Aus der Medizinischen Klinik mit Schwerpunkt Rheumatologie und
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DISSERTATION

Entwicklung und Zusammenhänge von Entzündungsparametern und Patientenskalen bei Patienten mit axialer SpA

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Inhalt

Abkürzungen

ADA	Adalimumab
AS	Ankylosierende Spondylitis
ASAS	*Assessment of Spondyloarthritis*
ASDAS	*Ankylosing Spondylitis Disease Activity Score*
axSpA	Axiale Spondyloarthritis
BASDAI	*Bath Ankylosing Spondylitis Disease Activity Index*
BASFI	*Bath Ankylosing Spondylitis Functional Index*
BASMI	*Bath Ankylosing Spondylitis Metrology Index*
BSG	Blutsenkungsgeschwindigkeit
CRP	C-reaktives Protein
ERS	Entzündlicher Rückenschmerz
ESTHER	*Effects of **E**tanercept versus **S**ulfasalazine in early axial spondyloar**TH**ritis on active inflammatory l**E**sions as detected by whole body M**RI***
ETA	Etanercept
GESPIC	***Ge**rman **Sp**ondyloarthritis **I**nception **C**ohort*
HLA-B27	*Human leukocyte antigen B27*
ICC	Intra-Class Korrelationskoeffizient
LSMEAN	*Least squares mean*
MRT	Magnetresonanztomografie
nr-axSpA	nichtröntgenologische axiale Spondyloarthritis
NSAR	Nichtsteroidales Antirheumatikum
PRO	*Patient reported outcome* (deutsch: vom Patienten berichteter Parameter)
r-axSpA	Röntgenologische axiale Spondyloarthritis
SIG	Sakroiliakalgelenke (deutsch: Kreuz-Darmbein-Gelenke)
SpA	Spondyloarthritis
SSZ	Sulfasalazin
STIR	*Short-Tau-Inversion-Recovery-Sequenz* (Basis-Puls-Sequenz beim MRT)
T1	Kontrastdarstellung von MRT-Bildern
TNF	Tumornekrosefaktor
WK	Wirbelkörper

1. Abstrakt (deutsch/englisch)

Zielstellung: Die Aktivität der axialen Spondyloarthritis (axSpA) lässt sich durch objektive Entzündungsparameter und subjektiv eingeschätzte Patientenskalen (PRO) messen. Die erste Arbeit untersucht den Zusammenhang zwischen entzündlicher Läsionen in der Magnetresonanztomographie (MRT) und der Neuentwicklung struktureller Veränderungen im Knochen bei früh erkrankten SpA-Patienten, die mit einem Biologikum Etanercept (ETA) oder einer konventionellen Basistherapie (Sulfasalazin) behandelt wurden. Die zweite Arbeit untersucht, ob die Krankheitsdauer von Patienten Auswirkungen auf die Stärke des Zusammenhangs zwischen objektiv messbaren Entzündungsparametern und PROs hat. Patienten dieser gepoolten Analyse wurden mit ETA oder Adalimumab behandelt. Die radiografische Progression der Sakroiliakalgelenke (SIG) und Prädiktoren für diese unter einer Tumornekrosefaktor (TNF)-Blocker Therapie werden in der dritten Arbeit untersucht.
Methoden: Es wurden Daten der Ganzkörper-MRTs und Röntgenbilder der SIG der ESTHER-Studie (1) ausgewertet und klinische Daten der ESTHER-Studie mit einer im Design analogen Studie, in der die Patienten ebenfalls mit einem TNF-Blocker behandelt wurden, gepoolt.
Ergebnisse: Es konnte ein signifikanter Zusammenhang zwischen der Reduktion einer Osteitis und dem Neuauftreten von Verfettung gezeigt werden. Wenn Osteitis zu Baseline vorhanden und anschließend verschwand, ist an 18% der WK und 11% der SIG Verfettung des Knochenmarks neu entstanden. Kürzer erkrankte Patienten verbessern sich deutlicher im BASDAI, BASFI, BASMI und ASDAS als länger erkrankte Patienten unter anti-TNF-Therapie. Keinen Unterschied gab es dagegen bei den objektiven Entzündungsparametern. Die größte Progression in den SIG konnte zwischen Baseline und Jahr 2 festgestellt werden (mean+-SD: 0,13+-0,73). Es gab einen signifikanten Unterschied in der Veränderung des SIG Summenscores zwischen Patienten, die im ersten Jahr mit ETA behandelt wurden und denen die Sulfasalazin bekommen hatten (p=0,04). Der CRP-Wert und MRT SIG Osteitisscore waren Prädiktoren für die Progression des SIG Summenscores.
Schlussfolgerung: Unsere Ergebnisse legen nahe, dass eine wirksame anti-TNF-Therapie, die Zeichen akuter Entzündung in den SIG oder der Wirbelsäule reduziert zur Entwicklung chronischer Veränderungen führen kann, dass es nach etwa vier Jahren Erkrankungsdauer eine Entkoppelung zwischen der Verbesserung subjektiver und der objektiver Parameter zur Messung der Krankheitsaktivität bei Patienten mit axSpA gibt und länger Erkrankte unter weiteren Folgen ihrer Krankheitsaktivität leiden. Erstmals konnten darüber hinaus Langzeitergebnisse zur radiografischen Progression in den SIG vorgelegt werden.

Introduction: The activity of axial spondyloarthritis (axSpA) can be assessed by objectively measurable parameters of inflammation and by patient reported outcomes (PRO). In the first paper the relation between active inflammatory lesions on magnetic resonance imaging (MRI) and the new development of chronic lesions in bone marrow was examined in patients with early axSpA who were treated with a an anti-TNF therapy (etanercept (ETA)) or a conventional treatment (sulfasalazine). The change of the strength of the correlation between objectively measurable parameters of inflammation and PROs was investigated in the second paper. Patients in this pooled analysis were treated with ETA or Adalimumab. Radiographic progression in sacroiliac joints (SIJ) and its predictors under therapy with tumor necrosis factor (TNF) inhibitor were examined in the third work. **Methods:** Data of whole body MRIs and SIJ radiographs of the ESTHER trial (1) were evaluated. Clinical data of the ESTHER trial were pooled with a study which was similar in design and were patients were treated with a TNF-inhibitor as well. **Results:** We found a significant correlation between reduction of osteitis and the development of new fatty lesions. If inflammation was present at baseline and was resolved afterwards fatty lesions newly occurred in 18% of vertebral units and 11% of SIJ. Patients with a short symptom duration improved more clearly in BASDAI, BASFI, BASMI and ASDAS than longer diseased patients under anti-TNF therapy. In contrast there was no difference in objective parameters of inflammation. The maximum progression in SIJ was assessed between baseline and year 2 (mean ±SD: 0.13±0.73). There was a significant difference in SIJ osteitis change score between patients who were treated with ETA in the first year and patients who were treated with sulfasalazine ($p=0.04$). The CRP value and MRI SIJ osteitis score were predictors for SIJ progression. **Conclusion:** These data suggest that an anti-TNF-therapy, which reduces signs of acute inflammation in SIJ or spine leads to the development of chronic changes. After about four years of symptom duration there is a disconnection between improvement in subjective and objective parameters in patients with axSpA. Longer diseased patients suffer under further outcomes of disease activity. Long term results of radiographic progression in SIJ were presented for the first time.

2. Einführung

Die axiale Spondyloarthritis (axSpA) ist eine entzündlich rheumatische Erkrankung der Wirbelsäule, bei der neben den Sakroiliakalgelenken (SIG) häufig auch die Wirbelkörper (WK) und Sehnenansatzstellen betroffen sind. Sind strukturelle Veränderungen einer Sakroiliitis auf dem Röntgenbild erkennbar, handelt es sich um eine röntgenologische axSpA (r-axSpA), welche nach früherer Nomenklatur als ankylosierende Spondylitis (AS) bezeichnet wurde. Die Erkrankung kann im fortgeschrittenen Stadium zu einer knöchernen Überbrückung der WK, sogenannte Ankylosen, führen. Dagegen spricht man von nicht-röntgenologischer axSpA (nr-axSpA), wenn noch keine Veränderungen im Röntgenbild erkennbar sind. Die axSpA tritt überwiegend zwischen im 3. und 4. Lebensjahrzehnt und nur gering häufiger bei Männern als bei Frauen auf. Häufig liegt eine positive Familienanamnese vor und die Patienten sind *Human leukocyte antigen* (HLA)-B27 positiv. Für die Diagnose wird in der Regel ein bildgebendes Verfahren wie Magnetresonanztomografie (MRT) oder Röntgen herangezogen. Das MRT dient in erster Linie dazu, aktiv-entzündliche Veränderungen (subchondrales Knochenmarksödem) darzustellen. Des Weiteren sind in einer speziellen MRT-Sequenz (T1) chronische Veränderungen der Gewebsstrukturen wie Verfettungen und Erosionen sichtbar. Im Röntgenbild sind strukturelle Veränderungen der Wirbelsäule und der SIG wie Erosionen nachweisbar. Bei den Klassifikationskriterien für die axSpA hat es in den letzten Jahren neue Entwicklungen gegeben. Die modifizierten New-York Kriterien (2) setzen für r-axSpA eine Sakroiliitis Grad II beidseits oder einseitig mindestens Grad III voraus, welche im fortgeschrittenen Stadium der Krankheit vorliegt. Neuere *Assessment of Spondyloarthritis* (ASAS) Klassifikationskriterien (3, 4) beziehen die MRT mit ein und erfassen Frühstadien der axSpA. Die Klassifikationskriterien unterstützen die Diagnosestellung, ersetzen diese aber nicht. Die Diagnosestellung ist komplexer, kann nicht alleine auf der Erfüllung oder Nichterfüllung von Klassifikationskriterien beruhen, sondern muss auch mögliche Differentialdiagnosen in die Entscheidungsfindung mit einbeziehen (5). Eine frühzeitige Diagnosestellung und damit eine frühe Erkennung der Erkrankung und deren zielgenaue Behandlung sind, wie auch in den hier diskutierten Arbeiten gezeigt wird für den Verlauf der axSpA entscheidend (6-8).

Zur Unterdrückung der Symptome bei entzündlichen Schmerzen der Wirbelsäule und SIG werden Tumornekrosefaktor (TNF)-alpha-Blocker wie Etanercept (ETA) und Adalimumab (ADA) eingesetzt, deren Wirksamkeit gut etabliert ist (9, 10). Dabei sind eine kurze Krankheitsdauer und ein jüngeres Alter gute Prädiktoren für ein erfolgreiches Therapieansprechen (11-14). Bisher konnte gezeigt werden (15), dass sich die Progression der

strukturellen Zerstörung der WK bei einer Langzeitbehandlung mit TNF-alpha-Blockern aufhalten lässt und sich dies positiv auf die Funktionalität der Patienten auswirkt. Die Verzögerung der radiografischen Progression der Sakroiliitis konnte bisher nur für Patienten gezeigt werden, die zwei Jahre mit ETA behandelt wurden (16).
In der vorliegenden Arbeit sollen als Erweiterung zum aktuellen Stand der Forschung die folgenden Fragestellungen beantwortet werden:

1. Gibt es einen Zusammenhang zwischen Entzündung und der Entstehung von Verfettungsstellen im subchondralen Knochenmark als erstes Zeichen der strukturellen Veränderung im Knochen?
2. Gibt es Unterschiede in der Stärke des Zusammenhangs zwischen den subjektiven vom Patienten berichteten Parametern (PRO) und objektiven Entzündungsparametern zwischen Patienten mit kürzerer und längerer Krankheitsdauer?
3. Gibt es Unterschiede in der Veränderung der Parameter für kürzer und länger erkrankte Patienten?
4. Lässt sich die radiografische Progression der SIG während einer Langzeitbehandlung mit TNF-alpha-Blockern aufhalten?
5. Gibt es Prädiktoren für die radiografische Progression der SIG?

3. Methodik

a) Zusammenhang zwischen aktiven entzündlichen Läsionen in der Wirbelsäule und den SIG und der Neubildung von Verfettungen

Studiendesign

Für diese Analyse wurden MRT-Daten der ESTHER-Studie (1) herangezogen. In dieser prospektiven, randomisierten, kontrollierten, klinischen Studie wurden Patienten mit der Diagnose axSpA eingeschlossen und mit dem TNF-alpha-Blocker ETA oder der konventionellen synthetischen Basistherapie Sulfasalazin (SSZ) behandelt. Es wurden Ganzkörper-MRTs zu Baseline, nach 24 und nach 48 Wochen angefertigt. Das Auftreten akuter Läsionen wurde mittels der STIR Sequenz, das chronischer Veränderungen, von Verfettungen, mittels T1 untersucht. Die MRT-Bilder der Wirbelsäule und der SIG wurden unabhängig von zwei für die Therapie und die zeitliche Reihenfolge der Bilder verblindeten Radiologen gescort. Für jeden WK wurde ein Score zwischen 0 und 3 für Verfettung und Ankylose und für Erosion ein Wert zwischen 0 und 2 vergeben. Die beiden SIG wurden in je vier Quadranten unterteilt und für jeden Quadranten Verfettung (0=keine Verfettung sichtbar, 1=Verfettung sichtbar), Erosion (0=normale Gelenkbegrenzung, 1=1-2 Erosionen, 2=3-5 Erosionen, 3=mehr als 5 Erosionen) und Ankylose

(0=keine Ankylose sichtbar, 1=Ankylose sichtbar) bestimmt. Ausgewertet wurden sowohl Einzelwerte als auch die Summe der WK und der SIG-Quadranten. Die statistische Auswertung bezog die Patienten ein, von denen MRTs zu Baseline und Woche 48 vorhanden waren.

Statistik

Die Hauptanalyseparameter waren Veränderungen der chronischen Läsionen wie Verfettung des Knochenmarks, Erosion und Ankylose in Relation zu vorausgegangenen aktiv entzündlichen Veränderungen. Wegen der schiefen Verteilung der Zielparameter wurde ein nichtparametrischer Ansatz zum Vergleich der Behandlungsgruppen gewählt. Die nicht-parametrische Kovarianzanalyse nach Brunner (17) ist ein für den Fall randomisierter Gruppenzuordnungen entwickeltes Verfahren, welches die Adjustierung um den Baselinestatus erlaubt und für diesen Fall trennscharf ist. Um den Zusammenhang zwischen akuten Läsionen und chronischen Veränderungen möglichst unverfälscht analysieren zu können wurde die Untersuchung auf WK- und Quadrantenebene mit eindeutig definierten Gruppen durchgeführt. Dieser Ansatz ist spezifischer und unverzerrter als ein Vergleich auf Patientenebene. Die WK und SIG-Quadranten wurden zu diesem Zweck in drei Gruppen eingeteilt: A) übereinstimmend sahen beide Radiologen keine Osteitis zu Baseline und Woche 48, B) beide Scorer sahen übereinstimmend Osteitis zu Baseline und keine zu Woche 48, C) weder Gruppe A noch B, aber eine Osteitis zu Woche 48 wurde von mindestens einem der beiden Radiologen gesehen. Für die Festlegung, ob eine neue chronische Läsion zwischen Baseline und Woche 48 an einer WK-Stelle oder in einem Quadranten entstanden ist, wurde ebenfalls eine strenge Definition benutzt: beide Reader mussten einen Score 0 zu Baseline und einen Score > 0 zu Woche 48 vergeben haben.

Zusammenhänge zwischen dem Status bzw. den Veränderungen akuter Läsionen und dem Entstehen von in der T1 Sequenz sichtbaren Verfettungen wurden mit verallgemeinerten Schätzgleichungen mit Logit-Link Funktion analysiert.

b) Veränderungen objektiver und subjektiver Entzündungszeichen bei Patienten mit kurzer und langer Erkrankungsdauer

Patienten

Patienten aus zwei randomisierten, kontrollierten, klinischen Studien (1, 11), die alle eine aktive axSpA mit einem *Bath Ankylosing Spondylitis Disease Activity Index* (BASDAI) ≥4 und entzündlichem Rückenschmerz (ERS) ≥4 (jeweils auf deiner numerischen Rating Skala 0-10) zu Studienbeginn hatten, wurden gepoolt. Alle Patienten wurden ein Jahr lang entweder mit ETA oder mit ADA behandelt. Patienten beider Studien erfüllten die ASAS Klassifikationskriterien

für axSpA. Gemäß ihrer Erkrankungsdauer zu Beginn der Studie wurden die Patienten zunächst in zwei Gruppen (<4 Jahre und ≥4 Jahre erkrankt) und zusätzlich in einer Sensitivitätsanalyse in vier Gruppen (<2 Jahre, 2-4 Jahre, 4-8 Jahre und ≥8 Jahre erkrankt) eingeteilt. Eine weitere Stratifizierung erfolgte nach dem C-reaktiven Protein (CRP) Status zu Baseline. Patienten mit einem CRP ≤5mg/l wurden der Gruppe der CRP negativen und jene mit einem CRP-Wert >5 mg/l in die Gruppe der CRP positiven Patienten zugeteilt.

