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DISSERTATION

Einflussfaktoren auf das Erreichen von Therapiezielen und die Sicherheit von Therapien bei rheumatoider Arthritis. Eine Analyse von Langzeitbeobachtungsdaten für ausgewählte Therapieoutcomes

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Abkürzungen

ABA	Abatacept
ACPA	Antikörper gegen citrullinierte Proteine
bDMARD	Biologic Disease-Modifying Anti-Rheumatic Drug
BSG	Blutsenkungsgeschwindigkeit
BMI	Body Mass Index
CAPEA	Course and Prognosis of Early Arthritis
CRP	C-reaktives Protein
csDMARD	Conventional synthetic Disease-Modifying Anti-Rheumatic Drug
DAS28	Disease-activity-score basierend auf 28 Gelenken
EMA	European Medicine Agency
EULAR	European League Against Rheumatism
FFbH	Funktionsfragebogen Hannover
HAQ	Health Assessment Questionnaire
HDA	Hohe Krankheitsaktivität (High Disease Activity)
HR	Hazardrate
IR	Inzidenzrate
JAKi	Januskinase Inhibitor
KI	Konfidenzintervall
LDA	Niedrige Krankheitsaktivität (Low Disease Activity)
MTX	Methotrexat
OR	Odds Ratio
PJ	Patientenjahre
RA	Rheumatoide Arthritis
RABBIT	Rheumatoide Arthritis: Beobachtung der Biologika Therapie
RF	Rheumafaktor
RTX	Rituximab
TCZ	Tocilizumab
TNFi	Tumornekrosefaktor-Inhibitor

Zusammenfassung / Abstract

Einleitung: Die rheumatoide Arthritis (RA) ist eine chronisch-entzündliche Erkrankung, bei der die Patienten in aller Regel einer dauerhaften medikamentösen Therapie bedürfen. Die Wahl der jeweiligen Therapie orientiert sich an der aktuellen Krankheitsaktivität, dem Vorliegen ungünstiger prognostischer Faktoren sowie dem bisherigen Krankheits- und Therapieverlauf. Mit Daten des deutschen Biologika-Registers RABBIT wurden unterschiedliche Aspekte der Prognose des Therapieansprechens sowie Faktoren, die die Wahl der Therapie beeinflussen können, untersucht: (1) Welchen Einfluss haben ungünstige prognostische Faktoren auf den Therapieerfolg? (2) Welche Rolle spielt die Zahl vorheriger Therapieversuche mit Biologika für die Wirksamkeit einer ausgewählten Biologikatherapie am Beispiel des IL-6-Inhibitors Tocilizumab (TCZ)? (3) Welches Risikoprofil zeigen einzelne Therapien im Hinblick auf inzidente oder rekurrente Psoriasis? Alle drei Arbeiten beziehen sich auf Aspekte, die von Relevanz für die klinische Entscheidungsfindung sind.

Methodik: Für alle drei Arbeiten wurden Daten aus dem deutschen Biologika-Register RABBIT verwendet, in welches Patienten mit Beginn einer neuen csDMARD-, bDMARD- oder JAKi -Therapie eingeschlossen werden. Für die erste Arbeit wurden zusätzlich Daten aus der Früharthritiskohorte CAPEA verwendet. Fehlende Daten wurden in allen Arbeiten mit Verfahren multipler Imputation ersetzt. Es wurden lineare (2) und generalisierte lineare (1) gemischte Modelle zur Analyse der Krankheitsaktivität, Kaplan-Meier-Methoden (2) zur Schätzung von Retentionsraten, sowie Cox-proportional-hazard Modelle zur Berechnung von Risiken für Therapieabbruch (2) und das Auftreten von Psoriasis (3) angewandt.

Ergebnisse: (1) Hohe Krankheitsaktivität, Funktionseinschränkungen, Komorbiditäten und Adipositas waren negativ mit dem Erreichen von niedriger Krankheitsaktivität (LDA) bzw. Remission innerhalb von 6 Monaten nach einem Therapiebeginn assoziiert. (2) Die Effektivität von TCZ über drei Jahre Beobachtung war für bionaive Patienten und Patienten mit einem oder zwei vorherigen bDMARD-Versagen vergleichbar. Dies unterscheidet diese Therapie von anderen Biologikatherapien. Lediglich Patienten mit mindestens drei bDMARDs in der Anamnese hatten ein signifikant höheres Risiko, die Therapie abzubrechen. (3) Inzidente Psoriasis war ein seltenes Ereignis bei RA (0,5-3/1.000 Patientenjahre), aber das Risiko unter TNF-Inhibitoren (TNFi) war 3,9-mal höher als unter csDMARDs. Eine Komedikation mit MTX scheint das Risiko zu verringern.

Schlussfolgerung: (1) Neben hoher Krankheitsaktivität ist auch bei Funktionseinschränkungen, Komorbiditäten und Adipositas eine frühzeitige Therapieintensivierung wichtig, um eine

ausreichende Krankheitskontrolle der RA zu erreichen (2) TCZ ist sowohl für bionaive als auch für Patienten mit mehreren bDMARD-Versagen eine effektive Therapie. (3) Unter TNFi besteht ein erhöhtes Risiko für inzidente Psoriasis, welches aber durch eine Komedikation mit MTX reduziert werden kann.

Introduction: Rheumatoid arthritis (RA) is a chronic inflammatory disease in which patients usually require anti-inflammatory therapy for many years. The choice of the respective therapy is based on the current disease activity, the presence of unfavorable prognostic factors and the previous course of the disease and therapy. Using data from the German Biologics Registry RABBIT, different aspects of the prognosis of the therapy response as well as factors that may influence the choice of therapy were investigated: (1) What influence do unfavorable prognostic factors have on the success of therapy? (2) What role does the number of previous therapy trials with biologicals play for the efficacy of a selected biologic therapy using the IL-6 inhibitor tocilizumab (TCZ) as an example? (3) What is the risk profile of individual therapies with regard to incident or recurrent psoriasis? All three papers refer to aspects that are relevant for clinical decision making.

Methods: In all three studies data from the German Biologics Register RABBIT were used, which includes patients starting a new csDMARD, bDMARD or JAKi therapy. In the first study, data from the early arthritis cohort CAPEA were used additionally. Missing data were replaced in all studies by multiple imputation procedures. Linear (2) and generalized linear (1) mixed models were used to analyze disease activity, Kaplan-Meier methods (2) to estimate retention rates, and Cox-proportional-hazard models to calculate risks for therapy discontinuation (2) and the occurrence of psoriasis (3).

Results: (1) High disease activity, functional limitations, comorbidities and obesity were negatively associated with the achievement of low disease activity (LDA) or remission within 6 months after a treatment start. (2) The effectiveness of TCZ over three years of observation was comparable for bionaive patients and patients with one or two previous bDMARD failures. This distinguishes this therapy from other biologic therapies. Only patients with at least three bDMARDs in their medical history had a significantly higher risk of discontinuing therapy. (3) Incident psoriasis was a rare event in RA (0.5-3/1,000 patient-years), but the risk under TNF inhibitors (TNFi) was 3.9 times higher than under csDMARDs. Comedication with MTX appears to reduce the risk.

Conclusions: (1) Besides high disease activity, also functional impairment, comorbidities and obesity, require early therapy intensification to achieve sufficient disease control of RA (2) TCZ is an effective therapy for bionaive as well as for patients with multiple bDMARD failure. (3) TNFi increases the risk of incident psoriasis, which can be reduced by comedication with MTX.

1. Einführung

Die rheumatoide Arthritis (RA) ist eine chronisch-entzündliche Erkrankung, die sich vor allem an den Gelenken, aber auch an inneren Organen manifestiert. Sie ist bis heute nicht heilbar und bedarf einer konsequenten Langzeittherapie, um Folgeschäden zu vermeiden. Das Therapieziel, welches in den deutschen [1] und europäischen Empfehlungen [2] zur Behandlung der RA genannt wird, ist das Erreichen niedriger Krankheitsaktivität (LDA) oder Remission. Das empfohlene First-line Basismedikament ist Methotrexat (MTX). Es gehört zur Klasse der konventionellen synthetischen krankheitsmodifizierenden Medikamente (csDMARDs). Erreicht ein Patient das Therapieziel nicht innerhalb von sechs Monaten, soll entweder ein anderes csDMARD, ein biologisches krankheitsmodifizierendes Medikament (bDMARD) oder ein Januskinase-Inhibitor (JAKi) verordnet werden. JAKi sind keine Biologika, sondern spezifische synthetische krankheitsmodifizierende Medikamente. Spricht ein Patient auch auf die zweite Therapie nicht an, wird der Wechsel auf ein anderes bDMARD oder einen JAKi empfohlen. Eine konkrete Empfehlung, welches Biologikum oder welcher JAKi gegeben werden sollte, besteht nicht. Die Entscheidung obliegt dem behandelnden Arzt, der die Therapie unter Gesichtspunkten des erwarteten Krankheitsverlaufs und der bisherigen Krankheits- und Therapiegeschichte auswählt. Biologika sind eine biotechnologisch hergestellte Medikamentenklasse, die direkt in die Prozesse des Immunsystems eingreift. Der genaue Mechanismus ist abhängig vom Wirkstoff. Tumornekrosefaktor-Inhibitoren (TNFi) hemmen entweder den zirkulierenden oder membranständigen Rezeptor des Zytokins, Tocilizumab (TCZ) führt zur Inhibition von Interleukin-6 Rezeptoren, Rituximab (RTX) depletiert B-Zellen und Abatacept (ABA) führt zur Suppression der T-Zell-Aktivierung. JAKi sind in Deutschland seit 2017 zugelassen und hemmen Januskinasen.

Im klinischen Alltag sieht sich der Arzt Patienten gegenüber, die unterschiedlich auf die Therapien ansprechen und eventuell schon mehrere Therapieversagen hatten. Nur ein kleiner Teil dieser Patienten erfüllt die Einschlusskriterien randomisierter klinischer Studien. Auch sind diese Studien meist zeitlich so beschränkt, dass Untersuchungen der Langzeiteffektivität über mehrere Jahre oder von Inzidenzen für seltene unerwünschte Ereignisse unter verschiedenen Therapien nicht möglich sind.

Zur Untersuchung der Langzeitwirkung und -sicherheit von Biologika wurden Beobachtungskohorten etabliert, wie das 2001 gegründete deutsche Register RABBIT (Rheumatoide Arthritis: Beobachtung der Biologika Therapie). Zusätzlich zu den Biologika und

den JAKi gibt es auch eine csDMARD-Vergleichsgruppe. Bislang wurden mehr als 18.000 Patienten eingeschlossen. In dieser Arbeit wurden Daten aus RABBIT genutzt, um anhand von drei verschiedenen Beispielen Therapiestrategien der RA im klinischen Alltag zu untersuchen. Zur Prüfung der externen Validität der Ergebnisse aus RABBIT wurden im ersten Beispiel Daten der deutschen Früharthritis-Kohorte CAPEA (Course and Prognosis of Early Arthritis) hinzugezogen.

1.1 Prognostisch ungünstige Faktoren für das Erreichen von LDA oder Remission

Die Kenntnis prognostisch ungünstiger Faktoren für das Erreichen der allgemein anerkannten Therapieziele ‚niedrige Krankheitsaktivität' (LDA) oder ‚Remission' soll Ärzte in der klinischen Entscheidungsfindung unterstützen. Die Empfehlungen der EULAR (European League Against Rheumatism) zum Management der rheumatoiden Arthritis mit synthetischen oder biologischen krankheitsmodifizierenden Medikamenten [2] beziehen sich explizit auf prognostisch ungünstige Faktoren. Falls sich die Krankheitsaktivität eines Patienten auf seiner ersten csDMARD Therapie (meist MTX) nach 3 Monaten noch nicht verbessert oder er nicht innerhalb von 6 Monaten das Therapieziel erreicht hat, soll bei Vorliegen von prognostisch ungünstigen Faktoren ein bDMARD oder JAKi begonnen werden. Folgende Faktoren werden genannt [2]: Moderate bis hohe Krankheitsaktivität, hohe Werte der Akute-Phase-Proteine, eine hohe Zahl geschwollener Gelenke, Seropositivität (Rheumafaktor (RF) und/oder ACPA (Antikörper gegen citrullinierte Proteine)), frühe Erosionen oder Versagen von mindestens 2 csDMARDs. Genaue Grenzwerte für befallene Gelenke oder Laborparameter werden nicht genannt. Die Wahl der Faktoren beruht größtenteils auf älteren Studien, bei denen als Outcome die radiographische Progression verwendet wurde [3-7]. Heutige Therapien zielen nicht nur auf die Verhinderung der Gelenkzerstörung, sondern insgesamt auf die konsequente Kontrolle der Krankheitsaktivität ab. Zudem sind die EULAR-Kriterien möglicherweise nicht ganz vollständig. So gibt es Studien, die zeigen, dass weitere Faktoren, wie Adipositas, physische Einschränkung, Komorbiditäten und Rauchen einen negativ-prädiktiven Wert für das Erreichen des Therapieziels haben können [8-10]. Die Hauptfragestellungen der ersten Publikation [11] lauteten daher:

(I) Welchen Einfluss haben die von der EULAR vorgeschlagenen Faktoren auf das Erreichen von LDA und Remission innerhalb von 6 Monaten nach Therapiebeginn?

(II) Wie hoch ist der Anteil von Patienten mit prognostisch ungünstigen Faktoren in den einzelnen Kohorten und wie viele Patienten erreichen die Therapieziele?

(III) Gibt es weitere relevante Faktoren?

1.2 Effektivität von TCZ bei Patienten stratifiziert nach Biologikaversagen

Ein prognostisch wichtiger Faktor für eine unzureichende Therapiewirksamkeit ist mehrfaches Therapieversagen in der Anamnese. Es ist bekannt, dass das Risiko einer unzureichenden Therapieresponse mit jedem vorhergehenden Therapieversagen steigt. Dies gilt für konventionelle synthetische ebenso wie für biologische DMARDs. Eine mögliche Ausnahme ist der Interleukin-6 Inhibitor Tocilizumab (TCZ). Damit würde sich diese Therapie insbesondere auch für Patienten eignen, die schon mehrere erfolglose Therapieversuche hinter sich haben. Die klinisch relevante Fragestellung war daher, ob Tocilizumab eine besonders geeignete Therapie für mehrfach therapierefraktäre Patienten darstellt.

TCZ ist seit 2009 für die Therapie der RA bei Patienten mit und ohne vorherige Biologikaversagen zugelassen. Klinische Studien haben gezeigt, dass TCZ auch nach TNFi Versagen effektiv ist [12-14]. Zudem ist TCZ im Gegensatz zu den meisten anderen Biologika auch in Monotherapie zugelassen. Eine Zulassung zur Kombination mit anderen csDMARDs außer MTX besteht nicht.

Die EULAR empfiehlt, dass bei nicht ausreichendem Ansprechen auf das erste bDMARD/ den ersten JAKi ein zweites bDMARD oder ein JAKi eingesetzt werden soll [2]. Es gibt Studien, die zeigen, dass ein zweiter TNFi effektiv sein kann [15, 16]. Es ist dem Arzt aber freigestellt, auch ein anderes der zugelassenen Medikamente einzusetzen. Versagt auch das zweite bDMARD hinsichtlich des Therapieziels LDA, soll das bDMARD oder der JAKi wieder gewechselt werden. In Deutschland ist es übliche klinische Praxis, TCZ nach Versagen von TNFi einzusetzen.

Eine britische Studie hat gezeigt, dass die Effektivität von TCZ bei Patienten ohne vorherige Biologikatherapie (bionaiv) und bei Patienten mit vorherigem Versagen eines oder mehrerer Biologika vergleichbar ist [17]. Allerdings beschränkte sich diese Studie auf einen Zeitraum von 6 Monaten und unterschied nur zwischen Patienten mit und ohne vorheriges Biologikaversagen. Es bleibt also offen, wie Patienten mit ansteigender Anzahl an Biologikaversagen auf TCZ ansprechen und wie sich die Wirksamkeit und Verträglichkeit über einen längeren Zeitraum verhält.

Die Hauptfragestellungen dieser Arbeit [18] waren:

(I) Vergleich der Therapiekontinuität von TCZ über 3 Jahre bei Patienten mit 0, 1, 2 oder ≥ 3 vorherigen Biologikaversagen

(II) Vergleich der mittleren Krankheitsaktivität über 3 Jahre für diese 4 Gruppen

Zusätzlich wurden

(III) Wahrscheinlichkeiten für das Erreichen von LDA berechnet,

(IV) Dropouts und Gründe für den Therapieabbruch und

(V) der Einfluss von Monotherapie bzw. Kombinationstherapie mit csDMARDs untersucht.

1.3 Risiko für Psoriasis unter verschiedenen Therapien bei RA-Patienten

Bei der Wahl einer Therapie spielt nicht nur die Effektivität eine Rolle, sondern auch ihre Sicherheit. Manche Erkrankungen, wie Leber- und Nierenerkrankungen, sind Kontraindikationen für einzelne Therapien, beispielsweise für MTX und Leflunomid. Bei malignen Tumoren gibt es Vorbehalte gegenüber einer Therapie mit TNFi, obwohl bisherige Publikationen ein erhöhtes Risiko nicht bestätigen [19, 20]. Für seltene nicht-schwerwiegende Ereignisse gibt es nur wenig Literatur bezüglich des Risikos unter verschiedenen Therapien. Bei Patienten mit RA ist das zusätzliche Auftreten einer Psoriasis ein solch seltenes und zumeist nicht-schwerwiegendes Ereignis. Unter der Therapie der RA mit TNFi wird das Auftreten von Psoriasis als paradoxe Reaktion beschrieben, da einige TNFi auch zur Therapie mittelschwerer bis schwerer Plaque-Psoriasis zugelassen sind. Bei Patienten mit RA wurde dennoch ein erhöhtes Risiko für die Entstehung einer Psoriasis unter TNFi beobachtet [21]. Zum Auftreten von Psoriasis unter anderen Therapien gibt es bisher nur Fallberichte [22-29]. Zum Zeitpunkt der Erstellung dieser Arbeit lief außerdem gerade ein Verfahren des Pharmacovogilance Risk Assessment Commitee der European Medical Agency (EMA) bezüglich eines eventuell erhöhten Risikos für Psoriasis unter TCZ [30]. Zusätzlich zur Therapie werden in der Literatur weitere mögliche Risikofaktoren beschrieben [31-33]. Diese wurden bisher nicht für Patienten mit RA bestätigt.

(I) Die klinisch relevante Fragestellungen in dieser Arbeit [34] waren, ob die verschiedenen konventionellen und biologischen DMARDs sich hinsichtlich des Risikos für das Auftreten einer inzidenten oder rekurrenten Psoriasis unterscheiden und

(II) welche anderen relevanten Risikofaktoren sich feststellen lassen.

Folgende zusätzliche Analysen wurden durchgeführt

(III) Einfluss der Komedikation von TNFi mit MTX

(IV) Überprüfung der Modellannahme des Cox-Modells und des

(V) Bias durch Channelling bestimmter Patienten zu bestimmten Therapien oder durch eventuelle Fehldiagnosen (RA statt Psoriasis Arthritis)

2. Methodik

Für alle drei Arbeiten wurden Daten aus der deutschen prospektiven Langzeitkohorte RABBIT verwendet. Seit 2001 werden Patienten mit gesicherter RA zu unterschiedlichsten Zeitpunkten im Krankheitsverlauf bei Therapiebeginn mit einem csDMARD, bDMARD oder JAKi nach Versagen mindestens eines csDMARDs eingeschlossen. Fragebögen werden von Rheumatologen und Patienten in regelmäßigen Abständen (Baseline, 3 Monate, 6 Monate und danach alle 6 Monate) ausgefüllt und umfassen unter anderem: Therapien inklusive Beginn- und Enddaten, Krankheitsaktivität, demographische Daten, physische Einschränkung und Komorbiditäten. Außerdem berichtet der Arzt aufgetretene unerwünschte Ereignisse und klassifiziert sie als schwerwiegend oder nicht schwerwiegend.

Durch die standardisierte Erhebung von Daten in vielen Patientengruppen ermöglicht diese Langzeitbeobachtungsstudie die Untersuchung und den Vergleich von Outcomes in verschiedenen Patientengruppen unter unterschiedlichen Therapien. Durch die lange Beobachtungszeit und die großen Fallzahlen sind auch Analysen von seltenen Ereignissen oder langfristiger Effektivität möglich.

Da fehlende Daten in Beobachtungsstudien nicht vermeidbar sind und einen starken Einfluss auf die Ergebnisse haben können, wurden in allen drei Arbeiten multiple Imputationsverfahren zur Ersetzung fehlender Werte verwendet. Um sicherzustellen, dass solche Verfahren verwendet werden können, müssen die Dropout- und Fehlmuster zuvor untersucht werden. Würden die Werte vollkommen zufällig fehlen, wäre ein Ersetzen nicht notwendig. Hängt das Fehlen eines Wertes von dem Wert selbst ab, also fehlen zum Beispiel vor allem DAS28- (Disease-Activity-Score basierend auf 28 Gelenken) Werte von Patienten, die eigentlich einen hohen DAS28 hätten und lässt sich das Fehlen nicht durch andere vorhandene Variablenwerte erklären, so ist ein Ersetzen nicht möglich. Dies wurde in allen Arbeiten zuvor geprüft.

