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Habilitationsschrift

Biologika-Register in der Rheumatologie als moderne Instrumente der Pharmakovigilanz

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von

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Abkürzungen

ACPA	Anti-Citrullinated Protein Antibodies
ACR	American College of Rheumatology
ARTIS	Anti-Rheumatic Therapies In Sweden
bDMARD	biologic Disease Modifying Anti-Rheumatic Drug
BSG	Blutsenkungsgeschwindigkeit
BSRBR	British Society for Rheumatology Biologics Register
COPD	Chronic Obstructive Pulmonal Disease
CRP	C-Reaktives Protein
csDMARD	conventional synthetic Disease Modifying Anti-Rheumatic Drug
DANBIO	Danish Rheumatologic Database (of Biologic Drugs)
DAS, DAS28	Disease Activity Score (basierend auf 28 Gelenken)
DGRH	Deutsche Gesellschaft für Rheumatologie
DMARD	Disease Modifying Anti-Rheumatic Drug
DRFZ	Deutsches Rheuma-Forschungszentrum Berlin
EMA	Europäische Arzneimittelbehörde
EULAR	European League Against Rheumatism
GEE	Generalized Estimating Equation
HR	Hazard Ratio
HZ	Herpes Zoster
ICEBIO	Iceland's Biologics Register
IL	Interleukin
IPTW	Inverse Probability of Treatment Weighting
JAK	Janus-Kinase-Inhibitor
KI (CI)	Konfidenzintervall
LEF	Leflunomid
LIP	Lower Intestinal Perforation
MCP	Metacarpophalangeal
MTX	Methotrexat
NSAR	Non-Steroidale Anti-Rheumatika
OR	Odds Ratio
RA	Rheumatoide Arthritis
RABBIT	Rheumatoide Arthritis Beobachtung der Biologika-Therapie
RF	Rheumafaktor
RATIO	Research Axed on Tolerance of bIOtherapies
SI	Schwerwiegende Infektion
TNF, TNFα	Tumornekrosefaktor α
tsDMARD	targeted synthetic Disease Modifying Anti-Rheumatic Drug
UAW	unerwünschte Arzneimittelwirkung

1 Einleitung

1.1 Rheumatoide Arthritis

1.1.1 Epidemiologie

Etwa 1,5 Millionen Menschen, das sind zwei Prozent der erwachsenen Bevölkerung, leiden unter einer der über 100 verschiedenen entzündlich-rheumatischen Erkrankungen (DGRH, Kommission Versorgung, 2017 [1]). Hinzu kommen 20.000 rheumakranke Kinder [2].

Das Lebenszeit-Risiko für die Entwicklung einer entzündlich-rheumatischen Erkrankung beträgt rund 8% für Frauen und 5% für Männer [3].

Bei den Erkrankungen des Erwachsenenalters unterscheidet man Erkrankungen

- die vorrangig die Gelenke, aber auch innere Organe, betreffen, mit der rheumatoiden Arthritis (RA) als wichtigster Einzeldiagnose,
- der Wirbelsäule, mit der ankylosierenden Spondylitis als wichtigster Erkrankung und
- der Gefäße und des Bindegewebes (Vaskulitiden und Kollagenosen) mit dem systemischen Lupus erythematodes als wichtigster Diagnose.

Das gemeinsame Charakteristikum ist die chronische, systemische Entzündung.

In Abbildung 1 ist das Diagnosespektrum entzündlich-rheumatischer Erkrankungen der Patienten dargestellt, die sich in rheumatologisch fachärztlicher Behandlung befinden. Die Daten stammen aus der Kerndokumentation, einer seit Beginn der 1990er Jahre bundesweit durchgeführten systematischen Erfassung von jährlich rund 13.000 Patienten. Sie ermöglicht es, die Situation von Patienten, die in Deutschland rheumatologisch versorgt werden, im Langzeitverlauf zu beschreiben [4].

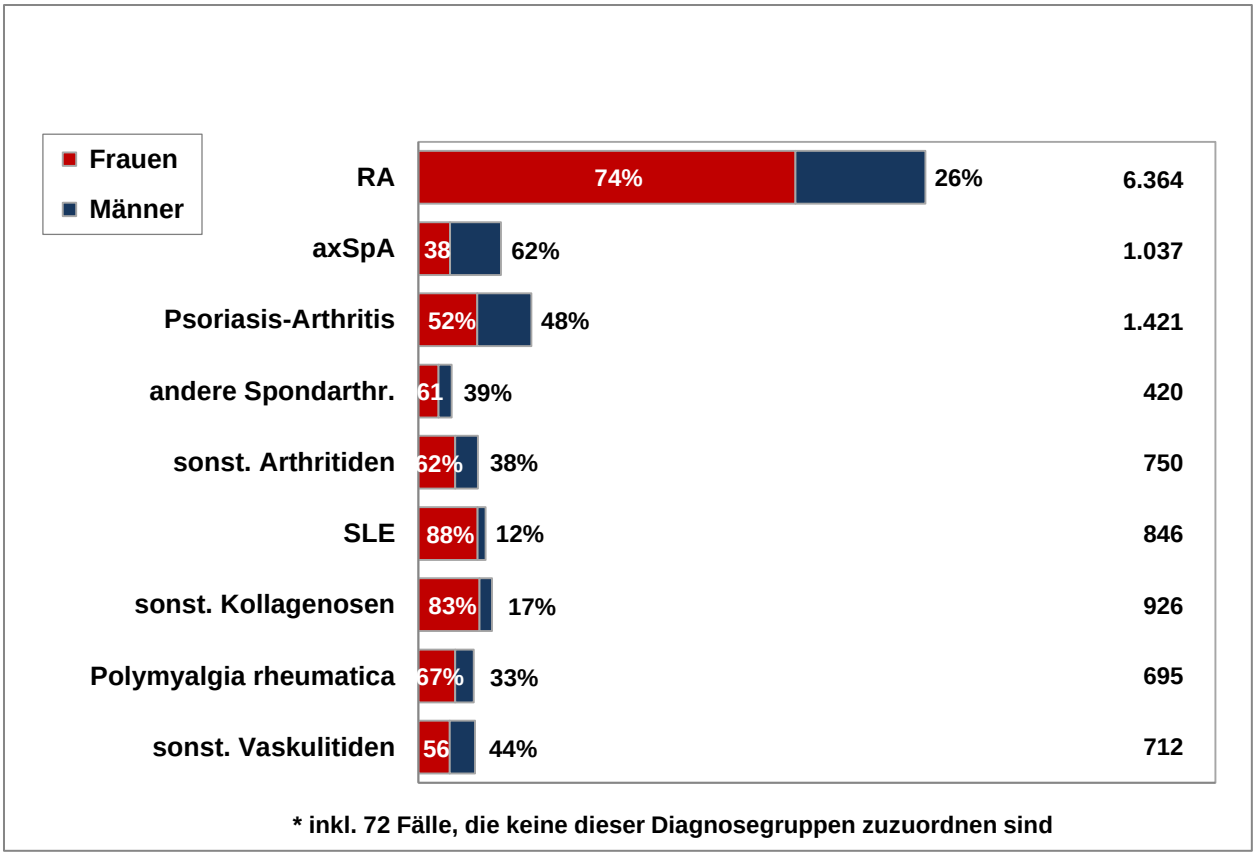

Abbildung 1. Diagnosespektrum entzündlich-rheumatischer Erkrankungen in der Kerndokumentation (n=13.243 ohne 72 Fälle, die keiner der Diagnosegruppen zugeordnet werden konnten)

(http://www.drfz.de/wp-content/uploads/Ergebnisse_Kerndokumentation_2016.pdf, letzter Zugriff 04/2019)

Die rheumatoide Arthritis (RA) ist die häufigste entzündlich-rheumatische Erkrankung. Ihre Prävalenz beträgt in Deutschland etwa 0,8% (0,3-1%) der erwachsenen Bevölkerung [5]. Frauen erkranken zwei- bis dreimal so häufig wie Männer [6], wobei sich das Geschlechterverhältnis mit zunehmendem Erkrankungsalter angleicht. Bis zum 45. Lebensjahr ist das Erkrankungsrisiko für Frauen gegenüber dem von Männern etwa um das 4fache erhöht, im höheren Alter ab 65 Jahren nur noch um das 1,4fache.

Bei der RA gibt es zwei Erkrankungsgipfel um das 55. und um das 75. Lebensjahr (Abbildung 2). Insgesamt liegt das mittlere Alter bei Erkrankungsbeginn für beide Geschlechter jenseits der 5. Lebensdekade, Männer erkranken etwa 5-8 Jahre später als

Frauen. Die jährliche Inzidenz beträgt insgesamt 20-40 Neuerkrankungen pro 100.000 Personen [7].

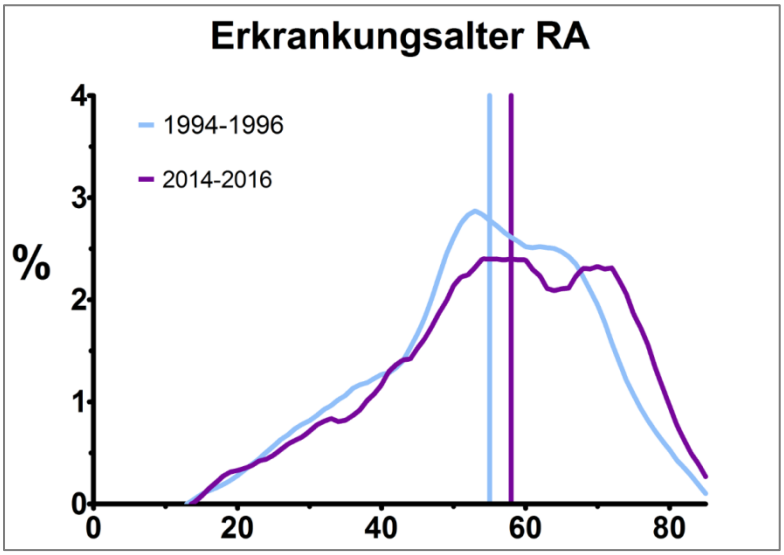

Abbildung 2. Alter bei Erkrankungsbeginn bei neu diagnostizierter RA in den Jahren 1994-96 und 2014-16 [8]

Risikofaktoren für die Entstehung einer RA sind neben einer genetischen Disposition („shared epitope“) [9, 10] auch Übergewicht [11] und Rauchen [12]. Ein dosisabhängiger Zusammenhang zwischen Intensität und Dauer der Rauch-Exposition (Pack-Years) ist gesichert. Dies gilt vor allem für Personen, die das HLA-DRB1 shared epitope [13] oder Autoantikörper gegen citrullinierte Proteine (ACPA) besitzen. Eine Studie aus den Niederlanden konnte zeigen, dass bei ACPA positiven Personen, die (noch) keine Arthritis hatten, das Risiko, eine Arthritis zu entwickeln, durch Rauchen auf das 9,6fache und durch Übergewicht auf das 5,6fache gesteigert wurde. Durch das Zusammentreffen beider Faktoren bei ACPA oder Rheumafaktor (RF) positiven Personen wurde das 28%ige Basisrisiko für die Entwicklung einer RA, auf 60% erhöht [14].

Da sowohl Rauchen als auch Übergewicht als Lebensstilfaktoren veränderbar sind, sollte bei familiärer Belastung oder bereits positivem Antikörperstatus eine entsprechende Beratung zur Primärprävention erfolgen.

1.1.2 *Krankheitsbild und Diagnose*

Die RA ist eine chronisch-entzündliche Gelenkerkrankung. Sie manifestiert sich meist an den kleinen Finger- und Zehengelenken, typischerweise sind Handwurzelknochen, Metacarpophalangealgelenke (MCP) und proximale Interphalangealgelenke (PIP) betroffen, aber auch andere Gelenke, wie Knie-, Schulter- und Hüftgelenke. Besonders kritisch ist der Befall der kleinen Wirbelgelenke im Bereich der Halswirbelsäule, der zu einer Instabilität und damit verbundener Rückenmarksschädigung führen kann.

Weitere Charakteristika der Erkrankung sind der symmetrische Befall, die ausgeprägte morgendliche Steifigkeit der Gelenke und der schubweise Verlauf mit Phasen höherer Krankheitsaktivität und Perioden dazwischen, in denen die Beschwerden milder sind. Unbehandelt kommt es durch die RA zu einer zunehmenden Zerstörung der Gelenke und zu weiteren Komorbiditäten. Besonders die anhaltende systemische Entzündung ist ein wichtiger Risikofaktor für, vor allem kardiovaskuläre, schwerwiegende Ereignisse und vorzeitige Mortalität. Das heutige gebräuchlichste Messinstrument zur Erfassung des Ausmaßes der systemischen Entzündung ist der ‘Disease Activity Score‘ (DAS)28, ein aus mehreren Parametern errechneter Score, in den sowohl die Anzahl der schmerzhaften und geschwollenen Gelenke (aus 28 definierten Gelenken) eingehen [15], als auch die Blutsenkungsgeschwindigkeit (BSG) und das globale Patientenurteil. Die ermittelten Werte zeigen geringe (DAS28 < 3,2), mittlere (3,2-5,1) oder hohe (> 5,1) Krankheitsaktivität an. Bei DAS28-Werten unter 2,6 spricht man von einer Remission der Erkrankung. Ein möglichst frühzeitiger Beginn der Therapie ist essentiell, um die systemische Inflammation kontrollieren zu können, bevor Schäden entstehen. Aus diesem Grund wurde in den letzten Jahren intensiv nach Möglichkeiten geforscht, um die Erkrankung in einem frühen Stadium identifizieren und sicher diagnostizieren zu können. Die 1987 vom American College of Rheumatology (ACR) publizierten Diagnosekriterien wurden 2010 von den ACR/EULAR (European League against Rheumatism) Kri-

terien abgelöst [16]. Ursprünglich als Klassifikationskriterien entwickelt, dienen sie zunehmend dazu, eine RA im Frühstadium zu diagnostizieren bzw. nicht-entzündliche Arthritiden sicher auszuschließen.

1.1.3 *Therapie der rheumatoiden Arthritis*

Das Ziel der RA-Therapie ist die Hemmung, im besten Fall das Beenden der systemischen Entzündung. Obwohl physikalische und Ergo-Therapie sowie Patientenschulung und Ernährungsumstellung wichtige Säulen der Behandlung von RA-Patienten darstellen, ist die medikamentöse Therapie essentiell für den Erhalt der Gelenkfunktionen und das Aufhalten des Krankheitsprozesses. Besonders zu Beginn der Erkrankung, aber auch in Phasen mit erhöhter Entzündungsaktivität werden verschiedene Therapieprinzipien kombiniert. Zur zügigen Schmerzlinderung und Entzündungshemmung kommen Glukokortikoide (systemisch oder als Gelenkinjektionen) und NSAR (Nicht-steroidale Antirheumatika) zum Einsatz. Ein langjähriger kontinuierlicher Gebrauch dieser Substanzen sollte jedoch wegen ihrer gastrointestinalen und kardiovaskulären Risiken vermieden werden.

Die Modifikation des Krankheitsverlaufs wird durch sogenannte Basistherapeutika ‚disease modifying anti-rheumatic drugs' (DMARDs) erreicht. Deren Wirkungseintritt ist häufig etwas verzögert, sie vermögen jedoch eine effiziente Eindämmung der Entzündung. Die am häufigsten verordneten konventionell synthetischen (cs)DMARDs sind Methotrexat (MTX) und Leflunomid (LEF). In leichteren Fällen oder bei Unverträglichkeiten können auch (Hydroxy-)Chloroquin, Azathioprin und Sulfasalazin eingesetzt werden. Auch eine Kombination verschiedener Basistherapeutika ist möglich.

Die Einführung von MTX in die Behandlung der RA Mitte der 1980er Jahre stellt einen Meilenstein in der Behandlung dar. Insbesondere bei frühem Einsatz lassen sich viele Krankheitsverläufe und damit die Prognose der Patienten günstig beeinflussen. Den-

noch sprechen 30-50% der Patienten im Verlauf der Erkrankung unzureichend auf MTX an. Die Zulassung der ersten Tumor-Nekrose-Faktor-Inhibitoren (TNFi) im Jahr 2001 und die in den Folgejahren auf den Markt gekommenen weiteren biotechnologisch entwickelten Antikörper, die spezifisch in das Immunsystem eingreifen, haben die Therapie der RA revolutioniert. In den letzten 15 Jahren hat sich durch den Einsatz dieser biologischen (b)DMARDs das Patientenbild in rheumatologischen Praxen stark gewandelt. Sie sind eine Option für Patienten, bei denen csDMARDs wegen Wirkversagen oder Unverträglichkeiten abgesetzt werden. Durch den Einsatz dieser Substanzen kann die Funktionsfähigkeit der Gelenke in vielen Fällen erhalten bleiben, was den Patienten den Verbleib im Berufsleben sowie die Teilhabe am normalen Leben ermöglicht.

Die Wirkprinzipien und Zielzellen der Antikörper-Therapien sind vielfältig, da es im Entzündungsprozess, ähnlich wie bei einem Orchester, mehrere Beteiligte gibt. Zum Einsatz bei der RA kommen deshalb B-Zell-depletierende Therapien (Rituximab/MabThera®) wie auch T-Zell-modulierende Therapien (Abatacept/Orencia®). Unter den Zytokin-inhibierenden Substanzen gibt es neben den TNF-Inhibitoren auch solche, die Interleukin (IL)-6 (Tocilizumab/RoActemra®) zum Ziel haben.

Nach dem Auslaufen der ersten TNFi Patente wurden ab dem Jahr 2015 auch Biosimilars für die Behandlung der RA zugelassen. Alle bDMARDs müssen parenteral verabreicht werden. Seit April/Mai 2017 sind mit den Januskinase (JAK)-Inhibitoren Baricitinib und Tofacitinib neue orale Therapieoptionen verfügbar.

1.2 Pharmakovigilanz

1.2.1 *Methoden der Pharmakovigilanz*

“Pharmakovigilanz ist die Gesamtheit der Maßnahmen zur Entdeckung, Erfassung, Bewertung und Vorbeugung von Nebenwirkungen sowie anderen arzneimittelbezogenen Problemen, die bei der Anwendung von Arzneimitteln auftreten.“ [17]

Die Erfassung unerwünschter Arzneimittelwirkungen (UAW) erfolgt meist anhand eines Spontanmeldesystems. In Deutschland sind Ärzte durch die Berufsordnung dazu verpflichtet, Verdachtsfälle von UAWs zu melden. Allerdings verhindern geringe Meldequoten von maximal 5-10% [18, 19] eine umfassende Analyse der UAWs. Ein zusätzlicher großer Nachteil von Spontanmeldesystemen ist, dass man den exakten Nenner, d.h. wie viele Personen gegenüber der Substanz exponiert waren, nicht kennt und somit keine Inzidenzen ermittelt oder verglichen werden können.

1.2.2 *Biologikaregister*

Zum Zeitpunkt der Zulassung der ersten TNFi zur Behandlung der rheumatoiden Arthritis im Jahr 2001 bestanden in der Rheumatologie erhebliche Bedenken bezüglich ihrer langfristigen Sicherheit. Insbesondere das Infektions- und Malignomrisiko, aber auch die Risiken des Auftretens neuer Autoimmunerkrankungen oder seltener schwerwiegender Ereignisse ließen sich aufgrund der Zulassungsstudien nicht beurteilen. Durch die randomisierten klinischen Studien hatte man eine gute Evidenz hinsichtlich der kurzfristigen Wirksamkeit und Sicherheit der Substanzen. Die Übertragbarkeit auf die in der täglichen Praxis behandelten Patienten war jedoch dadurch begrenzt, dass nur eine Minderheit dieser Patienten die Einschlusskriterien der klinischen Studien erfüllt [20]. Hinzu kommt, dass die Stichprobengrößen randomisierter klinischer Studien zu klein sind, um Risikoerhöhungen bei seltenen Ereignissen statistisch sichern zu können. Angesichts der Chronizität der rheumatoiden Arthritis müssen die Therapien in der Regel

langfristig, nicht selten lebenslang, angewandt werden. Die Zeithorizonte der klinischen Studien sind bei weitem zu kurz, um die Sicherheit in der Langzeitanwendung zu beurteilen.

Der neue, hochwirksame und zielgerichtet in das Immunsystem eingreifende, Wirkmechanismus und die ungeklärten Fragen im Hinblick auf die langfristige Sicherheit der ersten TNFi gaben 2001 den Anstoß für die Einrichtung von so genannten Biologika-Registern in verschiedenen europäischen Ländern. Obwohl die Studiendesigns durchaus unterschiedlich sind, haben alle das gemeinsame Ziel, die Sicherheit und Wirksamkeit der TNFi (und später weiterer bDMARDs, Biosimilars und JAK-Inhibitoren) im Vergleich zur csDMARD Therapie unter Alltagsbedingungen zu untersuchen [21]. Bei den meisten Registern handelt es sich um klinische Kohortenstudien, in die Patienten prospektiv eingeschlossen und über einen längeren Zeitraum dokumentiert werden. Einige dieser Register haben eine interne, csDMARD-therapierte Kontrollgruppe, wie das britische und das deutsche Biologikaregister, andere, z.B. die skandinavischen Register DANBIO, ARTIS und ICEBIO, können durch Verlinkung mit anderen Datenquellen die mit Biologika behandelten Patienten mit nicht exponierten Patienten oder mit Personen aus der Allgemeinbevölkerung vergleichen [22]. Dies ist besonders dann von Vorteil, wenn bei einer vermuteten erhöhten Inzidenz von Ereignissen beurteilt werden soll, ob diese Risikoerhöhung eher der zugrundeliegenden Erkrankung oder deren Therapie zugerechnet werden muss. Die Verlinkung der Daten mit den jeweiligen nationalen Krebsregistern ermöglicht robuste Analysen der Malignominzidenzen.

Der hohe Erfassungsgrad der Bevölkerung in den skandinavischen Registern, deren Daten zumeist aus klinischer Routinedokumentation stammen, wird durch eine geringere Tiefe und Vollständigkeit bei den klinischen Parametern erkauft. Das französische RATIO Register hat ein Alleinstellungsmerkmal, da es speziell zur Analyse von Lym-

phomen und schwerwiegenden bzw. opportunistischen Infektionen konzipiert wurde [23] und keine anderen unerwünschten Ereignisse erfasst .

Ein weiterer Unterschied zwischen den verschiedenen europäischen Registern besteht darin, ob die Dokumentation verpflichtend oder freiwillig ist. So war beispielsweise über viele Jahre hinweg in Großbritannien die Kostenerstattung der innovativen Therapien an die Bedingung gebunden, dass die Patienten im britischen Biologika-Register dokumentiert wurden. Damit wurde eine bis zu 90%ige Abdeckung der behandelten Patientengruppe erreicht, und das Register wies schnell große Patientenzahlen auf. Demgegenüber sind auf Freiwilligkeit basierende Register wie das deutsche RABBIT-Register einer möglichen Selektion ausgesetzt. Außerdem müssen deutlich mehr Anstrengungen unternommen werden, um vergleichbare Patientenzahlen zu erreichen.

Die bislang entstandenen rheumatologischen Biologika-Register sind entweder auf einzelne rheumatologische Erkrankungen fokussiert, wie z.B. das deutsche RABBIT-Register und das britische BSRBR-Register, die nur Patienten mit RA einschließen, oder sie erfassen Patienten mit unterschiedlichen entzündlich-rheumatischen Erkrankungen, wie das dänische DANBIO oder das tschechische ATTRA Register, die neben Patienten mit RA auch Patienten mit ankylosierender Spondylitis und solche mit Psoriasisarthritis beobachten. Der Vorteil krankheitsspezifischer Register liegt darin, dass in größerem Umfang auf einzelne Krankheitsbilder zugeschnittene Messinstrumente verwendet werden können. Zumindest war dies ein großer Vorteil, so lange die Dokumentation papierbasiert erfolgte. Die neueren Register sind web-basiert und können mit krankheitsspezifischen Modulen arbeiten. Diesen Weg gehen z.B. die in jüngerer Zeit ebenfalls am DRFZ initiierten Register RABBIT-SpA für axiale Spondyloarthritis und Psoriasisarthritis [24] oder das Schwangerschaftsregister Rhekiss [25], das Module für sieben verschiedene entzündlich-rheumatische Krankheiten enthält.

1.3 Fragestellung und Zielsetzung

Die in den klinischen Studien gewonnenen Daten zur Sicherheit und Wirksamkeit von Therapien, die unter anderem den Zulassungsbehörden als Bewertungsgrundlage dienen, sind durch geringe Patientenzahl und meist kurzer Studiendauer bis zu 6 Monaten unzureichend gepowert, um Sicherheitssignale seltener Ereignisse zu entdecken oder die Sicherheit der Therapien in der Langzeitanwendung zu überprüfen. Darüber hinaus sind Patienten durch die Ein- und Ausschlusskriterien klinischer Studien streng selektiert und entsprechen nicht denen des klinischen bzw. Praxisalltags. Letztere sind meist bedeutend älter, haben häufiger und mehr Komorbiditäten, deutlichere Funktionseinschränkungen und sind häufiger weiblich [20]. Wenn Therapien mit neuen Wirkprinzipien nach der Zulassung im Praxisalltag verschrieben werden, benötigt man deshalb gute Instrumente der Pharmakovigilanz, um deren Anwendungssicherheit für das gesamte Patientenspektrum und in der Langzeitanwendung zu belegen. Spontanmeldesysteme oder Sekundärdatenanalysen sind hierfür nur bedingt geeignet.

Ziel der vorliegenden Arbeit ist es, am Beispiel von Ergebnissen aus dem RABBIT Register die Bedeutung von Biologikaregistern als Instrumente der Pharmakovigilanz darzulegen sowie ihre Schwächen und Limitationen aufzuzeigen.

Für alle hier vorgestellten Arbeiten wurden Daten des deutschen Biologikaregisters RABBIT ausgewertet. Ihnen gemeinsam ist die Analyse von unerwünschten Ereignissen, die im Rahmen der medikamentösen Therapie der RA auftreten, sowie die Identifikation und Untersuchung weiterer Risikofaktoren, die mit diesen Ereignissen assoziiert sind oder sein könnten.

Das RABBIT Register ist eine prospektive Langzeitkohortenstudie, die 2001 initiiert wurde. Volljährige Patienten mit einer RA, die nach dem 16. Lebensjahr diagnostiziert wurde, können eingeschlossen werden, wenn sie entweder eine in Deutschland zur Be-

handlung der RA zugelassene Biologika-/Biosimilar-/oder JAK-Inhibitor-Therapie neu beginnen oder wenn sie nach mindestens einem csDMARD Versagen eine weitere cs-DMARD Therapie beginnen (=Kontrollgruppe).

Die hier vorgestellten Arbeiten verdeutlichen die methodischen Schwierigkeiten bei der Auswertung von Längsschnitt- und Beobachtungsdaten und zeigen Lösungsansätze, um für diese ‚Fehlerquellen' in der statistischen Analyse zu kontrollieren. Die Arbeiten sind in einen Gesamtkontext eingebettet und stellen jeweils Untersuchungen zu kurzfristig auftretenden unerwünschten Ereignissen, solchen mit langer Latenzzeit und sehr seltenen Ereignissen dar. Die beiden letzten Arbeiten verdeutlichen das Risiko für Komorbidität und vorzeitige Mortalität, das über eine hohe Krankheitsaktivität vermittelt wird.

2 Eigene Arbeiten

2.1 Ereignisse mit kurzer Latenz – Untersuchung des Risikos für virale und bakterielle Infektionen und deren Ausgang

2.1.1 Wie hoch ist das Risiko für Herpes zoster Reaktivierungen?

Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, Zink A. *Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents*. JAMA. 2009 Feb 18;301(7):737-44. doi: 10.1001/jama.2009.146. PubMed PMID: 19224750.

Zusammenfassung

Dass das Risiko für bakterielle Infektionen unter TNFi Therapie im Vergleich zu cs-DMARDs erhöht ist, wurde aus verschiedensten Studien berichtet, mehrere Fallbeispiele opportunistischer Infektionen waren publiziert worden. Im Gegensatz dazu war bis zum Zeitpunkt unserer Analyse wenig über die Reaktivierung latenter Virusinfektionen bei der Verordnung von TNFi unter Alltagsbedingungen bekannt.

Wir untersuchten die Häufigkeit und Ausprägungen der bis 1.11.2007 an das RABBIT Register gemeldeten Herpes zoster (Gürtelrose)-Ereignisse und analysierten die Assoziation zur verabreichten Therapie und zwar dahingehend, ob a) TNFi generell als Substanzklasse das Auftreten eines Herpes zoster (HZ) erhöhen und ob b) das Risiko unter einer Therapie mit den monoklonalen Antikörpern (Adalimumab (Humira®) und Infliximab (Remicade®)) sich von dem Risiko, das unter einer Etanercept (Enbrel®) Therapie besteht, unterscheidet. Unter den insgesamt 5040 in die Analyse einbezogenen Patienten, waren 86 HZ-Episoden bei 82 Patienten aufgetreten. N=18 Ereignisse waren schwerwiegend und führten in 12 Fällen zu einem Krankenhausaufenthalt.

Die rohen Inzidenzraten unter TNFi waren signifikant höher als unter csDMARD Therapie (10.1 vs. 5.6/1000 Patientenjahre). Vor allem die Inzidenzraten schwerwiegender

HZ-Ereignisse (multidermatomale und ophthalmische HZ) unterschieden sich deutlich: 0.8 (0.009-2.8) /1000 Patientenjahre unter Etanercept, 3.7 (2.0-6.3) unter Adalimumab/Infliximab und 0.9 (0.3-2.4) unter csDMARD Therapie.

In der multivariaten Cox-Regression fanden wir, adjustiert für Alter, Schwere der Erkrankung (mittels Propensity Score-Adjustierung) und Glukokortikoidgebrauch ein signifikant erhöhtes Risiko für das Auftreten eines HZ unter der Therapie mit monoklonalen Antikörpern im Vergleich zur Therapie mit csDMARDs (HR 1.82 [95%KI 1.1-3.2]), wohingegen für das Rezeptorfusionsprotein Etanercept keine Risikoerhöhung festgestellt werden konnte (HR1.36 [95%KI 0.7-2.6]). Dies führte dazu, dass für die Substanzklasse TNFi als Ganzes das Risiko für die Reaktivierung eines HZ im Vergleich zur Therapie mit csDMARDs nicht signifikant erhöht war (HR 1.63 [95%KI 0.97-2.7]). Da weitere Risikofaktoren wie höheres Alter und eine Therapie mit Glukokortikoiden häufig zur TNFi Therapie hinzukommen, sollten Patienten, die eine monoklonale TNFi-Therapie erhalten, aufmerksam auf erste Zeichen einer HZ Reaktivierung untersucht werden, um frühzeitig zu intervenieren und schwerwiegende Folgen zu vermeiden.

Risk of Herpes Zoster in Patients With Rheumatoid Arthritis Treated With Anti–TNF-α Agents

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Context The risk of bacterial infection is increased in patients treated with drugs that inhibit tumor necrosis factor α (TNF-α). Little is known about the reactivation of latent viral infections during treatment with TNF-α inhibitors.

Objective To investigate whether TNF-α inhibitors together as a class, or separately as either monoclonal anti–TNF-α antibodies (adalimumab, infliximab) or a fusion protein (etanercept), are related to higher rates of herpes zoster in patients with rheumatoid arthritis.

Design, Setting, and Patients Patients were enrolled in the German biologics register RABBIT, a prospective cohort, between May 2001 and December 2006 at the initiation of treatment with infliximab, etanercept, adalimumab, or anakinra, or when they changed conventional disease-modifying antirheumatic drug (DMARD). Treatment, clinical status, and adverse events were assessed by rheumatologists at fixed points during follow-up.

Main Outcome Measures Hazard ratio (HR) of herpes zoster episodes following anti–TNF-α treatment. Study aims were to detect a clinically significant difference (HR, 2.0) between TNF-α inhibitors as a class compared with DMARDs and to detect an HR of at least 2.5 for each of 2 types of TNF-α inhibitors, the monoclonal antibodies or the fusion protein, compared with conventional DMARDs.

Results Among 5040 patients receiving TNF-α inhibitors or conventional DMARDs, 86 episodes of herpes zoster occurred in 82 patients. Thirty-nine occurrences could be attributed to treatment with anti–TNF-α antibodies, 23 to etanercept, and 24 to conventional DMARDs. The crude incidence rate per 1000 patient-years was 11.1 (95% confidence interval [CI], 7.9-15.1) for the monoclonal antibodies, 8.9 (95% CI, 5.6-13.3) for etanercept, and 5.6 (95% CI, 3.6-8.3) for conventional DMARDs. Adjusted for age, rheumatoid arthritis severity, and glucocorticoid use, a significantly increased risk was observed for treatment with the monoclonal antibodies (HR, 1.82 [95% CI, 1.05-3.15]), although this risk was lower than the threshold for clinical significance. No significant associations were found for etanercept use (HR, 1.36 [95% CI, 0.73-2.55]) or for anti–TNF-α treatment (HR, 1.63 [95% CI, 0.97-2.74]) as a class.

Conclusion Treatment with monoclonal anti–TNF-α antibodies may be associated with increased risk of herpes zoster, but this requires further study.

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INHIBITION OF TUMOR NECROSIS FACTOR α (TNF-α) has been shown effective in the treatment of patients with active rheumatoid arthritis. For patients in whom the disease activity cannot be sufficiently controlled with conventional disease-modifying antirheumatic drugs (DMARDs), drugs targeting TNF-α have become indispensable. Increased use of anti–TNF-α agents for routine care of rheumatoid arthritis, as well as their use to treat an increasing number of other diseases such as ankylosing spondylitis, psoriatic arthritis, and inflammatory bowel disease, has led to the need to better understand their safety profiles. Obtaining such knowledge is a primary aim of the biologics registers established in several countries at the time these new agents were introduced.

There is evidence from randomized controlled trials (RCTs)[1,2] as well as observational cohort studies[3-5] and claims data[6] that patients treated with anti–TNF-α agents are at increased risk of bacterial infections. Furthermore, opportunistic infections of all etiologies have been reported in such patients. These data suggest that patients should be carefully monitored and that specific attention be paid to atypical sites or symptoms of infection.

Compared with bacterial infection, little is known about the risk of viral infections in patients with rheumatoid arthritis undergoing anti–TNF-α treatment.

For editorial comment see p 774.

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Herpes zoster, a neurocutaneous disease characterized by a painful vesicular dermatomal rash resulting from reactivation of the varicella zoster virus (VZV), is one of the most common adverse events reported in clinical trials of anti–TNF-α agents. Complications include bacterial superinfection and, more frequently, postherpetic neuralgia, which can cause substantial morbidity. Declining cellular immunity due to increasing age or immunosuppression is known to trigger reactivation of herpes zoster.[7] Immunodeficiency in any form was shown to strongly increase the risk of developing herpes zoster in studies of children with leukemia,[8,9] recipients of bone marrow transplants,[10] and individuals infected with human immunodeficiency virus.[11]

Patients with rheumatoid arthritis, systemic lupus erythematosus, or noninflammatory musculoskeletal disorders are at increased risk of herpes zoster compared with the general population.[12,13] In a retrospective study, Smitten et al analyzed a US claims database and the UK general practitioner database and found adjusted hazard ratios (HRs) of 1.91 (95% confidence interval [CI], 1.80-2.03) and 1.65 (95% CI, 1.57-1.75), respectively, for herpes zoster in patients with rheumatoid arthritis compared with patients without rheumatoid arthritis.[14] We analyzed data from the German biologics register RABBIT to investigate the contribution of various rheumatoid arthritis treatments, especially anti–TNF-α therapy, to the risk of VZV reactivation.

METHODS

RABBIT is an ongoing nationwide prospective cohort study initiated in 2001 with the purpose of investigating the long-term safety and effectiveness of biologic agents in treatment of rheumatoid arthritis. The study includes patients from more than 150 outpatient clinics and private practices specializing in rheumatology.[15] From May 1, 2001, to December 31, 2006, all patients with rheumatoid arthritis starting new treatment with either infliximab, etanercept, adalimumab, or anakinra and patients who were changing their DMARD treatment after at least 1 DMARD failure (control group) were asked by their rheumatologist to participate in the register. Once enrolled, data collection from the patients would continue until the end of 2011. The study protocol was approved in 2001 by the ethics committee of the Charité University School of Medicine, Berlin, Germany. Every patient participating in the study provided written informed consent before study entry.

At baseline and during fixed points of follow-up at 3, 6, 12, 18, 24, 30, and 36 months, data regarding treatment, disease activity (tender and swollen joint count, erythrocyte sedimentation rate, C-reactive protein level, and morning stiffness), comorbid conditions, and adverse events were recorded by the treating rheumatologist. Treatment information included the start and stop dates of DMARD therapy, as well as biologic therapies, reasons for treatment termination, and concomitant therapy with glucocorticoids, nonsteroidal anti-inflammatory drugs, or cyclooxygenase 2 selective inhibitors. The data recorded by the rheumatologist were complemented by patient questionnaires that also assessed functional capacity (measured by the Hannover Functional Status Questionnaire as percentage of full function[16]], global health status, pain, current disease activity, and adverse effects of the prescribed medications.

Adverse events were recorded and classified by the rheumatologist as serious or nonserious according to the International Conference on Harmonization E2A guidelines.[17] In addition, these events were graded as mild, moderate, or severe.[18] All adverse events were coded using the Medical Dictionary for Regulatory Affairs[19] by the study physician (A.S.).

All events reported from the treating rheumatologist prior to November 1, 2007, and coded as herpes zoster, herpes zoster multidermatomal, herpes zoster disseminated, herpes zoster oticus, herpes zoster ophthalmic, herpes zoster iridocyclitis, and herpes zoster infection neurological were included in the analysis. All patient reports of adverse effects were additionally screened to check the completeness of the physician reports. This procedure revealed 2 additional cases of herpes zoster treated with etanercept; these were included in the analysis after confirmation with the treating physician.

We considered a patient as receiving anti–TNF-α treatment at the time of the event if treatment was ongoing or was terminated 1 month or less prior to the event. The remaining treatment periods were regarded as periods under control conditions. Because of the low number of patient-years contributed to the data set, we excluded all events and observation periods after start of treatment with anakinra (76 patient-years) or rituximab (60 patient-years). Furthermore, we excluded 152 patients (2.9%) who did not have follow-up data.

Main Study Questions

The statistical analysis plan prespecified 2 hypotheses. First, that anti–TNF-α treatment is associated with an increased risk of herpes zoster. Second, that owing to different modes of action, the risk associated with treatment with the monoclonal antibodies (adalimumab or infliximab) differs from that conferred by the receptor fusion protein etanercept when compared with conventional DMARD treatment. This second hypothesis was suggested by data regarding the biology of granulomatous infections[20] and by our previous findings regarding all herpes infections.[3] The first hypothesis of a class effect may be inappropriate if the second hypothesis of a subclass effect is true. We did not adjust for multiple testing, because in a safety analysis it is more important to detect a possible risk (low β error) than to avoid an erroneous rejection of the null hypothesis (no association).

Statistical Analysis

Crude incidence rates were calculated as the number of herpes zoster infections per 1000 patient-years of follow-up (under specific treatment). Survival analysis methods (Cox regression,

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Andersen-Gill models[21]) were applied to identify risk factors for herpes zoster and to estimate the contribution of anti–TNF-α treatment to that risk. By Cox regression, the contribution of time-independent and time-dependent covariates to the first development of herpes zoster was investigated. The follow-up time following this event was not considered in this analysis. Patient characteristics at baseline (age, sex, comorbid conditions, and disease activity measured by the Disease Activity Score based on 28 joint counts [DAS28]) and parameters that varied with time during follow-up (treatment with glucocorticoids, treatment with anti–TNF-α agents, DAS28 at follow-up) were taken into account as possible risk factors.

To deal with confounding by indication, a propensity score (likelihood of being treated with anti–TNF-α agents) approach was applied. The propensity score was estimated by means of logistic regression with the covariates age, sex, number of previous DMARDs, DAS28, erythrocyte sedimentation rate, Hannover Functional Status Questionnaire score, and as additional markers of disease severity: osteoporosis (yes/no) and previous treatment with cyclosporine A (yes/no).[22] The tertiles of this score were used for stratification of the patients into 3 groups of equal size and increasing propensity score. These groups were then included as covariates in Cox and Andersen-Gill regression analyses for adjustment. This type of analysis allows showing the influence of the propensity score as a "severity indicator." We used tertiles instead of quintiles to increase the robustness of the model. Nevertheless, in a sensitivity analysis we also performed stratified regression analyses with quintiles, as proposed originally by D'Agostino.[23] Since the HRs of both analyses (stratified or with covariates) were very similar, we report only the results of the covariate adjustment. In a primary analysis, we analyzed the factors associated with the occurrence of herpes zoster in the total sample by means of Cox regression.

Based on our previous findings, we aimed to detect a 2-fold increase (HR, 2.0) in the hazard risk of developing herpes zoster in patients treated with anti–TNF-α agents. In the case of different risk profiles of anti–TNF-α agents, we aimed to detect at least a 2.5-fold increase in the hazard risk of patients treated with the monoclonal antibodies or with etanercept. To achieve 80% power for both hypotheses it was necessary to have observed 80 cases of herpes zoster, which occurred in November 2007. At that point we merged the data from the adverse events database with the clinical and treatment database and performed the current analysis.

In a secondary analysis, we selected a subsample of patients who switched treatments and had episodes while receiving anti–TNF-α therapy, as well as "control episodes" of more than 1 month of treatment with a traditional DMARD, glucocorticoids, or both. Applying Andersen-Gill models, we considered the complete follow-up time of these patients and investigated whether the first or second occurrence of herpes zoster was observed within an anti–TNF-α treatment episode or within a control episode.

Calculations were performed using the PHREG procedure in SAS version 9.1 (SAS Institute Inc, Cary, North Carolina). Furthermore, the invariance of the herpes zoster over time was investigated by means of a test developed by Thernau and Grambsch.[24] To check for possible incompleteness in our multivariate models, standard errors and CIs of the HRs were calculated by means of robust sandwich estimates.[25] These data are not shown, since they differed only slightly from the estimates calculated using the standard methods. All statistical tests performed were 2-sided; $P < .05$ was considered statistically significant.

RESULTS

A total of 5040 patients were included in the analysis. Baseline characteristics are shown in TABLE 1. Patients receiving anti–TNF-α treatment differed significantly from controls in regard to age, disease duration, rheu-

Table 1. Baseline Characteristics

Characteristic	Anti–TNF-α Agents				Controls (n = 1774)	*P* Value[a]
	Etanercept (n = 1252)	Infliximab (n = 591)	Adalimumab (n = 1423)	Total (n = 3266)		
Age, mean (SD), y	53.8 (12.5)	52.9 (12.7)	54.2 (12.0)	53.8 (12.3)	56.2 (11.4)	<.001
Women, No. (%)	975 (77.8)	433 (73.3)	1141 (80.2)	2549 (78.0)	1394 (78.6)	.66
Rheumatoid factor–positive, No. (%)	1008 (80.5)	469 (79.4)	1143 (80.4)	2620 (80.3)	1271 (71.7)	<.001
FFbH score, mean (SD)[b]	56.0 (22.9)	55.3 (21.6)	58.6 (23.4)	57.0 (22.9)	66.6 (21.5)	<.001
Disease duration, median (IQR), y	9 (4-16)	8.5 (4-14)	10 (5-17)	9 (5-16)	6 (3-12)	<.001
DAS28, mean (SD)	5.8 (1.3)	5.9 (1.2)	5.7 (1.3)	5.8 (1.3)	5.0 (1.3)	<.001
CRP, median (IQR), mg/L	16 (5-37)	17 (7-41)	13 (5-30)	17 (8-38)	8 (3-22)	<.001
Previous DMARD therapies, No. (%)	3.6 (1.4)	3.7 (1.5)	3.5 (1.4)	3.5 (1.4)	1.8 (1.1)	<.001
Glucocorticoids, No. (%)	1073 (86.1)	498 (84.4)	1154 (81.6)	2725 (83.8)	1354 (76.5)	<.001
Prednisolone ≥10 mg/d, No. (%)	440 (35.1)	217 (36.7)	416 (29.2)	1073 (32.9)	343 (19.3)	<.001

Abbreviations: CRP, C-reactive protein; DAS28, Disease Activity Score based on 28 joint counts; DMARD, disease-modifying antirheumatic drugs; FFbH, Hannover Functional Status Questionnaire; IQR, interquartile range; TNF, tumor necrosis factor.
SI conversion factor: To convert CRP values to nmol/L, multiply by 9.524.
[a] For comparison of anti–TNF-α agents total with controls.
[b] Functional capacity in percentage of full function.

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Table 2. Crude Incidence Rates of Herpes Zoster Events per 1000 Patient-years

	Anti–TNF-α Agent			
	Etanercept	Infliximab/ Adalimumab	Total	Controls
Observed patient-years	2588	3524	6112	4291
Herpes zoster				
No.	23	39	62	24
Incidence rate (95% CI)	8.9 (5.6-13.3)	11.1 (7.9-15.1)[a]	10.1 (7.8-13.0)[a]	5.6 (3.6-8.3)
Multidermatomal and ophthalmic zoster only				
No.	2	13	15	4
Incidence rate (95% CI)	0.8 (0.009-2.8)	3.7 (2.0-6.3)	2.5 (1.4-4.0)	0.9 (0.3-2.4)

Abbreviations: CI, confidence interval; TNF, tumor necrosis factor.
[a]Significantly different ($P<.05$) compared with controls.

matoid factor positivity, functional status, and number of previous DMARD failures. In addition, they had higher disease activity (as measured by the DAS28) at the time of inclusion in the study. No differences in demographic or clinical characteristics were found between patients treated with the 3 individual anti–TNF-α agents.

There were 86 cases of herpes zoster among 82 patients. Fifteen patients had multidermatomal zoster, and 4 had herpes zoster ophthalmicus. Eighteen events were serious, 12 of which required hospitalization due to either severe multidermatomal disease (n=8), eye involvement (n=1), or other reasons (n=3). Complications were reported in 3 patients. Postherpetic neuralgia occurred in 2 patients (1 while receiving etanercept and 1 while receiving adalimumab), and multidermatomal zoster with esophagitis and pulmonary involvement occurred in 1 patient (while receiving infliximab).

Compared with the control group, we found significantly higher crude incidence rates of herpes zoster in the patients receiving anti–TNF-α-treatment ($P=.01$), especially in those treated with the monoclonal antibodies (TABLE 2). Among the cases of multidermatomal herpes zoster, the crude incidence rate was highest for patients treated with the monoclonal antibodies (3.8 [95% CI, 1.0-9.7] per 1000 patient-years for patients treated with infliximab and 3.6 [95% CI, 1.7-6.9] per 1000 patient-years for patients treated with adalimumab). Five patients experienced recurrent episodes of herpes zoster that were not always located at the site of the primary occurrence. Two occurred in the control group, 2 in patients receiving etanercept, and 1 in a patient receiving unknown therapy. This last patient had been enrolled in an RCT after several years of observation in RABBIT and was excluded from our analyses because the exact treatment at the time of the herpes zoster epsiode was unknown.

Univariate Cox regression analysis (TABLE 3) showed a significantly increased risk of herpes zoster with increasing age (HR, 1.23 [95% CI, 1.02-1.49] per 10 years) and higher disease activity at baseline, as measured by the DAS28 (HR, 1.36 per unit increase [95% CI, 1.14-1.63]). An insignificant association was found for longer disease duration as a risk factor. We found a nonlinear increase in the risk of herpes zoster with increasing likelihood of being treated with biologics (propensity score tertiles). Patients with a high likelihood of being treated with biologics (patients with a propensity score >0.86, constituting the upper one-third of the propensity score tertiles) had a nearly 2-fold risk of herpes zoster compared with the remaining patients (10.9 [95% CI, 7.8-14.9] per 1000 patient-years vs 6.5 [95% CI, 4.7-8.7] per 1000 patient-years). Similar results were found by stratification of patients into quintiles of the propensity score, as proposed by D'Agostino.[23] Using this strategy, patients from the fourth and fifth quintiles had a 1.9-fold significantly higher risk for herpes zoster than the remaining patients, whereas patients from the first, second, and third quintiles did not differ significantly in their risk.

Baseline features that were not significantly associated with herpes zoster were female sex, positive rheumatoid factor, and functional capacity (as measured using the Hannover Functional Status Questionnaire) at study entry. No associations ($P>.90$) were found for specific comorbid conditions (eg, diabetes, renal insufficiency, and pulmonary disease; data not shown).

Treatment factors associated with an increased risk of herpes zoster were glucocorticoid use and treatment with anti–TNF-α agents, compared with conventional DMARD treatment. The corresponding incidence rates for episodes of herpes zoster during anti–TNF-α treatment and DMARD treatment were 9.8 (95% CI, 7.5-12.6) per 1000 patient-years and 5.1 (95% CI, 3.2-7.8) per 1000 patient-years. For the monoclonal antibodies and etanercept, the rates were 11.1 (95% CI, 7.9-15.1) per 1000 patient-years and 8.1 (95% CI, 5.0-12.4) per 1000 patient-years, respectively. There was no significant trend in HR over time; therefore, the application of Cox regression analysis was appropriate. We observed a greater risk of herpes zoster associated with increasing doses of glucocorticoids (Table 3). No significant associations were found for treatment with MTX ($P=.87$), leflunomide ($P=.12$), or azathioprine ($P=.13$). The corresponding incidence rates per 1000 patient-years were 7.8 (95% CI, 5.7-10.3), 5.5 (95% CI, 2.9-9.4), and 18.4 (95% CI, 3.8-53.8), respectively.