Statistik

Untersucht wurde der Zusammenhang zwischen Krankheitsdauer und der vom Patienten berichteten Parametern BASDAI und *Bath Ankylosing Spondylitis Functional Index* (BASFI), zwischen der Krankheitsdauer und den objektiven Entzündungsparametern CRP und dem MRT SIG Score, zwischen der Krankheitsdauer und dem aus Parametern der Wirbelsäulenbeweglichkeit zusammengesetzten Score *Bath Ankylosing Spondylitis Metrology Index* (BASMI) und zwischen der Krankheitsdauer und dem *Ankylosing Spondylitis Disease Activity Score* (ASDAS), welcher aus subjektiven Patienteneinschätzungen und dem objektiven (CRP) Parameter berechnet wurde.

Es wurden gemischte lineare Modelle für wiederholte Messungen angewendet, um die Parameter zwischen den Gruppen zu vergleichen, wobei nach dem Geschlecht, dem HLA-B27 Status und dem CRP Status zu Baseline adjustiert wurde. In den Vergleich wurden alle sechs Messzeitpunkte unter TNF-Blocker-Therapie einbezogen. Um den Einfluss einzelner sehr großer CRP-Werte auf das mittlere Behandlungsergebnis zu reduzieren wurden die schief verteilten CRP-Werte vor der Analyse logarithmiert. Partielle nicht-parametrische Spearman Korrelationskoeffizienten wurden angewendet, um die Zusammenhänge zwischen Veränderungen in vom Patienten berichteten Parametern und Entzündungsparametern zu untersuchen. Dieser Ansatz ermöglicht die Analyse des Zusammenhangs nach Adjustierung um den Einfluss der Ausgangswerte.

c) Verlauf der strukturellen Veränderung der SIG bei Patienten mit früher axialer SpA

Patienten

Für die Auswertung wurden Patienten aus der ESTHER-Studie (1) verwendet. Darin wurden Patienten mit früher axSpA sechs Jahre lang mit dem TNF-alpha-Blocker ETA behandelt. Zu Baseline, nach 2, 4 und 6 Jahren wurden Röntgenaufnahmen der SIG angefertigt. Für die Analyse wurden Patienten selektiert, von denen SIG Röntgenaufnahmen zu Baseline und mindestens einem weiteren Zeitpunkt vorhanden waren.

Bildgebungsparameter

Röntgenbilder der SIG wurden jeweils von zwei unabhängigen, geschulten Befundern gescort. Die Befunder waren in Bezug auf alle klinischen Daten und die zeitliche Reihenfolge der Bilder eines Patienten verblindet. Die Röntgenbilder wurden nach dem Graduierungssystem der modifizierten New York Kriterien (2) befundet (0=normales Gelenk, 1=Verdacht auf Veränderungen, 2=minimale Veränderungen, 3=eindeutige Veränderungen, 4=Ankylose). Auf Basis dieser Ergebnisse wurden die Patienten in r-axSpA, wenn beide Befunder eine radiografische Sakroiliitis von Grad 2 beidseitig oder von Grad 3 einseitig sahen und sonst in nr-axSpA eingeteilt.

Der SIG Osteitisscore im MRT wurde bereits in 3a) beschrieben.

Statistik

Für die Analyse wurde für jeden Patienten der Summenscore aus dem Wert des rechten und des linken SIG berechnet. Radiografische Progression wurde daraufhin definiert als

1. absolute Veränderung des SIG Summenscores
2. Veränderung von mindestens einem Grad im Summenscore
3. Veränderung von mindestens einem Grad in einem SIG nach Meinung beider Befunder
4. Veränderung von nr-axSpA in r-axSpA nach Meinung beider Befunder.

Um die Übereinstimmung zwischen beiden Befundern zu beurteilen wurde der Intra-Class-Korrelationskoeffizient (ICC) des SIG Summenscores berechnet. Welche Faktoren sich über die Zeit auf die radiografische Progression auswirken, wurde mittels gemischtem linearen Modell mit der Veränderung des Summenscores als Zielvariable untersucht. Die Veränderung wurde als Differenz der Summenscores zwischen zwei Jahren bestimmt (Baseline – Jahr 2, Jahr 2 – Jahr 4 und Jahr 4 – Jahr 6). Es wurde der Einfluss der Parameter Alter, Geschlecht, HLA-B27 Status, Behandlung mit SSZ im 1. Jahr, Behandlungsdauer mit ETA, Einnahme von nichtsteroidalem Antirheumatikum (NSAR), Symptomdauer, CRP, aktive und chronisch entzündliche Veränderung der SIG im MRT und radiografischer SIG Summenscore zu Baseline untersucht. Die Ergebnisse wurden als *least squares means* (LSMEAN) mit 95% Konfidenzintervall angegeben.

4. Ergebnisse

a) Zusammenhang zwischen aktiven entzündlichen Läsionen in der Wirbelsäule und den SIG und der Neubildung von Verfettungen

Zu Baseline zeigten 5% der WK und 39% der SIG-Quadranten Verfettungen des Knochenmarks. In ihrem Behandlungsergebnis nach 48 Wochen unterschieden sich die beiden Extremgruppen A

und B signifikant: In Quadranten oder an WK-Stellen an denen keine entzündlichen Läsionen in der STIR Sequenz nachweisbar waren, entstanden keine Verfettungen an SIG-Quadranten bzw. nur in 0,6% der WK. An jenen WK und SIG-Quadranten an denen akute Läsionen zu Baseline aber nicht zu Woche 48 vorhanden waren, war in der T1 Sequenz Verfettung in 18% der WK und 11% der SIG-Quadranten neu nachweisbar. Einen geringeren Anstieg der Verfettungsstellen gab es in Gruppe C (7% an den WK und 2% an den SIG), wenn die Entzündung nach Baseline noch vorhanden war. Für zu Baseline CRP positive Patienten war das Entstehen von Verfettung nicht korreliert mit einer Veränderung des CRP. Es gab kaum Stellen, an denen sich zu Baseline vorhandene Verfettung auflöste.
Der Vergleich der mittleren Verfettungsscores zwischen den beiden Behandlungsgruppen zeigte ein signifikant höheres Ansteigen des Scores in der ETA Gruppe im Vergleich zu den mit SSZ behandelten Patienten. Die Beurteilung der Entwicklung der Erosionen und der Ankylose von Baseline bis Woche 48 zeigte keine Veränderungen im mittleren Erosions- und Ankylosescore und keinen Unterschied zwischen den Behandlungsgruppen. Es verschwand keine der an den WK nachweisbaren Erosionen.

Die Ergebnisse sind in der folgenden Publikation ausführlicher dargestellt:
H Song, K G Hermann, H Haibel, C E Althoff, D Poddubnyy, J Listing, **A Weiß**, B Freundlich, M Rudwaleit, J Sieper, *Relationship between active inflammatory lesions in the spine and sacroiliac joints and new development of chronic lesions on whole-body MRI in early axial spondyloarthritis: results of the ESTHER trial at week 48*, Ann Rheum Dis, 2011

b) Veränderungen objektiver und subjektiver Entzündungszeichen bei Patienten mit kurzer und langer Erkrankungsdauer

Zu Baseline gab es signifikante Unterschiede zwischen den <4 Jahre und den ≥4 Jahre erkrankten Patienten im Alter, BASDAI, BASFI und CRP. Die Analyse der Daten im Verlauf von vier Jahren zeigte, dass sich die kürzer erkrankten Patienten deutlicher im BASDAI, BASFI, BASMI und ASDAS verbesserten als die länger Erkrankten nach Kontrolle um die Ausgangswertunterschiede. Keine signifikanten Unterschiede zwischen den Gruppen gab es dagegen bei den Veränderungen im CRP und dem MRT SIG Score.
In einer Sensitivitätsanalyse wurde eine weitere Unterteilung der Gruppen nach der Erkrankungsdauer vorgenommen. Diese zeigte keine weiteren Unterschiede zwischen den Subgruppen, so dass ein Trennpunkt bei vier Jahren am besten zwischen Patienten mit eindeutiger Verbesserung in PROs und denen mit weniger deutlichen Veränderungen

unterscheidet. Zur genaueren Untersuchung des möglichen Einflusses der Dauer der Erkrankung wurden im CRP positive und CRP negative Patienten getrennt untersucht.
Der Unterschied zwischen den kurz und lang erkrankten Patienten war für die CRP positiven nicht mehr so deutlich. Für CRP positive Patienten gab es keine signifikanten Unterschiede zwischen kurz und lang Erkrankten im BASDAI, BASFI, BASMI und ASDAS. Die kurz erkrankten CRP negativen Patienten zeigten dagegen deutlich größeres Ansprechen beim BASDAI, BASFI, BASMI und ASDAS als die länger erkrankten CRP negativen Patienten.
In einer weiteren Analyse wurden Veränderungen in objektiven Parametern mit Veränderungen in subjektiven Parametern korreliert. Nach Korrektur der Veränderungswerte für den jeweiligen Baselinewert des Parameters korrelierte die Verbesserung im BASDAI mit der Verbesserung des SIG Scores der kurz Erkrankten signifikant. Patienten mit ≥4 Jahre Erkrankungsdauer zeigten keinen signifikanten Zusammenhang zwischen den Verbesserungen im BASDAI und denen im MRT Score bzw. CRP.

Die Ergebnisse sind in der folgenden Publikation ausführlicher dargestellt:
A Weiß, I-H Song, H Haibel, J Listing, J Sieper, *Good correlation between changes in objective and subjective signs of inflammation in patients with short- but not long duration of axial spondyloarthritis treated with tumor necrosis factor-blockers*, Arthritis Research & Therapy, 2014

c) Verlauf der strukturellen Veränderung der SIG bei Patienten mit früher axSpA

Von 76 Patienten der ESTHER-Studie wurden 42 Patienten in die Analyse eingeschlossen, da für diese ein SIG Röntgenbild zu Baseline und mindestens zu einem weiteren Messzeitpunkt vorlag. 15 Patienten wurden als r-axSpA und 27 als nr-axSpA eingestuft. Die Übereinstimmung in Bezug auf die SIG Summenscores zwischen beiden Befundern war gut bis exzellent mit einem mittleren ICC zwischen 0,72 und 0,86.
Die mittlere Veränderung des SIG Summenscores im Röntgenbild von Baseline bis Jahr 2 lag bei 0,13, zwischen Jahr 2 und Jahr 4 bei -0,27 und zwischen Jahr 4 und Jahr 6 bei -0,09, damit lag die größte Progression zwischen Baseline und Jahr 2. Es gab einen signifikanten Unterschied in der Veränderung des SIG Summenscores zu Jahr 2 zwischen Patienten, die im ersten Jahr mit ETA (0,31 +-0,62) behandelt wurden und denen die SSZ (-0,11 +- 0,82) bekommen hatten (p=0,04). Dieser Effekt konnte in den folgenden Jahren nicht mehr beobachtet werden.

Die univariate Analyse der Prädiktoren für die Veränderung des SIG Summenscores ergab, dass sich sowohl der CRP-Wert als auch der MRT SIG Osteitisscore signifikant mit dem Anstieg des SIG Summenscores assoziiert ist. Die beiden Modelle der multivariaten Analyse, in der jeweils einer der beiden Entzündungsparameter aufgenommen wurde, zeigten einen noch deutlicheren Zusammenhang zwischen Entzündungsparameter und Veränderung des SIG.

Die Ergebnisse sind in der folgenden Publikation ausführlicher dargestellt:
V Rios Rodriguez, K Hermann, **A Weiß**, J Listing, H Haibel, C Althoff, F Proft, O Behmer, J Sieper, D Poddubnyy, *Progression of the structural damage in the sacroiliac joints in patients with early axial spondyloarthritis during a long-term anti-TNF treatment*, Arthritis Rheumatol, 2019

5. Diskussion

Ziel dieser Arbeit war die Analyse der Auswirkungen der Biologikatherapie mit ETA auf die Zusammenhänge zwischen Entzündung und dem Neuentstehen von Verfettungsstellen im subchondralen Knochenmark, auf die Zusammenhänge zwischen objektiv gemessenen Entzündungsparametern und PROs und auf die Progression der SIG.
Innerhalb der ersten Publikation konnte gezeigt werden, dass es einen Zusammenhang zwischen aktiver Entzündung und dem Neuentstehen von Verfettungsstellen gibt. Wenn Entzündung zurückgeht, kann es eher zu einer Verfettung im subchondralen Knochenmark kommen, was als Äquivalent eines Reparaturmechanismus angesehen werden muss (18). Da ETA die Entzündung effektiver als SSZ unterdrückt, kam es unter der ETA-Behandlung zu einem stärkeren Anstieg der Verfettung, was zu beweisen war. Bei mit ETA behandelten Patienten stieg der Verfettungscore von Baseline bis Woche 48 sowohl für die Wirbelsäule (von 1,9 auf 2,7) als auch für die SIG (von 4,0 auf 4,8) signifikant an, nicht jedoch bei der Kontrollgruppe mit SSZ behandelter Patienten (Wirbelsäule: von 1,1 auf 1,2 und SIG: von 3,0 auf 3,2). Diese Veränderungen konnten bereits nach sechs Monaten gezeigt werden. Verfettung gilt als erstes Zeichen chronischer Veränderungen im Knochen nach vorheriger Entzündung. In weniger als 1% der WK und SIG treten Verfettungen ohne vorherige Entzündung auf und Verfettung tritt weniger häufig auf, wenn die Entzündung noch anhält. Das MRT weist an dieser Stelle jedoch die technische Einschränkung auf, das Verfettung nicht gut sichtbar ist, solange eine Entzündung anhält. In einer weiteren Analyse müsste geprüft werden, ob das frühzeitige Unterdrücken der Entzündung nachweisbar chronische Veränderungen aufhält.