2.1 Prognostisch ungünstige Faktoren für das Erreichen von LDA oder Remission

Prognostisch ungünstige Faktoren werden in den EULAR Empfehlungen verwendet, um zu entscheiden, ob nach dem Versagen des ersten csDMARDs auf ein zweites gewechselt oder ein bDMARD oder JAKi begonnen werden sollte. Deshalb wurden in dieser Arbeit zwei Subkohorten der RABBIT-Studie verwendet mit Patienten, die zwischen 2009 und 2013 eingeschlossen wurden und entweder das zweite csDMARD oder direkt den ersten TNFi begonnen hatten. Um die Ergebnisse zu stützen, wurde zusätzlich noch eine Subgruppe von Patienten aus der Früharthritiskohorte CAPEA untersucht, die das erste csDMARD begonnen

hatte. In dieser von 2010 bis 2013 durchgeführten nicht-interventionellen Beobachtungsstudie wurden Patienten eingeschlossen, die weniger als 6 Monate RA-Symptome aufwiesen. Für diese Arbeit mussten die Patienten aus allen drei Kohorten bei Einschluss eine moderate bis hohe Krankheitsaktivität aufweisen (DAS28 ≥ 3,2).

Definition prognostisch ungünstiger Faktoren und Outcome

Die von der EULAR vorgeschlagenen prognostisch ungünstigen Faktoren „hohe Krankheitsaktivität", „frühe Erosionen" und „Seropositivität" wurden definiert als DAS28 > 5,1, das Vorhandensein von Erosionen bei Einschluss in die Beobachtungsstudie und Positivität von Rheumafaktor (RF) oder ACPA. Zusätzlich wurden physische Einschränkungen als HAQ (Health Assessment Questionnaire) ≥ 1,2, Adipositas als Body Mass Index (BMI) > 30 kg/m^2, Anzahl an Komorbiditäten (0 vs. 1, ≥ 2) und Rauchen (niemals/früher vs. aktuell) hinsichtlich ihres prognostischen Werts für das Erreichen der Therapieziele LDA oder Remission innerhalb von 6 Monaten untersucht. Der Outcome LDA wurde definiert als DAS28 < 3,2 und Remission als DAS28 < 2,6.

Fehlende Werte

Patienten, die die Therapie während der 6-monatigen Beobachtungszeit wechselten, wurden nur die DAS28-Werte zugeordnet, die sie unter ihrer Ausgangstherapie erreicht hatten. Fehlende Werte wurden mittels multipler Imputationen ersetzt. Genauso wurde mit fehlenden Werten von Kovariablen, wie Erosionen, verfahren.

Einfluss der prognostisch ungünstigen Faktoren

Häufigkeiten der prognostisch ungünstigen Faktoren sowie weitere Baseline Charakteristika wurden deskriptiv dargestellt. Unadjustierte Raten für das Erreichen von LDA bzw. Remission wurden für Subgruppen der Patienten sowie unterschiedliche Kombinationen von prognostischen Faktoren berechnet. Zur Schätzung des Einflusses der prognostischen Faktoren auf die Outcomes LDA und Remission innerhalb von 6 Monaten wurden in allen drei Kohorten generalisierte lineare gemischte Modelle für den binären Outcome verwendet. Diese Modelle ermöglichen es, die Informationen bezüglich der Outcomes nach 3 und 6 Monaten in einem Modell zu nutzen und sind dadurch robuster. Adjustiert wurden die Modelle bei beiden Outcomes für Alter (pro 5 Jahre, nur 1. csDMARD), Krankheitsdauer (2. csDMARD und 1.TNFi), DAS28 > 5.1, HAQ ≥ 1,2, RF/ACPA Positivität, Erosionen, Rauchen (aktuell), BMI > 30 und Anzahl an Komorbiditäten (1, ≥ 2).

2.2 Effektivität von TCZ bei Patienten stratifiziert nach Biologikaversagen

Für diese Analyse wurden Daten aller Patienten verwendet, die mit TCZ bis Oktober 2015 in RABBIT eingeschlossen wurden und mindestens einen Beobachtungszeitpunkt nach Baseline hatten. Die Patienten wurden anhand der Anzahl von Biologikaversagen zu Baseline in vier Gruppen unterteilt: bionaiv, ein Versagen, zwei Versagen und mindestens 3 Versagen.

Therapiekontinuität

Als Surrogat-Maß für Effektivität wurde die Zeit bis zum Abbruch von TCZ (Therapiekontinuität) verwendet. Mit Hilfe von Kaplan-Meier-Methoden wurde dies für die ersten 36 Monate nach Beginn der Therapie untersucht. Da es Patienten mit mehreren Therapieepisoden mit TCZ gab, wurde als Therapieende der erste Stopp einer TCZ-Therapie gewertet. Zusätzlich wurden Cox Proportional Hazards Modelle verwendet, um die Retentionsraten zwischen den Strata zu vergleichen. Therapieabbruchgründe wurden deskriptiv untersucht.

Fehlende Werte

Für die Analyse der Krankheitsaktivität wurden fehlende Werte des DAS28 mittels multipler Imputationsmethoden ersetzt. Genauso wurde mit DAS28-Werten von Patienten verfahren, die innerhalb des analysierten Zeitraums auf ein anderes bDMARD gewechselt sind, da man diese nicht mehr TCZ zuschreiben kann. Das Imputationsmodell für den DAS28 umfasste folgende Variablen: Krankheitsdauer, Anzahl an Komorbiditäten (0, 1, 2, ≥ 3), RF, Anzahl an Biologikaversagen (0, 1, 2, ≥ 3), der letzte zuvor vorhandene DAS28 (unter TCZ), physische Funktion gemessen mit dem Funktionsfragebogen Hannover (FFbH). Fehlende Werte zu den geschwollene Gelenken wurden mittels der Methode Last-Observation-Carried-Forward und nicht mit parametrischer multipler Imputation ersetzt, da die Verteilung mit Konzentration auf Null (keine geschwollenen Gelenke) sehr schief ist.

Krankheitsaktivität über 3 Jahre

Das Erreichen von LDA oder Remission wurde mit dem DAS28 basierend auf der BSG (Blutsenkungsgeschwindigkeit) berechnet. Analysiert wurde der Verlauf des DAS28 über 3 Jahre mittels zweier linearer gemischter Modelle. Das erste Modell entsprach einer Completer-Analyse. Es wurden also nur die Patienten einbezogen, die über ihren gesamten Verlauf von 3 Jahren auf der TCZ Therapie blieben. Im zweiten Modell hingegen wurden alle mit TCZ eingeschlossenen Patienten berücksichtigt. Beide Modelle wurden für Krankheitsdauer, FFbH, DAS28, Anzahl an Komorbiditäten (0, 1, 2, ≥ 3), Anzahl an Biologikaversagen (0, 1, 2, ≥ 3) und

einen Interaktionsterm zwischen Zeit seit Einschluss und Biologikaversagen adjustiert. Dieser Term dient der Untersuchung von unterschiedlichen Verläufen der Krankheitsaktivität in den 4 Gruppen. In einer Teilanalyse wurde zusätzlich noch eine zeitveränderliche Variable für Monotherapie, TCZ + MTX und TCZ + anderes csDMARD aufgenommen. So sollte der mögliche Einfluss der Begleittherapie untersucht werden. Außerdem wurden Wahrscheinlichkeiten für das Erreichen von LDA, hoher Krankheitsaktivität (HDA) bzw. ≥ 2 geschwollenen Gelenken geschätzt. Dazu fanden generalisierte lineare gemischte Modelle Anwendung.

2.3 Risiko für Psoriasis unter verschiedenen Therapien bei RA Patienten

Für die dritte Arbeit wurden Daten aller Patienten aus dem RABBIT Register verwendet, die seit Beginn des Registers am 1.5.2001 bis zum 30.04.2017 eingeschlossen worden waren. Bei der Analyse der gemeldeten schwerwiegenden und nicht-schwerwiegenden Psoriasis-Ereignisse wurden Patienten, bei denen während der Beobachtungszeit eine Psoriasis erstmalig auftrat von denjenigen unterschieden, bei denen diese Erkrankung schon zu Baseline bestanden hatte, es sich also um rekurrente Ereignisse handelte. Diese Ereignisse wurden zusätzlich von der Studienärztin anhand der genauen Ereignisbeschreibungen ohne Kenntnis der Therapie validiert. Im Anschluss erfolgte die Zuordnung zu der Therapie, die im Zeitraum von 3 Monaten vor dem Ereignis verabreicht wurde. Erhielt ein Patient kein bDMARD in dieser Zeit, so wurde das Ereignis der csDMARD Gruppe zugewiesen.

Dropout und fehlende Werte

Als Dropouts wurden hier Patienten gewertet, die aufgrund einer Diagnoseänderung im Verlauf nicht mehr weiter in der Kohorte beobachtet wurden. Diese Patienten (n=6 mit Psoriasisereignis im Verlauf und n=51 ohne) wurden aus der Analyse ausgeschlossen, da wir sicherstellen wollten, dass es sich wirklich um RA-Patienten und nicht eventuell um Patienten mit einer Psoriasis-Arthritis handelt. Für einige Patienten fehlte das Beginndatum des Psoriasisereignisses (n=9 bei inzidenten und n=3 bei rekurrenten Fällen). Da man davon ausgehen kann, dass das Fehlen der Daten nicht systematisch ist, wurden diese Daten mittels multipler Imputation ersetzt. Hierzu wurde eine Gleichverteilung zwischen dem Zeitpunkt vor dem Ereignis und dem Zeitpunkt, zu dem das Ereignis mitgeteilt wurde, verwendet.

Unadjustierte Inzidenzraten für Psoriasis unter verschiedenen Therapien

Es wurden unadjustierte Inzidenzraten pro 1000 Patientenjahre inkl. 95% Konfidenzintervalle (KI) für die verschiedenen Therapien berechnet. Hierfür wurden die TNFi zusammengefasst und

ABA, RTX und TCZ separat betrachtet. Diese Gruppeneinteilung wurde in den meisten nachfolgenden Analysen verwendet. Nur wenn eine getrennte Betrachtung der TNFi sinnvoll war, wie bei der Zeit bis zum Ereignis, wurden separate Angaben zu den TNFi gemacht. Außerdem wurden in einer Subanalyse die Inzidenzraten für die einzelnen TNFi verglichen. Um den Unterschied zwischen allen TNFi zu testen, wurde die Bonferroni-Korrektur für multiples Testen angewendet. JAKi wurden nicht analysiert, da es bis zum Zeitpunkt des Datenbankschlusses nicht genügend Daten gab.

Adjustierte Hazardraten und Risikofaktoren für inzidente und rekurrente Psoriasis

Zur Berechnung der adjustierten Hazardraten (HR) wurden Cox-proportional-hazard Modelle genutzt, wobei wir aufgrund der Fallzahl und der besseren Interpretationsmöglichkeiten die direkte Adjustierung gegenüber einem mit Propensity Scores gewichteten Modell vorzogen. Die notwendige Annahme proportionaler Hazards wurde mithilfe von Schoenfeld Residuen getestet [35]. Eine Verletzung der Annahme liegt vor, wenn sich die Residuen über die Zeit verändern. Dazu wurden die mittleren Korrelationen zwischen den Residuen und der Zeit bis zum Ereignis inkl. 95% KI berechnet. Aufgrund der vorliegenden Datenstruktur mit zeitveränderlichen Variablen wie der Therapie, konnten dafür keine vorhandenen Standardprozeduren verwendet werden. Deshalb wurde eine Prozedur dafür selbst implementiert. Univariate Cox-Modelle wurden berechnet für: Therapie, RF, Alter zu Baseline (pro 5 Jahre), Geschlecht, Glukokortikoiddosis pro 5 mg/d, Rauchverhalten zu Baseline (aktuell, früher/unbekannt, nie), Therapie mit MTX, Hautinfektionen innerhalb von 6 Monaten vor dem Ereignis, DAS28 gemittelt über 12 Monate vor dem Ereignis, Adipositas (BMI > 30 kg/m^2) und Depression zu Baseline. Die ersten acht Variablen gingen in das multiple Cox Modell ein. Die gleichen Kovariablen wurden auch in dem zusätzlich berechneten Cox Modell mit Propensity Score basierten Gewichten verwendet. Dieses Modell dient der Berücksichtigung eines eventuellen Channellings von bestimmten Patienten zu bestimmten Therapien. Bei Patienten mit inzidenter Psoriasis wurden außerdem Sensitivitätsanalysen durchgeführt: (1) Die Behandlung mit TNFi wurde aufgeteilt in TNFi + MTX und TNFi ohne MTX. (2) Es wurden nur Patienten mit seropositiver RA betrachtet, um einen Bias durch mögliche Fehldiagnosen zu vermeiden.

3. Ergebnisse

3.1 Prognostisch ungünstige Faktoren für das Erreichen von LDA oder Remission

Um die EULAR-Kriterien für prognostisch ungünstige Faktoren zu überprüfen, wurden Daten aus der Frühkohorte CAPEA sowie aus dem Biologikaregister RABBIT verwendet. Die 2.714 Patienten unterschieden sich hinsichtlich der Phase im Therapieverlauf: 713 begannen eine Therapie mit dem ersten csDMARD (CAPEA), 1.613 Patienten erhielten nach erstem Therapieversagen ein zweites csDMARD und 388 Patienten begannen eine Therapie mit dem ersten TNFi (beide Gruppen aus RABBIT). Das mittlere Alter lag in den drei Kohorten zwischen 55,6 und 58,9 Jahren. Die mittlere Krankheitsdauer betrug bei Patienten auf dem 1. csDMARD 13 Wochen, auf dem 2. csDMARD 4,8 Jahre und auf dem 1. TNFi 6,5 Jahre.

Häufigkeit von prognostisch ungünstigen Faktoren

Der in allen drei Kohorten häufigste prognostische Faktor war Rheumafaktor- oder ACPA-Seropositivität mit 65% (1.csDMARD) bis 75% (1.TNFi). Der am seltensten beobachtete Faktor war das Vorhandensein von Erosionen, welches von 17% (1. csDMARD) bis 46% (1. TNFi) variierte. Einen DAS28 > 5,1 hatten 53% (1. csDMARD), 35% (2.csDMARD) und 58% (1. TNFi) der Patienten, Funktionseinschränkungen 41% (1. csDMARD) bis 53% (1. TNFi) und mindestens 2 Komorbiditäten 31% (1. csDMARD) bis 54% (1. TNFi).

Unadjustierte Raten für das Erreichen von LDA oder Remission nach 6 Monaten

Der Anteil der Patienten, die LDA oder Remission nach 6 Monaten erreichten, sank mit der Zahl vorheriger Therapieversagen. Unter dem ersten csDMARD erreichten 58% bzw. 39% die Therapieziele LDA bzw. Remission, nach einem Therapieversagen waren es 45% und 26%. Nach Beginn einer Biologikatherapie mit einem TNFi erreichte ein etwas höherer Anteil von 48% bzw. 30% die Therapieziele. Etwas weniger Patienten in allen Gruppen erreichen die Therapieziele, wenn zu Beginn der Therapie eine hohe Krankheitsaktivität (DAS28 >5,1) bestanden hatte. Nahm man die Kriterien erosive Veränderungen und Seropositivität hinzu, änderten sich die Ergebnisse kaum.

Patienten mit der Kombination aus hohem DAS28, physischen Einschränkungen, ≥2 Komorbiditäten und Adipositas erreichten noch seltener LDA/Remission: 33% / 22% (1. csDMARD), 20%/11% (2. csDMARD), 21%/8% (1. TNFi)

Adjustierter Einfluss prognostisch ungünstiger Faktoren auf das Erreichen von LDA/Remission

In allen drei Kohorten zeigte sich ein signifikant negativer Einfluss eines DAS28 > 5,1 (Odds Ratio (OR) [95%-KI]: 0,45 [0,31; 0,65] (1. csDMARD) bis 0,33 [0,18; 0,63] (1. TNFi)) und eines HAQ ≥ 1,2 (OR [95%-KI]: 0,65 [0,44; 0,94] (1. csDMARD) bis 0,21 [0,11; 0,41] (1. TNFi)) auf das Erreichen von LDA innerhalb von 6 Monaten. In der Kohorte, die das erste csDMARD begann, zeigte sich außerdem für Adipositas ein signifikanter Zusammenhang mit dem Erreichen von LDA (OR [95%-KI]: 0,5 [0,33; 0,76]). Dies gilt auch für Patienten, die das zweite csDMARD begannen (OR [95%-KI]: 0,72 [0,58; 0,90]). In dieser Kohorte sind zusätzlich noch mindestens zwei Komorbiditäten ein signifikant ungünstiger Faktor (OR [95%-KI]: 0,64 [0,49; 0,84]), sowie bei Patienten auf dem 1.TNFi (OR [95%-KI]: 0,3 [0,15; 0,62]).

Für das Erreichen von Remission innerhalb von 6 Monaten waren hohe Krankheitsaktivität und Funktionseinschränkungen in allen drei Kohorten signifikante Faktoren. Bei Patienten auf dem zweiten csDMARD verringerten außerdem Adipositas, aktuelles Rauchen und mindestens zwei Komorbiditäten die Chance auf das Erreichen von Remission. Letzteres gilt genauso für Patienten auf dem ersten TNFi.

3.2 Effektivität von TCZ bei Patienten stratifiziert nach Biologikaversagen

Von 885 bei Einschluss mit TCZ behandelten Patienten waren 36% (n=318) bionaiv, 32% (n=286) hatten ein bDMARD Versagen vor Einschluss, 21% (n=186) hatten zwei Versagen und bei 11% (n=95) der Patienten hatten bereits mindestens drei bDMARDs versagt. Verglichen mit bionaiven Patienten waren Patienten mit vorherigem bDMARD Versagen jünger, aber länger krank, hatten mehr csDMARD-Versagen und häufiger Erosionen. Patienten mit mindestens drei Versagen hatten außerdem eine geringere physische Funktion und häufiger mindestens drei Komorbiditäten (47% bei Patienten mit mindestens drei vorherigen Versagen vs. 30% bei bionaiven Patienten).

Dropout und Follow-up

Aufgrund ihres Einschlussdatums konnten 288 Patienten nicht bis zum Datenbankschluss für drei Jahre beobachtet werden. Im Verlauf der drei Jahre beendeten 379 Patienten die TCZ Therapie, wurden aber unter anderen Therapien weiter beobachtet. Nur 60 der analysierten Patienten verließen das Register während des Follow-ups.

Therapiekontinuität

Für Patienten mit maximal zwei bDMARD Versagen waren die Kaplan-Meier-Schätzer der Retentionsraten nach drei Jahren ähnlich (bionaiv: 52%, 1 Versagen: 51%, 2 Versagen: 47%).

Für Patienten mit mindestens drei Versagen war die geschätzte Rate geringer (31%). Das Risiko für den Abbruch von TCZ war in dieser Gruppe ca. zweimal so groß wie für die anderen Gruppen (HR: 2,2 (verglichen mit bionaiv) bis 1,8 (verglichen mit 2 Versagen)). Eine Unterteilung in TCZ Monotherapie, TCZ + MTX und TCZ + andere csDMARDs beeinflusste die Retentionsraten nicht. In allen vier Strata waren die Hauptgründe für das Abbrechen der TCZ-Therapie unerwünschte Ereignisse und Ineffektivität. Die Inzidenzraten (IR) pro 1000 Patientenjahre (PJ) für schwerwiegende Infektionen waren für Patienten, die TCZ abbrachen höher als für Patienten, die auf der Therapie blieben (IR: 33 bis 49 vs. IR: 8 bis 27).

Krankheitsaktivität über 3 Jahre

Für die Completer-Analyse konnten Daten von 335 Patienten (130 bionaiv, 111 mit einem, 70 mit zwei und 24 mit mindestens drei Versagen) verwendet werden. Der Anteil an Patienten, die TCZ für die volle Beobachtungszeit erhielten, nahm also mit steigender Anzahl an vorherigen bDMARD Versagen ab (41% bis 25%). Im Mittel erreichten die Patienten in allen Strata LDA. Die mittlere Verbesserung der Krankheitsaktivität nach 3 Jahren lag zwischen 2,4 und 3,0 DAS28-Punkten. In der zweiten Analyse, in der alle mit TCZ eingeschlossenen Patienten verwendet wurden, war die Verbesserung geringer und variierte zwischen 2,0 und 2,7 DAS28-Punkten. Patienten mit weniger als drei Versagen erreichten auch hier im Mittel LDA nach 3 Jahren. Die geschätzten Wahrscheinlichkeiten für das Erreichen von LDA innerhalb von 3 Jahren lagen zwischen 66% für bionaive Patienten und 48% für Patienten mit mindestens drei Versagen. Es konnten keine Unterschiede der Effektivität für TCZ Monotherapie, TCZ + MTX und TCZ + anderes csDMARD festgestellt werden.