In the multivariate Cox regression analysis, anti–TNF-α treatment as a class was not significantly associated with an increased risk of herpes zoster (HR, 1.63 [95% CI, 0.97-2.74]). In subgroup analysis, we found no significantly increased risk of herpes zoster for patients treated with etanercept, whereas patients treated with either infliximab or adalimumab had a significantly increased risk (HR, 1.82 [95% CI, 1.05-3.15]) (Table 3), although this risk was lower than the study's predefined HR threshold of 2.5

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for clinical significance. The association for glucocorticoid use of 10 mg or more per day remained significant, even when the data were adjusted for age and disease severity using the propensity score (Table 3). Because of the high correlation of the DAS28 with both the propensity score and glucocorticoids use, it was not included in the multivariate model.

Subsample Analyses of Patients Who Switched Treatments

To investigate whether the adjustment by propensity score modeling was sufficient or whether selection bias resulting in higher risk for use of anti–TNF-α agents remained, we examined a subsample of 1344 patients who switched treatment at least once and therefore contributed data to the cohort while receiving anti–TNF-α treatment, as well as while receiving conventional DMARD treatment alone. On average, a patient from this subsample was treated for 15.8 months with anti–TNF-α therapy and 11.3 months with conventional DMARDs alone (TABLE 4). This subgroup of patients who had switched treatments had a higher risk of herpes zoster than the remaining sample (adjusted HR, 2.4 [95% CI, 1.5-3.9]).

We then considered the complete follow-up period of these patients and investigated whether herpes zoster was observed during control episodes or during episodes of treatment with anti–TNF-α agents. We observed incidence rates of 23.8 (95% CI, 15.5-34.8) per 1000 patient-years for treatment with monoclonal antibodies, 7.8 (95% CI, 2.5-18.2) per 1000 patient-years for treatment with etanercept, 17.9 (95% CI, 12.1-25.3) per 1000 patient-years for anti–TNF-α treatment as a class, and 6.9 (95% CI, 3.2-13.1) per 1000 patient-years for the control episodes. After adjustment for age and propensity score, treatment with anti–TNF-α agents was associated with a significantly increased risk of herpes zoster (TABLE 5). The association was highly significant for treatment with monoclonal antibodies (HR for adalimumab/infliximab vs controls, 2.91 [95% CI, 1.35-6.30]) and not significant for etanercept (HR, 1.09 [95% CI, 0.39-3.06]). Age remained a significant predictor in this analysis, whereas no association was found for treatment with glucocorticoids ($P > .70$ for any dosage).

Table 3. Risk of Herpes Zoster

Characteristic	Patients With Herpes Zoster, No.	Patient-years	Univariate Cox Regression		Multivariate Analysis	
			HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Characteristics at study entry						
Age, y[a]			1.23 (1.02-1.49)	.03	1.28 (1.05-1.55)	.01
Sex						
Men	17	2221	1 [Reference]			
Women	65	8260	1.04 (0.61-1.77)	.90		
Disease duration, y[b]			1.09 (0.98-1.22)	.10		
Rheumatoid factor						
Negative	20	2312	1 [Reference]			
Positive	62	8168	0.89 (0.54-1.48)	.66		
CRP[a]			1.04 (0.99-1.09)	.11		
DAS28			1.36 (1.14-1.63)	<.001		
FFbH[a]			0.96 (0.88-1.06)	.41		
Propensity score						
Tertile 1 (low)	19	3176	1 [Reference]			
Tertile 2 (moderate)	23	3324	1.26 (0.69-2.30)	.45		
Tertile 3 (high)	39	3571	2.06 (1.20-3.54)	.008		
High vs moderate/low	39	3571	1.84 (1.19-2.83)	.006	1.59 (1.00-2.52)	.05
Characteristics at follow-up						
Glucocorticoids, mg						
0	9	2317	1 [Reference]			
1-9	54	6681	2.06 (1.02-4.18)	.04	1.86 (0.92-3.78)	.09
≥10	19	1482	2.90 (1.30-6.47)	.01	2.52 (1.12-5.65)	.03
DAS28			1.21 (1.02-1.43)	.03		
DMARDs	22	4291	1 [Reference]			
Anti–TNF-α agents	60	6112	1.84 (1.13-3.00)	.02	1.63 (0.97-2.74)	.07
Etanercept	21	2588	1.55 (0.85-2.82)	.14	1.36 (0.73-2.55)	.33
Adalimumab/infliximab	39	3524	2.05 (1.22-3.45)	.007	1.82 (1.05-3.15)	.03

Abbreviations: CI, confidence interval; CRP, C-reactive protein; DAS28, Disease Activity Score based on 28 joint counts; DMARD, disease-modifying antirheumatic drug; FFbH, Hannover Functional Status Questionnaire; HR, hazard ratio; TNF, tumor necrosis factor.
[a] In steps of 10 units or years.
[b] In steps of 5 years.

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COMMENT

Although herpes zoster is a common disorder and is often reported as an adverse event during clinical trials, the association of various rheumatoid arthritis treatments with herpes zoster has been limited to a few published reports, mainly case reports. Serious herpes zoster episodes have been observed in RCTs and their open-label follow-up studies in patients with rheumatoid arthritis receiving the anti–TNF-α agents infliximab or adalimumab[26-29] but had not been reported from RCTs of patients with rheumatoid arthritis using etanercept.[30] However, it is not possible to generalize these findings, because sample sizes and follow-up times are too low. We investigated a hypothesis derived from these case reports and found a significant association between herpes zoster and treatment with the monoclonal anti–TNF-α antibodies infliximab and adalimumab; we found no significant association between herpes zoster and treatment with etanercept.

Patients with highly active rheumatoid arthritis and a history of more than 3 DMARD failures on average (and therefore a high likelihood of being treated with biologics [>85% in our data]) had a significantly increased risk of developing herpes zoster. Furthermore, a significantly higher risk was found for older age and, at least in the total sample, for treatment with glucocorticoids. The use of glucocorticoids is a known risk factor for several infections and has been shown to be associated with herpes zoster in other inflammatory diseases such as Crohn disease and ulcerative colitis.[31,32] In the present study we were not able to distinguish between the risk of herpes zoster due to the inflammatory activity of the disease itself as opposed to that due to the treatment with immunosuppressive drugs. If such an effect were present, it would be strongly confounded by treatment with glucocorticoids, which decrease cell-mediated immunity.

Our findings of an increased risk of VZV reactivation associated with anti–TNF-α antibody treatment are supported by the results of Smitten et al, who analyzed 2 large databases in the United States and United Kingdom[14] and reported an increased risk of herpes zoster in patients receiving biologic agents (odds ratio compared with patients with rheumatoid arthritis but not receiving DMARDs or glucocorticoids, 1.54) as well as for patients receiving DMARDs alone or glucocorticoids. Because Smitten et al were not able to adjust for the severity of rheumatoid arthritis, their comparator group might not be fully comparable.

In contrast, Wolfe et al[13] did not find an increased risk for infliximab, etanercept, or adalimumab in the National Data Bank for Rheumatic Diseases. The authors based their analysis on patient answers to a herpes zoster–specific question in the National Data Bank questionnaire; these answers were validated in a subsample by physician confirmation. We used physician diag-

Table 4. Baseline Characteristics of Patients Who Changed Treatment From Biologics to DMARDs or Vice Versa

Characteristic	Etanercept	Infliximab/ Adalimumab	Controls	Total
No.	361	677	306	1344
Age, mean (SD), y	55.2 (12.9)	54.5 (12.3)	53.7 (11.2)	54.5 (12.2)
Women, No. (%)	282 (78.1)	525 (77.6)	231 (75.5)	1038 (77.2)
Rheumatoid factor–positive, No. (%)	299 (82.8)	545 (80.5)	227 (74.2)	1071 (79.7)
DAS28, mean (SD)	5.8 (1.2)	5.9 (1.2)	5.5 (1.2)	5.8 (1.2)
CRP, median (IQR), mg/L	19 (9-38)	17 (7-40)	14 (6-33)	16 (7-37)
Previous DMARDs, No. (%)	3.7 (1.6)	3.7 (1.4)	2.2 (1.3)	3.4 (1.6)
Glucocorticoids, No. (%)	314 (87.0)	557 (82.5)	250 (82.0)	1121 (83.6)
Duration of treatment episodes, mean (SD), mo				
1st episode	9.4 (7.7)	8.8 (7.4)	15.8 (12.9)	9.8 (7.9)
2nd episode	8.2 (9.6)	7.6 (8.5)	14.5 (13.5)	8.6 (9.0)
With biologics per episode	16.9 (10.7)	16.2 (10.8)	13.8 (9.1)	15.8 (10.5)
Control periods, No. (%)	11.1 (9.7)	9.7 (8.8)	15.0 (9.2)	11.3 (9.4)

Abbreviations: CRP, C-reactive protein; DAS28, Disease Activity Score based on 28 joint counts; DMARD, disease-modifying antirheumatic drug; IQR, interquartile range.

Table 5. Risk of Herpes Zoster: Andersen-Gill Model[a]

	Herpes Zoster Episodes, No.	Patient-years	Adjusted HR (95% CI)[b]	*P* Value
Characteristics at study entry				
Age, y[c]			1.50 (1.12-2.01)	.006
Propensity score				
Tertiles 1 and 2 (moderate/low)	18	1727	1 [Reference]	
Tertile 3 (high)	22	1342	1.53 (0.82-2.83)	.18
Characteristics at follow-up				
DMARDs	9	1301	1 [Reference]	
Anti–TNF-α	31	1736	2.24 (1.05-4.75)	.04
Etanercept	5	642	1.12 (0.39-3.17)	.84
Adalimumab/infliximab	26	1094	2.91 (1.35-6.30)	.007
Analyses for single agents				
Etanercept	5	642	1.09 (0.39-3.06)	.87
Adalimumab	18	717	3.01 (1.36-6.64)	.007
Infliximab	8	377	2.43 (0.94-6.26)	.07

Abbreviations: CI, confidence interval; DMARD, disease-modifying antirheumatic drug; HR, hazard ratio.
[a] Includes only patients who changed treatment from biologics to DMARDs or vice versa. Four of the patients experienced 2 episodes.
[b] Adjusted for age and disease severity (propensity score).
[c] In steps of 10 years.

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noses for our analysis and checked them with the patient reports for completeness. Patients reported herpes simplex more frequently than physicians, but we found only 2 additional patient reports of herpes zoster.

Herpes zoster cases published in RCTs have been serious events[28] or associated with severe complications, including 1 case of encephalitis[28] and 1 death after secondary streptococcal A superinfection (necrotizing fasciitis).[29] In our data, only 20% of the herpes zoster epsiodes were classified as serious events, which could explain our higher rates in comparison to the RCTs. Recently it was reported that the risk of serious infections observed in patients with rheumatoid arthritis who are receiving biologics decreases with longer treatment duration.[4,5] However, we did not find a decrease in HRs for herpes zoster events with longer duration of anti–TNF-α treatment.

Our study has several limitations. First, though our results indicate a significant difference between monoclonal antibodies and conventional DMARD treatment, the HR of 1.8 did not reach our predefined threshold for clinical significance. Second, we cannot completely rule out a type I error greater than 5%, because we decided not adjust for multiple testing in order to be more sensitive in the detection of a possible risk. Third, our analyses are based on a limited number of herpes zoster episodes. Fourth, the observational character of the study may account for a possible residual confounding by indication.

To improve control of confounding factors, we applied Cox regression analyses in a robust way and, more importantly, examined a subsample of patients who experienced a change in therapy and therefore had been observed under different treatment regimens. The strength of this analysis was that each patient served as his or her own control, thus carrying his or her own risk factors while receiving different treatments. Furthermore, second occurrences of herpes zoster in the same patients could be taken into account. Compared with the multivariate Cox regression analysis, this analysis showed a stronger relationship between VZV reactivations and treatment with anti–TNF-α agents and supports the finding of different risk profiles of the individual anti–TNF-α agents.

It is possible that the observed effect of the different drugs on risk of herpes zoster is the consequence of their different molecular mechanisms of action. A similar difference has been observed in risk of tuberculosis reactivation, for which substantial differences have been found regarding treatment with the monoclonal antibodies compared with the soluble receptor fusion protein.[33,34] This idea is plausible, considering that etanercept is not effective to treat inflammatory bowel diseases such as Crohn disease, whereas infliximab and adalimumab are successful therapeutic options. These differing treatment effects could correspond with differing safety profiles.

Varicella and its reactivation as herpes zoster are vaccine-preventable diseases. The Shingle Prevention Study showed that vaccination of adults 60 years or older reduced the incidence of herpes zoster from 11.1 to 5.4 cases per 1000 person-years.[35] Additionally, the severity of herpes zoster and the number of complications were reduced significantly in those for whom the disease developed despite vaccination. Vaccination is therefore recommended for seronegative patients for whom immunosuppressive therapy is planned. The situation is less clear for patients with active rheumatoid arthritis who are in need of treatment with anti–TNF-α agents. The varicella vaccine contains live, attenuated virus. There have been reports of disseminated disease with fatal outcome caused by use of live vaccines in immunocompromised patients.[36,37] As a result, live vaccines are contraindicated during treatment with anti–TNF-α drugs. If immunization with live vaccine is indispensable, it should be given at least 3 weeks[38] before anti–TNF-α treatment is started or after anti–TNF-α treatment has been stopped for at least 5 half-lives.[39]

In contrast to the herpes zoster episodes reported in RCTs, our findings regarding serious complications such as bacterial superinfections, long-lasting postherpetic neuralgia, or ocular complications are reassuring; despite sometimes highly suppressed immunity and high disease activity, major complications were rare for all of the treatments. We believe that the efficient antiviral treatments currently available are mainly responsible for preventing the development of these complications.

Aside from age and disease severity, glucocorticoid use and treatment with the monoclonal anti–TNF-α antibodies adalimumab and infliximab appears to be associated with an increased risk of herpes zoster. Our data suggest that risk is not increased with the receptor fusion protein etanercept. Based on our data, we recommend careful monitoring of patients treated with monoclonal anti–TNF-α antibodies for early signs and symptoms of herpes zoster.

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Study concept and design: Strangfeld, Listing, Zink.
Acquisition of data: Strangfeld, Herzer, Liebhaber, Rockwitz, Richter.
Analysis and interpretation of data: Strangfeld, Listing, Zink.
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REFERENCES

1. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA*. 2006;295(19):2275-2285.

2. Strangfeld A, Listing J. Infection and musculoskeletal conditions: bacterial and opportunistic infections during anti-TNF therapy. *Best Pract Res Clin Rheumatol*. 2006;20(6):1181-1195.

3. Listing J, Strangfeld A, Kary S, et al. Infections in patients with rheumatoid arthritis treated with biologic agents. *Arthritis Rheum*. 2005;52(11):3403-3412.

4. Dixon WG, Symmons DP, Lunt M, Watson KD, Hyrich KL, Silman AJ; British Society for Rheumatology Biologics Register Control Centre Consortium; British Society for Rheumatology Biologics Register. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. *Arthritis Rheum*. 2007;56(9):2896-2904.

5. Askling J, Fored CM, Brandt L, et al. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF- antagonists. *Ann Rheum Dis*. 2007;66(10):1339-1344.

6. Curtis JR, Patkar N, Xie A, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. *Arthritis Rheum*. 2007;56(4):1125-1133.

7. Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? *Lancet Infect Dis*. 2004;4(1):26-33.

8. Glynn C, Crockford G, Gavaghan D, Cardno P, Price D, Miller J. Epidemiology of shingles. *J R Soc Med*. 1990;83(10):617-619.

9. Kost RG, Straus SE. Postherpetic neuralgia—pathogenesis, treatment, and prevention. *N Engl J Med*. 1996;335(1):32-42.

10. Locksley RM, Flournoy N, Sullivan KM, Meyers JD. Infection with varicella-zoster virus after marrow transplantation. *J Infect Dis*. 1985;152(6):1172-1181.

11. Veenstra J, Krol A, van Praag RM, et al. Herpes zoster, immunological deterioration and disease progression in HIV-1 infection. *AIDS*. 1995;9(10):1153-1158.

12. Pope JE, Krizova A, Ouimet JM, Goodwin JL, Lankin M. Close association of herpes zoster reactivation and systemic lupus erythematosus (SLE) diagnosis: case-control study of patients with SLE or noninflammatory musculoskeletal disorders. *J Rheumatol*. 2004;31(2):274-279.

13. Wolfe F, Michaud K, Chakravarty EF. Rates and predictors of herpes zoster in patients with rheumatoid arthritis and non-inflammatory musculoskeletal disorders. *Rheumatology (Oxford)*. 2006;45(11):1370-1375.

14. Smitten AL, Choi HK, Hochberg MC, et al. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. *Arthritis Rheum*. 2007;57(8):1431-1438.

15. Zink A, Listing J, Kary S, et al. Treatment continuation in patients receiving biological agents or conventional DMARD therapy. *Ann Rheum Dis*. 2005;64(9):1274-1279.

16. Lautenschlaeger J, Mau W, Kohlmann T, et al. Vergleichende Evaluation einer deutschen Version des Health Assessment Questionnaires (HAQ) und des Funktionsfragebogens Hannover (FFbH) [Comparative evaluation of a German version of the Health Assessment Questionnaire (HAQ) and the Hanover Functional Status Questionnaire (HFSQ)]. *Z Rheumatol*. 1997;56(3):144-155.

17. International Conference on Harmonisation. Clinical safety data mangement: definitions and standards for expedited reporting. European Medicines Agency Web site. http://www.emea.europa.eu/pdfs/human/ich/037795en.pdf. 1995. Accessed November 24, 2008.

18. Woodworth TG, Furst DE, Strand V, et al. Standardizing assessment of adverse effects in rheumatology clinical trials: status of OMERACT Toxicity Working Group March 2000: towards a common understanding of comparative toxicity/safety profiles for antirheumatic therapies. *J Rheumatol*. 2001;28(5):1163-1169.

19. MedDRA Maintenance and Support Services Organization. http://www.meddramsso.com. 2007. Accessed November 24, 2008.

20. Wallis RS, Ehlers S. Tumor necrosis factor and granuloma biology: explaining the differential infection risk of etanercept and infliximab. *Semin Arthritis Rheum*. 2005;34(5)(suppl1):34-38.

21. Andersen PK, Gill RD. Cox's regression model counting process:a large sample study. *Ann Stat*. 1982;10:1100-1120.

22. Listing J, Strangfeld A, Rau R, et al. Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low—results from RABBIT, the German biologics register. *Arthritis Res Ther*. 2006;8(3):R66.

23. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17(19):2265-2281.

24. Therneau TM, Grambsch PM. *Modelling Survival Data*. New York, NY: Springer; 2000.

25. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. *J Am Stat Assoc*. 1989;84:1074-1078.

26. Lipsky PE, van der Heijde DM, St Clair EW, et al; Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med*. 2000;343(22):1594-1602.

27. Maini RN, Breedveld FC, Kalden JR, et al; Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum*. 2004;50(4):1051-1065.

28. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum*. 2004;50(5):1400-1411.

29. Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol*. 2003;30(12):2563-2571.

30. Moreland LW, Weinblatt ME, Keystone EC, et al. Etanercept treatment in adults with established rheumatoid arthritis: 7 years of clinical experience. *J Rheumatol*. 2006;33(5):854-861.

31. Arvin AM. Varicella-zoster virus. *Clin Microbiol Rev*. 1996;9(3):361-381.

32. Gupta G, Lautenbach E, Lewis JD. Incidence and risk factors for herpes zoster among patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2006;4(12):1483-1490.

33. Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis*. 2004;38(9):1261-1265.

34. Wallis RS, Broder M, Wong J, Beenhouwer D. Granulomatous infections due to tumor necrosis factor blockade: correction. *Clin Infect Dis*. 2004;39(8):1254-1255.

35. Oxman MN, Levin MJ, Johnson GR, et al; Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352(22):2271-2284.

36. Kengsakul K, Sathirapongsasuti K, Punyagupta S. Fatal myeloencephalitis following yellow fever vaccination in a case with HIV infection. *J Med Assoc Thai*. 2002;85(1):131-134.

37. Schrauder A, Henke-Gendo C, Seidemann K, et al. Varicella vaccination in a child with acute lymphoblastic leukaemia. *Lancet*. 2007;369(9568):1232.

38. Pham T, Claudepierre P, Deprez X, et al; Club Rhumatismes et Inflammation, French Society of Rheumatology. Anti-TNF alpha therapy and safety monitoring: clinical tool guide elaborated by the Club Rhumatismes et Inflammations (CRI), section of the French Society of Rheumatology (Societe Francaise de Rhumatologie, SFR). *Joint Bone Spine*. 2005;72(suppl 1):S1-S58.

39. Vaccinations in the immunocompromised person—guidelines for the patient taking immunosuppressants, steroids and biologic therapies. British Society of Rheumatology Web site. http://www.rheumatology.org.uk/guidelines/guidelines_other/vaccinations/view. 2002. Accessed November 24, 2008.

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2.1.2 Entwicklung des RABBIT Risiko-Scores - ein Instrument zur Abschätzung des Risikos für schwerwiegende Infektionen

Strangfeld A, Eveslage M, Schneider M, Bergerhausen HJ, Klopsch T, Zink A, Listing J. *Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient?* Ann Rheum Dis. 2011 Nov;70(11):1914-20. doi: 10.1136/ard.2011.151043. PubMed PMID: 21791449.

Zusammenfassung

Analysen unterschiedlicher Registerdaten zeigten, dass RA Patienten unter einer TNFi Therapie ein höheres Risiko für das Auftreten schwerwiegender Infektionen haben als solche, die mit csDMARDs behandelt werden [26-28]. Sie zeigten darüber hinaus, dass das Risiko zu Beginn einer TNFi Therapie am höchsten war und mit zunehmender Beobachtungszeit abnahm [29, 30]. Das Ziel unserer Analyse war zu untersuchen, durch welche methodischen oder klinischen Aspekte dieser Rückgang erklärt werden kann und wie hoch der Einfluss jeweils ist. Des Weiteren wollten wir untersuchen, ob der Rückgang des Infektionsrisikos, der sich auf Kohortenebene zeigt, sich auch auf Patientenebene widerspiegelt. Hintergrund war die Zielsetzung, den behandelnden Rheumatologen ein Instrument an die Hand zu geben, mit dem das Infektionsrisiko eines Patienten anhand des individuellen, aktuellen Patientenprofils zu jedem Zeitpunkt der Therapieevaluation eingeschätzt werden kann.

Mit unserer Analyse konnten wir nachweisen, dass der Rückgang des Infektionsrisikos im Laufe der Beobachtungszeit im Wesentlichen auf zwei Effekten beruht: zum einen auf Kohortenebene durch den überproportionalen Dropout von Patienten mit hohem Risiko, ein generelles Problem von Langzeitstudien, aber zum anderen auch auf individueller Patientenebene durch den Rückgang des Infektionsrisikos bei effektiver Therapie.

Bei insgesamt 5044 RA Patienten, die zwischen dem 1.Mai 2001 und 31. Dezember 2006 mit dem Beginn einer TNFi (n=3271) oder csDMARD (n=1773) Therapie eingeschlossen worden waren und mindestens ein weiteres Follow-up hatten, konnten 392 schwerwiegende Infektionen untersucht werden: Patienten mit einem hohen Risiko für schwerwiegende Infektionen schieden deutlich häufiger aus der mit TNFi therapierten Patientengruppe aus, als Patienten mit einem geringeren Risiko („survival of the fittest“). Wir stellten weiterhin fest, dass sich bei Patienten durch eine effektive Therapie die Funktionsfähigkeit deutlich besserte und Glukokortikoide, die ihrerseits mit einem erhöhten Risiko für schwerwiegende Infektionen einhergehen, eingespart werden konnten.

Um dies statistisch modellieren und aufzeigen zu können, nutzten wir drei unterschiedliche Modelle zur Analyse der Daten. Im ersten Model (A) adjustierten wir lediglich für Unterschiede der mit TNFi oder csDMARD behandelten Patienten bei Therapiebeginn, im Model B bezogen wir zusätzlich die Veränderung der Glukokortikoiddosen und des Funktionsstatus als zeitveränderliche Variablen mit ein. Mit dem dritten Model (C) wurden durch die Verwendung von GEEs (Generalized Estimation Equations) in gewichteten Patientengruppen (IPTW-Schätzung) die unterschiedlichen Dropout Prozesse der verschiedenen Therapiegruppen berücksichtigt.

Mit Hilfe dieser komplexen Analyse, die sowohl für Selektionsprozesse als auch zeitlich sich verändernde Variablen adjustierte, war es uns möglich, Risikofaktoren für das Auftreten von schwerwiegenden Infektionen zu identifizieren, die zeitlich unabhängig waren. Für die Therapie mit TNFi zeigte sich eine zeitlich unabhängige Risikoerhöhung von 80% im Vergleich zur Therapie mit csDMARDs.

Dieses Risiko muss im Kontext konkurrierender Risiken betrachtet werden, d.h., wenn es gelingt, durch eine effektive Therapie die Krankheitsaktivität zu senken, die Funkti-

onsfähigkeit zu verbessern und die Komedikation mit Glukokortikoiden zu verringern oder gar zu beenden, kann eine TNFi Therapie auch zur Verminderung des Infektionsrisikos beitragen.

Basierend auf den Ergebnissen dieser Analyse entwickelten wir einen Risikoscore, der es dem behandelnden Rheumatologen erlaubt, das Risiko für schwerwiegende Infektionen unter verschiedenen Therapien für jeden Patienten anhand seines individuellen Risikoprofils (Alter, Komorbidität, Anzahl bisheriger Therapieversuche und aktuelle Begleitmedikation) zu jedem Zeitpunkt im Therapieverlauf zu berechnen.

Die Validität dieses Risikoscores evaluierten wir an einer unabhängigen Kohorte. Die Kohorte der (in dieser Arbeit nicht dargestellten) Evaluierung bestand aus 1522 mit TNFi und 1468 mit csDMARD behandelten Patienten, die nach dem 1.1.2009 in das RABBIT-Register eingeschlossen worden waren und aus 1343 mit Rituximab, 825 mit Tocilizumab und 444 mit Abatacept behandelten Patienten, die seit 2007 eingeschlossen worden waren. Hierdurch war es möglich, den Risikoscore auch auf die neueren Substanzen auszuweiten. Die Berechnung des Risikos unter TNFi und csDMARDs zeigte sich in der Evaluierung sehr robust [31].

Nach diesem sehr positiven Ergebnis entwickelten wir einen Rechner zur Kalkulation des Infektionsrisikos. Der „RABBIT Risikorechner“ ist auf der Webseite des RABBIT Registers unter http://www.biologika-register.de/home/risikoscore-fuer-infektionen/ frei zugänglich. Für die neuen Substanzen ist eine weitere Evaluierung geplant.

Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient?

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ABSTRACT

Objective To examine the risk of serious infection conveyed by tumour necrosis factor α (TNFα) inhibitors in the treatment of rheumatoid arthritis (RA).

Methods Data from patients with RA enrolled in the German biologics register RABBIT were used for analysis. Baseline patient characteristics, time-varying risk factors (treatment changes, functional capacity) and selection processes caused by dropout, death or switching to non-anti-TNF treatment were taken into account to estimate the adjusted incidence rate ratios (IRR_{adj}) of serious infection during treatment with TNF inhibitors compared with non-biological disease-modifying antirheumatic drug treatment.

Results Data were available on 5044 patients, in whom 392 serious infections occurred. The crude rates of serious infections in patients treated with TNF inhibitors declined over the first 3 years of observation (from 4.8 to 2.2/100 patient-years). This decline was driven by (1) treatment termination or loss to follow-up in patients at increased risk and (2) a risk reduction through decreasing glucocorticoid doses and improvement in function. Adjusted for selection processes and time-varying risk factors, the following parameters assessed at baseline (age, chronic diseases) or at follow-up prior to the infection were significantly associated with an increased risk: age >60 years, chronic lung or renal disease, low functional capacity, history of serious infections, treatment with glucocorticoids (7.5–14 mg/day, IRR_{adj} 2.1 (95% CI 1.4 to 3.2); ≥15 mg/day, IRR_{adj} 4.7 (95% CI 2.4 to 9.4)) and treatment with TNFα inhibitors (IRR_{adj} 1.8 (95% CI 1.2 to 2.7)).

Conclusion Reasons for the decline in infection rates observed at the group level were identified. The results enable expected infection rates to be calculated in individual patients based on their risk profiles.

INTRODUCTION

A decade ago tumour necrosis factor (TNF) inhibitors were approved for the treatment of rheumatoid arthritis (RA). Uncertainties regarding the specific risks of these new agents led to intensified efforts to investigate their safety. Meta-analyses of randomised controlled trials (RCTs) were undertaken, and various data sources including claims databases were used to assess the risk of serious adverse events (eg, serious infections) possibly associated with these agents.[1–11] One major innovation was the establishment of biologics registers to evaluate the safety and effectiveness of these drugs under the conditions of daily rheumatological care.[12] Upon analysis of these data, it became increasingly clear that the question of how a drug affects the risk of a specific adverse event is far more complex than evaluating the efficacy of the drug. Some of the methodological difficulties we faced while analysing real-world data will be described in this paper using the example of examining how anti-TNF therapy affects the risk of serious infection.

An increased rate of serious infections with anti-TNF therapy compared with conventional disease-modifying antirheumatic drug (DMARD) therapy was found in a meta-analysis of RCTs,[1] in an analysis of claims data[8] and in observational data.[3 6 9] Other findings were in contrast to these results[2 10 11] or reported a decline in the infection risk over time in patients treated with TNF inhibitors,[5 7 8 13] and therefore raised the question whether or not the risk is increased only during the first months of treatment.[5 7 13]

The first aim of our study therefore was to determine whether or not there is a methodological or clinical explanation for this decline in risk and, if so, what the relative contributions might be.

Our second question was how the risk reduction seen in the cohorts is reflected at the level of the individual patient. Patient demographics, clinical features and follow-up information such as treatment response and patient use of additional medications were studied to calculate the expected incidence rates of serious infections for defined subgroups of patients. The aim of this approach was to enable the treating physician to assess the magnitude of infection risk that he or she imposes on a patient when making specific treatment decisions.

METHODS

Patients

The analysis was based on patients with RA enrolled in the German biologics register RABBIT, an ongoing prospective cohort study, at the start of treatment with a biological agent or a conventional DMARD, between 1 May 2001 and 31 December 2006. Patients were followed up independent of any change in their treatment regimes. Observation time following a start of treatment with a non-anti-TNF biological agent was excluded. Patients treated with anakinra at baseline (n=89) and those for whom only baseline data were available (n=141) were excluded.

Assessments

At baseline and at predefined points of follow-up (at 3, 6 months and thereafter every 6 months), rheumatologists assessed the clinical status of the patient including the components of the disease activity score based on 28-joint counts (DAS28),[14] reported treatment details and adverse events. Patients assessed, among other items, their functional capacity as a percentage of full function by means of the Hannover Functional Status Questionnaire (Funktionsfragebogen Hannover (FFbH)).[15 16] Reasons for dropout from the study and causes of death were ascertained by contacting health authorities. Follow-up data (including serious infections) reported prior to 1 November 2009 were included. An infection was attributed to anti-TNF treatment when the treatment was either ongoing or terminated ≤3 months prior to infection. A patient who switched from anti-TNF treatment to treatment with non-biological DMARDs contributed to anti-TNF exposure time until 3 months after switching and to DMARD exposure time thereafter. A DMARD-treated patient who switched to anti-TNF treatment also contributed time to both exposure groups (for further details see Strangfeld *et al*[17] or Listing *et al*[3]).

Statistical analysis

Three different statistical models developed in a complementary fashion were used. In model A we adjusted the data only for differences between the anti-TNF and DMARD groups at the start of treatment (confounding by indication). A propensity score, as described earlier,[18] was used for adjustment. Further adjustment was made for risk factors for infection (table 3). In model B we also considered changes in glucocorticoid dosage and changes in functional status during follow-up as time-varying covariables. The differences between models A and B in the estimates of the trend parameter were used to calculate the relative contribution of clinical improvement to the decreased risk of infection. In the fully adjusted model C, generalised estimation equations (GEEs) were applied to a weighted sample of patients. In addition to model B, this model takes into account confounding by anti-TNF treatment termination, the impact of dropout and previous serious infections.[19] We defined 'dropout' as either loss to follow-up, death or switching to non-anti-TNF therapy.

For each patient and each 6-month follow-up period we calculated the probability of being in a certain status. Using logistic regression we estimated the probabilities of being a dropout with and without accounting for gender and patient characteristics at follow-up (occurrence of serious infections, DAS28, functional status). We calculated weights as ratios of both probabilities. The weights for different time periods were combined as described in detail by Molenberghs *et al*.[20] Again, for each 6-month period

Table 1 Baseline characteristics of patients

	Unweighted sample				Weighted sample		
	Anti-TNF	DMARD	Total	p Value	Anti-TNF	DMARD	p Value
N	3271	1773	5044		3271	1773	
Weights, mean (SD)	1 (0)	1 (0)	1 (0)	–	0.99 (0.8)	1.0 (1.2)	0.15
Female, n (%)	2556 (78.1)	1394 (78.6)	3950 (78.3)	0.69	2612.2 (78.8)	1519.4 (77.6)	0.29
Age	53.8 (12.3)	56.2 (11.5)	54.6 (12.1)	<0.0001	54.4 (12.3)	54.6 (12.1)	0.47
Median (IQR) disease duration, years	9 (5, 16)	6 (3, 12)	8 (4, 15)	<0.0001	8 (4, 15)	8 (4, 16)	0.45
Median (IQR) follow-up, years	3.1 (2.1, 4.9)	3.3 (2.5, 5.0)	3.1 (2.4, 5.0)	<0.0001	3 (2.2, 4.6)	3.5 (2.5, 5)	<0.0001
Rheumatoid factor positive, n (%)	2624 (80.2)	1271 (71.7)	3895 (77.2)	<0.0001	2620.4 (79.0)	1479.6 (75.5)	0.003
DAS28	5.7 (1.2)	5.1 (1.3)	5.5 (1.3)	<0.0001	5.5 (1.3)	5.6 (1.3)	0.20
FFbH	57.0 (23.0)	66.6 (21.5)	60.4 (22.9)	<0.0001	60.0 (22.8)	58.7 (24.3)	0.05
Smoking ever, n (%)	1027 (47.0)	585 (45.6)	1612 (46.4)	0.43	1036.1 (46.3)	621.1 (44.7)	0.36
No of previous DMARDs	3.3 (1.3)	1.8 (1.0)	2.8 (1.4)	<0.0001	2.8 (1.4)	2.9 (1.5)	0.01
No of previous biologics	0.23 (0.6)	0.01 (0.1)	0.14 (0.4)	<0.0001	0.17 (0.5)	0.10 (0.4)	<0.0001
Glucocorticoids 7.5–14 mg/day, n (%)	1027 (31.4)	386 (21.8)	1413 (28.0)	<0.0001	938.6 (30.0)	404.1 (25.4)	<0.0001
Glucocorticoids ≥15 mg/day, n (%)	491 (15.0)	147 (8.3)	683 (12.7)	<0.0001	465.5 (14.9)	146.6 (9.2)	<0.0001
COPD, n (%)	162 (5.0)	87 (4.9)	249 (4.9)	0.94	168.9 (5.1)	86.8 (4.4)	0.28
Chronic lung diseases total, n (%)	246 (7.5)	112 (6.3)	358 (7.1)	0.11	247.7(7.5)	135.9 (6.9)	0.47
Chronic renal disease, n (%)	139 (4.3)	31 (1.8)	170 (3.4)	<0.0001	156.1 (4.7)	56.8 (2.9)	0.001

Values are mean (SD) unless otherwise specified.
The weights estimated for the first time period (0–6 months) were used to calculate the weighted sample (columns 6 and 7).
COPD, chronic obstructive pulmonary disease; DAS28, disease activity score based on 28 joint counts; DMARD, disease-modifying antirheumatic drug; FFbH, Hannover Functional Status Questionnaire measuring functional capacity as percentage of full function; TNF, tumour necrosis factor.

Table 2 Crude rates of serious infections per 100 patient-years (pyrs)

		Serious infections			
	Exposure time (pyrs)	n	Per 100 pyrs	95% CI	Incidence rate ratio (IRR)
Year 1					
DMARD treatment	1765	40	2.3	1.6 to 3.1	2.13
Anti-TNF agents	3041	147	4.8	4.1 to 5.7	
Year 2					
DMARD treatment	1696	40	2.4	1.7 to 3.2	1.36
Anti-TNF agents	2564	82	3.2	2.9 to 4.0	
Year 3					
DMARD treatment	1397	35	2.5	1.8 to 3.5	0.88
Anti-TNF agents	2186	48	2.2	1.6 to 2.9	

DMARD, disease-modifying antirheumatic drug; TNF, tumour necrosis factor.

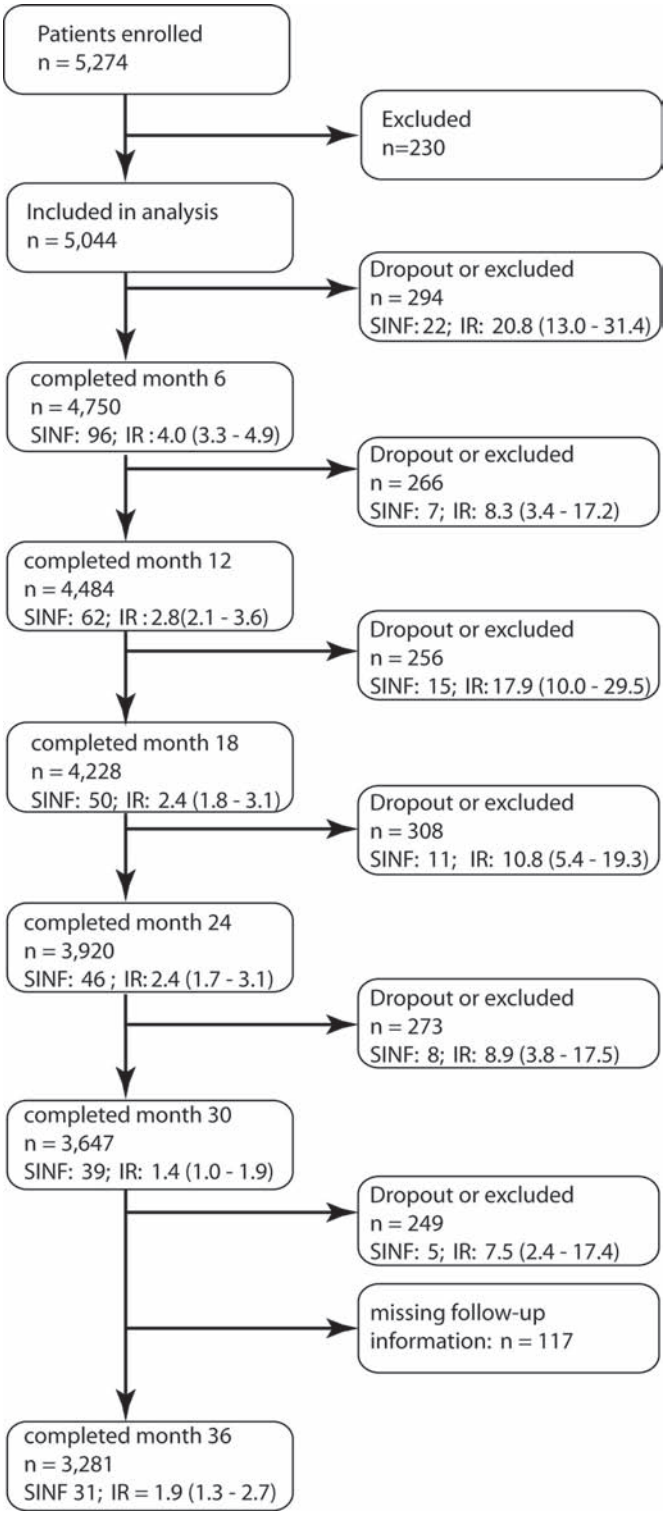

Figure 1 Flow chart of patients who dropped out of observation with rates of serious infections in patients who continued and those who dropped out. Dropouts include patients who switched to non-anti-tumour necrosis factor biological agents. IR, incidence rate; SINF, number of serious infections.

the likelihood of being treated with anti-TNF agents was calculated by taking and not taking into account covariables (age, number of DMARD failures and the patient characteristics listed above). This resulted in weights which account for treatment decisions.[19 20] Both types of weights (for dropout and treatment groups) were uncorrelated (|r|<0.1) and were then combined by multiplication to a final weight. By using this inverse probability weighting we obtained balanced samples of patients treated with or without TNFα inhibitors and of patients who continued or discontinued follow-up.

The application of multivariate GEE models requires a sufficient number of observed serious infections. We aimed to detect a ≥1.5-fold increase in infection risk caused by TNF inhibitors or a trend in risk of similar size (≤0.67=1/1.5) that would be comparable to other observations.[2] The number of serious infections observed in the first and second years would therefore ensure sufficient power (80%) for this analysis, whereas the total number of infections observed in the third year (n=83) was too low to achieve sufficient power. Because multiple infections in individual patients are not independent of each other, the GEE models require an estimate of intrapatient correlations. The number of these correlations increased considerably when the data were analysed for all 3 years. Therefore, a robust estimate of the 3-year infection risk was not possible. For both reasons (the small number of events and the high number of intracorrelations), we restricted the multivariate analysis to the first 2 years.

Owing to strict monitoring, information about DMARD or anti-TNF treatment exposure was complete in >99% of all patients. For all follow-up time points within the first 2 years (in dropouts before their last visit), 5.6% of DAS28 scores, 3.7% of FFbH scores and 3.6% of glucocorticoid dosages were missing. These values were replaced using statistical imputation methods based on the expectation maximation algorithm.[20] SAS software version 9.2 (PROC GLIMMIX, PROC MI) was used for the computations. p Values <0.05 were considered to be statistically significant.

RESULTS

Patient characteristics and treatment status at study entry

Between 1 May 2001 and 31 December 2006, 5274 patients were enrolled in RABBIT of whom 5044 met the inclusion criteria for this study. The average follow-up time was 2.6 years. Upon enrolment, patients treated with TNFα inhibitors differed significantly from those receiving conventional DMARDs with regard to age, disease duration, disease activity (DAS28), functional capacity (FFbH) or number of failed previous DMARD treatments (table 1, columns 2–5). The proportion of patients receiving higher doses of glucocorticoids was also significantly different. Inverse probability weighting was used for the final analysis and allowed for balanced anti-TNF and DMARD samples (table 1, columns 6–8).

Trends in crude infection rates

The crude rates of serious infections decreased significantly from the first to the second and third years in patients treated with TNF inhibitors, whereas these rates remained stable in the cohort of DMARD-treated patients (table 2). The decrease in the absolute rates of infection in patients treated with TNF inhibitors led to a decrease in the relative rates or incidence rate ratios (IRRs).

Changes in patient risk profiles over time

Overall, 1893 patients dropped out because of loss to follow-up, death or changing to non-anti-TNF biological agents within 3 years (figure 1). Dropouts experienced a significantly greater number of serious infections during the 6 months prior to dropping out than the patients who remained in the study. This association remained significant after adjustment for other risk factors of dropping out (male gender, elevated DAS28 scores, poor functional capacity) and repeated significance testing. The

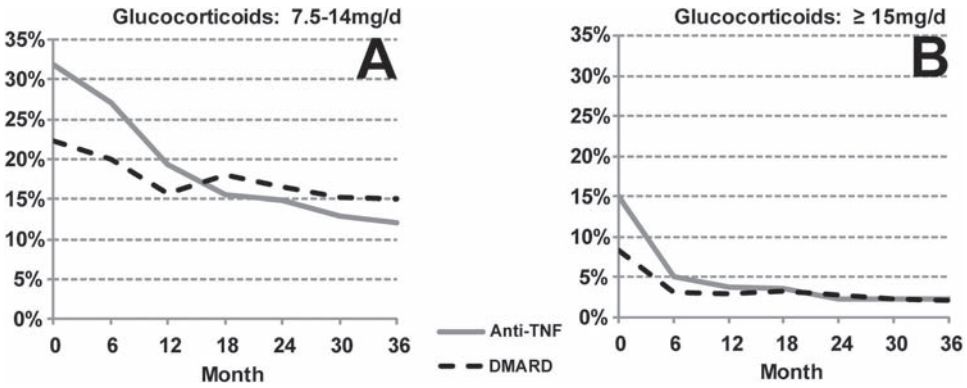

Figure 2 Decline in co-medication with glucocorticoids in patients who received a dose of (A) 7.5–14 mg/day or (&) ! 15 mg/day. DMARD, disease-modifying antirheumatic drug; TNF, tumour necrosis factor.

Table 3 Adjusted incidence rate ratios (IRR) of developing a serious infection in the first or second year

	Model A		Model B		Fully adjusted model C		
	IRR	95% CI	IRR	95% CI	IRR	95% CI	p Value
Age >60 years (yes vs no)	1.7	1.3 to 2.3	1.7	1.3 to 2.3	1.6	1.1 to 2.4	0.012
Chronic lung disease (yes vs no)	2.6	1.8 to 3.7	2.3	1.6 to 3.3	1.7	1.1 to 2.6	0.014
Chronic renal disease (yes vs no)	2.3	1.5 to 3.7	2.1	1.3 to 3.3	1.6	0.9 to 2.8	0.14
High number of treatment failures (>5) at baseline (yes vs no)	1.2	0.8 to 1.7	1.1	0.8 to 1.6	1.6	1.1 to 2.3	0.027
History of serious infection at follow-up (yes vs no)	–		–		2.1	1.0 to 4.3	0.038
FFbH (0–100%) per 10% at baseline	0.92	0.87 to 0.98					
FFbH (0–100%) per 10% at follow-up			0.90	0.86 to 0.95	0.90	0.85 to 0.96	0.0023
Glucocorticoids 7.5–14 mg/day at baseline (yes vs no)	1.0	0.7 to 1.4					
Glucocorticoids 7.5–14 mg/day at follow-up (yes vs no)			1.9	1.4 to 2.6	2.1	1.4 to 3.2	0.0002
Glucocorticoids ≥ 15 mg/day at baseline (yes vs no)	1.5	1.0 to 2.1					
Glucocorticoids ≥ 15 mg/day at follow-up (yes vs no)			3.6	2.2 to 5.7	4.7	2.4 to 9.4	<0.0001
Treatment with TNF inhibitors (yes vs no)	1.6	1.2 to 2.3	1.6	1.2 to 2.3	1.8	1.2 to 2.7	0.0027
Trend (IRR TNF year 2/IRR TNF year1)	0.69	0.50 to 0.96	0.79	0.57 to 1.10	(1.0)	(0.5 to 2.0)	(0.93)

Model A: only baseline characteristics were used for calculation and adjustment.
Model B: time-dependent use of glucocorticoids and FFbH were considered in the model. No adjustment for DMARD/anti-TNF treatment adaptations and dropout processes at follow-up.
Model C: fully adjusted model. Adjustment for time-varying risk factors as in model B and for treatment adaptations and dropout processes (see Methods section for further details).
DMARD, disease-modifying antirheumatic drug; FFbH, Hannover Functional Status Questionnaire measuring functional capacity as percentage of full function; TNF, tumour necrosis factor.

adjusted OR for dropping out after a serious infection calculated for each 6-month period ranged from 2.7 (95% CI 1.2 to 6.2) to 4.7 (95% CI 2.5 to 8.8).

Furthermore, patients who developed serious infections were more likely to switch from anti-TNF treatment to DMARD treatment. Since patients with prior serious infection were at increased risk of developing a further serious infection (see below), this switching led to changes in the risk profiles of the treatment groups (data not shown).

Another factor leading to a change in patient risk profile was the decreasing number of patients who received higher doses of glucocorticoids. The decline in the percentage of patients who needed this additional treatment was far more pronounced in the anti-TNF group (figure 2).

Multivariate analysis

To estimate the relative contributions of changes in the clinical status of the patients and of selection processes to the time-varying risk of infection, we applied three different statistical models (see Methods section). Based on model A which adjusted only for the baseline characteristics of the patients, we observed a statistically significant 31% decrease in the IRRs from year 1 to year 2 in the anti-TNF treatment group compared with the DMARD group (table 3). This decrease was comparable to the decrease in crude IRRs (table 2). However, model A disregards the considerable changes in glucocorticoid dose during the follow-up period (figure 2) and therefore misclassifies exposure at follow-up. Taking into account the time-varying change of glucocorticoid dose and the improvement in functional capacity (model B), approximately one-third (1 – (1 – 0.79)/(1 – 0.69)) of the decrease observed in model A can be attributed to the efficacy of TNF inhibitors. Dropout and treatment changes (either to non-anti-TNF biological agents or from anti-TNF to conventional DMARD treatment) in patients at risk of infection are responsible for the remaining two-thirds of the decline.