Die Beantwortung der Frage, ob es einen Zusammenhang zwischen PROs und objektiven Entzündungsparametern gibt, wurde in der zweiten Publikation untersucht. Für die axSpA sind die bisher veröffentlichten Ergebnisse unzureichend. Die Krankheitsaktivität wurde auf Basis von PROs wie BASDAI, ASAS-20, ASAS-40 und partiellen Remissionskriterien (19) bestimmt und der ASDAS (20) wurde als Instrument entwickelt, welches vom Patienten berichtete Parameter und CRP bzw. Blutsenkungsgeschwindigkeit (BSG) kombiniert. Ob es einen Zusammenhang zwischen subjektiven Patientenskalen und objektiven Entzündungsparametern gibt, wurde in dieser Arbeit sowohl zu Beginn der Behandlung mit anti-TNF-Behandlung mit ETA oder ADA berechnet als auch nach einem Jahr Behandlung mit einem TNF-alpha-Blocker. Zu Baseline waren PROs und Entzündungsparameter (CRP und MRT SIG) nicht korreliert. Nach einem Jahr anti-TNF-Behandlung konnte ein signifikanter Zusammenhang für Patienten, die <4 Jahre erkrankt waren, zwischen der Veränderung im BASDAI und der im CRP und der im MRT SIG Score nachgewiesen werden. Für länger Erkrankte war dieser Zusammenhang invers und schwächer (CRP: ρ=0,22, p=0,4 und MRT SIG: ρ=0,12, p=0,5). In dieser Analyse wurde der Baselinestatus berücksichtigt, da sich ein Patient mit einem höheren Ausgangswert mehr verbessern kann als einer, der zu Beginn eine niedrige Krankheitsaktivität hat.
Des Weiteren konnte gezeigt werden, dass mit TNF-alpha-Blockern behandelte Patienten mit einer Krankheitsdauer <4 Jahre sich signifikant in PROs verbessern (BASDAI p=0,001, BASFI p=0,0003) im Vergleich zu den Patienten, die ≥4 Jahre erkrankt sind (steht nicht im Artikel). Keine signifikanten Unterschiede zwischen beiden Gruppen gab es für die objektiven Entzündungsparameter MRT SIG Score und CRP. Eine weitere Unterteilung der Gruppen nach der Erkrankungsdauer in <2, 2 bis 4, 4 bis 8 und ≥8 Jahre erkrankt zeigte keine Veränderungen in diesen Ergebnissen, was deutlich macht, dass Patienten mit bis zu vier Jahren Krankheitsdauer besser auf eine Therapie mit einem TNF-alpha-Blocker ansprechen als länger als vier Jahre Erkrankte. Es liegt die Vermutung nahe, dass kürzer erkrankte Patienten in erster Linie durch Entzündungen beeinträchtigt sind, die sehr effektiv durch eine TNF-alpha-Blocker-Therapie unterdrückt wird, wogegen länger erkrankte Patienten neben Entzündungen weitere nicht-entzündliche Ursachen für ihre Symptome entwickelt haben.
In der dritten Arbeit wurde untersucht, ob sich die radiografische Progression der SIG aufhalten lässt. Progression tritt in der vorliegenden Studie vorwiegend in den ersten Jahren der anti-TNF-Behandlung auf. Die ESTHER Studie weist mit 7,1% Progression innerhalb der ersten beiden Jahre im Vergleich zu 3,8% innerhalb von zwei Jahren bei GESPIC (21) und 5,1% innerhalb von fünf Jahren in der DESIR Kohorte (16) die höchste Progressionsrate auf. Jedoch war eines der Einschlusskriterien in ESTHER, dass die Patienten eine aktive Entzündung der SIG bzw.

Wirbelsäule nachweisbar im MRT haben mussten. Des Weiteren wurden die Patienten in der ESTHER Studie, im Gegensatz zu GESPIC und DESIR, mit einem TNF-alpha-Blocker behandelt. Unter der Behandlung mit dem TNF-alpha-Blocker ETA waren die strukturellen Veränderungen in den SIG größer als in der Gruppe, die zunächst über ein Jahr mit SSZ behandelt wurden, eine Therapie, die allgemein als ineffektiv angesehen wird, könnte der Auslöser für die im Röntgenbild sichtbare Progression der strukturellen Zerstörung der SIG sein. Die hier erhobenen Befunde decken sich mit den in WS erhobenen: in den ersten 1-2 Jahren haben TNF-Blocker keinen oder evtl. sogar einen negativen Effekt auf strukturelle knöcherne Veränderungen, während ein hemmender Effekt auf die röntgenologische Progression bei längerfristiger Therapie mit einem TNF-Blocker sichtbar wird (15).

Als Prädiktoren für die radiografische Progression der SIG wurde die Erhöhung von Entzündungszeichen, gemessen durch CRP und durch vorhandene Osteitis der SIG im MRT identifiziert. Diese Parameter zeigten in der univariaten Analyse, dass sie sich signifikant auf den Sakroiliitis Summenscore nach zwei Jahren auswirken. Im multivariaten Modell, in dem für die Entzündung entweder der erhöhte CRP-Wert oder der Osteitisscore der SIG aufgenommen wurde, war dieser Zusammenhang sogar größer als im univariaten Modell.

Zusammenfassend zeigen die Ergebnisse der drei Analysen bei Patienten mit früher axSpA, dass es einen Zusammenhang zwischen der Entzündung, der anti-TNF-Therapie und dem Entstehen von Verfettungsstellen im Knochenmarksödem gibt. Zusammenhänge zwischen objektiv gemessenen Entzündungsparametern und PROs gibt es nur eindeutig für kurz erkrankte Patienten, nicht jedoch für Patienten, die länger als vier Jahre erkrankt sind. Die Langzeitbehandlung mit TNF-alpha-Blocker scheint die Progression der strukturellen Zerstörung der SIG zu verzögern. Der CRP-Wert und Osteitis im MRT stehen unabhängig voneinander im Zusammenhang mit der radiografischen Progression.

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Eidesstattliche Versicherung

„Ich, Anja Weiß, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Entwicklung und Zusammenhänge von Entzündungsparametern und Patientenskalen bei Patienten mit axialer SpA“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

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Meine Anteile an den ausgewählten Publikationen entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Betreuer, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o.) und werden von mir verantwortet.

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

_____ _____

Datum Unterschrift

Ausführliche Anteilserklärung

Anja Weiß hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: I-H Song, K G Hermann, H Haibel, C E Althoff, D Poddubnyy, J Listing, **A Weiß**, B Freundlich, M Rudwaleit, J Sieper, *Relationship between active inflammatory lesions in the spine and sacroiliac joints and new development of chronic lesions on whole-body MRI in early axial spondyloarthritis: results of the ESTHER trial at week 48*, Ann Rheum Dis, 2011
Beitrag im Einzelnen: Datenmanagement, Auswahl und Festlegung der anzuwendenden statistischen Methoden, Durchführung der Datenanalyse, Durchführung der statistischen Analyse, Erstellung der Ergebnisse, Grafiken und Tabellen, Prüfung des finalen Manuskripts

Publikation 2: **A Weiß**, I-H Song, H Haibel, J Listing, J Sieper, *Good correlation between changes in objective and subjective signs of inflammation in patients with short- but not long duration of axial spondyloarthritis treated with tumor necrosis factor-blockers*, Arthritis Research & Therapy, 2014
Beitrag im Einzelnen: Datenmanagement und Durchführung der Datenanalyse für beide Studien, Festlegung des Analyseplans, Festlegung der anzuwendenden statistischen Methoden und Einarbeitung in die nicht-parametrische Kovarianzanalyse nach Brunner, Durchführung der statistischen Analyse, Erstellung der Ergebnisse, Grafiken und Tabellen, Literaturrecherche, Verfassen des Manuskripts, Einreichung des Manuskriptes und Beantwortung der Reviewer-Fragen

Publikation 3: V Rios Rodriguez, K Hermann, **A Weiß**, J Listing, H Haibel, C Althoff, F Proft, O Behmer, D Poddubnyy, *Progression of the structural damage in the sacroiliac joints in patients with early axial spondyloarthritis during a long-term anti-TNF treatment*, Arthritis Rheumatol, 2019
Beitrag im Einzelnen: Datenmanagement und Durchführung der Datenanalyse, Festlegung des Analyseplans, Auswahl und Festlegung der anzuwendenden statistischen Methoden, Durchführung der statistischen Analyse, Prüfung des finalen Manuskripts

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers

Unterschrift der Doktorandin

Publikation 1: Relationship between active inflammatory lesions in the spine and sacroiliac joints and new development of chronic lesions on whole-body MRI in early axial spondyloarthritis: results of the ESTHER trial at week 48

I-H Song, K G Hermann, H Haibel, C E Althoff, D Poddubnyy, J Listing, A Weiß, B Freundlich, M Rudwaleit, J Sieper, *Relationship between active inflammatory lesions in the spine and sacroiliac joints and new development of chronic lesions on whole-body MRI in early axial spondyloarthritis: results of the ESTHER trial at week 48*, Ann Rheum Dis, 2011

Relationship between active inflammatory lesions in the spine and sacroiliac joints and new development of chronic lesions on whole-body MRI in early axial spondyloarthritis: results of the ESTHER trial at week 48

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ABSTRACT

Aim To investigate the relationship between active inflammatory lesions on whole-body MRI (wb-MRI) and new development of chronic lesions on T1 MRI in patients with early axial spondyloarthritis (SpA) treated either with etanercept (ETA) or sulfasalazine (SSZ).

Methods Wb-MRIs of 65 patients treated either with ETA (n=35) or SSZ (n=30) over 1 year were scored for active inflammation, fatty lesions, erosions and ankylosis in the 23 vertebral units (VUs) of the spine and in the sacroiliac joints (SI joints). Scoring was performed by two blinded radiologists.

Results If there was no previous inflammation in the bone no new fatty lesions occurred in SI joint quadrants and only a few (0.6%) in spine VUs. There was a significant relationship between disappearance of inflammation and the appearance of fatty lesions: if baseline inflammation resolved fatty lesions occurred in 10.5% of SI joint quadrants and 17.9% of VUs. If inflammation did not resolve over 1 year, fatty lesions occurred less frequently: 2.4% (SI joint quadrants) and 7.2% (VUs). There was a significantly higher increase of the mean fatty lesion score between baseline and week 48 in the ETA (4.0 vs 4.8 for the SI joints and 1.9 vs 2.7 for the spine) compared to the SSZ (3.0 vs 3.2 for the SI joints and 1.1 vs 1.2 for the spine, respectively) group (p=0.001 and p=0.020 for the differences). No significant changes in the erosion or ankylosis score were observed in any of the two groups during this time.

Conclusions These data indicate that there is a close interaction between inflammation, tumour necrosis factor blockade and the development of fatty lesions in subchondral bone marrow of patients with axial SpA.

INTRODUCTION

Treatment of patients with active ankylosing spondylitis (AS) with tumour necrosis factor α (TNFα)-blocking agents has been proven to be highly effective for signs and symptoms[1–3] and also for the suppression of active inflammation of sacroiliac joints (SI joints) and/or spine on MRI.[4 5] Against this background, the failure to retard the growth of syndesmophytes as shown on x-rays over a treatment period of 2 years was at first glance a surprise,[6–8] and has stimulated an intense discussion about the interaction between inflammation and new bone formation in general and especially in the context of AS.[9–11] Indeed, it has been shown that TNFα blocks the activity of osteoblasts and inhibition of TNFα stimulates osteoblast activity in a TNF transgenic mouse model of arthritis.[10 12] Thus, it has been postulated that TNF inhibits and TNF blockade stimulates new bone formation.[9 11 13] In several investigations the question was addressed as to whether inflammation is essential for the development of syndesmophytes or whether new bone formation occurs independently from previous inflammation.[11 14 15] Although a correlation between inflammation of vertebral corners at baseline with the growth of syndesmophytes at the same site 2 years later was found in these analyses, new bone formation also occurred at sites with no inflammation at baseline.

Inflammation of subchondral bone marrow (bone marrow oedema) can be demonstrated by the short tau inversion recovery (STIR) sequence of MRI, while chronic changes are seen better or are only visible on MRI T1 sequence.[16 17] The MRI T1 sequence is unique among imaging techniques for the detection of fatty lesions of the bone marrow, which is probably the earliest sign of chronic changes as a consequence of inflammation.[16 17] A correlation between the presence of active spondylitis on MRI and the subsequent occurrence of fatty lesions at the same sites on MRI T1 has been reported recently in a preliminary study.[18] Furthermore, a correlation between fatty lesions and the growth of syndesmophytes has been found[19] indicating that fatty infiltration might be a necessary step between inflammation and new bone formation.

In a recent study we reported a good efficacy of etanercept (ETA) treatment over 1 year in patients with early (symptom duration less than 5 years) axial spondyloarthritis (SpA) on active inflammation of SI joints and the spine as shown by MRI and on clinical parameters, in comparison to treatment over the same period with sulfasalazine (SSZ).[20] In this prospective study patients were randomised to one of the two treatment arms and whole-body MRI (wb-MRI) was read by two scorers blinded for treatment and time points.

In the present study we analysed the development of chronic changes in the bone on T1 MRI such as fatty lesions, erosions and ankylosis over 1 year, the effect of inflammation at baseline on

the development of chronic lesions and the effect of treatment on the development of chronic lesions in patients from this trial.

METHODS

Study design

Patients with axial SpA enrolled in a prospective randomised controlled trial were treated with ETA (n=40) versus SSZ (n=36) over 48 weeks.[20] All patients showed active inflammatory lesions (bone marrow oedema) on wb-MRI in either the SI joints and/or the spine at baseline (BL).[20]

For this analysis we included the 65 completers (35 patients on ETA and 30 on SSZ) in whom wb-MRI sets at baseline and week 48 were available. Patient characteristics are shown in table 1.

MRI

Wb-MRIs were performed at weeks 0, 24 and 48 on a 1.5 T scanner (Avanto TIM, Siemens, Erlangen, Germany) according to a previously described protocol.[20–22] The STIR images were acquired using the following parameters: repetition time (TR) 1660–4590, time to echo (TE) 25–83 and inversion time (TI) 150. The acquired T1 turbo spin-echo (TSE) images comprised a TR of 642–790 and a TE of 10.

Wb-MRIs were scored for active inflammation according to a recently described protocol[20] using the STIR sequences. Chronic changes were scored using the T1 sequences in the 23 vertebral units (VUs) of the spine and the 4 quadrants of each SI joint in case of fatty lesions; erosions and ankylosis were only scored for each SI joint as shown in detail in table 2. Scoring was performed by two radiologists, blinded for treatment arm and MRI time point. T1 and STIR images were scored at the same time.

At baseline, the agreement between both readers (KGH, CA) was high for osteitis and fatty lesions with intraclass correlation coefficients (ICCs) of 0.93 in the spine (SI joints 0.96) for osteitis and 0.97 (0.90) for fatty lesions. ICCs were lower for erosions: 0.82 (0.80) and ankylosis 0.75 (0.96).

Statistics

Main outcome parameters were changes in chronic lesions (fatty lesions, erosions, ankylosis) assessed by MRI T1 sequence and associations between the changes in chronic lesions and changes in active inflammation scores assessed by STIR sequences. To be able to investigate these associations the statistical analysis was restricted to n=65 completers (as described above). The non-parametric analysis of covariance (non-parametric ANCOVA) was used to compare the outcome of the treatment groups by taking the baseline status as covariable into account and the non-parametric Mann–Whitney test was applied to compare treatment groups at baseline. These analyses were based on means of the MRI scores of both readers (KGH, CA) on the patient level. Missing values at week 24 (n=3) were replaced by a so-called expectation maximization algorithm (replacement with an individual mean value from baseline and week 48 adjusted for the overall trend).[23]

To evaluate the associations between the changes in chronic lesions and changes in active inflammation scores in a very specific manner these possible associations were investigated in the spine on the VU level and in the SI joints on the level of four quadrants per SI joint in case of fatty lesions and per SI joints for erosions and ankylosis. Regarding changes in osteitis scores, three groups (VUs, or quadrants) were analysed separately; group A: both readers agree on no signs of osteitis in the STIR sequence in this unit at baseline and at week 48, group B: both readers agree regarding a resolution of inflammation in this unit, group C: units not assigned to A or B but inflammation present at week 48 according to at least one reader (group C was not further stratified because of insufficient sample size). Regarding the outcome, the development of a new chronic lesion between baseline and week 48, an agreement between both readers was required. Generalised estimation equation (GEE) models with a logit link function were applied to investigate the associations between changes in the MRI scores for fatty lesions and active inflammation. By means of these GEE models groups A, B and C were compared and the percentage of new chronic lesions and their corresponding 95% CIs were estimated by taking possible correlations between chronic and active changes in single VUs (or quadrants) within individual

Table 1 Baseline characteristics

	All	Etanercept	Sulfasalazine
Number of patients	65	35	30
Age in years, mean (SD)	33.0 (8.5)	33.5 (8.7)	32.4 (8.4)
Male, n (%)	39 (60.0)	22 (62.9)	17 (56.7)
Symptom duration in years, mean (SD)	2.7 (1.7)	2.5 (1.6)	3.0 (1.8)
HLA-B27 positive, n (%)	54 (83.1)	30 (85.7)	24 (80.0)
Fulfilled modified New York criteria,[37] n (%)	54 (50.8)	17 (48.6)	16 (53.3)
Fatty lesions on VU level, n (%)	67 (4.5)	49 (6.1)	18 (2.6)
Fatty lesions on SI joint quadrant level, n (%)	202 (38.8)	123 (43.9)	79 (32.9)
Erosions on VU level, n (%)	6 (0.4)	4 (0.5)	2 (0.3)
Erosions on SI joint level, n (%)	95 (73.1)	51 (72.9)	44 (73.3)
Ankylosis on VU level, n (%)	10 (0.7)	6 (0.7)	4 (0.6)
Ankylosis on SI joint level, n (%)	9 (6.9)	7 (10.0)	2 (3.3)

Mean values of fatty lesion scores, erosion scores and ankylosis scores shown in table 3.
HLA, human leucocyte antigen; SI joint, sacroiliac joint; VU, vertebral unit.

