Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: Psoriasis-Arthritis Secukinumab

Stand: August 2015

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Secukinumab 2015-B-087 zur Behandlung der aktiven Psoriasis-Arthritis	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	„nicht angezeigt“
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	- Therapiehinweise im Anwendungsgebiet liegen für folgende Wirkstoffe vor: o **Adalimumab** (Beschluss vom 21. November 2006) o **Leflunomid** (Beschluss vom 16. August 2007, zuletzt geändert am 15. Mai 2008) - Beschlüsse über die Nutzenbewertung nach § 35a SGB V: o **Apremilast** (Beschluss vom 6.August 2015)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Secukinumab L04AC10 Cosentyx®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Cosentyx, allein oder in Kombination mit Methotrexat (MTX), ist angezeigt für die Behandlung erwachsener Patienten mit aktiver Psoriasis-Arthritis, wenn das Ansprechen auf eine vorhergehende Therapie mit krankheitsmodifizierenden Antirheumatika (DMARD) unzureichend gewesen ist.
Biologika	
Etanercept L04AB01 Enbrel®	Psoriasis-Arthritis (Arthritis psoriatica) Behandlung der aktiven und progressiven Psoriasis-Arthritis bei Erwachsenen, wenn das Ansprechen auf eine vorhergehende Basistherapie unzureichend ist. Enbrel verbessert die körperliche Funktionsfähigkeit bei Patienten mit Psoriasis-Arthritis und reduziert das Fortschreiten der radiologisch nachweisbaren strukturellen Schädigungen der peripheren Gelenke bei Patienten mit polyartikulären symmetrischen Subtypen der Erkrankung.
Infliximab L04AB02 Remicade®/ Inflectra®	Psoriasis-Arthritis Inflectra™ ist indiziert zur Behandlung der aktiven und fortschreitenden Psoriasis-Arthritis bei erwachsenen Patienten, wenn deren Ansprechen auf eine vorhergehende krankheitsmodifizierende, antirheumatische Arzneimitteltherapie (DMARD-Therapie) unzureichend gewesen ist. Inflectra™ sollte verabreicht werden • in Kombination mit Methotrexat • oder als Monotherapie bei Patienten, die eine Unvertraglichkeit gegenuber Methotrexat zeigen oder bei denen Methotrexat kontraindiziert ist. Infliximab verbessert die korperliche Funktionsfahigkeit bei Patienten mit Psoriasis-Arthritis und reduziert die Progressionsrate peripherer Gelenkschaden, wie radiologisch bei Patienten mit polyartikularem symmetrischem Subtyp der Krankheit belegt wurde (siehe Abschnitt 5.1). (FI Inflectra® Stand 06/2015)
Adalimumab L04AB04 Humira®	Psoriasis-Arthritis Humira ist indiziert zur Behandlung der aktiven und progressiven Psoriasis-Arthritis (Arthritis psoriatica) bei Erwachsenen, die nur unzureichend auf eine vorherige Basistherapie angesprochen haben. Humira reduziert das Fortschreiten der radiologisch nachweisbaren strukturellen Schadigungen der peripheren Gelenke bei Patienten mit polyartikularen symmetrischen Subtypen der Erkrankung (siehe Abschnitt 5.1) und verbessert die korperliche Funktionsfahigkeit.
Golimumab	Psoriasis-Arthritis (PsA)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L04AB06 Simponi®	Simponi ist zur Anwendung als Monotherapie oder in Kombination mit MTX zur Behandlung der aktiven und fortschreitenden Psoriasis-Arthritis bei Erwachsenen indiziert, wenn das Ansprechen auf eine vorhergehende Therapie mit krankheitsmodifizierenden Antirheumatika (DMARD) unzureichend gewesen ist. Simponi verringert nachweislich die Progressionsrate der peripheren Gelenkschaden, bestimmt anhand von Rontgenaufnahmen bei Patienten mit polyartikularen polyartikularen symmetrischen Subtypen der Erkrankung (siehe Abschnitt 5.1) und verbessert die korperliche Funktionsfahigkeit.
Ustekinumab L04AC05 Stelara®	Psoriatische Arthritis (PsA)STELARA ist allein oder in Kombination mit MTX fur die Behandlung der aktiven psoriatischen Arthritis bei erwachsenen Patienten indiziert, wenn das Ansprechen auf eine vorherige nicht-biologische krankheitsmodifizierende antirheumatische (DMARD) Therapie unzureichend gewesen ist (siehe Abschnitt 5.1).
Certolizumab Pegol L04AB05. Cimzia ®	*Psoriasis-Arthritis* Cimzia ist in Kombination mit Methotrexat (MTX) fur die Behandlung der aktiven Psoriasis-Arthritis bei Erwachsenen angezeigt,wenn das vorherige Ansprechen auf eine Therapie mit DMARDS ungenugend war. In Fallen von Unvertraglichkeit gegenuber Methotrexat oder wenn die Fortsetzung der Behandlung mit Methotrexat ungeeignet ist, kann Cimzia als Monotherapie verabreicht werden. Fur Details zum therapeutischen Effekt, siehe Abschnitt 5.1.
Apremilast L04AA32 Otezla®	Psoriasis-Arthritis Otezla allein oder in Kombination mit krankheitsmodifizierenden antirheumatischen Arzneimitteln (DMARDs) ist indiziert zur Behandlung der aktiven Psoriasis-Arthritis (PsA) bei erwachsenen Patienten, die auf eine vorangegangene DMARD-Therapie unzureichend angesprochen oder diese nicht vertragen haben (siehe Abschnitt 5.1).

Quellen: AMIS-Datenbank, Fachinformationen

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: Secukinumab

Auftrag von: Abt. AM

bearbeitet von: Abt. FB Med

Datum: 11.08.2015

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Indikation für die Recherche:

Allein oder in Kombination mit Methotrexat (MTX) für die Behandlung erwachsener Patienten mit aktiver Psoriasis-Arthritis, wenn das Ansprechen auf eine vorhergehende Therapie mit krankheitsmodifizierenden Antirheumatika (DMARD) unzureichend gewesen ist.

Berücksichtigte Wirkstoffe/Therapien:

Übersicht zVT, Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation „Psoriasis-Arthritis“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 20.07.2015 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), arztbibliothek.de (ÄZQ), AWMF, Clinical Evidence, G-BA, GIN, IQWiG, NGC, NICE, TRIP.
Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der

Die Recherche ergab **310** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden **69** Quellen eingeschlossen. Insgesamt ergab dies **27** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

ACR	American College of Rheumatology criteria
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DMARD	Disease-modifying antirheumatic drug
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MTX	Methotrexat
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drugs
PsA	Psoriasis Arthritis
PsARC	Psoriatic Arthritis Response Criteria
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/ G-BA Beschlüsse

IQWiG, 2015 [15]. Apremilast – Nutzenbewertung gemäß § 35a SGB V	**Fragestellung/Ziele:** (Hinweis: nur die für das AWG relevante Fragestellung dargestellt) Bewertung des Zusatznutzens von Apremilast (allein oder in Kombination mit krankheitsmodifizierenden antirheumatischen Arzneimitteln [DMARDs]) im Vergleich zu einem Tumor-Nekrose-Faktor(TNF)-alpha-Hemmer (Etanercept oder Adalimumab oder Infliximab oder Golimumab) ggf. in Kombination mit Methotrexat als zweckmäßiger Vergleichstherapie bei erwachsenen Patienten mit aktiver Psoriasis-Arthritis, die auf eine vorangegangene DMARD-Therapie unzureichend angesprochen oder diese nicht vertragen haben. **Ergebnis /Fazit:** Der pU legt im Dossier keine Studien vor, die geeignet sind, Apremilast bei Patienten mit Psoriasis-Arthritis mit der zweckmäßigen Vergleichstherapie zu vergleichen. Ein Zusatznutzen von Apremilast im Vergleich zur zweckmäßigen Vergleichstherapie (TNF-alpha-Hemmer [Etanercept oder Adalimumab oder Infliximab oder Golimumab] ggf. in Kombination mit Methotrexat) ist damit für Patienten mit Psoriasis-Arthritis nicht belegt.
G-BA, 2015 [12]. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Apremilast	**Apremilast** (Otezla®) <u>Zugelassenes Anwendungsgebiet</u>: a) Psoriasis-Arthritis Otezla allein oder in Kombination mit krankheitsmodifizierenden antirheumatischen Arzneimitteln (DMARDs) ist indiziert zur Behandlung der aktiven Psoriasis-Arthritis (PsA) bei erwachsenen Patienten, die auf eine vorangegangene DMARD-Therapie unzureichend angesprochen oder diese nicht vertragen haben b) Plaque-Psoriasis […] <u>Zweckmäßige Vergleichstherapie:</u> a) Psoriasis-Arthritis Die zweckmäßige Vergleichstherapie für die Behandlung der aktiven Psoriasis-Arthritis bei erwachsenen Patienten, die auf eine vorangegangene DMARD-Therapie unzureichend angesprochen oder diese nicht vertragen haben, ist: • TNF-alpha-Hemmer (Etanercept oder Adalimumab oder Infliximab oder Golimumab) ggf. in Kombination mit Methotrexat. b) Plaque-Psoriasis […] <u>Ausmaß und Wahrscheinlichkeit des Zusatznutzens</u> a) Psoriasis-Arthritis (PsA) Der Zusatznutzen von Apremilast wird wie folgt bewertet: Der Zusatznutzen gegenüber der zweckmäßigen Vergleichstherapie (Etanercept oder Adalimumab oder Infliximab oder Golimumab, ggf. in Kombination mit MTX) ist nicht belegt.