The additional adjustment for dropout processes and treatment adaptations in model C led to changes in the IRRs compared with model B which were observed in the expected direction (table 3). Overall, these changes resulted in an IRR for trend of 1.0, suggesting that there is no time-dependent decline in the risk of infection with TNF inhibition if all risk factors are controlled for (table 3).

We found a significantly increased risk of serious infection in patients who had already developed a serious infection earlier in the observation period. Furthermore, older age, chronic lung disease, chronic renal disease and a high number of previous treatment failures increased the risk, whereas a good functional status reduced the risk. The risk was significantly increased in

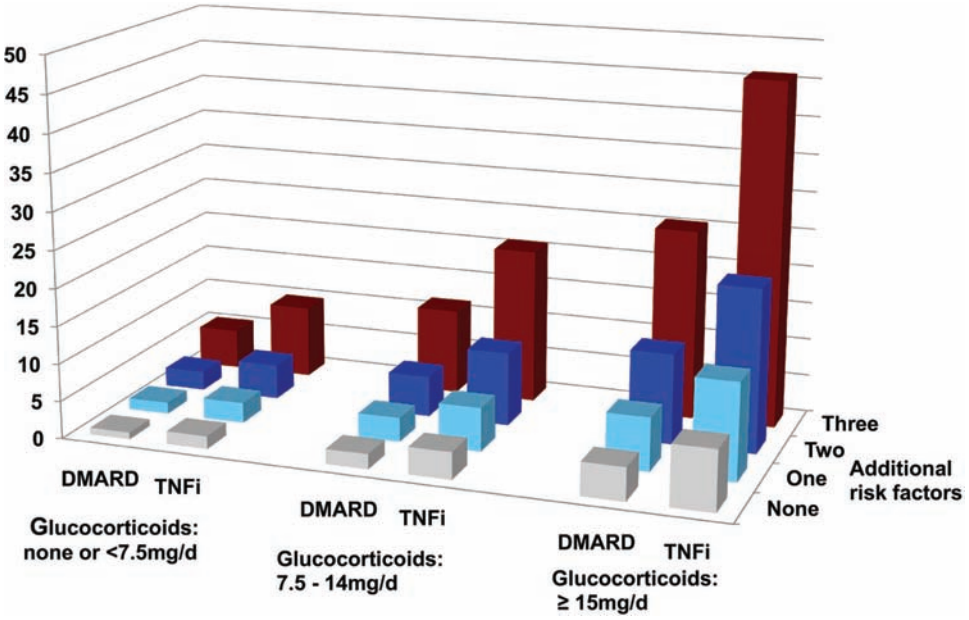

Figure 3 Estimated incidences of serious infections in 100 patients per year by treatment and risk profile. Additional risk factors are one or two of the following: age >60 years, chronic lung disease, chronic renal disease or high number of treatment failures; three risk factors: two of the above risk factors plus prior serious infections. DMARD, disease-modifying antirheumatic drug; TNFi, tumour necrosis factor inhibitor.

patients treated with glucocorticoids in a dose of ≥15 mg/day (IRR=4.7) or 7.5–14 mg/day (IRR=2.1) and in patients treated with TNF inhibitors (IRR=1.8). No significant increase in risk was observed for treatment with lower doses of glucocorticoids (IRR=1.1 (0.8; 1.7)) or in patients with other co-morbid conditions (eg, diabetes, IRR=1.3 (0.8; 2.0)). Higher disease activity was not directly associated with an increased infection risk but indirectly via the use of glucocorticoids and decline in function.

Absolute risks in different groups of patients

The fully adjusted model C allows estimation of relative risks (IRRs) and also the calculation of expected incidence rates of serious infection for individual patients depending on their risk profiles. As the IRRs of model C are not time-dependent, these incidence rates are also not time-dependent. They only change in a patient when the risk factors she or he is exposed to change.

The rates shown in figure 3 (and in file 1 in the online supplement) reflect how the infection risk in an individual patient is influenced by treatment with different doses of glucocorticoids or by treatment with anti-TNF agents compared with DMARDs. The rates further describe how the risk increases if a patient has one, two or three risk factors for serious infection (greater age, comorbid conditions such as chronic lung disease or chronic renal disease, or history of serious infection). The risk of infection increases steadily with the number of risk factors and with the dose of glucocorticoids, both in the anti-TNF and DMARD treatment groups.

The number of patients with two or more risk factors and treatment with glucocorticoids in a dose of ≥15 mg/day was rather low (70 exposed to anti-TNF, 39 treated with DMARDs). Nevertheless, the estimated incidence rates from model C were in accordance with the observed incidence rates in these patients. Taking into account the duration of exposure to high-dose glucocorticoids, the specific risk factors and the functional capacity of these patients, we would have expected 12.8 (95% CI 6.0 to 27.6) serious infections in patients exposed to anti-TNF agents. This modelling aligned well with the 13 serious infections that were actually observed in these 70 patients. A similar result was found for the 39 DMARD-treated patients in whom three serious infections were observed and 3.7 (95% CI 1.6 to 8.5) were predicted by the model.

DISCUSSION

Long-term safety data from observational studies reflect time-dependent changes in the risk profiles of individual patients as well as changes in the composition of the cohorts. Our study shows how variable the results from these studies can be, depending on the statistical model applied to adjust for differences between groups.

Using our statistical model A, we saw a similar decline in the absolute and relative risk of infection in the anti-TNF group in the second year of treatment, as has been reported from other observational data.[5 7 13] Taking into account changes in clinical status (model B) and the effect of treatment changes and dropouts (model C), we were able to explain this decrease and to estimate the relative contributions of both processes. We found that approximately one-third of the decrease in risk was caused by improvement in the clinical status and reduction of concomitant glucocorticoid therapy (mirroring a reduction of risk in individual patients). The remaining two-thirds of the decrease in risk could be explained by selective switching of patients who were at increased risk of infection. Both processes (clinical improvement and depletion of susceptible patients) led to a 'healthy drug survivor effect' in the anti-TNF cohort—that is, those patients who did well and responded to treatment remained under therapy. Of note, such a 'healthy drug survivor effect' is also present in extension studies of RCTs and might explain the contrasting results of two meta-analyses.[1 2] With regard to the question as to what are the risk factors of serious infection, we found that age, functional status and comorbidity contributed significantly to the overall infection risk, in addition to treatment with TNF inhibitors or glucocorticoids.

The adjusted relative risk of treatment with TNF inhibitors compared with that of conventional DMARDs was 1.8.

Furthermore, the adjusted relative risk of glucocorticoids was 2.1 for a dose of ≥7.5 mg/day and 4.7 for a dose of ≥15 mg/day. This result underlines the high risk conveyed by glucocorticoids that has also been addressed by other researchers.[8–11 21 22]

The risk imposed on a patient by one treatment must be balanced against the risk conferred by an alternative treatment. For example, consider a patient with highly active RA, aged 65, treated with methotrexate and 10 mg/day glucocorticoids. This patient has an 'average' risk of developing 0.032 serious infections per year. This risk increases to 0.058 if anti-TNF treatment is started, but it may decrease to 0.027 if glucocorticoid treatment can be reduced below 7.5 mg/day due to the response to anti-TNF treatment. The number needed to harm in this example decreases from 1 out of 31 with DMARD treatment plus 10 mg glucocorticoids to 1 out of 17 after start of anti-TNF and increases again to 1 out of 37 after stopping glucocorticoid treatment and maintaining TNF inhibition.

According to our data, improvement in function as a result of effective treatment can reduce the risk of serious infection significantly and to a greater extent than improvement in disease activity measured by the DAS28. This result is clinically plausible when one considers that immobility is a strong risk factor for developing comorbidities such as pneumonia or urogenital infections. Cardiovascular risk factors, as discussed prepviously,[7 10] are linked to age and were therefore not identified in our data.

Our analysis has some limitations. We investigated only the overall infection risk and were therefore not able to consider site-specific risk factors. There was also limited statistical power to analyse the data from the third year. We did not investigate the three TNF inhibitors separately. Although different effects on the reactivation of tuberculosis[23] and viral infections[17] have been reported for adalimumab, infliximab and etanercept, the overall infection risk appears to be similar.[3 5 13]

The important message from this study to the practising physician is that the time-dependent decline in risk seen in cohorts of patients treated with anti-TNF agents is partially caused by changes in the case mix of these cohorts and cannot directly be transferred to individual patients. Independent of treatment duration, TNF inhibition imposes an increased risk of serious infection on a patient which must be balanced against other risks resulting from co-medication, in particular higher doses of glucocorticoids and active disease.

Our data provide, for the first time, detailed information about the expected absolute risk of serious infection in subgroups of patients. This work therefore helps rheumatologists to identify patients at increased risk and to avoid combinations of treatments that confer a very high risk in predisposed patients.

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REFERENCES

1. **Bongartz T,** Sutton AJ, Sweeting MJ, *et al.* Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006;**295**:2275–85.
2. **Leombruno JP,** Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. *Ann Rheum Dis* 2009;**68**:1136–45.
3. **Listing J,** Strangfeld A, Kary S, *et al.* Infections in patients with rheumatoid arthritis treated with biologic agents. *Arthritis Rheum* 2005;**52**:3403–12.
4. **Dixon WG,** Watson K, Lunt M, *et al.* Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2006;**54**:2368–76.
5. **Dixon WG,** Symmons DP, Lunt M, *et al.* Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. *Arthritis Rheum* 2007;**56**:2896–904.
6. **Gómez-Reino JJ,** Carmona L, Valverde VR, *et al.* Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum* 2003;**48**:2122–7.
7. **Askling J,** Fored CM, Brandt L, *et al.* Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. *Ann Rheum Dis* 2007;**66**:1339–44.
8. **Curtis JR,** Patkar N, Xie A, *et al.* Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. *Arthritis Rheum* 2007;**56**:1125–33.
9. **Greenberg JD,** Reed G, Kremer JM, *et al.* Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. *Ann Rheum Dis* 2010;**69**:380–6.
10. **Wolfe F,** Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum* 2006;**54**:628–34.
11. **Schneeweiss S,** Setoguchi S, Weinblatt ME, *et al.* Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. *Arthritis Rheum* 2007;**56**:1754–64.
12. **Zink A,** Askling J, Dixon WG, *et al.* European biologicals registers: methodology, selected results and perspectives. *Ann Rheum Dis* 2009;**68**:1240–6.
13. **Galloway JB,** Hyrich KL, Mercer LK, *et al.* Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology (Oxford)* 2011;**50**:124–31.

14. **Prevoo ML,** van 't Hof MA, Kuper HH, *et al.* Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;**38**:44–8.
15. **Lautenschläger J,** Mau W, Kohlmann T, *et al.* [Comparative evaluation of a German version of the Health Assessment Questionnaire and the Hannover Functional Capacity Questionnaire]. *Z Rheumatol* 1997;**56**:144–55.
16. **Westhoff G,** Listing J, Zink A. Loss of physical independence in rheumatoid arthritis: interview data from a representative sample of patients in rheumatologic care. *Arthritis Care Res* 2000;**13**:11–22.
17. **Strangfeld A,** Listing J, Herzer P, *et al.* Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. *JAMA* 2009;**301**:737–44.
18. **Listing J,** Strangfeld A, Rau R, *et al.* Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low–results from RABBIT, the German biologics register. *Arthritis Res Ther* 2006;**8**:R66.
19. **Robins JM,** Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;**11**:550–60.
20. **Molenberghs G**, Kenward MG. *Missing Data in Clinical Studies*. Chichester: John Wiley & Sons, 2007.
21. **Smitten AL,** Choi HK, Hochberg MC, *et al.* The risk of hospitalized infection in patients with rheumatoid arthritis. *J Rheumatol* 2008;**35**:387–93.
22. **Bernatsky S,** Hudson M, Suissa S. Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis. *Rheumatology (Oxford)* 2007;**46**:1157–60.
23. **Dixon WG,** Hyrich KL, Watson KD, *et al.* Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Ann Rheum Dis* 2010;**69**:522–8.

2.1.3 Ausgang schwerwiegender Infektionen unter bDMARD- und csDMARD-Therapien

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Zusammenfassung

Ziel dieser Analyse war es, Risikofaktoren für die Entwicklung einer Sepsis und für Mortalität nach schwerwiegenden Infektionen (SI) bei RA Patienten zu untersuchen.

Patienten, die bis Oktober 2013 in das Register rekrutiert worden waren und von denen detaillierte Angaben zur Therapie, genügend Nachbeobachtungszeit sowie Informationen zu Beginn und Dauer der Infektion sowie deren Ausgang (Sepsis, Tod, Genesung) vorlagen, wurden eingeschlossen. Insgesamt hatten 859 Patienten 1017 schwerwiegende Infektionen erlitten. Die Patienten waren zum Zeitpunkt der Infektion entweder gegenüber TNFi, anderen Biologika oder csDMARDs exponiert. Eine der Infektion nachfolgende Sepsis wurde für 135 Patienten berichtet, von denen 85 verstarben. Weitere 53 Patienten waren nach der SI verstorben, ohne dass eine Sepsis diagnostiziert worden war.

Für die Analyse wurden generalisierte Schätzgleichungen (GEE Generalized Estimation Equations) für Längsschnittdaten angewandt.

Mit einem höheren Risiko für die Entwicklung einer Sepsis assoziiert waren höheres Alter, Herzinsuffizienz, Niereninsuffizienz und eine eingeschränkte Funktionsfähigkeit. Eine Glukokortikoidgabe von ≥10 mg/d erhöhte das Mortalitätsrisiko auf das 2,4fache. Im Vergleich zur csDMARD Therapie hatten Patienten mit einer TNFi Therapie ein signifikant niedrigeres Risiko, eine Sepsis zu entwickeln (OR=0,64 [95%Konfidenzintervall

(KI) 0,42-0,97]) oder danach zu versterben (OR=0,48 [95%KI 0,24-0,95]). Auch die Therapie mit anderen Biologika war im Vergleich zu csDMARDs mit einem signifikant geringeren Risiko für die Entwicklung einer Sepsis (OR 0,45 [95%KI 0,25-0,8]) oder dem Versterben (OR 0,16 [95%KI 0,05-0,54]) assoziiert.

Das Ergebnis erschien uns zunächst paradox, da das Risiko für schwerwiegende Infektionen unter TNFi und anderen Biologika im Vergleich zur csDMARD Therapie erhöht ist. Aus diesem Grund führten wir vier Sensitivitätsanalysen durch, die Faktoren, die das Ergebnis hätten beeinflussen können, berücksichtigten (beispielsweise ein unterschiedliches Keimspektrum in den Therapiegruppen mit unterschiedlichem Sepsisrisiko). Alle Sensitivitätsanalysen bestätigten jedoch das Ergebnis der Hauptanalyse und den Vorteil der Therapie mit bDMARD im Vergleich zur csDMARD Therapie.

Patienten, die ein bDMARD erhalten, aber mehr als 30 Tage vor der Infektion abgesetzt hatten, wiesen das gleiche Risiko einer Sepsis auf wie Biologika-naive csDMARD behandelte Patienten. Dieses Ergebnis reicht allerdings nicht aus, um die gängige Praxis des Absetzens/Pausierens eines bDMARDs beispielsweise vor Operationen in Frage zu stellen, da man in Beobachtungsstudien den Selektionsfehler, in diesem Fall das vorwiegende Absetzen der Therapie bei Patienten mit höherem Risiko, nicht sicher ausschließen kann. Dies könnte nur durch eine randomisierte Studie beantwortet werden.

Mit dieser Analyse gelang es erstmalig, einen zuvor im tierexperimentellen Versuch gezeigten Vorteil, der im humanen Therapieversuch scheiterte, anhand von qualitativ hochwertigen und methodisch belastbar ausgewerteten epidemiologischen Daten nachzuweisen [32].

OPEN ACCESS

EXTENDED REPORT

Impact of treatment with biologic DMARDs on the risk of sepsis or mortality after serious infection in patients with rheumatoid arthritis

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ABSTRACT

Objective This observational cohort study investigated the impact of biological (b) disease-modifying antirheumatic drugs (DMARDs) on the outcomes of serious infections (SIs) in patients with rheumatoid arthritis.

Methods We investigated outcomes of SIs observed in 947 patients enrolled in the German biologics register RABBIT(*R*heumatoid *a*rthritis: *o*bservation of *bi*ologic *t*herapy). Outcomes were (1) recovery without complication, (2) sepsis following SI (≤30 days), and (3) death after SI without known sepsis (≤90 days). We applied a multinomial generalised estimating equation model for longitudinal data to evaluate the risks of sepsis and death simultaneously.

Results Sepsis within 30 days after SI was reported in 135 out of 947 patients, 85 of these had a fatal outcome. Fifty-three patients died within 90 days after SI without known sepsis. The adjusted risk of developing sepsis increased with age and was higher in patients with chronic renal disease. Compared with conventional synthetic (cs)DMARDs, the risk was significantly lower when patients were exposed to bDMARDs at the time of SI (OR: 0.56, 95% CI 0.38 to 0.81). Risk factors of fatal SI were higher age, use of glucocorticoids at higher doses and heart failure. Patients treated with bDMARDs and those with better physical function had a significantly lower mortality risk.

Conclusions These results suggest a beneficial effect of bDMARDs on the risk of sepsis after SI and the risk of a fatal outcome. Successful immunosuppression may prevent an unregulated host response to SI, that is, the escalation to sepsis. Further investigation is needed to validate these results.

INTRODUCTION

Sepsis is a major concern in patients with serious infections (SIs) because it results in a case fatality rate of 30–50%.[1 2] Older patients are particularly susceptible to sepsis because of hospitalisation, comorbidity and impaired physical function.[3] Growing insights into the biological process of sepsis led to the improved management of this critical condition, but lethality remains high.[4] Waage *et al*[5] identified a potential target for the treatment of sepsis almost three decades ago. They found increased levels of tumour necrosis factor-α (TNF) in the serum of patients with sepsis. Tracey *et al*[6] blocked TNF (cachectin) in an experimental study in baboons and demonstrated clinically relevant improvements in survival of sepsis. Beutler *et al*[7] first reported a protective effect of immunisation against cachectin in mice. These promising findings demonstrated that TNF plays a key role in triggering sepsis. They prompted a sequence of randomised controlled trials wherein patients with sepsis were treated with different TNF inhibitors (TNFi).[8–11] Similarly, antagonists of the interleukin (IL) 1 receptor were targeted. An overview of trials is given in Remick *et al*.[12] Almost consistently, none of these trials showed a significant improvement in survival of patients treated with TNFi, which led to the conclusion that TNF blockade is not a useful treatment for sepsis. However, in these studies the biological cascade of sepsis had already started in all patients and the treatment may have been administered too late to stop this process.[1 12 13] The importance of the timing of TNF blockade was also shown in an experimental study with baboons.[6] Of three groups (no TNFi, TNFi 1 h prior or 2 h prior), only those baboons that were treated 2 h prior to infection survived.[6] This result corresponds with Beutler *et al*[7] who found that the timing between immunisation and infection was crucial for survival.

TNFi were established as first biologic disease-modifying antirheumatic drugs (bDMARDs) in the routine care of moderate to severe rheumatoid arthritis (RA) after failure of conventional synthetic (cs)DMARDs. Other bDMARDs have been approved since 2006 that target the CD20 antigen on B lymphocytes (rituximab), suppress T cell activation (abatacept) or inhibit the binding of IL-6 to its receptor (tocilizumab). Due to their immunosuppressive effect, bDMARDs increase the risk of SI in patients with RA who are per se at higher risk of SI due to comorbidities, complications of disease-related joint surgeries and impaired physical function.[14–19]

Notably, none of the above mentioned studies investigated the outcomes of SI such as (1) recovery from SI, (2) escalation of SI to sepsis or (3) death. The present investigation focuses on patients with RA who acquired SI after enrolment into the German biologics register RABBIT (*R*heumatoid *a*rthritis: *o*bservation of *bi*ologic *t*herapy). We examined the contribution of RA treatment and patient characteristics to the three different outcomes of SI using multinomial regression analysis. We also investigated the overall risk of death within 90 days after the onset of SI.

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STATISTICS AND METHODS

Patients and events of interest

The present study was conducted using data from the German biologics register RABBIT, which is an ongoing observational cohort study. Since May 2001, patients with RA have been eligible for enrolment at the start of treatment with a bDMARD or csDMARD after failure of at least one csDMARD.[20] A total of 12 097 patients were enrolled in RABBIT by 30 October 2013. The focus of this paper is the outcome of SIs. Therefore 947 patients who developed one or more infections that were classified as *serious* according to International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) definition[21] were included. In the main analysis we excluded 108 SIs in 88 patients with incomplete information on the SI. The main analysis is therefore based on all separable SIs (n=1017) of 859 patients. Patients were considered to be exposed to a particular DMARD when the SI occurred during active treatment with that DMARD, that is, no missed dose before the SI.

Assessments and follow-up

Clinical status was assessed at baseline, months 3 and 6, then every 6 months for 5–10 years.

Rheumatologists reported DMARD exposure (start and stop dates, doses), adverse events, disease activity (including components of the disease activity score based on a 28-joint-count (DAS28)) and comorbidities. Patients reported among other items on physical function using the Hannover Functional Status Questionnaire (FFbH). Its scores can be transformed to the Health Assessment Questionnaire values.[22] If serious adverse events were reported the rheumatologist was asked to provide detailed clinical information including hospital discharge letters.

Adherence to scheduled follow-ups was monitored and investigations of dropouts or the reasons for the discontinuation of study participation were performed. This includes inquiries to local administration offices regarding patients' vital status and cause of death. For further details see.[20]

Objective

The objective was to examine the impact of patients' clinical characteristics and RA treatment with TNFi, other bDMARDs, csDMARDs and glucocorticoids on the risk of developing sepsis or a fatal outcome of SI. Three approaches were applied. Approach A (figure 1) investigates the risks of sepsis and death after SI simultaneously and thus includes validated cases of fatal and non-fatal sepsis plus all deaths within 90 days after SI. With this approach we addressed possibly undetected and fatal cases of sepsis after SI. In approach B, the risk of death due to sepsis was investigated. The overall risk of death after SI, with and without sepsis, was addressed in approach C.

Statistical analyses

Model-based analyses

Units of investigation in this analysis were SIs. In approach A two possible outcomes of SI, sepsis (including death from sepsis) and mortality without known sepsis, were investigated simultaneously. These analyses are similar to analyses of competing risks in survival data.[23–25] It was crucial to include overall mortality in the analysis in order not to miss undetected cases of sepsis. In approach A (figure 1) we applied a recently introduced generalised estimating equations model for longitudinal and multinomial responses[26] to investigate the risks of sepsis and death as outcomes of SI simultaneously. This model class takes dependencies of subsequent SI in one patient into account. It is implemented in the statistical software R[27 28]. A similar approach was applied in time-discrete analyses of competing risks of hospital-acquired methicillin-resistant *Staphylococcus aureus* infections by Barnett *et al*.[29]

A generalised estimating equations model with the binary outcome mortality yes/no was used in approach C. However, since only two patients developed sepsis twice, in approach B the analysis was restricted to the last sepsis per patient and multiple logistic regression was applied.

Sensitivity analyses

The consistency of results was investigated in four different sensitivity analyses. Analysis I comprised the subset of patients with pneumonia. In a second analysis we aimed to detect the influence of bDMARD discontinuation and therefore restricted the group of patients on csDMARD treatment at the time of SI to those naïve to biologics. The third sensitivity analysis addressed the impact of incomplete data and uncertain DMARD exposure and included 108 additional SIs with incomplete information.

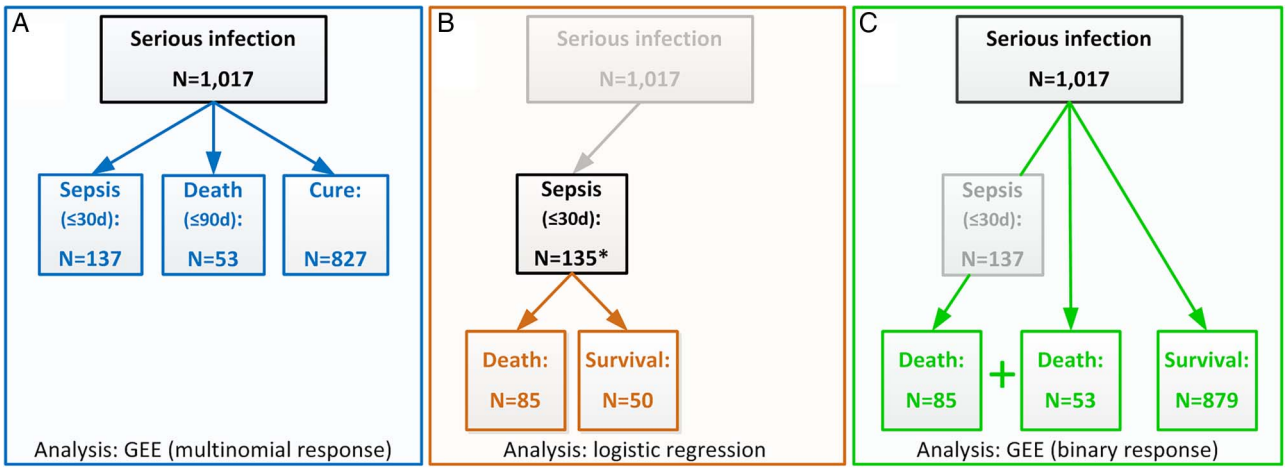

Figure 1 Investigation of SI outcomes. Boxes in colour indicate the outcomes of interest and boxes in black indicate the reference population. Approach A examined the risks of sepsis and death after SI simultaneously; this approach accounts for possibly undetected but fatal cases of sepsis (see: objectives & methods). Approach B focuses on the mortality risk of sepsis. Overall mortality after SI was examined in approach C. All sensitivity analyses were applied in the setting of approach A. GEE, generalised estimating equations; SI, serious infection.

In these patients we assumed that the last known DMARD exposure during follow-up in RABBIT persisted at the time of SI. Analysis IV comprises dropouts with no reported events of sepsis or death and a follow-up of less than 180 days after the last SI. In this most conservative approach, we assumed that dropout occurred due to sepsis only for bDMARD-treated patients and artificially imputed these events to the data.

RESULTS

Serious infection

Among all 1017 SIs with complete information, pneumonia was most frequent (n=332, 28.4%), followed by 131 infections of bones and joints (11.2%) and 120 respiratory infections other than pneumonia (10.3%). The complete spectrum of SIs is documented online (see online supplementary figures S1 and S2). We found no differences in the spectrum of SIs after stratification into (1) patients with and without subsequent sepsis and (2) bDMARD versus csDMARD treatment at the time of SI. 137 SIs escalated to sepsis within 30 days (11.7% of all SIs), two patients developed sepsis twice. The case fatality rate was 63% (85 deaths in 135 patients, figure 1). Out of 859 patients who did not develop sepsis, 53 died within 90 days following SI (6.2%).

Patient characteristics

Patients with SI were significantly older, had a longer disease duration, higher disease activity and more comorbidities at baseline than patients in the remaining cohort (table 1, p<0.01). Among patients with SI those who developed sepsis or died due to SI had significantly poorer clinical characteristics than patients with no further complications of SI, particularly heart failure and renal disease were considerably more frequent.

Baseline treatment was similar in patients with SI and the rest of the cohort. Disease activity (DAS28 and C reactive protein),

Table 1 Characteristics of patients with complete information of SI (n=859) at baseline and at the time of SI, compared with the remaining cohort and stratified by outcome of SI

		Patients with SI		
	Cohort	SI only	SI+sepsis	SI+death
At baseline/enrolment				
N	11 150	671	135	53
Age (years)	55.7 (12.5)	59.0 (11.6)	63.8 (10.3)	68.2 (7.1)
Sex (female, n (%))	8610 (77.2)	493 (73.5)	98 (72.6)	34 (64.2)
Symptom onset (years before enrolment)	10.1 (9.1)	12.2 (9.9)	15.1 (11.9)	12.4 (10)
Rheumatoid factor positive, n (%)	8026 (72.3)	527 (78.5)	115 (85.2)	44 (83.0)
CRP (mg/L)	18.7 (26.2)	25.8 (35.4)	31.5 (45.8)	30.0 (35.2)
DAS28	5.2 (1.3)	5.5 (1.3)	5.7 (1.2)	6.1 (1.3)
Comorbidities: heart failure, n (%)	207 (1.9)	39 (5.8)	19 (14.1)	10 (18.9)
Chronic renal disease, n (%)	353 (3.2)	57 (8.5)	25 (18.5)	10 (18.9)
COPD, n (%)	737 (6.6)	107 (16.0)	23 (17.0)	14 (26.4)
Diabetes, n (%)	1024 (9.2)	109 (16.2)	35 (25.9)	15 (28.3)
Smoking (never, n (%))	4813 (43.2)	290 (43.2)	52 (38.5)	20 (37.7)
No. of previous bDMARDs				
0, n (%)	8371 (75.1)	442 (65.9)	91 (67.4)	44 (83)
≥2, n (%)	1250 (11.2)	107 (15.9)	19 (14.1)	3 (5.7)
TNFi, n (%)	5384 (48.3)	356 (53.1)	76 (56.3)	27 (50.9)
Other bDMARDs, n (%)	2203 (19.8)	182 (27.1)	28 (20.7)	8 (15.1)
Glucocorticoids				
<5 mg, n (%)	3671 (32.9)	156 (23.3)	30 (22.2)	11 (20.8)
≥10 mg, n (%)	2256 (20.2)	181 (26.8)	34 (25.2)	14 (26.4)
At the time of first serious infection:				
Age at SI	–	60.8 (11.7)	66.0 (10.1)	70.5 (7.3)
CRP mg/L	–	17.4 (26.4)	24.3 (36.9)	17.0 (23.5)
DAS28	–	4.3 (1.5)	4.6 (1.4)	4.6 (1.6)
Comorbidities				
Heart failure, n (%)	–	46 (6.9)	21 (15.6)	19 (35.8)
Chronic renal disease, n (%)	–	68 (10.1)	32 (23.7)	14 (26.4)
TNFi, n (%)	–	297 (44.3)	44 (32.6)	14 (26.4)
Other bDMARDs, n (%)	–	129 (19.2)	17 (12.6)	3 (5.7)
Glucocorticoids				
<5 mg, n (%)	–	257 (38.3)	40 (29.6)	16 (30.2)
≥10 mg, n (%)	–	100 (14.9)	26 (19.3)	14 (26.4)

Other bDMARD (tocilizumab, rituximab, abatacept). Numbers represent mean (sd) or frequencies (%). Amount of missing data: at baseline most frequent missings were found in CRP (5.0%) and DAS28 (3.1%), at the last study visit prior to SI the CRP was missing in 8.9%.
COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; DAS28, disease activity score (28 joint count); DMARD, disease-modifying antirheumatic drug; bDMARD; biologic DMARD; N, number; SI, serious infection; TNFi, tumor necrosis factor-α inhibitors (adalimumab, etanercept, infliximab, golimumab, certolizumab),

at the last regular time point before the SI, was significantly reduced compared with baseline. The median time from the last regular study visit to SI was 3.7 months (IQR: 1.9 to 6.2). Treatment with bDMARDs was significantly less frequent at the time of SI than at baseline, especially in patients who developed sepsis or died after SI (table 1, p<0.01).

We categorised patients according DMARD exposure at the time of SI to investigate a possible patient channelling between enrolment and the SI (table 2). We found significant differences between treatment regimens only for age (p<0.01). Disease activity, physical function, erythrocyte sedimentation rate (ESR), CRP and prevalence of heart failure or chronic renal disease did not vary significantly between groups of DMARDs. Among patients treated with csDMARDs at the time of SI almost two-thirds (63.7%) were previously treated with bDMARDs.

In the subpopulation of patients with pneumonia, male patients were more frequent in the csDMARD and other bDMARD groups. Further, patients treated with csDMARDs only were significantly older than those treated with bDMARDs (p<0.01). Other disease characteristics, for example, DAS28 and physical function, were not different (see online supplementary table S2).

Risk of sepsis and mortality

The adjusted OR of developing sepsis increased significantly with age. Risk was higher in patients with chronic renal disease and lower in patients with better function. The risk was significantly reduced when patients were exposed to TNFi or other bDMARDs at the time of the SI (table 3). Risk of death after SI was significantly higher in patients with congestive heart failure and in older patients. Treatment with any class of bDMARDs and better physical function (FFbH) had significant protective effects regarding mortality. No significant association with the risk of sepsis or death was found for sex. Disease activity (DAS28) was not included in the adjusted model because it was not associated with sepsis or mortality in the univariate analysis (see online supplementary table S1). Diabetes was significantly associated only in the univariate analysis, therefore we excluded diabetes from the multiple regressions for model sparsity and included only the strongest predictors, renal disease and heart failure (see online supplementary table S1). Similar results were obtained in a subsample of patients with pneumonia (n=298, see online supplementary table S3).

Table 2 Characteristics of patients stratified by the class of DMARD exposure at the time of SI

	TNFi	Other bDMARDs	csDMARDs
No. of SIs	399	174	444
No. of patients	370	159	388
Age at SI (mean (SD), years)	60.7 (11.9)	62.6 (11.0)	64.7 (11.0)
Sex (female, n (%))	298 (74.7)	123 (70.7)	314 (70.7)
RF positive (n (%))	335 (84.0)	139 (79.9)	353 (79.5)
Disease duration at SI (mean (SD), years)	14.5 (10.1)	16.5 (10.7)	14.5 (11.2)
CRP (mean (SD))	16.7 (27.5)	22.3 (33.2)	20.9 (29.3)
DAS28 (mean (SD))	4.4 (1.5)	4.5 (1.6)	4.4 (1.4)
% of physical function (SD)	56.6 (25.5)	51.0 (24.0)	54.5 (25.9)
Follow-up (years, mean (SD))	5.2 (2.9)	3.8 (2.1)	4.3 (2.5)
Hospitalisations due to SI* (n (%))	283 (83.7)	128 (83.1)	275 (82.1)
Selected comorbidities:			
Heart failure, n (%)	36 (9.0)	24 (13.8)	44 (9.9)
Chronic renal disease, n (%)	51 (12.8)	23 (13.2)	66 (14.9)
Events of interest			
Death (≤90 days) w/o sepsis, n (%)	15 (3.8)	3 (1.7)	35 (7.9)
Sepsis (≤30 days, n)	46 (11.5)	17 (9.8)	74 (16.7)
Death after sepsis, n (%)	20 (43.5)	11 (64.7)	54 (74.0)

No. of patients in DMARD strata exceeds n=859 since patients with >1 SI may contribute to different treatment episodes (DMARD strata). The median time between the last study visit and the SI was 3.7 months (first quartile: 1.9 months, third quartile: 6.2 months). *Hospitalisation rates refer to SI which did not escalate to sepsis or death. bDMARD, biologic DMARD; csDMARD, conventional synthetic DMARD; CRP, C reactive protein; DAS28, disease activity score (28 joint count); DMARD, disease-modifying antirheumatic drug; RF, rheumatoid factor; SI, serious infection; TNFi, tumor necrosis factor-α inhibitor (adalimumab, etanercept, infliximab, golimumab, certolizumab), other bDMARD (tocilizumab, rituximab, abatacept); w/o, without.

Table 3 Results of the GEE model for longitudinal multinomial regression on the risks of sepsis (n=137) and death (n=53) after SI (n=1017)

	Sepsis		Death	
	OR	95% CI	OR	95% CI
Age (by 10 years)	1.41	1.15 to 1.74	2.47	1.61 to 3.79
Sex (male vs female)	0.99	0.63 to 1.55	1.45	0.74 to 2.83
FFbH (by 10% improvement)	0.92	0.84 to 1.00	0.86	0.76 to 0.98
GC (<5 mg/day=reference)	Ref.	.	Ref.	.
GC (5 to <10 mg/day vs ref.)	1.26	0.82 to 1.93	0.93	0.47 to 1.83
GC (≥10 mg/day vs ref.)	1.66	0.96 to 2.88	2.40	1.04 to 5.55
csDMARD	Ref.	.	Ref.	.
TNFi	0.64	0.42 to 0.97	0.48	0.24 to 0.95
Other bDMARD	0.45	0.25 to 0.80	0.16	0.05 to 0.54
Heart failure (yes vs no)	1.38	0.74 to 2.56	3.56	1.73 to 7.33
Chronic renal disease (yes vs no)	1.93	1.19 to 3.14	1.51	0.72 to 3.17

The adjusted ORs specify the increase or decrease in the risk of developing the outcome (sepsis or death).
bDMARD, biologic DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; GC, glucocorticoids; GEE, generalised estimating equation; SI, serious infection; TNFi, tumor necrosis factor-α inhibitor (adalimumab, etanercept, infliximab, golimumab, certolizumab), other bDMARD (tocilizumab, rituximab, abatacept). Physical function (FFbH) and doses of GC refer to measurements of most recent study visit, DMARD exposure is the current exposure at SI. The median time between the last study visit and the SI was 3.7 months (first quartile: 1.9 months, third quartile: 6.2 months).

Discontinuation of bDMARDs and the risk of sepsis

In the analysis above, the sepsis and mortality risks of patients exposed to bDMARDs at the time of SI were compared with those unexposed. In this approach we had pooled bDMARD-naïve patients and those who discontinued bDMARDs during follow-up. In the following analysis we considered first SIs only and categorised patients into (A) biologic-naïve, (B) exposed to bDMARDs and (C) bDMARD withdrawn prior to first SI. The restriction to first SI was applied to omit an effect of treatment decisions based on previous SI.

In bDMARD-naïve patients 133 first SIs were observed, 515 in patients exposed to bDMARDs and 211 in patients who had discontinued bDMARDs >1 month prior to the first SI. The latter patients had significantly longer disease duration, lower physical function, higher disease activity (DAS28) and were more often affected by heart failure and renal disease than bDMARD-naïve patients (see online supplementary table S4). Sepsis occurred in 39 (18.4%) out of 211 SIs which was similar to biologic-naïve patients (23/133, 17.3%) and more frequent than in patients exposed to bDMARDs at the time of the first SI (58/515, 11.3%).

Table 4 ORs of multiple logistic regression for mortality after sepsis (85 deaths in 135 patients, approach B) and of a GEE-type regression model for all-cause mortality (138 deaths in 859 patients, approach C)

	Death from sepsis		All-cause mortality after SI	
	OR	CI	OR	CI
Age (by 10 years)	1.53	1.04 to 2.26	1.85	1.43 to 2.40
Sex (male vs female)	1.56	0.65 to 3.72	1.40	0.89 to 2.19
FFbH (by 10% improvement)			0.86	0.79 to 0.94
GC (<5 mg/d=reference)			.	.
GC (5– <10 mg/d vs ref.)			1.08	0.69 to 1.70
GC (≥10 mg/d vs ref.)			1.67	0.95 to 2.96
csDMARDs	Ref.		.	.
TNFα	0.28	0.12 to 0.63	0.34	0.21 to 0.55
Other bDMARD	0.76	0.22 to 2.67	0.27	0.14 to 0.51
Heart failure (yes vs no)	3.25	0.95 to 11.13	2.13	1.19 to 3.81
Chronic renal disease (yes vs no)			1.65	1.00 to 2.73

csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; GC, glucocorticoids; GEE, generalised estimating equations; SI, serious infection; TNFi, tumor necrosis factor-α inhibitor (adalimumab, etanercept, infliximab, golimumab, certolizumab), other bDMARD (tocilizumab, rituximab, abatacept). Physical function (FFbH) and doses of GC refer to measurements of most recent study visit, DMARD exposure is the current exposure at SI. The median time between the last study visit and the SI was 3.7 months (first quartile: 1.9 months, third quartile: 6.2 months).

Adjustment for age, sex, comorbid conditions (heart failure, renal disease), physical function and glucocorticoid dose by means of multinomial regression resulted in a similar risk of sepsis (adjusted OR: 0.97, 95% CI (0.56 to 1.70)) and mortality (adjusted OR: 0.96, 95% CI (0.42 to 2.17)) for patients who discontinued bDMARDs prior to first SI compared with biologic-naïve patients (reference category). The adjusted risks were significantly lower for patients exposed to bDMARDs at SI (OR (sepsis): 0.57 (0.34 to 0.97), OR (death): 0.34 (0.15 to 0.80)) compared with biologic-naïve patients (see online supplementary table S5).

Mortality after SI and sepsis

Adjustment in the analyses of mortality after sepsis was restricted to age, sex, treatment with bDMARDs and comorbid heart failure because of the low number of fatal outcomes of sepsis. Treatment with TNFi, but not with other bDMARDs, was significantly associated with a lower case fatality rate of sepsis (approach B). All-cause mortality after SI, irrespective of the development of sepsis, was significantly reduced for the use of TNFi and other bDMARDs (approach C, table 4).

Sensitivity analyses

ORs of the risk of sepsis and death for exposure to bDMARDs compared with csDMARDs remained consistently below 1 throughout all four sensitivity analyses (figure 2). The reduction of the study population in analyses 1 and 2 produced wider CIs but consistent estimates. Analysis 3, incorporating 108 SIs with incomplete information, strengthened the results. In the most conservative analysis 4 we imputed the event of sepsis only to those 29 out of 50 dropouts who were exposed to bDMARDs (TNFi: n=17, other bDMARDs: n=12). However, the overall protective effect of bDMARDs remained significant.

DISCUSSION

This is the first study that investigated simultaneously the risks of sepsis and mortality as possible outcomes of SIs in patients with RA. An SI escalated to sepsis or preceded the patient's death in one of five patients. Patients with heart failure, renal disease and at higher age exhibited an increased risk of both adverse outcomes. Patients who were exposed to bDMARDs at the time of SI had a significantly reduced risk of developing sepsis. Similarly, bDMARD treatment significantly lowered the risk of a fatal outcome of SI. A similar result concerning overall

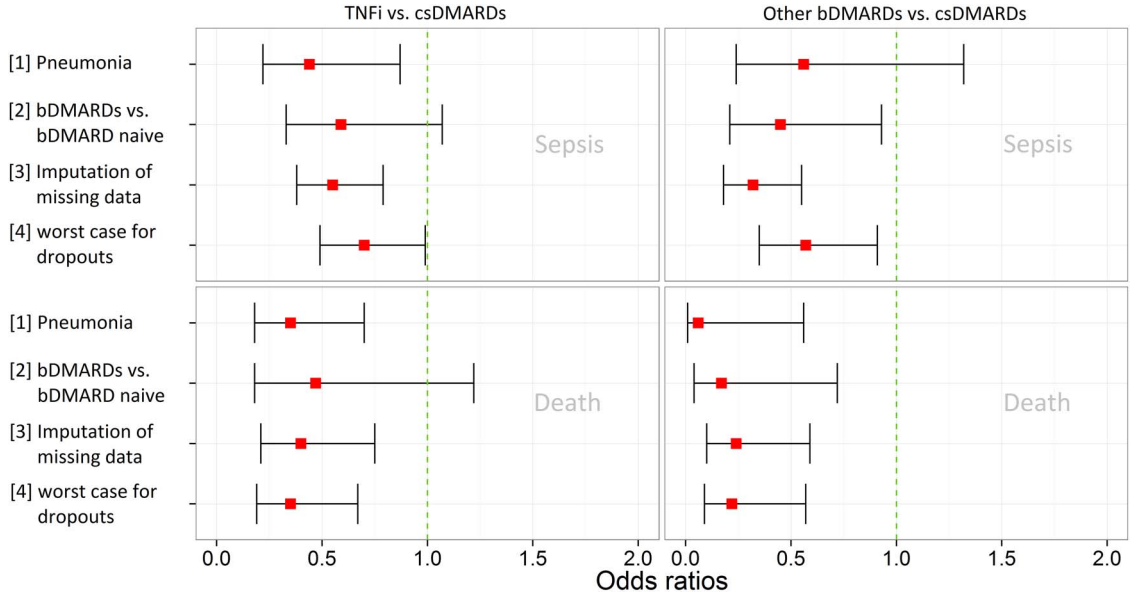

Figure 2 Results of sensitivity analyses show ORs and respective confidence intervals of TNFi vs. csDMARDs and other bDMARDs vs. csDMARDs. Approach [1]: analysis in a subsample of patients with pneumonia, approach [2]: patients at csDMARD treatment were restricted to biologic naïve patients; approach [3]: 108 infections with unknown date and exposure were included, the last known DMARD exposure was 'carried forward' to the respective event of sepsis (n=47) or death (n=19), in approach [4] we assumed in a most conservative manner that all patients who dropped out but were previously treated with bDMARDs had a sepsis (n=29). bDMARD, biologic DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; TNFi, tumour necrosis factor α inhibitors.

mortality after SI was made by Galloway *et al*[30] with data from the British Society of Rheumatology: Biologics Register (BSRBR); they found for TNFi versus csDMARD an adjusted OR of 0.50 (95% CI (0.3 to 0.8)). We also found that mortality after sepsis was significantly lower when patients were exposed to bDMARDs at the time of SI. These findings are consistent with experimental studies in animals[6 7] which suggest that TNFi effectively prevents sepsis.

A secondary but important result of this study addresses the impact of discontinuing bDMARD treatment on the risk of sepsis and death after SI. It is common knowledge that initiation of bDMARD therapy increases the risk of SI.[14–19] Further, discontinuation of bDMARDs is supposed to decrease the risk of SI. Regarding the risks of sepsis or death after SI our results suggest a different mechanism: adverse outcomes of SI (sepsis and death) were more likely in biologic-naïve patients than in patients exposed to bDMARDs at the time of SI (see online supplementary table S5, Sensitivity analysis 2) which could indicate a protective effect of bDMARDs. This double-edged effect of bDMARDs has been described very recently as the 'dual' role of TNFi regarding septic arthritis.[31] The authors referred to an experimental study which showed protective effects of TNFi against septic arthritis.[32] In our study the protective effect receded when bDMARDs were discontinued: the risk of developing sepsis or of dying after SI was similar in patients who had discontinued bDMARDs at least 30 days before the SI and in biologic-naïve patients (see online supplementary table S5).

We performed four sensitivity analyses to test the robustness of the results. The most conservative, or worst-case scenario, which assumed that all bDMARD-treated patients with insufficient follow-up had developed sepsis (Sensitivity analysis 4, figure 2) did not reveal diverging results.

A strength of our study is the simultaneous investigation of sepsis and mortality after SI. This approach prevented the omission of cases which died from undetected sepsis. Furthermore, we adjusted for possible imbalances between DMARD groups in all analyses (age, sex and important risk factors).

There are possible shortcomings of our study. We have found a similar spectrum of SIs across bDMARDs and csDMARDs (see online supplementary figure S2), but a residual chance remains that subtypes of SI are differentially distributed. To minimise this bias we performed a subanalysis of patients with pneumonia which showed consistent results. However, our data do not comprise sufficient pathogen classification to investigate bacterial pneumonia and viral pneumonia separately. Additionally, the numbers of patients and events did not permit discrimination between effects of particular bDMARDs.

Another uncertainty rests with the complexity of the clinical course, the symptoms and the severity of SI and sepsis. There could be a suspicion bias, meaning that patients treated with bDMARDs who develop an SI could be hospitalised faster than those on csDMARDs. This would lead to earlier detection and treatment and thus better outcome of sepsis. We have no indication of such bias since the hospitalisation rates and the spectrum of SIs were equal among the treatment groups. In addition, in RABBIT all diagnoses and serious adverse events are validated and classified by the study physician in a blinded manner, that is, unaware of the DMARD exposure of the respective patient.

In conclusion, this study suggests that patients exposed to bDMARDs at the time of SI have a reduced risk of sepsis and mortality. The effective immunosuppression via bDMARDs may prevent an unregulated host response to SI and the development of sepsis. Discontinuation of bDMARDs seems to shift the risk from an increased susceptibility to SI to more severe outcomes. Nonetheless, we cannot conclude from our study that bDMARDs should be continued in case of an SI since this is the first study showing these results. They have to be confirmed by other studies before any clinical consequences can be drawn.

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Contributors AR, JL, AZ and AS had full access to all data of this study and take responsibility for data integrity and accuracy of the analysis. Study concept and design: JL, AZ, AS. Acquisition of the data: MS, AK, TK, JK. Analysis and interpretation of the data: AR, JL, AZ, AS. Drafting the manuscript: AR. Critical revision of the manuscript for important intellectual content: AR, JL, MS, AK, TK, JK, AZ, AS. Obtained funding: JL, AZ, AS. Study supervision: JL, AZ, AS, MS.

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REFERENCES

1 Cohen J. The immunopathogenesis of sepsis. *Nature* 2002;420:885–91.
2 Stearns-Kurosawa DJ, Osuchowski MF, Valentine C, *et al*. The pathogenesis of sepsis. *Annu Rev Pathol* 2011;6:19-
3 Destarac LA, Ely EW. Sepsis in older patients: an emerging concern in critical care. *Adv Sepsis* 2001;2:15–22.
4 Schorr CA, Zanotti S, Dellinger RP. Severe sepsis and septic shock: management and performance improvement. *Virulence* 2014;5:190–9.
5 Waage A, Halstensen A, Espevik T. Association between tumour necrosis factor in serum and fatal outcome in patients with meningococcal disease. *Lancet* 1987;329:355–7.
6 Tracey KJ, Fong Y, Hesse DG, *et al*. Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. *Nature* 1987;330:662–4.
7 Beutler B, Milsark IW, Cerami AC. Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effect of endotoxin. *Science* 1985;229:869–71.
8 Reinhart K, Karzai W. Anti-tumor necrosis factor therapy in sepsis: update on clinical trials and lessons learned. *Crit Care Med* 2001;29:S121–5.
9 Charles JF, Opal SM, Dhainaut JF, *et al*. Influence of an anti-tumor necrosis factor monoclonal antibody on cytokine levels in patients with sepsis. *Crit Care Med* 1993;21:318–27.
10 Abraham E, Anzueto A, Gutierrez G, *et al*. Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. *Lancet* 1998;351:929–33.