3.3 Risiko für Psoriasis unter verschiedenen Therapien bei RA Patienten

Baselinecharakteristika für Patienten ohne Psoriasis zu Baseline

Für die Analyse der inzidenten Psoriasis wurden Daten von 14.525 Patienten mit insgesamt 63.221 Patientenjahren genutzt, die bis zum 31.10.2017 in RABBIT eingeschlossen wurden und keine Psoriasis zu Baseline aufwiesen. Von den Patienten waren 75% weiblich und 64% (TNFi) bis 84% (RTX) waren RF-positiv. Das Alter variierte von 55 (TNFi) bis 59 (RTX) Jahren und die mittlere Glukokortikoiddosis von 3,7 mg/d (csDMARDs) bis 5,6 mg/d (TNFi, RTX). Eine Komedikation mit MTX erhielten nur 36% der TCZ Patienten, aber 80% der ABA Patienten.

Anzahl der Ereignisse, Inzidenzraten und Hazardraten für inzidente Psoriasis

Insgesamt wurden 117 inzidente Ereignisse (112 nicht schwerwiegende, 5 schwerwiegende) von den Rheumatologen berichtet: 85 unter TNFi, 10 unter RTX, 6 unter ABA, 3 unter TCZ und 14

unter csDMARDs (ein Patient war doppelexponiert gegenüber RTX und ABA). Die unadjustierten Inzidenzraten pro 1.000 Patientenjahre lagen für csDMARDs bei 0,7 und für die Biologika zwischen 0,5 (TCZ) und 3,0 (TNFi, signifikant höher als für csDMARDs). Die Inzidenzraten für die einzelnen TNFi unterschieden sich nicht signifikant.

In der univariaten Analyse waren TNFi und aktuelles Rauchen signifikant mit der Entstehung einer inzidenten Psoriasis assoziiert, wohingegen Behandlung mit MTX das Risiko signifikant reduzierte. Kein Einfluss zeigte sich für die Krankeitsaktivität (DAS28). Im multiplen Modell wurde es deshalb vorgezogen, die Glukokortikoiddosis statt des DAS28 aufzunehmen. Ein signifikant erhöhtes Risiko ergab sich im multiplen Modell nur für TNFi (HR [95%-KI]: 3,87 [2,31; 6,51]), aktuelles Rauchen (HR [95%-KI]: 2,07 [1,28; 3,35]) und weibliches Geschlecht (HR [95%-KI]: 1,69 [1,002; 2,87]). Hingegen reduzierte die Behandlung mit MTX das Risiko signifikant (HR [95%-KI]: 0,5 [0,34; 0,73]). Dieses Ergebnis wurde durch die erste Sensitivitätsanalyse nochmals unterstützt: Sie zeigte für Patienten, die TNFi in Kombination mit MTX erhielten, ein deutlich geringeres Risiko als für Patienten, die TNFi ohne MTX erhielten (HR [95%-KI]: 2.83 [1.54; 5.20] vs. 6.61 [3.79; 11.55]).

Baselinecharakteristika für Patienten mit Psoriasis zu Baseline

Für die Analyse der rekurrenten Psoriasis lagen Daten von 375 Patienten mit 1.521 Patientenjahren vor, für die zu Baseline die Komorbidität Psoriasis durch den Rheumatologen berichtet wurde. Von diesen Patienten waren 70% (TNFi) bis 89% (RTX) weiblich und 56% (csDMARDs) bis 78% (ABA) RF-positiv. Das mittlere Alter zu Baseline lag zwischen 54 (TCZ) und 60 (RTX) Jahren und die mittlere Glukokortikoiddosis zwischen 3,9 mg/d und 6,5 mg/d. Der Anteil der Patienten mit MTX-Komedikation war mit 36% in der TCZ Gruppe am geringsten und bei mit ABA eingeschlossene Patienten mit 79% am höchsten.

Anzahl der Ereignisse, Inzidenzraten und Hazardraten für rekurrente Psoriasis

Es wurden 37 rekurrente Psoriasis Ereignisse gemeldet, welche sich wie folgt auf die Therapien verteilten: 20 TNFi, 6 RTX, 7 ABA, 2 TCZ und 2 csDMARDs. Die unadjustierten Inzidenzraten pro 1.000 Patientenjahre für RTX (IR: 51,4) und ABA (IR: 66,1) waren signifikant höher als jene für csDMARDs (IR: 5,3). Für TCZ (IR: 15,7) und TNFi (IR: 28,0) war der Unterschied nicht signifikant. Auch die adjustierten HRs zeigten ein signifikant höheres Risiko für RTX (HR [95%-KI]: 4,85 [1,53; 15,35]) und ABA (HR: 6,56 [2,28; 18,89]) und keinen signifikanten Zusammenhang mit TNFi (HR [95%-KI]: 2,37 [0,93; 6,03]) und TCZ (HR [95%-KI]: 1,23 [0,25; 6,07]). Es konnten keine weiteren signifikanten Zusammenhänge mit möglichen

Risikofaktoren gezeigt werden. Das gewichtete Modell führte nicht zu nennenswerten Veränderungen.

4. Diskussion

In dieser Dissertation wurde unter Nutzung von Daten aus Langzeitbeobachtungsstudien untersucht, welchen Einfluss Merkmale der Patienten auf die Wirksamkeit und Sicherheit ausgewählter Therapieoptionen haben. Alle drei Arbeiten verfolgen das Ziel, aufgrund belastbarer empirischer Daten Hinweise für die klinische Entscheidungsfindung zu geben.

Die Daten stammen von konsekutiv in der rheumatologischen Routineversorgung beobachteten Patienten. Im Vergleich zu randomisierten klinischen Studien sind die Ergebnisse daher gut in den Versorgungsalltag übertragbar [36]. Gleichzeitig ermöglicht der lange der Follow-up die Untersuchung von Langzeiteffektivität und –sicherheit sowie von seltenen unerwünschten Ereignissen.

Zunächst wurden die in europäischen Therapieempfehlungen verwendeten prognostischen Faktoren für das Therapieansprechen mit empirischen Daten aus drei Kohorten verglichen. Da die Therapiehistorie von entscheidender Bedeutung für den weiteren Therapieverlauf ist, wurden drei Gruppen von Patienten in unterschiedlichen Phasen ihrer Behandlung verglichen: Beginn einer Behandlung mit einem ersten csDMARD, einem zweiten csDMARD oder einem ersten TNFi.

Einen unabhängigen signifikanten Zusammenhang mit dem Erreichen von LDA und Remission fanden wird für folgende Baselinefaktoren: hohe Krankheitsaktivität, physische Einschränkungen, Komorbiditäten und Adipositas. Erosionen und Seropositiviät hatten in allen drei Gruppen keinen Einfluss auf das Erreichen von LDA bzw. Remission innerhalb von 6 Monaten. Eine Studie, die ein ähnliches Ergebnis fand, empfahl, dass traditionelle prognostische Faktoren nicht zur Vorhersage für das Erreichen von LDA oder Remission verwendet werden sollten [37]. Ursprünglich wurden diese traditionellen Faktoren für die Vermeidung der radiographischen Progression als Therapieziel entwickelt und nicht für das Erreichen von LDA oder Remission, wofür sie nun aber von der EULAR als prognostische Faktoren vorgeschlagen werden. Hohe Krankheitsaktivität ist der einzige Faktor aus den Therapieempfehlungen, der in unserer Studie bestätigt werden konnte. Physische Einschränkungen, Adipositas und Komorbiditäten werden nicht als prognostischer Faktor in den Empfehlungen genannt. Andere Studien kamen zu ähnlichen Ergebnissen wie wir [8, 9, 37]. Da für die Faktoren ein unabhängiger signifikanter Zusammenhang festgestellt werden konnte, ist es als sinnvoll zu

erachten, all diese Faktoren als prognostisch ungünstige Faktoren zu verwenden und bei Vorliegen die Therapie frühzeitig zu intensivieren, um eine ausreichende Krankheitskontrolle der RA zu erreichen. Für Rauchen hingegen können wir bisherige Ergebnisse, die Tabakkonsum einen prognostischen Wert zuschreiben [38], nicht stützen. Lediglich für Patienten auf dem zweiten csDMARD ergab sich ein signifikanter Zusammenhang von Rauchverhalten mit dem Erreichen von Remission. Eine Limitation dieser Studie ist, dass Erosionen vom Rheumatologen berichtet und nicht extern beurteilt wurden. Auch gab es keine Follow-up-Informationen bezüglich Erosionen, sondern lediglich Werte zu Baseline.

In der zweiten Arbeit wurde untersucht, welchen Einfluss die Therapiehistorie auf die Wirksamkeit einer ausgewählten Biologikatherapie hat. Hierzu wurde die Effektivität von TCZ im Verlauf von drei Jahren bei bionaiven Patienten sowie Patienten mit einem, zwei und mindestens drei vorherigen bDMARD-Versagen verglichen. RA-Patienten benötigen oft ihr Leben lang eine medikamentöse Therapie. Aus verschiedenen Gründen, zumeist Wirkversagen oder Nebenwirkungen, kommen im Krankheitsverlauf oft mehrere unterschiedliche Therapien zum Einsatz. Deshalb ist es wichtig, wirksame Therapieoptionen auch für Patienten nach mehreren Therapieversagen zu haben. Wir konnten zeigen, dass Patienten mit bis zu zwei vorherigen bDMARD-Versagen unter TCZ im Mittel LDA erreichten und es zu einer mittleren Senkung des DAS28 um mindestens zwei Punkte kam. Zwei Studien aus Großbritannien und den USA zeigten ebenfalls, dass TCZ nach Biologikaversagen eine sehr effektive Therapieoption ist [17, 39]. Patienten mit mindestens drei vorherigen Therapieversagen wurden in beiden Arbeiten allerdings nicht separat analysiert. In unseren Daten hatten diese Patienten nach drei Jahren einen im Mittel signifikant höheren DAS28 als bionaive Patienten. Dies unterstützt die Ergebnisse einer klinischen Studie, die zeigte, dass Patienten mit mindestens drei TNFi-Versagen eine geringere Response auf TCZ haben als Patienten mit einem oder zwei TNFi-Versagen [13]. Allerdings erreichten in unserer Analyse trotzdem noch fast 50% der Patienten mit mindestens drei Versagen nach drei Jahren LDA. Das ist beachtlich, wenn man berücksichtigt, dass diese Patienten im Mittel bereits 15 Jahre erkrankt waren. Die Schwere der Erkrankung zeigte sich u.a. an der hohen Zahl bereits durchgeführter Gelenkoperationen. In dieser Patientengruppe traten auch während der Beobachtungszeit mehr als doppelt so viele Gelenkoperationen auf als in den anderen Gruppen. Diese sind sehr wahrscheinlich als Folge der langanhaltenden aktiven Erkrankung anzusehen und nicht auf die Behandlung mit TCZ zurückzuführen. Ein ähnliches Bild wie für die Krankheitsaktivität zeigte sich auch für die Retentionsraten über drei Jahre. Sie waren für Patienten mit bis zu zwei Versagen nahezu

identisch. Für Patienten mit ≥ 3 Versagen waren die Retentionsraten deutlich geringer und das Risiko für den Therapieabbruch signifikant höher, was nicht nur die geringere Effektivität in dieser Gruppe widerspiegelt, sondern auch das häufigere Auftreten von unerwünschten Ereignissen. Eine Stratifizierung der Patienten in TCZ Monotherapie, TCZ + MTX und TCZ + anderes csDMARD beeinflusste die Retentionsraten und die Ergebnisse zur Krankheitsaktivität nicht nennenswert. Dies unterstützt die Ergebnisse einer Studie, die zeigte, dass begleitende MTX-Therapie keinen Einfluss auf die Effektivität von TCZ hat [17]. Eine Limitation unserer Studie ist, dass als Maß für die Krankheitsaktivität der DAS28 basierend auf der BSG verwendet wurde, denn bei einer Therapie mit TCZ führt nicht nur die Reduktion der Entzündung zur Senkung der BSG, sondern TCZ verringert diese auch direkt [40]. Ein Vergleich des unter TCZ erreichten DAS28 mit anderen Therapien erscheint unzulässig, zwischen Patienten unter TCZ ist der Vergleich aber möglich.

In der dritten Arbeit wurde die Zielsetzung, belastbare Daten für die klinische Entscheidungsfindung zu gewinnen, durch eine vergleichende Analyse des Risikos für ein ausgewähltes unerwünschtes Ereignis unter verschiedenen Therapieoptionen verfolgt. Es wurde das Auftreten von inzidenter oder rekurrenter Psoriasis unter verschiedenen Therapien verglichen. Für ein solches, zumeist nicht-schwerwiegendes, Ereignis gibt es neben Fallberichten oft nur wenig Literatur. Wir konnten zeigen, dass eine inzidente Psoriasis bei RA-Patienten selten auftritt: Die höchste unadjustierte IR trat unter TNFi auf und lag bei 3,0 / 1000 PJ. Die IR für TNFi war im Gegensatz zu ABA, RTX, und TCZ signifikant höher als für csDMARDs. Das adjustierte Modell lieferte ein ähnliches Ergebnis: Das Risiko für inzidente Psoriasis unter TNFi war fast 4-mal so hoch wie für csDMARDs (HR [95%-KI]: 3,97 [2,3; 6,6]). Dies galt nicht für die anderen Biologika RTX, ABA und TCZ. Da die Pathogenese der Psoriasis immer noch nicht gänzlich geklärt ist, ist es schwer zu erklären, woraus der Nachteil der TNFi resultiert. Es gibt die Hypothese, dass es durch die TNFi zu einem Überschuss von Interferon-alpha kommt [41]. Dies scheint für die Entstehung von Psoriasis relevant zu sein [42, 43]. Neben der Therapie ergaben sich keine weiteren Risikofaktoren aus der Analyse: Bei aktuellen Rauchern und bei Frauen war das Risiko für die Entstehung einer inzidenten Psoriasis 2-fach bzw. 1,5-fach höher. In der Allgemeinbevölkerung ist Rauchen als Risikofaktoren für das Entstehen einer Psoriasis aus mehreren Studien bekannt [31-33]. Im Gegensatz zu den genannten Risikofaktoren halbierte die Medikation mit MTX das Risiko für inzidente Psoriasis, insbesondere auch als Komedikation bei Behandlung mit TNFi. Für rekurrente Psoriasis konnten wir neben der Therapie keine weiteren Risikofaktoren identifizieren. Im Gegensatz zur inzidenten Psoriasis fanden wir hier ein

signifikant höheres Risiko unter ABA und RTX verglichen mit csDMARDs. Auch die HRs für TNFi und TCZ waren größer als 1, aber nicht signifikant. Aufgrund der recht geringen Fallzahl sind weitere Studien nötig, um Behandlungsempfehlungen für RA-Patienten mit Psoriasis zu geben. Eine Limitation dieser Studie ist, dass es nicht ganz auszuschließen ist, dass Patienten mit Psoriasis-Arthritis falsch mit der Diagnose RA eingeschlossen wurden. Um dies zu überprüfen, wurde eine Subanalyse nur mit RF-positiven Patienten durchgeführt. Diese zeigte jedoch vergleichbare Ergebnisse, was die Fehlklassifikation unwahrscheinlich macht. Außerdem wurden Patienten, deren Diagnose im Verlauf geändert wurde, ausgeschlossen und alle Fälle, die eine Psoriasis entwickelten, wurden von der Studienärztin validiert. Ein Channelling von Patienten zu bestimmten Therapien wurde mit einem Propensity-Score-gewichteten Modell berücksichtigt. Auch dieses führte zu vergleichbaren Ergebnissen.

Eine Limitation, die alle drei Arbeiten gemein haben, sind die auch bei intensivem Monitoring nicht ganz vermeidbaren fehlenden Werte. In allen drei Arbeiten wurden fehlende Werte nach Überprüfung der Voraussetzungen mittels multipler Imputationsmethoden ersetzt.

Die Ergebnisse aller drei Arbeiten zeigen die Vorteile der longitudinalen Kohorten-Struktur der verwendeten Daten. Sie ermöglicht die Analyse ganz verschiedener Outcomes wie zum Beispiel das Erreichen von Therapiezielen, die Wirksamkeit von Therapien in unterschiedlichen Patientengruppen oder das Risiko von unerwünschten Ereignissen unter verschiedenen Therapien. Für solche Analysen benötigt man Daten von Patienten, die sich in unterschiedlichen Therapiestadien befinden, die idealerweise aus der gleichen Datenquelle stammen und die über längere Zeiträume sorgfältig beobachtet wurden.

Alle drei hier zusammengefassten Arbeiten sind deshalb von Relevanz für die Entwicklung von Therapieempfehlungen und für die klinische Entscheidungsfindung. Sie stellen selbstverständlich nur einen kleinen Ausschnitt dessen dar, was mit großen, langfristig beobachteten klinischen Kohorten möglich ist.

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Eidesstattliche Versicherung

„Ich, Lisa Baganz, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: **„Einflussfaktoren auf das Erreichen von Therapiezielen und die Sicherheit von Therapien bei rheumatoider Arthritis. Eine Analyse von Langzeitbeobachtungsdaten für ausgewählte Therapieoutcomes“** selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. 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.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

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Datum Unterschrift

Anteilserklärung an den erfolgten Publikationen

Lisa Baganz hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1:

Baganz L, Richter A, Albrecht K, Schneider M, Burmester GR, Zink A, Strangfeld A*: Are prognostic factors adequately selected to guide treatment decisions in patients with rheumatoid arthritis? A collaborative analysis from three observational cohorts.*
Semin Arthritis Rheum. 2019 Jun;48(6):976-982.
Impact factor: 5.072

Beitrag im Einzelnen: Datenmanagement und Nacherhebung von Daten für CAPEA. Definition der Patientengruppen. Recherchen zu möglichen prognostischen Faktoren. Wahl der statistischen Methoden (u.a. Imputationsmodell für fehlende Werte, Gemischte Modelle zur Bachtung mehrerer Zeitpunkte pro Patient im Verlauf). Durchführung der Datenanalysen für alle drei Kohorten. Interpretation und Vergleich der Ergebnisse für alle drei Kohorten. Erstellung des Manuskripts. Erstellung von Abbildungen und Tabellen. Einreichung des Manuskripts. Beantwortung der Reviewer-Fragen. Erstellung und Einreichung der Revision.

Publikation 2:

Baganz L, Richter A, Kekow J, Bussmann A, Krause A, Stille C, Listing J, Zink A, Strangfeld A: *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, 38(4):579-587.
Impact Factor: 2.200

Beitrag im Einzelnen: Festlegung des Analyseplans. Ausführliche Analyse zu fehlenden Werten und Dropouts. Wahl und Anwendung der statistischen Methoden (u.a. Imputationsmodell für fehlende Werte im Zeitverlauf, Kaplan-Meierschätzer zur anschaulichen grafischen Darstellung der Retentionsraten).

Durchführung der Datenanalyse. Interpretation der Ergebnisse. Erstellung des Manuskripts. Erstellung von Abbildungen und Tabellen. Einreichung des Manuskripts. Beantwortung der Reviewer-Fragen. Erstellung und Einreichung der Revision.

Publikation 3:

Baganz L, Listing J, Kekow J, Eisterhues C, Wassenberg S, Zink A, Strangfeld A: *Different risk profiles of biologic agents for new-onset psoriasis in patients with rheumatoid arthritis.* Semin Arthritis Rheum. 2019
Impact factor: 5.072

Beitrag im Einzelnen: Festlegung des Analyseplans. Wahl und Anwendung der statistischen Methoden (u.a. Gewichtung mit Propensity Scores zur Vermeidung eines Channeling Bias, Imputation fehlender Beginndaten). Schreiben eines SAS-Makros zur Überprüfung der Modellannahmen des Cox-proportinal-hazard Modells. Präzise Prüfungen zu Diagnoseänderungen und Therapieverläufen. Durchführung der Datenanalyse. Interpretation der Ergebnisse. Erstellung des Manuskripts. Erstellung von Abbildungen und Tabellen. Einreichung des Manuskripts. Beantwortung der Reviewer-Fragen. Erstellung und Einreichung der Revision.

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers/der betreuenden Hochschullehrerin

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Unterschrift des Doktoranden/der Doktorandin

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Publikation 1:

Baganz L, Richter A, Albrecht K, Schneider M, Burmester GR, Zink A, Strangfeld A*: Are prognostic factors adequately selected to guide treatment decisions in patients with rheumatoid arthritis? A collaborative analysis from three observational cohorts.* Semin Arthritis Rheum. 2019 Jun;48(6):976-982.