Table 2 Scores for chronic inflammatory changes on MRI

Finding on MRI	Spine score per VU	SI joint score per quadrant/joint
Fatty lesion	0: normal bone marrow	0: fatty lesions absent
	1: fatty lesions of <25% of VU area	1: fatty lesions present
	2: fatty lesions of ≥25% and <50% of VU area	NA
	3: fatty lesions of ≥50% of VU area	NA
Erosions*	0: no erosion	0: normal joint margin
	1: erosion <25% of vertebral end plate	1: 1–2 erosions
	2: erosion ≥25% of vertebral end plate	2: 3–5 erosions
	NA	3: >5 erosions
Ankylosis*	0: no ankylosis	0: ankylosis absent
	1: syndesmophyte growth, not bridging	1: ankylosis present
	2: syndesmophyte growth, bridging (anterior/posterior)	NA
	3: transdiscal ankylosis	NA

Maximum fatty lesion score per patient: 69 for spine and 8 for SI joints; maximum erosion score per patient: 46 for spine and 6 for SI joints; maximum ankylosis score per patient 69 for spine and 2 for SI joints.
*Erosions and ankylosis in the spine were scored on the VU level; in the SI joints erosions and ankylosis were scored for left and right SI joint (not per quadrant).
NA, not applicable; SI joint, sacroiliac joint; VU, vertebral unit.

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patients into account.[24] SAS software (PROC GLIMMIX; SAS, Cary, North Carolina, USA) was used for calculations. p Values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics

The inclusion criteria and the patients' characteristics for this trial have been described recently in detail.[20] Patients' characteristics including chronic MRI lesions at baseline are shown in table 1. In the whole group (n=65) fatty lesions were found in 4.5% of VUs (in 26.2% of patients) and in 38.8% of SI joint quadrants (in 69.2% of patients). Erosions were found in only 0.4% of VUs but in 73.1% of SI joints. Ankylosis of VUs occurred in 0.7% in contrast to 6.9% of SI joints.

Occurrence of fatty lesions over 1 year in relation to inflammation

New fatty lesions at week 48 developed in 23 VUs and in 17 SI joint quadrants in all patients. There was a very low rate of new fatty lesions of <1% (0.6% for VUs and 0% for SI joint quadrants) if there was no previous inflammation in the bone (figure 1A for spine VUs and figure 1B for SI joint quadrants). In the presence of baseline inflammation and disappearance of inflammation at all subsequent time points fatty lesions occurred in 17.9% (VUs) and 10.5% (SI joint quadrants), while fatty lesions occurred much less frequently if inflammation was present at week 48: 7.2% in VUs and 2.4% in SI joint quadrants (figure 1A,B). Appearance of new fatty lesions in the SI joints and the spine did not correlate with a change in C reactive protein (SI joints: correlation

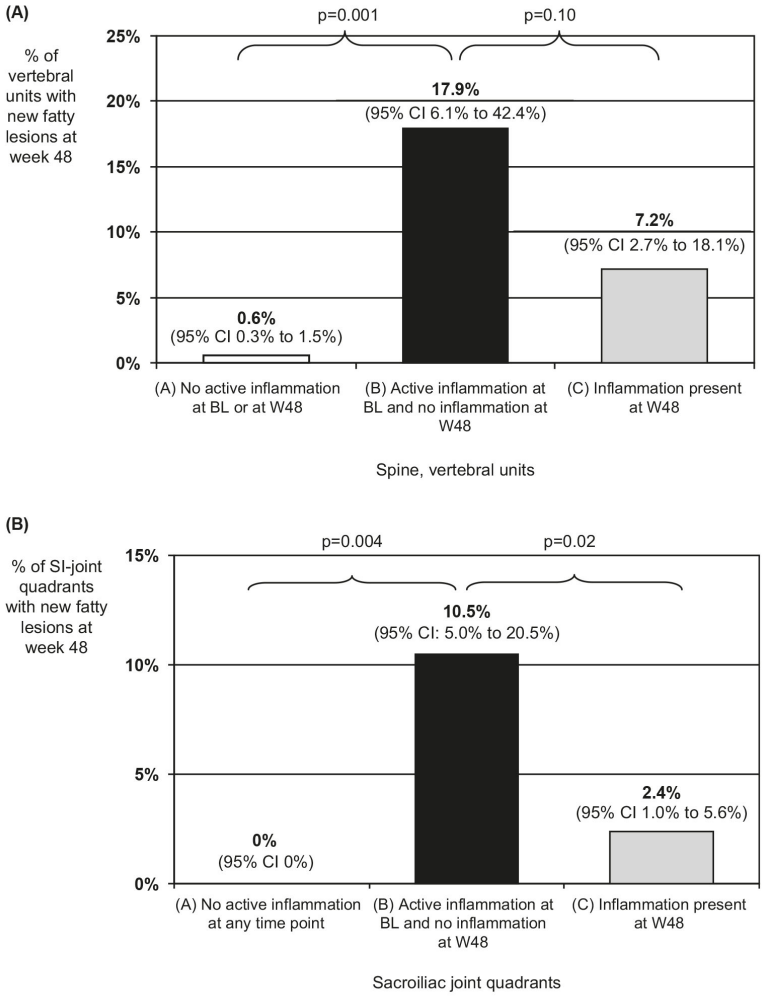

Figure 1 Frequency of newly developed fatty lesions at the vertebral units of (A) the spine and (B) the sacroiliac joint quadrants at week 48 in relation to active inflammatory lesions. Percentages shown in the three groups in which (A) there was no active inflammation at baseline (BL) and no inflammation at week 48 (W48) vs (B) there was active inflammation at baseline but no inflammation at week 48 (disappearance of active inflammation) vs (C) there was inflammation present at week 48.

coefficient=0.018, p=0.34; spine: correlation coefficient=0.055, p=0.95).

Fatty lesions present at baseline did not disappear over 48 weeks: 0 out of 67 (0%) at VUs and 2 out of 202 (1%) at SI joint quadrants.

When the change of active inflammation was plotted against the change of the fatty lesion score also on a patient level the correlation between reduction of active inflammation and increase of fatty lesions can be seen (see supplementary figure S1). There was a significant correlation between reduction of active inflammation and increase of fatty lesions in the spine (correlation coefficient=–0.39, p=0.001) as well as in the SI joints (correlation coefficient=–0.76, p=0.0015).

Occurrence of fatty lesions compared between the two treatment groups

There was a significantly higher increase of the mean fatty lesion score in the ETA group (4.0 at baseline vs 4.8 at week 48 for the SI joints and 1.9 vs 2.7 for the spine) compared to the SSZ group (3.0 at baseline vs 3.2 at week 48 for the SI joints and 1.1 vs 1.2 for the spine, respectively) (p=0.001 and p=0.020 for the differences between the treatment groups) (table 3). The increase in the fatty lesion score in the ETA group was already visible after 24 weeks (table 3).

The corresponding increase of the fatty lesion score on the patient level is shown in the probability plots in figure 2A (for the spine) and figure 2B (for the SI joints).When the nine patients who already had a maximal fatty lesion score of 8 in the SI joints at baseline were excluded from this analysis, the mean baseline values were the same (mean value 2.8) and again the increase in the mean fatty lesion score between baseline and week 48 was significantly (p=0.001) higher in the ETA (from 2.8 to 3.9) as compared to the SSZ group (from 2.8 to 3.0).

Figure 3 shows MRI examples without (figure 3A) and with (figure 3B) development of fatty lesions in the spine after suppression of active inflammation.

Table 3 Mean MRI SI joint and spine scores for fatty lesions, erosions and ankylosis at baseline, week 24 and week 48 in patients with axial spondyloarthritis treated with etanercept (ETA) or sulfasalazine (SSZ)

Location	MRI parameter	Study time point	ETA (n=35)	SSZ (n=30)	p Value*
Spine	Fatty lesion score (0–69) (mean (SD))	Baseline†	1.9 (5.0)	1.1 (2.6)	
		Week 24	2.6 (5.6)	0.9 (2.1)	0.033
		Week 48	2.7 (5.8)	1.2 (2.7)	0.020
	Erosion score (0–46) (mean (SD))	Baseline†	0.2 (0.4)	0.3 (0.7)	
		Week 24	0.2 (0.4)	0.3 (0.8)	0.49
		Week 48	0.2 (0.5)	0.3 (0.8)	0.21
	Ankylosis score (0– 69) (mean (SD))	Baseline†	0.6 (2.4)	0.3 (1.1)	
		Week 24	0.6 (2.3)	0.2 (1.1)	0.10
		Week 48	0.7 (2.5)	0.3 (1.1)	0.52
SI joints	Fatty lesion score (0–8) (mean (SD))	Baseline†	4.0 (3.2)	3.0 (2.8)	
		Week 24	4.6 (3.4)	3.2 (2.9)	0.018
		Week 48	4.8 (3.2)	3.2 (2.9)	0.001
	Erosion score (0–6) (mean (SD))	Baseline†	3.9 (2.2)	3.5 (2.0)	
		Week 24	3.8 (2.2)	3.6 (2.1)	0.060
		Week 48	3.8 (2.2)	3.5 (2.2)	0.41
	Ankylosis score (0–2) (mean (SD))	Baseline†	0.2 (0.6)	0.1 (0.4)	
		Week 24	0.2 (0.6)	0.1 (0.4)	0.12
		Week 48	0.2 (0.6)	0.1 (0.4)	0.48

*p Values for comparison of changes in the MRI scores between both groups by analysis of covariance.
†No significant differences at baseline between ETA and SSZ: (a) spine: fatty lesions (p=0.65), erosions (p=1.0), ankylosis (p=0.35); (b) SI joints: fatty lesions (p=0.24), erosions (p=0.346), ankylosis (p=0.50).
SI joints, sacroiliac joints.

Development of erosions and ankylosis over 1 year

As shown in table 3 there was no change in the mean erosion score in the whole group and also no change in the two subgroups (ETA vs SSZ), either in the spine or in the SI joints. The same was true for the mean ankylosis score.

Furthermore, none of the six erosions present in all VUs disappeared (0%). Also, there was no change in the ankylosis score in any of the two groups.

DISCUSSION

In this study we have clearly shown that significant changes of fatty lesions in the SI joints and the spine can be observed over 1 year, but not other changes on T1 MRI: (1) fatty lesions did not occur without previous inflammation in the subchondral bone marrow, (2) the score for fatty lesions increased in patients treated with the TNF blocker ETA but not in patients in the control group treated with SSZ and (3) significant changes in the fatty lesion score could already be seen after 6 months. Finally, (4) no changes in the erosion and ankylosis score were seen over 1 year in any of the two treatment groups. These findings might cast some new light on the interaction between inflammation, chronic bony changes and the development of new bone formation in AS.

Fatty lesions seem to be the first sign of chronic damage in the bone after previous inflammation. This was clearly demonstrated in the current study because fatty lesions occurred only at sites that showed subchondral bone marrow oedema as a sign of active osteitis at baseline, confirming previously reported preliminary results.[18] Fatty lesions without previous inflammation occurred very rarely. These few cases might be explained by the fact that MRI might have a sensitivity limit in the detection of inflammation, as was shown in a previous study correlating MRI inflammation and histological inflammation.[25] Interestingly, fatty lesions occurred less frequently if inflammation persisted, indicating that the presence of inflammation might inhibit the occurrence of 'fatty lesions'. However, we cannot exclude a technical problem for this part of the analysis because fatty lesions might not be detectable on an MRI T1 sequence (hyperintense signal) if inflammation is still present (hypointense signal).

The histological correlate of the rather imprecise MRI finding of 'fatty lesions' is not clear at this moment, but probably reflects replacement of subchondral bone marrow by some repair tissue through expansion and/or activation of mesenchymal cells such as adipocytes, fibroblasts and osteoblasts.[26 27]

Fatty lesions at vertebral edges on T1 MRI have also recently been described as early chronic bony changes, which are relatively specific for SpA if they occur at several sites though they do not appear to be different from controls if present only as single lesions in the spine.[28 29] Thus, although fatty lesions seem to be useful for following up the sequence of events in SpA from inflammation to chronic damage, they are not unique for SpA unless they show a certain pattern.

The significant increase of fatty lesions in the group of patients treated with ETA over 1 year in comparison to the SSZ-treated group is a very interesting result of the current study. Although such a result seems to be a logical consequence, because ETA was very effective in suppressing active bone inflammation on MRI in the SI joints and the spine in comparison to treatment with SSZ, and active suppression of inflammation was strongly associated with the appearance of fatty lesions, this has not been shown before. Most interestingly, such a (significant) difference between two treatment groups was already visible after 6 months of treatment with a further increase of the difference

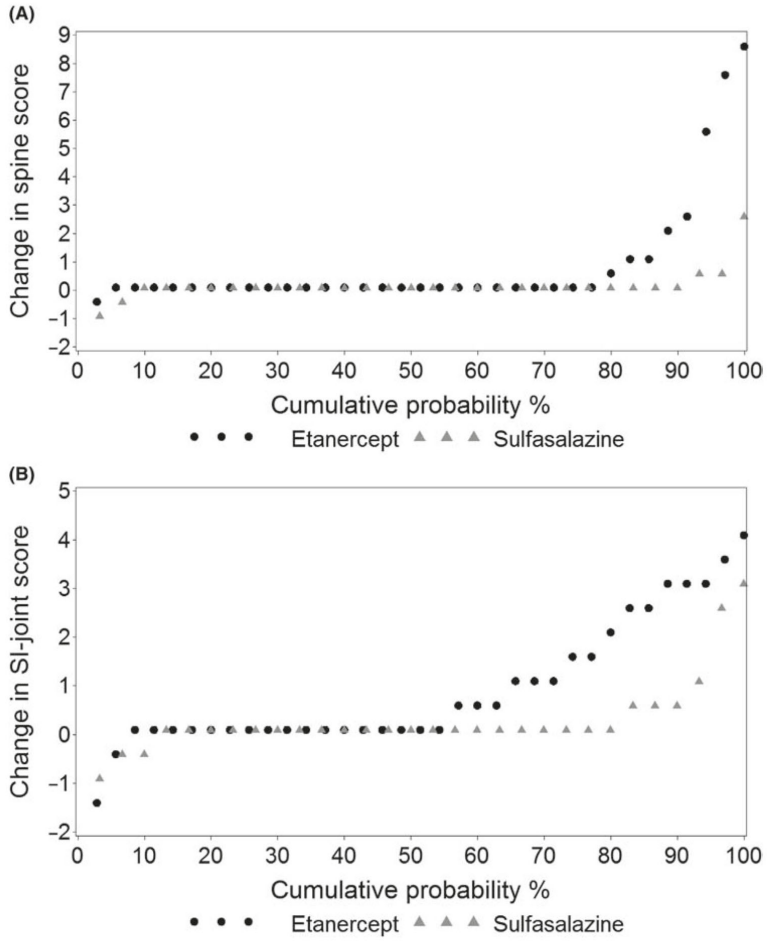

Figure 2 Cumulative probability of changes in MRI fatty lesion scores of (A) the spine and (B) the sacroiliac joints from baseline to week 48 in the etanercept and sulfasalazine treatment groups at the patient level. Each data point in figure 2A,B represents an individual patient.

after 12 months. These data suggest that fatty lesions might prove to be an important early outcome parameter to assess whether suppression of inflammation comes early enough to avoid chronic changes. However, fatty lesions occurred only at about 10% to 20% of cleared inflammatory sites, thus in 80% to 90% of inflammatory sites inflammation was cleared without the occurrence of fatty lesions. We did not find an improvement of fatty lesions in the spine in any of the treatment groups which is in contrast to results from the already mentioned preliminary study.[19] However it is difficult to envisage by which mechanism TNF blockade would reverse the presence of fatty lesions.