	Begründung: Um Studien zum Nachweis des Zusatznutzens von Apremilast zur Behandlung der Psoriasis-Arthritis gegenüber der zweckmäßigen Vergleichstherapie zu identifizieren, führte der pharmazeutische Unternehmer eine bibliographische Literaturrecherche als auch eine Recherche in Studienregistern durch. Dabei wurden ausschließlich placebokontrollierte Studien gefunden. Es liegen folglich keine direkt vergleichenden Studien von Apremilast gegenüber der zweckmäßigen Vergleichstherapie (Etanercept oder Adalimumab oder Infliximab oder Golimumab, ggf. in Kombination mit MTX) vor. Der pharmazeutische Unternehmer unternimmt jedoch auch keine Anstrengungen Studien zu identifizieren, mit denen gegebenenfalls ein indirekter Vergleich von Apremilast gegenüber einer der Vergleichstherapien möglich gewesen wäre. Somit lässt sich der Stellenwert von Apremilast im Verhältnis zu anderen Therapieoptionen zur Behandlung der Psoriasis-Arthritis nicht beurteilen. In Ermangelung eines direkten Vergleiches stellt der pharmazeutische Unternehmer in seinem Dossier zur Nutzenbewertung die (gepoolten) Ergebnisse der placebokontrollierten Studien PSA-002, PSA-003, PSA-004 dar. Da diese Placebo-Vergleiche jedoch keinen Vergleich gegenüber einer zweckmäßigen Vergleichstherapie zulassen, sind aus den dargestellten Analysen keine Aussagen zum Zusatznutzen ableitbar. Folglich ist der Zusatznutzen von Apremilast zur Behandlung der Psoriasis-Arthritis nicht belegt. Für die Indikation Psoriasis-Arthritis wurden die placebokontrollierten Studien PSA-002 (PALACE 1), PSA-003 (PALACE 2), PSA-004 (PALACE 3) im Rahmen des Zulassungsverfahren von der Europäischen Zulassungsbehörde bewertet. Die Studien PSA-002, PSA-003 und PSA 004 schlossen vorbehandelte erwachsene Patienten mit aktiver PsA (≥ 3 geschwollene Gelenke und ≥ 3 druckschmerzempfindliche Gelenke) ein. An die 24- wöchige placebokontrollierte Phase schloss sich eine aktive Behandlungsphase mit Apremilast für alle Patienten für mindestens 28 Wochen und eine offene Langzeit – Beobachtungsphase mit einer angestrebten Dauer von 4 Jahren an. Für die Zulassung lagen die Daten nach 24 Wochen und 52 Wochen vor. Apremilast wurde in diesen Studien sowohl als Monotherapie (34,8 %) als auch in Kombination mit stabilen Dosen niedermolekularer DMARDs (65,2 %, darunter Methotrexat, Sulfasalazin und Leflunomid allein oder in Kombination) angewendet. Es wurde seitens der EMA im öffentlichen Bewertungsbericht angemerkt, dass ein Placebo-Vergleich zwar den EMA – Empfehlungen in dieser Indikation entspräche, jedoch ein Vergleich gegenüber einer aktiven Kontrolle für die Bewertung von Apremilast in der Zusammenschau mit anderen Therapieoptionen in dieser Indikation hilfreich gewesen wäre. Die vom pharmazeutischen Unternehmer diesbezüglich im Rahmen der Zulassung eingebrachten historischen Vergleiche gegenüber klassischen DMARDs wurden im EPAR nicht weiter kommentiert, da die geforderten Endpunkte, die einen Vergleich der Wirksamkeit von Apremilast gegenüber diesen Therapieoptionen erlaubt hätten, nicht verfügbar waren. Zudem wurde im EPAR ausgeführt, dass die Ergebnisse des Studienprogramms nicht hinreichend für die ursprünglich angestrebte Zusatzformulierung „[…] Otezla verbessert die körperliche Funktionsfähigkeit.“4 waren. Für den diese Aussage stützenden Endpunkt HAQ-DI (Fragebogen zur Bewertung des Gesundheitszustandes) sei die minimal clinical important difference

	(MCID) für die Indikation Psoriasis-Arthritis nicht ausreichend etabliert und die Unterschiede zur Placebo-Gruppe waren nur gering ausgeprägt.
G-BA, 2006 [10]. Bekanntmachung des Beschlusses über eine Änderung der Arzneimittel-Richtlinie/AMR in Anlage 4: Therapiehinweis zu Adalimumab	**Adalimumab (Humira®)** Bei Rheumatoider Arthritis und Psoriasis-Arthritis (Arthritis psoriatica), Empfehlungen zur wirtschaftlichen Verordnungsweise Beschluss vom: 21.11.2006; In Kraft getreten am: 12.07.2007 **Indikation** Adalimumab ist ein rekombinanter humaner monoklonaler Antikörper. Adalimumab ist zugelassen zur Behandlung − der mäßigen bis schweren aktiven Rheumatoiden Arthritis bei Erwachsenen, die nur unzureichend auf krankheits-modifizierende Antirheumatika, einschließlich MTX, angesprochen haben, − der schweren, aktiven und progressiven Rheumatoiden Arthritis bei Erwachsenen, die zuvor nicht mit MTX behandelt wurden, − der aktiven und progressiven Psoriasis-Arthritis (Arthritis psoriatica) bei Erwachsenen, die nur unzureichend auf die vorherige Therapie mit krankheitsmodifizierenden Antirheumatika angesprochen haben, − der schweren aktiven ankylosierenden Spondylitis bei Erwachsenen, die nur unzureichend auf eine konventionelle Therapie angesprochen haben. … Die Behandlung mit TNF-alpha-Hemmern stellt dabei eine Alternative zur Reduktion der Symptomatik und Verbesserung der körperlichen Funktionsfähigkeit bei Patienten mit aktiver Rheumatoider Arthritis oder Arthritis psoriatica dar, wenn eine Therapie mit allen individuell indizierten DMARDs und deren Kombinationen, mindestens jedoch 2 einschließlich Methotrexat (MTX) - soweit keine Kontraindikationen dafür vorliegen - bis zur individuell angezeigten Höchstdosis (in der Regel 20 bis 25 mg pro Woche, ggf. als Injektion und ggf. Folsäure- bzw. Folinsäurepräparate), erfolglos geblieben ist. Diese müssen lange genug (in der Regel je nach DMARD mindestens jeweils 3 bis 6 Monate) in adäquater Dosis und unter fachlich kompetenter Überwachung eingesetzt worden sein. Für einen breiten Einsatz von Adalimumab als erstes DMARD bei neu diagnostizierter Rheumatoider Arthritis fehlen derzeit u. a. evaluierte prädiktive Faktoren für den Krankheits-verlauf, die eine ausreichend sichere Auswahl der Patienten mit schwerer progressiver Arthritis in frühen Krankheitsstadien ermöglichen würde. In der Regel ist die Primäranwendung daher bei der derzeitigen Studienlage nicht angezeigt. Bei seltenen individuellen Besonderheiten (Kontraindikationen gegen alle DMARDs oder hohe Krankheitsprogression) kann ein frühzeitiger Einsatz von TNF-alpha-Hemmern angemessen sein. Bei der Wahl eines TNF-alpha-Hemmers können aus medizinisch-therapeutischer Sicht aufgrund der derzeitigen Studienlage oder evidenzbasierter Leitlinien bei der Indikation Rheumatoide Arthritis keine allgemeinen Prioritäten gesetzt werden. Bei der Indikation Psoriasis-Arthritis ist der unterschiedliche Zulassungsstatus bzgl. der Hautmanifestation der Psoriasis zu beachten, insbesondere da die Zulassung von Etanercept und Infliximab die Anwendung bei Arthritis psoriatica und bei therapieresistenter mittelschwerer bis schwerer Plaque psoriasis abdeckt. Die voraussichtlichen Therapiekosten für das ausgewählte Präparat stellen damit bei Beginn einer TNF-alpha-Therapie den wesentlichen Gesichtspunkt bei der Produktwahl dar. Davon kann