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Are prognostic factors adequately selected to guide treatment decisions in patients with rheumatoid arthritis? A collaborative analysis from three observational cohorts

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ABSTRACT

Objective: To investigate the impact of indicators of unfavorable prognosis ("poor prognostic factors") on the achievement of low disease activity (LDA)/remission in patients with rheumatoid arthritis (RA).
Methods: Biologic DMARD-naïve patients with RA from three observational cohorts were examined. $N = 713$ patients started their 1st csDMARD, $n = 1613$ switched to the 2nd csDMARD and $n = 388$ to the 1st TNF-inhibitor. High disease activity (DAS28 > 5.1), autoantibodies (RF/ACPA positive), prevalent erosions, functional limitation (HAQ ≥ 1.2), comorbidities, obesity (BMI > 30 kg/m^2), and smoking were evaluated as prognostic factors. Generalized regression analyses were applied to investigate prognostic factors regarding the achievement of LDA (DAS28 < 3.2) or remission (DAS28 < 2.6) within six months.
Results: At baseline, RF/ACPA positivity was most frequent in all cohorts (60.3–75.3%), followed by DAS28 > 5.1 (35–57.7%), HAQ ≥ 1.2 (40.5–52.5%), ≥ 2 comorbidities (31.4–54.1%) and erosions (17.1–46.1%). Remission was achieved by 39% (1st-csDMARD), 26% (2nd-csDMARD) and 30% (1st-TNFi). In adjusted regression models DAS28 > 5.1 (OR: 0.41 [0.30;0.56]), HAQ ≥ 1.2 (0.56 [0.42;0.74]), current smoking (0.72 [0.53;0.97], obesity (0.66 [0.49;0.89] and ≥ 2 comorbidities (0.57 [0.40;0.80]) were independently associated with a lower chance to achieve remission within six months (ORs for 2nd-csDMARD). The proportion of patients in LDA/remission declined by 6–12%-points if DAS28 > 5.1 was present at baseline and by 15–27%-points if functional limitation, comorbidities and obesity were additionally present. In all cohorts RF/ACPA positivity and erosions were not associated with achieving LDA/remission.
Conclusions: While RF/ACPA status and erosions do not affect the achievement of LDA/remission, high disease activity, functional limitation, comorbidities and obesity should be considered as unfavorable prognostic factors in patients starting the 1st or 2nd DMARD strategy.

Introduction

Clinical decision making is based on data on prognosis and expected clinical outcome in groups of patients with a defined disease. Factors associated with an unfavorable prognosis play a prominent role in therapeutic decision making in various medical disciplines [1,2]. In rheumatoid arthritis (RA), so-called poor prognostic factors have been incorporated in almost all treatment recommendations [3]. The most commonly used prognostic factors are high disease activity, early presence of erosions and autoantibody positivity [3,4]. Functional limitation and extraarticular disease were additionally reported traditionally as poor prognostic factors in the former guidelines of the American College of Rheumatology (ACR) [5]. Disease duration at treatment initiation, early treatment response and functional limitation were found to have an impact on disease activity in studies [5–8]. The 2016 update of the European League Against Rheumatism (EULAR) recommendations for the management of RA highlights autoantibodies, high disease activity, and early erosions, and has introduced the failure of two conventional synthetic (cs) DMARDs as additional poor prognostic factor. It is proposed to use these characteristics in clinical decision-making at six months when the first strategy and target attainment have failed [4]. In the absence of poor prognostic factors, switching or adding another csDMARD is suggested, and initiation of a biologic (b) DMARD or JAK-inhibitor is recommended when poor prognostic factors are present [4]. This decision algorithm turns the presence of poor prognostic factors into a door opener for the start with a bDMARD

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therapy but at the same time, withholds treatment intensification from patients without autoantibodies or erosions. In contrast, the 2015 ACR guidelines dispense with poor prognostic factors for therapeutic decisions and recommend a decision exclusively based on disease activity [9]. The treatment target, addressed in both recommendations, is low disease activity (LDA) or remission.

The development of the concept of prognostic factors was mainly based on risk models developed for the outcome of radiologic progression and not LDA or remission [10–14]. The assumption of an exchangeability of outcomes has not been examined. Numerous studies analyzed prognostic factors for remission in RA [15–18] but these studies do not give guidance to clinicians on how to proceed in decision making. So far, prognostic factors are utilized to identify patients with a high risk for disease progression in order to intensify treatment once these factors have manifested. However, this approach does not fully reflect todays possibilities to achieve early sustained remission [19].

Regarding risk estimation in RA, it has been proposed to use data from cohorts of patients representative of a wider RA population instead of selective RCT populations, to investigate additional variables in prediction models and to consider patients undergoing different treatment strategies [20]. Based on this target, the aim of the present study was to investigate the impact of the traditionally used prognostic factors for the outcomes of LDA or remission in large RA cohorts of patients at the time of one of the following treatment decisions: starting the 1st csDMARD, switching to a 2nd csDMARD or switching to the 1st TNF-inhibitor. In addition to the prognostic factors mentioned above, we decided to investigate functional limitation, comorbidities, obesity, and smoking as risk factors for achieving LDA/remission since all of them had shown predictive value in previous studies [16–18].

Methods

Patients

Data from two data sources were used.

The 'Course And Prognosis of Early Arthritis' (CAPEA) inception cohort is a prospective multicenter, non-interventional, observational study investigating the prognostic value of early symptoms for the development of a chronic disease course in patients with early arthritis. Newly referred patients with symptom duration of less than six months were included in CAPEA between 2010 and 2013 [21].

The German biologics register RABBIT (Rheumatoid arthritis: observation of biologic therapy) is an ongoing prospective, observational cohort study on the long-term safety and effectiveness of treatment with bDMARDs and other new therapies in RA patients [22]. In addition, patients treated with csDMARDs are recruited to a control group. Irrespective of the initial treatment and treatment changes, all patients are followed under the same protocol. Patients are eligible for enrolment at the start of treatment with a cs- or bDMARD after failure of at least one DMARD.

Data reported by rheumatologists and patients comprise demographics, clinical status including joint counts, treatment, laboratory tests, and patient-reported outcomes. All patients give their informed consent before enrolment.

Both data bases received approval by the Ethics Committee of the Charité University Medicine, Berlin.

The inclusion criteria were:

- CAPEA: DMARD-naïve RA patients starting the 1st csDMARD
- RABBIT: bDMARD-naïve RA patients switching either to a 2nd csDMARD or to a TNFi after one previous csDMARD failure, enrolled from 01.01.2009 to 31.10.2016 (at least 6 months prior to data closing date: 30.04.2017)
- Both: at least moderate disease activity at baseline, defined by the disease activity score with 28 joints (DAS28) $\geq$ 3.2 and with at least one follow up visit

Prognostic factors and outcome

In both data sources, rheumatologists at baseline report the parameters proposed by EULAR as poor prognostic factors [4]. High disease activity (DAS28-ESR > 5.1), autoantibody positivity, defined as positive rheumatoid factor (RF) or anti-citrullinated protein antibody (ACPA) and presence of erosions on radiographs. In addition to these factors, functional limitation, obesity, number of comorbidities and tobacco use were assessed. The number of comorbidities is a sum of more than 20 selected comorbidities of a tick list in the questionnaire checked by the rheumatologist at baseline, including amongst others hypertension, diabetes, chronic obstructive pulmonary, cardiovascular, renal and psychological diseases. In both databases, the Hannover Functional Ability Questionnaire (FFbH) which can be transformed into HAQ values [23] was used to assess functional limitation. HAQ values $\geq$ 1.2 were regarded as considerable functional limitation [24]. Obesity was classified according to the definition of the World Health Organization (WHO) as BMI > 30 kg/m^2 [25]. Having one or $\geq$ 2 comorbid conditions was examined as a poor prognostic factor. Tobacco use was reported as current, former or never smoking, and current smoking was assessed for its potential prognostic value. Age (1st csDMARD cohort) and disease duration (2nd csDMARD, 1st TNFi cohorts) were assessed as covariates.

The outcomes were achievement of LDA (DAS28 < 3.2) or remission (DAS28 < 2.6) within six months.

Statistical analysis

Baseline characteristics and frequencies of prognostic factors are reported for the three patient groups: 1st csDMARD, 2nd csDMARD, 1st TNFi. The number of patients presenting with different combinations of prognostic factors are graphically displayed, using UpSetR [26].

To consider unequal dropout in patients with different treatments, an intention-to-treat (ITT) approach was used for the outcomes LDA and remission. In general, the DAS28-ESR was used to evaluate disease activity. If DAS28-ESR was missing (n = 126) but DAS28-CRP was available at baseline, DAS28-CRP was also used at follow up and converted to DAS28-ESR values [27]. In patients who switched from enrolment therapy to another DMARD therapy within six months only DAS28 values were considered that were achieved under the enrolment therapy. Missing values of the DAS28 and of covariates such as erosions were imputed using multiple imputations. Both imputation models included the baseline variables age and rheumatoid factor and additionally previous values of DAS28 and physical function for DAS28.

Generalized linear mixed models were applied to estimate the impact of the proposed prognostic factors regarding the achievement of LDA/remission (at months 3 and 6). This method takes correlation between repeated measurements into account and leads to more robust results because it not only uses the information after 6 months but also the one from the 3 months visit. The full model comprised age (by 5 years) for the 1st csDMARD cohort, disease duration in years for 2nd csDMARD and 1st TNFi cohorts, DAS28 > 5.1, HAQ $\geq$ 1.2, RF/ACPA positivity, erosions, current smoking, BMI > 30 kg/m^2 and number of comorbidities (none, 1, $\geq$ 2). Due to the high correlation between DAS28 and glucocorticoids we decided not to include glucocorticoid dosage in the final model.

Uncertainty of results is indicated by 95% confidence intervals (CI). Missing values are reported in Table 1. Data comprising multiple imputations were analyzed using SAS [28].

Results

Patient characteristics

A total of 713 patients starting the 1st csDMARD (CAPEA), 1613 patients switching to the 2nd csDMARD therapy (RABBIT) and

Table 1
Patient characteristics and frequency of poor prognostic factors at baseline

	1st csDMARD (n = 713)	Missing values	2nd csDMARD (n = 1613)	Missing values	1st TNFi (n = 388)	Missing values
Sex, female, N (%)	442 (62)	0	1193 (74)	0	249 (64.2)	0
Age in years, mean (SD)	57.1 (13.9)	0	58.9 (12.7)	0	55.6 (14.6)	0
Disease duration in weeks, mean (SD)	12.6 (6.8)	1	–	–	–	–
Disease duration in years, mean (SD)	–	–	4.8 (6.1)	2	6.5 (7.5)	1
ESR	35.5 (24.1)	36	29 (20.4)	71	32.6 (22.4)	19
CRP	22.1 (33.1)	29	12.9 (19.1)	139	16.8 (18.9)	18
SJC	6.7 (5.1)	0	4.5 (4)	0	6.5 (5.3)	0
DAS28	5.3 (1.1)	0	4.8 (1)	0	5.3 (1.1)	0
DAS28 3.2– 5.1, N (%)	337 (47.3)	0	1049 (65)	0	164 (42.3)	0
>5.1, N (%)	376 (52.7)	0	564 (35)	0	224 (57.7)	0
RF or ACPA positive (%)	460 (65.2)	7	971 (60.3)	3	287 (75.3)	7
RF and ACPA positive (%)	271 (52.4)	196	610 (41.4)	138	198 (59.1)	53
Radiologic erosions, N (%)	104 (17.1)	104	413 (27.2)	95	175 (46.1)	8
HAQ	1.1 (0.6)	0	1.2 (0.6)	37	1.3 (0.6)	3
HAQ ≥ 1.2, N (%)	289 (40.5)	0	697 (44.2)	37	202 (52.5)	3
BMI	27.1 (5)	0	28.1 (5.4)	0	27.2 (5.6)	0
BMI > 30, N (%)	168 (23.6)	0	521 (32.3)	0	92 (23.7)	0
Smoking, current, N (%)	241 (33.8)	0	414 (25.7)	0	126 (32.5)	0
GC dose at enrolment mg/d, mean (SD)	15 (17.1)	0	7.8 (9.9)	0	6.7 (6.8)	0
GC dose last 6 months mg/d, mean (SD)	–	–	3.1 (4.5)	1	4.4 (6)	0
No comorbidities, N (%)	268 (37.6)	0	487 (30.2)	0	98 (34.3)	0
One comorbidity, N (%)	221 (31)	0	528 (32.7)	0	80 (20.6)	0
Two or more comorbidities, N (%)	224 (31.4)	0	598 (37.1)	0	210 (45.1)	0

388 patients switching to the 1st TNFi (RABBIT) were included. The mean age in patients on the 1st csDMARD was 57.6 years and the mean disease duration was 13 weeks. Patients switching to the 2nd csDMARD were on average 58.9 years old and had a mean disease duration of 4.8 years. In the third group (1st TNFi), patients were on average 55.6 years old and had a mean disease duration of 6.5 years. All baseline characteristics are reported in Table 1.

Frequency of poor prognostic factors

At baseline, DAS28 > 5.1 was present in 53% (1st csDMARD), 35% (2nd csDMARD) and 58% (1st TNFi) of all patients. 41% (1st csDMARD) to 53% (1st TNFi) had functional limitation (HAQ > 1.2) and 31–54% had two or more comorbidities. RF or ACPA was present in 65% (1st csDMARD) to 75% (1st TNFi). The number of patients with radiologic erosions was highest in patients starting 1st TNFi (46.1%) and lowest in those starting the 1st csDMARD (17.1%) The frequencies of all prognostic factors are listed in Table 1.

Of all patients with DAS28 > 5.1, 53% (1st csDMARD) to 62% (1st TNFi) also had functional limitation (HAQ > 1.2). 33% (1st csDMARD) to 52% (1st TNFi) had DAS28 > 5.1 and ≥ 2 comorbidities. A combination of DAS28 > 5.1, erosions, and RF/ACPA positivity were found in 7% (8%) of the patients enrolled with the 1st (2nd) csDMARD and in 23% of patients who started the 1st TNFi. Fig. 1 shows the coincident presence of two or three prognostic factors. In all cohorts, RF or ACPA positivity was the most common single and also the most common combined factor. All other factors predominately occurred in combination.

Crude rates of achievement of LDA or remission at six months

LDA/remission were achieved by 58%/39% (1st csDMARD), 45%/26% (2nd csDMARD) and 48%/30% (1st TNFi) of patients. The proportion of patients in LDA/remission was lowered by 6–12%-points if a DAS28 > 5.1 had been present at baseline. If patients had high disease activity, functional limitation, comorbidites and obesity at baseline, the frequency of achieving LDA/remission dropped to 33%/22% (1st csDMARD), 20%/11% (2nd csDMARD) and 21%/8% (1st TNFi). The unadjusted percentages of LDA/remission achievement at six months are reported in Table 2.

Within six months, a total of 2% (1st csDMARD) and 9% (2nd csDMARD) switched to a bDMARD strategy and 1% of patients who started their first TNFi switched to a non-TNFi.

Regression results for achievement of LDA or remission within six months

In patients enrolled with their 1st csDMARD, high disease activity (DAS28 > 5.1), functional limitation (HAQ ≥ 1.2) and obesity (BMI > 30 kg/m^2) were independently significantly associated with a lower chance to achieve LDA within six months. In patients enrolled with the 2nd csDMARD, comorbidities were an additional significant factor for the outcome LDA. In the third group (1st TNFi), high disease activity, functional limitation and comorbidities were significantly associated with outcome LDA. Autoantibody status, erosions and current smoking were not significantly associated with the achievement of LDA in any of the cohorts (Table 3). In patients starting the 1st csDMARD, ORs for comorbidities were lower than 1 but not significant. The same applies to current smoking in this subgroup.

Regarding remission, the results are comparable to the ones for LDA (Table 4) with the difference that in patients starting the 1st csDMARD the negative effect of obesity was not significant. In patients enrolled with the 2nd csDMARD, current smoking was an additional significant factor associated with the achievement of remission.

When including the DAS28-components instead of the DAS28 itself, we found that higher tender joint counts lead to a lower chance to achieve LDA in all three cohorts and a lower chance for remission in the 2nd csDMARD and 1st TNFi cohort. In all cohorts a higher ESR value decreased the chance of achieving LDA or remission and in the 2nd csDMARD cohort a worse value of patient global was associated with a lower chance to achieve LDA/remission (data not shown).

Discussion

This study examined the impact of those factors that are included in current treatment recommendations for RA to predict an unfavorable prognosis regarding the achievement of LDA or remission after six months of treatment. We used three patient groups from two different data sources to model typical treatment situations: Initiation of a first csDMARD therapy, using data from the early arthritis cohort

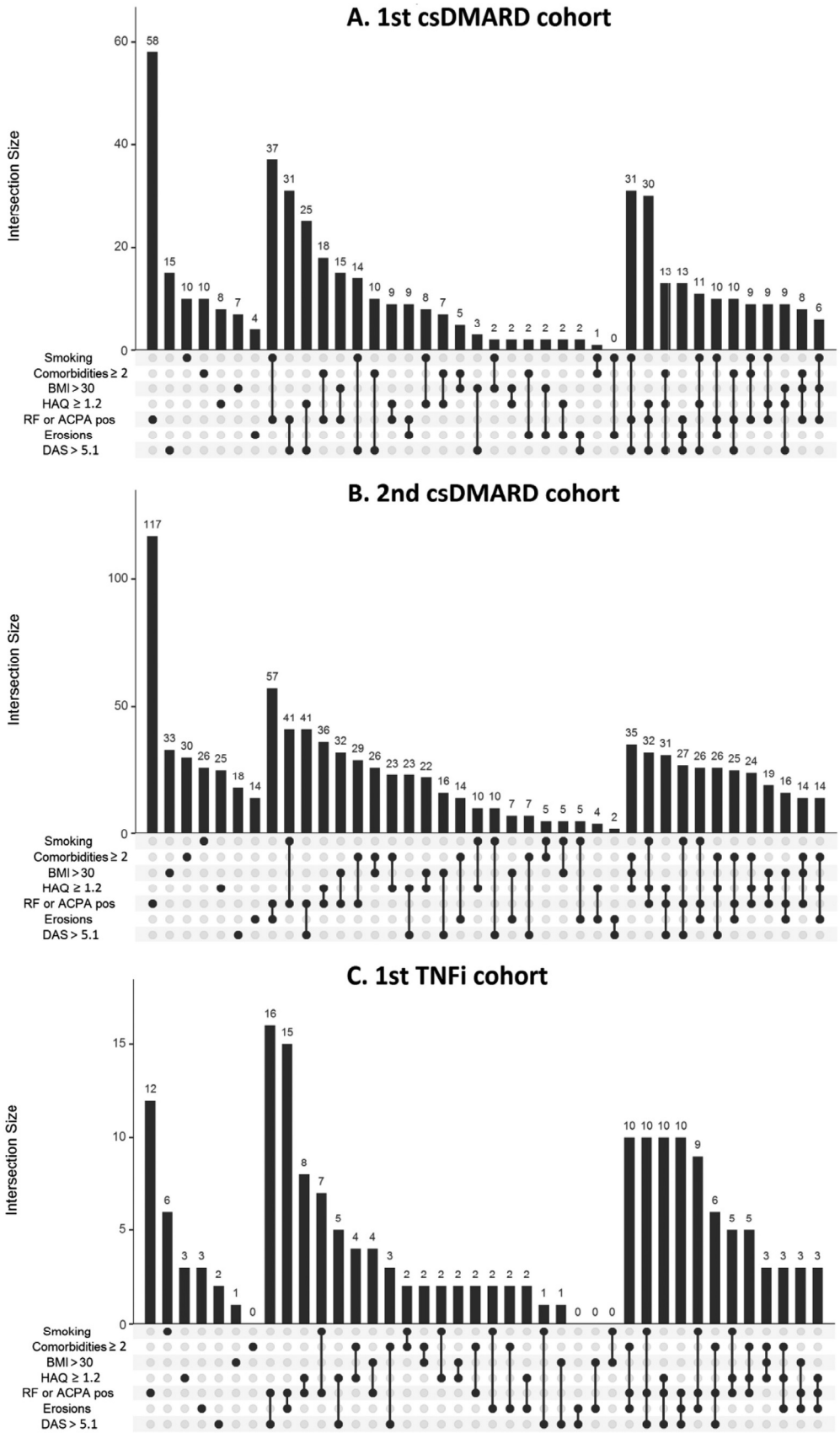

Fig. 1. Number of patients with one or several prognostic factors at baseline.

The bars show the number of patients with exclusively one, two or three prognostic factors (Intersection size).

Abbreviations: BMI > 30 Body mass index > 30, HAQ ≥ 1.2 Health Assessment Questionnaire ≥ 1.2, RF Rheumatoid Factor, ACPA anti-citrullinated protein antibodies, pos positive, DAS > 5.1 Disease activity score > 5.1.