The key data presented here are further supported by the very similar results obtained for the SI joints and spine, both read blinded to time points. Furthermore, the availability of a control treatment group over 1 year, which was prospectively randomised at baseline, made it possible to compare fatty lesion scores between the two groups.

Beside fatty lesions, erosions and ankylosis are other manifestations of chronic damage in AS.[16 17] Erosions were observed in 73% of SI joints but only in 0.4% of VUs in this early axial SpA group. After 1 year of follow-up, we could neither find a change in erosions nor in ankylosis in either of the two treatment groups. If these patients treated with ETA are followed up longer than 1 year, an improvement of an erosion score might be detectable.[19] There was a low frequency of ankylosis at baseline, and no change was observed over 1 year. Though MRI is not the method of choice for assessing ankylosis it has been used before for this[17 30] and for SI joints;[16] however the role of MRI for the assessment of ankylosis has to be evaluated in future studies.

Long-term outcome in AS is determined by new bone formation (ankylosis) in the spine. Therefore the question arises as to how the occurrence of fatty lesions might be connected to this. We postulate that fatty lesions are the first chronic changes after inflammation and that they are necessary for the later development of syndesmophytes. Thus, if fatty lesions can be avoided this might be an early (in the first 6–12 months) indicator that new bone formation can also be avoided. Indeed, in one investigation radiographic syndesmophytes after 2 years were present in 12%

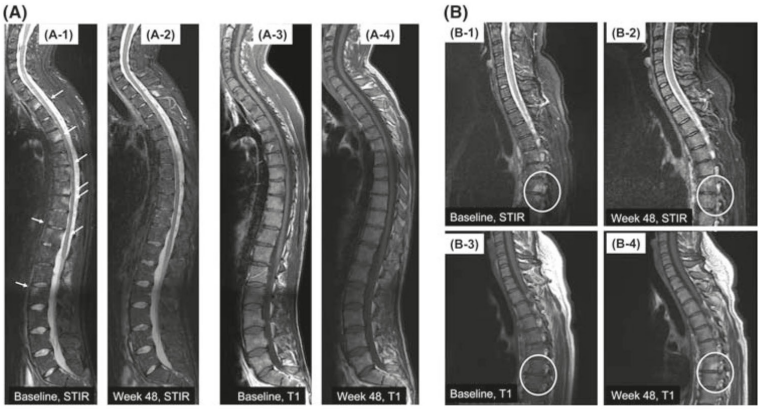

Figure 3 Illustration of spine MRI of two patients treated with etanercept. (A) In patient A active inflammation (as shown by hyperintense signals in short tau inversion recovery sequence) in the spine decreased between (A-1) baseline and (A-2) week 48 but no new fatty lesions developed between (A-3) baseline and (A-4) week 48. (B) Patient B: active inflammatory lesions also decreased between (B-1) baseline and (B-2) week 48 and fatty lesions (as shown by hyperintense sequence in T1 sequence) newly occurred between (B-3) baseline and (B-4) week 48.

of the vertebral edges that showed fatty lesions at baseline but only in 2% of patients without fatty lesions at baseline,[31] supporting the proposed link between inflammation, occurrence of fatty lesions and new bone formation. The patients in the current study will be treated long term with ETA and followed up yearly by wb-MRI and by x-rays every 2 years, which will allow this question to be addressed in more detail in the future.

The molecular basis for the link between inflammation and new bone formation in AS is still not clear. It has recently been shown that low serum levels of the molecules sclerostin[10] and Dickkopf 1 (DKK1),[32] which are both important for osteoclast activation and osteoblast inhibition, are associated with the formation of new syndesmophytes in patients with AS. Thus, taking all imaging and molecular data in AS together, inhibition and/or low levels of inflammation are necessary for the development of chronic lesions such as fatty lesions in subchondral bone marrow and the development of syndesmophytes. The results reported here on fatty lesions in axial SpA that might provide a missing link between these events.

With regard to TNF blocker treatment of patients with axial SpA, we propose the following scenario: early treatment might prevent the occurrence of early chronic changes such as fatty lesions, which was the case in about 80% of inflammatory lesions that were successfully cleared by ETA treatment. Whether or not syndesmophytes will develop from these fatty lesions may no longer be dependent on TNF blocker treatment but rather on the genetic background of the patients and on other treatments such as non-steroidal anti-inflammatory drugs, which might have an effect on new bone formation.[33–35] However, because continuous successful treatment with TNF blockers may avoid or reduce the occurrence of new inflammatory sites[20 36] new chronic lesions may not occur or their appearance may be reduced, because chronic lesions depend on inflammation initially, as shown in the current study. Thus, a reduction of syndesmophytes growth should be detectable in patients treated long term with TNF blockers. However, because the development of the events discussed is a slow process it may take several years of follow-up to prove this. Future long-term follow-up of patients with AS treated with TNF blockers are necessary to confirm the here-proposed concept.

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Competing interests I-HS: consulting fees or other remuneration from Wyeth/Pfizer Pharmaceuticals, Merck Sharp Dohme/Schering Plough, Abbott Immunology Pharmaceuticals. KGH: None. HH: consulting fees or other remuneration from Wyeth/Pfizer, Merck Sharp Dohme/Schering Plough, Abbott Immunology Pharmaceuticals. CA: None. DP: consulting fees or other remuneration from Merck Sharp Dohme/Schering Plough, Abbott Immunology Pharmaceuticals. JL: None. AW: None. BF: former employee of Pfizer/Wyeth. MR: consulting fees or other remuneration from Wyeth/Pfizer, Merck Sharp Dohme/Schering Plough, Abbott Immunology Pharmaceuticals, UCB. JS: consulting fees or other remuneration from Wyeth/Pfizer, Merck Sharp Dohme/Schering Plough, Abbott Immunology Pharmaceuticals, UCB.

Ethics approval This study was conducted with the approval of the Local ethics committee: Landesamt für Gesundheit und Soziales, Geschaeftsstelle der Ethik-Kommission des Landes Berlin, Saechsische Straße 28, 10707 Berlin, Germany.

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Relationship between active inflammatory lesions in the spine and sacroiliac joints and new development of chronic lesions on whole-body MRI in early axial spondyloarthritis: results of the ESTHER trial at week 48

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Notes

Publikation 2: Good correlation between changes in objective and subjective signs of inflammation in patients with short- but not long duration of axial spondyloarthritis treated with tumor necrosis factor-blockers

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Good correlation between changes in objective and subjective signs of inflammation in patients with short- but not long duration of axial spondyloarthritis treated with tumor necrosis factor-blockers

Anja Weiß[1*], In-Ho Song[2], Hildrun Haibel[2], Joachim Listing[1] and Joachim Sieper[1,2]

Abstract

Introduction: The aim of this study was to investigate the influence of symptom duration on treatment response and on the correlation between improvements in patient reported outcomes (PRO) and objective inflammation in patients with axial spondylarthritis (SpA) treated with etanercept (ETA) or adalimumab (ADA).

Methods: Data from 112 patients with axial SpA originally enrolled in two randomized controlled clinical trials were pooled and analyzed after one year of treatment with ETA (n = 66) or ADA (n = 46). Patients with <4 years and ≥4 years of disease were compared for improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Disease Activity Score (ASDAS), C-reactive protein (CRP) and magnetic resonance imaging (MRI) score for sacroiliac joints (SIJ).

Results: Patients with <4 years of disease showed a significantly better improvement than longer diseased patients in BASDAI (3.2 (95% confidence interval (CI): 2.7 to 3.7) vs. 1.7 (1.1 to 2.2)), BASFI, BASMI and ASDAS (1.6 (1.4 to 1.8) vs. 0.9 (0.7 to 1.1)). The change in BASDAI showed a significant correlation with the change in SIJ score (Spearman's rank correlation coefficient (rho) = 0.37, $P = 0.01$) and the change in CRP (rho = 0.45, $P = 0.001$) in patients with <4 years of disease. For long diseased patients this correlation was poor and did not achieve statistical significance (rho = 0.13, $P = 0.46$; rho = 0.22, $P = 0.13$ respectively).

Conclusion: The low correlation between change of PROs and change of objective signs of inflammation seen in axial SpA patients with longer symptom duration treated with tumor necrosis factor-blocker seems to indicate that inflammation is not the only cause of the patients' symptoms, while inflammation seems to be the major cause in short diseased patients.

Trial registration: Clinical Trials.gov NCT00844142 (Trial 1); NCT00235105 (Trial 2)

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Introduction

Recently new classification criteria have been developed for axial spondyloarthritis (axSpA) [1] which cover both patients with ankylosing spondylitis (AS), with typical radiographic changes of the sacroiliac joints (SIJ) according to the modified New York criteria [2], and patients without the presence of radiographic sacroiliitis, thus, before the development of chronic structural changes. This latter group has been labeled as non-radiographic axial SpA (nr-axSpA) [3]. These criteria allow earlier classification, diagnosis and treatment of these patients, and reduction in the reported unacceptably long delay of between 5 and 10 years between onset of symptoms and making a diagnosis [4].

In patients with established AS who failed to respond to conventional treatment with non-steroidal anti-inflammatory drugs (NSAIDs) TNF-blockers have been proven to be highly effective. Similar or even higher response rates were recently found in patients with nr-axSpA [5,6]. Younger age, shorter symptom duration or elevated C-reactive protein (CRP) values were found to be predictive of a Bath ankylosing spondylitis disease activity index (BASDAI)-50 response or an assessment of the SpondyloArthritis International Society (ASAS)-40 [5,7-9] response to TNF-blockers [5,10].

Currently, it is not clear why patients earlier in the course of their disease respond better to TNF-blockade in comparison to longer diseased patients, especially in the subgroup of nr-axSpA patients who have, by definition, not yet developed relevant structural damage in the axial skeleton.

Measurement of disease activity in axSpA currently relies predominantly on patient-reported outcome (PRO) measures such as the BASDAI and the ASAS-20, ASAS-40 and partial remission criteria [3]. Only recently was a new ankylosing spondylitis disease activity score (ASDAS) developed, which incorporates the CRP value in addition to PRO measures, or - alternatively - the erythrocyte sedimentation rate [11]. Until now the influence of symptom duration on PROs, such as the BASDAI and the Bath ankylosing spondylitits functional index (BASFI), inflammation parameters, such as CRP and magnetic resonance imaging (MRI) score, or changes in these measurements, has not been well investigated. A recent analysis of TNF-blocker trials in AS patients suggests that there is only weak correlation between improvement of objective parameters of inflammation, such as CRP or active inflammation on MRI, and improvement in clinical parameters [12].

In the present study we pooled data from two TNF-blocker trials to investigate such a possible dissociation between PROs and objective parameters of inflammation in more detail. In the first one, nr-axSpA patients with no limitation for symptom duration were treated with adalimumab (ADA) and in the second one axSpA patients, including both AS and nr-axSpA, with a symptom duration of less than 5 years were treated with etanercept (ETA). This gave us the opportunity to investigate the time dependency of treatment response and the association or dissociation between PROs and objective signs of inflammation in more detail.

Methods

Patients

Patients of both randomized controlled clinical trials had an active axSpA defined as BASDAI ≥4 and a back pain score ≥4, despite concurrent treatment or intolerance to NSAIDs. Treatment periods of one year in patients receiving ETA or ADA were considered. Patients with at least two visits under treatment were included in the analysis. Signed informed consent was obtained from each patient before any study-related procedures were performed.

In the etanercept trial [13] 76 patients with active axSpA (BASDAI ≥4, active inflammatory lesions on MRI in the SIJs (sacroiliac joints) or the spine) and a symptom duration of less than 5 years were randomized to receive ETA (n = 40) or sulfasalazine (SSZ) treatment (n = 36) for one year. SSZ patients who completed week 48 in a status of active disease (n = 26) switched to treatment with ETA. For further details see Song *et al.* [13]. To investigate the influence of symptom duration on the outcome, only treatment episodes under ETA were considered. We included data from 40 patients who received ETA during the first year (48 weeks) and outcome data for 26 patients from the SSZ group who received ETA during the second year (week 48 was used as baseline visit and the visits at weeks 50 to 108 as the outcome assessment).

In another trial, 46 patients with early axSpA without radiological sacroiliitis were randomized to receive ADA (n = 22) or placebo (n = 24). ADA was given for one year until week 44. Patients who were randomly assigned to placebo received it for the first 12 weeks and then switched to ADA for one further year [5]. For this analysis we included data from 22 patients who received ADA during the first year and data for 24 patients who were treated with ADA from week 12 until week 52 (week 12 was taken as the baseline visit). Retrospectively, patients from both trials fulfilled the new ASAS classification criteria for axSpA [1].

Patients from both studies were pooled for further analysis and stratified according to their symptom duration into two (<4 years and ≥4 years) or four groups (<2 years, 2 to 4 years, 4 to 8 years and ≥8 years). Out of all patients, 34 patients fulfilled the New York criteria for AS, of those patients with symptom duration <4 years, and 18 and 16 of those patients with symptom duration ≥4 years.

Patients were additionally stratified according to their CRP status at baseline: CRP value ≤5 mg/l (CRP-negative) and with a baseline CRP value >5 mg/l (CRP-positive).

The different groups were analyzed for PROs such as BASDAI and BASFI, for objective inflammation parameters, such as CRP and MRI SIJ score, and for parameters that combine subjective patient assessments and objective clinical assessments, such as the Bath ankylosing spondylitis metrology index (BASMI) and ASDAS. In both studies, MRI of the SIJ was performed and inflammation was scored by the Berlin MRI score, as described previously. Differences between baseline and week 48 were analyzed for all parameters.

The 1-year etanercept trial was approved by *Landesamt für Gesundheit und Soziales, Geschäftsstelle der Ethik-Kommission des Landes*, Berlin, Germany. The ethics approval for the 1-year adalimumab trial was granted by *Ethik-Kommission der Charité - Universitätsmedizin*, Berlin, Germany.

Statistics

Mixed linear models were used to compare the outcome in PROs, and objective and combined measures after one year of treatment with ETA or ADA between groups of different symptom duration. An adjustment for possible differences at baseline was made, including gender, human leukocyte antigen (HLA)-B27 status, and CRP status at baseline as co-variables in these models. By their nature these mixed models adjust for confounding by a dropout process. To apply the same type of model for example, for the outcome in BASDAI as well as the outcome in non-normally heavily-skewed distributed CRP values, the CRP values were log transformed. The mixed model was then applied to these log-transformed data. For better understanding, adjusted mean scores (so called least square LS means) with 95% confidence intervals are shown and, for CRP, the corresponding CRP values transformed back from the log CRP are reported in the tables.

For the analysis of the association between the change in scores for the different parameters during TNF-blockade, partial non-parametric Spearman coefficients for correlation between changes in PROs and changes in inflammation scores were calculated. By this method the dependency of the baseline status is calculated by linear regression, and the change not explained by the baseline status is calculated as the correlation between two parameters. The variation of change in BASDAI (or BASFI) and MRI (or CRP), adjusted for differences in the BASDAI and MRI status at baseline, is presented in the figures. For correlation of baseline values, the Spearman correlation coefficient was calculated. The non-parametric Mann-Whitney test, Chi-square test and *t*-test was used to compare groups according to symptom duration at baseline. *P*-values <0.05 were considered statistically significant.

Results

Baseline characteristics

The mean symptom duration for the patients pooled from both studies was 4.7 years, with a similar number of patients in the <4-years group (58 patients) and the ≥4-years group (54 patients). Patients' baseline characteristics differed in age, BASDAI, BASFI and CRP but were similar for the other parameters in the two groups (Table 1). Baseline data are also shown separately in Table 1 for the ETA and the ADA trial.

Improvement in patients with short versus longer duration of symptoms

Patients with a symptom duration <4 years improved to a significantly higher extent in the BASDAI ($P = 0.001$), BASFI ($P = 0.0003$), BASMI ($P = 0.01$) and ASDAS ($P = 0.001$) than patients with longer-duration disease after adjustment for differences in the baseline status (Table 2). Such differences were not observed for inflammatory parameters, such as CRP ($P = 0.09$) and MRI SIJ assessment ($P = 0.28$). These results were confirmed when the ETA and the ADA trials were analyzed separately, with the exception of MRI SIJ assessment, which improved to a significantly higher extent in patients with short- than in long-duration disease in the ADA trial (Table 2). In a sensitivity analysis a further sub-classification of the two groups was made into patients with less than 2 years or 2 to 4 years of symptoms on the one hand, and into patients with 4 to 8 years or ≥8 years of symptom duration on the other hand (Figure 1). This analysis suggested that the cutoff of 4 years differentiates best between patients with a very clear and a less clear improvement in PROs.