	abgewichen werden, wenn individuelle klinische Faktoren (z.B. Neben- und Wechselwirkungen) bzw. die spezifischen Eigenschaften oder die Anwendungsmodalitäten des Arzneimittels eine nachvollziehbare Kontraindikation darstellen oder die bevorzugte Anwendung im Einzelfall begründen. Auch die Praxisausstattung (z.B. Lagerungsmöglichkeit für Infusionen und Nachüberwachung beim Einsatz von Infliximab) begründet keine unwirtschaftliche Produktwahl. Ein Ansprechen auf die Therapie ist bereits nach 1 bis 2 Wochen zu erwarten. Soweit auch nach 3 Monaten kein deutliches klinisches Ansprechen (klinische Symptomatik, DAS-Score, Labor) zu verzeichnen ist, ist die Therapie mit Adalimumab abzusetzen.
G-BA, 2007 [11]. Tragende Gründe zum Beschluss über eine Änderung der Arzneimittel-Richtlinie in Anlage 4: Therapiehinweis zu Leflunomid	**Leflunomid (Arava®)** Empfehlungen zur wirtschaftlichen Verordnungsweise; Beschluss vom: 16.08.2007 / 15.05.2008; In Kraft getreten am: 21.12.2007 / 03.09.2008 **Indikation:** Leflunomid ist ein antirheumatisches Basistherapeutikum. Es ist zugelassen zur Behandlung Erwachsener mit aktiver rheumatoider Arthritis und aktiver Psoriasis-Arthritis. **Psoriasis-Arthritis** Die Wirkung aller bisher untersuchten DMARDs bei der Psoriasis-Arthritis wird generell als gering bis mittelmäßig eingeschätzt. Im Gegensatz zur rheumatoiden Arthritis konnte für kein DMARD in dieser Indikation eine Verzögerung der Progression von Gelenkdestruktionen belegt werden. Es existieren bisher keine vergleichenden Studien von Leflunomid mit anderen Basistherapeutika zur Wirksamkeit bei Psoriasis-Arthritis. Patienten mit Psoriasis-Arthritis, die gleichzeitig systemisch behandlungsbedürftige Hautläsionen aufweisen, sollten primär mit MTX oder Ciclosporin behandelt werden, da bei diesen Substanzen eine gute Wirksamkeit nicht nur bezüglich der dermatologischen Symptome, sondern auch bezüglich der arthritischen Symptome belegt ist. Bei der kleinen Gruppe von Patienten mit Psoriasis-Arthritis ohne wesentliche dermatologische Symptomatik kommt, sofern eine Therapie mit NSAR nicht ausreichend ist, unter Berücksichtigung des Zulassungsstatus der Einsatz von Leflunomid oder MTX in Betracht.

Cochrane Reviews

Colebatch AN, et al. 2011 [6]. Safety of non-steroidal anti-inflammatory drugs, including aspirin and paracetamol (acetaminophen) in people receiving methotrexate for inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis)	1. Fragestellung To systematically assess and collate the scientific evidence on the safety and adverse effects of using NSAIDs, including aspirin, or paracetamol, or both, with methotrexate in inflammatory arthritis. To identify gaps in the current evidence, assess the implications of those gaps and to make recommendations for future research to address these deficiencies.
	2. Methodik **Population:** Adults with a diagnosis of inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and other forms of spondyloarthritis) receiving treatment with methotrexate, any dose, duration or route **Intervention:** Methotrexate monotherapy **Komparator:** Methotrexate with concurrent NSAIDs, including aspirin, or paracetamol, or both **Endpunkte** • Increased methotrexate toxicity as evidenced by gastrointestinal, hepatic, pulmonary, haematological, or renal adverse events; Withdrawals due to adverse events • All adverse events, including mortality **Suchzeitraum** (Aktualität der Recherche): May 2010 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 17 (n = 1809) **Qualitätsbewertung der Studien:** Cochrane Risk of Bias Tool
	3. Ergebnisdarstellung • All Studies included people with rheumatoid arthritis using various NSAIDs, including aspirin. • There were no identified studies for other forms of inflammatory arthritis (e.g. psoriatic arthritis)
	4. Anmerkungen/Fazit der Autoren -

Systematische Reviews

Rodgers M, et al.	1. Fragestellung To determine the clinical effectiveness, safety and cost-

2011 [22]. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation	effectiveness of etanercept, infliximab and adalimumab
	2. Methodik **Population** Patients with active and progressive PsA who have an inadequate response to standard treatment (including DMARD therapy). **Intervention** • etanercept, • infliximab • adalimumab **Komparator** placebo, another of the three listed agents, or conventional management strategies for active and progressive PsA that have responded inadequately to previous DMARD therapy, excluding TNF inhibitors. **Endpunkte** • measures of anti-inflammatory response (PsARC, ACR 20/50/70), skin lesion response (PASI) and functional status (HAQ), radiological assessments of disease progression or remission, QoL assessments [e.g. Dermatology Life Quality Index (DLQI)] and overall global assessments. • incidence of serious adverse events. **Suchzeitraum** (Aktualität der Recherche): up to June 2009. **Anzahl eingeschlossene Studien** (Gesamt): 6 **Qualitätsbewertung der Studien:** The quality of RCTs and other study designs were assessed using standard checklists. Centre for Reviews and Dissemination (CRD). Manual for selecting reviews and writing abstracts for the Database of Abstracts of Reviews of Effects (DARE). 2008. URL: www.crd. york.ac.uk/crdweb/html/help.htm
	3. Ergebnisdarstellung Note: direct and indirect comparisons! All trials (n=6) were double blind and placebo-controlled RCTs and rated ‘good’ by the quality assessment. *Efficacy:* • Pooled estimates of effect demonstrated a significant improvement in patients with PsA for all joint disease and functional status outcomes at 12–14 weeks’ follow-up. • The biologic treatment significantly reduced joint symptoms assessed by PsARC for etanercept [relative risk (RR) 2.60, 95% confidence interval (CI) 1.96 to 3.45], infliximab (RR 3.44, 95% CI

	2.53 to 4.69) and adalimumab (RR 2.24, 95% CI 1.74 to 2.88). This was consistent with the results from the pooled estimates of ACR 20. • Furthermore, the statistically significant reduction in HAQ score also indicated a beneficial effect of these biologic therapies on patients' functional status. • Significant heterogeneity was observed only in the outcome of PsARC in infliximab. • The 24-week data for all three biologics demonstrated that the treatment effects are maintained. Trial data demonstrate a significant effect of all three biologics on skin disease in terms of PASI response, at 12 or 24 weeks. • The results of evidence synthesis found that infliximab appears to be the most effective of the three biologics. Across all outcomes of joint and skin disease at 12 weeks, infliximab is associated with the highest probabilities of response. The response in joint disease (PsARC and ACR) is greater with etanercept than with adalimumab, whereas the response in skin disease (PASI) is greater with adalimumab than with etanercept, although these differences are not statistically significant. • In those patients who achieve a PsARC response to treatment the highest mean reductions in the functional and psychological impact of the disease, measured by HAQ, are seen with infliximab and etanercept (–0.657 for infliximab and –0.630 for etanercept). • For all three biologics the changes in HAQ for those patients who did not respond to treatment were below the minimum clinically significant threshold (–0.3). • Short-term radiographic measures indicate that these agents can slow disease progression in the short term (< 24 weeks). The available follow-up data, although promising, are inadequate to determine if these effects persist in the longer term. *Safety:* • Thirty-two relevant studies were identified for the evaluation of safety of these biologics. • The rates of serious infection were etanercept 0.6%–13.2%, infliximab 0.8%–13.8% and adalimumab 0.4%–5.1%. The rates of malignancy were etanercept 1%–5.7%, infliximab 0.16%–5.1% and adalimumab 0.1%–1.1%. The rates of activation of TB for the treatment were etanercept 0%–1.4%, infliximab 0.06%–4.6% and adalimumab 0%–0.4%.
	4. Anmerkungen/Fazit der Autoren Limited available efficacy data and difficulty in assessing PsA