Table 2
Unadjusted percentages of patients achieving Low disease activity or remission at six months

	1st csDMARD (*N* = 713)	2nd csDMARD (*N* = 1613)	1st TNFi (*N* = 388)
LDA			
of all patients	58% (*n* = 416)	45% (*n* = 725)	48% (*n* = 186)
of patients with			
DAS28 > 5.1	52% (*n* = 194)	33% (*n* = 187)	37% (*n* = 82)
DAS28 > 5.1 + erosions + RF/ACPA positivity	58% (*n* = 28)	30% (*n* = 38)	35% (*n* = 31)
DAS28 > 5.1 + HAQ ≥ 1.2 + ≥ 2 comorbidities + BMI > 30	33% (*n* = 10)	20% (*n* = 16)	21% (*n* = 7)
Remission			
all patients	39% (*n* = 278)	26% (*n* = 415)	30% (*n* = 117)
of patients with			
DAS28 > 5.1	31% (n = 118)	16% (n = 92)	22% (n = 49)
DAS28 > 5.1, erosions, and RF/ACPA positivity	32% (*n* = 16)	16% (*n* = 20)	22% (*n* = 20)
DAS28 > 5.1, HAQ ≥ 1.2, ≥ 2 comorbidities, BMI > 30	22% (*n* = 7)	11% (*n* = 9)	8% (*n* = 3)

Table 3
Achievement of low disease activity within six months: results of generalized linear mixed models

	1st csDMARD OR (95% CI)	2nd csDMARD OR (95% CI)	1st TNFi OR (95% CI)
Age (by 5 years)	1.00 (0.93–1.07)		
Disease duration in years		1.00 (0.99–1.02)	1.00 (0.96–1.04)
DAS28 > 5.1	**0.45 (0.31–0.65)**	**0.42 (0.33–0.53)**	**0.33 (0.18–0.63)**
HAQ ≥ 1.2	**0.65 (0.44–0.94)**	**0.55 (0.44–0.70)**	**0.21 (0.11–0.41)**
RF/ACPA positive	0.77 (0.54–1.10)	0.93 (0.75–1.15)	1.28 (0.63–2.57)
Erosions	0.82 (0.52–1.30)	0.83 (0.65–1.07)	1.06 (0.60–1.89)
Smoking, current	0.71 (0.48–1.04)	0.85 (0.66–1.10)	1.04 (0.55–1.94)
BMI > 30 kg/m^2	**0.50 (0.33–0.76)**	**0.72 (0.58–0.90)**	0.87 (0.45–1.70)
One comorbidity	0.72 (0.47–1.10)	0.93 (0.72–1.20)	**0.40 (0.18–0.89)**
Two or more comorbidities,	0.70 (0.45–1.10)	**0.64 (0.49–0.84)**	**0.30 (0.15–0.62)**

Achievement of low disease activity within three and six months determined by poor prognostic factors in patients with baseline DAS28 ≥ 3.2.
Abbreviations: ACPA antibodies to citrullinated proteins, BMI body mass index, CI confidence interval, DAS28 Disease Activity Score of 28 joints, HAQ health assessment questionnaire, LDA low disease activity (DAS28 < 3.2), No. number, RF rheumatoid factor, OR odds ratio.

Table 4
Achievement of remission within six months: Results of generalized linear mixed models

	1st csDMARD OR (95% CI)	2nd csDMARD OR (95% CI)	1st TNFi OR (95% CI)
Age (by 5 years)	1.01 (0.94–1.08)		
Disease duration in years		1.00 (0.98–1.03)	1.01 (0.97–1.05)
DAS28 > 5.1	**0.46 (0.32–0.67)**	**0.41 (0.30–0.56)**	**0.53 (0.29–0.99)**
HAQ ≥ 1.2	**0.55 (0.37–0.82)**	**0.56 (0.42–0.74)**	**0.25 (0.13–0.49)**
RF/ACPA positive	0.78 (0.54–1.14)	0.86 (0.66–1.13)	0.76 (0.37–1.54)
Erosions	0.77 (0.48–1.25)	0.97 (0.72–1.31)	0.84 (0.44–1.60)
Smoking, current	0.67 (0.46–1.00)	**0.72 (0.53–0.97)**	0.75 (0.39–1.46)
BMI > 30 kg/m^2	0.71 (0.46–1.07)	**0.66 (0.49–0.89)**	0.67 (0.32–1.38)
One comorbidity	0.71 (0.46–1.09)	0.90 (0.65–1.26)	**0.35 (0.15–0.79)**
Two or more comorbidities,	0.65 (0.41–1.02)	**0.57 (0.40–0.80)**	**0.27 (0.13–0.56)**

Legend: Achievement of low disease activity within three and six months determined by poor prognostic factors in patients with baseline DAS28 ≥ 3.2.
Abbreviations: ACPA antibodies to citrullinated proteins, BMI body mass index, CI confidence interval, DAS28 Disease Activity Score of 28 joints, HAQ health assessment questionnaire, LDA low disease activity (DAS28 < 3.2), No. number, RF rheumatoid factor, OR odds ratio.

CAPEA, and start of a second csDMARD or a first TNFi in the observational cohort study RABBIT. This approach ensured the investigation of a broad spectrum of treatment situations which are closely linked to the concept of prognostic factors. We found that the proportion of patients achieving LDA or remission declined considerably if high disease activity, functional limitation, comorbidities and obesity were present. Each of these factors was independently and significantly associated with a lower chance to achieve LDA or remission. In contrast, RF/ACPA status and the presence of erosions did not affect the outcome LDA or remission.

Overall, the rates of patients achieving LDA or remission are relatively low, reflecting real-world data from patients who differ in their clinical characteristics and remain on DMARD strategies longer compared to patients included in clinical trials.

High disease activity is the dominating prognostic factor in all current treatment recommendations [3]. In our data, high disease activity at baseline was confirmed to be a robust prognostic marker in all cohorts and for both outcomes LDA and remission, being present in half of all patients on the first csDMARD and first TNF-inhibitor and in little less than half of all patients starting the second csDMARD. However, if disease activity alone is considered as prognostic marker, as suggested by the ACR [9], the independent impact of functional limitation, comorbidities and obesity is neglected.

Functional limitation has been recognized as a relevant factor for the achievement of remission in the ESPOIR cohort [7]. Our results confirm the potential to capture patients with a lower probability to achieve LDA or remission by using the HAQ-questionnaire.

Comorbidities are increasingly noticed as important predictors of RA outcomes. Recent data from an Italian RA cohort indicate the relevance of comorbidity as a negative predictor of LDA or remission in patients who started TNF-inhibitors [17]. While in patients on the 1st csDMARD comorbidities did not influence the six months outcome, our results support the negative association of comorbidities with the achievement of LDA or remission in patients on the 2nd DMARD strategy. Treatment limitations with an increasing number of comorbidities may particularly affect 2nd and further treatment strategies.

Obesity was associated with a lower chance to achieve LDA in patients on the 1st and 2nd csDMARD but not on the 1st TNF inhibitor. A recent meta-analysis found obesity to reduce the chances to achieve remission (defined by DAS28 < 2.6) in patients with RA receiving treatment with cs- or bDMARDs [16]. Since the influence of obesity was independent to HAQ and disease activity, we conclude that obesity should also be considered as a factor of prognostic relevance.

Smoking is often discussed as a relevant prognostic factor associated with activity and severity of RA, radiologic progression and a lower treatment response [29]. The present results do not support an independent effect of current smoking on achieving LDA. Smoking was associated only with remission in patients on the 2nd csDMARD strategy. However, the association of smoking and disease activity in patients on the 1st csDMARD may lead to an attenuated effect of smoking in the fully adjusted approach through collinearity.

Autoantibodies and erosions are known predictors for structural progression [10–14]. However, in this study of three groups of RA patients at different stages of treatment escalation, none of these factors was associated with achieving LDA or remission within six months. This is in line with the results from the ESPOIR cohort that remission cannot be predicted by the presence of autoantibodies or erosions [7]. These confirming results suggest that traditional prognostic factors derived from prediction models for rapid radiographic progression are not suitable for predicting the non-achievement of LDA or remission. It has been recognized for years that clinical outcomes of RA such as mortality or work disability are predicted primarily by poor functional status and also by comorbidities more significantly compared to laboratory tests or radiographs [30–32] but

these findings were not implemented in treatment recommendations.

The coincident presence of several factors has rarely been used for stratification to date [33]. The present results show that in all cohorts RF or ACPA positivity and any combination thereof with other prognostic factors is very common while erosions alone hardly ever occur in any cohort. This supports the assumption that structural damage is closely linked to disease activity and usually considered a consequence thereof [29]. There is robust evidence that achievement of low disease activity or remission in an early stage of RA is able to prevent radiographic progression [34]. Therefore, erosions as a criterion for therapy escalation should be the exception and appear to be outdated in today's treatment recommendations [29,35]. Similarly, focusing on autoantibodies may mask high disease activity and/or functional limitation in seronegative patients and impede necessary escalation of therapy [33,36–38]. The mean disease duration was more than four years in patients switching to a 2nd DMARD strategy. This contrasts with trial data or recommendations that suggest an early switch to a 2nd treatment strategy if LDA or remission is not achieved. This real-world data from RABBIT shows that most patients remain considerably long on their first csDMARD. One reason may be a secondary loss of effectiveness of the 1st csDMARD after years of treatment which made it difficult to assess disease duration as a prognostic marker in these cohorts. Sufficient evidence exists to confirm short disease duration at treatment initiation and early response as predictors of remission in RA [8,39,40]. However, treatment decisions need to be made also in patients with previous treatment failures. In a previous paper, based on the comparison of RA cohorts at different treatment stages, we observed that the percentage of patients with autoantibodies and erosions increased with the number of treatment failures [41].

In agreement with the treat-to-target principle and all current treatment recommendations [3] we selected LDA and remission as outcomes. If high disease activity, functional limitation, comorbidities and obesity are considered as relevant prognostic factors, 58% of patients without any poor prognostic factor, 49% of patients with one, but only 19% of patients with all four factors achieved LDA. These results confirm that specific prognostic factors as well as the number of factors in an individual patient are relevant for the achievement of LDA as treatment target.

Limitations and strengths

By including patients from the CAPEA cohort, starting on the first csDMARD, and two patient groups from RABBIT, starting on the 2nd DMARD or 1st TNFi, our analyses cover the main situations concerning treatment initiation or escalation in early and established disease that are addressed in treatment recommendations. All cohorts had considerable sample sizes while drop out of patients was very rare. Nonetheless, missing information was considered by multiple imputations. A limitation of the study is that baseline erosions were not evaluated by independent readers but reported by the rheumatologists. The proportion of erosions was comparable to other RA cohorts indicating sufficient quality of reporting [26]. No information on new erosions during follow-up were available. This condition represents routine rheumatologic care outside clinical trials. The frequently missing data on erosions and their inconsistent assessment are additional reasons for the assumption that erosions are not the best markers to guide treatment decisions in daily care. Using only the sum of over 20 selected comorbidities is a coarsened approach compared to examining the effects of individual comorbidities since the impact of cardiovascular comorbidities vs. psychological disorders might be different. However, evaluation of specific effects of comorbidities is beyond the scope of this study.

In conclusion, high disease activity, functional limitation, comorbidities and obesity may be considered as negative prognostic factors for achieving LDA or remission within six months after starting the first or second DMARD strategy. Current smoking was additionally negatively associated with the achievement of remission. Of the traditional poor prognostic factors to predict radiologic progression, only disease activity remained associated with the achievement of LDA. Autoantibodies and erosions are of limited value to guide decisions on treatment escalation when LDA/remission is the target.

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Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2018.09.003.

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COHORT STUDIES

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

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Abstract

In Germany, Tocilizumab (TCZ) is used for the treatment of rheumatoid arthritis both in biologic-naïve patients and those with previous failures of biologic disease-modifying antirheumatic drugs (bDMARDs). The long-term effectiveness and retention rates of TCZ in patients with different numbers of prior bDMARD failures has rarely been investigated. We included 885 RA patients in the analyses, enrolled with the start of TCZ between 2009 and 2015 in the German biologics register RABBIT. Patients were stratified according to prior bDMARD failures: no prior bDMARD or 1, 2 or ≥ 3 bDMARD failures. We applied Kaplan–Meier methods and Cox-regression to examine treatment adherence as well as linear mixed effects models to investigate effectiveness over 3 years of follow-up. Compared to biologic-naïve patients, those with prior bDMARD failures at start of TCZ were younger but had significantly longer disease duration and more comorbidities. DAS28 at baseline and loss of physical function were highest in patients with ≥ 3 bDMARD failures. During follow-up, patients with up to two bDMARD failures on average reached low disease activity (LDA, DAS28 < 3.2). Those with ≥ 3 prior bDMARDs had a slightly lower response. However, after 3 years, nearly 50% of them achieved LDA. Treatment continuation on TCZ therapy was similar in patients with ≤ 2 bDMARD failures but significantly lower in those with ≥ 3 bDMARD failures. TCZ seems to be similarly effective in patients with no, one or two prior bDMARD failures. The majority of patients achieved LDA already after 6 months and maintained it over a period of 3 years. TCZ proved effective even in the high-risk group of patients with more than two prior bDMARD failures.

Keywords Observational cohort study · Treatment strategy · Biologics register · IL-6 blockade · Line of therapy

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Introduction

With the advent of biologic disease-modifying antirheumatic drugs (bDMARDs), the treatment options for the management of rheumatoid arthritis (RA) have improved tremendously. The availability of treatments with different mechanisms of action addresses the need for therapies targeting different components of the immune system since patients may not respond to a specific bDMARD therapy but to another mode of action. Since 2013, the EULAR guidelines entitle remission or low disease activity (LDA) to be the primary treatment target in all RA patients [1]. If the target cannot be reached within 6 months after initiating treatment, the therapy should be altered by adding conventional synthetic (cs)DMARDs, switching to a bDMARD and consequently also between bDMARDs. Expedited therapy decisions involve sequential use of different DMARDs. Therefore, more recently licensedbDMARDs representing new modes of action are often prescribed as second-, third- or fourth-line therapies after failure of a tumor necrosis factor α inhibitor (TNFi). This practice reflects limited long-term data about safety and effectiveness of new drugs rather than evidence of effectiveness after bDMARD failure.

Determining an optimal treatment algorithm for RA patients is methodologically complex. Various studies compared the effectiveness of switching to a second TNFi or to a bDMARD with another mode of action after one TNFi failure [2–5]. The studies showed that in patients who switched to a bDMARD with a different mode of action the drug survival [2, 3], improvement in DAS28 (Disease Activity Score based on 28 joint counts) [5] and the remission rates [4] were higher [2–5]. Other studies showed that a second TNFi can be effective, specifically after discontinuation because of adverse events [6, 7], and no differences in outcomes (CDAI, ACR responses, mHAQ) were found for patients with prior TNFi exposure who received either another TNFi or abatacept [8]. It has been recommended to use different mechanisms of action at least after the second TNFi-failure [9, 10]. Heretofore, no clear recommendation about the optimal sequence of different DMARDs is available [1].

TCZ is a humanised monoclonal antibody targeting the IL-6 receptor. This bDMARD has been approved in 2009 for the treatment of RA and is administered either intravenously or subcutaneously (since 2014). Recommended doses of TCZ are 8 mg/kg once every 4 weeks (intravenously) or 162 mg every week irrespective of the patient's weight (subcutaneously). Studies show that besides a higher incidence of injection side reactions, the safety and efficacy of subcutaneous TCZ are similar to intravenous treatment [11, 12] and also switching from intravenous to subcutaneous injection seems to have no influence on safety and efficacy [13, 14]. While TCZ is approved both as monotherapy and in combination with methotrexate (MTX), combinations with other csDMARDs are not. The recommendation is to use TCZ in combination with MTX [1]. The usage of TCZ as second line bDMARD after failure of TNFi which was shown to be an effective treatment option by several RCTs [15–17] is common in Germany. A recent study showed that in short-term use (6-months follow-up) TCZ was equally effective in biologic-naïve patients and patients with prior bDMARD failures [18]. However, it is not clear if in the long run response to treatment with TCZ is lower in patients with prior bDMARD failure compared to biologic-naïve patients. Furthermore, outcome and safety of TCZ treatment in patients with more than two bDMARD failures have been insufficiently investigated.

The aim of this study was to examine the effectiveness of TCZ over 3 years of follow-up depending on the patients' prior exposure to bDMARDs. Due to the observational design of this study differences of patients' baseline characteristics are taken into account as well as concomitant treatment with csDMARDs and time-varying doses of glucocorticoids (GCs). Furthermore, the impact of attrition in this cohort of RA patients is examined as well as reasons for discontinuing treatment with TCZ.

Subjects and methods

Data source

We analysed data from the German biologics register RABBIT (Rheumatoid Arthritis: Observation of Biologic Therapy) which is an ongoing observational cohort study initiated in 2001. RA patients can be included if they start a licensed bDMARD, biosimilar or a csDMARD therapy after at least one csDMARD failure. At baseline, after 3, 6 and then every 6 months, rheumatologists report start and stop dates of actual DMARD therapies, prior DMARD therapies, glucocorticoid doses, comorbidities (at baseline, after 2.5, 5 and 7.5 years), adverse events and features of the clinical status such as the disease activity measured by DAS28 and its components [including erythrocyte sedimentation rate (ESR)]. Patient-reported outcomes are recorded at the same visits. Physical function is captured by a German instrument [Funktionsfragebogen Hannover (FFbH)] similar to the Health Assessment Questionnaire [19]. If patients stop their baseline therapy, they are not excluded but they will be observed for up to 10 years regardless of their treatment.

If patients have not visited the rheumatologist for more than 1 year without information, extensive dropout investigations are carried out including enquiries to doctors, patients themselves or their relatives. Vital status and causes of death are requested from the local administration and health

offices. Further details of design and conduct of the RABBIT study were reported elsewhere [20].

Patient selection

The enrolment of patients initiating TCZ treatment started in 2009. Until 31 October 2015, 950 patients were enrolled into RABBIT. We excluded 65 patients from the analysis for whom currently only baseline data were available. In total, 885 patients contributed to the analyses. Patients who missed at least two scheduled visits were considered as dropouts.

Statistical analysis

Patients were stratified into four groups according to the number of bDMARD failures prior to initiation of TCZ. We compared baseline characteristics of patients with one or more bDMARD failures with those of biologic-naïve patients (reference group).

Therapy discontinuation within 36 months of follow-up was examined using Kaplan–Meier methods; Cox-proportional hazard models were applied to compare retention rates between strata of bDMARD failures. We defined discontinuation as the end of the first TCZ therapy after the enrolment in RABBIT. In addition, we investigated the time to stop TCZ with different concomitant csDMARD therapies.

The effectiveness of TCZ was evaluated using the DAS28-ESR over the first 3 years after treatment initiation. We applied two different linear mixed models: the first model is a completer analysis including only patients who maintained TCZ treatment throughout their complete follow-up. In the second model, we considered all patients initiating TCZ treatment at baseline (intent-to-treat (ITT) approach). Since the dropout processes as well as the numbers of patients who switched to another bDMARD were not equally distributed between the strata, we applied multiple imputations for the DAS28 for those patients who switched to another bDMARD (stopped TCZ therapy) during follow-up or were lost to follow-up. The imputation model included age, number of comorbidities (0, 1, 2, ≥ 3), rheumatoid factor, number of prior bDMARD failures (0, 1, 2, ≥ 3), DAS28 and FFbH scores prior to the start of another bDMARD or dropout. Both linear mixed models were adjusted for the following baseline covariates: disease duration, functional status, DAS28, number of comorbidities (0, 1, 2, ≥ 3), number of prior bDMARD failures (0, 1, 2, ≥ 3). Additionally, we tested for a different course of the disease activity (DAS28) between strata of bDMARD failures by an interaction term of follow-up time and the number of bDMARD failures. In a subanalysis, we included the dose of TCZ (≤ 6 vs. > 6 mg/kg) in the model. To examine whether the use of concomitant csDMARDs had an influence on the effectiveness, we included a time-varying categorical variable for csDMARD therapy in the linear mixed model with imputed data for the DAS28. We distinguished between TCZ monotherapy, TCZ + MTX and TCZ + other csDMARD.

In addition, we applied generalized linear mixed models (glimmix procedure in SAS 9.4) to calculate mean predicted probabilities for (a) low disease activity, (b) high disease activity and (c) ≤ 2 swollen joints. In model (a) and (b), we used the same covariates for adjustment as in the analyses of effectiveness (DAS28). In model (c) we additionally adjusted for baseline SJC. Instead of multiple imputation techniques for missing values of the swollen joint counts, we used last-observation-carried-forward (LOCF) since the joint counts follow a highly skewed distribution with a concentration on zeros, i.e., imputation of negative values are likely. The same approach (LOCF) was used for missing doses of concomitant glucocorticoids. In a linear mixed model, we investigated whether the glucocorticoid doses differed between the strata during follow-up. We adjusted for time (discrete follow-up visits), number of prior bDMARD failures (0, 1, 2, ≥ 3) and the interaction of time and bDMARD failures. For analysis, we used software from the SAS Institute, version 9.4.