11 Abraham E, Laterre PF, Garbino J, *et al*. Lenercept (p55 tumor necrosis factor receptor fusion protein) in severe sepsis and early septic shock: a randomized, double-blind, placebo-controlled, multicenter phase III trial with 1,342 patients. *Crit Care Med* 2001;29.
12 Remick DG. Cytokine therapeutics for the treatment of sepsis: why has nothing worked? *Curr Pharm Des* 2003;9:75–82.
13 Waage A. Tumour necrosis factor and septic shock. *Lancet* 1998;351:603.
14 Strangfeld A, Eveslage M, Schneider M, *et al*. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? *Ann Rheum Dis* 2011;70:1914–20.
15 Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. *Rheumatology* 2013;52:53–61.
16 Listing J, Strangfeld A, Kary S, *et al*. Infections in patients with rheumatoid arthritis treated with biologic agents. *Arthritis Rheum* 2005;52:3403–12.
17 Dixon WG, Symmons DP, Lunt M, *et al*. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: Lessons from interpreting data from observational studies. *Arthritis Rheum* 2007;56:2896–904.
18 Askling J, Fored CM, Brandt L, *et al*. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF-antagonists. *Ann Rheum Dis* 2007;66:1339–44.
19 Bongartz T, Sutton AJ, Sweeting MJ, *et al*. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006;295:2275–85.
20 Zink A, Listing J, Kary S, *et al*. Treatment continuation in patients receiving biological agents or conventional DMARD therapy. *Ann Rheum Dis* 2005;64:1274–9.
21 Brown E. Using MedDRA. *Drug-Safety* 2004;27:591–602.
22 Lautenschlaeger J, Mau W, Kohlmann T, *et al*. [Comparative evaluation of a German version of the Health Assessment Questionnaire and the Hannover Functional Capacity Questionnaire]. *Z Rheumatol* 1997;56:144–55.
23 Andersen PK, Abildstrom SZ, Rosthoj S. Competing risks as a multi-state model. *Stat Methods Med Res* 2002;11:203–15.
24 Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. *Springer Science & Business Media*, 2000.
25 Beyersmann J, Allignol A, Schumacher M. Competing risks and multistate models with R. *Springer Science & Business Media*, 2011.
26 Touloumis A, Agresti A, Kateri M. GEE for multinomial responses using a local odds ratios parameterization. *Biom* 2013;69:633–40.
27 Touloumis A. R package multgee: a generalized estimating equations solver for multinomial responses. arXiv preprint arXiv:1410 5232 2014.
28 R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0. 2005.
29 Barnett AG, Batra R, Graves N, *et al*. Using a longitudinal model to estimate the effect of methicillin-resistant staphylococcus aureus infection on length of stay in an intensive care unit. *Am J Epidemiol* 2009;170:1186–94.
30 Galloway JB, Hyrich KL, Mercer LK, *et al*. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology (Oxford)* 2011;50:124–31.
31 Lee SI, Kim WU. Dual effects of tumor necrosis factor α inhibitors on septic arthritis: from a "bad friend" to a "good enemy". *Arthritis Rheumatol* 2015;67:11–13.
32 Ali A, Zhu X, Kwiecinski J, *et al*. Antibiotic-killed staphylococcus aureus induces destructive arthritis in mice. *Arthritis Rheumatol* 2015;67:107–16.

2.2 Ereignisse mit langer Latenzzeit und sehr seltene Ereignisse

2.2.1 Risiko für inzidente und rekurrente Tumore

Strangfeld A, Hierse F, Rau R, Burmester GR, Krummel-Lorenz B, Demary W, Listing J, Zink A. *Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT*. Arthritis Res Ther. 2010;12(1):R5. doi: 10.1186/ar2904. PubMed PMID: 20064207.

Zusammenfassung

Bei Einführung der TNF Inhibitoren war man aufgrund der tumorsuppressiven Wirkung des TNFα [33] besorgt über ein möglicherweise erhöhtes Risiko für die Entwicklung von Malignomen unter diesen Substanzen, zumal sie durch den chronischen Verlauf der rheumatischen Erkrankung über lange Zeit, wenn nicht gar lebenslang, verabreicht werden müssen. Zwei von Bongartz et al. [34, 35] veröffentlichte Meta-Analysen der im Vorfeld der Zulassung durchgeführten klinischen Studien fanden im Vergleich zu der mit Placebo behandelten Patientengruppe ein signifikant erhöhtes Risiko für Tumore unter der Therapie mit Adalimumab (gepoolte OR 3.3 [95%KI 1.2-9.1]) und eine, wenngleich nicht signifikante, Erhöhung des Tumorrisikos unter der Therapie mit Etanercept (HR 1.84 [95%KI 0.8-4.3]). Da im rheumatologischen Alltag eher davon ausgegangen werden muss, dass die behandelten Patienten nicht so sorgfältig selektiert und überwacht werden, wie dies im Rahmen klinischer Studien der Fall ist, stellte sich die Frage, ob hier nicht noch ein viel höheres Risiko unter Therapie mit bDMARDs zu erwarten sei.

Angesichts der Bedeutung der Fragestellung führten wir bereits 2007 eine erste Analyse zum Risiko für inzidente und rekurrente Malignome unter TNFi im Vergleich zu csDMARDs durch. Insgesamt konnten 5,120 Patienten analysiert werden, die bis 31.12.2006 in die Kohorte eingeschlossen worden waren und bei denen ausreichende Follow-up-Informationen vorhanden waren. 122 Patienten hatten eine Tumor-

anamnese. Bei 4998 Patienten ohne Tumoranamnese wurde das Risiko für inzidente Tumore untersucht. 1719 waren mit csDMARD, die restlichen mit bDMARDs behandelt worden. Die aufgetretenen Raten wurden organspezifisch mit alters- und geschlechtsstandardisierten Raten der Normalbevölkerung verglichen. Für einige Organe (Brust-, Geschlechtsorgane und Kolon) wurden geringere Tumorraten als in der Bevölkerung festgestellt, für andere (Lunge und Lymphome) höhere.

Die Untersuchung der Risikofaktoren für eine erhöhte Tumorinzidenz erfolgte zunächst mit allen Patienten durch eine multivariate Cox-Regression und in einer weiteren Analyse durch eine eingebettete Fall-Kontroll-Studie, in die als Matching-Kriterien außer Alter, Geschlecht und Rauchstatus auch Begleiterkrankungen einbezogen wurden. Als Risikofaktoren wurden höheren Alter, hohe Krankheitsaktivität und COPD oder chronische Magen-Darm-Erkrankungen identifiziert. Die Therapie mit TNFi war im Vergleich zur Therapie mit csDMARDs nicht mit einem höheren Risiko für die Tumorentwicklung assoziiert.

Patienten, die mit einer Tumoranamnese in das Register eingeschlossen worden waren, hatten kein höheres Risiko für eine Rekurrenz des Tumors unter TNFi oder Anakinra im Vergleich zu Patienten unter csDMARD Therapie.

Mit dieser Analyse war RABBIT das erste Biologika- Register, in dem das Risiko für rekurrente Tumore untersucht wurde. Eine Limitation ist, dass zu dieser Zeit die Zahl der Patienten mit Tumoranamnese im Register noch relativ klein war. Da es sich bei diesen Patienten um eine in der rheumatologischen Praxis relevante Gruppe handelt, deren Teilnahme an klinischen Studien von vornherein ausgeschlossen ist, wird diese Analyse derzeit mit deutlich höheren Patientenzahlen und einer tumorspezifischen Differenzierung der Analyse wiederholt.

Für zwei Tumorarten, für die bei RA mit einem erhöhten Risiko gerechnet werden muss, maligne Melanome und Lymphome, wurde die Inzidenz inzwischen in internationaler Zusammenarbeit von sieben bzw. elf Registern untersucht. Zu diesen Analysen, die bestätigen konnten, dass bei einer Therapie mit Biologika mit keiner signifikanten Risikoerhöhung zu rechnen ist, hat das RABBIT-Register federführend beigetragen [36, 37].

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RESEARCH ARTICLE Open Access

Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT

Anja Strangfeld*[1], Franka Hierse[1], Rolf Rau[2], Gerd-Ruediger Burmester[3], Brigitte Krummel-Lorenz[4], Winfried Demary[5], Joachim Listing[1] and Angela Zink[1,3]

Abstract

Introduction: We used the data of the German biologics register RABBIT, a nationwide prospective cohort study, to investigate the risk of new or recurrent malignancy in patients with rheumatoid arthritis (RA) receiving biologics compared to conventional disease modifying anti-rheumatic drugs (DMARDs).

Methods: The analysis was based on patients with RA enrolled in RABBIT at the start of a biologic or conventional DMARD therapy between 01 May 2001 and 31 December 2006. Incidences of first or recurrent malignancies were analysed separately. A nested case-control design was used to investigate the risk of developing a first malignancy. Matching criteria were: age, gender, follow-up time, disease activity score based on 28 joint counts (DAS28) at study entry, smoking status, and selected chronic co-morbid conditions (obstructive or other lung disease, kidney, liver or gastrointestinal disease, psoriasis).

Results: A prior malignancy was reported in 122 out of 5,120 patients. Fifty-eight of these patients had received anti-TNFα agents, 9 anakinra, and 55 conventional DMARDs at study entry. In 14 patients (ever exposed to anti-TNFα: eight, to anakinra: one) 15 recurrent cancers were observed. The average time period since the onset of the first malignancy was nine years. Crude recurrence rates per 1,000 patient-years (pyrs) were 45.5 for patients exposed to anti-TNFα agents, 32.3 for anakinra patients and 31.4 for patients exposed to DMARDs only (Incidence rate ratio anti-TNFα vs. DMARD = 1.4, $P = 0.6$.). In patients without prior cancer, 74 patients (70% female, mean age: 61.3) developed a first malignancy during the observation. This corresponds to an incidence rate (IR) of 6.0/1,000 pyrs. Forty-four of these patients were ever exposed to anti-TNFα treatment (IR = 5.1/1,000 pyrs). In a nested case-control study comparing cancer patients to cancer-free controls, 44 of the cancer patients and 44 of the cancer-free controls were ever exposed to anti-TNFα agents ($P = 1.0$).

Conclusions: No significant differences in the overall incidence of malignancies in patients exposed or unexposed to anti-TNFα or anakinra treatment were found. The same applied to the risk of recurrent malignancies. However, in particular this last finding needs further validation in larger data sets.

Introduction

Patients with rheumatoid arthritis (RA) and other chronic inflammatory diseases are often subject to prolonged treatment with immunosuppressive drugs which modify the immunologic pathways involved in the pathogenesis of RA. Tumor necrosis factor alpha (TNFα) is among the cytokines that play a major role in the inflammatory process of rheumatic diseases. Its inhibition leads to substantial improvement in clinical signs and symptoms in a majority of patients. To date three different agents are available as monoclonal antibodies or receptor fusion antagonists of TNFα. The finding that TNFα is able to induce tumor cell apoptosis led it to be named TNF before its role in the

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inflammatory process was revealed [1]. TNFα or rather its nuclear factor-kappa B pathway acts as an early tumor suppressor [2]. This property led to concerns about a possibly increased risk of malignancies when drugs blocking TNFα will be used for long-term treatment.

These concerns were supported by two meta-analyses of randomized controlled trial data. In their first aggregate data meta-analysis of nine randomized controlled trials (RCTs) of anti-TNFα antibody therapies (infliximab and adalimumab) versus placebo in patients with rheumatoid arthritis, Bongartz et al. [3] found a significantly increased risk for malignancies in anti-TNFα versus placebo treated patients with a pooled odds ratio of 3.3 (95% CI: 1.2 to 9.1). In their second meta-analysis Bongartz et al. [4] found a higher malignancy risk also in patients treated with etanercept as compared to the control group, although the relative risk estimate did not achieve statistical significance (Hazard ratio (HR) of 1.84 [95% CI: 0.79 to 4.28]).

Considering the strict criteria for the inclusion of patients and the thorough monitoring process preceding controlled trials there might be an even higher risk when unselected RA patients are treated with anti-TNFα agents in daily rheumatologic care. Therefore, real-world data from studies systematically observing patients treated with these agents for long periods are of high importance.

Patients with prior malignancy are usually excluded from participation in RCTs and most clinical recommendations do not encourage treating these patients with anti-TNFα. However, this treatment might be the best therapeutic option for their inflammatory disease. Information regarding the safety of biologic agents prescribed to patients with prior malignancies is available only from two abstracts from the British Society of Rheumatology Biologics Register (BSRBR) [5,6], one of them indicating a possibly increased recurrence risk for melanoma [6].

According to the national recommendations of the German Society of Rheumatology biologic agents should be prescribed after failure of at least six months of treatment with two conventional DMARDs (including methotrexate (MTX)) alone or in combination [7].

The German biologics register RABBIT is an ongoing, nationwide prospective cohort study started in 2001 with the approval of the first biologic agents in Germany. It was established with the aim to assess the long-term safety of biologic agents including TNFα blockers. Time points of follow-up and assessments are identical for patients treated with biologic agents and for those under therapy with conventional DMARDs.

We used the data from RABBIT to investigate the frequency of developing a first malignancy in patients treated with anti-TNFα agents compared to those treated with conventional DMARDs and to study the risk of patients with a history of malignancy receiving anti-TNFα therapy.

Materials and methods

Patients

Patients aged 18 to 75 years meeting the American College of Rheumatology (ACR) criteria for RA are eligible to be enrolled in RABBIT at the start of treatment with a biologic agent or a conventional DMARD after failure of at least one other DMARD. Prior to enrollment all patients gave their informed consent. Patients enrolled between 01 May 2001 and 31 December 2006 (end of recruitment to this cohort) were included in the following analyses provided at least one follow-up visit and the baseline status regarding co-morbid conditions were available. Patients were followed up independent of any change in their treatment regimes. Information about patients who missed two or more consecutive follow-up visits was obtained by contacting the treating physicians, and if necessary the patients themselves, their relatives or the local health authorities to determine the patient's vital status. The reasons for dropout and the causes of death were ascertained. Details of inclusion criteria for RABBIT were previously reported [8,9]. The ethics committee of the Charité University School of Medicine, Berlin, approved the study protocol.

Assessments

At baseline and at predefined time points of follow-up (3, 6, 12, 18, 24, 30, 36, 48, 60 months) rheumatologists assessed the clinical status including the components of the disease activity score based on 28 joint counts (DAS28) and reported treatment details and serious and non-serious adverse events according to the International Conference on Harmonization E2A guidelines [10]. All adverse events were coded using the Medical Dictionary for Regulatory Affairs (MedDRA) [11] by one of the authors (AS). Reported malignancies were considered as *events of interest*, and an additional query asking for diagnostic and treatment details and cancer history was sent to the reporting rheumatologist. Only in five cases we did not receive any further information. In 50% of the cases hospital discharge letters with the exact histopathologic results were sent to us.

At study entry rheumatologists reported co-morbidities for every patient on a list of 23 diseases which include among others: prior malignancy or lymphoma, chronic obstructive pulmonary disease (COPD), other chronic lung disease, chronic renal disease, chronic gastrointestinal disease, chronic liver disease, psoriasis, and chronic viral disease. Patients assessed their pain, general health, disability and socioeconomic status. The Hannover Functional Status Questionnaire (Funktionsfragebogen Hannover, FFbH) was used to assess disability. Scores are expressed as percentage of full function (range 0 to 100) and can be transformed into Health Assessment Questionnaire (HAQ) values [12]. Smoking habits were not assessed at baseline but only after 24, 48, 60 months. Since this resulted in a high percentage of missing smoking information we did not include smok-

ing in the multivariate analyses. Nevertheless, in the nested case control study we were able to include smoking by using the missing information as one matching criterion.

Statistical analysis

Prior malignancies and tumor recurrence. All patients meeting the study inclusion criteria were stratified by their prior malignancy status. For all patients prior malignancies were reported by the rheumatologist at study entry. Patients with or without prior malignancy were compared with respect to patient characteristics and treatment. In patients with a recurrent malignancy during the observation in RABBIT we analysed whether treatment was associated with recurrence. We defined recurrency as development of any cancer after a history of a prior malignancy, irrespective of the type of the recurrent tumor.

Tumor incidence

We analysed the tumor incidence during the observation period in all patients without prior malignancy. We included all types of cancer except for basal cell carcinomas. One M. Bowen was reported and included. There was no report of other carcinomas in situ. The observed number of incident cancers was compared with the expected number calculated from population data [13]. Cox regression was used to analyse the effects of treatment and to adjust for demographic and clinical data. Only exposure times after enrollment in the RABBIT register were taken into account. Patients were considered to be exposed to anti-TNFα treatment for the time period from the start of anti-TNFα treatment to the end of follow-up (*ever exposed*-approach). The same definition was used for anakinra exposure. Because of the applied *ever exposed*-approach patients could have been exposed to both, anti-TNFα agents and anakinra. Patients (or follow-up time of patients) not (yet) exposed to anti-TNFα or anakinra were considered as exposed to DMARDs only.

The following baseline characteristics were included in the risk assessment: age, gender, disease duration, rheumatoid factor, functional capacity (measured by the FFbH), selected previous treatment exposures (cyclosporine or azathioprine) [14], and co-morbid conditions.

Since nearly all (98.3%) of our patients were ever exposed to methotrexate and only a small minority (0.6%) to cyclosphosphamide we were not able to investigate a specific cancer risk associated with these agents. A preliminary analysis blinded for treatment assignment revealed associations between the frequency of cancer and COPD, chronic gastrointestinal diseases and chronic renal diseases. Other co-morbidities, such as chronic lung diseases in general, are known to be associated with increased cancer risk. Therefore, the following comorbid conditions were included in the Cox regression analysis: COPD, other chronic lung disease, chronic renal disease, chronic gastrointestinal disease, chronic liver disease, and psoriasis. Furthermore, we investigated the impact of exposure to anti-TNFα agents as well as the impact of long-term high disease activity (measured by time-averaged DAS28 scores) on the risk of cancer. For this analysis, the mean of all DAS28 scores measured more than six months before an event were included as time-dependent co-variables into the Cox regression analysis. Disease activity during the six months prior to a malignancy diagnosis was not considered since it may have been influenced by the carcinogenesis. For malignancies that developed within the first six months of observation, the DAS28 measured at study entry was used. On average 7% of the DAS28 values at follow-up were missing. To minimize possible bias missing values were imputed before the time-averaged scores were calculated. The expectation-maximisation (EM) algorithm most appropriate for approximately normally distributed variables such as the DAS28 was applied for estimation and imputation [15]. Calculations were performed using the SAS procedures MI and PHREG. A test based on the analysis of Schoenfeld residuals of Cox regression was used to investigate the invariance of the HR over time [16].

The control for confounding factors by Cox regression analysis may be insufficient since smoking could not be included and two possible risk factors found in our preliminary analysis (see above) were observed in less than 5% of the patients. Our statistical analysis plan therefore stipulated to perform a nested case control study as our main analysis of the risk of incident cancer. For each case with an incident cancer, a cancer-free control patient was selected who was compatible with the following matching criteria: gender, smoking status, and six co-morbid conditions (same as those used in the Cox regression). Cases with valid data of smoking status were matched to controls with the same smoking status and patients with missing information regarding smoking status were matched to controls who also had no smoking status data. After matching for eight categorical variables, a control patient was selected who fitted best to the case concerning age, follow-up time and DAS28 at baseline. Standardized Mahalanobis metric was used for measuring similarity. The availability of 4,923 possible controls permitted use of this detailed matching algorithm. Mc Nemar test was used to compare the numbers of patients exposed to biologics (anti-TNFα agents or anakinra) between patients and matched controls. For further comparisons within the nested case control study, paired t-test and Wilcoxon test were applied as appropriate. Chi-square test, t-test and Mann-Whitney test were used for statistical comparisons of patient's characteristics at baseline. *P*-values < 0.05 were considered statistically significant.

Results

Patient characteristics and treatment status at study entry

Between 01 May 2001 and 31 December 2006, 5,279 patients were enrolled in RABBIT. One hundred fifty-nine patients were excluded from this analysis because of miss-

ing follow-up information or missing co-morbid condition status (Figure 1). Their baseline characteristics (age, DAS28, function, co-morbidity status) were not statistically different from the remaining 5,120 patients. Those were stratified according to their prior malignancy status, and both groups were analysed separately. A total of 124 prior malignancies were found in 122 patients: 6 lymphomas (DMARDs: 2, anti-TNFα: 4), and 118 solid tumors (DMARDs: 54, anakinra: 9, anti-TNFα: 55)]. Patients with prior malignancies were significantly older ($P < 0.001$), had a lower functional capacity (56% of full function vs. 60% of full function) and a higher frequency of chronic gastrointestinal disease than patients without prior malignancy (Table 1). Within both strata, we found that patients receiving biologics had significantly more active disease, and were more limited in activities of daily living (FFbH). As reported previously, there were no significant differences in the clinical characteristics of patients receiving etanercept, adalimumab, or infliximab [17], whereas anakinra patients had more treatment failures with DMARDs and a lower functional capacity (FFbH) than anti-TNFα patients. Because of the differing modes of action and the differences in the clinical characteristics, separate results are provided in the following analyses for patients receiving anti-TNFα agents and patients receiving anakinra.

Patients with a prior malignancy were insignificantly less frequently treated with anti-TNFα agents or anakinra at inclusion than patients without prior malignancy (Figure 1, Table 1). The adjusted OR to receive biologics (adjusted for age, sex, disability, disease activity) for patients with prior malignancies compared to those without was 0.7 (95%CI: 0.5 to 1.1). Detailed information including the exact type of malignancy was reported in 54 of the 124 prior malignancies. We found some differences regarding the spectrum of those malignancies in anti-TNFα vs. DMARD treated patients: At study entry all nine cases with prior prostatic

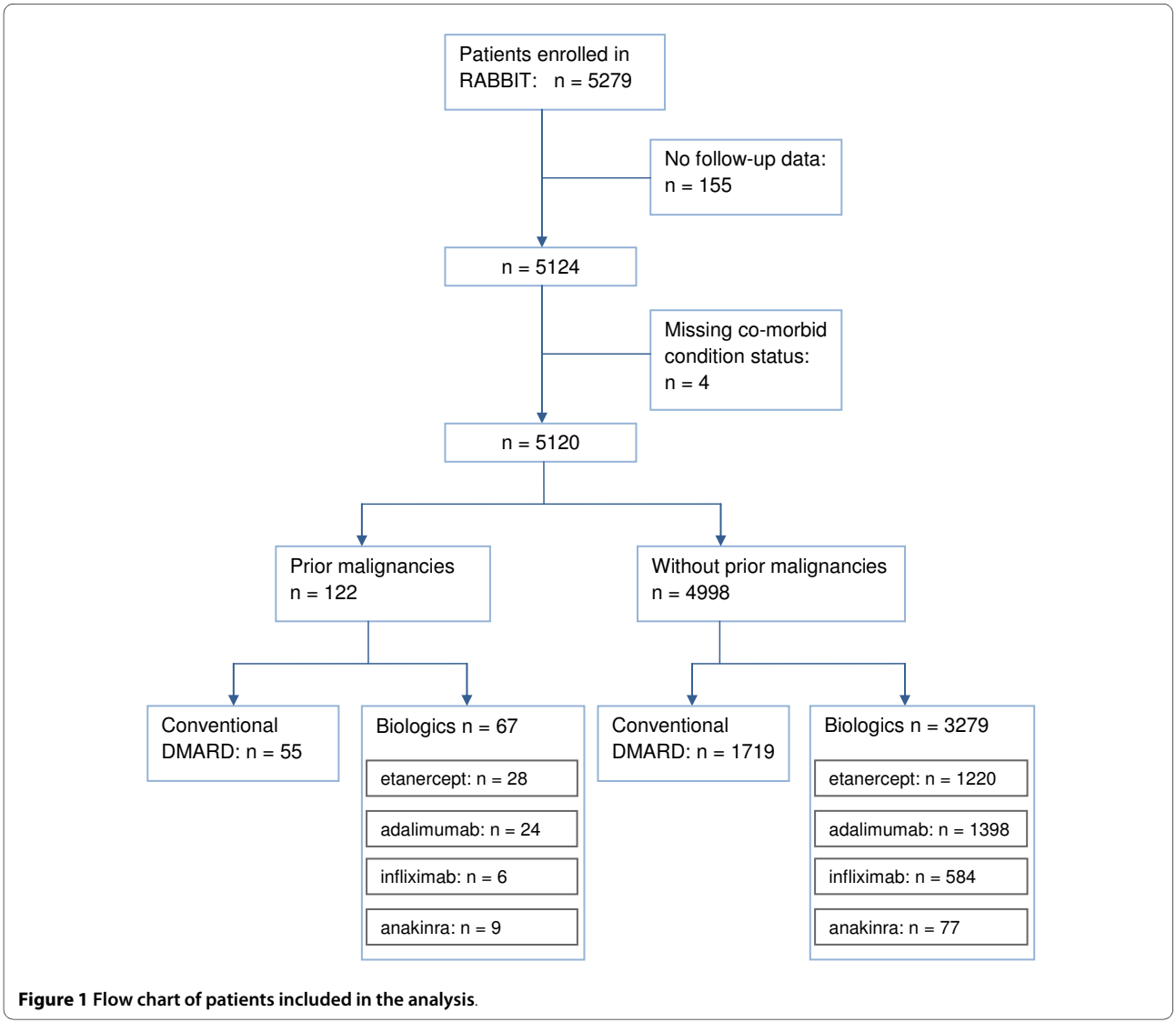

Figure 1 Flow chart of patients included in the analysis.

Table 1: Baseline characteristics of patients

	Patients with prior malignancy				Patients without prior malignancy				
	Biologic	**Control**	**Total**	**P #**	**Biologic**	**Control**	**Total**	**P #**	**P ##**
n	67	55	122		3279	1719	4998		
Female n (%)	45 (67.2)	41 (74.5)	86 (70.5)	0.43	2564 (78.2)	1353 (78.7)	3917 (78.4)	0.671	0.047
Age (mean, SD)	64.0 (9.0)	63.2 (7.7)	63.7 (8.4)	0.62	53.6 (12.3)	55.9 (11.5)	54.4 (12.1)	< 0.0001	< 0.001
Disease duration (yrs), median (IQR)	10 (6, 16.5)	7 (3, 13)	9 (4, 16)	0.02	9 (5, 17)	6 (2.5, 12)	8 (4, 15)	< 0.0001	0.286
Time from prior cancer to study entry (yrs), median (IQR)	5 (2, 9)	5 (3, 11)	5 (2, 10)	0.77					
Follow-up time (yrs), median (IQR)	2.1 (1.4, 3.0)	2.5 (1.0, 4.0)	2.1 (1.1, 3.1)	0.43	2.4 (1.4, 3.1)	2.5 (1.3, 3.3)	2.4 (1.3, 3.1)	0.081	0.611
Rheumatoid factor positive n (%)	53 (79.1)	46 (83.6)	99 (81.1)	0.64	2629 (80.2)	1225 (71.3)	3854 (77.1)	< 0.0001	0.327
DAS28 (mean, SD)	5.7 (1.3)	5.4 (1.1)	5.6 (1.2)	0.04	5.8 (1.3)	5.0 (1.3)	5.5 (1.3)	< 0.0001	0.282
ESR (mm/h), median (IQR)	38 (18, 51)	26 (15, 42)	32 (17, 50)	0.12	30 (16, 48)	22 (12, 38)	27 (14, 44)	< 0.0001	0.080
CRP (mg/L), median (IQR)	25 (10, 46)	15 (8, 30)	19 (9, 43)	0.07	17 (8, 38)	12 (5, 27)	15 (7, 34)	< 0.0001	0.146
FFbH (mean, SD)	52.1 (21.3)	59.9 (23.5)	55.7 (22.5)	0.02	57.0 (23.0)	66.8 (21.4)	60.4 (22.9)	< 0.0001	0.025
Smoking ever n (%)	23 (57.5)	15 (55.6)	38 (56.7)	1.00	878 (46.9)	473 (46.4)	1351 (46.7)	0.328	0.13
No. of previous DMARDs (mean, SD)	3.7 (1.5)	1.9 (1.0)	2.9 (1.6)	< 0.001	3.6 (1.4)	1.9 (1.1)	2.9 (1.5)	< 0.0001	0.656
COPD n (%)	3 (4.4)	6 (10.9)	9 (7.3)	0.30	163 (5)	81 (4.7)	244 (4.9)	0.685	0.205
Chronic renal disease n (%)	4 (5.9)	1 (1.8)	5 (4.1)	0.38	134 (4.1)	29 (1.7)	163 (3.3)	< 0.0001	0.603
Chronic lung disease n (%)	5 (7.4)	1 (1.8)	6 (4.9)	0.22	93 (2.8)	29 (1.7)	122 (2.4)	0.012	0.129
Chronic gastrointest. disease n (%)	**12 (17.6)**	**5 (9.1)**	**17 (13.9)**	**0.2**	**281 (8.6)**	**138 (8.0)**	**419 (8.4)**	**0.510**	**0.047**

Values are means and standard deviations if not otherwise specified. IQR = inter quartile range; FFbH = Hannover Functional Status Questionnaire measuring functional capacity in percent of full function; DAS28: disease activity score based on 28 joint counts;
= *P*-value for comparison between biologic and control group within strata according to prior malignancy status, ## = comparison between strata

cancer were treated with biologics (seven with anti-TNFα and two with anakinra) whereas three patients with prior bladder cancer were found in the DMARD treated group and one patient was treated with anakinra. Patients with prior breast cancer were less frequently treated with biologics (n = 11) than with DMARDs (n = 14) at inclusion. The time between onset of the prior malignancy and study entry did not differ between the treatment groups. The median time was five years (IQR: 2 to 9) for patients receiving biologics (anti-TNFα: four years (2 to 10); anakinra: six years (5 to 9)) and five years (3 to 11) for patients receiving conventional DMARDs (P = 0.77). In 28 (45.9%) of the patients treated with biologics (27 with anti-TNFα and 1 with anakinra) and in 22 (40.7%) patients in the DMARD group the time since the last tumor diagnosis was less than five years when treatment with the respective agent started.

Recurrence of a prior malignancy

During follow-up 15 recurrent cancers were observed in 14 patients including 14 recurrences of the same type and site as the prior tumor and one metastasis of unknown origin (Table 2). Nine recurrences were seen in eight patients under treatment with anti-TNFα agents, one in an anakinra patient and five in patients exposed to DMARDs only. The corresponding crude incidence rates were 45.5 (95%CI: 20.8 to 86.3)/1,000 patient years (pyrs) for patients receiving anti-TNFα agents, 32.3 (95%CI: 0.8 to 179.7)/1,000 pyrs for patients treated with anakinra and 31.4 (95%CI: 10.2 to 73.4)/1,000 pyrs for DMARD treated patients (incidence rate ratio anti-TNFα agents vs. DMARDs: 1.4 (95% CI: 0.5 to 5.5) P = 0.63).

The mean time span between the prior tumor and the diagnosis of the new tumor was 9.5 (SD: 7.8), 9.1, and 9.2 (8.8.) years for patients exposed to anti-TNFα agents, anakinra, or conventional DMARDs, respectively. Three patients developed a recurrent cancer less than five years after the previous cancer (two in the anti-TNFα treated group, one in the DMARD group).

Four of the five patients who were treated with conventional DMARDs only and experienced a recurrence of their prior malignancy died (signet-ring-cell carcinoma, metastasis of unknown origin, breast cancer, lung cancer). One out of the eight patients under treatment with anti-TNFα died (breast cancer), and the one patient under treatment with anakinra (lung cancer) died. All other patients with recurrences were still alive at the time of the analysis.

Incidence of tumors in patients without a prior malignancy

Comparison of the tumor incidence with the general population

Seventy-four patients among the 4,998 patients who did not have a prior malignancy developed an incident tumor. This is an overall incidence rate of 6.0 per 1,000 pyrs [95% CI: 4.7 to 7.6]. The figures were 5.1 per 1,000 pyrs (95% CI: 3.7 to 6.9) for patients exposed to anti-TNFα, 7.2 per 1,000 pyrs (95% CI: 2.4 to 16.9) for patients exposed to anakinra and 8.4 per 1,000 pyrs (95% CI: 5.7 to 12.0) for patients exposed to conventional DMARDs. For some of the cancer sites the observed incidence rates in both groups were lower than the age and sex adjusted rates as expected from the general population (for example, breast, male and female reproductive organs and colon cancer) [13] (Figure 2). Higher rates were observed for non-Hodgkin's lymphoma in patients exposed to biologics and for pancreatic cancer in the group not exposed to biologics. None of the site specific differences were statistically significant when the P-values were adjusted for repeated significance testing. Taking into account all malignancies, the number of observed cancers in patients exposed to anti-TNFα agents was non-significantly lower than the expected number from the general population (standardized incidence rate ratio: 0.75, 95% CI: 0.54 to 1.01). No difference was found for patients not exposed to biologics.

Comparison of patients with and without incident tumors in patients with no prior cancer

Overall, patients who developed malignancies during the study period had more co-morbidities than those who did not (mean = 2.5 (SD = 2.1) vs. 1.7(1.9)). Higher rates were observed for COPD (11/74 (14.9%) vs. 223/4924 (4.5%), P < 0.0001), chronic gastrointestinal diseases ((13/74 (17.6%) vs. 406/4924 (8.2%), P = 0.008), and chronic renal diseases (4/74 (5.4%) vs. 159/4924 (3.2%), P = 0.22). Furthermore, site specific associations were observed for gastric/colorectal cancer in 2/419 patients with a chronic gastrointestinal disease vs. 3/4579 in the remaining patients (P = 0.06), and for bladder cancer/renal cancer in 1/163 patients with chronic renal diseases vs. 3/4835 in the remaining patients (P = 0.12).

Crude cancer incidence rates were therefore higher in patients with specific comorbid conditions but also in those with a highly active disease (Table 3).

The univariate analysis showed that patients with a very active disease (DAS28 >5.1, mean: 5.93) during follow-up had a two times higher cancer risk than those with low disease activity (DAS28 <3.2, mean: 2.75) (Table 4).

In the multivariate analysis the development of an incident tumor was strongly associated with age (HR = 1.71; 95% CI: 1.3 to 2.2 per 10 years increase in age, P < 0.0001) and COPD (HR = 2.63; 95% CI: 1.4 to 5.0, P = 0.004) (Table 4). A higher cancer risk was also observed for patients with chronic gastrointestinal diseases whereas no significant associations were found for other co-morbid conditions (other chronic lung diseases, psoriasis, chronic liver disease) or for gender (HR (males vs. females) = 1.46; 95% CI: 0.9 to 2.4, P = 0.14). Likewise, associations for patients ever exposed to cyclosporine (n = 582, P = 0.24) or azathioprine (n = 599, P = 0.32) were not statistically significant.

In patients exposed to anti-TNFα agents we observed a non-significantly decreased risk for developing a malignancy compared to patients treated with conventional DMARDs (adjusted HR = 0.70; 95% CI: 0.44 to 1.12, P = 0.13).

Time dependency of the hazard risk in patients without prior cancer

The mean time until the onset of the malignancy was 25.0 (16.8) months for patients exposed to anti-TNFα agents, 14.8 (9.1) for anakinra and 17.4 (15.7) months for patients not exposed to biologics. Ten of the 44 malignancies of anti-TNFα-exposed patients developed in the first year compared to 15 of 30 malignancies in non-exposed patients. This corresponds to adjusted hazard ratios of 0.4 for the first and 1.0 for the second to fourth year. We analysed this possible time trend in the hazard ratio by means of an analysis of standardized Schoenfeld residuals of the Cox regression. The trend was, however, not statistically significant (P = 0.13).

Nested case-control study

The main analysis to assess the risk of developing an incident tumor under treatment with anti-TNFα agents was conducted as a nested case control study. Each case with an incident malignancy was matched to one control patient without malignancy (see Methods). Due to the high number of possible matching partners, matching was successful for all parameters involved. Cases with incident malignancy had lower baseline functional capacity than those without cancer (Table 5). There was no significant difference concerning treatment exposure: Forty-four (59.5%) of the cases and 45 (60.8%) of the controls had ever been exposed to biologics. The numbers of cases ever exposed to etanercept, adalimumab, infliximab, or anakinra (n = 22; n = 20; n = 16; n = 5, respectively) did not differ significantly from the numbers of controls ever exposed to these therapies (n = 27; n = 24; n = 10; n = 5, respectively). A separate analysis of malignancies observed in the first year (anti-TNFα exposed 10/25 cases vs. 11/25 controls) and in the second to fourth year (anti-TNFα exposed: 34/49 cases vs. 33/49 controls) did not show any significant difference between the groups or a significant time trend.

An insignificantly higher rate of exposure to anti-TNFα agents was found in patients who developed non-Hodgkin's lymphoma.

Discussion

First, in patients with prior malignancy we did not find a significant increase in the risk of recurrent tumors under treatment with anti-TNFα agents compared to conventional DMARDs, even though there was a higher recurrence rate under anti-TNFα treatment (IRR = 1.4, P = 0.6).

Table 2: Recurrence of prior malignancy by type and treatment

		Ever exposed to		
	Total	**Anti-TNFα**	**Anakinra**	**Conventional DMARD only**
N with prior malignancy	122	72	11	43
Patient-years of follow-up	379	198	31	159
Recurrent malignancies	15	9 (5 f, 4 m)	1 (m)	5 (4 f, 1 m)
Breast cancer	5	4 (f)	-	1(f)
Lung cancer	3	1 (m)	1 (m)	1 (f)
Bladder cancer	2	1 (m)[#]	-	1 (f)
Liposarcoma	1	1 (m)	-	-
Melanoma	1	1 (f)		
Signet-ring cell carcinoma	1	-	-	1 (f)
Testicular cancer	1	1 (m)[#]	-	-
Metastasis of unknown origin	1			1 (m)

M = male, f = female, [#]testicular cancer and bladder cancer in one patient

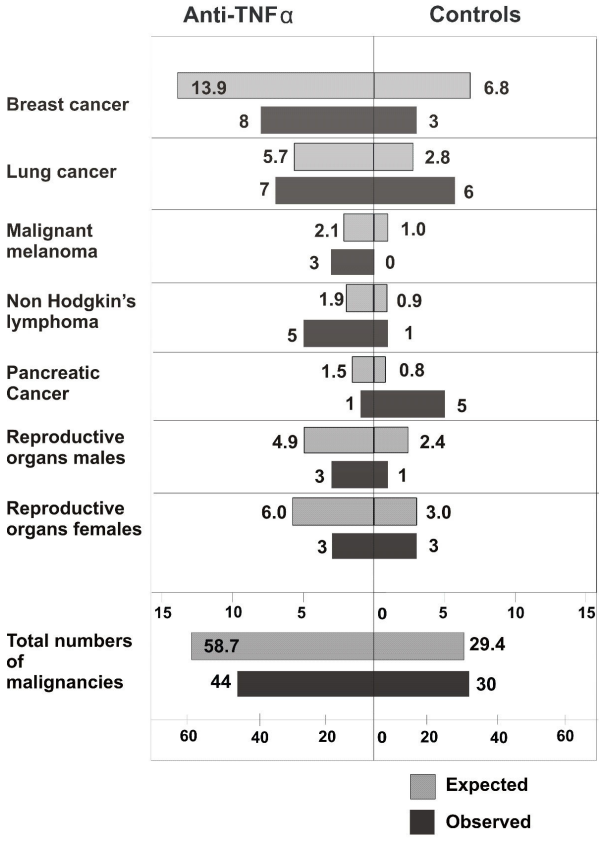

Figure 2 Observed numbers of cancers and expected numbers from the general population, standardized by age and sex.

Second, patients without prior malignancy did not have higher rates of incident tumors when they were exposed to biologics compared to unexposed patients.

The strength of our study is that all data on incident and recurrent tumours originate from a prospective, closely monitored observational cohort study established for the purpose of pharmacovigilance. Data were collected in an identical manner and by the same physicians for patients treated with biologic agents or with conventional DMARDs. Due to stringent and close monitoring, drop-out rates were less than 5% per year. Additionally, for all patients lost to follow-up the vital status was ascertained or, if appropriate, the cause of death.

To investigate the occurrence of incident malignancies, we followed three different methodological approaches: a nested case-control study, a multivariate Cox regression and a comparison with population data.

Of note, we excluded basal cell carcinoma from all types of our analysis since no age and sex specific population rates were available.

The design of the nested case control study allowed us to adjust for differences in clinical and demographic parameters (for example, selected co-morbidities, smoking status) which are related to treatment assignment but which are also associated with the risk of cancer. We therefore consider the nested-case control analysis our central assessment of the risk of incident malignancies under treatment with anti-TNFα agents. However, since only a very small proportion of the patients were included in the nested case control analysis and therefore information of a large number of patients was not used, we decided to apply a multivariate Cox regression analysis in addition.

A potential weakness of this study is that we only investigated the overall cancer risk. The risk for site-specific cancers has not been analyzed due to the limited numbers of events. In addition, due to the relatively short time of observation no conclusions can be drawn beyond the scope of four years of exposure.

Limitations of the analysis of tumor recurrence include the relatively small sample size and the fact that physicians were less likely to prescribe cytokine inhibitors for patients with prior malignancy than for those without such a history. Furthermore, our data indicate that physicians might have made different treatment decisions for patients with different prior tumors. We therefore must exhibit caution in drawing firm conclusions.

The same applies for the interpretation of the data for anakinra treated patients: only a few patients in the cohort were ever treated with anakinra, most of them were also exposed to anti-TNFα agents. Therefore, malignancies occurring in this group must be interpreted carefully, taking patient selection (also seen in differing baseline characteristics) into account.

Our results differ from those reported by the British Society for Rheumatology Biologics Registry (BSRBR) [6]. Dixon and co-workers analyzed 177 patients with prior malignancies treated with anti-TNFα agents with a median follow-up of three years and found no increased risk for recurrent malignant diseases compared to 118 patients with prior malignancies treated with conventional DMARDs and followed-up for 1.9 years. Their crude incidence rates were 25.3 and 41.9 per 1,000 patient-years for patients treated with anti-TNFα agents and conventional DMARDs, respectively, compared to 45.5 and 31.4 per 1,000 patients-years in our study. In an earlier analysis of the BSRBR [5] a total of 154 patients in the anti-TNFα cohort had a previous malignancy and six (4%) developed a new malignancy. However, of these malignancies only one was a local recurrence which is in contrast to our findings. In our study, in 14 out of the 15 recurrences the observed malignancies were *true* recurrences of the prior tumor with the same type and site. Only in one of our patients with pulmonary and bone metastases the origin of the malignancy remained unknown. This patient had a history of testicular cancer 20 years before.

Our investigations regarding the risk of developing an incident malignancy were motivated by two meta-analyses of randomized controlled trials which suggested an

Table 3: Crude incidence rates of malignancies

	n of CA	n	pyrs	IR
Characteristics at baseline				
Age (per 10 yrs increase)				
Female	52	3,917	9,687	5.4
Male	22	1,081	2,554	8.6
Co-morbid conditions:				
COPD				
No	63	4,754	11,677	5.4
Yes	11	244	564	19.5
Gastrointestinal disease				
No	61	4,579	11,153	5.5
Yes	13	419	1,088	11.9
Renal disease				
No	70	4,835	11,884	5.9
Yes	4	163	357	11.2
Characteristics at follow-up				
DAS28				
<3.2	6	787	2,165	2.8
3.2 to 5.1	34	2,823	7,341	4.6
>5.1	34	1,388	2,735	12.4
Ever exposed to				
Conventional DMARDs only	30	1,684 #	3,561	8.4
Anti-TNF agents	44	3,651 *	8,558	5.1
Anakinra	5	247 $	690	7.2

CA: malignancies, n = number of cases, pyrs = follow-up time in patient years, IR = crude incidence rate per 1,000 pyrs.
#35 of the patients in the DMARD cohort were exposed to anti-TNF agents before inclusion in the study. According to the ever exposed approach their follow-up time was assigned to the anti-TNF treated group.
* Patients included in this group are patients who were included in the study with the start of an anti-TNF agent (n = 3,201) and patients who changed during follow-up from DMARD or anakinra treatment to anti-TNF treatment
$223 of the 247 pts were exposed to anakinra and anti-TNF agents, they experienced five malignancies.

increased risk of malignancies associated with the treatment with one of the TNFα blocking agents: adalimumab, infliximab, or etanercept [3,4]. The results of these meta-analyses are in contrast with those from observational cohort studies or national cancer registries, in which such an increased risk was not observed [18,19]. The methodological weaknesses of the first meta-analysis investigating the risk for treatment with adalimumab or infliximab have already been discussed elsewhere [20]. However, the repeated finding of an increased cancer risk also in patients treated with etanercept [3,4] requires further research, even if it did not achieve statistical significance. These meta-analyses support the *early mobilization hypothesis* implying a high risk within the first months of treatment with anti-TNFα agents.

However, our results for the first year are in contrast to the meta-analyses reported by Bongartz et al. [3,4]. In the first year of treatment patients receiving biologics had a lower risk for developing an incident malignancy than those

Table 4: Hazard ratios of developing a malignancy

	Univariate Cox regression			Multivariate analysis		
	HR	**95% CI**	**P**	**adjusted HR**	**95% CI**	**P**
Characteristics at baseline						
Age (per 10 yrs increase)	1.82	1.44 to 2.31	< 0.0001	1.71	1.35 to 2.17	< 0.0001
Male vs. female	1.61	0.98 to 2.65	0.062	1.47	0.89 to 2.43	0.13
Co-morbid conditions:						
COPD	3.64	1.92 to 6.91	< 0.0001	2.63	1.37 to 5.04	0.004
Gastrointestinal disease	2.19	1.20 to 3.98	0.010	1.81	0.99 to 3.30	0.0534
Renal disease	1.93	0.70 to 5.28	0.20			
Characteristics at follow-up						
DAS28 (per unit increase)	1.24	1.02 to 1.50	0.034			
DAS28						
< 3.2	*Referent*					
3.2 to 5.1	1.28	0.54 to 3.06	0.58			
> 5.1	2.00	0.82 to 4.86	0.13			
Ever exposed to						
Conventional DMARDs only	*Referent*			*Referent*		
Anti-TNF agents	0.61	0.39 to 0.97	0.039	0.70	0.44 to 1.12	0.133
Anakinra	1.16	0.47 to 2.89	0.75	1.39	0.56 to 3.48	0.480

receiving conventional DMARDs. This may be due to a selection bias evoked by the screening process for malignancies following the physician's decision that a patient should receive biologic treatment. Screening for latent TB by chest x-ray as recommended in guidelines [21] may reveal asymptomatic lung cancers and only those patients who screen negative for current malignancies will receive biologic treatment and be included in the biologics group in the RABBIT register. No such general screening occurs in patients who will receive a new DMARD therapy. Therefore the rate for malignancies in the DMARD group represents the *true* unselected rate that can be expected for RA patients under conventional DMARD treatment. Indeed this concept is supported by our findings that the observed number of cancer cases in the DMARD treated group (n = 30) was equal to the expected number (n = 30.8), whereas the observed number in the biologics group (n = 44) was lower than what would have been expected based on the rates from the general population (n = 64.3).