	activity and its response to biologic therapy. 5. Hinweise durch FB Med Monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable amount of data that was deemed commercial-in-confidence and academic-in-confidence. The full report was used by the Appraisal Committee at NICE in their deliberations (→ NICE 2010)
Thaler KJ, et al. 2012 [25]. Drug Class Review Targeted Immune Modulators. Final Update 3 Report	1. Fragestellung To compare the efficacy, effectiveness, and safety (adverse events) of abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, tocilizumab, and ustekinumab in patients with rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis. Hier: psoriatic arthritis
	2. Methodik **Population:** Patients with psoriatic arthritis **Intervention** abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, tocilizumab, and ustekinumab **Kontrolle** Included interventions or placebo **Endpunkte** Efficacy and safety parameter, QoL **Suchzeitraum** (Aktualität der Recherche): to 2011 (October) **Anzahl eingeschlossene Studien** (Gesamt): 2 SR, 4 RCTs, 1 **Qualitätsbewertung der Studien:** • "We assessed the internal validity (quality) of trials based on predefined criteria developed by the United States Preventive Services Task Force (ratings: good-fair-poor) and the National Health Service Centre for Reviews and Dissemination.External validity (generalizability) was assessed and reported but did not influence quality ratings. We did not rate the quality of pooled data-analyses." • Grading the strength of evidence (high – moderate – low - insufficient) based on the methods guidance established for the Evidence-based Practice Center program of the Agency for Healthcare Research and Quality (only for major

	comparsions and major outcomes); criteria: risk of bias, consistency, directness, and precision
	3. Ergebnisdarstellung • Inclusion of 2 systematic reviews and meta-analyses (Saad et al. 2008; Rodgers et al. 2011) that analyzed the same six trials of adalimumab, etanercept, and infliximab (providing indirect comparisons) • Additionally; inclusion of 4 placebo-controlled trials assessing the efficacy of abatacept (Mease et al. 2011), alefacept (Mease et al. 2006), golimumab (Kavanaugh et al. 2009), and ustekinumab (Gottlieb et al. 2009)and 1 open-label registry study (Saad et al. 2010) of adalimumab, etanercept, and infliximab for data on quality of life. • All trials consisted of patients who had previously failed a disease-modifying antirheumatic drug. **Summary of finding** (→ Tab. 11, 12) • No direct evidence from head-to-head randomized controlled trials on the comparative effectiveness of targeted immune modulators for the treatment of psoriatic arthritis in adults or children exists. • 2 SR/MA suggested that adalimumab, etanercept, and infliximab are more efficacious than placebo but no statistically significant differences among adalimumab, etanercept, and infliximab could be detected. • One prospective observational registry study of 595 patients with psoriatic arthritis showed that adalimumab, etanercept, and infliximab have similar positive effects on quality of life. The strength of the evidence for the comparative effectiveness of adalimumab, etanercept, and infliximab was low. • In addition, evidence indicated that alefacept combined with methotrexate is more efficacious than methotrexate alone • Abatacept, golimumab, and ustekinumab are more efficacious than placebo. • At this time there are no studies, placebo or head-to-head, that evaluate the use of targeted immune modulators in children with psoriatic arthritis

Table 11. Summary of efficacy trials in adult patients with psoriatic arthritis

Author Year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
ABATACEPT									
Mease et al. 2011[178]	RCT	170	6 months	Abatacept 3-30 mg/kg vs. placebo	ACR 20	HOQ, SF-36, PASI	Active PsA despite DMARD therapy and one target skin lesion	Abatacept had statistically significantly better response than placebo for doses 10-30 mg/kg	Fair
ADALIMUMAB									
Saad et al. 2008[176]	SR and MA	413	12-24 weeks	Adalimumab + methotrexate vs. placebo + methotrexate	ACR 20/50/70 PsARC	PASI 50/75/90 SF-36, HAQ-DI	Adults with PsA	Adalimumab had statistically significantly better outcomes than placebo	Good
Rodgers et al., 2011[177]	SR and MA	982	12 weeks	Adalimumab + methotrexate vs. placebo + methotrexate	PsARC	ACR20	Adults with PsA	Adalimumab had statistically significantly better outcomes than placebo	Good
ALEFACEPT									
Mease et al. 2006[179]	RCT	185	24 weeks (12 weeks treatment, 12 weeks observation)	Alefacept + methotrexate vs. placebo + methotrexate	ACR 20	ACR 50/70, PASI, PGA	Active PsA; failed at least 1 DMARD; mean disease duration: NR	Alefacept had statistically significantly better ACR 20 than placebo	Fair
ETANERCEPT									
Saad et al. 2008[176]	SR and MA	265	12-24 weeks	Etanercept + methotrexate vs. methotrexate + placebo	ACR 20/50/70 PsARC	PASI 50/75/90	Adults with PsA	Etanercept had statistically significantly better outcomes than placebo	Good

Direct and indirect comparison

Author Year	Study design	N	Duration	Comparisons	Primary outcome	Secondary outcomes	Population	Results	Quality rating
Rodgers et al., 2011[177]	SR and MA	982	12 weeks	Etanercept + methotrexate vs. placebo + methotrexate	PsARC	ACR20	Adults with PsA	Etanercept had statistically significantly better outcomes than placebo	Good
GOLIMUMAB									
Kavanaugh et al., 2009[180]	RCT	405	16 weeks	Golimumab vs. placebo	ACR20	ACR50/70, PsARC, DAS28, SF-36	Adults with PsA	Golimumab had statistically significantly better outcomes than placebo	Fair
INFLIXIMAB									
Saad et al. 2008[176]	SR and MA	304	12-24 weeks	Infliximab + methotrexate vs. placebo + methotrexate	ACR 20/50/70 PsARC	PASI 50/75/90	Adults with PsA	Infliximab had statistically significantly better outcomes than placebo	Good
Rodgers et al., 2011[177]	SR and MA	982	12 weeks	Infliximab + methotrexate vs. placebo + methotrexate	PsARC	ACR20	Adults with PsA	Infliximab had statistically significantly better outcomes than placebo	Good
USTEKINUMAB									
Gottlieb et al., 2009.[181,182]	RCT	146	12 weeks	ustekinumab vs. placebo	ACR 20	PASI 75, DLQI	Adults with PsA	Significantly more ustekinumab patients achieved ACR20 and DLQI than placebo	Fair

Abbreviations: ACR, American College of Rheumatology; DAS, disease activity score; DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; HAQ-DI, Health Assessment Questionnaire Disability Index; MA, meta-analysis; NR, not reported; PASI, Psoriasis Arthritis Severity Index; PGA, Physician Global Assessment; PsA, psoriatic arthritis; PsARC, psoriatic arthritis response criteria; RCT, randomized controlled trial; SF-36, Medical Outcomes Study Short Form 36 Health Survey; SR, systematic review.

Table 12. Characteristics and results of studies conducting direct and adjusted-indirect comparisons

Author, year	Comparisons	Primary outcome	Conclusion	Quality
Saad et al., 2010[183]	Adalimumab, etanercept, infliximab	QoL	Adalimumab, etanercept, and infliximab have similar positive effects on quality of life	Fair
Saad et al., 2008[176]	Adalimumab, etanercept, infliximab	ACR and PsARC	No statistically significant differences between adalimumab, infliximab, and etanercept	Good
Rodgers et al., 2011[177]	Adalimumab, etanercept, infliximab	PsARC	No statistically significant differences between adalimumab, infliximab, and etanercept for probability of achieving PsARC response	Good

Abbreviations: ACR, American College of Rheumatology; PsARC, psoriatic arthritis response criteria; TIM, targeted immune modulator; QoL, quality of life.

4. Anmerkungen/Fazit der Autoren
   -

AHRQ, 2012 [2].

Drug Therapy for Psoriatic Arthritis in Adults: Update of a 2007 Report. Comparative Effectiveness Review Number 54

1. Fragestellung

This report summarizes the evidence on the comparative efficacy, effectiveness, and harms of corticosteroids, oral DMARDs, and biologic DMARDs in the treatment of patients with Psoriatic arthritis (PsA)

Prepared by: RTI International–University of North Carolina Evidence-based Practice Center Research Triangle Park, NC

2. Methodik

Population:
Adults with PsA

Intervention
Corticosteroids, oral DMARDs, biologic DMARDs

Kontrolle

	Included interventions or placebo **Endpunkte** Efficacy, safety, QoL **Suchzeitraum** (Aktualität der Recherche): up to Jan 2011 **Anzahl eingeschlossene Studien** (Gesamt): 16 (0 head-to-head RCTs, 0 head-to-head non-RCTs, 10 placebo-controlled trials, 3 meta-analyses or systematic reviews, and 3 observational studies.) **Qualitätsbewertung der Studien:** • We rated the quality of individual studies using the predefined criteria based on those developed by the U.S. Preventive Services Task Force (ratings: good, fair, poor) and the National Health Service Centre for Reviews and Dissemination. We gave a good-quality rating to studies that met all criteria. We gave a poor-quality rating to studies that had a fatal flaw defined as a methodological shortcoming that leads to a very high risk of bias) in one or more categories and excluded them from our analyses. • Grading the strength of evidence as high, moderate, low, or insufficient based on methods guidance for the EPC program for the most important outcomes (measures of disease activity (e.g., ACR 20/50/70, DAS), radiographic changes, functional capacity, quality of life, withdrawals due to adverse events, and specific adverse events if data were available (e.g.,injection-site reactions, infections, malignancy).
	3. Ergebnisdarstellung **Key Comparisons**: <u>Oral DMARDs</u> <u>Leflunomide</u> **Efficacy and Effectiveness** No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of leflunomide and other treatments. → Strength of Evidence Grade: INSUFFICIENT Compared with placebo in one study, leflunomide produced better improvement in health-related quality of life and statistically significant, but not clinically significant, improvement in disease activity and functional capacity. → Strength of Evidence Grade: LOW **Harms** No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative harms of leflunomide and other treatments. → Strength of Evidence Grade: INSUFFICIENT