Improvement in CRP-positive and CRP-negative patients

Quite interestingly, the differences between patients with short and longer symptom duration became less evident in CRP-positive patients. The differences in BASDAI ($P = 0.11$), BASFI ($P = 0.23$), BASMI ($P = 0.3$) and ASDAS ($P = 0.07$) were no longer significant. In contrast to CRP negative patients who showed a significantly better response for PRO parameters (BASDAI, $P = 0.001$; BASFI, $P = 0.001$; BASMI, $P = 0.01$, and ASDAS, $P = 0.001$) in the case of short symptom duration (Table 3).

Correlation between improvement in patient-reported outcomes and improvement in objective measures

At the start of treatment the PROs and measures of inflammation (CRP and MRI) were not correlated. Nevertheless, to investigate whether there was at least

Table 1 Baseline characteristics of patients by study and symptom duration group

	Pooled data			Etanercept			Adalimumab		
	<4 years	≥4 years	*P*-value	<4 years	≥4 years	*P*-value	<4 years	≥4 years	*P*-value
	n = 58	n = 54		n = 42	n = 24		n = 16	n = 30	
Symptom duration mean (SD)	2 (1.1)	7.7 (5)		2 (1.1)	5.2 (0.9)		1.9 (1)	9.7 (5.9)	
Age, years, mean (SD)	31.7 (8.1)	37.8 (8.4)	0.001	31.6 (8.2)	37 (7.7)	0.01	31.8 (8.1)	38.5 (9.1)	0.02
Male, n (%)	30 (51.7)	28 (51.9)	0.99	25 (59.5)	12 (50)	0.45	5 (31.3)	16 (53.3)	0.15
HLA-B27-positive, n (%)	45 (77.6)	41 (75.9)	0.84	33 (78.6)	22 (91.7)	0.17	12 (75)	19 (63.3)	0.42
Joints with arthritis, mean (SD)	1.1 (3.3)	1.7 (6.4)	0.30	1.4 (3.9)	1.9 (6)	0.33	0.4 (0.7)	1.6 (6.7)	0.86
Joints with enthesitis, mean (SD)	2.5 (3.6)	3.5 (3.8)	0.095	2.7 (4)	3.7 (4.6)	0.41	2 (2.7)	3.3 (3.1)	0.16
BASDAI, mean (SD)	4.9 (1.9)	6 (1.8)	0.004	5 (1.7)	5.5 (2)	0.29	4.7 (2.4)	6.3 (1.5)	0.009
BASFI, mean (SD)	3.8 (2.4)	5 (2.1)	0.007	3.9 (2.2)	4.4 (2.3)	0.34	3.6 (2.8)	5.4 (1.9)	0.01
BASMI mean (SD)	1.5 (1.3)	2.1 (1.8)	0.057	1.7 (1.4)	2.6 (2)	0.04	1.1 (0.9)	1.7 (1.6)	0.16
ASDAS, mean (SD)	3.1 (0.9)	3.1 (0.8)	0.95	3.2 (0.8)	3 (1)	0.49	2.9 (0.9)	3.2 (0.6)	0.22
CRP, mg/l, mean (SD)	9 (9.3)	6.9 (9.6)	0.018	9.7 (10.4)	8.8 (13.4)	0.18	7.4 (6)	5.4 (5.2)	0.14
log CRP, mg/l, mean (SD)	2 (0.7)	1.7 (0.8)	0.018	2.1 (0.8)	1.8 (0.8)	0.26	1.9 (0.7)	1.5 (0.8)	0.16
CRP-negative, n (%)	26 (46.4)	37 (71.2)	0.009	18 (42.9)	16 (66.7)	0.04	8 (50)	21 (70)	0.18
MRI SIJ score, mean (SD)	6.2 (6.1)	4.1 (4.7)	0.08	6.4 (6)	5 (5.7)	0.21	5.4 (7)	3.2 (3.4)	0.61

P-value <0.05 was taken to indicate statistically significant differences between two groups. HLA-B27, human leukocyte antigen-B27; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; BASMI, Bath ankylosing spondylitis metrology index; ASDAS, ankylosing spondylitis disease activity score; CRP, C-reactive protein; MRI, magnetic resonance imaging; SIJ, sacroiliac joint.

correlation between improvement in PROs and the improvement in inflammations scores (MRI and CRP levels in CRP-positive patients), the baseline values of these parameters had to be taken into account. This analysis resulted in significant correlation only in patients with short symptom-duration. In this subgroup an improvement in the BASDAI correlated significantly with an improvement in the SIJ score (rho = 0.37, $P = 0.01$) and with a decrease in CRP values (rho = 0.52, $P = 0.005$, analyzed for CRP-positive patients only) (Table 4). In contrast, these correlations were poor and not significant (rho = 0.12, $P = 0.46$, for change in the BASDAI versus change in MRI-SIJ score; rho = 0.22, $P = 0.42$, for change in BASDAI versus change in CRP) (Table 4 and Figure 2) for patients with long disease-duration.

The differences in correlation between the adjusted change scores can also be clearly seen in Figure 2A and B. In both groups there was a clear variation in the improvement, which could not yet be explained by the baseline status of high or lower active disease. In patients with short symptom-duration, improvement in BASDAI and improvement in MRI went parallel, whereas in longer disease-duration virtually no correlation was found between the improvement scores (Figure 2A). Similar results were found in the subgroup of CRP-positive patients (Figure 2B). Although the overall direction of the association (regression

Table 2 Improvement from baseline after one year treatment with etanercept or adalimumab

	Pooled data			Etanercept			Adalimumab		
	Adjusted mean changes (95% CI)		*P*-value	Adjusted mean changes (95% CI)		*P*-value	Adjusted mean changes (95% CI)		*P*-value
	<4 years	≥4 years		<4 years	≥4 years		<4 years	≥4 years	
BASDAI	3.2 (2.7, 3.7)	1.7 (1.1, 2.2)	0.001	3.1 (2.6, 3.6)	1.8 (1.1, 2.6)	0.008	3.2 (2.2, 4.3)	1.6 (0.9, 2.3)	0.02
BASFI	2.4 (2, 2.9)	1.2 (0.7, 1.6)	0.001	2.4 (1.9, 2.8)	1.2 (0.5, 1.8)	0.006	2.5 (1.5, 3.5)	1.3 (0.5, 2)	0.06
BASMI	0.3 (0, 0.6)	−0.1 (−0.4, 0.2)	0.09	0.4 (0.1, 0.7)	−0.02 (−0.5, 0.4)	0.16	0.02 (−0.6, 0.6)	−0.1 (−0.5, 0.3)	0.74
ASDAS	1.6 (1.4, 1.8)	0.9 (0.7, 1.1)	0.001	1.5 (1.3, 1.8)	1.1 (0.8, 1.4)	0.04	1.7 (1.2, 2.1)	0.8 (0.5, 1.1)	0.003
CRP*	1.6 (1.5, 2)	1.6 (1.4, 1.8)	0.72	1.5 (1.4, 1.8)	1.6 (1.4, 2.0)	0.60	2.2 (1.6, 3.0)	1.5 (1.2, 1.8)	0.06
MRI SIJ	3.5 (2.9, 4.1)	3 (2.3, 3.6)	0.28	3.9 (3.3, 4.6)	3.7 (2.8, 4.6)	0.71	7.0 (3.8, 10.1)	2.7 (0.7, 4.7)	0.04

*Log-transformed CRP results were back transformed; p-value <0.05 was taken to indicate statistically significant differences between two groups; adjusted mean changes from baseline under treatment with etanercept or adalimumab (95% CI). Outcome differences were adjusted for baseline status (see Methods). BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; BASMI, Bath ankylosing spondylitis metrology index; ASDAS, ankylosing spondylitis disease activity score; CRP, C-reactive protein in mg/l; MRI, magnetic resonance imaging; SIJ sacroiliac joint.

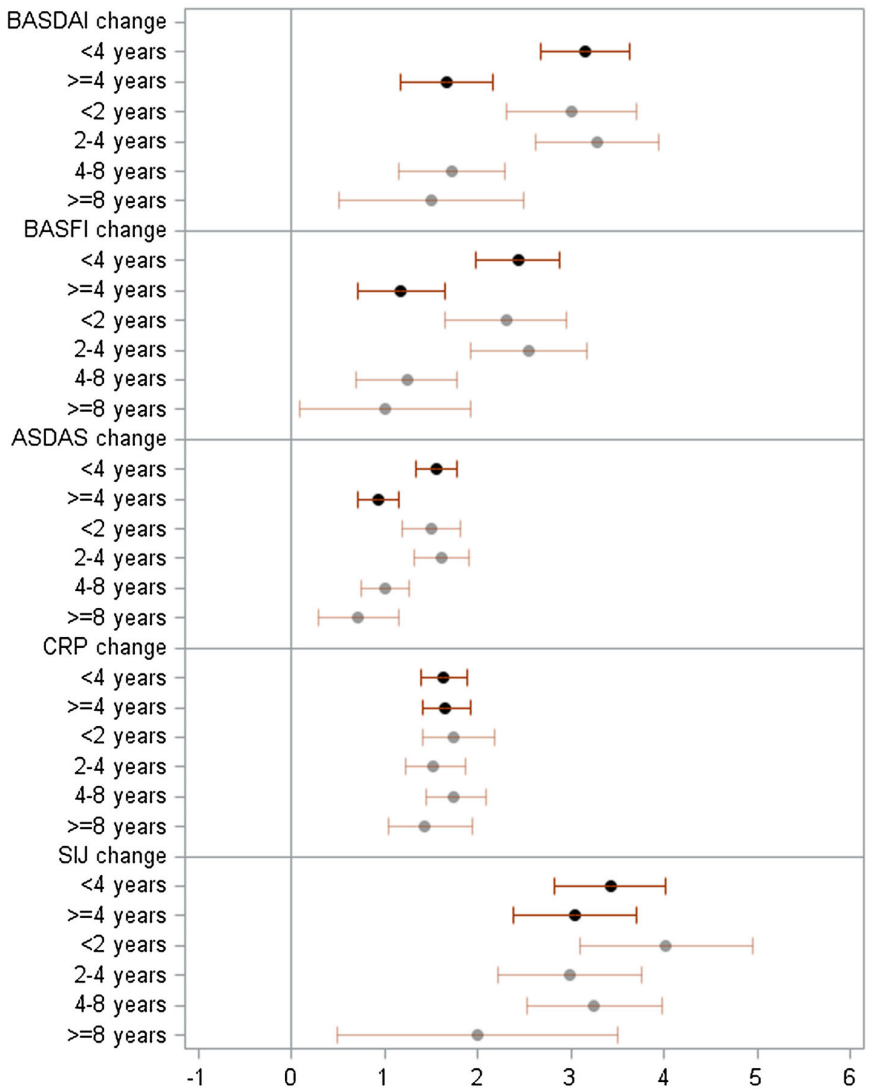

Figure 1 Adjusted mean changes from baseline. Adjusted mean changes from baseline are shown for two (<4 and ≥4 years) and four groups of symptom duration (<4, 2 to 4, 4 to 8 and ≥8 years). BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; ASDAS, ankylosing spondylitis disease activity score; CRP, C-reactive protein and SIJ, sacroiliac joint.

line) was similar for both groups the green dots showing changes in patients with short disease-duration were closer to the regression line, whereas the red dots showing patients with longer disease-duration varied, indicating a stronger dissociation between change in CRP and change in BASDAI in the second group.

Discussion

We differentiated between improvement in PROs and improvement in objective parameters. According to the findings of others we assumed patients with a shorter duration of symptoms improved more clearly in PROs than patients with longer symptom duration. However, we did not expect to observe a similar difference in objective parameters. Therefore, the main objective of this study was to investigate the associations between the improvement in subjective and objective measures within groups of patients with axSpA with different symptom duration.

We could confirm earlier data that the response rate to TNF-blocker therapy measured by PROs is indeed clearly better if axSpA patients are treated early in the course of their disease [10,14]. Findings of others described higher BASDAI-50, ASAS-20 or ASAS-40 response rates in patients with shorter symptom duration or in patients of younger age [5,8,10,12,14,15]. We focused on early disease

Table 3 Results for CRP-positive and CRP-negative patients

	CRP-positive patients				CRP-negative patients			
	Baseline value	Adjusted mean changes (95% CI)		*P*-value	Baseline value	Adjusted mean changes (95% CI)		*P*-value
		<4 years	≥4 years			<4 years	≥4 years	
		n = 30	n = 15			n = 26	n = 37	
BASDAI	5.4	3.3 (2.7, 4.0)	2.4 (1.5, 3.3)	0.11	5.5	3 (2.3, 3.7)	1.3 (0.7, 1.9)	0.001
BASFI	4.2	2.4 (1.8, 3.0)	1.8 (0.9, 2.7)	0.23	4.5	2.4 (1.8, 3.1)	0.9 (0.4, 1.5)	0.001
BASMI	1.5	0.1 (−0.3, 0.4)	0.4 (−0.1, 0.9)	0.30	2.0	0.5 (0, 1)	−0.3 (−0.6, 0.1)	0.01
ASDAS	3.6	1.9 (1.6, 2.2)	1.5 (1.1, 1.9)	0.07	2.8	1.3 (1, 1.6)	0.6 (0.3, 0.8)	0.001
CRP*	13.8	2.7 (2.2, 3.3)	2.1 (1.5, 3)	0.20	3.6	1.2 (1, 1.5)	1.2 (1, 1.4)	0.86
MRI SIJ	6.6	4.6 (3.6, 5.7)	3.5 (2, 4.9)	0.19	3.8	2.5 (1.8, 3.2)	2.5 (1.9, 3.1)	0.96

*Log-transformed CRP results were back-transformed; *P*-value <0.05 was taken to indicate statistically significant differences between two groups; adjusted mean changes from baseline under treatment with etanercept or adalimumab (95% CI). Outcome differences were adjusted for baseline status (see Methods). BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; BASMI, Bath ankylosing spondylitis metrology index; ASDAS, ankylosing spondylitis disease activity score; CRP, C-reactive protein in mg/l; MRI, magnetic resonance imaging; SIJ, sacroiliac joint.

and found that axSpA patients with less than 4 years of symptom duration had significantly better improvement in PROs (BASDAI, $P = 0.001$; BASFI, $P = 0.001$) than patients with longer symptom duration (Table 2). No significant differences were observed between the subgroups of <2 years and 2 to 4 years of symptom duration. Although these subgroups were of small size these results suggest a cutoff of around 4 years can be used to identify a window of opportunity for early therapy regarding a good treatment response to TNF-blockers. Indeed, symptom duration of less than 3 years [6,16] or less than 5 years [13] have been associated with a clinical remission rate of about 50% in axSpA patients treated with TNF-blockers, and a cutoff of 5 years of symptoms differentiated good and bad responders in an nr-axSpA trial with ADA [10].

As expected we found no difference in the improvement of objective parameters of inflammation such as MRI inflammation ($P = 0.28$) and CRP ($P = 0.72$) between the disease groups. Previous studies suggest that the degree of inflammation measured by CRP or MRI is predictive for BASDAI or ASAS response [8,14]. For the first time, we separately analyzed the influence of symptom duration on treatment response for CRP-positive and CRP-negative patients. Quite interestingly, the difference in the treatment response in favor of patients with short-duration disease was less clear in CRP-positive patients with only a non-significant trend in favor of the latter group. In contrast, all PRO parameters were significantly, and most probably with more clinical relevance, better in patients with short symptom-duration in the CRP-negative group, indicating that the probability of a good clinical response is rather low in TNF-blocker-treated patients with long symptom-duration who are CRP-negative.