Results

Baseline characteristics

Most of the 885 patients enrolled with TCZ (64.1%) had one or more bDMARD failures (Table 1): 318 (35.9%) were biologic-naïve (first-line TCZ), 286 (32.3%) had one bDMARD failure (second-line TCZ), 186 (21.0%) two (third-line TCZ), and 95 (10.7%) ≥ 3 prior bDMARD failures (fourth-line TCZ). Patients with prior bDMARD failures were significantly different from biologic-naïve patients: they were younger, had longer disease duration, more csDMARD failures, more erosive changes and more severe fatigue. The functional status was significantly lower in patients with one or at least three bDMARD failures and more patients had three or more comorbidities compared to biologic-naïve patients. In the group with ≥ 3 prior bDMARD failures, nearly 50% of the patients had three or more comorbidities, in particular significantly more osteoporosis, diabetes and heart failure than biologic-naïve patients. No difference was found for fibromyalgia, psoriasis and depression.

Patient follow-up

Overall, 379 patients (first-line: 118, second-line: 119, third-line: 83, fourth-line: 59) terminated TCZ but were still under observation in the register with other DMARD treatments. In contrast, only 60 out of 885 patients (6.8%)

Table 1 Baseline characteristics of patients enrolled with tocilizumab

	Tocilizumab as			
	1st line	2nd line	3rd line	4th line
Number of patients	318	286	186	95
Female patients, *n* (%)	239 (75.2)	227 (79.4)	149 (80.1)	77 (81.1)
Age	58 ± 12.5	56.4 ± 12.4	55.7 ± 12.7	54.6 ± 14.8*
Disease duration in years	8 ± 7.4	11.6 ± 8.5*	13.3 ± 9.2*	15.3 ± 9.9*
TCZ dose mg/kg	7.1 (2.1)	7.3 (2.0)	7.4 (1.8)	7.2 (2.2)
TCZ dose ≤ 6 mg/kg, *n* (%)	54 (17.1)	38 (13.5)	20 (10.9)	14 (15.2)
Prev. TNFi, *n* (%)	0	262 (91.6)	185 (99.5)	95 (100)
Prev. other bDMARDs, *n* (%)	0	24 (8.4)	24 (15.1)	57 (64.2)
Concomitant csDMARD, *n* (%)	170 (53.5)	141 (49.3)	97 (52.2)	47 (49.5)
There of MTX only, *n* (%)	102 (60.0)	96 (68.09)	69 (71.13)	35 (74.47)
GC dose mg/d	8.2 ± 5.1	7.5 ± 4.0	8.9 ± 8.6	7.8 ± 4.3
No GCs, *n* (%)	121 (38.1)	103 (36)	63 (33.9)	29 (30.5)
DAS28	5.1 ± 1.3	5.2 ± 1.3	5.2 ± 1.3	5.5 ± 1.3*
ESR in mm/h	34.2 ± 26.2	31.1 ± 23	33.5 ± 25.6	36.5 ± 25.9
CRP in mg/L	16.5 ± 22	17.9 ± 26.5	19.8 ± 32.1	20.7 ± 24
SJC	6.7 ± 5.2	6.5 ± 5.1	6.2 ± 5.3	7.3 ± 6.6
TJC	8.5 ± 6.5	9.1 ± 6.9	8.7 ± 6.8	10.2 ± 7.8*
ACPA pos., *n* (%)	165 (68.5)	151 (72.9)	104 (73.8)	52 (73.2)
RF pos., *n* (%)	217 (71.9)	208 (75.1)	132 (72.9)	64 (68.1)
Erosive RA, n (%)	164 (53.9)	188 (68.1)*	110 (64.3)*	66 (75)*
FFbH	65.8 ± 23	60.5 ± 24.5*	62.1 ± 23.6	56.1 ± 23.9*
Pain (NRS: 0–10)	5.9 ± 2.3	6.3 ± 2.2*	6.2 ± 2.1	6.8 ± 1.9*
PGA (NRS: 0–10)	5.9 ± 2.1	6.2 ± 2	6.2 ± 1.9	6.7 ± 1.9*
Fatigue (NRS: 0–10)	5 ± 2.9	5.5 ± 2.8*	5.6 ± 2.5*	6.3 ± 2.4*
Comorbidities				
Osteoporosis, *n* (%)	53 (16.7)	64 (22.4)	29 (15.6)	28 (29.5)*
Diabetes, *n* (%)	33 (10.4)	34 (11.9)	14 (7.5)	22 (23.2)*
Heart failure, *n* (%)	10 (3.1)	5 (1.7)	4 (2.2)	8 (8.4)*
Hypertension, *n* (%)	134 (42.1)	122 (42.7)	67 (36)	37 (38.9)
1 comorbidity, *n* (%)	83 (26.1)	65 (22.7)	59 (31.7)	14 (14.7)
2 comorbidities, *n* (%)	57 (17.9)	50 (17.5)	35 (18.8)	16 (16.8)
≥ 3 comorbidities, *n* (%)	96 (30.2)	111 (38.8)*	51 (27.4)	45 (47.4)*

Values are mean ± SD unless otherwise specified

No number, *SD* standard deviation, *prev* previous, *TNFi* tumor necrosis factor inhibitor, *bDMARDs* biologic disease modifying antirheumatic drugs, *csDMARDs* conventional synthetic disease modifying antirheumatic drugs, *GC* glucocorticoid, *DAS28* disease activity score based on 28 joints, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *SJC* swollen joint counts, *TJC* tender joint counts, *ACPA*, citrullinated peptide/protein antibodies, *pos* positive, *RF* rheumatoid factor, *FFbH* Funktionsfragebogen Hannover, *NRS* numerical rating scale, *PGA* patient global assessment

* Significantly different from patients with first line TCZ ($p < 0.05$)

were lost to follow-up over 3 years of observation (first-line: 19, second-line: 17, third-line: 21, 4th-line: 3). Apart from discontinuation and dropout, a total of 288 patients (1st-line: 120, 2nd-line: 87, 3rd-line: 63, fourth-line: 18) were enrolled later than 3 years prior to October 31 2015 and could therefore not complete 3 years of follow-up.

Therapy adherence

Retention rates

After the first year, 65–70% of the patients with ≤ 2 prior bDMARD failures were still on TCZ therapy compared to only 43% in the group with ≥ 3 bDMARD failures

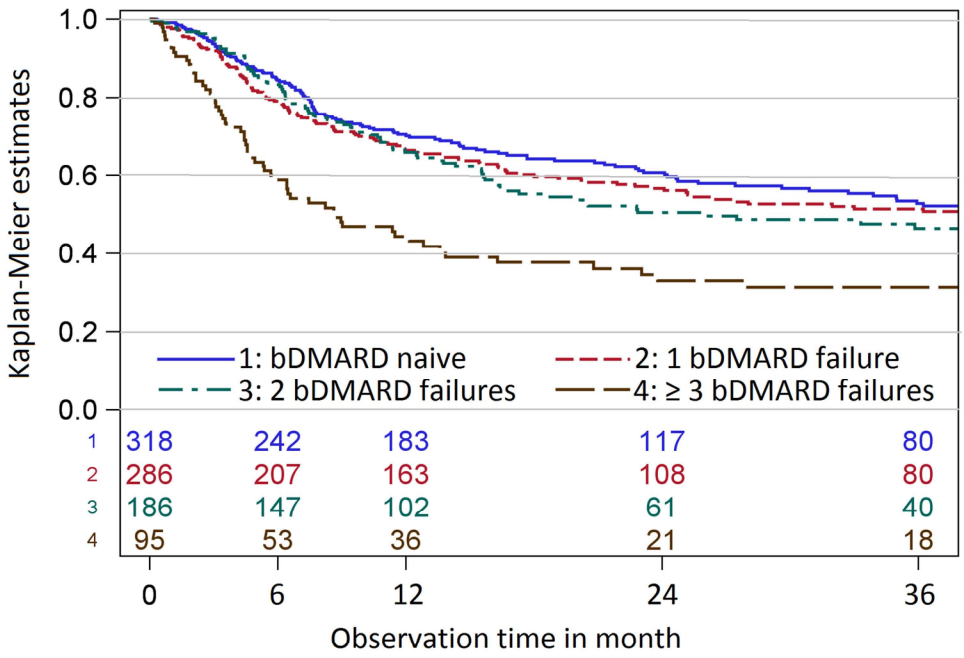

Fig. 1 Kaplan–Meier curves for retention of tocilizumab therapy over 3 years. The patients were stratified by the number of prior bDMARD failures. The numbers on top of the x-axis represent the number of patients at risk at the corresponding time point

(Fig. 1). The Kaplan–Meier estimates after 3 years of follow-up were also similar in the first three strata: 52.2% (bDMARD naïve), 50.8% (1 bDMARD failure) and 46.5% (2 bDMARD failures) compared to 31.3% in the group with ≥ 3 bDMARD failures. In the group with three or more bDMARD failures, 41% of patients stopped TCZ therapy already during the first 6 months.

Characteristics of patients discontinuing TCZ

The unadjusted hazard ratios show that the probability for stopping TCZ therapy was 2.2 times higher in patients with at least three prior bDMARD failures compared to biologic-naïve patients and 1.8 times higher compared to patients with two prior bDMARD failures.

Patients who discontinued TCZ had higher doses of TCZ at baseline (> 6 mg/kg) than those who maintained their treatment. They also had higher DAS28 at baseline and more often three or more comorbidities, especially diabetes. Besides biologic-naive patients, those who discontinued had a lower functional status.

Reasons for terminations

The most frequent reasons for discontinuation were adverse events and ineffectiveness (multiple reasons could be named). In biologic-naïve patients who discontinued TCZ treatment, 32% stopped because of ineffectiveness and 47% due to adverse events (AEs). After one failure (2 failures, ≥ 3 failures), 38% (46, 42%) stopped due to ineffectiveness and 57% (47, 53%) due to AEs. During the first 6 months the percentage of patients who stopped TCZ due to AEs was 15% (17, 35%) higher for patients with no (1; ≥ 3) prior failures than during the following 2.5 years. Overall, the most frequent serious adverse event was "hospitalized surgery". In patients with ≥ 3 bDMARD failures, this event occurred 14.9 times per 100 patient-years, whereas the incidence rates in the other three groups were 3–7 per 100 patient-years. More than 75% of the surgeries were bone and joint surgeries in all strata. In patients who stopped TCZ therapy, the rates for serious infections were 36.5 (first-line), 33.4 (second), 48.5 (third), and 49.2 (fourth) per 1000 py, and rates for neoplasms were 14.6 (first-line), 20.0 (second), 19.4 (third), and 0 (fourth). This was higher than in patients who continued therapy (serious infections: IR: 7.8–27.3; neoplasms: IR: 4.8 in third-line and no event in all other patients). There was no difference regarding the occurrence of major cardiovascular events. Four patients died under TCZ therapy.

Effectiveness

In both approaches, all patients had significant DAS28 improvements, irrespective of the number of prior bDMARD failures. In the first approach, only 335 patients who remained on TCZ were included (completers). Of them, 130 (39%) were biologic-naïve, 111 (33%) had one

Table 2 Adjusted baseline DAS28 and least-square means of the course of the DAS28 over 3 years of follow-up separated by the number of prior bDMARD-failures

	N	Baseline	Month 6	Month 12	Month 24	Month 36
Model 1: Completers						
1st-line	130	5.2	2.42 [2.18;2.66]	2.51 [2.26;2.77]	2.26 [1.97;2.55]	2.23 [1.91;2.55]
2nd-line	111	5.2	2.81 [2.55;3.07]	2.82 [2.56;3.09]	2.74 [2.45;3.03]	2.55 [2.24;2.87]
3rd-line	70	5.2	2.96 [2.63;3.28]	2.84 [2.49;3.18]	2.64 [2.27;3.01]	2.61 [2.18;3.03]
4th-line	24	5.2	2.62 [2.04;3.19]	2.68 [2.07;3.28]	2.81 [2.10;3.51]	2.87 [2.14;3.60]
Model 2: ITT						
1st-line	318	5.2	2.79 [2.62;2.96]	2.84 [2.66;3.02]	2.84 [2.65;3.02]	2.50 [2.25;2.74]
2nd-line	286	5.2	3.00 [2.82;3.17]	3.06 [2.86;3.25]	2.97 [2.78;3.15]	2.86 [2.64;3.07]
3rd-line	186	5.2	3.08 [2.85;3.30]	3.06 [2.83;3.29]	3.04 [2.76;3.32]	2.70 [2.39;3.00]
4th-line	95	5.2	3.48 [3.18;3.78]	3.55 [3.22;3.87]	3.14 [2.72;3.56]	3.27 [2.83;3.70]

We adjusted for the following baseline variables: disease duration, functional status, DAS28 and the number of comorbidities

bDMARD failure, 70 (21%) had two and 24 (7%) had three or more prior failures. The percentage of completers after 3 years of follow-up was 41% in biologic-naive patients, 39% in second line, 38% in third line and 25% in fourth line users. The average improvement after 3 years of follow-up varied between 2.4 and 3.0 DAS28 units. On average, the patients reached LDA (Table 2).

In approach 2 (ITT analysis), the DAS28 was reduced by 2.0–2.7 points on average after 3 years. Consequently, the estimated means of the DAS28 were higher than in the first model. After 36 months, patients with less than three bDMARD failures on average reached LDA, whereas patients with ≥ 3 bDMARD failures remained on average in moderate disease activity. The difference in the DAS28 scores after 3 years between biologic-naïve patients and those with three or more prior bDMARD failures is larger than in the completer analysis but still not significant (Table 2). Additional adjustment for the dose had no influence on the results. However, the overall mean of the DAS28 averaged over 3 years was significantly higher in patients with ≥ 3 prior bDMARD failures compared to biologic-naïve patients or patients with 1 bDMARD failure [first-line: 2.79 (2.67;2.91), second-line: 2.96 (2.84;3.09), third-line: 3.00 (2.84;3.15), fourth-line: 3.34 (3.10;3.59)]. This result is supported by the predicted probability for achieving LDA over 3 years. It was decreasing from 66 to 48% with the number of prior bDMARD failures. A similar result was also obtained for swollen joint counts (SJC): the mean probability over 3 years for ≤ 2 SJC decreased from 74 to 62% (Table 3). The probability for remaining in high disease activity was 10% in patients with ≥ 3 bDMARD failures.

Concomitant therapy

Conventional synthetic DMARDs

Overall, 430 patients (first-line: 148, second-line: 145, third-line: 89, fourth-line: 48) started TCZ as monotherapy. Of them, 73 (17%, first-line: 12%, second-line: 20%, third-line: 16%, fourth-line: 25%) added a csDMARD during observation. There was no difference in effectiveness between TCZ monotherapy or TCZ in combination with MTX or another csDMARD or more than one csDMARD. Compared to concomitant MTX only use, TCZ monotherapy resulted on average in an insignificantly higher DAS28 of 0.03 [− 0.1; 0.2] points and the effect of other combinations was 0.04 [− 0.1; 0.2]. Moreover, the time to stop TCZ therapy was similar for the three groups (data not shown).

Table 3 Mean baseline SJC and adjusted least-square means of the percentage of patients with SJC ≤ 2 for all strata of prior bDMARD failures

	N	Baseline	Month 6	Month 12	Month 24	Month 36
1st-line	318	6.6	75 [70;80]	80 [76;85]	76 [71;82]	78 [72; 84]
2nd-line	286	6.6	65 [59;71]	67 [61;73]	66 [60;72]	69 [62; 76]
3rd-line	186	6.6	64 [56;71]	67 [59;74]	66 [58;74]	66 [58; 75]
4th-line	95	6.6	59 [48;70]	60 [49;71]	70 [59; 81]	68 [56;80]

We adjusted for the following baseline variables: disease duration, functional status, DAS28, SJC and the number of comorbidities

ITT intention-to-treat

Glucocorticoids

Overall, 9.6% [95%-KI:(7.7; 11.7%)] of patients were enrolled with a high GC dose (> 10 mg/d) and 38.3% did not receive GCs at baseline. However, the mean GC doses during follow-up barely differed between the strata: 3.1 (first-line), 3.4 (second-line), 4.1 (third-line), and 4.1 mg/d (fourth-line).

During follow-up, the percentage of patients with high GC doses decreased and the percentage of patients without GCs increased (Fig. 2). The changes were larger for the patients who were enrolled later.

Discussion

We investigated the effectiveness of TCZ in 885 RA patients over 3 years stratified by the number of prior bDMARD failures incorporating third- and fourth-line bDMARD therapies. To our knowledge, there is little data on this issue. However, due to the chronicity of RA and an increasing number of patients with numerous treatment failures, more analyses of this kind are necessary.

Our results show that TCZ is an effective treatment in the majority of biologic-naïve patients as well as in those with up to three prior bDMARD failures. Particularly,

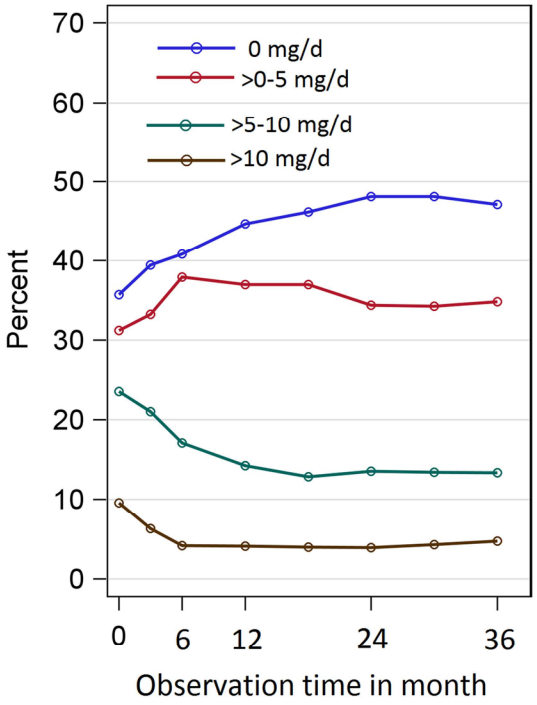

Fig. 2 Time-varying percentage of patients who received either no concomitant glucocorticoids, > 0–5, > 5–10 or > 10 mg/d. Missing glucocorticoid doses and doses of patients who switched to another biologic where imputed using LOCF

TCZ completers achieved an average disease activity corresponding to LDA. However, after adjustment for therapy switches and dropout processes (ITT analysis), we did also find no major differences between strata: the mean DAS28 was reduced by at least 2 units and on average LDA was reached in patients with ≤ 2 bDMARD failures. Similar results have been reported by Harrold et al. regarding the median decrease in CDAI, improvement in mHAQ and mACR20/50/70 responses [21] and Kihara et al. who also found no differences in EULAR response and DAS28-remission at month 6 for TCZ-treated patients being either biologic-naïve or after at least one bDMARD failure [18].

In our analysis, merely the patient group with ≥ 3 bDMARD failures had a slightly lower response in the ITT approach. This result is in line with RCT data showing a similar ACR20 response in patients with one, two or three prior TNFi-failures but lower ACR50 and ACR70 responses for patients with ≥ 3 TNFi failures [16]. It is likely that the latter patients form a risk group for non-response and adverse events irrespective of the therapy [22]. This was also apparent in our data: although patients with ≥ 3 prior bDMARDs were younger, they had significantly longer disease duration, nearly two-thirds had already been exposed to non-TNFi prior to TCZ, and about 50% had three or more comorbidities. In addition, these patients developed more SAEs involving especially surgeries (there of 75% bone and joint-related surgeries) with an incidence of 14.9 per 100 patients-years which was more than twice as high as in the other groups. However, the disease-related bone and joint surgeries are very likely not associated with the recently initiated TCZ treatment. They will rather be a consequence of a long-standing and insufficiently controlled disease. A similar observation was made in the study of Kihara et al., wherein patients with subsequent-line TCZ had more often a history of joint replacement, longer disease duration, lower physical function and more comorbidities [18]. On the other hand, our study also shows that in a considerable proportion of patients with ≥ 3, bDMARD failure disease activity (DAS28) was significantly reduced; in the ITT analysis, 48% of these patients achieved LDA. Overall, the results on effectiveness and incidence of SAEs are summarized by our time-to-event analysis. Assuming that time-to-event is a combined surrogate marker for effectiveness and safety, we found similar survival curves for patients with 0, 1 or 2 bDMARD failures and a significantly lower retention rate for patients with ≥ 3 bDMARD failures.

Our results are not compromised by a differential use of concomitant GCs or csDMARDs. The impact of concomitant methotrexate or other csDMARDs was marginal and insignificant compared to TCZ monotherapy. This is in contrast to the EULAR guidelines recommending TCZ in combination with MTX [1] but supported by the study of Kihara et al., wherein concomitant MTX therapy was

not associated with a better response to TCZ. Regarding concomitant GCs, we could not find systematically different doses between strata. In all strata, doses of concomitant GCs were significantly reduced during follow-up. This is in agreement with two recent studies [23, 24]. In patients enrolled after 2012, more than 50% completely withdrew GCs under TCZ treatment. This is in line with the EULAR recommendations to withdraw concomitant GCs as soon as possible [1].