	Current evidence was limited to placebo controlled trials. Compared with placebo, leflunomide led to higher rates of withdrawals because of adverse events, diarrhea, and clinically significant increases in alanine aminotransferase. → Strength of Evidence Grade: INSUFFICIENT <u>Methotrexate</u> **Efficacy and Effectiveness** No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of MTX and other treatments. →Strength of Evidence Grade: INSUFFICIENT Current evidence was limited to placebo-controlled trials. Compared with placebo in one fair study, MTX resulted in greater improvement in physician assessment of disease activity than placebo. Strength of Evidence Grade: LOW **Harms** No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative harms of MTX and other treatments. →Strength of Evidence Grade: INSUFFICIENT <u>Sulfasalazine</u> **Efficacy and Effectiveness** No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of sulfasalazine and other treatments. →Strength of Evidence Grade: INSUFFICIENT Current evidence was limited to placebo-controlled trials. Compared with placebo in one good systematic review study, sulfasalazine reduced disease activity. →Strength of Evidence Grade: MODERATE **Harms** No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative harms of sulfasalazine and other treatments. →Strength of Evidence Grade: INSUFFICIENT <u>Biologic DMARD + Oral DMARD vs. Biologic DMARD or Oral DMARD</u> **Efficacy and Effectiveness** The current evidence was limited to two cohort studies. Compared to anti-TNF monotherapy (adalimumab, etanercept, or infliximab), MTX plus anti-TNF produced similar disease activity response rates. → Strength of Evidence Grade: LOW One systematic review of TNF inhibitors found that both TNF inhibitors and sulfasalazine are effective (similar withdrawals due to lack of efficacy); however, the data were insufficient to determine if the effect reached MCID. → Strength of Evidence Grade: INSUFFICIENT **Harms**

	No head-to-head evidence met inclusion criteria; unable to draw conclusions on the comparative harms of biologic DMARD + oral DMARD and other treatments. → Strength of Evidence Grade: INSUFFICIENT <u>Biologics</u> **Efficacy and Effectiveness** No head-to-head trials met inclusion criteria; unable to draw conclusions on the comparative efficacy of biologics and other treatments. →Strength of Evidence Grade: INSUFFICIENT Compared with placebo, adalimumab, etanercept, golimumab, and infliximab led to greater improvement in disease activity, functional capacitya and health-related quality of life. → Strength of Evidence Grade: LOW to MODERATE (Low for golimumab and moderate for adalimumab, etanercept, and infliximab) **Harms** Etanercept had a lower rate of withdrawals because of adverse events than infliximab in a prospective cohort study →Strength of Evidence Grade: LOW Additional evidence was limited to placebo-controlled trials, where adverse events were not the primary outcome. Overall adverse event profiles appeared to be similar for biologic DMARDs and placebo. However, compared with placebo, we noted the following: adalimumab and etanercept had more injection-site reactions and adalimumab had fewer events of aggravated psoriasis than placebo →Strength of Evidence Grade: LOW Golimumab was associated with more malignancies than placebo in one RCT →Strength of Evidence Grade: INSUFFICIENT
	4. Fazit der Autoren Overall, the data are quite limited and the evidence is insufficient to draw firm conclusions on comparative efficacy, effectiveness, and harms of either oral or biologic DMARDs for PsA. This report's findings did not reveal any differences with current standard of care. Head-to-head (RCTs) are needed to establish the comparative efficacy and safety of different treatments with and without corticosteroids, oral DMARDs, and biologic DMARDs, to determine the best therapy to prevent or minimize debilitating joint damage and optimize quality of life for people with PsA. 5. Hinweise FBMed In terms of applicability to populations, the studies were generally multicenter involving adults with diagnosed PsA. Prior medications tried before these studies were variable, but in general patients had failed a DMARD prior to starting any of the biologic agents
Thorlund K, et al.	1. Fragestellung To evaluate the comparative effectiveness of available tumor

2012 [26]. Anti-tumor necrosis factor (TNF) drugs for the treatment of psoriatic arthritis: an indirect comparison meta-analysis	necrosis factor-α inhibitors (anti-TNFs) for the management of psoriatic arthritis (PsA) in patients with an inadequate response to disease-modifying antirheumatic drugs (DMARDs).
	2. Methodik: indirect comparison MA **Population:** Adults with active and progressive PsA with an inadequate response to previous DMARD therapy **Intervention** anti-TNFs (adalimumab, etanercept, golimumab, and infliximab**)** **Kontrolle** Placebo **Endpunkte** PsARC Response, HAQ (change from baseline for responder and non-responder), PASI **Suchzeitraum** (Aktualität der Recherche): up to 2012 **Anzahl eingeschlossene Studien** (Gesamt): 7 • Adalimumab: n= 2 • Etanercept: n= 2 • Infliximab: n= 2 • Golimumab: n= 1 **Qualitätsbewertung der Studien:** modified Jadad scale
	3. Ergebnisdarstellung *Study characteristics:*

Results:

Direkter Vergleich vs Placebo:

Table 1 Characteristics of the included trials

Trial	Intervention	Setting	Blinded period	No of patients randomized	Quality score	Outcomes of interest
Mease et al[8]	ETN (25 mg twice weekly)	NS	12 weeks	60	5/5	HAQ, PASI, PsARC
Mease et al[25–27]	ETN (25 mg twice weekly)	17 sites in USA	24 weeks	205	4/5	PASI, PsARC
IMPACT[10–12]	INF (5 mg/kg at weeks 0, 2, 6, 14)	9 sites in Europe, Canada, USA	16 weeks	104	4/5	HAQ, PsARC
IMPACT 2[21–24]	INF (5 mg/kg at weeks 0, 2, 6, 14, 22)	36 sites in Europe, Canada, USA	16 weeks	200	4/5	HAQ, PASI, PsARC
ADEPT[14–18]	ADA (40 mg every other week)	50 sites in Europe, Australia, Canada, USA	24 weeks	313	3/5	HAQ, PASI, PsARC
Genovese et al[19]	ADA (40 mg every other week)	16 sites in Canada, USA	24 weeks	100	5/5	HAQ, PsARC
GO-REVEAL[20]	GOL (50 mg or 100 mg every fourth week)	52 sites in Europe, Canada, USA	24 weeks	405	5/5	HAQ, PASI, PsARC

Abbreviations: ADA, adalimumab; ADEPT, Adalimumab Effectiveness in Psoriatic Arthritis Trial; ETN, etanercept; GOL, golimumab; GO-REVEAL, Golimumab-Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody; HAQ, Health Assessment Questionnaire; IMPACT, Infliximab Multinational Psoriatic Arthritis Controlled Trial; INF, inflizimab; NS, not stated; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria.

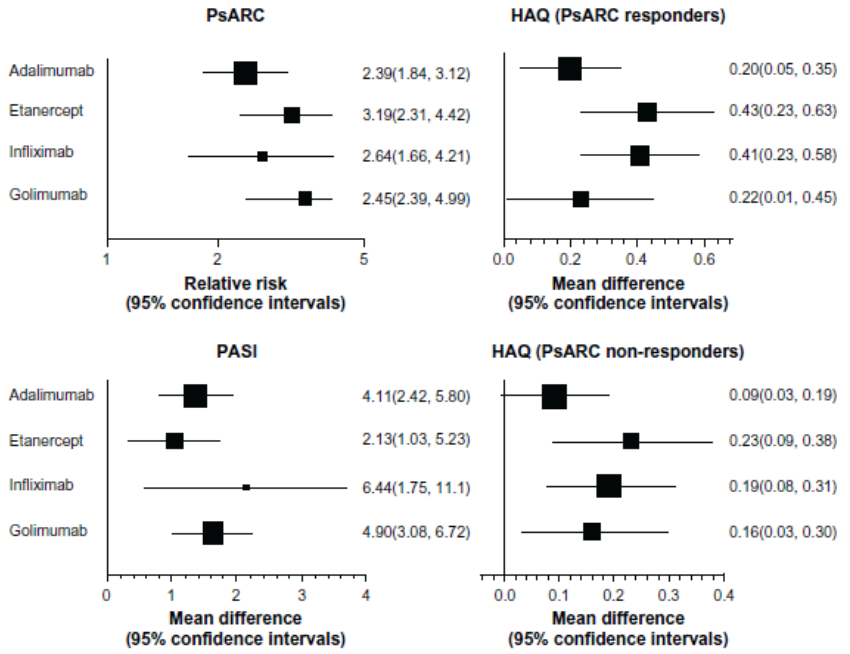


Figure Forest plots of direct estimates for anti-TNFs versus placebo comparisons.