In contrast to an increased risk, it is also possible that inhibition of TNFα has beneficial or even preventive effects regarding cancer. TNFα is important in all steps of cancer development, for example, initiation, promotion, and survival. Elevated levels of TNFα are linked to a poor prognosis and increased invasiveness in certain human cancers [22,23]. However, the results of first trials to treat breast or ovarian cancer with TNFα inhibitors have been, so far, inconclusive [24,25]. The increased risk of non-Hodgkin's lymphoma in RA patients treated with biologic agents is well established [26,27] and has been shown to be strongly associated with long-term high disease activity [28] which is more likely in the history of patients subsequently treated with biologic agents. Nevertheless, in our nested case control study where we controlled for disease activity and duration we still found a higher proportion of anti-TNFα

Table 5: Patient characteristics of cases and matched controls

	Cases (with incident malignancy)	Matched controls	P
N	74	74	
Characteristics at study entry			
Females[#] n (%)	52 (70.3)	52 (70.3)	n.a.
Age[#] (mean, SD)	61.3 (8.9)	61.4 (8.5)	0.97
Observation time[#] (years) (median, IQR)	2.9 (1.8, 4.0)	2.9 (1.6, 3.9)	0.25
DAS28[#] (mean, SD)	5.6 (1.0)	5.7 (1.0)	0.31
Smoking status[#]			
Nonsmoker	16 (21.6)	16 (21.6)	n.a.
Smoker n (%)	19 (25.7)	19 (25.7)	
Unknown status n (%)	39 (52.7)	39 (52.7)	
Disease duration (years) (median, IQR)	7 (3,14)	9 (5,16)	0.22
Functional status, FFbH (mean, SD)	57.1 (22.3)	63.2 (22.6)	0.058
Characteristics at follow-up			
DAS28 (mean, SD)[$]	5.0 (1.2)	4.9 (1.2)	0.41
Ever exposed to biologics n (%)	44 (59.5)	45 (60.8)	1.0
Ever exposed to anti-TNFα agents [&]	44 (59.5)	44 (59.5)	1.0
Ever exposed to anakinra[&]	5 (6.8)	5 (6.8)	1.0
Among them			
Cases with solid tumors (n = 68)			
Ever exposed to biologics	39 (57.4)	43 (63.2)	0.56
Ever exposed to anti-TNFα agents	39 (57.4)	42 (61.8)	0.70
Ever exposed to anakinra	5 (7.4)	5 (7.4)	**1.0**
Cases with non-Hodgkin's Lymphoma (n = 6)			
Characteristics at study entry			
Females# n(%)	5 (83.3)	5 (83.3)	**n.a.**
Age# (mean, SD)	65.2 (6.5)	66.8 (8.0)	**0.13**
Disease duration	5.5 (4,13)	7 (5,11)	**0.53**
Functional status, FFbH (mean, SD)	52.8 (31.4)	54.2 (27.5)	**0.90**
DAS28# (mean, SD)	5.9 (0.6)	6.2 (0.5)	**0.29**
Characteristics at follow-up			
DAS28 (mean, SD)$	5.2 (0.7)	5.5 (0.7)	**0.14**
Ever exposed to anti-TNFα agents	**5 (83.3)**	**2 (33.3)**	**0.38**

[#] matching criteria (further matching criteria not shown in the table = COPD, other chronic lung disease, chronic renal disease, chronic gastrointestinal disease, chronic liver disease, and psoriasis)
[&]five cases and four controls received anti-TNFα agents and anakinra (at different points in time)
[$]cases = mean of DAS28 values over time points until six months prior to the cancer diagnosis, matched controls: mean of DAS28 values over time points of the corresponding case

exposure in patients with incident non-Hodgkin's lymphomas vs matched controls. This difference was not found for solid tumors.

Conclusions

Our data add to the growing evidence of no overall increased cancer risk for patients treated with anti-TNFα agents during the first years of treatment. This does not preclude that there may be an increased risk for specific cancer types such as lymphoma or skin cancer.

Taking the limitations of the currently available evidence into account there is a need for further large-scale prospective studies investigating risk modifications for different cancer sites as well as investigating the cancer risk after long-term exposure to biologic agents above four years.

Further, this study provides first but limited evidence regarding the risk of patients with a prior malignancy treated with anti-TNFα agents. The finding of an insignificantly increased risk of recurrence under anti-TNFα treatment supports the current practice of carefully balancing treatment decisions in these patients.

Abbreviations

ACR: American College of Rheumatology; BSRBR: British Society of Rheumatology Biologics Register; CI: confidence interval; COPD: chronic obstructive pulmonary disease; DAS28: disease activity score based on 28 joint counts; DMARDs: disease modifying anti-rheumatic drugs; FFbH: Hannover Functional Status Questionnaire (Funktionsfragebogen Hannover); HAQ: Health Assessment Questionnaire; HR: hazard ratio; IQR: interquartile range; IR: incidence rate; IRR: incidence rate ratio; MedDRA: Medical Dictionary for Regulatory Affairs; OR: odds ratio; pyrs: patient-years; RA: rheumatoid arthritis; RABBIT: (German biologics register) acronym for: rheumatoid arthritis observation of biologic therapies; RCT: randomized controlled trial; SD: standard deviation; TB: tuberculosis; TNFα: tumor necrosis factor alpha.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AS, JL and AZ had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. AZ, JL and AS determined the study concept and design. AS, GRB, BK-L and WD acquired the data. AS, JL and AZ analysed and interpreted the data. AS, JL and AZ drafted the manuscript. RR, GRB, BK-L, WD and FH critically revised the manuscript for important intellectual content and final approval. FH and JL did the statistical analysis. AZ obtained the funding and supervision. AS supervised adverse events reporting, verifications and MedDRA coding. All authors gave final approval of the version to be published.

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References

1. Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B: **An endotoxin-induced serum factor that causes necrosis of tumors.** *Proc Natl Acad Sci USA* 1975, **72:**3666-3670.
2. Perkins ND: **NF-kappaB: tumor promoter or suppressor?** *Trends Cell Biol* 2004, **14:**64-69.
3. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V: **Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials.** *JAMA* 2006, **295:**2275-2285.
4. Bongartz T, Warren FC, Mines D, Matteson EL, Abrams KR, Sutton AJ: **Etanercept therapy in rheumatoid arthritis and the risk of malignancies. A systematic review and individual patient data meta-analysis of Randomized Controlled Trials.** *Ann Rheum Dis* 2008, **68:**1177-1183.
5. Watson KD, Dixon WGHK, Lunt M, Symmons DP, Silman AJ, BSRBR Control Centre Consourtium: **Influence of anti-TNF therapy and previous malignancy on cancer incidence in patients with rheumatoid arthritis (RA): Results from the BSR Biologics Register.** *Ann Rheum Dis* 2006, **65:**512.
6. Dixon WG, Watson KD, Lunt M, BSRBR Control Centre Consortium, Hyrich KL, Symmons DPM: **The influence of anti-TNF therapy upon cancer incidence in patients with rheumatoid arthritis (RA) who have had prior malignancy: Results from the BSRBR.** *Arthritis Rheum* 2008, **58:**S638-S639.

7. Deutsche Gesellschaft für Rheumatologie: **[Recommendations of the German Society of Rheumatology for therapy with tumor necrosis factor inhibitors. Pharmacotherapy Committee of the German Society of Rheumatology].** [http://dgrh.de/fileadmin/media/Qualitaetssicherung/Therapie-Empfehlungen/TNF-Blocker_06.pdf]. (last access 2/11/2009)
8. Zink A, Listing J, Kary S, Ramlau P, Stoyanova-Scholz M, Babinsky K, von Hinueber U, Gromnica-Ihle E, Wassenberg S, Antoni C, Herzer P, Kekow J, Schneider M, Rau R: **Treatment continuation in patients receiving biological agents or conventional DMARD therapy.** *Ann Rheum Dis* 2005, **64:**1274-1279.
9. Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, Zink A: **Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF (alpha) agents.** *JAMA* 2009, **301:**737-744.
10. International Conference on Harmonisation: **Clinical Safety Data Mangement: Definitions and standards for expedited reporting.** 1995 [http://www.emea.europa.eu/pdfs/human/ich/037795en.pdf]. (last access at 16/06/2009)
11. **MedDRA Maintenance and Support Services Organization** 2007 [http://www.meddramsso.com]. (last access 16/06/09)
12. Lautenschlaeger J, Mau W, Kohlmann T, Raspe HH, Struve F, Bruckle W, Zeidler H: **[Comparative evaluation of a German version of the Health Assessment Questionnaire and the Hannover Functional Capacity Questionnaire].** *Z Rheumatol* 1997, **56:**144-155.
13. Robert-Koch-Institut (publisher): **Krebsneuerkrankungen in Deutschland (Cancer incidence in Germany).** 2009 [http://www.rki.de]. (last access 07.06.2009)
14. Jones M, Symmons D, Finn J, Wolfe F: **Does exposure to immunosuppressive therapy increase the 10 year malignancy and mortality risks in rheumatoid arthritis? A matched cohort study.** *Br J Rheumatol* 1996, **35:**738-745.
15. Dempster AP, Laird NM, Rubin DB: **Maximum Likelihood from Incomplete Data Via Em Algorithm.** *Journal of the Royal Statistical Society Series B-Methodological* 1977, **39:**1-38.
16. Therneau TM, Grambsch PM: **Modelling Survival Data.** New York: Springer; 2000.
17. Zink A, Strangfeld A, Schneider M, Herzer P, Hierse F, Stoyanova-Scholz M, Wassenberg S, Kapelle A, Listing J: **Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials.** *Arthritis Rheum* 2006, **54:**3399-3407.
18. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N, Cöster L, Geborek P, Jacobsson LT, Lindblad S, Lysholm J, Rantapää-Dahlqvist S, Saxne T, Klareskog L: **Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists.** *Ann Rheum Dis* 2005, **64:**1421-1426.
19. Wolfe F, Michaud K: **Biologic treatment of rheumatoid arthritis and the risk of malignancy - Analyses from a large US observational study.** *Arthritis Rheum* 2007, **56:**2886-2895.
20. Dixon W, Silman A: **Is there an association between anti-TNF monoclonal antibody therapy in rheumatoid arthritis and risk of malignancy and serious infection? Commentary on the meta-analysis by Bongartz et al.** *Arthritis Res Ther* 2006, **8:**111.
21. Ledingham J, Wilkinson C, Deighton C: **British Thoracic Society (BTS) recommendations for assessing risk and managing tuberculosis in patients due to start anti-TNF-{alpha} treatments.** *Rheumatology (Oxford)* 2005, **44:**1205-1206.
22. Sethi G, Sung B, Aggarwal BB: **TNF: a master switch for inflammation to cancer.** *Front Biosci* 2008, **13:**5094-5107.
23. Balkwill F: **TNF-alpha in promotion and progression of cancer.** *Cancer Metastasis Rev* 2006, **25:**409-416.
24. Madhusudan S, Muthuramalingam SR, Braybrooke JP, Wilner S, Kaur K, Han C, Hoare S, Balkwill F, Ganesan TS: **Study of etanercept, a tumor necrosis factor-alpha inhibitor, in recurrent ovarian cancer.** *J Clin Oncol* 2005, **23:**5950-5959.
25. Madhusudan S, Foster M, Muthuramalingam SR, Braybrooke JP, Wilner S, Kaur K, Han C, Hoare S, Balkwill F, Talbot DC, Ganesan TS, Harris AL: **A phase II study of etanercept (Enbrel), a tumor necrosis factor alpha inhibitor in patients with metastatic breast cancer.** *Clin Cancer Res* 2004, **10:**6528-6534.
26. Baecklund E, Ekbom A, Sparen P, Feltelius N, Klareskog L: **Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study.** *BMJ* 1998, **317:**180-181.
27. Prior P, Symmons DP, Hawkins CF, Scott DL, Brown R: **Cancer morbidity in rheumatoid arthritis.** *Ann Rheum Dis* 1984, **43:**128-131.
28. Baecklund E, Iliadou A, Askling J, Ekbom A, Backlin C, Granath F, Catrina AI, Rosenquist R, Feltelius N, Sundström C, Klareskog L: **Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis.** *Arthritis Rheum* 2006, **54:**692-701.

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2.2.2 Risiko für Perforationen des unteren Darmtraktes unter Tocilizumab

Strangfeld A, Richter A, Siegmund B, Herzer P, Rockwitz K, Demary W, Aringer M, Meißner Y, Zink A, Listing J. *Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs.* Ann Rheum Dis 2017,76 (3): 504-510. doi: 10.1136/annrheumdis-2016-209773. PubMed PMID: 27405509.

Zusammenfassung

Perforationen des unteren Darmtraktes (lower intestinal perforations (LIP)) sind in der Normalbevölkerung mit einer Inzidenz von etwa 0,04/1.000 Personenjahren (PJ) selten [38]. Während der 6-monatigen randomisierten klinischen Studien mit Tocilizumab waren in der Verumgruppe Perforationen des Darmtraktes aufgefallen mit einer Häufigkeit von 2.8/1000 PJ, während in der Placebo+csDMARD-Gruppe keine Fälle aufgetreten waren [39]. Die Relevanz dieses Vergleichs war allerding begrenzt durch wenige und zum Teil nur sehr kurz beobachtete Patienten in der Placebo+csDMARD-Gruppe (insgesamt nur 872 PJ). Obwohl die Rate der LIP unter Tocilizumab im Vergleich zur Normalbevölkerung deutlich erhöht war, konnte man diese Beobachtung nicht adäquat einordnen, da Vergleichszahlen über das Basisrisiko für LIP bei Patienten mit rheumatoider Arthritis (RA) fehlten.

Diese Wissenslücke konnte mit der vorgestellten Analyse geschlossen werden. Das RABBIT-Register hat den Vorteil, dass Patienten mit allen in Deutschland zur Behandlung der RA zugelassenen bDMARDs eingeschlossen werden können und auf die gleiche Weise wie die mit csDMARD behandelten Kontrollpatienten dokumentiert werden. Dadurch ist es möglich, echte Therapievergleiche innerhalb eines Studiendesigns und eines Versorgungssystems durchzuführen. Das Ziel der Analyse war, Risikofaktoren für LIP zu identifizieren und zu untersuchen, ob unter einer Therapie mit Tocilizumab die klinischen Symptome einer LIP verändert sind.

Bei insgesamt 13.310 RA Patienten mit 53.972 PJ Beobachtung waren 37 LIPs bis Datenbankschluss am 31.Oktober 2015 berichtet worden. Unter einer Therapie mit Tocilizumab waren die Inzidenzraten von LIPs (2,7/1000 PJ) im Vergleich zu csDMARDs und anderen Biologika (0,2-0,6/1000 PJ) signifikant erhöht.

Mit einem signifikant höheren Risiko für das Auftreten einer LIP waren Alter, Glukokortikoide und NSAR assoziiert. Auch eine Therapie mit Tocilizumab erhöhte das Risiko für eine LIP, im Vergleich zur csDMARD Therapie, fast um das 5fache (HR 4,5 [95%KI 2,0-10,0]), während dies für andere Biologika nicht zutraf (TNFi 1,04 [0,5-2,3], andere Biologika 0,33 [0,1-1,4]).

Eine weitere wichtige Erkenntnis der Analyse war, dass Patienten unter einer Therapie mit Tocilizumab meist nur sehr abgeschwächte Symptome einer LIP aufwiesen sowie keine oder nur eine leichte CRP Erhöhung. Dadurch wird die Diagnose einer LIP deutlich erschwert, besonders, wenn der Arzt, der dies beurteilen soll (z.B. Diensthabender in der Rettungsstelle) nicht über die Therapie mit Tocilizumab und die dadurch hervorgerufene Unterdrückung der Akute-Phase-Reaktion (mit fehlendem CRP-Anstieg) informiert ist, was zu einer Fehleinschätzung der Schwere des Ereignisses führen kann.

Dies ist möglicherweise auch der Grund dafür, dass bei einigen der in RABBIT beobachteten und mit Tocilizumab behandelten Patienten die LIPs nicht rechtzeitig erkannt wurden, denn die 30-Tage-Mortalität war unter Tocilizumab deutlich höher mit 46% (5 von 11) der Patienten im Vergleich zu 9% unter csDMARDs (1 von 11) und 23% unter TNFi (3 von 13).

OPEN ACCESS

EXTENDED REPORT

Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs

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ABSTRACT

Objective To investigate the risk of developing lower intestinal perforations (LIPs) in patients with rheumatoid arthritis (RA) treated with tocilizumab (TCZ).

Methods In 13 310 patients with RA observed in the German biologics register *R*heumatoid *A*rthritis: *O*bservation of *Bi*ologic *T*herapy, 141 serious gastrointestinal events possibly associated with perforations were reported until 31 October 2015. All events were validated independently by two physicians, blinded for treatment exposure.

Results 37 LIPs (32 in the colon/sigma) were observed in 53 972 patient years (PYs). Only two patients had a history of diverticulitis (one in TCZ). Age, current/cumulative glucocorticoids and non-steroidal anti-inflammatory drugs were significantly associated with the risk of LIP. The crude incidence rate of LIP was significantly increased in TCZ (2.7/1000 PYs) as compared with all other treatments (0.2–0.6/1000 PYs). The adjusted HR (ref: conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs)) in TCZ was 4.48 (95% CI 2.0 to 10.0), in tumour necrosis factor-α inhibitor (TNFi) 1.04 (0.5 to 2.3) and in other biologic DMARDs 0.33 (0.1 to 1.4). 4/11 patients treated with TCZ presented without typical symptoms of LIP (acute abdomen, severe pain). Only one patient had highly elevated C reactive protein (CRP). One quarter of patients died within 30 days after LIP (9/37), 5/11 under TCZ, 2/13 under TNFi and 2/11 under csDMARD treatment.

Conclusions The incidence rates of LIP under TCZ found in this real world study are in line with those seen in randomised controlled trials of TCZ and higher than in all other DMARD treatments. To ensure safe use of TCZ in daily practice, physicians and patients should be aware that, under TCZ, LIP may occur with mild symptoms only and without CRP elevation.

INTRODUCTION

Lower intestinal perforations (LIPs) are rare in the general population with an incidence rate of about 0.04/1000 persons/year in the European population.[1] The incidence of LIP increases with age and is higher in women than in men. In most cases, perforations appear as a result of infected or inflamed diverticular disease. Lethality is high, with rates of around 30%[2] and increases with age.[3]

In patients with rheumatoid arthritis (RA), perforations of the gastrointestinal (GI) tract have been a concern for quite a long time. In the prebiologic era, GI complications were among the most common causes of death in patients with RA.[4] At that time, concerns mainly referred to perforations of the upper GI tract, for which non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs) are the most important risk factors.[5] However, in addition to risks for the upper GI tract, for the lower GI tract a higher risk for diverticular complications was found on NSAIDs in several case-control studies with ORs ranging from 1.8 to 11.2.[6–8]

Similarly, GCs were found to be strongly associated with lower GI perforations[9–11] with HRs in patients with RA of 2.8 (95% CI 1.3 to 6.1) compared with non-users[9] or 4.7 (95% CI 1.9 to 12.0) when GCs and NSAIDs were used concomitantly.

Since the approval of the first biologics, the incidence of GI tract complications in RA was expected to decrease with the decreasing use of NSAIDs and high-dose GCs. However, this is only the case if concomitant GCs can be reduced by effective therapy. Curtis *et al* investigated the risk for GI tract complications on tumour necrosis factor-α inhibitors (TNFi) and found a higher incidence of hospitalised GI perforation with concomitant GCs (1.12 (95% CI 0.5 to 2.5)/1000 patient years (PYs)) than without (0.47 (95% CI 0.2 to 0.98)).[9] The British Biologics Register (BSRBR)[12] compared the risk of GI perforations in patients treated with TNFi and those on conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs) only. While there was no statistically important elevation of the risk associated with TNFi with an incidence rate of lower GI perforations of 0.39/1000 PYs, concomitant GCs were the most important risk factor, conveying a 2.9 (95% CI 1.5 to 5.3) times higher risk, confined to lower GI perforations with a HR of 8.0 (95% CI 2.6 to 24.1).

The clinical development programme of tocilizumab (TCZ) for the treatment of RA identified GI perforations as important risk. An integrated safety analysis of eight trials and long-term extension studies with TCZ reported that no GI perforation had occurred in the group treated with csDMARDs only, but 26 such cases were identified in patients of the group ever exposed to TCZ, resulting in an

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incidence rate of 2.8/1000 PYs.[13] Eighteen of these perforations occurred in the colon. Due to the early escape design of the trials, only 825 PYs were available in the csDMARD group, limiting the significance of the finding.

Since there is little information on the overall incidence of LIP in patients with RA exposed to specific treatments, no robust comparisons of the incidence rate of GI perforations could be made between TCZ-treated patients and those on other therapies. Several other factors, such as diverticular disease, high disease activity or long-standing high-dose GC or NSAID use, could also have accounted for the higher incidence in TCZ-treated patients. Further, the few studies existing in this field differ considerably in study design, case definition and population studied, the latter impacting on the background risk.

Prospective observational cohort studies, such as the German biologics register *R*heumatoid *A*rthritis *Ob*servation of *Bi*ologic *T*herapy (RABBIT), have the advantage that all patients who start treatment with one of the approved biologic agents are eligible to be enrolled. In addition, a control group treated with csDMARDs only is observed under the same protocol. This design enables studying differences in incidence rates of adverse events occurring under different treatments. The aim of this study was to identify risk factors for LIP within the RABBIT register, taking concomitant (time varying) dosages of NSAIDs and GCs into account. We thereby aimed to examine the clinical signs and symptoms of LIP events to inform treating physicians how to advise their patients when starting a new treatment.

METHODS

Patients

We used data of the German biologics register RABBIT captured and validated until 31 October 2015.

RABBIT is an ongoing observational cohort study that started in May 2001. Since then, patients with RA are enrolled when starting a treatment with a biologic DMARD (bDMARD), or csDMARD after failure of at least one csDMARD. Once enrolled, patients are observed for at least 5 years regardless of treatment terminations and changes (with the option to extend observation for another 5 years, if the patient agrees).

The study protocol was approved in 2001 by the ethics committee of the Charité University School of Medicine, Berlin. Each patient participating in the study gave written informed consent before study entry.

Assessments and procedures

During follow-up, information from rheumatologists and patients is captured at regular intervals: at baseline, after 3 and 6 months, and thereafter every 6 months. Data collected include clinical status, disease activity (including disease activity score based on 28 joints (DAS28)), details on DMARD treatment (substance, dosage, application, start and stop dates, reasons for stopping) and concomitant treatments like NSAIDs (yes/no) and GCs (actual dose and mean dose since last questionnaire). At every time point of follow-up, all adverse events that occurred since last questionnaire are reported. At baseline and every 2 years, rheumatologists report comorbid conditions in predefined groups and in plain text. Patients report, among other items, physical function (using the Hannover Functional Status Questionnaire, FFbH).

Adherence to scheduled visits is monitored closely. Investigations of dropouts (defined as two missing follow-ups) are performed regularly. This includes inquiries to local administration offices regarding patient's vital status and, if the patient had died, obtaining the causes of death from the health authorities. Complete details have been published.[14]

Outcomes

Primary outcome

Incidence of LIPs in patients exposed to TCZ, csDMARDs, TNFi, abatacept or rituximab.

Secondary outcomes

Clinical signs and symptoms of LIPs in these patients.
Thirty-day mortality after LIPs.

Outcome validation

To capture all LIPs, we first identified all events that might be associated with GI perforations (including also haemorrhages and bleedings of the intestinal tract) via a predefined group of MedDRA terms. These included all events of the standard MedDRA query (SMQ) 'GI perforation' plus 51 additional MedDRA codes (see online supplementary table S1). Based on medical records and specific queries to the treating rheumatologists, all events were validated first by the leading physician of RABBIT (AS). An additional external validation was done by the Head of the Department for Gastroenterology of the Charité University Medicine (BS). At time of validation, both reviewers were blinded for the patient's treatment exposure. Only events with a definite, non-iatrogenic and non-traumatic LIP were selected for the analysis. We only counted perforations localised below the duodenojejunal junction (ligament of Treitz) as lower GI perforation. The topmost localised perforation included in the analysis was in the terminal ileum.

Definition of DMARD exposure

Treatment was assigned using a risk window for exposure to bDMARDs: a patient was considered exposed to a certain bDMARD at the time of the event if he/she had received at least one dose of the drug within 3 months (rituximab 9 months) prior to the event. Patients unexposed to bDMARDs in this risk window were assigned to the csDMARD group.

All substances targeting TNF (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) were subsumed under TNFi since we had not seen any differences in incidence rates.

Statistical analysis

Multiple Cox regression was applied to compare the risks of LIPs between the treatment groups. Adjustment was made for age, sex, treatment with GCs and NSAIDs. We distinguished current (Cox regression 1) and cumulative (Cox regression 2) treatment with NSAIDs and GCs. For each patient, the portion of visits with new or ongoing NSAIDs treatment was used as a proxy for NSAID use (range: 0 to 1). Regarding cumulative treatment with GCs, we proceeded in a similar way, but considered each month with a dose of >5–10 mg/day with a weight of 0.5 and each month with a dose of >10 mg/day with a weight of 1. Further covariables (body mass index (BMI), number of bDMARD failures, DAS28) were additionally investigated in univariate Cox regression. We applied two sensitivity analyses: (a) we restricted the cohort to a subgroup of patients recruited after 2009 and (b) we repeated Cox regression 1 and 2 but restricted the reference group to biologic naïve patients. Exact Poisson and Clopper-Pearson binomial CIs were calculated for incidence rates and proportions. The uncertainty of HRs is shown in 95% CIs.

RESULTS

Patients

Until 31 October 2015, 13 310 patients had been enrolled in the RABBIT register. Patients in the csDMARD-treated biologic naïve control group were older and had shorter disease duration at inclusion than TNFi-treated patients. Patients starting treatment with non-TNFi biologics had the longest disease duration and the highest number of prior treatment failures (table 1). Most of them (66.1%) had prior TNFi treatment.

The prevalence of chronic GI disease at baseline was lowest in the csDMARD-treated group and highest in patients starting treatment with abatacept. Chronic diverticulosis was reported in 33 patients. In two patients, a history of diverticulitis was known to the rheumatologist, one of these patients had a perforated diverticulum before inclusion in the register. None of the patients with chronic GI disease at baseline developed an intestinal perforation during follow-up.

Incidence of GI perforations

In 53 972 PYs of follow-up, 141 adverse events possibly describing GI perforations were reported. After internal and external medical review, 44 GI perforations were identified (figure 1). Seven were localised in the upper GI tract: three under TNFi resulting in an incidence rate of 0.12 (95% CI 0.02 to 0.35)/1000 PYs and four under csDMARD (0.22 (95% CI 0.06 to 0.57)/1000 PYs).

Thirty-seven GI perforations were localised in the lower GI tract: 32 in the colon/sigma, 4 in the appendix, and 1 in the terminal ileum. Similar incidence rates were observed for patients exposed to csDMARDs (0.6 (95% CI 0.3 to 1.1) /1000 PYs), TNFi (0.5 (95% CI 0.3 to 0.9)/1000 PYs), abatacept (0.5 (95% CI 0.01 to 2.8)/1000 PYs) and rituximab (0.2 (95% CI 0.01 to 1.1)/1000 PYs), whereas the incidence rate for patients exposed to TCZ was significantly higher (2.7 (95% CI 1.4 to 4.8)/1000 PYs) (figure 2). These crude incidence rates correspond to numbers needed to harm of 1647, 1911 and 371 in patients treated with csDMARDs, TNFi and TCZ, respectively. Sensitivity analysis (a) showed similar rates (see online supplementary figure S1).

Univariate and multivariate risk evaluation of LIP

Twenty-eight of the 37 patients who developed LIP had concomitant GCs, with a daily dose of ≥7.5 mg in 12 patients. Compared with those treated with TCZ, the average dose of GCs was higher in patients treated with TNFi and lower in csDMARD-treated patients (table 2). Further characteristics of patients who developed perforations did not differ significantly between the various treatment groups.

In the univariate analysis higher age, treatment with TCZ, current as well as cumulative GCs, and cumulative NSAIDs but none of the other risk factors (eg, sex, disease activity (DAS28), BMI and number of previous biologics) were significantly associated with LIP. In the multivariate analysis, higher age, current and cumulative use of GCs and NSAIDs were significantly associated with a higher risk of LIP, in addition to treatment with TCZ (table 3). Compared with csDMARDs, exposure to TCZ was associated with a 4.5 times higher risk for LIP (95% CI 2.01 to 9.99) (table 3, Cox regression 2), whereas no association was found for TNFi, abatacept or

Table 1 Patient characteristics at inclusion in the RABBIT register

Parameter	csDMARDs	TNFi	TCZ	ABA	RTX
N	4423	6711	877	371	928
Patient years, sum	18 113	24 851	4082	1976	4950
Age, years, mean (SD)	57.6 (12.3)	54.9 (12.6)	56.7 (12.8)	58.1 (12.9)	58.7 (12.1)
Female	3345 (75.6)	5113 (76.2)	685 (78.1)	282 (76.0)	719 (77.5)
Rheumatoid factor positive	2763 (62.6)	4983 (74.9)	608 (72.2)	267 (74.2)	764 (82.9)
No. of previous csDMARDs, mean (SD)	1.4 (0.9)	2.7 (1.4)	2.2 (1.1)	2.4 (1.3)	2.6 (1.2)
No. of previous bDMARDs, mean (SD)	0 (0.2)	0.2 (0.6)	1.0 (1.1)	1.4 (1.3)	1.4 (1.1)
NSAIDs	1497 (33.8)	2695 (40.2)	293 (33.4)	151 (40.7)	351 (37.8)
Glucocorticoids, not available	9 (0.2)	18 (0.3)	0	0	9 (1.0)
Glucocorticoids, <5 mg/day	1412 (31.9)	1682 (25.1)	240 (27.4)	80 (21.6)	215 (23.2)
Glucocorticoids, 5–10 mg/day	2057 (46.5)	3058 (45.6)	389 (44.4)	182 (49.1)	386 (41.6)
Glucocorticoids, ≥10 mg/day	945 (21.4)	1953 (29.1)	248 (28.3)	109 (29.4)	318 (34.3)
Disease duration, years, mean (SD)	7.2 (8.0)	10.7 (9.2)	10.6 (8.7)	12.0 (9.0)	13.8 (9.9)
DAS28, mean (SD)	4.7 (1.3)	5.4 (1.3)	5.2 (1.3)	5.4 (1.3)	5.3 (1.3)
CRP, mg/L, mean (SD)	14.1 (20.5)	21.2 (29.4)	18.0 (26.1)	19.6 (26.3)	18.3 (24.6)
FFbH, mean (SD)	69.4 (21.7)	61.4 (23.3)	62.6 (24.2)	58.6 (23.6)	55.9 (23.8)
BMI, mean (SD)	27.4 (5.3)	26.4 (5.3)	26.7 (5.4)	26.8 (5.8)	26.3 (5.1)
BMI ≥30 kg/m^2	1167 (26.4)	1412 (21.0)	218 (24.9)	81 (21.8)	181 (19.5)
Diabetes mellitus	436 (9.9)	668 (10.0)	102 (11.6)	46 (12.4)	111 (12.0)
Hyperlipoproteinemia	315 (7.1)	557 (8.3)	82 (9.4)	44 (11.9)	106 (11.4)
Diverticulosis/prior diverticulitis	12 (0.3)	11 (0.2)	3 (0.3)	4 (1.1)	5 (0.5)
Gastrointestinal diseases	159 (3.6)	339 (5.1)	43 (4.9)	26 (7.0)	59 (6.4)
Chronic renal disease	102 (2.3)	295 (4.4)	49 (5.6)	24 (6.5)	61 (6.6)

Values are numbers of patients (%) unless otherwise specified.
ABA, abatacept; bDMARDs, biologic disease-modifying anti-rheumatic drugs; BMI, body mass index; CRP, C reactive protein; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; DAS28, disease activity score based on 28 joints; FFbH, Funktionsfragebogen Hannover (physical function in %); NSAIDs, non-steroidal anti-inflammatory drugs; RABBIT, *R*heumatoid *A*rthritis *O*bservation of *Bi*ologic *T*herapy; RTX, rituximab; TCZ, tocilizumab; TNFi, tumour necrosis factor-α inhibitor.

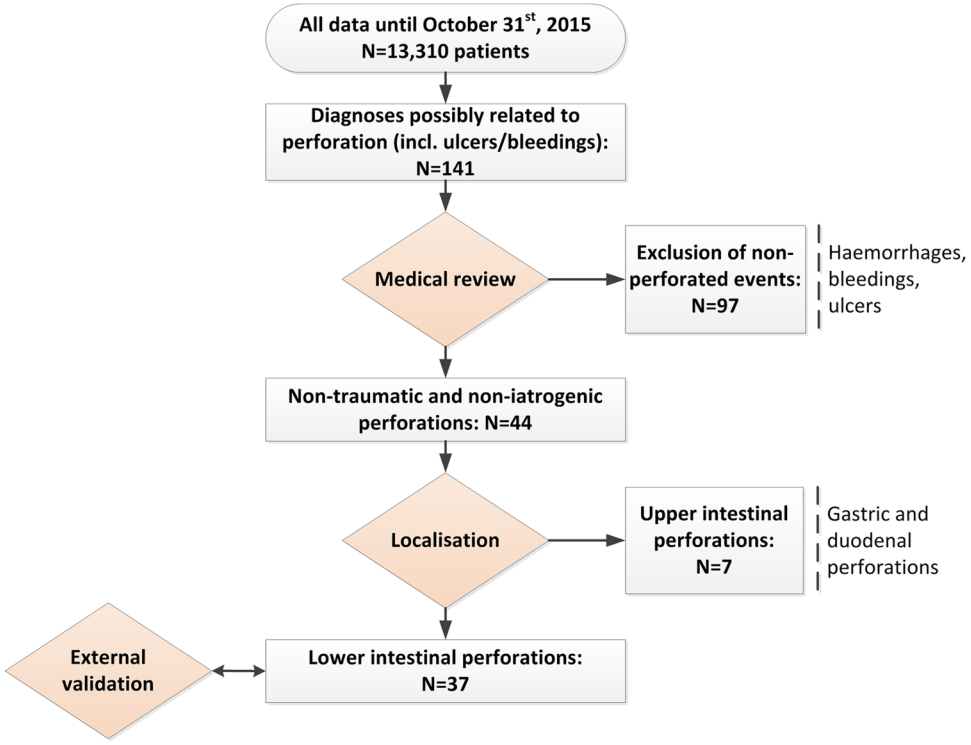

Figure 1 Flowchart of case selection and validation process.

rituximab. Sensitivity analyses (b) did not show different results (see online supplementary table S3).

Clinical signs and outcome of LIPs

While 90% of the patients with csDMARD and 60% of those on TNFi reported acute abdominal pain, this was only the case for 27% (three cases) on TCZ. The majority of patients treated with csDMARDs or other bDMARDs had very high C reactive protein (CRP) values (above 100 mg/L). In contrast, this was the case in only one patient treated with TCZ.

Online supplementary table S2 shows demographics, CRP values, features of clinical presentation and comedication with GC of each patient who developed LIP on TCZ.

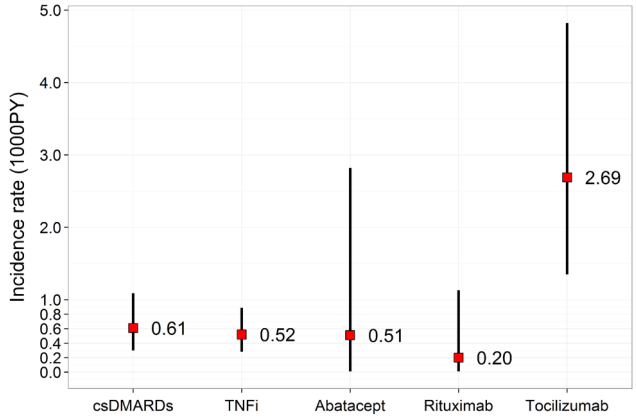

Figure 2 Incidence rates of lower intestinal perforation stratified by DMARDs. Events/patient years (PYs): csDMARDs=11/18 113; TNFi=13/24 851 (adalimumab=6, etanercept=6, infliximab=1); Abatacept=1/1976; Rituximab=1/4950; Tocilizumab=11/4082. csDMARD, conventional synthetic DMARD; TNFi, tumour necrosis factor-α.

According to classifications of colonic diseases, LIPs are considered as complicated diverticulitis (in contrast to diverticulitis without perforation). In total, 92 events of diverticulitis were reported during follow-up. The proportion of patients who developed a perforation was higher in patients treated with TCZ than in all other treatment groups (see table 4).

The 30-day mortality after perforation was 24% in all groups (9/37 patients). The mortality in patients on TCZ (46%) was considerably elevated, although not statistically significant (p=0.09, Fisher's exact test) (table 4).

DISCUSSION

Our objective was to evaluate the risk for LIP under various treatments by using the data of a large German RA cohort. We observed a significantly elevated risk for LIP in patients treated with TCZ compared with patients treated with csDMARD and also as compared with patients treated with TNFi or other biologics. LIPs are uncommon events that occurred in patients exposed to TCZ with an incidence of 2.7 per 1000 PYs only, but were associated with a 30-day mortality of 46%.

In patients treated with TCZ, symptomatic diverticulitis was more often associated with perforation than in other treatments. In these patients, the clinical presentation tended to be milder than in other patients. This might explain the finding from van Vollenhoven *et al*[15] that in the majority of patients in the TCZ clinical development programme who had a perforation, the diverticulitis was recognised only after the perforation had occurred.

The incidence rate of LIP in patients treated with TCZ in our cohort was comparable to that reported from randomised controlled trials with TCZ, postmarketing surveillance studies, spontaneous reports or US-based healthcare data in which per 1000 PYs 2.8, 2.4 and 2–2.3 LIPs, respectively, were observed.[13 16 17] Observational cohort studies reported lower incidence rates in patients with RA not treated with TCZ: in the

Table 2 Clinical characteristics during follow-up of patients who developed LIP

Parameter	csDMARDs	TNFi	TCZ	ABA	RTX
N	11	13	11	1	1
Age at LIP, years, mean (SD)	66.8 (4.8)	67.3 (8.3)	69.2 (7.6)	[73]	[61]
Female	7 (63.6)	7 (53.8)	9 (81.8)	[1 (100)]	[1 (100)]
Rheumatoid factor positive	11 (100)	12 (92.3)	6 (54.5)	[1 (100)]	[1 (100)]
No. of previous bDMARDs, mean (SD)	0.7 (1.3)	1.8 (0.8)	3.3 (1.6)	[4]	[4]
Cumulative NSAID treatment*, mean (SD)	0.4 (0.4)	0.4 (0.3)	0.3 (0.4)	[1]	[0.5]
Disease duration at LIP, years, mean (SD)	13.2 (9.1)	13.0 (7.5)	15.7 (8.4)	[13]	[12]
DAS28 prior to LIP					
≤6 months, mean (SD)	3.8 (0.7)	4.0 (1.7)	3.5 (2.1)	[5.0]	[5.4]
≤12 months, mean (SD)	3.8 (0.7)	4.0 (1.6)	3.7 (2.0)	[5.0]	[5.5]
CRP (mg/L) prior to LIP					
≤6 months, mean (SD)	8.1 (7.9)	25.8 (33.4)	11.5 (17.6)	[0.7]	[3.8]
≤12 months, mean (SD)	10.6 (8.5)	28.3 (33.0)	16.0 (21.5)	[0.7]	[4.2]
ESR (mm/hour) prior to LIP					
≤6 months, mean (SD)	19.4 (11.6)	36.0 (27.6)	14.8 (15.8)	[12.0]	[12.0]
≤12 months, mean (SD)	18.8 (11.3)	36.0 (27.1)	16.3 (13.9)	[12.0]	[13.7]
Glucocorticoids prior to LIP					
Average over 6 months, mean (SD)	5.6 (3.8)	9.7 (9.3)	7.5 (7.5)	[5.0]	[10.0]
Average over 12 months, mean (SD)	5.6 (3.4)	9.6 (9.0)	8.1 (7.3)	[5.0]	[10.0]

*Cumulative treatment with NSAID (range: 0 to 1) was calculated for each patient as: no. of follow-ups with concomitant NSAID use divided by the total no. of follow-ups.
ABA, abatacept; bDMARDs, biologic disease-modifying anti-rheumatic drugs; CRP, C reactive protein; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; DAS28, disease activity score based on 28 joints; ESR, erythrocyte sedimentation rate; LIP, lower intestinal perforation; NSAID, non-steroidal anti-inflammatory drug; RTX, rituximab; TCZ, tocilizumab; TNFi, tumour necrosis factor-α inhibitor.

Table 3 Univariate HRs and results of multiple Cox regression

	Univariate		Multiple Cox regression 1		Multiple Cox regression 2	
	HR	95% CI	HR	95% CI	HR	95% CI
Age at event (by 5 years)	1.48	(1.25 to 1.75)	1.55	(1.30 to 1.84)	1.57	(1.32 to 1.87)
Male	1.68	(0.84 to 3.34)	1.58	(0.79 to 3.20)	1.45	(0.72 to 2.90)
BMI	1.00	(0.94 to 1.06)				
bDMARD failures (reference: 0)						
1 bDMARD	1.54	(0.67 to 3.52)				
≥2 bDMARDs	0.71	(0.17 to 3.00)				
DAS28 (current)	1.14	(0.92 to 1.42)				
DAS28 (average last 12 months)	1.16	(0.91 to 1.48)				
DMARD (reference: csDMARDs)						
TNFi	0.84	(0.39 to 1.80)	1.00	(0.46 to 2.20)	1.04	(0.48 to 2.26)
Other bDMARDs	0.40	(0.09 to 1.78)	0.41	(0.09 to 1.84)	0.33	(0.08 to 1.44)
Tocilizumab	4.17	(1.87 to 9.27)	5.11	(2.31 to 11.3)	4.48	(2.01 to 9.99)
GCs						
Current GC (by 5 mg)	1.22	(1.13 to 1.31)	1.28	(1.18 to 1.38)		
Cumulative GCs*	1.81	(1.47 to 2.22)			1.87	(1.50 to 2.33)
NSAIDs						
Current NSAID	1.80	(0.92 to 3.53)	2.18	(1.11 to 4.31)		
Cumulative NSAIDs†	2.71	(1.20 to 6.12)			3.00	(1.33 to 6.82)

In Cox regression 1, we adjusted for current doses of GCs and NSAIDs, whereas in Cox regression 2 for cumulative doses.
*Concomitant GC use (range: 0 to 1) was calculated for each patient as the area under curve of follow-up month with medium doses (>5 to 10 mg/day, weight of 0.5) plus follow-up month with high doses (>10 mg/day, weight of 1) and then divided by total no. of follow-up months.
†Cumulative treatment with NSAIDs (range: 0 to 1) was calculated for each patient as: no. of follow-ups with concomitant NSAIDs use divided by the total no. of follow-ups.
bDMARD, biologic disease-modifying anti-rheumatic drug; BMI, body mass index; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; DAS28, disease activity score based on 28 joints; GC, glucocorticoid; NSAIDs, non-steroidal anti-inflammatory drugs; other bDMARDs, abatacept and rituximab; TNFi, tumour necrosis factor-α inhibitor.

Rochester cohort, a rate of 1.3/1000 PYs[18] in 813 patients diagnosed with RA between 1980 to 2008 (and followed until 2009) was observed. Only 17% of the patients had ever been exposed to bDMARDs and 77% had concomitant GCs. From US claims data,[19] a rate of 0.87/1000 PYs in patients with RA was reported. In the British Biologics Register, an incidence of LIP of 0.39/1000 PYs in patients on TNFi treatment and of 0.15/1000 PYs in biologic naïve csDMARD-treated patients was

Table 4 Incident diverticulitis, perforations and lethal perforations

	PYs	Total no. of diverticulitis (Incidence rate/1000 PYs (95% CI))	Thereof: no. of LIP (proportion, (95% CI*))	No. of patients died within 30 days after LIP (proportion, (95% CI*))
csDMARDs	18 113	34 (1.9 (1.3 to 2.6))	11 (32.4 (17.4 to 50.5))	1 (9.1 (0.0 to 41.3))
TNFi	24 851	37 (1.5 (1.1 to 2.1))	13 (35.1 (20.2 to 52.5))	3 (23.1 (5.0 to 53.8))
Tocilizumab	4082	16 (3.9 (2.2 to 6.4))	11 (68.7 (41.3 to 89.0))	5 (45.5 (16.8 to 76.6))
Abatacept	1976	1 (0.5 (0.0 to 2.8))	1 (100 (2.5 to 100))	0 (0 (0 to 97.5))
Rituximab	4950	4 (0.8 (0.2 to 2.1))	1 (25.0 (0 to 80.6))	0 (0 (0 to 97.5))
Total	53 972	92 (1.7 (1.4 to 2.1))	37 (40.2 (30.1 to 31.0))	9 (24.3 (11.8 to 41.2))

*Exact Clopper-Pearson 95% CI for the proportion.
csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; IR, incidence rate per 1000 PYs; LIP, lower intestinal perforations; PYs, patient years; TNFi, tumour necrosis factor-α inhibitor.

found.[12] GCs were the most important risk factor for LIP in this study.

Comparable to other studies, we also observed a higher risk for patients who were older, male or treated with GCs in higher dosages or NSAIDs in higher frequency. Minor differences in the distribution of these risk factors between the treatment groups did, however, not explain the higher incidence of LIPs in TCZ-treated patients. Adjustment for these factors did not decrease the HR for developing a LIP under TCZ.

Biological mechanisms may also support the increased risk of LIP in patients treated with TCZ: the interleukin 6 (IL-6) receptor targeted by TCZ seems to have an important function of the intestinal barrier. It is hypothesised that locally accumulated fat tissue may cover inflamed diverticula, similar to creeping fat in Crohn's disease which covers inflamed intestinal segments and where IL-6 is predominantly found.[20 21] Creeping fat may limit the transmural intestinal inflammation to the intestine.[22 23]

Our study has strengths and limitations. An important risk factor of LIP is previous diverticulitis that was likely underreported at enrolment into RABBIT. Adjustment for this risk factor was not possible since none of the patients with a history of diverticulitis, diverticulosis or another chronic GI disease developed a LIP. However, patients with prior diverticulitis are unlikely to be overrepresented in patients treated with TCZ since first clinical trials of TCZ reported a higher risk of LIP and the German Society for Rheumatology recommended not using TCZ in patients with a history of diverticulitis (http://dgrh.de/rheumatocilizumab.html). This may have caused a lower reporting threshold for LIP under TCZ treatment. Nevertheless, we do not assume different reporting behaviour for LIPs due to the severity of the events requiring hospitalisation and possibly leading to severe sequelae. An underreporting of LIPs is therefore not likely under any treatment. The rather constant reporting rates over time support this assumption. In addition, all LIPs were diagnosed by treating gastroenterologists or surgeons of general hospitals and not the rheumatologists participating in RABBIT.

The low numbers of LIPs observed in the register were another limitation which restricted the number of covariables in the Cox regression to adjust for confounding by indication. In addition, the risk conveyed by cumulative NSAID use could only be considered by a proxy since exact doses and start/stop dates of NSAIDs as well as the exposure prior to enrolment in RABBIT are not comprised in our data. The effect of long-term NSAID use in high doses might therefore be inadequately estimated.

The strengths of our study are the prospective design, the comprehensive case validation with independent external validation, the availability of clinical information on the course and outcome of LIP and the long-term follow-up of patients exposed to different treatments including treatment switches which allows comparative analyses.

CONCLUSION

This is the first comparative analysis of real-life data on the risk of LIP, covering all DMARDs available in Germany for the treatment of RA. In agreement with the results from the TCZ clinical development programme which qualified LIP as important identified risk, we found a rate of 2.7/1000 PYs in patients treated with TCZ. This rate was significantly higher than in other biologic agents or csDMARDs. It is of clinical importance that the majority of patients who experienced a LIP on TCZ did not have a history of diverticulitis. Further, some patients with LIP presented with relatively mild symptoms. In combination with the suppressed values of CRP under TCZ treatment, this may lead to a delayed diagnosis by non-specialised physicians not familiar with TCZ. Rheumatologists should be aware that IL-6 inhibition can be associated with an increased risk of LIP in patients with prior diverticulitis. Patients should be advised to observe signs and symptoms of LIP carefully and to inform non-specialised doctors that CRP, in their case, cannot be interpreted as a marker of diverticular inflammation. This could contribute to reduce a rare but serious risk in daily care.

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Contributors AS, AR, JL and AZ had full access to all data of this study and take responsibility for data integrity and accuracy of the analysis. JL, AZ and AS: study concept and design. PH, KR, WD, MA, YM and BS: acquisition of the data. BS: external validation of diagnoses. AR, JL, AZ and AS: analysis and interpretation of the data.