Additionally we investigated the associations between objective and subjective measures at start of treatment and after one year of treatment with a TNF-blocker. Similar to others [17,18], we observed only weak, or in patients with longer symptom-duration, even inverse

Table 4 Correlation coefficients

		Correlation coefficient (*P*-value)		
		All patients	<4 years	≥4 years
Baseline[1]	BASDAI versus SIJ	−0.1 (0.3)	0.1 (0.3)	−0.3 (0.02)
	BASDAI versus CRP[3]	0.04 (0.8)	0.1 (0.7)	−0.1 (0.8)
	BASFI versus SIJ	−0.04 (0.7)	0.2 (0.2)	−0.3 (0.1)
	BASFI versus CRP[3]	−0.2 (0.2)	−0.2 (0.4)	−0.2 (0.6)
	SIJ versus CRP[3]	−0.4 (0.01)	−0.5 (0.005)	0 (0.995)
Differences[2]	BASDAI versus SIJ	0.2 (0.1)	0.4 (0.01)	0.12 (0.5)
	BASDAI versus CRP[3]	0.4 (0.02)	0.5 (0.01)	0.22 (0.4)
	BASFI versus SIJ	0.1 (0.3)	0.4 (0.01)	0.1 (0.7)
	BASFI versus CRP[3]	0.1 (0.5)	0.3 (0.2)	0.03 (0.9)
	SIJ versus CRP[3]	0.4 (0.02)	0.04 (0.9)	0.8 (0.01)

[1]Spearman correlation coefficient. [2]Partial Spearman correlation coefficients of differences adjusted for the baseline status of the corresponding parameters. [3]CRP-positive patients. BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; BASMI, Bath ankylosing spondylitis metrology index; ASDAS, ankylosing spondylitis disease activity score; CRP, C-reactive protein; SIJ, sacroiliac joint assessment on MRI.

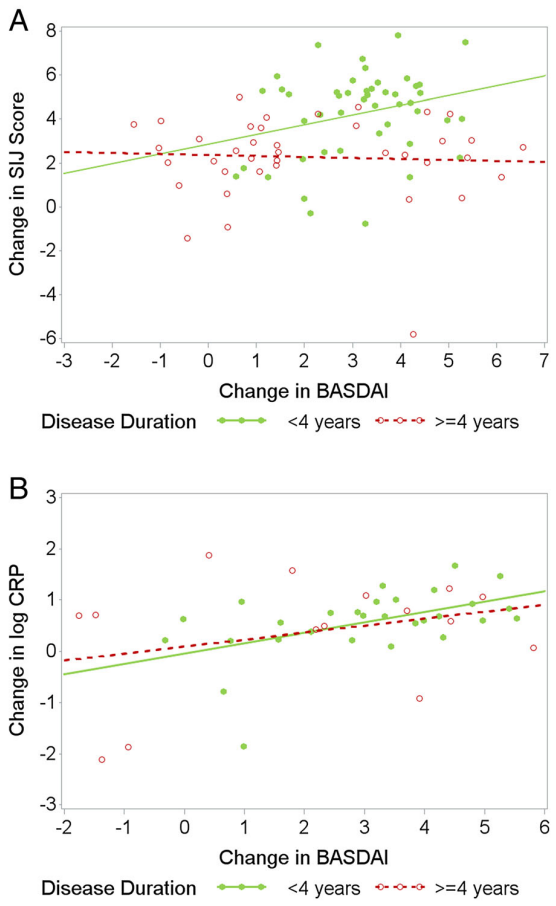

Figure 2 Correlation between change in Bath ankylosing spondylitis disease activity index (BASDAI) and change in sacroiliac joints (SIJs) (A), and change in C-reactive protein (CRP) score (B). (A) Improvement in BASDAI and SIJ score is presented after one year of treatment adjusted for baseline. **(B)** Improvement in BASDAI and log CRP values is presented for CRP-positive patients after one year of treatment adjusted for baseline.

correlation between the baseline status of PROs (BASDAI and BASFI) and objective measures of inflammation (CRP and MRI inflammation score). The interesting question is whether the improvement in BASDAI and BASFI is also unrelated to the improvement measured in MRI scores or CRP. To address this question, the fact that a patient with high CRP or high BASDAI score at baseline had a higher chance of a significant improvement than patients with moderate disease activity. Therefore, we adjusted the observed changes for differences in the baseline values.

We show here for the first time that these correlations were clearly better in axSpA patients with short symptom-duration. In the patients with short-duration disease, improvement in PROs such as BASDAI and objective parameters of inflammation, such as the amount of MRI inflammation (Figure 2A) or CRP (Figure 2B) was in the same positive direction in all patients. These correlations were only statistically significant in this group of patients. In patients with longer symptom-duration these correlations were very weak, indicating clear dissociation between change in PROs and changes in objective parameters. Worsening of the BASDAI despite improvement of inflammatory parameters was found only for some patients in the long-duration disease group. Machado *et al.* found good correlation between change in MRI and CRP but no correlation between MRI change and change in PROs, such as the BASDAI [12]. However, they did not take the influence of the baseline status into account and they could not differentiate between patients with long- and short-term disease because the number of patients with short symptom-duration was only small in this study.

The data presented here indicate that early in the course of the disease the patient's symptoms are predominantly caused by inflammation, whereas later in the course, symptoms might additionally be due to various other causes, among which inflammation is only one. This might also explain why TNF-blockers, which are highly effective anti-inflammatory drugs, work less well in these patients. Ongoing, often insufficiently treated inflammation of the axial skeleton over years might result in other causes of pain, such as secondary fibromyalgia, chronic muscle imbalance, non-physiological stress or impact on joints and enthuses, and other less well-defined causes. These data also stress the importance of early diagnosis and early treatment of axial SpA patients to achieve the best improvement in patients' symptoms. Whether such an early diagnosis and early treatment also has an effect on the prevention of structural bony damage has yet to be shown [19].

Conclusion

Our data suggest there is already a disconnection between improvement in subjective and objective signs of disease activity in patients with axial spondyloarthritis after four years of symptom duration. We only found clear correlation between changes in inflammation scores and changes in patient-reported outcomes in patients with short disease-duration. These results add a new perspective to earlier findings on low association between signs and symptoms and CRP positivity/MRI inflammation in axSpA patients.

Abbreviations

ADA: adalimumab; AS: ankylosing spondylitis; ASAS: assessment of SpondyloArthritis International Society; ASDAS: ankylosing spondylitis disease activity score; axSpA: axial spondyloarthritis; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; BASMI: Bath ankylosing spondylitis metrology index; CRP: C-reactive protein; ETA: etanercept; HLA: human leukocyte antigen; MRI: magnetic resonance imaging; nr-axSpA: non-radiographic axial spondylarthritis; NSAID: non-steroidal anti-inflammatory drug; PRO: patient-reported outcome; SIJ: sacroiliac joint; SpA: spondylarthritis; TNF: tumor necrosis factor.

Competing interests
AW and JL have nothing to disclose. JS received consulting fees or other renumeration from Pfizer, Merck, AbbVie, and UCB. IS received consulting fees or other renumeration from Pfizer, Merck, and AbbVie. HH received consulting fees or other renumeration from Pfizer, Merck, and AbbVie. Etanercept was tested in trial 1, which was supported by an unrestricted grant from Wyeth, which was acquired by Pfizer Inc in October 2009. Etanercept is marketed as Enbrel and Wyeth is listed as a collaborator in the trial registration. Adalimumab was tested in trial 2 and is marketed by AbbVie under the name HUMIRA. AbbVie is part of Abbot and funded the trial. Abbot is listed as a collaborator in the trial registration.

Authors' contributions
AW, JL had full access to all of the data and take responsibility for the integrity and accuracy of the data analysis. AW performed the statistical analysis, interpreted the data and wrote manuscript. IHS and HH were involved in the study design of the two randomized controlled trials, the acquisition and interpretation of the data. JL was involved in the interpretation of the data and reviewed the manuscript. JS was responsible for the study concept and design of this study and the two randomized controlled trials and was involved in data interpretation, and review of the manuscript. All authors read and approved the final manuscript.

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Publikation 3: Progression of the structural damage in the sacroiliac joints in patients with early axial spondyloarthritis during a long-term anti-TNF treatment

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Progression of Structural Damage in the Sacroiliac Joints in Patients With Early Axial Spondyloarthritis During Long-Term Anti–Tumor Necrosis Factor Treatment: Six-Year Results of Continuous Treatment With Etanercept

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Objective. To evaluate radiographic progression in the sacroiliac (SI) joints and to identify its predictors during long-term treatment (up to 6 years) with the tumor necrosis factor (TNF) inhibitor etanercept in patients with early axial spondyloarthritis (SpA).

Methods. Patients with early axial SpA who were treated with etanercept for up to 6 years in the Etanercept versus Sulfasalazine in Early Axial Spondyloarthritis (ESTHER) trial were selected based on the availability of radiographs of the SI joints. Two readers who were blinded with regard to clinical data scored the radiographs according to the modified New York criteria (range 0–4 per SI joint). A sacroiliitis sum score (total range 0–8) was calculated as the mean of the scores of the 2 readers. Active and chronic inflammatory changes in the SI joints on magnetic resonance imaging (MRI) performed at baseline, year 2, and year 4 were assessed according to the Berlin MRI scoring system.

Results. Of the 76 patients originally included in the study, 42 had radiographs of the SI joints available at baseline and at least 1 follow-up time point (year 2, 4, or 6). The mean ± SD change in the sacroiliitis sum score was 0.13 ± 0.73, −0.27 ± 0.76, and −0.09 ± 0.68, in the time intervals baseline to year 2, year 2 to year 4, and year 4 to year 6, respectively. In the longitudinal mixed model analysis, elevated C-reactive protein level (β = 0.58 [95% confidence interval 0.24, 0.91]) and MRI SI joint osteitis score (β = 0.06 [95% confidence interval 0.03, 0.10]) were independently associated with progression of the sacroiliitis sum score.

Conclusion. Our findings indicate that long-term anti-TNF therapy decelerates the progression of structural damage in the SI joints. Elevated CRP level and presence of osteitis on MRI were independently associated with radiographic sacroiliitis progression.

INTRODUCTION

For years researchers have undertaken a detailed investigation of the progression of structural damage in the spine in patients with axial spondyloarthritis (SpA). Recent insights have heightened interest in the investigation of the progression of structural damage in the sacroiliac (SI) joints. First, the emerging concept of axial SpA as one disease with two stages (1,2), nonradiographic axial SpA and radiographic axial SpA, depending on the absence or presence of definite radiographic sacroiliitis according

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to the modified New York criteria for ankylosing spondylitis (AS) (3), requires more data about progression from one stage to the other. Second, with improvement in the early diagnosis of axial SpA, there is increased interest in the natural course of the disease at an early stage. Third, recent data suggest that structural damage in the SI joint might have functional relevance in patients with axial SpA independently of structural damage in the spine (4). Finally, biologic therapy retards spinal progression, raising the question of whether it also has such an effect on the SI joint. Until now, observational studies have suggested a natural low, but still detectable, level of progression of radiographic sacroiliitis over a period of 2–5 years (5–7).

So far, only one study has shown some deceleration of radiographic sacroiliitis progression over 2 years of treatment with the tumor necrosis factor (TNF) inhibitor etanercept in patients with nonradiographic axial SpA as compared to a historical control group (8). No long-term studies have addressed this question to date, although it has been shown that in the case of the spine the progression rate might decrease over time in patients receiving long-term anti-TNF therapy (9). The aim of the present study was to investigate the long-term course (up to 6 years) of radiographic progression in the SI joint in patients with early active axial SpA treated with the TNF inhibitor etanercept and to explore factors associated with such progression.

PATIENTS AND METHODS

Study design and patient selection. The design of the Etanercept versus Sulfasalazine in Early Axial Spondyloarthritis (ESTHER) trial (ClinicalTrials.gov identifier: NCT00844142), including detailed clinical and magnetic resonance imaging (MRI) outcome data, has been reported elsewhere (10–13). Briefly, a total of 76 patients with early axial SpA (with a disease duration of ≤5 years) who had active inflammatory lesions (osteitis) on MRI in either the SI joint or the spine were randomized to receive treatment with etanercept (n = 40) or sulfasalazine (n = 36) for 1 year. At the end of year 1, all patients who were not in remission continued with or (for those receiving sulfasalazine therapy) switched to etanercept until the end of year 6. Patients in remission discontinued therapy and were followed up until the end of year 2. If a patient experienced a disease flare, etanercept was introduced or re-introduced and continued until the end of year 6. Patients were selected for the present analysis based on the availability of radiographs of the SI joints, which were obtained at baseline and every 2 years thereafter.

Radiographic assessment. Two trained readers (VRR and DP), who had good interreader reliability (were well calibrated) and were blinded with regard to all clinical data and time points, independently scored the SI joint radiographs (obtained at up to 4 time points per patient: baseline, year 2, year 4, and year 6). Radiographs were scored according to the grading system of the modified New York criteria for AS (3), where 0 = normal, 1 = suspicious changes, 2 = minimal abnormality (small localized areas with erosion or sclerosis, without alteration in the joint width), 3 = unequivocal abnormality (moderate or advanced sacroiliitis with erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis), and 4 = severe abnormality (total ankylosis). Patients were classified as having radiographic axial SpA if both readers recorded the presence of definite radiographic sacroiliitis of at least grade 2 bilaterally or at least grade 3 unilaterally. Otherwise, patients were classified as having nonradiographic axial SpA.

MRI assessment. MRIs of the SI joints, as part of whole-body MRIs, were obtained at baseline, year 2, and year 4 in all patients. Two trained and calibrated readers (K-GH and CA), who were blinded with regard to all clinical data and time points, evaluated the images according to the Berlin MRI scoring system (14) with minor modifications concerning the fatty deposition subscore (13). Briefly, osteitis and fatty deposition in the bone marrow were scored per SI joint quadrant from 0 (no lesion) to 3 (≥66% of the quadrant involved), resulting in an entire score range for every lesion type of 0–24. Erosions were graded on a scale of 0–3 per joint, ankylosis on a scale of 0–2 per joint, and subchondral sclerosis on a scale of 0–1 per joint. The mean of the 2 readers' scores was calculated.

Ethics committee approval. The study was approved by the central ethics committee of the federal state of Berlin (Landesamt für Gesundheit und Soziales, Ethikkommission Berlin; approval number ZS EK 14 EA4/100/05). Written consent was obtained from all patients.

Statistical analysis. The sacroiliitis sum score was calculated as the sum of the grades for the left and right SI joints (ranging from 0 [no signs of radiographic sacroiliitis in either SI joint] to 8 [total ankylosis of both SI joints]). The mean of 2 readers' sacroiliitis sum scores was used in the subsequent analysis. The following definitions of radiographic sacroiliitis progression were used: 1) absolute change in the sacroiliitis sum score, 2) progression of at least 1 grade in the absolute sacroiliitis sum score, 3) progression of at least 1 grade in at least 1 SI joint in the opinion of both readers, and 4) progression from nonradiographic axial SpA to radiographic axial SpA in the opinion of both readers. For definitions 2, 3, and 4, corresponding rates of "regression" were calculated.

To determine the interreader reliability of the radiographic sacroiliitis assessment, we calculated the intraclass correlation coefficients (ICCs) for the sacroiliitis sum score. To identify factors associated with radiographic sacroiliitis progression over time, a longitudinal linear mixed model analysis was performed. The change in the sacroiliitis sum score over a 2-year interval (with up to 3 such intervals per patient) was used as an outcome variable. Possible predictors of progression assessed at the

beginning of each 2-year interval were explored in the univariable and multivariable analyses. Predictor candidates included age, sex, HLA–B27 status, treatment with sulfasalazine in the first study year, duration of treatment with etanercept, intake of nonsteroidal antiinflammatory drugs (NSAIDs), symptom duration, C-reactive protein (CRP) level, active and chronic inflammatory changes on MRI of the SI joints, and radiographic sacroiliitis sum score. Parameter estimates (β) with corresponding 95% confidence intervals (95% CIs) were calculated. Statistical analysis was performed using SPSS version 25 (IBM) and SAS version 9.4 (SAS Institute).