→All anti-TNFs were significantly better than placebo

Indirect comparision:

Table 2 Head-to-head indirect estimates of the anti-TNF drugs

Comparison	PsARC RR (95% CI)	HAQ MD (95% CI)		PASI MD (95% CI)
		Responders	Nonresponders	
ADA versus ETN	0.75 (0.49, 1.24)	−0.23 (−0.51, 0.05)	−0.15 (−0.33, 0.03)	0.98 (−1.72, 3.68)
ADA versus INF	0.91 (0.53, 1.32)	−0.21 (−0.48, 0.06)	−0.11 (−0.27, 0.05)	−2.33 (−7.30, 2.64)
ADA versus GOL	0.69 (0.44, 1.26)	−0.03 (−0.33, 0.27)	−0.08 (−0.25, 0.09)	−0.79 (−3.27, 1.69)
ETN versus INF	1.21 (0.69, 1.34)	0.02 (−0.26, 0.30)	0.04 (−0.15, 0.23)	−3.31 (−8.44, 1.82)
ETN versus GOL	0.92 (0.57, 1.28)	0.20 (−0.10, 0.50)	0.07 (−0.13, 0.26)	−1.77 (−4.55, 1.01)
INF versus GOL	0.76 (0.42, 1.35)	0.18 (−0.11, 0.47)	0.03 (−0.15, 0.21)	1.54 (−3.48, 6.56)

Abbreviations: ADA, adalimumab; anti-TNF, anti-tumor necrosis factor; CI, confidence interval; ETN, etanercept; GOL, golimumab; HAQ, Health Assessment Questionnaire; INF, infliximab; MD, mean difference; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria; RR, relative risk.

→indirect comparison did not reveal any statistically significant difference between the anti-TNFs.

4. Anmerkungen/Fazit der Autoren

Our indirect comparison did not demonstrate any significant difference between anti-TNF drugs for the treatment of PsA. In

	some instances, the magnitudes of effect in our indirect comparison differed from others.
Goulabchand R, et al. 2013 [14]. Effect of tumour necrosis factor blockers on radiographic progression of psoriatic arthritis: a systematic review and meta-analysis of randomised controlled trials	1. Fragestellung • to examine the effect of tumour necrosis factor (TNF) blockers on radiographic progression • to determine whether treatment combining TNF blocker with methotrexate (MTX) was superior to TNF-blocker monotherapy.
	2. Methodik **Population:** Adults with active and progressive PsA with an inadequate response to previous DMARD therapy **Intervention** anti-TNFs (adalimumab, etanercept, golimumab, and infliximab**)** **Kontrolle** Placebo **Endpunkte** • proportion of patients without radiographic evidence of disease progression at treatment week 24 (non-progressors). • Proportion of non-progressors at week 48, • mean change in mTSS at week 24 modified total Sharp score (mTSS) has been used to evaluate radiographic evidence of damage in PsA **Suchzeitraum** (Aktualität der Recherche): up to December 2012 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 5 (n=1110) **Qualitätsbewertung der Studien**: Jadad scale
	3. Ergebnisdarstellung • The studies involved 1110 patients, 584 receiving TNF blockers with or without MTX, and 526 placebo with or without MTX. • No study compared a TNF blocker with a synthetic DMARD. • In total, 494/584 (84.5%) of patients receiving TNF blockers for PsA were considered non-progressors at week 24 as compared with 362/526 (68.8%) receiving placebo (OR 2.68 (95% CI 1.99 to 3.60), p<0.001), without significant heterogeneity (I2=3%, p=0.39) • At week 24, patients in both groups started receiving TNF blockers: at week 48, one group had received TNF blockers for 24 weeks, and the other for 48 weeks. At week 48, results again favoured TNF blockers (OR 2.42 (1.57 to 3.71); I2=0%; p=0.91) • Only a few data were available for TNF blocker therapy

	combined with MTX. No RCT directly compared the three groups of treatment: TNF blockers combined with synthetic DMARDs and each therapy alone. • No study evaluated the effect of biologics added to MTX on radiographic and clinical outcomes in PsA. *Mease et al. in a subanalysis, found no difference in structural progression between two groups (ETN treatment alone vs ETN with MTX) after 24 weeks, but no statistical analysis was available. Gladman et al., in a subanalysis, found no difference in radiographic disease progression between ADA alone and ADA with MTX (mean difference in mTSS at 24 weeks −0.2±1.17 vs −0.2±1.59*
	4. Anmerkungen/Fazit der Autoren Our meta-analysis of RCTs of PsA revealed that the TNF blockers ETN, IFX, ADA and GLM all led to better control of structural damages than non-biologic therapy after 24 and 48 weeks of treatment. The role of the therapy combined with MTX could not be clearly determined because of limited available data. 5. Hinweise FBMed Results based on radiographic assessment
Lemos LL, et al. 2014 [16]. Treatment of psoriatic arthritis with anti-TNF agents: a systematic review and meta-analysis of efficacy, effectiveness and safety	1. Fragestellung • To provide a comprehensive and up to date review on the efficacy and safety of the anti-TNF drugs adalimumab, etanercept, golimumab and infliximab used in active PsA. • Additionally, to present results of observational studies aiming to reveal the results of these anti- TNFs in real life settings.
	2. Methodik **Population:** Patients with PsA older than 18 y **Intervention** anti-TNFs **Kontrolle** other anti-TNFs or controls **Endpunkte** • Improvements of 20, 50 and 70 % in the American College of Rheumatology (ACR) criteria; • PsARC, the EULAR response, PASI70/75, DAS28, HAQ, SF-36, FACIT-F • adverse events **Suchzeitraum** (Aktualität der Recherche): from inception to 11/08/2013, **Anzahl eingeschlossene Studien** (Gesamt): 15 , davon 9 RCT, 6 Observationsstudien

Qualitätsbewertung der Studien: Jadad Score, Cochrane Risk of Bias Tool

3. Ergebnisdarstellung
   - Quality of studies based on Jadad sore: 7 RCT high quality, 2 RCT fair quality

Anti-TNF vs Placebo

ACR20 response

Comparison	Number of studies	Risk Ratio (95% CI)	I^2
Adalimumab vs Placebo	2 (n=413)	3.42 (2.08; 5.63)	38%
Etanercept vs Placebo	2 (n=265)	4.15 (2.71; 6.36)	0%
Golimumab vs Placebo	1 (n=259)	4.20 (2.51; 7.03)	n.a
Infliximab vs Placebo	3 (n=403)	3.50 (0.76;16.13)	96%

ACR50 response

Comparison	Number of studies	Risk Ratio (95% CI)	I^2
Adalimumab vs Placebo	2 (n=413)	10.02 (4.71; 21.28)	0%
Etanercept vs Placebo	2 (n=265)	9.12 (4.06; 20.49)	0%
Golimumab vs Placebo	1 (n=259)	6.81 (2.79; 16.62)	n.a.
Infliximab vs Placebo	3 (n=414)	8.24 (0.85; 79.73	91%

ACR70 response

Comparison	Number of studies	Risk Ratio (95% CI)	I^2
Adalimumab vs Placebo	2 (n=413)	4.81(0.69; 33.42)	10%
Etanercept vs Placebo	2 (n=265)	14.75 (1.97;110.51)	0%
Golimumab vs Placebo	1 (n=259)	3.48 (0.77; 15.80)	n.a.
Infliximab vs Placebo	3 (n=414)	7.93 (1.24; 50.57)	71%

Direct comparison (1 RCT, n=100): ACR20

- Adalimumab vs infliximab: RR 0.92 (95%CI 0.69;1.23)
- Etanercept vs infliximab: RR 0.94 (95%CI 0.71;1.25)
- Adalimumab vs etanercept: RR 0.98 (95%CI 0.73; 1.32)

→ no stat. sign. difference

Safety

There was no difference between anti-TNF and control groups in the occurrence of AEs and serious AEs. The analysis of AEs had substantial heterogeneity. Treatment discontinuation due to AEs was not different between anti-TNF and control groups, except for the subgroup of patients who used infliximab.