This study has limitations inherent to the observational design. We observed different dropout rates across strata of bDMARD failures which may have led to biased estimates. Therefore, we considered missing values and dropouts by multiple imputations. An imputation model will not nullify the impact of non-random dropouts but the comparison of ITT (model 2) versus completer analyses (model 1) showed an expected upwards correction of values of the DAS28 over time in model 2. In addition, the overall low rates of missing values and the low attrition rate in RABBIT support the significance of the findings [20]. Due to the suppression of ESR by TCZ [25], the outcomes DAS28-ESR and LDA may overestimate the treatment effect. Our results should, therefore, not directly be compared to data on other substances. Nevertheless, comparisons of the DAS28-ESR among users of TCZ remain valid. In order to estimate treatment effectiveness without the impact of ESR, we analysed the percentage of patients achieving ≤ 2 swollen joints over 3 years which was between 74 (bio-naïve) and 62% (≥ 3 bDMARD failures) (data not shown). This underlines our results on clinical effectiveness.

Strengths of this study are the large number of patients receiving TCZ, enabling stratified analyses, and the follow-up of 3 years. Further, since all patients are from the same country, similar prescription guidelines and treatment patterns can be assumed. This is specifically important regarding the analysis of concomitant therapies since use and doses in daily practice may vary considerably between countries [26]. Moreover, regarding the use of glucocorticoids, the RABBIT study comprises not only doses at baseline but also during follow-up. Although the overall amount of missing data and dropouts was low, we implied imputation methods to control for this possible confounder.

Conclusions

In conclusion, the results from this study indicate that TCZ is equally effective in patients with no, one or two previous bDMARD failures. The majority of patients achieved LDA and maintained it over a period of 3 years. In patients with more than two prior bDMARD failures overall effectiveness was lower, compared to the other patient groups. Nevertheless, nearly 50% of these patients reached LDA at follow-up. This is remarkable since these patients had a mean disease duration of 15 years, and a large number of previous joint surgeries, indicating a severe course of disease. Effective treatment options such as TCZ are needed for these difficult-to-treat patients.

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Compliance with ethical standards

Ethical approval The study protocol of RABBIT was approved by the ethics committee of the Charité University Medicine Berlin (reference number: 1508/2001). Prior to enrolment, all patients have to give their informed consent.

Conflict of interest Lisa Baganz: No competing interest. Adrian Richter: Honoraria from Pfizer outside the submitted work. Jörn Kekow: No competing interests. Arnold Bussmann: No competing interests. Andreas Krause: Grants and personal fees from Roche/Chugai outside the submitted work. Carsten Stille: No competing interests. Joachim Listing: No competing interests. Angela Zink: Grants and personal fees from AbbVie, BMS, MSD, Pfizer, Roche, and UCB outside the submitted work. Anja Strangfeld: Personal fees from AbbVie, BMS, MSD, Pfizer, Roche, Sanofi-Aventis and UCB outside the submitted work.

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Different risk profiles of biologic agents for new-onset psoriasis in patients with rheumatoid arthritis

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ABSTRACT

Objective: To investigate rates and risk factors for incident and recurrent psoriasis in rheumatoid arthritis (RA) patients treated with different biologic (b) and conventional synthetic (cs) disease-modifying antirheumatic drugs (DMARDs).
Methods: RA patients enrolled in the German biologics register RABBIT without (n = 14,525) or with a history of psoriasis (n = 375) were analyzed separately. All first events of psoriasis reported until October 2017 were assigned to the treatments prescribed in the previous 3 months. Crude incidence rates (IR) of psoriasis were calculated per 1000 patient-years. To investigate risk factors for psoriasis, cox regressions with and without inverse probability weights were applied to adjust for confounding by indication.
Results: 117 incident and 37 recurrent psoriatic events were reported. Patients exposed to TNFi had a significantly higher incidence rate (IR = 3.04/1,000 PY) than those exposed to csDMARDs only (IR = 0.65), whereas IRs for abatacept, rituximab and tocilizumab did not differ significantly from csDMARDs. Adjusted Cox regression confirmed a higher risk for TNFi. Female sex (HR: 1.7) and smoking (HR: 2.1) were significantly associated with incident psoriasis while methotrexate decreased the risk (HR: 0.5). For recurrent psoriasis, IRs for TNFi, abatacept and rituximab were significantly higher than for csDMARDs.
Conclusions: Our data confirm a previously observed increased risk of incident psoriasis in patients exposed to TNFi compared to csDMARDs. However, the overall risk is low and the event is usually non-serious. Comedication of TNFi with methotrexate seems to lower the risk of incident psoriasis. In patients with a history of psoriasis, recurrence as adverse event is rare.

Introduction

It is standard of care to use biologic agents in patients with rheumatoid arthritis (RA) after failure of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) [1]. Since first approval of tumor necrosis factor alpha inhibitors (TNFi) nearly two decades ago and of non-TNFi substances such as rituximab (RTX), abatacept (ABA) and tocilizumab (TOC) more than 10 years ago, rheumatologists have acquired extensive experience with these agents. Observational data from biologic registers and the regular analysis of safety data have cleared out major concerns on adverse events possibly associated with the use of biologics such as an increase in the incidence of malignancies [2–6].

The comprehensive information on drug safety available from the biologic registers allows in-depth analysis not only of serious but also of non-serious adverse events. This also applies to the so-called paradoxical reactions described under treatment with TNFi, such as the occurrence of psoriasis. An association between the treatment with TNFi and new-onset psoriasis was observed ten years ago [7], but it is still not clear whether TNFi rather triggers exacerbations of prevalent psoriasis or whether it induces incident psoriasis as an adverse drug reaction. There have been various reports and case series of psoriatic skin lesions in patients exposed to TNFi, in particular from gastroenterology [8,9].

One recent review of the clinical features, histopathological findings, and management experience of psoriasis occurring under TNFi treatment [10] came to the conclusion that stopping the TNFi treatment led to improvement of the psoriasis in about half of the patients.

Regarding the incidence of psoriasis among non-TNFi biologic therapies there is even less evidence than for TNFi. After approval of RTX, several case reports were published [11, 12], different from the clinical trials where no such cases were reported. The French AIR register did not find an association of psoriatic events with RTX

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treatment [13]. In patients treated with ABA the occurrence of psoriatic events in individual patients was reported [14–16] but not systematically studied.

While there were no psoriatic events reported during the clinical studies with TOC, four cases of psoriasis were published after its approval [17–19] and a total of 12 suspected cases were reported to the European Database of suspected adverse drug reaction reports (www.adrreports.eu). This led to a publication of the Drug Commission of the German Physicians of a possible association of psoriasis with TOC treatment [20]. In September 2018 the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency included psoriasis in the list for safety signals under tocilizumab [21]. Market authorization holders are expected to monitor those lists regularly, take action and change their product information sheets accordingly.

There are very few publications on recurrent psoriasis under biological treatments. A review described two studies with 4 and 2 patients that reported exacerbation of psoriasis [22]. And there is one case report on recurrent psoriasis in a patient with spondylarthropathy, treated with ABA [23].

Using data of the German Biologics Register RABBIT, we analysed incident and recurrent psoriasis in RA patients treated with biologic agents compared csDMARDs.

Methods

Patients

RABBIT is a prospective longitudinal cohort study initiated in 2001. Patients are enrolled at start of a biologic DMARD, Janus Kinase inhibitor or csDMARD after at least one csDMARD treatment [24]. Patients are observed for a minimum of five and up to ten years irrespective of treatment changes. Information is regularly collected from rheumatologists and patients on disease activity, treatment including start and stop dates, co-morbidities, functional capacity and the occurrence of adverse events. Prior to enrolment, all patients give their informed consent. RABBIT received approval by the Ethics Committee of the Charité University Medicine, Berlin.

Definition of outcome "psoriasis"

Two outcomes were examined separately:

1. Incident psoriasis (main analysis): Only patients without a reported psoriasis at baseline
2. Recurrent psoriasis: Only patients with a psoriasis reported as comorbidity at baseline

Recurrent events include both new episodes of psoriasis after skin remission and significant worsening of a pre-existing psoriasis. To identify serious and non-serious psoriatic events we searched our adverse event database for the MedDRA terms 'Juvenile psoriatic arthritis', 'Dermatitis psoriasiformis', 'Psoriasis', 'Psoriatic arthropathy', 'Nail psoriasis', 'Erythrodermic psoriasis', 'Guttate psoriasis', 'Pustular psoriasis', 'Rebound psoriasis'. In all patients only the first psoriasic event reported until October 31st, 2017 was selected and either assigned to biologic treatments administered within 3 months prior to the event (exposure to two biologics was possible) or to the csDMARD group. Based on the description of the event by the rheumatologist, the study physician (AS) validated all events, blinded for treatment assignment. If a prior psoriatic event was reported during observation but not as comorbidity at baseline ($n = 13$), further events were counted as recurrent psoriasis.

Dropout due to change of diagnosis

RABBIT enrols patients with RA only. There were 5 cases where psoriasis was not known to be a pre-existing condition and one case with psoriasis at baseline in whom the diagnosis was changed to psoriatic arthritis ($n = 5$) or psoriatic spondyloarthritis ($n = 1$) after psoriasis had occurred. These six patients were excluded. In patients without psoriatic event, $n = 51$ were excluded due to change of diagnosis.

Statistical analysis

For the analyses, all substances targeting TNF were combined in one group. The follow-up time in patients treated with Janus Kinase inhibitors was too small to be included in the analysis. Crude incidence rates (IR) of psoriatic events were calculated per 1000 patient-years (PY) including 95% confidence intervals (CI). In a sub-analysis we calculated incidence rates for individual TNFi (adalimumab (ADA), certolizumab (CZP), etanercept originator (oETA), etanercept biosimilar (bsETA), golimumab (GLM), infliximab (INF)) and tested the differences between all therapies using Bonferroni adjustment of p-values to control for multiple testing. Since the number of psoriatic events was rather low, we used direct adjustments of Cox regression (standard Cox model) to allow direct examination of the covariates. To check the proportional hazard assumption of the Cox regression model, Schoenfeld residuals [25] were calculated. A violation of the proportional hazard assumption is indicated if these residuals change over time. This was tested by means of the correlation coefficient between residuals and time to event (including 95% confidence intervals).

Univariate Cox models were calculated for 11 covariates: treatment (TNFi, ABA, RTX, TOC), rheumatoid factor, baseline age (per 5 years), sex, glucocorticoid dosage per 5 mg/d [26], baseline smoking status (current, previous/unknown, never) [27–29], treatment with methotrexate (MTX), skin infections 6 months prior to the event [29], DAS28 averaged over 12 months prior to the event, baseline obesity (BMI≥30) [27,28] and baseline depression as an indicator of increased vulnerability to stressful life events [27]. All of these variables are reported by the rheumatologist. Due to the limited number of events, the multiple Cox model was adjusted for the first eight of these covariates only.

A second multiple Cox regression model with the same covariates as above was applied using propensity score based inverse probability weights (IPW) to control for confounding by indication. Two different propensity scores (PS1, PS2) were calculated to model treatment changes over time using the baseline covariates age, sex, comorbidities, rheumatoid factor, functional capacity (Functional status questionnaire Hanover, FFbH), DAS28, number of treatment failures, year of enrollment (PS1: until 2006, PS2: from 2007) and interaction terms between the last three.

For the analysis of incident psoriasis, the following sensitivity analyses were conducted: (1) The Cox model was adjusted for different covariates. One by one, we incorporated prior csDMARD failures, obesity, and baseline depression and replaced the glucocorticoid dose by DAS28. (2) We stratified TNFi therapy into TNFi with or without MTX. (3) Not only skin infections 6 months prior to the psoriatic event were considered but all prior skin infections that had occurred during the observation. (4) The Cox regression model was applied only to patients with positive rheumatoid factor to avoid bias due to a misspecification of the RA diagnosis.

For a small number of events (incident psoriasis: $n = 9$; recurrent psoriasis: $n = 3$) the event date was missing. These missing values were replaced by multiple imputations using a uniform distribution between the date of the visit prior to the event and the one at which the event was reported. Information on the rheumatoid factor was missing in 1% of the patients but none of these experienced a psoriatic event during follow up.

Results

Until October 2017, 14,525 patients had at least one follow-up and no psoriasis at baseline, providing 63,221 patient years (PY) of

observation. For 375 patients, providing 1521 PY, psoriasis was reported as comorbidity at baseline.

Baseline characteristics

Patient characteristics at inclusion in the register are shown in Table 1.

Patients without psoriasis at baseline were on average 55 (TNFi) to 59 (RTX) years old, and about 75% were female. A total of 64% (csDMARD) to 84% (RTX) of patients were rheumatoid factor positive. The mean glucocorticoid dose 6 months prior to inclusion varied between 3.7 mg/d (csDMARD) and 5.6 mg/d (TNFi, RTX). Major differences were found regarding co-medication with MTX, which was prescribed to 36% of TOC and up to 70% of ABA treated patients.

Patients with psoriasis at baseline were on average 54 (TOC) to 60 (RTX) years old, and 70% (TNFi) to 89% (RTX) were female. Co-medication with MTX was applied in 36% of TOC and up to 79% of ABA treated patients.

Incident psoriasis and recurrent psoriatic events (new episodes after skin remission or significant worsening of pre-existing psoriasis)

A total of 117 incident psoriatic events were reported including 5 classified as serious. Thereof 85 occurred under TNFi therapy, 10 under RTX (1 patient was exposed to RTX and ADA), 6 under ABA, 3 under TOC and 14 under csDMARD. In patients with prevalent psoriasis at baseline, 37 recurrent events (3 of them classified as serious) were reported: 20 patients were exposed to TNFi, 6 to RTX, 7 to ABA, 2 to TOC and 2 to csDMARDs. Examining patient reports on adverse events did not reveal additional events.

The median time between enrolment in the cohort and incident psoriasis was 18 months (25%-quartile: 11 months, 75%-quartile: 46 months). The median time between start of the treatment under which the new psoriasis occurred and the event varied from 4.5 months under CZP to 17 months under ETA. In patients with psoriasis at baseline the median time from enrolment to the first reoccurrence was 11 months (25%-quartile: 4months, 75%-quartile: 36months).

A total of 14 (12%) incident psoriatic events were palmoplantar manifestations, 19 (16%) were pustular and 7 (6%) were reported as palmoplantar pustulosis. Of the recurrent psoriatic events 3 (8%) were reported as palmoplantar, 2 (5%) as pustular and 1 (3%) as palmoplantar pustulosis.

Crude incidence rates (IR) and adjusted hazard ratios (HR) for patients without psoriasis at baseline

The crude IR per 1000 PY for incident psoriasis was 3.04 under TNFi treatment and significantly higher than in the csDMARD control group (IR 0.65, Fig. 1). The IRs for ABA, RTX and TOC did not differ significantly from the IR under csDMARDs. Across TNFi, the IRs varied insignificantly (see Figure S1 in supplement).

The results of the univariate Cox models are shown in Table 2. A significantly increased risk for psoriasis was found for treatment with TNFi (HR: 3.97, 95%-CI: [2.38;6.64]) and a decreased risk for co-medication with MTX (HR: 0.51, CI: [0.35;0.76]). DAS28 was not significantly associated (HR: 1.07, CI: [0.92; 1.25]), and the HR became smaller with additional adjustment for DMARD-treatment (HR: 1.04, CI: [0.89;1.21]). Multiple Cox regression analysis showed a higher risk for TNFi (HR: 3.87, CI: [2.31; 6.51]; Table 2). Other significant risk factors for incident psoriasis were female sex and current smoking. Age, glucocorticoids per 5 mg/d increase, and skin infections during the 6 months prior to the psoriatic event were not significantly associated. In patients treated with TNFi+MTX the risk was lower than in patients treated with TNFi without MTX (HR: 2.83, CI: [1.54;5.20] vs. 6.61 [3.79;11.55]). Analyses among RF positive patients only did not lead to different results. Also including all skin infections observed prior to the psoriatic event, incorporating prior csDMARD failures, obesity or depression at baseline or replacing the glucocorticoid dose by DAS28 did not change the findings. Sex was the only covariate for which Schoenfeld residuals indicated a possible violation of the proportional hazards assumption. This finding is likely attributable to the low fraction of men with psoriatic events (19 of 117).

The IPW Cox regression model (Table S1 in supplement) did not show divergent results. The HRs were similar to the unweighted analysis. A noteworthy difference was found for ABA where the IPW model resulted in a lower HR (1.8 vs 2.4). The significantly increased risks for females and smokers remained as did the beneficial effect of MTX as co-medication.

Restricting the model to RF positive patients did not have an impact on the results.

Crude incidence rates and adjusted hazard ratios for patients with psoriasis as comorbidity at baseline

The IR for recurrent psoriasis in patients treated with csDMARDs was 5.3 per 1000 PY (Fig. 2). For ABA and RTX the incidence rates

Table 1
Baseline characteristics stratified by treatment at enrolment for patients with and without psoriasis as comorbidity at baseline

	Patients without psoriasis as comorbidity at baseline					Patients with psoriasis as comorbidity at baseline				
Parameter	csDMARD	TNFi	RTX	ABA	TOC	csDMARD	TNFi	RTX	ABA	TOC
N	5082	7009	929	485	1020	92	204	27	24	28
Age in years	57.7 (12.3)	55.3 (12.6)	58.7 (11.9)	58.4 (12.9)	56.8 (12.9)	55.2 (11)	54.5 (11.8)	60.1 (11.7)	54.8 (13.4)	54.4 (12.1)
Female, N(%)	3858 (75.9)	5301 (75.6)	711 (76.5)	362 (74.6)	786 (77.1)	74 (80.4)	142 (69.6)	24 (88.9)	17 (70.8)	20 (71.4)
Disease Duration in years	7.4 (8.1)	10.3 (9)	13.7 (9.8)	11.7 (9.3)	10.8 (9.1)	9.5 (8.6)	10.5 (9.7)	10.7 (8.7)	9.9 (7.4)	10.1 (6.3)
ESR mm/h	26.6 (20.4)	32 (23.1)	32.3 (23.7)	32.1 (25.3)	32.5 (25)	32.7 (24.4)	29.3 (22.9)	33.8 (26.3)	35.3 (29.4)	44.3 (30.9)
DAS28-ESR	4.7 (1.3)	5.3 (1.3)	5.3 (1.3)	5.3 (1.3)	5.2 (1.3)	5.1 (1.4)	5.1 (1.3)	4.9 (1.5)	5.2 (1)	5.6 (1.3)
No. previous csDMARDs	1.6 (1)	2.7 (1.2)	2.5 (1.1)	2.5 (1.2)	2.3 (1)	1.9 (1.1)	2.5 (1.3)	2.6 (0.9)	2.5 (1.1)	2.3 (0.8)
RF, positive N(%)	3215 (63.5)	5149 (74.5)	772 (83.7)	350 (74.2)	725 (74.4)	55 (59.8)	112 (55.7)	17 (63)	18 (78.3)	14 (53.8)
FFbH, 0–100	69 (22.1)	62.3 (23.2)	56.6 (23.6)	58.9 (23.5)	63.2 (23.8)	63.8 (21.1)	60.2 (22)	45.1 (26.3)	61.2 (24.2)	59.9 (23.8)
Smoking, current N(%)	1169 (23)	1585 (22.6)	210 (22.6)	121 (24.9)	284 (27.8)	26 (28.3)	49 (24)	7 (25.9)	8 (33.3)	7 (25)
Smoking, never N(%)	2212 (43.5)	2957 (42.2)	394 (42.4)	208 (42.9)	425 (41.7)	37 (40.2)	80 (39.2)	11 (40.7)	8 (33.3)	15 (53.6)
Smoking, other N(%)	1701 (33.5)	2467 (35.2)	325 (35)	156 (32.2)	311 (30.5)	29 (31.5)	75 (36.8)	9 (33.3)	8 (33.3)	6 (21.4)
GC dose last 6 months mg/d	3.7 (4.5)	5.6 (6.6)	5.6 (6.5)	4.7 (5.9)	4.6 (5.3)	4.9 (5)	4.5 (6.3)	6.5 (5.3)	3.9 (4.5)	5.2 (6.7)
(co-)medication MTX, N(%)	3390 (66.7)	3697 (52.7)	502 (54)	339 (69.9)	367 (36)	51 (55.4)	98 (48)	14 (51.9)	19 (79.2)	10 (35.7)
Depression, N (%)	272 (5.4)	414 (5.9)	56 (6)	35 (7.2)	84 (8.2)	2 (2.2)	16 (7.8)	3 (11.1)	5 (20.8)	3 (10.7)
Obesity, N (%)	1379 (27.2)	1540 (22.1)	189 (20.6)	119 (24.7)	255 (25.2)	22 (23.9)	49 (24)	5 (18.5)	7 (29.2)	5 (17.9)

Values are means (SD) if nothing other was stated. Abbreviations: ESR erythrozyte sedimentation rate, DAS28 disease activity score based on 28 joints, No. Number, RF rheumatoid factor, GC glucocorticoid, MTX metothrexate.