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REFERENCES

1 Hart AR, Kennedy HJ, Stebbings WS, *et al*. How frequently do large bowel diverticula perforate? An incidence and cross-sectional study. [Article]. *Eur J Gastroenterol Hepatol* 2000;12:661–5.
2 Morris CR, Harvey IM, Stebbings WSL, *et al*. Anti-inflammatory drugs, analgesics and the risk of perforated colonic diverticular disease. *Br J Surg* 2003;90:1267–72.
3 Svenningsen P, Manoharan T, Foss NB, *et al*. Increased mortality in the elderly after emergency abdominal surgery. *Dan Med J* 2014;61:A4876.
4 Prior P, Symmons DP, Scott DL, *et al*. Cause of death in rheumatoid arthritis. *Br J Rheumatol* 1984;23:92–9.
5 Henry DA, Johnston A, Dobson A, *et al*. Fatal peptic ulcer complications and the use of non-steroidal anti-inflammatory drugs, aspirin, and corticosteroids. *Br Med J (Clin Res Ed)* 1987;295:1227–9.
6 Laine L, Smith R, Min K, *et al*. Systematic review: the lower gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther* 2006;24:751–67.
7 Lanas A, Serrano P, Bajador E, *et al*. Evidence of aspirin use in both upper and lower gastrointestinal perforation. *Gastroenterology* 1997;112:683–9.
8 Langman MJ, Morgan L, Worrall A. Use of anti-inflammatory drugs by patients admitted with small or large bowel perforations and haemorrhage. *Br Med J (Clin Res Ed)* 1985;290:347–9.
9 Curtis JR, Xie F, Chen L, *et al*. The incidence of gastrointestinal perforations among rheumatoid arthritis patients. *Arthritis Rheum* 2011;63:346–51.
10 Mpofu S, Mpofu CMA, Hutchinson D, *et al*. Steroids, non-steroidal anti-inflammatory drugs, and sigmoid diverticular abscess perforation in rheumatic conditions. *Ann Rheum Dis* 2004;63:588–90.
11 Piekarek K, Israelsson LA. Perforated colonic diverticular disease: the importance of NSAIDs, opioids, corticosteroids, and calcium channel blockers. *Int J Colorectal Dis* 2008;23:1193–7.
12 Závada J, Lunt M, Davies R, *et al*. The risk of gastrointestinal perforations in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the BSRBR-RA. *Ann Rheum Dis* 2014;73:252–5.
13 Schiff MH, Kremer JM, Jahreis A, *et al*. Integrated safety in tocilizumab clinical trials. *Arthritis Res Ther* 2011;13:1–13.
14 Listing J, Kekow J, Manger B, *et al*. Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab. *Ann Rheum Dis* 2015;74:415–21.
15 van Vollenhoven RF, Keystone EC, Furie R, *et al*. Gastrointestinal safety in patients with rheumatoid arthritis treated with tocilizumab: data from Roche clinical trials. *Arthritis Rheum* 2009;60:1613.
16 Yamamoto K, Goto H, Hirao K, *et al*. Longterm safety of tocilizumab: results from 3 years of followup postmarketing surveillance of 5573 patients with rheumatoid arthritis in Japan. *J Rheumatol* 2015;42:1368–75.
17 Curtis JR, Perez-Gutthann S, Suissa S, *et al*. Tocilizumab in rheumatoid arthritis: A case study of safety evaluations of a large postmarketing data set from multiple data sources. *Semin Arthritis Rheum* 2015;44:381–8.
18 Myasoedova E, Matteson EL, Talley NJ, *et al*. Increased incidence and impact of upper and lower gastrointestinal events in patients with rheumatoid arthritis in Olmsted County, Minnesota: a longitudinal population-based study. *J Rheumatol* 2012;39:1355–62.
19 Curtis JR, Lanas A, John A, *et al*. Factors associated with gastrointestinal perforation in a cohort of patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012;64:1819–28.
20 Siegmund B, Lehr HA, Fantuzzi G. Leptin: a pivotal mediator of intestinal inflammation in mice. *Gastroenterology* 2002;122:2011–25.
21 Siegmund B, Sennello JA, Jones-Carson J, *et al*. Leptin receptor expression on T lymphocytes modulates chronic intestinal inflammation in mice. *Gut* 2004;53:965–72.
22 Peyrin-Biroulet L, Gonzalez F, Dubuquoy L, *et al*. Mesenteric fat as a source of C reactive protein and as a target for bacterial translocation in Crohn's disease. *Gut* 2012;61:78–85.
23 Zulian A, Cancello R, Micheletto G, *et al*. Visceral adipocytes: old actors in obesity and new protagonists in Crohn's disease? *Gut* 2012;61:86–94.

2.3 Die Bedeutung der Krankheitsaktivität als Risikofaktor für Komorbidität

2.3.1 Mortalität von RA-Patienten unter bDMARD- und csDMARD-Therapien

Listing J, Kekow J, Manger B, Burmester GR, Pattloch D, Zink A, **Strangfeld A**. *Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab.* Ann Rheum Dis. 2015 Feb;74(2):415-21. doi:10.1136/annrheumdis-2013-204021. PubMed PMID: 24291654.

Zusammenfassung

Im Vergleich zur Normalbevölkerung haben RA Patienten ein deutlich erhöhtes Mortalitätsrisiko [40]. Dies zeigte sich auch in unseren Registerdaten mit einer 1,5fachen höheren Mortalitätsrate im Vergleich zur alters- und geschlechtsstandardisierten Bevölkerung. Welche Faktoren in welchem Maße zu dieser Erhöhung beitragen, war Gegenstand dieser Arbeit.

Wir fanden, dass neben den aus der Normalbevölkerung bekannten klassischen Risikofaktoren, die auch bei RA Patienten die Lebenszeit verringern (männliches Geschlecht, höheres Alter, kardiovaskuläre Erkrankungen, Rauchen, Diabetes etc.), zusätzlich krankheitsspezifische Charakteristika wie verringerte Funktionskapazität und dauerhaft erhöhte Krankheitsaktivität mit einem höheren Mortalitätsrisiko assoziiert waren. Patienten, die in mehr als 80% der Beobachtungszeit eine hohe Krankheitsaktivität (DAS28>5.1) aufwiesen, hatten im Vergleich zu denjenigen mit geringer Krankheitsaktivität (DAS28<3.2) eine um 10 Jahre kürzere Lebenserwartung. Ein weiterer Risikofaktor war die Glukokortikoidtherapie: 15 mg/d erhöhten das Mortalitätsrisiko um das 3,6fache, aber auch Dosierungen >5 mg/d waren mit einem 1,5fach erhöhten Risiko assoziiert.

Verglichen mit den Patienten, die mit MTX behandelt wurden, hatten Patienten unter einer Therapie mit TNFi, Rituximab oder anderen bDMARDs ein signifikant geringeres Mortalitätsrisiko, selbst wenn man die bessere Wirksamkeit dieser Biologika einrechne-

te und nur Patienten miteinander verglich, die dasselbe Niveau der Krankheitsaktivität hatten (ungeachtet der verwendeten DMARD-Therapie).

OPEN ACCESS

EXTENDED REPORT

Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab

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ABSTRACT

Objectives To investigate the impact of disease activity, the course of the disease, its treatment over time, comorbidities and traditional risk factors on survival.

Methods Data of the German biologics register RABBIT were used. Cox regression was applied to investigate the impact of time-varying covariates (disease activity as measured by the DAS28, functional capacity, treatment with glucocorticoids, biologic or synthetic disease modifying antirheumatic drugs (DMARDs)) on mortality after adjustment for age, sex, comorbid conditions and smoking.

Results During 31 378 patient-years of follow-up, 463 of 8908 patients died (standardised mortality ratio: 1.49 (95% CI 1.36 to 1.63)). Patients with persistent, highly active disease (mean DAS28 > 5.1) had a significantly higher mortality risk (adjusted HR (HR_{adj})=2.43; (95% CI 1.64 to 3.61)) than patients with persistently low disease activity (mean DAS28 < 3.2). Poor function and treatment with glucocorticoids > 5 mg/d was significantly associated with an increased mortality, independent of disease activity. Significantly lower mortality was observed in patients treated with tumour necrosis factor α (TNFα) inhibitors (HR_{adj}=0.64 (95% CI 0.50 to 0.81), rituximab (HR_{adj}=0.57 (95% CI 0.39 to 0.84), or other biologics (HR_{adj}=0.64 (95% CI 0.42 to 0.99), compared to those receiving methotrexate. To account for treatment termination in patients at risk, an HR_{adj} for patients ever exposed to TNFα inhibitors or rituximab was calculated. This resulted in an HR_{adj} of 0.77 (95% CI 0.60 to 0.97).

Conclusions Patients with long-standing high disease activity are at substantially increased risk of mortality. Effective control of disease activity decreases mortality. TNFα inhibitors and rituximab seem to be superior to conventional DMARDs in reducing this risk.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease leading to increased mortality, as shown already in 1953 by Cobb *et al*[1] and subsequently by several longitudinal observational studies.[2–4] Early mortality was attributed to poor functional capacity, co-morbid conditions, and markers of RA severity or activity, such as rheumatoid factor or erythrocyte sedimentation rate.[5–8]

There is evidence from cardiovascular research that persistent systemic inflammation leads to increased mortality.[9 10] Additionally, we know that successful control of disease activity by treatment with methotrexate reduces mortality in RA.[11 12]

During the last decades, treatment strategies in RA have fundamentally changed, favouring early intensive treatment to reach remission as a major therapeutic goal.[13] With the approval of tumour necrosis factor α (TNFα) inhibitors (infliximab, etanercept, adalimumab, certolizumab, and golimumab), rituximab and other biologic agents (abatacept, tocilizumab, and anakinra), seminal advances in treatment options were made, and their efficacy was convincingly shown in randomised clinical trials. So far, six observational studies and one meta-analysis have investigated the impact of TNFα inhibitors on mortality, with conflicting results. Three of them suggested a reduced mortality,[14–16] whereas the other four did not.[17–20] All but one study compared treatment decisions rather than the direct effects of the drugs. If confounding by indication was adjusted for, only those patient characteristics known at the start of an index treatment were used for adjustment. As shown in one of these studies,[19] such an approach is prone to biased estimates. For the analysis of long-term outcomes such as mortality, the impact of changes in exposure and in the risk profiles of the patients over time have to be considered. In our study, we therefore took into account changes in the activity of RA, in functional capacity, fluctuating dosages of glucocorticoids, and changes in the treatment with synthetic or biologic disease modifying anti-rheumatic drugs (DMARDs) over time. We aimed to estimate the impact of each factor on premature mortality. Our main objectives were (A) to estimate the association between persistent highly active disease and mortality and (B) to evaluate the mortality risk of patients treated with TNFα inhibitors or rituximab compared with patients receiving methotrexate (alone or in combination with other synthetic DMARDs).

METHODS

Patients and study design

Data from RABBIT (acronym for: *RA ob*servation of *bi*ologic *t*herapy), an ongoing prospective cohort study initiated in May 2001 in Germany, were used for the analysis. Patients with RA, according to the American College of Rheumatology 1987 criteria,[21] were eligible for enrolment at start of treatment with a biologic or a synthetic DMARD after at least one termination of a treatment with a synthetic DMARD. The enrolment of patients starting

infliximab, etanercept, adalimumab, anakinra, rituximab, abatacept, tocilizumab, golimumab, or certolizumab began after the approval of the respective biological agent in Germany in 2001, 2003, 2007 or 2009. Participating rheumatologists were asked to enrol consecutive patients with RA who fulfilled the inclusion criteria: age at onset of RA >15 years, start of a new treatment with biologic or synthetic DMARDs after a failure of at least one DMARD treatment, patient scheduled for continuous care. All patients enrolled in RABBIT between May 2001 and June 2011 were included. For the investigation reported here, follow-up ended at 31 December 2011 or at month 108 of follow-up, whichever came first.

The study protocol was approved in 2001 by the ethics committee of the Charité University School of Medicine, Berlin. Each patient participating in the study gave written informed consent before study entry.

Procedures

At baseline and at predefined time points of follow-up (at 3 and 6 months, and thereafter every 6 months), rheumatologists assessed the clinical status, including the disease activity score (DAS28),[22] based on four parameters including the erythrocyte sedimentation rate. The rheumatologists further reported treatment details (start and stop dates, dosages) and serious and non-serious adverse events. Patients assessed, among other items, their functional capacity in percent of full function by means of the Hannover Functional Status Questionnaire (Funktionsfragebogen Hannover, FFbH,[23 24] see Strangfeld *et al*[25 26] for further details of our study). Vital status was ascertained in patients who had missed two subsequent study visits (n=2568) by contacting first, the rheumatologist; second, the patient or his/her relatives and third, the local registration office. In 58 (2.3%) patients, the vital status could not be ascertained. The procedure systematically covered a period of 24 months after the last visit. All deaths occurring during this period were taken into account. Most of the deaths occurred during the first six (262/463 (56.6%)) or first 12 months (380/463 (82.1%)) after the last study visit.

Main study hypotheses

The following prespecified hypotheses were investigated:

- Hypothesis 1: patients with RA with high disease activity over time (mean DAS28 > 5.1) are at increased risk of premature death compared to patients with low disease activity (mean DAS28 < 3.2).
- Hypothesis 2: patients treated with TNFα inhibitors during the last 6 months, or rituximab during the last 12 months, do not have an increased mortality compared to patients treated with methotrexate.
- Hypothesis 3: patients ever exposed to TNFα inhibitors or rituximab do not have a higher mortality than biologics-naive patients treated with methotrexate.

Statistical analysis

To control for the family-wise α-error, hypotheses 1–3 were tested in a sequential manner according to a closed test principle. The primary analyses were based on multiple Cox regression analysis including prespecified fixed and time-dependent risk factors. Fixed risk factors were recorded at baseline (T_0) and included: age, sex, smoking and six groups of comorbid conditions—chronic lung disease, diabetes, coronary heart disease, chronic renal disease, prior malignancy and osteoporosis (as an indicator of a severe course of the disease prior to baseline). Time-dependent risk factors were updated at each time point of follow-up (T_x) and included: mean DAS28 and mean FFbH scores between T_0 and T_x, treatment with glucocorticoids during the last 12 months, exposure to synthetic DMARDs, TNFα inhibitors, rituximab, or other biologic DMARDs.

Mean DAS28 scores were categorised into: low disease activity (DAS28 <3.2), moderate disease activity type A (DAS28: 3.2–4.1) and type B (DAS28 4.1–5.1), and high disease activity (DAS28 > 5.1).

Two conservative definitions of exposure to biologics were considered: first, a risk-window approach, considering a patient exposed to a biologic agent if the patient had received the agent

Table 1 Baseline characteristics by treatment group at inclusion

	MTX	sDMARDs no MTX	TNFα inhibitors	Rituximab	Other biologics	Total
n	2060	928	4649	703	568	8908
Follow-up (months)*	43.9 (32.7)	39.4 (31.7)	46.5 (32.3)	28.0 (14.6)	25.4 (23.1)	42.4 (31.6)
Female	1565 (76.0)	744 (80.2)	3584 (77.1)	552 (78.5)	438 (77.1)	6883 (77.3)
Age	56.4 (12.0)	58.5 (12.4)	54.5 (12.4)	58.5 (12.0)	56.4 (12.9)	55.8 (12.4)
Disease duration	7.2 (7.7)	8.8 (9.3)	11.2 (9.3)	13.6 (10.2)	12.9 (9.0)	10.3 (9.2)
Rheumatoid factor positive	1361 (66.1)	591 (63.7)	3614 (78.0)	578 (82.3)	416 (73.9)	6560 (73.8)
DAS28	4.9 (1.3)	4.8 (1.3)	5.6 (1.3)	5.5 (1.3)	5.6 (1.3)	5.3 (1.3)
Percent of full function (FFbH)	69.2 (21.6)	67.7 (22.0)	59.2 (23.1)	53.8 (23.6)	58.1 (23.9)	61.9 (23.3)
Glucocorticoids	1260 (61.1)	516 (55.6)	3456 (73.3)	523 (74.4)	400 (70.4)	6155 (69.1)
Prednisone dose (mg/d)	4.2 (5.4)	3.6 (4.4)	6.4 (7.0)	6.3 (5.9)	6.0 (6.0)	5.6 (6.3)
Diabetes	175 (8.5)	101 (10.9)	418 (9.0)	76 (10.8)	58 (10.2)	828 (9.3)
Coronary heart disease	114 (5.5)	70 (7.5)	324 (7.0)	84 (12.0)	51 (9.0)	643 (7.2)
Among them: heart failure	20 (1.0)	11 (1.2)	110 (2.4)	41 (5.8)	24 (4.2)	206 (2.3)
Chronic lung disease	111 (5.4)	77 (8.3)	349 (7.5)	65 (9.3)	36 (6.3)	638 (7.2)
Chronic renal disease	23 (1.1)	26 (2.8)	188 (4.0)	45 (6.4)	30 (5.3)	312 (3.5)
Prior malignancy	69 (3.4)	32 (3.5)	96 (2.1)	82 (11.7)	28 (4.9)	307 (3.4)
Osteoporosis	291 (14.1)	157 (16.9)	986 (21.2)	194 (27.6)	138 (24.3)	1766 (19.8)
Smoker	501 (24.3)	178 (19.2)	1077 (23.2)	161 (23.0)	136 (24.0)	2053 (23.1)

Values are means (SDs) or numbers (%) as appropriate. Methotrexate (MTX) group: patients treated with MTX alone or in combination with other synthetic disease modifying anti-rheumatic drugs (sDMARD), sDMARD no MTX group: treatment with sDMARDs without MTX.
*Follow-up of patients per treatment group at inclusion.

during the last six (rituximab: during the last 12) months. Second, an ever-exposed approach was applied to take into account terminations of biologic treatments in patients at increased risk of premature mortality. In this analysis, a patient is considered to be exposed to a biologic after having received the first dose. Since nearly all patients ever exposed to rituximab were also ever exposed to TNFα inhibitors, a distinction between both exposures was not made in this approach. A sustained biologic treatment discontinuation (>6 months, rituximab >12 months) despite active disease (DAS28 >4.1) was considered as an additional risk factor in the primary ever-exposed analysis.

The aim of both approaches was to show non-inferiority of TNFα inhibitors and rituximab compared to treatment with methotrexate (alone or in combination with synthetic DMARDs) regarding fatal outcomes. A non-inferiority margin of 20% was used, and treatment with TNFα inhibitors or rituximab was considered not inferior to treatment with methotrexate (and synthetic DMARDs) whenever the upper bound of the 95% CI of the corresponding adjusted HR was <1.2. After showing non-inferiority, superiority was tested in a closed test procedure. Hypotheses regarding the influence of single anti-TNF agents, or the group of other biologics (abatacept, tocilizumab and anakinra) were investigated in an exploratory manner.

Power considerations were made for hypothesis 1. We expected to observe a more than 50% increase in mortality when comparing patients with DAS28 > 5.1 to those with DAS28 < 3.2 and, therefore, at least 80% power to detect this difference. In this power calculation, the decrease in the power by risk factors which were correlated with DAS28 scores was taken into account. Since there was only a weak correlation between the mean DAS28 scores of the patients and their mean glucocorticoid dosages, which ranged for the different time points between 0.2 and 0.3, it was considered to be possible to distinguish between both effects. Nevertheless, to achieve sufficient power, functional capacity was not used for adjustment when hypothesis 1 was tested, because of a correlation of about 0.5 between mean DAS28 and mean FFbH scores. To test hypotheses 2 and 3, functional capacity was considered as a risk factor of premature mortality and an additional adjustment for this factor was made.

In a secondary analysis, a comparison with the German general population was conducted: patients were classified into four groups according to their DAS28 scores averaged over follow-up. Age-standardised and sex-standardised mortality ratios (SMR) were calculated with the German population rates from 2001 to 2010 as the reference. Life table methods were used to calculate the life expectancy of groups of patients. For each sex and age stratum (5-year bands) the likelihood of surviving was calculated. This estimate was used to calculate the remaining life expectancy taking into account that all patients were living at age 20 years. Comparing these results with the German general population, the life-years lost were calculated. We furthermore estimated 5 years survival rates by means of Cox regression for patients with either a low (mean DAS28 < 3.2) or a high disease activity (mean DAS28 > 5.1) during at least 80% of their available 5-year follow-up time. In sensitivity analyses we excluded patients with a prior malignancy (solid tumour or lymphoma) or heart failure to investigate the influence of a possible channelling bias on the adjusted HRs for biologics. Since we excluded patients with a high mortality risk, the power of this analysis was lower than the power of the primary analysis.

Owing to strict monitoring, treatment data were complete in 99%, and clinical data in 94% of the patients per visit.[26] Except in cases for whom we knew that the treatment was discontinued, we assumed that patients who died had continued the treatment until the last months prior to death. Missing smoking information was, however, more frequent (14%). A 10-fold multiple imputation was used to fill in all missing clinical and smoking data; p values <0.05 were considered to be statistically significant. SAS V.9.3 was used for the analysis.

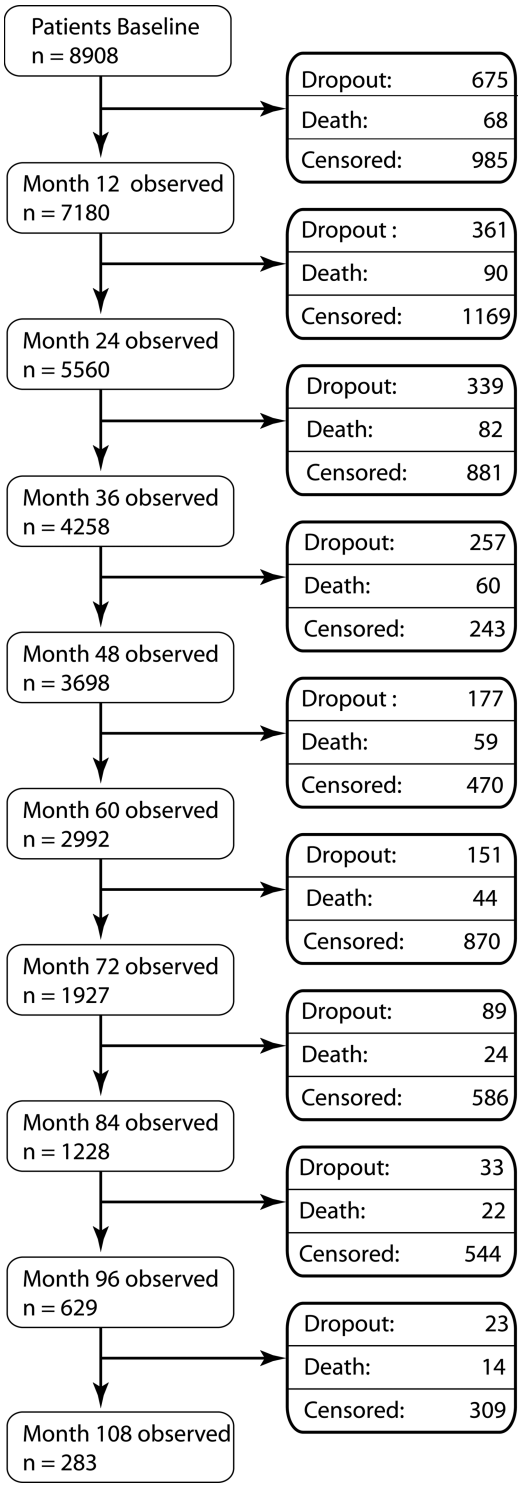

Figure 1 Flow chart of patients enrolled. Censored: patients who were in this study on 31 December 2011 but did not complete a follow-up period of 9 years since they were enrolled after January 2003. The follow-up time of these patients was censored at the last regular study visit. Dropouts: patients lost to follow-up.

RESULTS

Between 1 May 2001 and 30 June 2011, a cohort of 8908 patients with RA, with a mean age of 55.8 (SD 12.4) years at baseline was enrolled. The mean follow-up was 3.5 years (SD: 2.6; IQR: 1.2–5.4). Follow-up of five, seven, or 8 years was available for 2992, 1228 and 629 patients, respectively. Patients receiving anti-TNF agents, rituximab, or other biologic drugs, had a significantly more active disease, and they were more limited in activities of daily living than patients treated with synthetic DMARDs only (table 1).

Within an observation period of 31 378 patient-years, a total of 463 patients died (figure 1). Patients who dropped out of the observation had, on average, a 0.3 units higher DAS28 score (4.2) at their last study visit than patients who completed the corresponding visit. This difference was even higher (0.6 units) in patients who died (mean last DAS28: 4.4). Causes of death are shown in the online supplementary table ST1.

Significantly elevated standardised mortality ratios were observed in men and women (table 2). The increase was associated with patients having highly active disease (DAS28 > 5.1), on average, over time, whereas, no increase was found in patients with low disease activity (DAS28 < 3.2). In terms of remaining life expectancy at age 20 years, women RABBIT patients generally expected 59.9 further life years (men 55.3), which is about 2 years less than the agematched and sexmatched population (table 2). In the case of highly active disease (DAS28 > 5.1), women patients lost 10.3 years (men 10.7) compared with the population (table 2).

The results found in comparison to the German population were confirmed by multiple Cox regression analysis. Patients who, on average, remained in a state of highly active disease (DAS28 > 5.1) over time had a more than twofold mortality risk (HR: 2.43; 95% CI 1.64 to 3.61, table 3) compared to those with low disease activity (DAS28 < 3.2).

This association was significant after control for treatment with glucocorticoids, and remained significant after additional adjustment for functional capacity, a disease outcome which is correlated with DAS28 (table 4 column 4–6). Patients treated with higher dosages of glucocorticoids had a significantly higher mortality, whereas, those exposed to TNFα inhibitors (during the last 6 months), rituximab (during the last 12 months) or other biologics (last 6 months) had a significantly lower risk of dying early (table 4 column 4–6).

Even using a conservative 'ever exposed' approach, we found a significantly lower mortality in patients ever exposed to TNFα inhibitors or rituximab, compared to methotrexate therapy (HR=0.77; 95% CI 0.60 to 0.97), whereas, sustained treatment discontinuation (>6 months see Methods) despite active disease was associated with a significantly higher risk of dying (HR=2.08; 95% CI 1.59 to 2.72). When attributing the risk resulting from sustained treatment discontinuation to the biologic the patient had received before, we found in this secondary analysis no increase in the mortality risk in patients ever exposed to TNFα inhibitors or rituximab (HR=0.85; 95% CI 0.67 to 1.08).

Table 3 Adjusted HRs of death by categories of mean disease activity of the patients at follow-up

	PYRS	Adjusted HR (95%CI)	p Value
DAS28<3.2	6730	Referent	
DAS28 3.2–4.1	8875	1.29 (0.85 to 1.93)	0.21
DAS28>4.1–5.1	8773	1.42 (0.96 to 2.10)	0.073
DAS28>5.1	6999	2.43 (1.64 to 3.61)	0.0001

The risk window approach was used to calculate the adjusted HRs. Adjustments were made for age, sex, smoking, comorbid conditions (chronic lung disease, diabetes, coronary heart disease, chronic renal disease, prior malignancy and osteoporosis) and as time-dependent risk factors treatment with glucocorticoids, treatment with methotrexate, other synthetic disease modifying antirheumatic drugs, TNFα inhibitors, rituximab, or other biologics. Updated FFbH scores were not included in the risk set. (PYRS: patient-years).

Similar results were found in the sensitivity analyses. When we excluded patients with prior malignancies (solid tumours or lymphoma) we could still confirm hypotheses 2 and 3, that treatment with TNFα inhibitors or rituximab was not inferior to treatment with methotrexate (data not shown). A similar result was found after additional exclusion of patients with prior heart failure.

Comparing the individual treatments, the HRs for individual biologic agents with methotrexate as reference group are shown in the online supplementary table ST2. In the online supplementary table ST3 HRs for TNFα inhibitors are given with etanercept as reference. No significant differences between the anti-TNF agents were seen in the '6-months risk window' or the 'ever exposed' approaches.

To put the relative risks into context, we furthermore estimated 5 years survival rates according to the overall disease activity status of the patients. Figure 2 shows the results for women and men at ages 50 and 65 years. The difference in survival between patients with low and high disease activity were significant and ranged from 3% to 23%, depending on age, sex, smoking and comorbidity status.

DISCUSSION

We found evidence for a significant association between highly active RA and mortality. Patients with a persistent, highly active disease had a significantly higher mortality than those with a mean DAS28 < 3.2. Patients with low functional capacity, with diabetes, chronic lung or chronic renal diseases, cardiac disorders as well as those treated with higher dosages of

Table 2 Standardised mortality ratios (SMR) and life-years lost, in comparison with the German general population by groups of patients with different mean disease activity (DAS28) scores at follow-up

	Women			Men		
DAS28	Deaths	SMR (95% CI)	Lost life years (95% CI)	Deaths	SMR (95% CI)	Lost life years (95% CI)
<3.2	29	0.86 (0.58 to1.24)	−1.5 (−3.0 to 0.0)	13	0.54 (0.29 to 0.92)	−2.4 (−6.1 to1.3)
3.2–4.1	60	0.94 (0.72 to1.22)	0.0 (−1.4 to 1.4)	39	1.11 (0.79 to 1.52)	0.1 (−2.1 to 2.3)
>4.1–5.1	88	1.35 (1.09 to 1.67)	3.0 (1.1 to 4.9)	42	1.34 (0.96 to 1.81)	0.5 (−1.3 to 2.1)
>5.1	132	3.33 (2.79 to 3.95)	10.3 (8.9 to 11.6)	60	3.33 (2.54 to 4.30)	10.7 (8.9 to 12.6)
Total	309	1.53 (1.37 to 1.71)	2.7 (2.0 to 3.4)	154	1.41 (1.20 to 1.65)	1.9 (0.8 to 3.0)

Table 4 Adjusted HRs ; Adjustments were made for all parameters shown in the table

	Unadjusted HR		Adjusted HR: 6 (rituximab 12) months risk window approach			Adjusted HR: Ever exposed approach				
	HR	95% CI	HR	95% CI	p Value	HR	95% CI	p Value	Deaths	PYRS
At baseline										
Male	1.85	1.53 to 2.25	1.75	1.40 to 2.18	<0.0001	1.72	1.38 to 2.14	<0.0001	154	6718
Age per 5 years	1.66	1.57 to 1.75	1.49	1.40 to 1.59	<0.0001	1.50	1.41 to 1.60	<0.0001		31 378
Diabetes	3.43	2.77 to 4.26	1.84	1.46 to 2.33	<0.0001	1.85	1.46 to 2.33	<0.0001	108	2633
Chronic lung disease	3.31	2.63 to 4.17	1.68	1.31 to 2.17	0.0003	1.71	1.32 to 2.20	0.0002	89	2125
Chronic renal disease	4.90	3.71 to 6.47	1.94	1.43 to 2.63	0.0001	1.92	1.41 to 2.61	0.0002	57	926
Prior malignancy	3.15	2.27 to 4.37	1.26	0.88 to 1.80	0.20	1.27	0.89 to 1.81	0.18	39	927
Osteoporosis	2.86	2.38 to 3.43	1.43	1.16 to 1.76	0.0015	1.41	1.15 to 1.73	0.0020	199	6718
Coronary heart disease	4.94	4.00 to 6.10	1.43	1.12 to 1.83	0.006	1.46	1.14 to 1.86	0.0036	115	2017
Smoker	0.82	0.62 to 1.07	1.37	1.02 to 1.85	0.038	1.36	1.01 to 1.83	0.042	86	6936
At follow-up										
DAS28* <3.2	Ref.		Ref.			Ref.			42	6730
DAS28* 3.2–4.1	1.81	1.21 to 2.71	1.15	0.76 to 1.74	0.49	1.11	0.74 to 1.68	0.59	99	8875
DAS28* >4.1 to 5.1	2.29	1.57 to 3.33	1.17	0.78 to 1.75	0.43	1.08	0.72 to 1.61	0.70	130	8773
DAS28>5.1	4.86	3.35 to 7.04	1.75	1.14 to 2.68	0.013	1.54	1.00 to 2.38	0.0499	192	6999
Prednisone most recent 12 months: 0 mg/d	Ref.		Ref.			Ref.			88	9036
1–5 mg/d	1.33	1.00 to 1.76	1.05	0.80 to 1.38	0.71	1.04	0.79 to 1.37	0.77	177	13 615
>5–10 mg/d	2.22	1.65 to 2.98	1.46	1.09 to 1.95	0.013	1.41	1.06 to 1.89	0.021	140	7086
>10–15 mg/d	3.95	2.61 to 5.98	2.00	1.29 to 3.11	0.0033	2.01	1.30 to 3.11	0.0030	37	1170
>15 mg/d	6.68	4.06 to 11.0	3.59	2.11 to 6.13	<0.0001	3.43	2.01 to 5.86	<0.0001	21	448
FFbH* in % of full function per 10% improvement	0.76	0.73 to 0.79	0.88	0.84 to 0.93	<0.0001	0.89	0.85 to 0.93	<0.0001		31 378
Methotrexate	Ref.		Ref.			Ref.			96†/78‡	7012†/6469‡
Other synth. DMARDs	2.53	1.95 to 3.28	1.14	0.86 to 1.51	0.36	0.98	0.60 to 1.59	0.92	126†/31‡	3513†/1581‡
TNFα inhibitors	0.77	0.61 to 0.98	0.64	0.50 to 0.81	0.0007	NA			182†	16 843†
Rituximab	1.01	0.70 to 1.46	0.57	0.39 to 0.84	0.0062	NA			36†	2599†
TNFα inhibitors or rituximab	NA		NA			0.77	0.60 to 0.97	0.0312	330‡	22 370‡
Other biologics	1.02	0.68 to 1.52	0.64	0.42 to 0.99	0.043	0.91	0.66 to 1.25	0.54	25†/51‡	1654†/2806‡
DAS28>4.1 for > 6 (12) months after discon- tinuation of a biologic without start of a new one	NA		NA			2.08	1.59 to 2.72	<0.0001	86‡	1812‡

*Average of single DAS28 or FFbH scores between baseline and last time point prior to the event, FFbH: Function questionnaire (see Methods) (range 0–100%).
†Risk window approach.
‡Ever exposed approach.
DMARD, disease modifying antirheumatic drugs; PYRS: patient years; Ref., referent.

glucocorticoids, were at a further increased risk. Treatment with more than 5 mg/d glucocorticoids was significantly associated with an increased mortality risk in a dose-dependent manner. Patients treated with TNFα inhibitors or rituximab had a significantly reduced premature mortality compared to those treated with methotrexate alone or in combination with other synthetic DMARDs. No significant differences between the individual TNFα inhibitors were seen, which is in agreement with a recent study from the Swedish biologics register.[27]

The strength and novelty of our study is that it took into account changes in patient characteristics (disease activity, functional capacity) and treatment details (eg, fluctuating glucocorticoid dosages) at all time points during long-term follow-up, in order to achieve valid estimates of the risk of mortality conveyed by biologic agents in comparison with conventional DMARD therapy. This approach is more robust than an approach adjusting only for patient's baseline characteristics, for example, by propensity score methods.[19]

To our knowledge, our study is the first to differentiate the impact of inflammation on all-cause mortality from the impact of glucocorticoids. Since the mean disease activity of individual patients and the mean glucocorticoid dose they received for the treatment of RA were only weakly correlated, we were able to distinguish between both risk factors. The clinical relevance of the findings is expressed by the number of lost life years and by 5-year survival rates, which substantially differ between patients in low and high disease activity. The findings are in concordance with reports on the impact of inflammation on premature death from cardiovascular diseases,[9] chronic lung diseases[28] and lymphoma.[29]

Significant associations between mortality and glucocorticoid use (as time-varying yes/no parameter) were described by Mikuls *et al*[5] and Jacobsson *et al*.[15] A dose-related association is supported by findings of an increased cardiovascular as well as all-cause mortality associated with the use of glucocorticoids.[30–32] When analysing the incidence of serious infections in our biologics register, we recently found a significant association between the glucocorticoid dose and the magnitude of the risk.[26] One might object that glucocorticoid use is an indicator for severe disease, and that the association between increased mortality and higher dosages of glucocorticoids found in our data and in those of others only relates to a persistently high disease activity. This view is, however, not supported by our data since we already adjusted for disease activity, functional capacity and

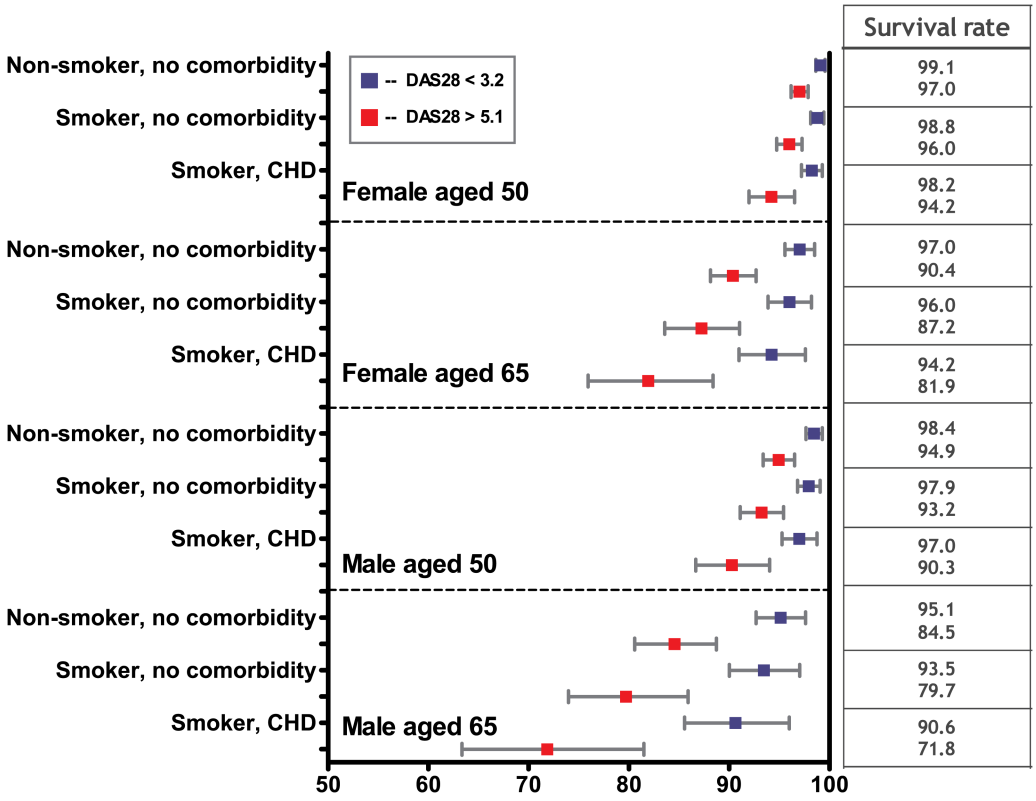

Figure 2 Five-year survival rates (in %) for patients with highly active disease (DAS28 scores >5.1 at ≥80% of the observation time (18% of patients) and low disease activity (DAS28 scores <3.2 for ≥80% of the observation time (9% of patients) CHD: coronary heart disease.

comorbidities. Nevertheless, we cannot rule out unmeasured confounding, and we therefore invite other researchers to re-examine our findings.

We observed a reduced mortality in patients treated with TNFα inhibitors or rituximab. Since we compared patients by taking their disease activity on treatment into account, a potential additional benefit of biologics resulting from their higher efficacy was not considered. However, this strengthens rather than weakens our findings.

Our study has some limitations. It was underpowered to show significant effects for infliximab, etanercept, certolizumab, golimumab, abatacept, tocilizumab, or anakinra separately. We were so far only able to show the effects for the group of TNFα inhibitors and for rituximab. Further, generalisability of the results to the German population is limited since our register includes patients on the upper end of the disease severity spectrum. Patients with RA who do well on methotrexate monotherapy are not included in the control group. We might, therefore, have underestimated beneficial effects of methotrexate. Finally, due to the observational nature of the study, and due to a rather long list of risk factors and confounders, residual confounding with an impact on the results cannot be ruled out.

CONCLUSION

Taking the course of disease into account, we observed an increased mortality in patients with persistent, highly active disease, and in patients treated with higher dosages of glucocorticoids. We further found that TNFα inhibitors and rituximab, and possibly other biologics, reduced the mortality compared to treatment with methotrexate (alone or in combination with other synthetic DMARDs).

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Contributors JL DP, AZ, and AS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the analysis. Study concept and design: JL, AZ, AS. Acquisition of the data: JK, BM, G-RB, DP. Analysis and interpretation of the data: JL, DP, AZ, AS. Drafting the manuscript: JL, AZ, AS. Critical revision of the manuscript for important intellectual content: JL, JK, BM, G-RB, DP, AZ, AS. Obtained funding and Study supervision: JL, AZ, AS.

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REFERENCES

1 Cobb S, Anderson F, Bauer W. Length of life and cause of death in rheumatoid arthritis. *N Engl J Med* 1953;249:553–6.
2 Wolfe F, Mitchell DM, Sibley JT, *et al*. The mortality of rheumatoid arthritis. *Arthritis Rheum* 1994;37:481–94.
3 Bjornadal L, Baecklund E, Yin L, *et al*. Decreasing mortality in patients with rheumatoid arthritis: results from a large population based cohort in Sweden, 1964–95. *J Rheumatol* 2002;29:906–12.
4 Gonzalez A, Maradit KH, Crowson CS, *et al*. The widening mortality gap between rheumatoid arthritis patients and the general population. *Arthritis Rheum* 2007;56:3583–7.
5 Mikuls TR, Fay BT, Michaud K, *et al*. Associations of disease activity and treatments with mortality in men with rheumatoid arthritis: results from the VARA registry. *Rheumatology (Oxford)* 2011;50:101–9.
6 del Rincon ID, Williams K, Stern MP, *et al*. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001;44:2737–45.
7 Gonzalez-Gay MA, Gonzalez-Juanatey C, Lopez-Diaz MJ, *et al*. HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. *Arthritis Rheum* 2007;57:125–32.
8 Wolfe F, Michaud K, Gefeller O, *et al*. Predicting mortality in patients with rheumatoid arthritis. *Arthritis Rheum* 2003;48:1530–42.
9 Sattar N, McCarey DW, Capell H, *et al*. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation* 2003;108:2957–63.
10 Sattar N, Murray HM, McConnachie A, *et al*. C-reactive protein and prediction of coronary heart disease and global vascular events in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). *Circulation* 2007;115:981–9.
11 Choi HK, Hernan MA, Seeger JD, *et al*. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002;359:1173–7.
12 Krause D, Schleusser B, Herborn G, *et al*. Response to methotrexate treatment is associated with reduced mortality in patients with severe rheumatoid arthritis. *Arthritis Rheum* 2000;43:14–21.
13 Smolen JS, Aletaha D, Bijlsma JW, *et al*. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010;69:631–7.
14 Carmona L, Descalzo MA, Perez-Pampin E, *et al*. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. *Ann Rheum Dis* 2007;66:880–5.
15 Jacobsson LT, Turesson C, Nilsson JA, *et al*. Treatment with TNF blockers and mortality risk in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007;66:670–5.
16 Burmester GR, Panaccione R, Gordon KB, *et al*. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis* 2013;72:517–24.
17 Lunt M, Watson KD, Dixon WG, *et al*. No evidence of association between anti-tumor necrosis factor treatment and mortality in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2010;62:3145–53.
18 Al-Aly Z, Pan H, Zeringue A, *et al*. Tumor necrosis factor-alpha blockade, cardiovascular outcomes, and survival in rheumatoid arthritis. *Transl Res* 2011;157:10–18.
19 Lunt M, Solomon D, Rothman K, *et al*. Different methods of balancing covariates leading to different effect estimates in the presence of effect modification. *Am J Epidemiol* 2009;169:909–17.
20 Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. *Ann Rheum Dis* 2009;68:1136–45.
21 Arnett FC, Edworthy SM, Bloch DA, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
22 Prevoo ML, van't Hof MA, Kuper HH, *et al*. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44–8.
23 Lautenschlaeger J, Mau W, Kohlmann T, *et al*. [Comparative evaluation of a German version of the Health Assessment Questionnaire and the Hannover Functional Capacity Questionnaire]. *Z Rheumatol* 1997;56:144–55.
24 Westhoff G, Listing J, Zink A. Loss of physical independence in rheumatoid arthritis: interview data from a representative sample of patients treated in tertiary rheumatologic care. *Arthr Care Res* 2000;13:11–21.
25 Strangfeld A, Listing J, Herzer P, *et al*. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. *JAMA* 2009; 301:737–44.
26 Strangfeld A, Eveslage M, Schneider M, *et al*. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? *Ann Rheum Dis* 2011;70:1914–20.
27 Simard JF, Neovius M, Askling J. Mortality in patients with rheumatoid arthritis treated with TNF inhibitors: drug-specific comparisons in the swedish biologics register. *Arthritis Rheum* 2012.
28 Sin DD, Anthonisen NR, Soriano JB, *et al*. Mortality in COPD: role of comorbidities. *Eur Respir J* 2006;28:1245–57.
29 Baecklund E, Iliadou A, Askling J, *et al*. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis Rheum* 2006;54:692–701.
30 Davis JM III, Maradit KH, Crowson CS, *et al*. Glucocorticoids and cardiovascular events in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum* 2007;56:820–30.
31 Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. *Ann Intern Med* 2004;141:764–70.
32 Sihvonen S, Korpela M, Mustonen J, *et al*. Mortality in patients with rheumatoid arthritis treated with low-dose oral glucocorticoids. A population-based cohort study. *J Rheumatol* 2006;33:1740–6.

2.3.2 Einflussfaktoren auf die Entwicklung eines Myokardinfarkts

Meissner Y, Zink A, Kekow J, Rockwitz K, Liebhaber A, Zinke S, Gerhold K, Richter A, Listing J, **Strangfeld A**. *Impact of disease activity and treatment of comorbidities on the risk of myocardial infarction in rheumatoid arthritis.* Arthritis Res Ther. 2016 Aug 5;18(1):183. doi:10.1186/s13075-016-1077-z. PubMed PMID:27495156.

Zusammenfassung

Das Risiko für einen Myokardinfarkt bzw. das Versterben an einer ischämischen Herzerkrankung ist für RA-Patienten eineinhalb bis zweimal höher als für Menschen der Normalbevölkerung [41-43].

Zusätzlich zu traditionellen Risikofaktoren erhöhen proinflammatorische Zytokine das Risiko, und auch dem Entzündungsmarker CRP werden zytotoxische Eigenschaften zugeschrieben [44]. Eine Analyse, wie stark das Herzinfarktrisiko durch die verabreichte Therapie beeinflusst wird, ist aufgrund der Vielzahl der Risikofaktoren nicht einfach. In dieser Arbeit untersuchten wir die Bedeutung RA-spezifischer Risikofaktoren (wie Therapie und chronische Entzündung) unter Kontrolle traditioneller, auch aus der Bevölkerung bekannter Risikofaktoren, für die Inzidenz des Myokardinfarkts. Als adäquates Studiendesign hierfür wählten wir eine in das Register eingebettete Fall-Kontroll-Studie. Wir konnten für viele Störfaktoren kontrollieren, indem wir sie als Matchingkriterien vorgaben. Dieses intensive Matching war nur möglich, weil die RABBIT-Kohorte, aus der wir Fall- und Kontroll-Patienten rekrutierten, groß genug ist. Jedem RA-Patienten mit einem Myokardinfarkt während der Beobachtung in RABBIT konnte eine Kontrolle zugeordnet werden, die in Alter, Geschlecht und verschiedenen kardiovaskulären Komorbiditäten und Risikofaktoren (wie Hypertonie, Hyperlipoproteinämie, Koronare Herzkrankheit, Herzinsuffizienz, zerebrovaskuläres Ereignis in der Anamnese) übereinstimmte. Hinsichtlich der verabreichten Therapien unterschieden sich Patienten mit My-

okardinfarkt (Fälle) und Kontrollen nicht. Fälle hatten aber signifikant höhere BSG- und CRP-Werte als Kontrollen ohne Infarkt, sowohl bei Einschluss in das Register und in den ersten 6 Monaten Beobachtung, als auch in der Zeit vor dem Infarkt (Fälle) bzw. Indexdatum (Kontrollen). Dies spiegelte sich im DAS28 nicht wider, in den zusätzlich weitere Parameter wie das Patientenurteil, eingehen. Einen Hinweis darauf, dass Patienten, die einen Myokardinfarkt entwickelten, eine schwerer zu kontrollierende Erkrankung haben, könnte auch die Anzahl der verabreichten Therapien geben. Fallpatienten wechselten ihre DMARD Therapie signifikant häufiger als Kontrollen.

Ein weiterer Unterschied zwischen Fällen und Kontrollen bestand in der Therapie der bestehenden kardiovaskulären Begleiterkrankung. Bei Patienten, die einen Myokardinfarkt entwickelten, waren Begleiterkrankungen deutlich seltener therapiert worden (64%) als dies bei den Kontrollen (83%) oder den Patienten der restlichen Kohorte (79%) der Fall war.

Auch diese Analyse zeigt, wie groß der Einfluss der Krankheitsaktivität auf die Entwicklung unerwünschter Ereignisse und Komorbiditäten ist. Sie verdeutlicht darüber hinaus aber auch, dass mit dem aus mehreren Parametern zusammengesetzte Krankheitsaktivitätsscore das kardiovaskuläre Risiko weniger gut abgeschätzt werden kann als mit den unspezifischen Entzündungsmarkern CRP und BSG.

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Impact of disease activity and treatment of comorbidities on the risk of myocardial infarction in rheumatoid arthritis

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Abstract

Background: The aim was to estimate the impact of individual risk factors and treatment with various disease-modifying antirheumatic drugs (DMARDs) on the incidence of myocardial infarction (MI) in patients with rheumatoid arthritis (RA).

Methods: We analysed data from 11,285 patients with RA, enrolled in the prospective cohort study RABBIT, at the start of biologic (b) or conventional synthetic (cs) DMARDs. A nested case–control study was conducted, defining patients with MI during follow-up as cases. Cases were matched 1:1 to control patients based on age, sex, year of enrolment and five cardiovascular (CV) comorbidities. Generalized linear models were applied (Poisson regression with a random component, conditional logistic regression).

Results: In total, 112 patients developed an MI during follow-up. At baseline, during the first 6 months of follow-up and prior to the MI, inflammation markers (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)) but not 28-joint-count disease activity score (DAS28) were significantly higher in MI cases compared to matched controls and the remaining cohort. Baseline treatment with DMARDs was similar across all groups. During follow-up bDMARD treatment was significantly more often discontinued or switched in MI cases. CV comorbidities were significantly less often treated in MI cases vs. matched controls (36 % vs. 17 %, $p < 0.01$). In the adjusted regression model, we found a strong association between higher CRP and MI (OR for log-transformed CRP at follow-up: 1.47, 95 % CI 1.00; 2.16). Furthermore, treatment with prednisone ≥10 mg/day (OR 1.93, 95 % CI 0.57; 5.85), TNF inhibitors (OR 0.91, 95 % CI 0.40; 2.10) or other bDMARDs (OR 0.85, 95 % CI 0.27; 2.72) was not associated with higher MI risk.