	Subgroup analysis: Use of methotrexate In most of the included studies, the concomitant use of MTX by patients in the anti-TNF group provided no additional benefit.
	4. Anmerkungen/Fazit der Autoren It was not possible to draw conclusions of efficacy differences between anti-TNF agents since the few studies comparing biologicals with each other were included, and in addition, these studies were not designed for such a purpose. All the same, the results suggest that there are no differences among the anti-TNF drugs and other factors should be taken into account in the choice of medication, such as costs and patient convenience, since these drugs have different dosing and schemes regimens and different routes of administration.
Coates LC, et al. 2014 [4]. Systematic Review of Treatments for Psoriatic Arthritis: 2014 Update for the GRAPPA =Summary based on Acosta Felquer ML, 2014 [1], Nash P, 2014 [17], Orbai AM, 2014 [21], Rose S, 2014 [23]	1. Fragestellung To performed a systematic review of current literature on the efficacy of different therapies, management, and therapeutic strategies for PsA, in order to provide information for the development of the new GRAPPA treatment recommendations.
	2. Methodik **Population:** patients with PsA **Intervention:** all therapies used in PsA (nonsteroidal antiinflammatory drugs (NSAID), disease modifying anti-rheumatic drugs/DMARDs; biologics) **Komparator:** Included interventions **Endpunkte** Efficacy (e.g. ACR response, measures of enthesitis, dactylitis) safety **Suchzeitraum** (Aktualität der Recherche): up to February 2013/ March 2014 **Qualitätsbewertung der Studien:** k.A. Grading of the body evidence using GRADE
	3. Ergebnisdarstellung **Summary** ***Peripheral arthritis (Acosta Felquer et al 2014)*.** Although nonsteroidal anti-inflammatory drugs (NSAID) have been commonly prescribed for peripheral arthritis, little new evidence supporting efficacy could be documented. However, new data were reported on traditional use of disease-modifying

	antirheumatic drugs (DMARD), specifically methotrexate (MTX), where results from 2 RCT suggested its potential efficacy. Limited data from observational and open-label studies provide additional lower-level evidence for the efficacy of MTX, leflunomide, and cyclosporine in PsA. Higher levels of evidence support the use of anti-tumor necrosis factor (TNF) agents in PsA. Statistically significant improvements in measures of joint disease were demonstrated with etanercept, adalimumab, infliximab, golimumab, and certolizumab pegol compared with placebo, although effect sizes were not always available. Other biological DMARD, specifically ustekinumab, abatacept, brodalumab, and secukinumab, also demonstrated statistically significant improvements compared to placebo. Apremilast, a small molecule that specifically inhibits phosphodiesterase 4, was superior to placebo in a series of 4 Phase III studies. Results with combination therapies were also reported, particularly MTX in combination with anti-TNF therapies and other biologics in trials without placebo controls. (siehe Tab.)

Table 1. Effect size and number needed to treat (NNT) in controlled trials in patients with psoriatic arthritis.

	MTX[9]	CSA[19]	LFN[17]	ADA[28]	ADA[23] ADEPT	ADA[29]	ETA[20]	INF[31] IMPACT	INF[30] IMPACT 2	GOL[34]	CZP[37]	UST[39]	ABAT[39]	Apremilast[52]
Patients (n) on treatment/ control	16/19	38/34	95/91	51/49	151/ 162	58/55	101/ 104	52/52	100/ 100	146/ 113	138/ 136	76/70	40/42	67/68
Mean dose	10 mg / wIM	2.5–4 mg/k/d	20 mg /d	40 mg eow	40 mg eow	40 mg eow	25 mg biw	5 mg/kg	5 mg /kg	50 mg/mo	200 q2w	90 mg qw	10 mg/kg	20 mg bid, 40 mg qd
Comparator	NSAID	PBO	PBO	PBO	PBO	CSA 2.5–3.75 mg/kg/d +ADA	PBO	PBO	PBO	PBO	PBO	PBO	PBO	PBO
Followup, weeks	24	48	24	12	24	48	24	16	24	24	24	12	24	12
Tender joint score, ES			0.22											
Swollen joint score, ES			0.17											
Pain, VAS; ES	–0.15	0.26		0.64	0.94			1.74	1.96			0.65		
HAQ, ES		–0.18	0.29	0.49	0.67			0.87	1.17	0.65				
Tender joint count, 0–78; ES				0.25				1.14	1.14					
Swollen joint count, 0–76; ES	0.33	0.13		0.3				1.17	0.81					
ACR20, NNT				5	3		3	2	3	3	3	4	4	4 bid 5 qd
PsARC, NNT			4			10								
Primary endpoint		Tender Joint Index (Ritchie)	PsARC	ACR20 wk 12	ACR20 wk 12 and x-ray	PsARC 12 mo	ACR20 wk 12	ACR20 wk 16	ACR20 wk 14	ACR20 wk 14 and vdH-S wk 24	ACR20 wk 12 and x-ray	ACR20 wk 12	ACR20 day 169	ACR20 wk 12

MTX: methotrexate; CSA: cyclosporine; LFN: leflunomide; ADA: adalimumab; ETA: etanercept, INF: infliximab; GOL: golimumab; CZP: certolizumab pegol; UST: ustekinumab; ABAT: abatacept; ES: effect size; NNT: number needed to treat; ACR20: American College of Rheumatology 20% response; PsARC: Psoriatic Arthritis Response Criteria; VAS: visual analog scale; vdH-S Sharp/van der Heijde score; eow: every other week; biw: twice weekly; q2w: every 2 weeks; q4w: every 4 weeks; bid: twice/daily; qd : once daily.

Axial disease (Nash et al. 2014)

Scant data are available on traditional therapies for axial disease in PsA (e.g., NSAID, MTX, etc.), but limited new data are available for targeted biologics and novel agents. Although improvement in axial disease is not often specified as an endpoint, significant benefits have been noted in RCT of anti-TNF therapies in AS, psoriasis, and PsA, particularly regarding disease activity, range of motion, physical function, and quality of life, both as monotherapy and in combination with other DMARD. Other biologics (e.g., ustekinumab, brodalumab) have reported some success in axial PsA in small open-label studies.

Enthesitis (Orbai et al 2014): 12 studies

Effectiveness of Various Agents for Enthesitis in PsA (level of

	evidence). • Effective (1b): Infliximab; golimumab; certolizumab; ustekinumab; apremilast (30 mg twice daily). • Not effective (1b): Sulfasalazine (2 g daily). • Not adequately studied: Adalimumab; other disease-modifying antirheumatic drugs (including methotrexate); nonsteroidal antiinflammatory drugs; physiotherapy. ***Dactylitis (Rose, et al 2014): 29 studies*** Traditionally, NSAID, local corticosteroid injections, and DMARD have been used to treat dactylitis. In this review, the authors found large variabilities in study designs, outcome measures, and availability of primary data. However, significant improvements in dactylitis were observed with the use of ustekinumab, certolizumab, and infliximab. One etanercept study demonstrated improvement in dactylitis scores, but a placebo-controlled trial is required that targets dactylitis as an endpoint. The role of anakinra remains uncertain.
	4. Fazit/Amerkungen der Autoren Treatment recommendations from GRAPPA will follow, based on this systematic assessment of the literature 5. Hinweise durch FBMed • Bewertung der internen Validität (Risk of Bias) der Primärstudien unklar • Aktualisierte Therapie-Empfehlungen (GRAPPA) bisher nicht publiziert
Adverse Events	
Dommasch ED, et al. 2011 [9]. The risk of infection and malignancy with rumor necrosis factor antagonists in adult patients with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials.	1. Fragestellung To examine the risks of infection and malignancy with the use of TNF antagonists in adult patients with psoriatic disease
	2. Methodik **Population:** Adults patients with moderate to severe PsO and/or PsA **Intervention** etanercept, infliximab, adalimumab, golimumab, certolizumab, **Kontrolle** Anti-TNF or placebo **Endpunkte** • infection • malignancy **Suchzeitraum** (Aktualität der Recherche): from inception to July 30th, 2009 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 20