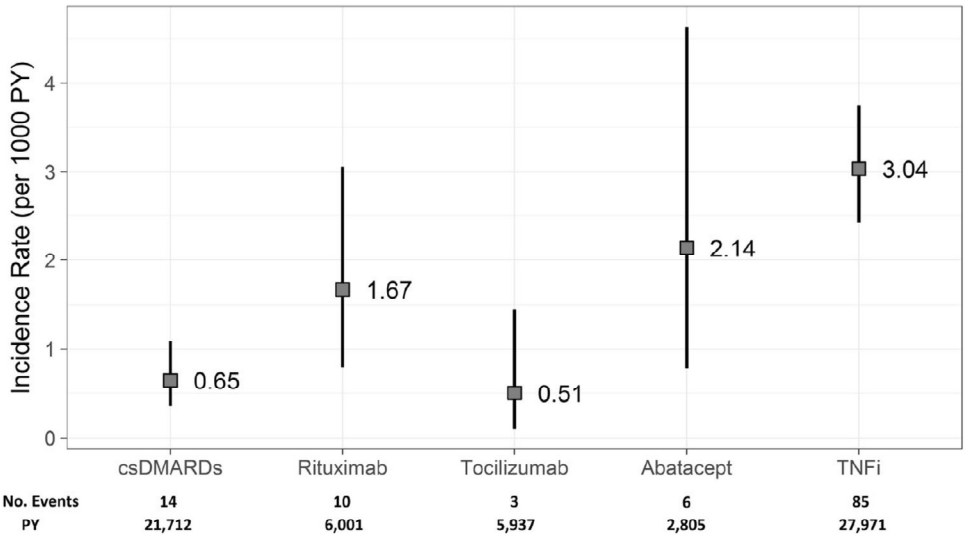

Fig. 1. Crude Incidence rates per 1000 patient years (PY) and 95% confidence intervals for incident psoriasis in patients without psoriasis as comorbidity at baseline.

were significantly higher, whereas the higher rates for TOC and TNFi did not reach significance. The IRs for individual TNFi therapies are shown in Figure S2 in the supplement.

The Cox regression revealed a significantly higher risk for patients receiving ABA (HR: 6.6) or RTX (HR: 4.8, Table 3). The HR for patients treated with TNFi was 2.4 but not significantly increased. None of the other risk factors examined was significantly associated with the risk of recurrent psoriatic events.

Results from the IPW-adjusted cox regression were similar.

Discussion

In this study from the German RA cohort RABBIT, treatment with TNFi was associated with a significantly higher risk of incident psoriasis compared to csDMARDs. An earlier study with observational data reported an incidence rate of 1.04 [CI:0.67–1.54] in patients treated with infliximab, etanercept or adalimumab [7] with a significantly higher incidence in patients treated with adalimumab than with etanercept. We could not confirm the latter finding. For ABA and RTX we found HRs >1 which were not significant. For TOC the risk was insignificantly lower than for csDMARDs.

The pathogenesis of psoriasis is still incompletely understood and it is unclear how its occurrence may be induced by different biologic agents. The most common hypothesis regarding TNFi is that the inhibition of TNF-alpha may result in an overload of interferon-alpha [30] which plays an important role in the development of psoriasis [31,32]. A study suggested that cortisone also plays a role in the development of psoriasis [26], which could not be confirmed with our analysis. However, other risk factors like female sex were identified in our analyses, which is in accordance with a recent study describing the incidence and prevalence of psoriasis in the general population of Germany [33].

Three studies examined risk factors for psoriasis in the general population. All three reported a higher risk for smoking [27–29] and two of them for obesity or higher BMI [27,28]. For RA patients we could confirm a higher risk for current smoking but not for obesity or higher BMI. For the other proposed factors including beta blockers, statins [28] and stressful life events [27] our cohort lacks the necessary data. However, in a sensitivity analysis depression was not significantly associated with the occurrence of psoriasis. We also could not confirm the observation of skin infections as a risk factor [29]. Though, we did find an insignificantly elevated risk for prior skin infections.

Table 2
Hazard Ratios for incident psoriasis in patients without psoriasis as comorbidity at baseline

	all patients				RF positive patients	
	univariate HR	95% CI	multiple HR	95% CI	multiple HR	95% CI
TNFi	**3.97**	**(2.38;6.64)**	**3.87**	**(2.31;6.51)**	3.20	**(1.71;5.98)**
Abatacept	2.31	(0.92;5.79)	2.41	(0.96;6.03)	2.73	(0.97;7.69)
Rituximab	1.98	(0.91;4.31)	1.94	(0.89;4.25)	1.73	(0.70;4.26)
Tocilizumab	0.54	(0.16;1.87)	0.46	(0.13;1.60)	0.62	(0.17;2.24)
RF positive	0.82	(0.54;1.23)	0.74	(0.49;1.12)		
Age (by 5 years)	0.93	(0.86;1.00)	0.97	(0.90;1.05)	0.96	(0.87;1.05)
Females	1.56	(0.93;2.60)	**1.69**	**(1.002;2.87)**	1.81	(0.96;3.42)
Glucocorticoids per 5 mg/d	1.10	(0.96;1.25)	1.08	(0.94;1.24)	0.95	(0.71;1.26)
Methotrexate	**0.51**	**(0.35;0.76)**	**0.50**	**(0.34;0.73)**	**0.48**	**(0.30;0.77)**
Smoking, current	**1.79**	**(1.13;2.85)**	**2.07**	**(1.28;3.35)**	**2.64**	**(1.47;4.75)**
Smoking, other	1.29	(0.82;2.05)	1.41	(0.89;2.25)	1.66	(0.93;2.97)
Prior skin infections	1.90	(0.44;8.23)	1.74	(0.40;7.56)	1.42	(0.18;11.24)
DAS28*	1.07	(0.92;1.25)				
Obesity	0.88	(0.55;1.40)				
Depression	1.16	(0.52;2.58)				

*DAS28 is the averaged DAS28-ESR over the past 12 months; Abbreviations: RF rheumatoid factor, DAS28 disease activity score based on 28 joints.

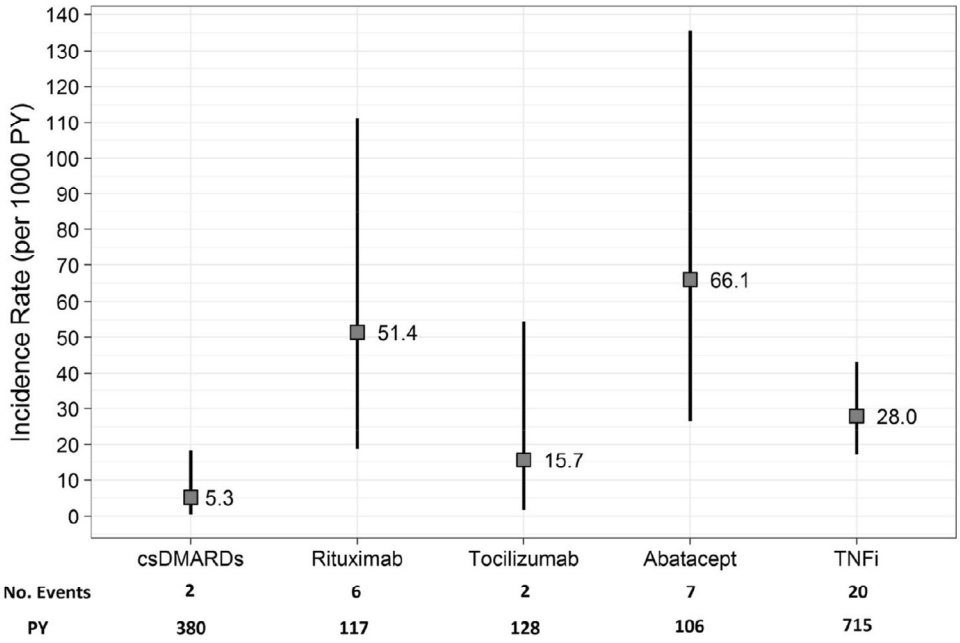

Fig. 2. Crude Incidence rates per 1000 patient years (PY) and 95% confidence intervals for recurrent* psoriasis in patients with psoriasis as comorbidity at baseline.
*includes new episodes of psoriasis after skin remission and significant worsening of pre-existing psoriasis.

Methotrexate is recommended as anchor drug for the treatment of RA either as first csDMARD or as co-medication with bDMARDs in European and US-guidelines [34,35]. In contrast to a review that did not find a protective effect of methotrexate concerning new-onset psoriasis [22] we found a significantly reduced risk for incident psoriasis in patients treated with methotrexate, both in combination as well as in mono-therapy.

For recurrent psoriasis (new episodes after skin remission or significant worsening of pre-existing), we found a significantly higher risk in patients treated with ABA and RTX. For TNFi treated patients the HR was insignificantly increased. Other risk factors for recurrent psoriasis could not be identified.

Limitation and strengths

The inclusion criteria for the RABBIT cohort require the patient to have a confirmed rheumatoid arthritis diagnosis. Patients whose diagnosis was changed after enrolment were excluded from the analysis. Still there is a risk of misdiagnosis as in daily care some patients have overlapping syndromes or a clear differentiation between RA and other inflammatory rheumatic diseases cannot be made (yet). We addressed this with a sensitivity analysis with rheumatoid factor positive patients. The results were comparable to the main analysis. To address a possible channeling bias regarding preferential selection of TNFi in patients with unclear or overlapping psoriasis diagnosis, an inverse probability weight model was calculated which led to similar results. This model was used only as sensitivity analysis because there are difficulties for inverse-probability weighting with propensity scores, especially with more than two treatments. Patients treated with substances atypical for their characteristics will receive very high weights. In an analysis of an infrequent disease, this may lead to an overestimation of occurrence.

The strengths of this study are the long follow up in the cohort which allows to study outcomes that may occur late in the treatment course. In addition, all licensed RA treatments are observed with exact start and stop dates, and all adverse events reported by the rheumatologist are documented irrespective of their classification as serious or non-serious events.

Table 3
Hazard Ratios for recurrent* psoriasis in patients with psoriasis as comorbidity at baseline

	Multiple HR	95% CI
TNF	2.37	(0.93;6.03)
Abatacept	**6.56**	**(2.28;18.89)**
Rituximab	**4.85**	**(1.53;15.35)**
Tocilizumab	1.23	(0.25;6.07)
RF positive	0.96	(0.46;1.97)
Age (by 5 years)	0.96	(0.81;1.12)
Females	1.29	(0.55;3.01)
Glucocorticoids per 5 mg/d	1.05	(0.75;1.47)
Methotrexate	0.70	(0.35;1.41)
Smoking, current	0.95	(0.36;2.52)
Smoking, other	1.79	(0.81;3.95)
Prior skin infections	1.87	(0.22;15.80)

Abbreviations: RF rheumatoid factor.
*Includes new episodes of psoriasis after skin remission and significant worsening of pre-existing psoriasis.

Conclusion

This study examined the risk of incident and recurrent psoriasis in RA patients treated with biologics or csDMARDs. Physicians should be aware that there is a small, but significantly increased risk of incident psoriasis under TNFi treatment and that comedication with MTX can probably lower this risk. Recurrence of pre-existing psoriasis seems to be more frequent in patients treated with ABA or RTX. This result should be seen against the background of low patient numbers and requires further validation.

Key messages

- Under TNFi treatment the risk for incident psoriasis in RA patients is increased.
- Comedication with methotrexate seems to lower this risk.
- Additional risk factors for incident psoriasis in RA patients are female sex and current smoking.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2019.07.004.

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Supplement

Table S1 Weighted hazard ratios for incident psoriasis in patients without psoriasis as comorbidity at baseline.

	all patients				**RF positive patients**	
	univariate HR	**95% CI**	**multiple HR**	**95% CI**	**multiple HR**	**95% CI**
TNFi	4.11	(2.34; 7.19)	**4.14**	**(2.37;7.25)**	**3.13**	**(1.63;5.99)**
Abatacept	1.76	(0.63; 4.89)	1.82	(0.66;5.03)	2.44	(0.78;7.65)
Rituximab	1.81	(0.78; 4.21)	1.98	(0.85;4.60)	1.63	(0.58;4.60)
Tocilizumab	0.31	(0.06; 1.49)	0.26	(0.05;1.28)	0.38	(0.08;1.91)
RF positive	0.59	(0.40; 0.87)	**0.55**	**(0.37;0.82)**		
Age (by 5 years)	0.96	(0.89; 1.03)	1.01	(0.94;1.09)	0.99	(0.90;1.09)
Females	1.88	(1.10; 3.21)	**1.95**	**(1.13;3.37)**	1.75	(0.89;3.45)
Glucocorticoids per 5 mg/d	0.97	(0.78; 1.21)	0.97	(0.77;1.21)	0.79	(0.56;1.10)
Methotrexate	0.57	(0.39; 0.83)	**0.55**	**(0.38;0.81)**	**0.38**	**(0.23;0.63)**
Smoking, current	1.73	(1.12; 2.68)	**2.17**	**(1.37;3.43)**	**1.90**	**(1.04;3.46)**
Smoking, other	0.95	(0.60; 1.52)	1.08	(0.67;1.74)	1.23	(0.69;2.18)
Prior skin infections	2.39	(0.72; 7.94)	2.13	(0.64;7.11)	0.95	(0.07;12.21)
DAS28*	0.99	(0.86; 1.15)				
Obesity	0.82	(0.51; 1.31)				
Depression	0.74	(0.29; 1.90)				

** DAS28 is the averaged DAS28-ESR over the past 12 months; Abbreviations: RF rheumatoid factor, DAS28 disease activity score based on 28 joints*

Table S2 Weighted Hazard Ratios for recurrent* psoriasis in patients with psoriasis as comorbidity at baseline.

	multiple HR	**95% CI**
TNF	2.43	(0.80 ;7.34)
Abatacept	**7.05**	**(1.90;26.20)**
Rituximab	4.35	(0.91;20.72)
Tocilizumab	1.67	(0.32;8.76)
RF positive	0.89	(0.38;2.06)
Age (by 5 years)	0.97	(0.80;1.17)
Females	1.15	(0.44;3.03)
Glucocorticoids per 5 mg/d	1.05	(0.72;1.53)
Methotrexate	0.47	(0.20;1.07)
Smoking, current	0.67	(0.21;2.10)
Smoking, other	1.46	(0.58;3.69)
Prior skin infections	2.23	(0.17;29.51)

Abbreviations: RF rheumatoid factor

**includes new episodes of psoriasis after skin remission and significant worsening of pre-existing psoriasis*

Figure S1: Crude Incidence rates per 1000 patient years (PY) and 95% confidence intervals for incident psoriasis in patients without psoriasis as comorbidity at baseline.

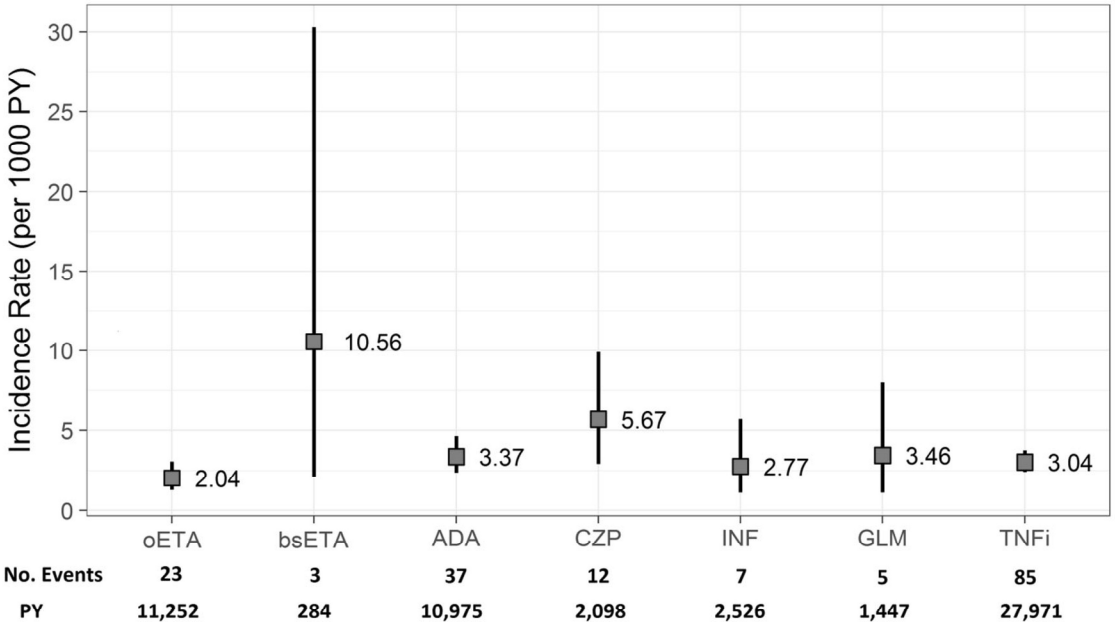
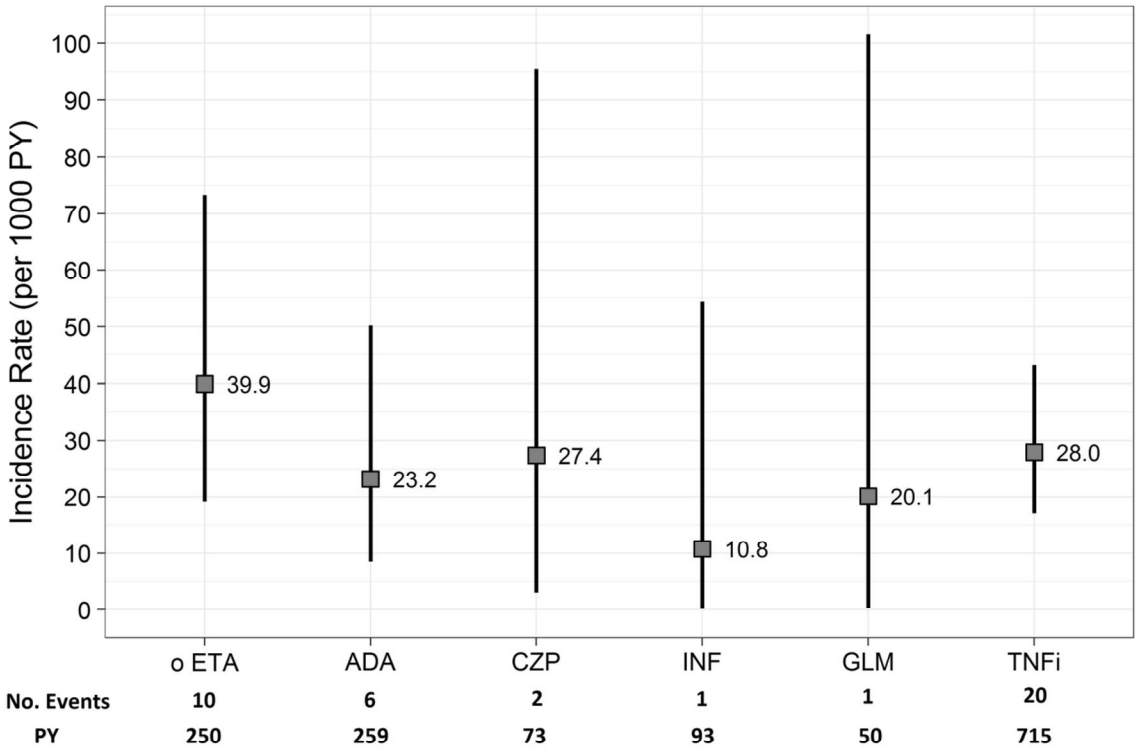


Figure S2: Crude Incidence rates per 1000 patient years (PY) and 95% confidence intervals for recurrent* psoriasis in patients with psoriasis as comorbidity at baseline.



**includes new episodes of psoriasis after skin remission and significant worsening of pre-existing psoriasis*

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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Publikationsliste

Baganz L, Listing J, Kekow J, Eisterhues C, Wassenberg S, Zink A, Strangfeld A: *Different risk profiles of biologic agents for new-onset psoriasis in patients with rheumatoid arthritis.* Semin Arthritis Rheum. 2019
Impact Factor: 5.072

Baganz L, Richter A, Albrecht K, Schneider M, Burmester GR, Zink A, Strangfeld A*: Are prognostic factors adequately selected to guide treatment decisions in patients with rheumatoid arthritis? A collaborative analysis from three observational cohorts.* Semin Arthritis Rheum. 2019 Jun;48(6):976-982.
Impact Factor: 5.072

Baganz L, Richter A, Kekow J, Bussmann A, Krause A, Stille C, Listing J, Zink A, Strangfeld A: *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, 38(4):579-587.
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Impact Factor: 9.002

Albrecht K, Richter A, Meissner Y, Huscher D, **Baganz L**, Thiele K, Schneider M, Strangfeld A, Zink A: *[How frequent are poor prognostic markers in rheumatoid arthritis? : An estimate based on three epidemiologic cohorts].* Z Rheumatol 2017, 76(5):434-442.
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