RESULTS

Patient characteristics. Of the 76 patients enrolled in the ESTHER study, a total of 55 patients had radiography of the SI joints performed at baseline. For 42 patients, at least 1 follow-up radiograph was available to assess progression of radiographic sacroiliitis. Radiographs were available to assess progression for 42 patients between baseline and year 2, for 32 patients between year 2 and year 4, and for 27 patients between year 4 and year 6. Fifteen patients (35.7%) were classified as having radiographic axial SpA and 27 patients (64.3%) were classified as having nonradiographic axial SpA at baseline based on radiographs of the SI joints. The characteristics of the patients included in this analysis were similar to those of the 76 patients in the ESTHER study (10). Table 1 summarizes the baseline characteristics of the patients.

Agreement between readers. There was good to excellent agreement between the 2 readers regarding the sacroiliitis sum score at all time points: baseline (ICC 0.83 [95% CI 0.71, 0.90]), year 2 (ICC 0.82 [95% CI 0.67, 0.90]), year 4 (ICC 0.72 [95% CI 0.45, 0.86]), and year 6 (ICC 0.76 [95% CI 0.49, 0.89]).

Radiographic sacroiliitis progression. The distribution of sacroiliitis sum scores at baseline is shown in Figure 1. The majority of the patients had low-level sacroiliitis and none of the patients had a complete ankylosis of SI joints (sacroiliitis sum score of 8), reflecting an early stage of the disease in the patients included in this analysis. The mean ± SD change in sacroiliitis sum score was 0.13 ± 0.73, –0.27 ± 0.76, and –0.09 ± 0.68 from baseline to year 2, year 2 to year 4, and year 4 to year 6, respectively. The highest level of progression was observed in the period from baseline to year 2 and was clearly lower in the following years according to all 4 definitions of progression (Table 2). Similar results were obtained when progression was analyzed only in those patients for whom radiographs for all time points were available (n = 27) (change in sacroiliitis sum score 0.20 ± 0.72 between baseline and year 2, –0.22 ± 0.8 between year 2 and year 4, and –0.09 ± 0.68 between year 4 and year 6).

The change in the sacroiliitis sum score was higher over the first 2 years in patients who received etanercept during this period (n = 24) than in patients who were treated with sulfasalazine in the first year and then switched to etanercept in the second year (n = 18) (0.31 ± 0.62 versus –0.11 ± 0.82; P = 0.04). In the following years, no impact of sulfasalazine treatment in the initial study phase on radiographic sacroiliitis progression was observed.

Predictors of radiographic sacroiliitis progression. A longitudinal mixed model analysis was performed in the entire group of patients with data on 2-year intervals from baseline till year

Table 1. Baseline characteristics of the patients with axial SpA in the ESTHER study who were included in the present analysis*

	All patients (n = 42)	Patients with nonradiographic axial SpA (n = 27)	Patients with radiographic axial SpA (n = 15)
Sex, no. (%) male	26 (62)	17 (63)	9 (60)
Age, mean ± SD years	34.1 ± 7.9	34.3 ± 7.8	33.7 ± 8.2
Symptom duration, mean ± SD years	3.1 ± 1.6	2.6 ± 1.6	4.0 ± 1.1†
No. (%) HLA–B27 positive	34 (81)	19 (70.4)	15 (100)‡
CRP, mean ± SD mg/liter	11.2 ± 15.4	10.2 ± 15.5	13.0 ± 15.7
Elevated CRP (>5 mg/liter), no. (%)	22 (52)	12 (44.4)	10 (66.6)
BASDAI, mean ± SD (range 0–10)	5.6 ± 1.2	5.6 ± 1.2	5.5 ± 1.2
ASDAS, mean ± SD	3.3 ± 0.8	3.3 ± 0.8	3.4 ± 0.6
No. treated with etanercept/no. treated with sulfasalazine during the first year	24/18	17/10	7/8

* The Mann-Whitney U test was used for statistical analysis of continuous variables, and Fisher's exact test was used for categorical variables. ESTHER = Etanercept versus Sulfasalazine in Early Axial Spondyloarthritis; CRP = C-reactive protein; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; ASDAS = Ankylosing Spondylitis Disease Activity Score.
† P = 0.01 versus patients with nonradiographic axial spondyloarthritis (SpA).
‡ P = 0.04 versus patients with nonradiographic axial SpA.

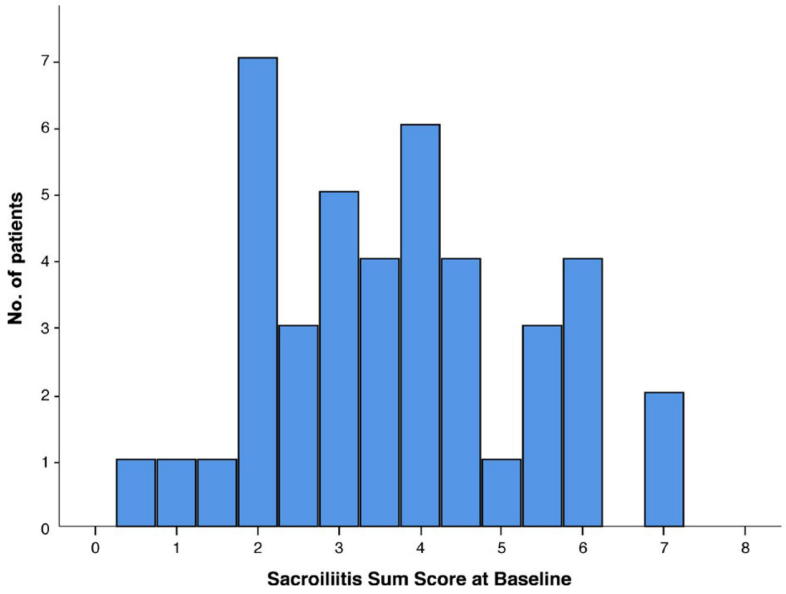

Figure 1. Distribution of the sacroiliitis sum score at baseline in patients with early axial spondyloarthritis from the Etanercept versus Sulfasalazine in Early Axial Spondyloarthritis trial (n = 42). Values are the mean of the scores from 2 readers.

6 to determine possible factors associated with a change in the total sacroiliitis sum score. In the univariable analysis, elevated CRP level (β = 0.45 [95% CI 0.14, 0.75]) and the SI joint osteitis score on MRI (β = 0.05 [95% CI 0.02, 0.08]) were significantly associated with an increase in the sacroiliitis sum score after 2 years.

For the multivariable analysis, we created 2 models; each one included one of the parameters reflecting inflammatory activity (CRP level or osteitis on MRI) that showed a significant association in the univariable analysis. Both models were adjusted for age, sex, HLA–B27 positivity, symptom duration, duration of treatment with etanercept, NSAID intake, and the sacroiliitis sum score. The strength of the association for elevated CRP level and SI joint osteitis score on MRI was even greater than in the univariable analysis, with β = 0.58 (95% CI 0.24, 0.91) and β = 0.06 (95% CI 0.03, 0.10), respectively (Table 3).

DISCUSSION

This is the first study to analyze the long-term (up to 6 years) progression of radiographic sacroiliitis in patients with axial SpA

Table 2. Progression of radiographic sacroiliitis in patients with early axial SpA treated with etanercept for up to 6 years*

Definition of progression	Baseline to year 2 (n = 42)	Year 2 to year 4 (n = 32)	Year 4 to year 6 (n = 27)
Change in the sacroiliitis sum score, mean ± SD	0.13 ± 0.73	−0.27 ± 0.76	−0.09 ± 0.68
Progression ≥1 grade in the sacroiliitis sum score			
Progression	9/42 (21.4)	2/32 (6.3)	3/27 (11.1)
Regression	4/42 (9.5)	7/32 (21.9)	5/27 (18.5)
Progression ≥1 grade in at least 1 SI joint in the opinion of both readers			
Progression	5/42 (11.9)	1/32 (3.1)	0/27 (0)
Regression	1/42 (2.4)	4/32 (12.5)	1/27 (3.7)
Progression from nonradiographic axial SpA to radiographic axial SpA			
Progression	5/27 (18.5)	1/24 (4.1)	0/19 (0)
Regression	2/15 (13)	1/8 (12.5)	1/8 (12.5)

* Except where indicated otherwise, values are the number of patients/number for whom data were available (%). SpA = spondyloarthritis; SI = sacroiliac.

Table 3. Longitudinal mixed model analysis of the association between progression of radiographic sacroiliitis (change in the sacroiliitis sum score) and disease-related parameters in patients with early axial SpA treated with etanercept for up to 6 years*

Parameter	Univariable analysis, β (95% CI)	Multivariable analysis model 1, β (95% CI)	Multivariable analysis model 2, β (95% CI)
Age, years	0.00 (−0.02, 0.02)	−0.01 (−0.03, 0.01)	−0.01 (−0.03, 0.01)
Male sex	−0.04 (−0.35, 0.27)	−0.25 (−0.59, 0.09)	−0.05 (−0.37, 0.28)
Symptom duration, years	−0.01 (−0.08, 0.06)	0.06 (−0.04, 0.15)	0.06 (−0.03, 0.15)
HLA–B27 positivity	−0.08 (−0.47, 0.32)	−0.26 (−0.72, 0.20)	−0.33 (−0.78, 0.13)
CRP, mg/liter	0.01 (0.00, 0.03)	–	–
Elevated CRP (>5 mg/liter)	0.45 (0.14, 0.75)	–	0.58 (0.24, 0.91)
SI joint osteitis score on MRI (range 0–24)	0.05 (0.02, 0.08)	0.06 (0.03, 0.10)	–
SI joint fatty deposition score on MRI (range 0–24)	0.00 (−0.03, 0.02)	–	–
SI joint erosion score on MRI (range 0–6)	−0.01 (−0.09, 0.07)	–	–
SI joint sclerosis score on MRI (range 0–2)	−0.04 (−0.29, 0.22)	–	–
Treatment with sulfasalazine in the first study year	−0.15 (−0.46, 0.16)	–	–
Duration of etanercept treatment, years	−0.04 (−0.13, 0.04)	−0.06 (−0.20, 0.09)	−0.06 (−0.19, 0.06)
NSAID intake (yes versus no)	0.21 (−0.08, 0.51)	−0.03 (−0.41, 0.36)	−0.01 (−0.35, 0.34)
Sacroiliitis sum score (range 0–8)	−0.08 (−0.17, 0.01)	−0.17 (−0.28, −0.06)	−0.17 (−0.28, −0.06)

* Sacroiliac (SI) joint ankylosis score on magnetic resonance imaging (MRI) was not included in the analysis because ankylosis was not recorded in any of the cases. SpA = spondyloarthritis; 95% CI = 95% confidence interval; CRP = C-reactive protein; NSAID = nonsteroidal antiinflammatory drug.

treated with an anti-TNF agent, in this case with etanercept. Our results suggest that long-term treatment with a potent antiinflammatory drug like a TNF inhibitor may influence the evolution of the disease by decelerating radiographic progression in the SI joints in patients with early axial SpA.

In our analysis, progression of radiographic sacroiliitis occurred mostly in the first years of anti-TNF treatment; these results were consistent among all 4 definitions of progression used. For instance, progression from nonradiographic axial SpA to radiographic axial SpA occurred only in the first years of anti-TNF treatment. In 5 of 27 patients with nonradiographic axial SpA, the disease evolved into radiographic axial SpA in the first 2 years of the study, while in 2 of 15 patients radiographic axial SpA regressed to nonradiographic axial SpA over the same time period, giving a net progression (calculated according to the methodology of the Devenir des Spondylarthropathies Indifférenciées Récentes [DESIR] cohort) (7) of 7.1% ([5 – 2]/[27 + 15]). In the following time intervals (year 2 to year 4 and year 4 to year 6), the progression rate did not exceed the measurement error.

The net progression rate of 7.1% within the first 2 years of the ESTHER study was higher than the 3.8% net progression over 2 years in the German Spondyloarthritis Inception Cohort (GESPIC) and the 5.1% net progression over 5 years in the DESIR cohort (5,7). This might be related to 1) a higher degree of inflammation in the SI joints in the present study (the presence of active osteitis on MRI of the SI joint or spine was an inclusion criterion of the ESTHER study), and 2) treatment with a TNF inhibitor (which was not the case in the GESPIC and DESIR cohorts) that might have triggered a faster bone repair visible on radiographs as progression of structural damage. Our data also indicate a faster progression of radiographic sacroiliitis over 2 years in patients who received etanercept for 2 years compared to patients who received etanercept for 1 year following a 1-year treatment with sulfasalazine.

In another analysis of the 2-year progression rate from nonradiographic axial SpA to AS in patients treated with etanercept, the Study Comparing Etanercept Against a Placebo for Etanercept on a Background Nonsteroidal Antiinflammatory Drug in the Treatment of Early Spondyloarthritis Patients Who Do Not Have X-ray Structural Changes (EMBARK), almost no progression was reported over 2 years (8). This might again be related to a lower proportion of patients with active inflammation or a lower extent of inflammation on MRI of the SI joints, a known risk factor for pro-

gression of radiographic sacroiliitis (8,15), in the EMBARK study (16) as compared to the ESTHER population. The evidence of a deceleration of structural damage progression in the SI joint with increasing duration of anti-TNF therapy shown here seems congruent with the retardation of the spine progression seen in AS patients treated long-term with TNF inhibitors (9,17,18).

There is some evidence of the effect of NSAIDs on radiographic progression of the spine (19,20); however, its role is still a subject of debate (21). Currently, there are no data on its effect on radiographic progression in the SI joints; therefore, further studies are needed. In the ESTHER study, NSAID intake was recorded at every study visit for 1 previous week only. Thus, we could not quantify the NSAID intake using the Assessment of SpondyloArthritis international Society NSAIDs index (22), but we could include the NSAID intake itself (yes/no) recorded at each study visit in the longitudinal analysis. As a result, no association with radiographic progression in the SI joint was observed.

Our data from the longitudinal analysis, consistent with the findings of previous studies (5,8,15), showed a positive and independent association between elevated CRP level, the presence of osteitis on MRI, and progression of radiographic sacroiliitis in patients with early axial SpA. The level of osteitis on MRI could be reduced in these patients after 3 years of continuous treatment with etanercept, as previously described (23). Thus, these findings support the hypothesis that long-term treatment with TNF inhibitors could reduce new bone formation by preventing the development of new inflammatory lesions resulting in structural damage (24,25). The negative association between the baseline sacroiliitis sum score and its subsequent progression can be explained by a higher probability of progression within a given timeframe in patients with low-grade sacroiliitis (grade 0–1) compared to those with high-grade sacroiliitis (grade 2 and especially grade 3).

The clinical relevance of our results is related to the fact that evidence of inhibition of progression of structural damage in the SI joints (i.e., progression of radiographic sacroiliitis, progression from nonradiographic axial SpA to radiographic axial SpA) would mean disease modification in axial SpA. This is important in light of recent data suggesting that structural damage in the SI joint might have an impact on functional status and spinal mobility in patients with axial SpA, independent of structural damage to the spine (4).

The strength of our study is mainly related to the longitudinal analysis of data collected from a homogeneous group of patients with definite early axial SpA treated with a TNF inhibitor etanercept for up to 6 years; this aspect of the study is, to date, unique.

The major limitation of any analysis of radiographic progression in the SI joints, including ours, is the low reliability of radiographic assessment even in the case of well-trained and calibrated readers (26). Another limitation of our study is the small number of patients included in the analysis, due to the requirement of availability of radiographs from baseline and at least year 2, and the number of dropouts during the study. Nonetheless, 42 patients were assessed at up to 4 time points (3 two-year time intervals), allowing a robust modeling of radiographic sacroiliitis progression and the identification of strong predictors. A further limitation of our study is related to the absence of a control group. Our data can only be indirectly compared to historical data from the GESPIC or DESIR cohorts, for instance. Patients enrolled in the ESTHER study had high disease activity and active inflammation confirmed by MRI despite the use of NSAIDs, which would have made a control group not treated with TNF inhibitors for years almost impossible.

In conclusion, the results presented here could indicate a reduction in radiographic progression in the SI joints over time in patients who received long-term anti-TNF treatment (for up to 6 years). An elevated CRP level and the presence of osteitis on MRI were the strongest predictors of radiographic sacroiliitis progression.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Rios Rodriguez had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Rios Rodriguez, Sieper, Poddubnyy.
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Pfizer had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Pfizer provided the study drug etanercept. Publication of this article was not contingent upon approval by Pfizer.

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Lebenslauf

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

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