Conclusions: CRP was associated with risk of MI. Our results underline the importance of tight disease control taking not only global disease activity, but also CRP as an individual marker into account. It seems irrelevant with which class of (biologic or conventional) DMARD effective control of disease activity is achieved. However, in some patients the available treatment options were insufficient or insufficiently used - regarding DMARDs to treat RA as well as regarding the treatment of CV comorbidities.

Keywords: Myocardial infarction, Cardiovascular disease, Inflammation, Disease activity, Tumour necrosis factor inhibitors, Biologicals

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Background

In rheumatoid arthritis (RA), increased morbidity and mortality due to myocardial infarctions (MI) cannot entirely explained by traditional cardiovascular (CV) risk factors [1–3]. There is evidence that the rheumatic disease itself contributes to the risk of CV events [1, 4–6], with inflammation as the link between RA and CV disease (CVD). Some of the pivotal pro-inflammatory mediators, including the cytokines tumour necrosis factor (TNF), interleukin 1 (IL-1) and interleukin 6 (IL-6) [7, 8], as well as the acute-phase reactant C-reactive protein (CRP), are involved in atherogenesis and eventually in the development of coronary artery diseases like MI [9].

A recent meta-analysis of studies investigating single nucleotide polymorphisms (SNPs) hypothesized a causal role of the IL6R-gene signalling via the inflammatory markers CRP and fibrinogen in the development of coronary heart disease (CHD) [10]. The awareness of even relatively low levels of CRP as a risk factor for MI has increased in the rheumatologic community. A few studies of MI in RA examined prospectively collected CRP [11–15]. Nevertheless, other studies have identified erythrocyte sedimentation rate (ESR) as a relevant inflammation marker in CVD [16–19]. Similarly, high disease activity measured by the composite score based on 28 joints (DAS28) is discussed to have an important influence on the risk of MI [17, 19]. The European League Against Rheumatism (EULAR) recommendations for CV risk management require "adequate control of disease activity" [20]. However, global disease activity might not be sensitive enough in patients at increased risk of MI. Therefore, the question remains whether CRP and/or ESR should be taken into account as additional targets in a treat-to-target approach. Randomised clinical trials are unable to answer this question due to the long latency to the outcome of MI, the restricted follow-up time and the exclusion of patients with major CVD. Observational studies, on the other hand, should be suitable to investigate risk factors for MI. However, comparisons between patients with RA who develop MI and the rest of the cohort are difficult to interpret in observational studies, due to significant differences in age, sex and CV comorbidities [12, 19].

To control for these confounding factors, a few studies applied a matched case-control design [21, 22], but the results are conflicting. Radovits et al. could neither confirm CRP nor DAS28 as risk factors for MI [22], whereas Mantel et al. observed significantly elevated ESR, CRP and DAS28 in cases compared to controls [21]. These contradictory results may be caused by sparse matching procedures: matching for disease duration only [22] and matching for sex, year of RA diagnosis and rheumatologic unit [21].

We pursued two aims with this study: First, to show the influence of risk factors, especially the effect of inflammation, on the incidence of MI in patients with RA. Second, we were interested in the impact of treatment: (1) the treatment of RA with disease-modifying antirheumatic drugs (DMARDs) and concomitant glucocorticoids and (2) the treatment of CV comorbidities. To preclude distorting effects we applied a case–control study with an extended matching algorithm comprising traditional CV risk factors such as age, sex and CV comorbidities.

Methods

Data source

Data from the German biologics register Rheumatoid Arthritis: Observation of Biologic Therapy (RABBIT) were used. RABBIT is an ongoing observational cohort study in which patients are included at the start of treatment with a biologic (b)DMARD or a conventional synthetic (cs)DMARD after failure of at least one prior csDMARD [23, 24]. In brief, once enrolled, patients stay in the cohort for at least the next 5 (if possible, 10) years. At regular predefined times (0, 3 and 6 months, and then every 6 months) rheumatologists complete assessment forms at clinical routine visits capturing current clinical status, treatment and all adverse events that have occurred since the last follow-up. Additionally, weight, height as well as existing comorbidities and their treatment are assessed at baseline. At all follow-up visits patients report their global health status using numerical rating scales and their disability by the Hannover Functional Status Questionnaire (FFbH), in which 100 % indicates full functional capacity [25]. Smoking habits are stated at baseline. The study protocol of RABBIT was approved by the ethics committee of the Charité University Medicine Berlin.

Study design and matching algorithm

We performed a nested case–control analysis based on exact matching where each case was randomly matched to one control patient from the same original cohort. Matching criteria were sex, age at baseline (±3 years) and CV comorbidity at baseline (hypertension, CHD, heart failure, prior cerebrovascular event and hyperlipoproteinaemia). To ensure similar availability of treatment options for each case–control pair, the year of inclusion into RABBIT (±2 years) was also added as matching criteria. Eligible controls had to to be still under observation and without a CV event at follow-up prior to the index date of the corresponding case (calendar date of the MI).

Case definition

Cases were defined as patients observed in RABBIT with an MI as the first CV event after enrolment up to

October 2013. The case definition included the following reported diagnoses: MI (acute, silent or not otherwise specified), ST segment elevation MI, non ST segment elevation MI and anterior or posterior wall infarction. For all reported MIs supplemental information on clinical symptoms, cardiac biomarkers, electrocardiographic changes and imaging results were requested on standardized forms from the rheumatologist. If available, hospital discharge letters and death certificates were reviewed. Individual patients were eligible as a case if their first ever MI had occurred prior to enrolment in RABBIT. These events are possibly subsumed in the comorbidity defined as CHD.

Validation of cases and controls

In a subgroup of patients (MIs reported to RABBIT until October 2011 and their matching controls, $n_{pairs} = 75$), on-site visits were performed to revalidate CV events and to verify the control status of the corresponding controls. During these on-site visits, the entire patient records or electronic patient files were reviewed. This comprised inpatient and outpatient records, laboratory results and hospital discharge letters. A CV event listed in the patient record during follow-up, which had not been previously reported to RABBIT, was considered as an event for the analysis. If this event was an MI and had occurred in a control patient, this patient was recategorized as a case patient and a new control patient was matched for that case. After data collection in the rheumatologic units, the diagnoses of all reviewed patients were validated in a blinded process by a physician (KG) to verify the case and control status. Only confirmed events were included.

DMARD exposure and concomitant treatment

Data on DMARD treatment are captured in RABBIT at every follow-up time point, and include agent, dose, frequency of administration and start/stop-dates. Concomitant treatment with oral glucocorticoids including dosage in prednisone-equivalents, nonsteroidal anti-inflammatory drugs (NSAIDs) and inhibitors of cyclooxygenase-2 (COX-2) are prospectively collected. In addition, rheumatologists report comorbidities and their medical treatment at baseline. Patients with hypertension, CHD, heart failure or hyperlipoproteinaemia, but without respective treatment, were labelled as having no CV treatment.

For the analysis, bDMARDs were categorized into (1) TNF inhibitor (TNFi) (adalimumab, certolizumab, etanercept, golimumab and infliximab), (2) other bDMARDs (abatacept, anakinra, rituximab and tocilizumab) and (3) csDMARDs. In groups (1) and (2) combination with csDMARD treatment was possible; group (3) was exclusively treated with one or more csDMARDs. We applied two different definitions of bDMARD exposure: to examine treatment changes in the use of bDMARDs and to determine length and frequency of bDMARD episodes we considered the first missed dose or the switch between bDMARDs as discontinuation. In contrast, in the multivariable analysis of the influence of RA treatments on the risk of MI we considered patients as being exposed to a certain DMARD class or glucocorticoid if at least one dose of the drug was prescribed within the last 6 months prior to the MI/index date.

Statistical analysis

For baseline comparison of MI cases and the remainder of the RABBIT cohort we used the *t* test and Chi-squared test. Comparisons in the matched case–control design were drawn using the paired *t* test or McNemar's test. CRP, ESR and DAS28 were analysed at different times: at baseline, within the first 6 months after enrolment and up to 18 months before the MI/index date. Persistence with enrolment therapy was investigated using Kaplan-Meier estimates. In addition, we were interested in the cumulative number of treatment changes (sequence of DMARD episodes). The switch from a csDMARD to a bDMARD or the reverse and any switch between bDMARDs were counted as treatment changes and were used to calculate treatment episodes. We assumed that the number of switches follow a Poisson distribution and applied a generalized linear mixed model with a random component for the matched case–control design.

Multiple conditional logistic regression analysis was applied to investigate the impact of risk factors on the likelihood of developing an MI (cases vs. controls). The regression model was additionally adjusted for non-matching criteria: CRP, smoking, diabetes and insufficient treatment of underlying CVD. CRP was included as reported values within 6 months prior to the MI/index date (analysis I) and as the average of all reported values from baseline until the MI/index (analysis II). Due to the skewed distribution of CRP values, log-transformed CRP values (logCRP) were calculated. A sub-analysis was applied, excluding patients with a reported CHD at baseline (N_{pairs} for the analysis = 77).

The most frequently missing data among case–control pairs were on patient-reported smoking status (25/224, 11.2 %) at baseline. In subsequent analyses these patients were considered in a separate category (unknown smoking status) and not excluded. Missing data on ESR (CRP) were less frequent: 1.4 % (0 %) at baseline and during follow-up 9.5 % (8.1 %) at most in case–control pairs. In the 6 months prior to MI, values of CRP were not available for seven pairs (six (5.4 %) cases and one (0.9 %) control). For the analysis of the course of disease activity we applied multiple imputations ($n_{Imputation} = 5$) of missing values. In conditional logistic regression we considered only pairs with observed values of ESR (CRP).

P values <0.05 were regarded as statistically significant without adjustment for multiple testing in univariate comparisons. The matching was applied using the R-package Optmatch of the freely available software R [26]. All other analyses were applied using the Statistical Analysis System (SAS) version 9.4.

Results

Between 1 May 2001 and 31 October 2013, a total of 11,285 patients were enrolled into the RABBIT register (Fig. 1). Within that period of time, rheumatologists reported 115 MIs as a first CV event. Due to the exact matching algorithm matching controls were not found for four male cases (aged 62, 64, 68 and 76 years) with heart failure as a comorbidity. They were matched to controls with heart failure but were allowed to differ from their corresponding case in no more than two comorbidities (differences in hypertension in one pair, in CHD in two pairs, in previous cerebrovascular events in two pairs and in hyperlipoproteinaemia in one pair). For two further male MI cases no appropriate controls were found, due to their comorbidity status. These two patients were excluded. Similarly, patients with non-confirmed MI (n = 3) were excluded. During on-site visits, patients with non-reported MI (n = 2) were identified and included with a matching control. In total 112 eligible case–control pairs remained for the analyses (Fig. 1).

Characteristics of matched pairs and the remainder of the cohort at baseline

Case–control pairs differed significantly from other patients in the RABBIT cohort in all matching parameters except for previous cerebrovascular events. In addition, cases differed from the cohort in most of the non-matching criteria (Table 1). Cases had significantly higher CRP, ESR and DAS28, and more impaired physical function (FFbH) and comorbidities (diabetes and chronic lung or renal disease). Compared to the cohort, MI cases were more often treated with oral glucocorticoids (93.6 % vs. 79.6 %, $p < 0.01$).

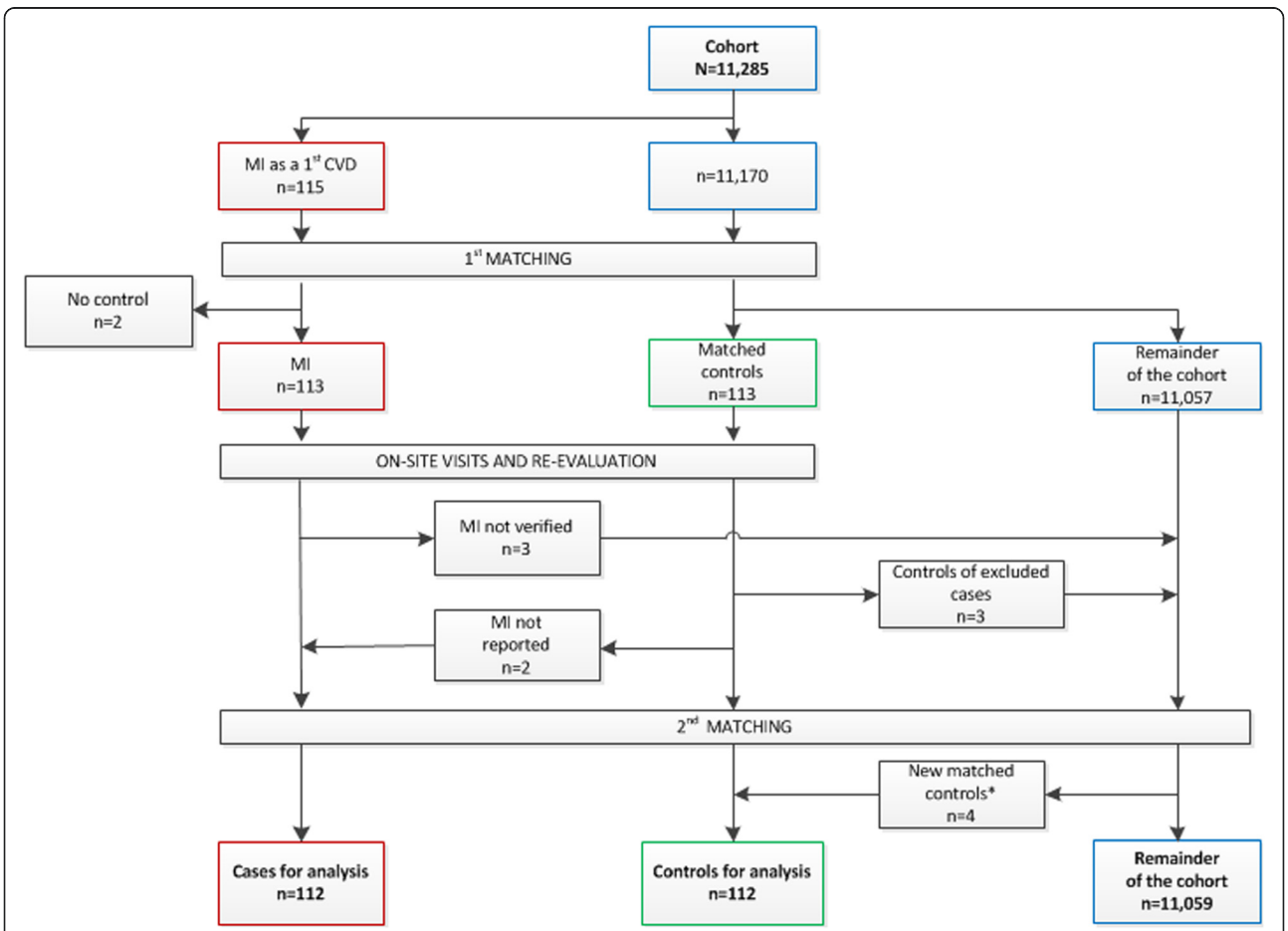

Fig. 1 Flow chart for patient selection. *Because two controls turned out to be cases, four new controls had to be found in the second matching. *MI* myocardial infarction, *CVD* cardiovascular disease

Table 1 Baseline characteristics of cases, controls and the remainder of the RABBIT cohort

	Cases n = 112	Controls n = 112	Remainder of the cohort[a] n = 11,059
Matching criteria			
Sex, male	48 (42.9)	48 (42.9)	2536 (22.9)‡
Age, years, mean (SD)	63.7 (9.1)	63.7 (9.1)	55.9 (12.5)‡
Hypertension	67 (60.4)	68 (60.7)	4102 (37.1)‡
Coronary heart disease	28 (25.2)	26 (23.2)	622 (5.6)‡
Heart failure	7 (6.3)	7 (6.3)	242 (2.2)‡
Previous cerebrovascular event	0 (0)	2 (1.8)	146 (1.3)
Hyperlipoproteinemia	19 (17.1)	18 (16.1)	869 (7.9)‡
Time to MI/index date, month, mean (SD)	31.0 (24.9)	29.5 (23.9)	NA
Unmatched criteria			
Observation time, months, mean (SD)	52.6 (28.6)	60.2 (28.0)†	44.4 (32.7)‡
Disease duration, years, mean (SD)	11.4 (10.6)	11.4 (9.4)	10.0 (9.1)
Rheumatoid factor positive	83 (74.1)	85 (75.9)	7942 (72.1)
CRP, mg/L, mean (SD)	23.5 (27.0)	16.5 (22.1)†	18.4 (26.6)‡
ESR, mm/h, mean (SD)	39.2 (28.9)	30.7 (20.6)†	31.3 (23.0)‡
DAS28, mean (SD)	5.6 (1.3)	5.5 (1.3)	5.2 (1.3)‡
FFbH, mean (SD)	53.1 (24.8)	58.4 (23.3)	63.0 (23.3)‡
Smoking, current	25 (22.3)	19 (17.0)	2355 (21.3)
Smoking, former	35 (31.3)	24 (21.4)	2589 (23.4)
Smoking, never	35 (31.3)	61 (54.5)	4698 (42.5)
Smoking, unknown	17 (15.2)	8 (7.1)	1417 (12.8)
BMI, mean (SD)	28.1 (5.6)	26.7 (4.0)†	26.6 (5.3)‡
BMI ≥30 kg/m^2	34 (30.4)	19 (17.0)†	2514 (22.7)
Diabetes mellitus	26 (23.4)	14 (12.5)†	1075 (9.7)‡
Chronic renal disease	11 (9.9)	8 (7.1)	397 (3.6)‡
COPD	12 (10.8)	13 (11.6)	495 (4.5)‡
No. of previous csDMARDs, mean (SD)	2.6 (1.4)	2.8 (1.5)	2.4 (1.3)
No. of previous bDMARDs, mean (SD)	0.5 (1.0)	0.4 (0.9)	0.3 (0.7)
Oral glucocorticoids	103 (93.6)	87 (77.7)†	8788 (79.6)‡
Glucocorticoids, <5 mg/day	12 (10.9)	29 (25.9)	2981 (27.0)
Glucocorticoids, 5–10 mg/day	64 (58.2)	46 (41.1)	4997 (45.3)‡
Glucocorticoids, ≥10 mg/day	34 (30.9)	37 (33.0)	3048 (27.6)‡
Non-selective NSAIDs	47 (42.0)	39 (34.8)	4260 (38.5)
COX-2 inhibitors	17 (15.2)	23 (20.5)	1699 (15.4)
Any NSAIDs	62 (55.4)	62 (55.4)	5895 (53.3)
No CV treatment[b]	27/75 (36.0)	13/75 (17.3)†	967/4584 (21.1)‡

Values are numbers of patients (%) unless otherwise specified. [a]Patients without myocardial infarction (*MI*) at follow-up and patients who were not matched controls. [b]No cardiovascular (*CV*) treatment: one or more of the reported cardiovascular disease (*CVD*) at baseline (hypertension, coronary heart disease, heart failure or hyperlipoproteinaemia) is not reported as being treated

BMI body mass index, *SD* standard deviation, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *DAS28* disease activity score based on 28 joints, *FFbH* Hannover Functional Status Questionnaire, *COPD* chronic obstructive pulmonary disease, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *bDMARD* biologic DMARD, *NSAID* nonsteroidal anti-inflammatory drug, *COX-2* cyclooxygenase-2, *NA* not applicable. †$P < 0.05$ for comparison with cases (paired *t* test or Mc Nemar´s test). ‡$P < 0.05$ for comparison with cases (unpaired *t* test or chi-squared test)

The enrolment therapies (TNFi, other bDMARDs or csDMARDs) were similarly distributed between cases, controls and the cohort, with 45.5 % of cases on TNFi, 21.4 % on other bDMARDs and 33.1 % on csDMARDs; the corresponding figures among controls were 42.9 %, 21.4 % and 35.7 %, and among the cohort, 50.8 %, 16.2 % and 33.0 %, respectively.

Despite good agreement in the matching criteria, there were significant differences between cases and controls in CRP and ESR, obesity (body mass index (BMI) ≥30 kg/m^2), diabetes and use of glucocorticoids. Importantly, among 75 case–control pairs with at least one baseline CV comorbidity, those patients who developed an MI during follow-up (cases) were significantly less likely to receive medical treatment for their CV comorbidity than their corresponding controls (36 % vs. 17 %, $p < 0.01$, Table 1).

Treatment with DMARDs during follow-up

The number of different DMARD episodes was significantly higher in patients with MI than in matched controls, with one episode in 51 cases (45.5 %), two episodes in 30 cases (26.8 %) and ≥3 episodes in 31 cases (27.7 %); in controls the corresponding figures were 77 (68.8 %), 19 (16.9 %) and 16 (14.3 %), respectively ($p < 0.01$, paired t test).

Persistence with bDMARD enrolment therapy was significantly lower in cases compared to controls ($p < 0.01$, log rank test). In 50 pairs who started simultaneously with a bDMARD, 54.9 % (95 % CI 38.5; 68.5) of the cases compared to 76.5 % (95 % CI 60.4; 86.7) of the controls were still on the enrolment therapy at month 12. In addition, prior to the MI/index date the number of treatment switches (between different DMARDs) was about 53 % higher in cases (Poisson regression 1.53, 95 % CI 1.04; 2.27) than in respective controls. The median duration of a DMARD episode was 7 months in cases (IQR 4–17) and 13 months in controls (IQR 6–23).

Disease activity and inflammation during follow-up

During the first 6 months from baseline, the inflammation markers CRP and ESR were significantly elevated in MI cases (Fig. 2, left; Table 2). In contrast, matched controls achieved similar improvements to the rest of the cohort (Table 2).

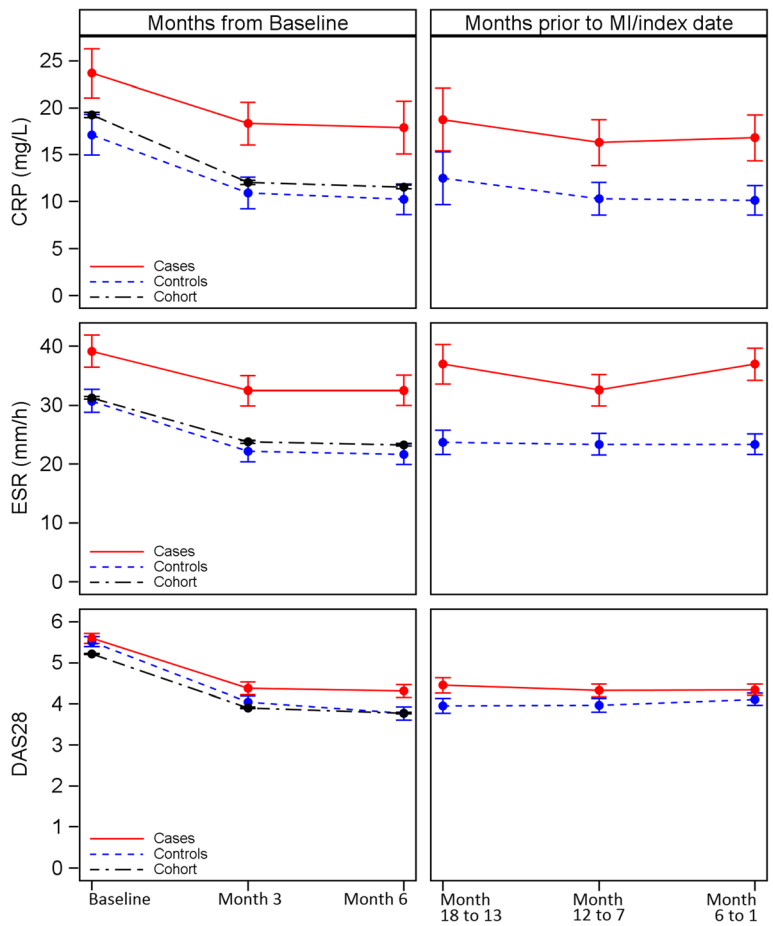

Fig. 2 Development of mean C-reactive protein (*CRP*, mg/L), mean erythrocyte sedimentation rate (*ESR*, mm/h) and mean disease activity score based on 28 joints (*DAS28*) (all presented with *error bars*) at baseline, month 3 and month 6 in cases, matched controls and the remainder of the RABBIT cohort (*left*) and 18 months prior to the myocardial infarction (*MI*)/index date in cases and matched controls (*right*)

Table 2 Development of inflammation and disease activity in cases, controls and the remainder of the RABBIT cohort stratified by enrolment therapy

	Treatment at baseline	Number	Mean at baseline (95 % CI)	Mean at month 3 (95 % CI)	Mean at month 6 (95 % CI)
CRP (mg/L)					
Cases	csDMARD	37	21.6 (12.4; 30.8)	16.3 (9.0; 23.6)	14.3 (7.3; 21.2)
	bDMARD	75	24.4 (18.2; 30.6)	19.5 (14.5; 24.5)	19.4 (13.5; 25.4)
Controls	csDMARD	40	10.2 (6.1; 14.3)	9.8 (5.1; 14.5)	8.0 (4.7; 11.3)
	bDMARD	72	20.0 (14.1; 25.9)	11.4 (7.4; 15.4)	11.0 (6.9; 15.0)
Cohort remainder	csDMARD	3656	14.1 (13.5; 14.8)	11.4 (10.8; 11.9)	11.0 (10.4; 11.5)
	bDMARD	7403	20.75 (20.1; 21.4)	12.9 (12.4; 13.3)	12.7 (12.2; 13.1)
ESR (mm/h)					
Cases	csDMARD	37	30.4 (23.9; 36.9)	27.7 (20.9; 34.5)	31.4 (23.8; 39.0)
	bDMARD	75	43.2 (35.9; 50.4)	36.8 (30.5; 43.2)	34.7 (28.7; 40.7)
Controls	csDMARD	40	26.8 (20.2; 33.4)	22.4 (16.5; 28.2)	19.4 (13.1; 25.7)
	bDMARD	72	32.8 (28.1; 37.5)	22.7 (18.4; 27.1)	22.6 (18.8; 26.4)
Cohort remainder	csDMARD	3656	27.4 (26.7; 28.0)	23.9 (23.3; 24.5)	23.5 (22.8; 24.2)
	bDMARD	7403	33.3 (32.7; 33.8)	24.4 (24.0; 24.9)	24.4 (24.0; 25.0)
DAS28					
Cases	csDMARD	37	5.2 (4.8; 5.5)	4.0 (3.5; 4.4)	3.9 (3.4; 4.3)
	bDMARD	75	5.8 (5.5; 6.1)	4.6 (4.2; 5.0)	4.6 (4.2; 5.0)
Controls	csDMARD	40	4.8 (4.4; 5.3)	4.0 (3.6; 4.5)	3.5 (3.0; 4.0)
	bDMARD	72	5.9 (5.6; 6.1)	4.1 (3.7; 4.4)	3.9 (3.6; 4.3)
Cohort remainder	csDMARD	3656	4.8 (4.7; 4.8)	3.8 (3.7; 3.8)	3.7 (3.6; 3.7)
	bDMARD	7403	5.4 (5.4; 5.5)	4.0 (3.9; 4.0)	3.9 (3.8; 3.9)

Mean values are averaged over five imputations and CI were corrected for the imputation variance
CI confidence interval, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *DAS28* disease activity score based on 28 joints, *bDMARD* biologic disease-modifying antirheumatic drug, *csDMARD* conventional synthetic DMARD

The distinct differences between cases and controls were still observed during the last 6 months (Table 3) and the last 18 months prior to the MI/index date (Fig. 2, right). Notably, no differences were found in DAS28.

The exclusion of patients with underlying CHD at baseline did not alter the course of inflammation and disease activity (Additional file 1).

Evaluation of risk factors for MI

In the univariate logistic comparison of cases and controls there was an increased risk of MI with an increase of CRP per 5 mg/L (OR 1.13 (95 % CI 1.02; 1.22) based on values obtained within 6 months prior to the MI/index date). The association with risk of MI was stronger with log-transformed CRP (1.75 (1.24; 2.46)). Similarly, averaged and log-transformed CRP over the total observation time was significantly associated with risk of MI (1.75 (1.26; 2.43)). Other significant predictors were absence of baseline CV treatment (3.60 (1.28; 12.40)) and glucocorticoids at a dosage of 5–10 mg/day (1.97 (0.98; 4.11) and ≥10 mg/day (3.02 (1.11; 8.25) vs. glucocorticoids <5 mg/day). Previous or current smoking (3.15 (1.47; 7.34)) and unknown smoking status (2.68 (1.06; 7.30)) were significant risk factors compared to not smoking. There was no significant association between increased risk of MI and TNFi or other bDMARD treatment (reference csDMARDs). The adjusted multiple conditional logistic regression revealed no association between risk of MI and treatment with TNFi or other bDMARDs, and no significantly higher risk with glucocorticoid treatment of 5–10 mg/day or ≥10 mg/day (Table 4). There was a strong association between log CRP and MI, but not between raw CRP values and MI, confirming the expected non-linear association. Smoking was confirmed as another significant risk factor.

The risk imposed by elevated CRP remained in a sub-analysis of patients without CHD at baseline, although this was no longer statistically significant for values averaged over the complete observation period (until the MI/index date).

Discussion

We investigated the risk of MI in a large observational cohort study of 11,285 patients with established RA. An in-depth comparison of patients who developed MI with the remaining cohort revealed wide-ranging differences in patient characteristics and exemplified the need for an

Table 3 Characteristics of cases and matched controls within six months before the MI/index date

	Cases n = 105	Controls n = 105	*P* value
CRP, mg/L, mean (SD)	17.6 (25.0)	10.4 (14.6)	0.011
ESR, mm/h, mean (SD)	36.1 (26.5)	22.6 (16.2)	<0.001
DAS28, mean (SD)	4.3 (1.4)	4.0 (1.5)	0.22
Tender joint count, mean (SD)	4.2 (5.0)	4.4 (5.6)	0.71
Swollen joint count, mean (SD)	3.8 (5.0)	4.6 (5.4)	0.17
NRS patient global health 0–10, mean (SD)	5.1 (2.2)	4.9 (2.0)	0.41
FFbH, mean (SD)	58.7 (27.1)	61.0 (24.2)	0.32
TNFi	50 (47.6 %)	55 (52.4 %)	0.41
Other bDMARDs	21 (20.0 %)	23 (21.9 %)	0.66
csDMARDs only	33 (31.4 %)	23 (21.9 %)	0.11
Glucocorticoids, <5 mg/day	44 (41.9 %)	62 (59.6 %)	
Glucocorticoids, 5–10 mg/day	45 (42.9 %)	34 (32.7 %)	0.008
Glucocorticoids, ≥10 mg/day	16 (15.2 %)	8 (7.7 %)	
Non-selective NSAIDs	60 (57.1 %)	62 (59.0 %)	0.77
COX-2 inhibitors	28 (26.7 %)	36 (34.3 %)	0.19
Any NSAID	72 (68.6 %)	78 (74.3 %)	0.33

Case–control pairs with missing C-reactive protein (*CRP*) values were not included in this analysis. Data represent averages of all reported values within 6 months before the myocardial infarction (*MI*)/index date. All values are numbers of patients (%) unless otherwise specified. Tumour necrosis factor inhibitors (*TNFi*), other biologic disease-modifying antirheumatic drugs (*bDMARDs*) and conventional synthetic DMARDS (*csDMARDs*) were counted if the patient received at least one dose of the drug within 6 months before the MI/index date. For nonsteroidal anti-inflammatory drugs (*NSAIDs*) and cyclooxygenase-2 (*COX-2*) inhibitors, data represent use in the 24 months before the MI/index date

SD standard deviation, *ESR* erythrocyte sedimentation rate, *DAS28* disease activity score based on 28 joints, *NRS* numeric rating scale, *FFbH* Hannover Functional Status Questionnaire

Table 4 Multivariate odds ratios for the risk of MI in the nested case–control analysis

	All matched case–control pairs				Subset of cases and controls without CHD			
	I		II		I		II	
	OR	(95 % CI)	OR	(95 % CI)	OR	(95 % CI)	OR	(95 % CI)
Log CRP, prior MI[a]	1.58	(1.07; 2.33)			1.60	(1.04; 2.46)		
Log CRP, total observation[a]			1.47	(1.00; 2.16)			1.44	(0.94; 2.19)
csDMARDs only	Ref.		Ref.		Ref.		Ref.	
TNFi	0.96	(0.41; 2.22)	0.91	(0.40; 2.10)	1.24	(0.49; 3.16)	1.22	(0.49; 3.05)
Other bDMARDs	1.13	(0.34; 3.71)	0.85	(0.27; 2.72)	0.86	(0.19; 3.84)	0.53	(0.13; 2.18)
Glucocorticoids <5 mg/day	Ref.		Ref.		Ref.		Ref.	
5–10 mg/day	1.33	(0.61; 2.89)	1.22	(0.56; 2.68)	1.42	(0.59; 3.43)	1.32	(0.55; 3.17)
≥10 mg/day	2.17	(0.69; 6.81)	1.83	(0.57; 5.85)	2.48	(0.72; 8.59)	2.18	(0.61; 7.79)
No CV treatment[b]	2.76	(0.91; 8.32)	2.66	(0.88; 8.00)	2.42	(0.55; 10.77)	2.66	(0.60; 11.72)
Smoking never	Ref.		Ref.		Ref.		Ref.	
Smoking ever	3.33	(1.45; 7.63)	2.93	(1.29; 6.66)	2.13	(0.85; 5.32)	2.03	(0.69; 5.93)
Smoking status unknown	2.15	(0.82; 5.66)	2.12	(0.80; 5.65)	1.74	(0.62; 4.88)	1.84	(0.65; 5.21)
Diabetes	2.08	(0.84; 5.18)	2.32	(0.94; 5.71)	1.95	(0.68; 5.63)	1.92	(0.67; 5.51)

Case–control pairs with missing C-reactive protein (*CRP*) values were not considered in this analysis. [a]All CRP values were log-transformed. Analysis I: CRP values of the last 6 months prior to the myocardial infarction (*MI*)/index date, Analysis II: averaged CRP values from baseline until the MI/index date. [b]No CV treatment: one or more of the types of reported cardiovascular disease (CVD) at baseline (hypertension, coronary heart disease, heart failure and hyperlipoproteinaemia) is not reported as being treated. Baseline information was used for no CV treatment, smoking and diabetes. All other treatments are values within 6 months before the MI/index date

OR odds ratio, *CI* confidence interval, *CHD* coronary heart disease, *bDMARD* biologic disease-modifying anti-rheumatic drug, *csDMARD* conventional synthetic DMARD, *TNFi* tumour necrosis factor inhibitor

appropriate study design beyond covariate adjustment. To account for these differences we applied a nested case–control design using an extensive matching algorithm that enabled us to link homogeneous case–control pairs.

In a setting that controlled for traditional risk factors, we found that inflammation and smoking were significantly associated with the risk of MI in patients with RA. At baseline, during the first 6 months of follow-up and, more importantly, prior to the MI/index date (Fig. 2), there was a distinct difference in CRP and ESR levels between cases and controls. The significant differences in CRP values remained throughout the period of observation. This result confirms recent findings of others who report that the risk of MI is highest for patients with RA who have high CRP [15]. Similar to the results of the Emerging Risk Factors Collaboration [27], our data suggest a nonlinear increase in risk of MI with rising CRP. Compared with the significantly increased risk of MI with high sensitivity CRP values above 1 mg/L among the general population [28], our data suggest that the complete suppression of systemic inflammation in RA may reduce the risk of MI.

Others have reported lower risk of MI in TNFi responders vs. TNFi non-responders [29, 30]. However, based on the DAS28, patients can respond even when CRP remains high [31], which is in line with our data. Patients with MI presented with similar values of the DAS28 prior to the MI/index date compared to control patients, but with significantly elevated CRP and ESR. We conclude that the evaluation of RA disease activity solely based on the DAS28 may not be sufficient to predict risk of MI. The assessment should also comprise the inflammatory marker CRP, particularly in patients with present CVD or at increased risk of CVD.

We identified comparable treatment with DMARDs in patients who developed MI and in the matched controls at baseline only. During follow-up there were significant differences: rheumatologists switched the bDMARD treatment in cases significantly more often than in respective controls, which indicates continuous attempts to adapt the DMARD treatment. Nevertheless, switches remained ineffective in reducing CRP (Fig. 2). This result suggests that the available RA treatment options for these patients were insufficient. New biologic drugs with alternative targets have been available since 2007. A recent meta-analysis discussed IL-6 inhibition as a possible treatment target to prevent CVD [10]. This may be appropriate for patients not responding to other bDMARDs and with high average CRP. Due to the small number of tocilizumab episodes (13 of 242 cases (5.4 %) and 9 of 184 controls (4.9 %)), we could not study the impact of this treatment separately.

There are conflicting results from previous studies regarding the influence of glucocorticoid treatment on the risk of CVD. Some studies report a risk associated with higher doses of glucocorticoids [32–36]. As expected, in the univariate analysis we observed stronger association between prednisone dose and MI risk than in the multivariate analyses after adjustment for average CRP. These results suggest that the harmful effects of glucocorticoids reported by others are likely partly a result of patient channelling: patients who did not respond to the primary treatment with bDMARDs were consequently treated with glucocorticoids in higher doses. In this matter, concomitant glucocorticoids were used by rheumatologists as a kind of rescue therapy. We observed that the risk remained with glucocorticoid use ≥10 mg/day, but this was not statistically significant and needs to be investigated further in studies with sample sizes larger than ours.

An obvious but rather unexpected risk factor was detected in our data: in patients with a future MI, preexisting CV comorbidities were less frequently treated than in the corresponding control patients. This suggests that insufficient consideration of CV risk in patients with known CV comorbidities is a further risk factor for MI. There seems to be a gap between the knowledge about CV risk in RA, respective recommendations [20, 37] and the daily management of patients. Our findings confirm suboptimal risk management of CVD [38, 39]. One of the weaknesses of this study is the uncertainty about the first-ever MI. In some of the patients the information about the first MI was subsumed in the comorbidity of CHD at baseline. Therefore, we performed a sub-analysis in patients without reported CHD at baseline. We calculated consistent estimates. A strength of this study is the comprehensive on-site validation process, which revealed low numbers of underreported MI in patients with elevated risk of a CV event. However, on-site validation was stopped after reviewing 75 case–control pairs, as very little additional information was obtained on laboratory parameters or CV treatment. The size of the nested case–control study was too small to estimate the separate effects of abatacept, rituximab and tocilizumab [40, 41], or those of methotrexate, leflunomide or other csDMARDs. The total amount of missing data during follow-up was low (<10 %). Nevertheless, we applied multiple imputations but the impact on estimates was statistically and clinically insignificant when compared to an analysis of pairs with observed data only.

Conclusion

In conclusion, our results underline the importance of a treat-to-target approach, which has to take the global disease activity and CRP into account. As inflammation is the link to CVD, we consider CRP the most reliable marker to assess the risk of MI. For many patients it

seems less important by which DMARD treatment (TNFi, other bDMARD or csDMARD) the treatment target is reached. In some patients however, the available treatment options were insufficient or insufficiently used. This adds to the evidence indicating the necessity of tight disease control and adequate treatment of comorbidities.

Additional file

Additional file 1: Figure S1. Course of RA disease represented by CRP, ESR and DAS28, and restricted to patients without coronary heart disease at baseline. (DOCX 128 kb)

Abbreviations

bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COX-2, cyclooxygenase-2; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, cardiovascular; CVD, cardiovascular disease; DAS28, disease activity score based on 28 joints; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; FFbH, Hannover Functional Status Questionnaire; IL, interleukin; IQR, interquartile range; logCRP, log-transformed C-reactive protein; MI, myocardial infarction; NRS, numeric rating scale; NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; RABBIT, Rheumatoid Arthritis Observation of Biologic Therapy; SD, standard deviation; SNP, single nucleotide polymorphism; TNF, tumour necrosis factor

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Authors' contributions

YM, AZ, KG, AR, JL and AS had full access to all data in this study and take responsibility for data integrity and accuracy of the analysis. Study concept and design: AZ, JL and AS. Acquisition of the data: YM, JK, KR, AL and SZ. Analysis and interpretation of the data: YM, AZ, AR, JL and AS. Drafting the manuscript: YM. Critical revision of the manuscript for important intellectual content: YM, AZ, JK, KR, AL, SZ, KG, AR, JL and AS. Obtaining funding: AZ, JL and AS. Study supervision: AZ, JL, AS and JK. All authors read and approved the manuscript.

Competing interests

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Ethical approval and consent to participate

The study protocol of RABBIT was approved by the ethics committee of the Charité University Medicine Berlin. Prior to enrolment, all patients have to give their written informed consent.

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References

1. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365:2205–19.
2. Meune C, Touze E, Trinquart L, Allanore Y. High risk of clinical cardiovascular events in rheumatoid arthritis: levels of associations of myocardial infarction and stroke through a systematic review and meta-analysis. Arch Cardiovasc Dis. 2010;103:253–61.
3. Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis. 2012;71:1524–9.
4. del Rincon I, Freeman GL, Haas RW, O'Leary DH, Escalante A. Relative contribution of cardiovascular risk factors and rheumatoid arthritis clinical manifestations to atherosclerosis. Arthritis Rheum. 2005;52:3413–23.
5. Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation. 2003;108:2957–63.

6. Gonzalez A, Maradit Kremers H, Crowson CS, Ballman KV, Roger VL, Jacobsen SJ, O'Fallon WM, Gabriel SE. Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients? Ann Rheum Dis. 2008;67:64–9.
7. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? Atherosclerosis. 2000;148:209–14.
8. Skeoch S, Bruce IN. Atherosclerosis in rheumatoid arthritis: is it all about inflammation? Nat Rev Rheumatol. 2015;11:390–400.
9. Fordjour PA, Wang Y, Shi Y, Agyemang K, Akinyi M, Zhang Q, Fan G. Possible mechanisms of C-reactive protein mediated acute myocardial infarction. Eur J Pharmacol. 2015;760:72–80.
10. The I. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. Lancet. 2012;379:1214–24.
11. Zhang J, Chen L, Delzell E, Muntner P, Hillegass WB, Safford MM, Millan IY, Crowson CS, Curtis JR. The association between inflammatory markers, serum lipids and the risk of cardiovascular events in patients with rheumatoid arthritis. Ann Rheum Dis. 2014;73:1301–8.
12. Ajeganova S, Andersson ML, Frostegard J, Hafstrom I. Disease factors in early rheumatoid arthritis are associated with differential risks for cardiovascular events and mortality depending on age at onset: a 10-year observational cohort study. J Rheumatol. 2013;40:1958–66.
13. Gonzalez-Gay MA, Gonzalez-Juanatey C, Lopez-Diaz MJ, Pineiro A, Garcia-Porrua C, Miranda-Filloy JA, Ollier WE, Martin J, Llorca J. HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. Arthritis Rheum. 2007;57:125–32.
14. Goodson NJ, Symmons DP, Scott DG, Bunn D, Lunt M, Silman AJ. Baseline levels of C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis: a ten-year follow up study of a primary care-based inception cohort. Arthritis Rheum. 2005;52:2293–9.
15. Navarro-Millan I, Yang S, DuVall SL, Chen L, Baddley J, Cannon GW, Delzell ES, Zhang J, Safford MM, Patkar NM, Mikuls TR, Singh JA, Curtis JR. Association of hyperlipidaemia, inflammation and serological status and coronary heart disease among patients with rheumatoid arthritis: data from the National Veterans Health Administration. Ann Rheum Dis. 2016;75:341–7.
16. Wallberg-Jonsson S, Johansson H, Ohman ML, Rantapaa-Dahlqvist S. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. J Rheumatol. 1999;26:2562–71.
17. Innala L, Moller B, Ljung L, Magnusson S, Smedby T, Sodergren A, Ohman ML, Rantapaa-Dahlqvist S, Wallberg-Jonsson S. Cardiovascular events in early RA are a result of inflammatory burden and traditional risk factors: a five year prospective study. Arthritis Res Ther. 2011;13:R131.
18. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2005;52:722–32.
19. Arts EE, Fransen J, den Broeder AA, Popa CD, van Riel PL. The effect of disease duration and disease activity on the risk of cardiovascular disease in rheumatoid arthritis patients. Ann Rheum Dis. 2015;74:998–1003.
20. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, McInnes IB, Haentzschel H, Gonzalez-Gay MA, Provan S, Semb A, Sidiropoulos P, Kitas G, Smulders YM, Soubrier M, Szekanecz Z, Sattar N, Nurmohamed MT. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis. 2010;69:325–31.
21. Mantel A, Holmqvist M, Nyberg F, Tornling G, Frisell T, Alfredsson L, Askling J. Risk factors for the rapid risk increase of acute coronary events in patients with new-onset rheumatoid arthritis: a nested case–control study. Arthritis Rheumatol. 2015;67:2845–54.
22. Radovits BJ, Popa-Diaconu DA, Popa C, Eijsbouts A, Laan RF, van Riel PL, Fransen J. Disease activity as a risk factor for myocardial infarction in rheumatoid arthritis. Ann Rheum Dis. 2009;68(8):1271–6.
23. Zink A, Listing J, Kary S, Ramlau P, Stoyanova-Scholz M, Babinsky K, von Hinueber U, Gromnica-Ihle E, Wassenberg S, Antoni C, Herzer P, Kekow J, Schneider M, Rau R. Treatment continuation in patients receiving biological agents or conventional DMARD therapy. Ann Rheum Dis. 2005;64:1274–9.
24. Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, Zink A. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA. 2009;301:737–44.
25. Lautenschlager J, Mau W, Kohlmann T, Raspe HH, Struve F, Bruckle W, Zeidler H. Comparative evaluation of a German version of the Health Assessment Questionnaire and the Hannover Functional Capacity Questionnaire. Z Rheumatol. 1997;56:144–55.
26. Hansen BB, Klopfer SO. Optimal full matching and related designs via network flows. J Comput Graph Stat. 2006;15:609–27.
27. Emerging Risk Factors C, Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, Danesh J. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010;375:132–40.
28. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med. 2002;347:1557–65.
29. Dixon WG, Watson KD, Lunt M, Hyrich KL, British Society for Rheumatology Biologics Register Control Centre C, Silman AJ, Symmons DP, British Society for Rheumatology Biologics R. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2007;56:2905–12.
30. Ljung L, Rantapaa-Dahlqvist S, Jacobsson LT, Askling J. Response to biological treatment and subsequent risk of coronary events in rheumatoid arthritis. Ann Rheum Dis. 2016;doi: 10.1136/annrheumdis-2015-208995. [Epub ahead of print].
31. Graf J, Scherzer R, Grunfeld C, Imboden J. Levels of C-reactive protein associated with high and very high cardiovascular risk are prevalent in patients with rheumatoid arthritis. PloS One. 2009;4, e6242.
32. Greenberg JD, Kremer JM, Curtis JR, Hochberg MC, Reed G, Tsao P, Farkouh ME, Nasir A, Setoguchi S, Solomon DH, Investigators C. Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. Ann Rheum Dis. 2011;70:576–82.
33. Zhang J, Xie F, Yun H, Chen L, Muntner P, Levitan EB, Safford MM, Kent ST, Osterman MT, Lewis JD, Saag K, Singh JA, Curtis JR. Comparative effects of biologics on cardiovascular risk among older patients with rheumatoid arthritis. Ann Rheum Dis. 2016;doi: 10.1136/annrheumdis-2015-207870. [Epub ahead of print].
34. Avina-Zubieta JA, Abrahamowicz M, De Vera MA, Choi HK, Sayre EC, Rahman MM, Sylvestre MP, Wynant W, Esdaile JM, Lacaille D. Immediate and past cumulative effects of oral glucocorticoids on the risk of acute myocardial infarction in rheumatoid arthritis: a population-based study. Rheumatology. 2013;52:68–75.
35. Davis III JM, Maradit Kremers H, Crowson CS, Nicola PJ, Ballman KV, Therneau TM, Roger VL, Gabriel SE. Glucocorticoids and cardiovascular events in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum. 2007;56:820–30.
36. del Rincon I, Battafarano DF, Restrepo JF, Erikson JM, Escalante A. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. Arthritis Rheumatol. 2014;66:264–72.
37. Baillet A, Gossec L, Carmona L, Wit M, van Eijk-Hustings Y, Bertheussen H, Alison K, Toft M, Kouloumas M, Ferreira RJ, Oliver S, Rubbert-Roth A, van AS, Dixon WG, Finckh A, Zink A, Kremer J, Kvien TK, Nurmohamed M, van der Heijde D, Dougados M. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. Ann Rheum Dis. 2016;doi: 10.1136/annrheumdis-2016-209233. [Epub ahead of print].
38. Gossec L, Salejan F, Nataf H, Nguyen M, Gaud-Listrat V, Hudry C, Breuillard P, Dernis E, Boumier P, Durandin-Truffinet M, Fannius J, Fechtenbaum J, Izou-Fouillot MA, Labatide-Alanore S, Lebrun A, LeDevic P, LeGoux P, Sacchi A, Salliot C, Sparsa L, d'Andre FL, Dougados M, Network RR. Challenges of cardiovascular risk assessment in the routine rheumatology outpatient setting: an observational study of 110 rheumatoid arthritis patients. Arthritis Care Res. 2013;65:712–7.
39. Desai SS, Myles JD, Kaplan MJ. Suboptimal cardiovascular risk factor identification and management in patients with rheumatoid arthritis: a cohort analysis. Arthritis Res Ther. 2012;14:R270.
40. Provan SA, Berg IJ, Hammer HB, Mathiessen A, Kvien TK, Semb AG. The impact of newer biological disease modifying anti-rheumatic drugs on cardiovascular risk factors: a 12-month longitudinal study in rheumatoid arthritis patients treated with rituximab, Abatacept and Tociliziumab. PloS One. 2015;10, e0130709.
41. Rao VU, Pavlov A, Klearman M, Musselman D, Giles JT, Bathon JM, Sattar N, Lee JS. An evaluation of risk factors for major adverse cardiovascular events during tocilizumab therapy. Arthritis Rheumatol. 2015;67:372–80.

3 Diskussion

In der vorliegenden Arbeit wurden wichtige Ergebnisse einer großen klinisch-epidemiologischen Kohortenstudie zusammengefasst, die seit 2001 die Sicherheit und Wirksamkeit neuer Therapien in der Behandlung der rheumatoiden Arthritis untersucht. Ausgangspunkt des RABBIT-Registers war die Entwicklung und Marktzulassung biotechnologisch hergestellter Substanzen, die auf vollkommen neuen Wirkprinzipien beruhen. Im Gegensatz zu den bis dahin angewandten synthetischen Therapien, deren Wirksamkeit bei der rheumatoiden Arthritis eher zufällig gefunden und pharmakologisch nie ganz erklärt worden war, wusste man hier sehr genau, an welchem Zytokin die jeweilige Substanz ansetzt und konnte damit gezielt einzelne Abschnitte des pathophysiologischen Ablaufs der Entzündungsreaktion beeinflussen. Die beiden ersten zur Zulassung gelangten Substanzen waren Tumor-Nekrose-Faktor-α (TNFα) Inhibitoren, die entweder als Fusionsprotein (Etanercept) oder als monoklonaler Antikörper (Infliximab) das bei der rheumatoiden Arthritis vermehrt gebildete TNFα binden und damit die Entzündung unterdrücken. Die in den ersten klinischen Studien untersuchte gezielte Zytokinhemmung zeigte eine bis dato nicht gekannte Wirksamkeit im Hinblick auf die Verringerung der Krankheitsaktivität. Da TNFα aber in vielen physiologischen Prozessen eine relevante Bedeutung zukommt, bestand zugleich die Befürchtung, sich mit der starken Immunsuppression schwerwiegende unerwünschte Wirkungen wie inzidente Tumore oder schwere Infektionen zu erkaufen. In der Folge wurde von der europäischen rheumatologischen Dachorganisation EULAR die Einrichtung sogenannter Biologikaregister empfohlen mit dem Ziel, die Therapiesicherheit der neuen Substanzen mit epidemiologischen Methoden und unter Berücksichtigung von krankheitsspezifischen Einflussfaktoren wie Krankheitsaktivität, Schweregrad der Erkrankung und Komorbiditäten zu untersuchen [45]. In dieser Situation erreichten die Deutsche Gesellschaft für Rheumatologie und das Deutsche Rheuma-Forschungszentrum (DRFZ), dass die Her-

steller der neuen Medikamente sich zu einer langfristigen Förderung einer unabhängigen Beobachtung der Sicherheit und Wirksamkeit der neuen Substanzen unter Alltagsbedingungen bereit erklärten. Der gemeinsame Vertrag sichert die volle akademische Freiheit für die Studienleitung am DRFZ sowie eine langfristige Finanzierung, die eine Laufzeit der Beobachtungsstudie über mehrere Jahrzehnte ermöglicht. Dem zum Start des Registers dreiseitigen Vertrag zwischen zwei Herstellern und dem DRFZ sind inzwischen zehn weitere Firmen jeweils mit der Marktzulassung von insgesamt 20 innovativen Substanzen beigetreten. Hierzu gehören auch Nachahmerprodukte nach dem Patentablauf der Originalsubstanzen, die sogenannten Biosimilars und neue zielgerichtete synthetische Therapien, die sogenannten targeted synthetic (ts)DMARDs. Die europäische Arzneimittelbehörde EMA unterstützt die Beobachtung neuer Substanzen in Registern seit 2007, indem sie allen Firmen, die die Marktzulassung für ein Medikament zur Behandlung der rheumatoiden Arthritis beantragen, die Teilnahme an den drei größten europäischen Registern, also dem deutschen, britischen und schwedischen Register, im Rahmen der Pharmakovigilanzpläne nachhaltig empfiehlt.

Auf diese Weise ist die einzigartige Situation entstanden, dass zu einem Krankheitsbild alle zugelassenen Medikamente einer sehr langfristigen, prospektiven und vergleichenden Beobachtung unterzogen werden können. Solche Vergleiche sind üblicherweise nur mit Hilfe von Sekundärdaten beispielsweise von Krankenkassen oder Kassenärztlichen Vereinigungen möglich. Diese Daten haben neben den Vorteilen der schnellen und einfachen Verfügbarkeit, hohen Patientenzahlen und (meist) guten Abdeckung der Gesamtbevölkerung jedoch auch große Schwächen. Da die Daten nicht zu Forschungszwecken gesammelt wurden, fehlen wichtige klinische Parameter, die zur Einschätzung des Schweregrades der Erkrankung notwendig sind, die Validität der Diagnosen ist nicht gesichert bzw. bedarf der Entwicklung aufwändiger Algorithmen und es fehlen sämtliche patienten-berichteten Outcomes, die gerade in der Rheumatologie

großen Stellenwert besitzen. Besonders kritisch ist aber, dass der bei entzündlich rheumatischen Erkrankungen deutliche Einfluss der Krankheitsaktivität bei der Auswertung von Sekundärdaten vernachlässigt werden muss. Analysen wie die hier vorgelegten erfordern zwingend Primärdatenerhebungen unter Einbeziehung krankheitsspezifischer Messinstrumente der Entzündungsaktivität. Durch die steigenden Dokumentationspflichten der Ärzte ist aber auch die Primärdatenerhebung mit dem großen Nachteil behaftet, dass die Datenerhebung für das Register zusätzlich zur bereits geleisteten Dokumentation geschehen muss. Durch die Anforderungen im Praxisalltag ergeben sich auch hier häufig Erhebungslücken, denen nur durch sorgfältiges Monitoring zu begegnen ist. Um eine hohe Datenqualität bei möglichst geringer Belastung des Arztes zu erreichen, bedarf es gut definierter Routinen im Monitoring, damit unverzichtbare Parameter möglichst vollständig verfügbar gemacht werden. Durch den mehrstufigen Monitoringprozess in RABBIT liegt beispielsweise der Anteil der fehlenden Daten zur Krankheitsaktivität bei nur 3%. Für die gründliche Analyse der Arzneimittelsicherheit müssen über das reguläre Monitoring hinaus Details der aufgetretenen schwerwiegenden unerwünschten Ereignisse erhoben werden und bei Nichtvorhandensein von Epikrisen oder Unkenntnis des Rheumatologen über den Verbleib der Patienten weitere Schritte (auch unter Einbeziehung der Behörden) unternommen werden. So zeigte jüngst eine in Britisch Columbia (Kanada) durchgeführte Analyse von Labordaten, Krankenhausakten und Sterberegisterdaten, dass die Zahl der Todesfälle nach schwerwiegenden Infektionen deutlich unterschätzt wird, wenn nur die hospitalisierten (Todes-)Ereignisse gezählt werden [46]. Im Falle der nordischen Register (Dänemark, Norwegen, Schweden, Finnland und Island) ist eine Zusammenführung der Daten klinischer Register mit anderen nationalen Registern (bspw. zu Malignomen, Todesursachen oder Geburtsdefekten) möglich. Trotz der zum Teil erheblichen logistischen und methodischen Herausforderungen bei der Zusammenführung von Daten aus verschiedenen Datenquellen können

hiermit klinische Daten valide ergänzt und komplettiert werden [47]. In Deutschland müssen wir durch die meist fehlende Möglichkeit der Datenzusammenführung verschiedener Datenquellen hohe Anforderungen an die Datenqualität der Primärerhebungen stellen, um die bei Beobachtungsdaten häufig vorkommenden Lücken und Verzerrungen bestmöglich zu minimieren.

Wenn man die Ergebnisse aus 18 Jahren RABBIT-Register zusammenfasst, so kann heute im Hinblick auf die bei Beginn der Zulassung hauptsächlichen Besorgnisse weitgehend Entwarnung gegeben werden. Zumindest für die bereits seit Längerem auf dem Markt befindlichen Biologika kann man heute mit hoher Sicherheit sagen, dass die gezielte Unterdrückung wesentlicher Bestandteile des Immunsystems nicht zu gravierenden Folgen wie Erhöhung des Tumorrisikos oder Entstehung neuer Autoimmunerkrankungen führt. Auch andere Risiken können aufgrund der Daten aus RABBIT nun quantifiziert werden: Das wesentliche Risiko ist eine Erhöhung der Inzidenz schwerwiegender Infektionen um etwa 60%. Wie mit Hilfe des RABBIT Risikoscores für schwerwiegende Infektionen gezeigt werden konnte, muss diese Risikoerhöhung jedoch im Kontext anderer, durch die wirksame Unterdrückung der Krankheitsaktivität erreichter, Wirkungen gesehen werden. So kann durch das nach Beginn einer Biologika-Therapie in der Regel rasch mögliche Absetzen oder die Dosisreduktion von Glukokortikoiden ein Infektionsrisiko erreicht werden, das geringer ist als es unter einer konventionell synthetischen DMARD-Therapie mit begleitend gegebenen Glukokortikoiden zu erwarten wäre. Die Zusammenschau der verschiedenen Risiken eines Patienten –von individuellen Merkmalen wie Alter oder Komorbidität bis zu Begleitmedikation und Infektionsanamnese – ermöglicht es, ein individualisiertes Risikoprofil für jeden einzelnen Patienten zu gewinnen und personalisierte Therapieentscheidungen zu fällen. Die Tatsache, dass der RABBIT Risiko-Rechner für schwerwiegende Infektionen im Internet rund 30.000 Mal pro Jahr aufgerufen wird, zeigt seine breite Verwendung in der täglichen rheumatologi-

schen Praxis. Auch Patienten können so in die Therapieentscheidung einbezogen werden, indem verschiedene Therapieoptionen simuliert werden.

Eine weitere sehr eindrückliche Erkenntnis aus dem RABBIT-Register ist die große Bedeutung der unzureichend kontrollierten Krankheitsaktivität. Der Vergleich von Patienten mit kontinuierlich hoher oder kontinuierlich niedriger Krankheitsaktivität über längere Zeiträume zeigte deutlich, dass eine mangelhafte Unterdrückung der Entzündungsaktivität mit bis zu zehn verlorenen Lebensjahren sowie einem hohen Risiko für Schlaganfall, Herzinfarkt oder Verschlechterung einer Herzinsuffizienz verbunden ist. Diese Erkenntnis unterstreicht die Bedeutung einer zielgerichteten Therapie, die als „treat-to-target"-Strategie im Rahmen klinischer Versuche nachgewiesen worden ist [48] und nun mit den Ergebnissen aus RABBIT auch mit Beobachtungsdaten eindrucksvoll gezeigt werden konnte.

Die dritte wichtige Erkenntnis aus RABBIT ist, dass sich große Langzeit-Beobachtungsstudien gut dazu eignen, sehr seltene Risiken zu quantifizieren und in den Kontext vergleichbarer Therapien zu stellen. Die signifikante und relevante Risikoerhöhung für Perforationen des unteren Darmtraktes unter IL6-Blockade, zusammen mit der veränderten klinischen Präsentation und hohen Letalität, macht deutlich, dass solche Beobachtungsstudien auch geeignet sind, Klinikern Hinweise auf besondere Risikokonstellationen und deren rasche Erkennung zu geben. Aber auch Patienten, die mit diesen Substanzen behandelt werden, profitieren von dem Wissen, dass bestimmte Symptome der erhöhten Aufmerksamkeit bedürfen und Laborwerte wie z.B. C-reaktives Protein, unter dieser Therapie keine Aussagekraft haben und somit als diagnostische Marker ungeeignet sind.

Schließlich können mit solchen umfassenden Beobachtungsstudien auch Untersuchungen nachgebildet werden, die niemals experimentell hergestellt werden könnten. Die im

Tierversuch festgestellte protektive Wirkung der TNF-Blockade hinsichtlich der Entwicklung einer Sepsis und des Versterbens daran ließ sich in keinem randomisierten klinischen Versuch abbilden, da Infektionen bei Menschen aus ethischen Gründen nicht experimentell herbeigeführt werden können. Die Verabreichung von TNF-Inhibitoren zum Zeitpunkt einer bereits eingetretenen Sepsis ist aber zu spät, um die Entzündungskaskade noch wirksam unterdrücken zu können [49].

In RABBIT konnte nun gezeigt werden, dass – analog zum Tierexperiment – eine wirksame Immunsuppression durch TNFi und andere Biologika zum Zeitpunkt der Infektion das Risiko für Morbidität und Mortalität durch Sepsis signifikant verringert. Welche klinischen Konsequenzen diese Erkenntnis für das Verhalten bei Infektion oder vor geplanten Operationen hat, wird sich in Zukunft zeigen. Zumindest wird inzwischen deutlich kritischer diskutiert, ob im Falle einer schwerwiegenden Infektion reflexhaft die Therapie abgesetzt werden muss, oder ob das lange Zeit empfohlene Absetzen einer Biologikatherapie vor geplanten Operationen notwendig ist [50].

3.1 Stärken des Register-Ansatzes und Beispiele für weitere Erkenntnisse aus RABBIT

In dieser Arbeit wurden wichtige Ergebnisse aus RABBIT mit dem Fokus Arzneimittelsicherheit zusammengefasst. Die Möglichkeiten einer solchen prospektiven Langzeitbeobachtung gehen noch weit darüber hinaus. So konnten mit RABBIT innovative Erkenntnisse im Hinblick auf die Wirksamkeit unterschiedlicher Therapien und zu Einflussfaktoren hierauf gewonnen werden. Durch die Beobachtung der unter Alltagsbedingungen verabreichten Therapien und Therapiekombinationen konnten durch Survival- und Wirksamkeitsanalysen auch Ergebnisse über den Einfluss vorheriger Therapien (bzw. deren Versagen) [51] und den Stellenwert und die Wirksamkeit verschiedener Komedikationen gewonnen werden. Wir zeigten, dass nicht nur Methotrexat ein geeigneter syn-

thetischer Kombinationspartner von TNF-Inhibitoren und Rituximab ist, sondern ebenso das nicht für diese Kombination zugelassene Leflunomid [52, 53], da auch hierunter Wirksamkeit und Therapiekontinuität, verglichen mit einer Monotherapie, deutlich besser waren. Da randomisierte klinische Studien fehlen, kommt diesem Ergebnis für die Behandlung von chronisch kranken Patienten mit mehreren Therapieversagen in der Vorgeschichte und zum Teil substantieller Komorbidität große Bedeutung zu.

Auch im Hinblick auf weitere, die Therapiewirksamkeit beeinflussende, Faktoren konnten aus RABBIT wichtige Erkenntnisse gewonnen werden. So zeigte sich bei Patienten unter einer Rituximab Therapie ein deutlich besseres Ansprechen, bei ACPA oder RF-positiven Patienten im Vergleich zu seronegativen Patienten [53]. Die inzwischen vorliegenden umfangreichen Längsschnittdaten mit mehr als 70.000 Patientenjahren erlauben es, den Einfluss weiterer Patientencharakteristika auf die Wirksamkeit der Therapien zu untersuchen. Hier konnte gezeigt werden, dass Übergewicht die Wirksamkeit der meisten Therapien signifikant verringert, wobei ein zusätzlicher geschlechtsspezifischer Zusammenhang besteht mit einem größeren Einfluss der Adipositas bei Frauen [54]. Ziel dieser umfassenden Analysen patientenspezifischer und klinischer Parameter ist es, eine bessere Prädiktion des Therapieansprechens zu erreichen und in Zukunft frühzeitig im Krankheitsverlauf gezieltere und individualisierte Therapieentscheidungen, einschließlich der Wahl optimaler Therapiekombinationen, zu ermöglichen.

Durch die Analyse von Daten zur Lebensqualität [55], zu den Differenzen zwischen Patienten in klinischen Studien und in der Versorgungspraxis [20] oder zu der Bedeutung prognostisch ungünstiger Faktoren [56] konnten weitere wichtige Erkenntnisse für die Prognose der Erkrankung und Therapiesteuerung gewonnen werden.

Momentan untersuchen wir mit Daten des RABBIT Registers, ob auch ein höheres Alter über 70 Jahre als unabhängiger Einflussfaktor die Therapiewirksamkeit mindert und ob

es spezifische Aspekte bezüglich der Therapiesicherheit bei dieser Patientengruppe gibt, auf die besonders zu achten wäre. Diesbezüglich sind keine Daten aus den randomisierten klinischen Studien zu erwarten, obwohl die Bedeutung für den klinischen Alltag enorm ist und durch den demographischen Wandel zunehmen wird.

3.2 Schwächen und Limitationen des Registeransatzes

Die zentrale Schwäche von Beobachtungsdaten von Krankheits- und Therapieverläufen liegt in dem nicht-randomisierten Studienansatz. Wenn es um den direkten Vergleich der Wirksamkeit unterschiedlicher Therapien geht, ist ein randomisierter Head-to-Head-Vergleich überlegen, weil er nicht mit einem Indikationsbias umgehen muss. Allerdings sind solche Studien aufwändig und kaum geeignet, belastbare Aussagen zur Arzneimittelsicherheit zu gewinnen. Bei der Analyse von Beobachtungsdaten sind die Fehlerquellen durch Attrition bzw. Selektionsbias (Indikationsbias) besonders zu berücksichtigen, da sowohl die Einleitung einer Therapie als auch das Absetzen einer bestehenden Therapie (meist) auf der Entscheidung der behandelnden Ärzte oder einer gemeinsamen Entscheidung mit dem Patienten beruhen. Mögliche Ansätze, um dem Indikationsbias zu begegnen, sind propensity score Methoden [57], die es ermöglichen, weitgehend vergleichbare Gruppen von Patienten zu bilden. Auch die Selektion der Therapie von Patienten aufgrund ihrer Komorbiditäten muss bei der Analyse berücksichtigt werden. Dies kann beispielsweise durch ein möglichst exaktes Matching einzelner Patienten geschehen, die sich nur in der im Fokus stehenden Eigenschaft unterscheiden. In einer sehr großen Kohorte wie dem RABBIT Register ist dies gut möglich [58]. Nicht garantiert werden kann hingegen, dass die teilnehmenden Ärzte hinsichtlich ihres Patienten- und Therapiespektrums vollständig repräsentativ für die rheumatologische Versorgung in Deutschland sind. Insofern bilden die Register zwar ein wesentlich breiteres und aussagefähigeres Spektrum von Patienten ab als randomisierte klinische Studien, sind aber

ebenfalls mit Selektionseffekten behaftet.

Zu den Limitationen des Ansatzes gehört weiterhin, dass die in dieser Arbeit vorgestellten Ergebnisse ausschließlich mit Daten aus Deutschland gewonnen wurden. Die Analysen hatten vorrangig häufige Ereignisse wie Infektionen oder solche mit ungewöhnlich großer Risikoerhöhung, wie im Falle der Perforationen des unteren Darmtraktes unter der Therapie mit Tocilizumab, im Fokus. Inwieweit andere sehr seltene Ereignisse von einzelnen Registern ausreichend untersucht werden können, ist fraglich. Zur Analyse seltener Ereignisse bedarf es der Intensivierung internationaler Kooperationen. Mit der registerübergreifenden, gemeinsamen Analyse des Auftretens maligner Melanome [36] und Lymphome [37] von jeweils elf bzw. zwölf Registern wurde hier ein wichtiger Schritt unternommen. Während der Zusammenarbeit wurde aber deutlich, dass unter anderem unterschiedliche Erhebungsmodalitäten, Datenquellen und bevölkerungsbezogene Hintergrundrisiken eine große Herausforderung für die Analyse darstellen. Ein reines Pooling der Daten würde eine Verzerrung in Richtung der Ergebnisse desjenigen Registers mit dem größten Effekt und/oder den höchsten Patientenzahlen bewirken. Die gemeinsame Analyse muss daher andere, z.B. metaanalytische, die Hetorogenität einbeziehende Methoden [59] einsetzen. Doch auch hier können (zu) große Unterschiede im Kohortendesign die Ergebnisse verzerren. Aus diesem Grund gibt es seit einigen Jahren intensive Bestrebungen, zumindest im europäischen Rahmen eine Harmonisierung der erhobenen Daten und deren Instrumente zu erreichen, um zumindest einige der Störquellen zu beseitigen [60]. Die Arbeitsgruppe „Register und Beobachtungsstudien“ der EULAR, der das RABBIT-Register angehört, hat hier eine Vorreiterrolle. Sie veranstaltet seit mehr als 15 Jahren regelmäßige Treffen und alle zwei Jahre einen eigenen europäischen Kongress. Diese umfangreichen internationalen Bemühungen dienen der gemeinsamen Zielsetzung, die in den verschiedenen Registern gewonnenen Daten optimal zu nutzen, um auch für seltene Risiken oder sehr spezifische Risikogruppen be-

lastbare Aussagen treffen zu können. Dies dient einer besseren klinischen Entscheidungsfindung und einer höheren Arzneimittelsicherheit für eine große Zahl chronisch kranker Patienten.

3.3 Fazit und Ausblick

Die Diskussion der Ergebnisse abschließend, kann festgehalten werden, dass sorgfältig durchgeführte klinisch-epidemiologische Langzeitkohorten („Register“) zur Sicherheit und Wirksamkeit von Therapien unter Alltagsbedingungen unverzichtbare Bestandteile einer evidenzbasierten Therapie und klinischen Entscheidungsfindung sind. Die hier vorgestellten Erkenntnisse sind klinisch relevant und hätten weder durch randomisierte klinische Studien noch durch die Analyse von Routinedaten gewonnen werden können.

Dieser Erkenntnis folgend, muss mit dem Blick in die Zukunft eine Modernisierung der bislang in RABBIT noch rein papierbasierten Datenerhebung stattfinden. Durch den deutlich höheren Dokumentationsaufwand, der heute bereits in der normalen ärztlichen Alltagsroutine erfolgt, muss der Aufwand für zusätzliche Erhebungen minimiert werden. Auch das personal- und kostenintensive Monitoring der Papierversion ist auf die Dauer kaum mehr zu leisten. Seit 2015 wurden im DRFZ zwei webbasierte Registerplattformen etabliert: RABBIT-SpA für axiale Spondyloarthritiden und Psoriasisarthritis [24] sowie Rhekiss [25], ein Register für die Erfassung des Verlaufs und Outcome von Kinderwunsch und Schwangerschaften bei Patientinnen mit entzündlich rheumatischen Erkrankungen. In jedes der Register wurden bereits mehr als 1.000 Patienten eingeschlossen. Es wurden Routinen in den Erhebungsprozess eingebunden, die die komplexen Anforderungen an das Monitoring (s. oben, hohe Datenqualität bei möglichst geringer zusätzlicher Belastung des Arztes) erfüllen. Derzeit wird evaluiert, wie gut die

Performance der web-basierten Register ist, auch im Vergleich zu den bislang bei RABBIT etablierten Prozessen zur Sicherung der Datenqualität.

Mit dem Wandel des Gesundheitssystems, der Digitalisierung in der Medizin und der flächendeckenden Einführung der elektronischen Patientenakte bieten sich neue Möglichkeiten, Forschungsdaten zu generieren. Voraussetzung sind Plattformen für Kohortenstudien, die einerseits die bereits in der Routine erhobenen Daten abgreifen können und es andererseits erlauben, für die in Kohorten eingeschlossenen Patienten zusätzliche Parameter durch studienspezifische Module zu erheben. Ziel ist es, durch die Integration der Register in bestehende Systeme die Doppelerhebung zu vermeiden und die Belastung der dokumentierenden Ärzte deutlich zu verringern. Dies würde auch die Durchführung pragmatischer Trials auf Basis von Registern erleichtern.

Die Nutzung der in den Einrichtungen vorliegenden personenbezogenen Daten für Forschungszwecke kann nur entsprechend der geltenden Datenschutzgesetzgebung erfolgen. Es geht nicht nur um den einmaligen Transfer pseudonymisierter Daten, sondern es müssen Längsschnitterhebungen und externes Monitoring möglich sein. Diese Anforderungen können nur durch eine web-basierte Plattform mit doppelter Pseudonymisierung der Daten entsprechend den Vorgaben der Telematikplattform und Schnittstellen zu den gängigen Praxissystemen gelöst werden. In der Rheumatologie gibt es daher aktuell intensive Bemühungen, die Zersplitterung in unterschiedliche Dokumentationssysteme zu überwinden und eine einheitliche Plattform für Beobachtungsstudien, klinische Studien und die Dokumentation im Rahmen neuer Versorgungsmodelle zu schaffen, die Schnittstellen zur elektronischen Patientenakte und gängigen Praxissystemen aufweist. Neben der Deutschen Gesellschaft für Rheumatologie und dem Berufsverband deutscher Rheumatologen ist hieran wesentlich das Deutsche Rheuma-

Forschungszentrum (DRFZ) beteiligt, um die Anforderungen der verschiedenen Register- und Kohortenstudien von Anfang an einzubringen.

4 Zusammenfassung

Die in dieser Arbeit vorgestellten Ergebnisse aus dem RABBIT Register unterstreichen die Bedeutung der Biologikaregister als Instrumente der Pharmakovigilanz. Für die Generierung zuverlässiger Ergebnisse kommt es jedoch neben sorgfältiger Erhebung der Primärdaten und intensiver Qualitätssicherung durch umfassendes Monitoring darauf an, die spezifischen Limitationen von Beobachtungs- und Kohortenstudien zu berücksichtigen und ihnen mit adäquaten statistischen Mitteln zu begegnen.

Alle hier vorgestellten Arbeiten berichten über Analysen unerwünschter Ereignisse mit kurzer oder langer Latenzzeit, die im Rahmen des RABBIT-Registers beobachtet wurden. Durch die Anwendung geeigneter statistischer Methoden konnte nicht nur das Risiko für das Auftreten dieser Ereignisse unter verschiedenen Therapien verglichen werden, sondern es war auch möglich, weitere assoziierte Risiken zu untersuchen.

In der ersten Arbeit wurde ein höheres Risiko für das Auftreten eines Herpes zoster (HZ) unter der Therapie mit TNF Inhibitoren im Vergleich zu csDMARD gezeigt. Dieses beruhte im Wesentlichen auf einer Risikoerhöhung unter der Therapie mit monoklonalen Antikörpern, während für die Therapie mit dem TNF inhibierenden Rezeptorfusionsprotein keine solche Erhöhung nachgewiesen werden konnte [61]. Bereits bei dieser Arbeit stellte sich heraus, dass der Komedikation (vor allem der Therapie mit Glukokortikoiden) eine große Bedeutung zukommt.

Mit der zweiten hier vorgestellten Arbeit wurde das Risiko für schwerwiegende Infektionen unter bDMARD Therapien untersucht [62]. Darüber hinaus gingen wir der Frage nach, welche methodischen oder klinischen Umstände für den in verschiedenen Registern beobachteten Rückgang des Infektionsrisikos mit längerer Beobachtungszeit verantwortlich sind. Wir konnten nachweisen, dass dies im Wesentlichen auf zwei Effekten beruht: Zum einen zeigt sich auf Kohortenebene ein Selektionsprozess mit einem über-

proportionalen Dropout von Patienten mit hohem Risiko für schwerwiegende Infektionen aus der mit bDMARDs behandelten Patientengruppe („survival of the fittest“). Zum anderen ändert sich das Risiko auf der individuellen Patientenebene, da mit dem Wirkungseintritt einer effektiven Therapie auch das Risiko für schwerwiegende Infektionen durch verbesserte Funktionsfähigkeit und die Reduktion der risikobehafteten Komedikation mit Glukokortikoiden sinkt. Durch die Anwendung geeigneter statistischer Methoden konnte ein Risikomodell etabliert werden, das es erlaubte, sowohl die zeitliche Veränderung von klinischen Parametern als auch das selektive Dropout in den Therapiegruppen zu berücksichtigten. Eine TNFi Therapie geht demnach, zeitunabhängig, mit einer etwa 80%igen Erhöhung des Risikos für schwerwiegende Infektionen im Vergleich zur Therapie mit csDMARDs einher. Im Kontext weiterer konkurrierender Risiken kann das Risiko für schwerwiegende Infektionen unter einer TNFi Therapie aber geringer sein als zuvor unter einer weniger effektiven csDMARD Therapie, wenn durch die TNFi Therapie Glukokortikoide eingespart und die Funktionsfähigkeit verbessert werden können. Basierend auf den Ergebnissen dieser Analyse entwickelten wir einen Risikorechner, der nach seiner Evaluierung an einer unabhängigen Kohorte auf der RABBIT-Webseite zur Verfügung steht.

Wie groß der Einfluss der zum Zeitpunkt des Auftretens der schwerwiegenden Infektion erhaltenen Therapie auf den Ausgang des Ereignisses ist, wurde in der dritten hier vorgestellten Arbeit untersucht [63]. Es zeigte sich, dass Patienten, die zum Zeitpunkt des Auftretens einer schwerwiegenden Infektion eine bDMARD Therapie erhielten, im Vergleich zu denjenigen unter csDMARDs ein signifikant geringeres Risiko hatten, eine Sepsis zu entwickeln, oder zu versterben. Überraschend war, dass das Ergebnis mit einem im Tierversuch gezeigten Überlebensvorteil übereinstimmte, der im humanen Therapieversuch bislang nicht reproduziert werden konnte.

Der Aspekt der bei der Markteinführung der TNF Inhibitoren bestehenden Besorgnis über ein möglicherweise erhöhtes Risiko für die Entwicklung von Malignomen wurde gemeinsam mit der Analyse des Risikos für rekurrente Tumore in der vierten hier vorgestellten Arbeit untersucht [64]. Dabei fanden wir kein erhöhtes Risiko für die Entwicklung von Tumoren unter einer TNFi Therapie im Vergleich zur csDMARD Therapie. Auch bei Patienten mit einer Tumoranamnese, die mit TNFi oder Anakinra behandelt wurden, muss kein erhöhtes Risiko für eine Tumorrekurrenz oder das Auftreten eines zweiten Tumors befürchtet werden.

Dass bei Entdeckung eines möglichen Sicherheitssignals in klinischen Studien oftmals der Vergleich fehlt, um die beobachteten Ereignisraten in einen Kontext zu bringen, war Hintergrund für die fünfte der hier vorgestellten Arbeiten, die Perforationen des unteren Darmtraktes unter der Therapie mit Tocilizumab untersuchte [65]. Ein in klinischen Studien beobachtetes Signal konnte nicht bewertet werden, da geeignete Vergleichsdaten fehlten. Es blieb daher ungeklärt, ob Perforationen des unteren Darmtraktes bei Patienten mit rheumatoider Arthritis generell häufiger auftreten, oder unter Biologikatherapie oder der Therapie mit Tocilizumab erhöht sind. RABBIT konnte zeigen, dass Perforationen des unteren Darmtraktes unter einer Therapie mit Tocilizumab deutlich häufiger auftraten, als unter allen anderen bDMARD Therapien und dass das Risiko für eine solche Perforation im Vergleich zu einer synthetischen DMARD Therapie sogar um das 5-fache erhöht ist. Darüber hinaus gelang es aufzuzeigen, dass unter der Therapie mit Tocilizumab die Unterdrückung der akute Phase Parameter und die undeutliche Symptomatik häufig zu einer Diagnoseverzögerung führen, was ein deutlich erhöhtes Risiko zur Folge hat, an diesem Ereignis zu versterben.

Mit den beiden letzten vorgestellten Arbeiten zur Mortalität [66] und zum Auftreten des Myokardinfarktes [67] konnte die große Bedeutung einer unzureichend kontrollierten

Krankheitsaktivität als Risikofaktor eindrücklich gezeigt werden. Patienten mit einer hohen Krankheitsaktivität hatten im Vergleich zu denjenigen mit gleichem Risikoprofil, aber einer gut kontrollierten, geringeren Krankheitsaktivität eine um 10 Jahre verkürzte Lebenserwartung. Auch eine begleitende Glukokortikoidtherapie wurde in dieser Analyse abermals als Risikofaktor identifiziert. Auffällig war, dass nicht nur höhere Glukokortikoiddosen, sondern bereits solche über 5 mg/d das Risiko vorzeitiger Mortalität signifikant erhöhten. Das Risiko für das Auftreten eines Myokardinfarktes wurde mit einer Fall-Kontroll-Studie mit detaillierten Matching (nach Alter, Geschlecht, sowie 5 kardiovaskulären Komorbiditäten) untersucht. Auch hier zeigte sich, wie bedeutend die Kontrolle eines zu hohen Entzündungsniveaus ist. Darüber hinaus fiel auf, dass kardiovaskuläre Komorbiditäten bei Patienten, die einen Myokardinfarkt entwickelten, weniger häufig zuvor therapiert worden waren als bei Patienten ohne Myokardinfarkt.

In der Zusammenschau aller aus RABBIT gewonnen Ergebnisse kann weitestgehend Entwarnung gegeben werden hinsichtlich des befürchteten Risikos inzidenter Autoimmun- oder maligner Tumorerkrankungen durch Biologika-Therapien. Über die ursprünglich im Fokus stehenden Risiken der medikamentösen Therapien hinaus konnten mit zunehmender Patientenzahl und Beobachtungszeit auch differenzierte Analysen des Zusammenwirkens von klinischen und soziodemografischen Charakteristika der Patienten und deren Einfluss auf das Auftreten unerwünschter Ereignisse durchgeführt werden.

Die Ergebnisse aus RABBIT sind zu einem wichtigen Bestandteil der klinischen Routine in der Rheumatologie geworden. Aus der heutigen Pharmakovigilanzforschung sind die als sorgfältige Kohortenstudien geplanten und durchgeführten Register nicht mehr wegzudenken. Die Erfahrungen aus RABBIT haben darüber hinaus Eingang gefunden in

den Aufbau von Registern in anderen Fachgebieten der Medizin wie Dermatologie, Neurologie, Pneumologie oder Kinderheilkunde.

5 Literaturangaben

1. Zink A, Braun J, Gromnica-Ihle E, Krause D, Lakomek HJ, Mau W, et al. Memorandum der Deutschen Gesellschaft für Rheumatologie zur Versorgungsqualität in der Rheumatologie - Update 2016. [Memorandum of the German Society for Rheumatology on the quality of treatment in rheumatology - Update 2016]. Z Rheumatol. 2017 Apr; 76(3):195-207.

2. Minden K, Niewerth M. Rheumakranke Kinder und Jugendliche: Kerndokumentation und Prognose. Monatsschr Kinderheilkd. 2012 2012; 160(3):237-243.

3. Crowson CS, Matteson EL, Myasoedova E, Michet CJ, Ernste FC, Warrington KJ, et al. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. Arthritis Rheum. 2011 3/2011; 63(3):633-639.

4. Zink A. Versorgungsforschung in der Rheumatologie. Aktueller Stand. [Healthcare research in rheumatology : Current state]. Z Rheumatol. 2014 3/2014; 73(2):115-122.

5. Zink A, Albrecht K. Wie häufig sind muskuloskeletale Erkrankungen in Deutschland? [How frequent are musculoskeletal diseases in Germany?]. Z Rheumatol. 2016 5/2016; 75(4):346-353.

6. Silman AJ, Hochberg MC. Descriptive epidemiology of rheumatoid arthritis. In: MC H, AJ S, JS S, ME W, MH W, eds. *Rheumatoid Arthritis*. Philadelphia: Mosby Elsevier; 2009:15-22.

7. Eriksson JK, Neovius M, Ernestam S, Lindblad S, Simard JF, Askling J. Incidence of rheumatoid arthritis in sweden: a nationwide population-based assessment of incidence, its determinants, and treatment penetration. Arthritis Care Res (Hoboken). 2013 6/2013; 65(6):870-878.

8. Albrecht K CJ, Zink A. Langzeit-Trends in der rheumatologischen Versorgung: Erfolge und Defizite im Spiegel von 25 Jahren rheumatologischer Kerndokumentation. Z Rheumatol. 2019 (im Druck)(78: Heft 8).

9. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum. 1987 11/1987; 30(11):1205-1213.

10. Klareskog L, Alfredsson L, Rantapaa-Dahlqvist S, Berglin E, Stolt P, Padyukov L. What precedes development of rheumatoid arthritis? Ann Rheum Dis. 2004 11/2004; 63 Suppl 2:ii28-ii31.

11. Crowson CS, Matteson EL, Davis JM, 3rd, Gabriel SE. Contribution of obesity to the rise in incidence of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2013 1/2013; 65(1):71-77.

12. Stolt P, Bengtsson C, Nordmark B, Lindblad S, Lundberg I, Klareskog L, et al. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. Ann Rheum Dis. 2003 9/2003; 62(9):835-841.

13. Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum. 2006 1/2006; 54(1):38-46.

14. de Hair MJ, Landewe RB, van de Sande MG, van Schaardenburg D, van Baarsen LG, Gerlag DM, et al. Smoking and overweight determine the likelihood of developing rheumatoid arthritis. Ann Rheum Dis. 2013 Oct; 72(10):1654-1658.

15. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995 1995; 38:44-48.

16. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, III, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010 9/2010; 69(9):1580-1588.

17. Aly A-F. Definitionen zu Pharmakovigilanz und Arzneimitteltherapiesicherheit. Themenheft Arzneimitteltherapiesicherheit. 2015; 42(3):99-104.

18. Martin RM, Kapoor KV, Wilton LV, Mann RD. Underreporting of suspected adverse drug reactions to newly marketed ("black triangle") drugs in general practice: observational study. BMJ. 1998 7/11/1998; 317(7151):119-120.

19. Begaud B, Martin K, Haramburu F, Moore N. Rates of spontaneous reporting of adverse drug reactions in France. JAMA. 2002 Oct 2; 288(13):1588.

20. Zink A, Strangfeld A, Schneider M, Herzer P, Hierse F, Stoyanova-Scholz M, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials. Arthritis Rheum. 2006 11/2006; 54(11):3399-3407.

21. Curtis JR, Jain A, Askling J, Bridges SLJ, Carmona L, Dixon W, et al. A comparison of patient characteristics and outcomes in selected European and U.S. rheumatoid arthritis registries. Semin Arthritis Rheum. 2010 8/2010; 40(1):2-14.

22. Zink A, Askling J, Dixon WG, Klareskog L, Silman AJ, Symmons DP. European biologicals registers: methodology, selected results and perspectives. Ann Rheum Dis. 2009 8/2009; 68(8):1240-1246.

23. Tubach F, Salmon-Ceron D, Ravaud P, Mariette X, Group RS. The RATIO observatory: French registry of opportunistic infections, severe bacterial infections, and lymphomas complicating anti-TnFalpha therapy. Joint Bone Spine. 2005 Dec; 72(6):456-460.

24. Regierer AC, Weiss A, Baraliakos X, Zink A, Listing J, Strangfeld A. RABBIT-SpA: ein neues Krankheitsregister fur axiale Spondyloarthritis und Psoriasisarthritis. [RABBIT-SpA: a new disease register for axial spondyloarthritis and psoriatic arthritis]. Z Rheumatol. 2019 Mar 12.

25. Strangfeld A, Bungartz C, Richter J, Zink A, Schneider M, Listing J, et al. First results from the prospective German pregnancy register RHEKISS. EULAR, London, 8 - 11 June 2016. Ann Rheum Dis. 2016 2016; 75(Suppl. 2):119.

26. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from

the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 Aug; 54(8):2368-2376.

27. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum. 2003; 48(8):2122-2127.

28. Greenberg JD, Reed G, Kremer JM, Tindall E, Kavanaugh A, Zheng C, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis. 2010 2/2010; 69(2):380-386.

29. Dixon WG, Symmons DP, Lunt M, Watson KD, Hyrich KL, Silman AJ. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. Arthritis Rheum. 2007 Sep; 56(9):2896-2904.

30. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N, et al. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. Ann Rheum Dis. 2007; 66(10):1339-1344.

31. Zink A, Manger B, Kaufmann J, Eisterhues C, Krause A, Listing J, et al. Evaluation of the RABBIT Risk Score for serious infections. Ann Rheum Dis. 2014 9/2014; 73(9):1673-1676.

32. Strangfeld A. Sepsis und Mortalitat nach schwerwiegenden Infektionen : Wie epidemiologische Daten tierexperimentelle Ergebnisse bestatigen. [Sepsis and mortality after severe infections : How epidemiological data confirm results of animal experiments]. Z Rheumatol. 2017 Aug 31; doi: 10.1007/s00393-017-0374-5.

33. Dreyer L, Mellemkjaer L, Andersen AR, Bennett P, Poulsen UE, Juulsgaard Ellingsen T, et al. Incidences of overall and site specific cancers in TNFalpha inhibitor treated patients with rheumatoid arthritis and other arthritides - a follow-up study from the DANBIO Registry. Ann Rheum Dis. 2013; 72(1):79-82.

34. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and

malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006 5/17/2006; 295(19):2275-2285.

35. Bongartz T, Warren FC, Mines D, Matteson EL, Abrams KR, Sutton AJ. Etanercept therapy in rheumatoid arthritis and the risk of malignancies. A systematic review and individual patient data meta-analysis of Randomized Controlled Trials. Ann Rheum Dis. 2008 11/19/2008; 68(7):1177-1183.

36. Mercer LK, Askling J, Raaschou P, Dixon WG, Dreyer L, Hetland ML, et al. Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: results from a collaborative project of 11 European biologic registers. Ann Rheum Dis. 2017 Feb; 76(2):386-391.

37. Mercer LK, Regierer AC, Mariette X, Dixon WG, Baecklund E, Hellgren K, et al. Spectrum of lymphomas across different drug treatment groups in rheumatoid arthritis: a European registries collaborative project. Ann Rheum Dis. 2017 Dec; 76(12):2025-2030.

38. Hart AR, Kennedy HJ, Stebbings WS, Day NE. How frequently do large bowel diverticula perforate? An incidence and cross-sectional study. Eur J Gastroenterol Hepatol. 2000 Jun; 12(6):661-665.

39. Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF. Integrated safety in tocilizumab clinical trials. Arthritis Res Ther. 2011; 13(5):R141.

40. Gonzalez A, Maradit KH, Crowson CS, Nicola PJ, Davis JM, 3rd, Therneau TM, et al. The widening mortality gap between rheumatoid arthritis patients and the general population. Arthritis Rheum. 2007 11/2007; 56(11):3583-3587.

41. Gabriel SE. Cardiovascular morbidity and mortality in rheumatoid arthritis. Am J Med. 2008 Oct; 121(10 Suppl 1):S9-14.

42. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation. 2003 Mar 11; 107(9):1303-1307.

43. Wolfe F, Freundlich B, Straus WL. Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis. J Rheumatol. 2003 1/2003; 30(1):36-40.

44. Fordjour PA, Wang Y, Shi Y, Agyemang K, Akinyi M, Zhang Q, et al. Possible mechanisms of C-reactive protein mediated acute myocardial infarction. Eur J Pharmacol. 2015 Aug 5; 760:72-80.

45. Silman A, Klareskog L, Breedveld F, Bresnihan B, Maini R, van Riel P, et al. Proposal to establish a register for the long term surveillance of adverse events in patients with rheumatic diseases exposed to biological agents: the EULAR Surveillance Register for Biological Compounds. Ann Rheum Dis. 2000 6/2000; 59(6):419-420.

46. Laupland KB, Pasquill K, Parfitt EC, Dagasso G, Gupta K, Steele L. Inhospital death is a biased measure of fatal outcome from bloodstream infection. Clin Epidemiol. 2019; 11:47-52.

47. Chatzidionysiou K, Hetland ML, Frisell T, Di Giuseppe D, Hellgren K, Glintborg B, et al. Opportunities and challenges for real-world studies on chronic inflammatory joint diseases through data enrichment and collaboration between national registers: the Nordic example. RMD Open. 2018; 4(1):e000655.

48. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis. 2016 1/2016; 75(1):3-15.

49. Remick DG. Cytokine therapeutics for the treatment of sepsis: why has nothing worked? Curr Pharm Des. 2003; 9(1):75-82.

50. George MD, Baker JF, Hsu JY, Wu Q, Xie F, Chen L, et al. Perioperative Timing of Infliximab and the Risk of Serious Infection After Elective Hip and Knee Arthroplasty. Arthritis Care Res (Hoboken). 2017 Dec; 69(12):1845-1854.

51. Baganz L, Richter A, Kekow J, Bussmann A, Krause A, Stille C, et al. Long-term effectiveness of tocilizumab in patients with rheumatoid arthritis, stratified by number of previous treatment failures with biologic agents: results from the German RABBIT cohort. Rheumatol Int. 2018 Apr; 38(4):579-587.

52. Strangfeld A, Hierse F, Kekow J, von Hinueber U, Tony HP, Dockhorn R, et al. Comparative effectiveness of tumour necrosis factor alpha inhibitors in combination with either methotrexate or leflunomide. Ann Rheum Dis. 2009 12/2009; 68(12):1856-1862.

53. Richter A, Strangfeld A, Herzer P, Wilden E, Bussmann A, Listing J, et al. Sustainability of rituximab therapy in different treatment strategies: results of a 3-year followup of a German biologics register. Arthritis Care Res (Hoboken). 2014 Nov; 66(11):1627-1633.

54. Schäfer M MY, Kekow J, Berger S, Remstedt S, Manger B, Listing J, Strangfeld A, Zink A. Obesity reduces the real-world effectiveness of cytokine but not cell-targeted disease-modifying agents in rheumatoid arthritis. Rheumatology (Oxford). 2019 (accepted).

55. Gerhold K, Richter A, Schneider M, Bergerhausen HJ, Demary W, Liebhaber A, et al. Health-related quality of life in patients with long-standing rheumatoid arthritis in the era of biologics: data from the German biologics register RABBIT. Rheumatology (Oxford). 2015 10/2015; 54(10):1858-1866.

56. Albrecht K, Richter A, Meissner Y, Huscher D, Baganz L, Thiele K, et al. Wie häufig sind prognostisch ungunstige Faktoren bei Patienten mit rheumatoider Arthritis? : Eine Abschatzung anhand von 3 epidemiologischen Kohorten. [How frequent are poor prognostic markers in rheumatoid arthritis? : An estimate based on three epidemiologic cohorts]. Z Rheumatol. 2017 Jun; 76(5):434-442.

57. Rosenbaum PR, Rubin DB. The Central Role of the Propensity Score in Observational Studies for Causal Effects. Biometrika. 1983 1983; 70(1):41-55.

58. Hansen BB KS. Optimal full matching and related designs via network flows. Journal of Computational and Graphical Statistics. 2006; 15(3):306-627.

59. Bohning D, Sarol J, Rattanasiri S, Viwatwongkasem C, Biggeri A. A comparison of non-iterative and iterative estimators of heterogeneity variance for the standardized mortality ratio. Biostatistics. 2004 Jan; 5(1):61-74.

60. Radner H, Chatzidionysiou K, Nikiphorou E, Gossec L, Hyrich KL, Zabalan C, et al. 2017 EULAR recommendations for a core data set to support observational research and clinical care in rheumatoid arthritis. Ann Rheum Dis. 2018 Apr; 77(4):476-479.

61. Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA. 2009 2/18/2009; 301(7):737-744.

62. Strangfeld A, Eveslage M, Schneider M, Bergerhausen HJ, Klopsch T, Zink A, et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Ann Rheum Dis. 2011 11/2011; 70(11):1914-1920.

63. Richter A, Listing J, Schneider M, Klopsch T, Kapelle A, Kaufmann J, et al. Impact of treatment with biologic DMARDs on the risk of sepsis or mortality after serious infection in patients with rheumatoid arthritis. Ann Rheum Dis. 2016 9/2016; 75(9):1667-1673.

64. Strangfeld A, Hierse F, Rau R, Burmester GR, Krummel-Lorenz B, Demary W, et al. Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. Arthritis Res Ther. 2010 2010; 12(1):R5.

65. Strangfeld A, Richter A, Siegmund B, Herzer P, Rockwitz K, Demary W, et al. Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs. Ann Rheum Dis. 2017; 76(3):504-510.

66. Listing J, Kekow J, Manger B, Burmester GR, Pattloch D, Zink A, et al. Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFalpha inhibitors and rituximab. Ann Rheum Dis. 2015 2/2015; 74(2):415-421.

67. Meissner Y, Zink A, Kekow J, Rockwitz K, Liebhaber A, Zinke S, et al. Impact of disease activity and treatment of comorbidities on the risk of myocardial infarction in rheumatoid arthritis. Arthritis Res Ther. 2016; 18(1):183.

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Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,
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- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

.....29.04.2019.....
Datum

…… Anja Strangfeld.....
Unterschrift