	(n=6810 including 1383 patients with PsA) Seven trials specifically included patients with active PsA unresponsive to DMARDs and/or non-steroidal anti-inflammatory drugs (NSAIDS), although five of these trials additionally required that patients have active psoriatic skin lesions and/or a documented history of PsO. 6. **Qualitätsbewertung der Studien:** Jadad score (Jadad score of 3 or greater was required for inclusion)
	3. Ergebnisdarstellung Malignancies • The pooled OR for malignancies in patients with PsO and PsA using anti-TNF agents was 1.48 (95% CI: 0.71, 3.09), no heterogeneity • 70.6% of malignancies were non-melanoma skin cancers (NMSC). • The OR for NMSC in patients using anti-TNF agents across all trials was 1.33 (95% CI: 0.58, 3.04). The IRR for NMSC was 0.72 (95% CI: 0.42, 1.24). • OR for all malignancies excluding NMSC was 1.28 (95% CI: 0.39, 4.15). IRR was 0.56 (95% CI: 0.31, 1.01). • Subgroup analysis by disease also indicated no differences between anti-TNF and placebo Infections • The OR for any infectious event in patients with PsA or PsO treated with an anti-TNF agent was 1.18 (95% CI: 1.05, 1.33), with 97.6% of infections being non-serious, i.e., not recorded as an SAE. • Serious infections: no stat. sig. differences between anti-TNF and placebo • Subgroup analysis by disease also indicated no differences between anti-TNF and placebo *Publication Bias* • No evidence of publication bias with Egger tests for malignancy (P = 0.54),NMSC (p = 0.29), malignancies excluding NMSC (p = 0.48), overall infection (p = 0.18),non-serious infection (p = 0.16), or serious infection (p = 0.14). • Funnel plots were also created for the above outcomes, all of which were found to be symmetrical.
	4. Anmerkungen/Fazit der Autoren There is a small increased risk of overall infection with the short-term use of TNF antagonists for psoriasis that may be attributable to differences in follow-up time between treatment and placebo groups. There was no evidence of an increased risk of serious infection and a statistically significant increased risk in cancer was not observed with short-term use of TNF inhibitors. *Limitations:* Short duration of follow-up and rarity of malignancies and serious

	infections. 5. Hinweise durch FBMed • Subgruppenanalysen zu den beiden unterschiedlichen Krankheitsformen wurden durchgeführt. • Studien in der Metaanalyse waren teilweise sehr heterogen hinsichtlich: Studienmedikation, Design, Krankheitsbild, vorherige und begleitende Therapie, Krankheitsdauer.
Conway R, et al. 2015 [8]. Risk of liver injury among methotrexate users: A meta-analysis of randomized controlled trials	1. Fragestellung To evaluate the relative risk and severity of liver disease among patients treated with methotrexate.
	2. Methodik **Population:** Adults with rheumatoid arthritis, psoriasis, psoriatic arthritis or inflammatory bowel disease **Intervention:** MTX **Komparator:** No MTX **Endpunkte** Liver adverse events **Suchzeitraum** (Aktualität der Recherche): April 2014 **Anzahl eingeschlossene Studien** (Gesamt): 32 including 1 RCT on PsA **Qualitätsbewertung der Studien:** Cochrane Risk of Bias tool
	3. Ergebnisdarstellung 1 RCT on PsA: MTX vs placebo (n=221), study duration 24 w Increased risk of total liver adverse events with MTX: RR 6.17 (95%CI 1.41-26.91)
	4. Fazit der Autoren Our study found an increased risk of elevated transaminases but not liver failure, cirrhosis or death with methotrexate compared to other agents. We were unable to assess long-term liver toxicity due to the short duration of included clinical trials.
Conway R, et al. 2015 [7]. Methotrexate use und risk of lung disease in psoriasis, psoriatic arthritis, and inflammatory bowel disease: systematic literature review and	1. Fragestellung To evaluate the relative risk of pulmonary disease among patients with psoriasis, psoriatic arthritis, and inflammatory bowel disease treated with methotrexate.
	5. Methodik **Population:** Adults with rheumatoid arthritis, psoriasis, psoriatic arthritis or inflammatory bowel disease **Intervention:**

meta-analysis of randomized controlled trials	MTX **Komparator:** No MTX **Endpunkte** Liver adverse events **Suchzeitraum** (Aktualität der Recherche): Jan 2014 **Anzahl eingeschlossene Studien** (Gesamt): 7 RCTs including 1 RCT on PsA **Qualitätsbewertung der Studien:** Cochrane Risk of Bias tool
	6. Ergebnisdarstellung 1 RCT on PsA: MTX vs placebo (n=221), study duration 24 w: No increased risk of total adverse respiratory events with MTX (RR 1.27 [95%CI 0.81-2.01])
	7. Fazit der Autoren Findings suggested that there was no increased risk of lung disease in methotrexate treated patients with non-malignant inflammatory diseases. Given the limitations of the study, however, we cannot exclude a small but clinically important risk.

SIGN, 2010 [24].

Diagnosis and management of psoriasis and psoriatic arthritis in adults

Scottish Intercollegiate Guidelines Network (SIGN)

Fragestellung:
Diagnosis and management of psoriasis and PsA in adults:

Early diagnosis of PsA, screening for comorbidities, assessment of disease severity, non-pharmacological treatment, psychological interventions, occupational health, topical treatment, phototherapy, systemic therapy, biologic treatment, referral pathways and the provision of patient information.

Hier relevant:

What evidence is there for the efficacy and safety of specific therapies for PsA?

- NSAIDS and corticosteroids, DMARDs (auranofin, azathioprine, ciclosporin, D-penicillamine, hydroxychloroquine, leflunomide, methotrexate, mycophenolate mofetil, sulfasalazine), biologic therapies, combination therapies (MTX + biologic)
- peripheral PsA, axial PsA, enthesitis, dactylitis

Methodik

Grundlage der Leitlinie

- developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development
- methodology are contained in 'SIGN 50: A Guideline Developer's Handbook', available at www.sign.ac.uk.
- Suchzeitraum: bis 2008

LoE

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of
1+	well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 -	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies, high quality case contr cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and moderate probability that the relationship is causal
2 -	Case control or cohort studies with a high risk of confounding or bias and a significant ris the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GoR

A - At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

	B - A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+ **C -** A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++ **D-** Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+ **[✓] -** Recommended best practice based on the clinical experience of the guideline development group
	Empfehlungen ***Treatment of psoriatic arthritis in secondary care:*** <u>pharmacological treatment</u> *NSAIDS:* • NSAIDs are recommended for short term symptom relief in patients with psoriatic arthritis where not contraindicated. (LoE: C) *Kortikosteroide:* • The judicious use of intra-articular corticosteroids to treat persistent synovitis of a given joint is recommended, particularly for mono- or oligoarthritis, or for bridging therapy whilst waiting for systemic therapy to become effective. (LoE: ✓) *DMARDS:* • Leflunomide is recommended for the treatment of active peripheral psoriatic arthritis (LoE: A) • Sulfasalazine may be considered as an alternative in the treatment of peripheral psoriatic arthritis. (LoE: C) • Methotrexate may be considered in the treatment of psoriatic arthritis. (LoE: C) • The addition of ciclosporin to methotrexate in the treatment of psoriatic arthritis is not recommended for routine therapy. (LoE: D) • Patients should not be expected to fail ciclosporin before being eligible for biologic therapy for psoriatic arthritis. (LoE: ✓) • The use of intramuscular or oral gold in the treatment of psoriatic arthritis is not recommended where less toxic treatments are an option. (LoE: B) • Choice of DMARD and sequence of DMARD should take into account: o patient preference o severity of joint disease

	○ severity of skin disease ○ comorbidities ○ risk of adverse reactions. (LoE: ✓) *Biologic therapy:* • Adalimumab, etanercept or infliximab are recommended for treatment of active psoriatic arthritis in patients who have failed to respond to, are intolerant of, or have had contraindications to, at least two disease-modifying therapies.(LoE: A) • Appropriate patients on biologic therapies should be offered the opportunity to join the BADBIR long term safety register.(LoE: ✓) The use of biologic treatments in psoriatic arthritis should conform to British Society for Rheumatology guidelines.(LoE: ✓)
Gossec L, et al. 2012 [13]. **EULAR** European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies Zu Grunde liegender SR: Ash Z, 2012 [3]	European League Against Rheumatism (EULAR) To provide recommendations for the treatment of PsA with systemic or local (non-topical) symptomatic and disease-modifying antirheumatic drugs (DMARD). Methodik Grundlage der Leitlinie: evidence and consensus based GL – systematic literature reviews performed for non-steroidal anti-inflammatory drugs (NSAID), glucocorticoids, synthetic DMARD and biological DMARD (Ash et al., 2012) – evidence was discussed, summarized and recommendations were formulated by a task force comprising 35 representatives (28 rheumatologists, 2 patients, 1 infectious disease specialist, 1 dermatologist, 1 physiotherapist and 2 rheumatology fellows) and providing levels of evidence, strength of recommendations and levels of agreement. – Suchzeitraum: 1962 - January 2010 **LoE**

Table 2 Categories of evidence

Category	Evidence
1A	From meta-analysis of randomised controlled trials
1B	From at least one randomised controlled trial
2A	From at least one controlled study without randomisation
2B	From at least one type of quasi-experimental study
3	From descriptive studies, such as comparative studies, correlation studies, or case-control studies
4	From expert committee reports or opinions and/or clinical experience of respected authorities

GoR

Table 3 Strength of recommendations

Strength	Directly based on:
A	Category I evidence
B	Category II evidence or extrapolated recommendations from category I evidence
C	Category III evidence or extrapolated recommendation from category I or II evidence
D	Category IV evidence or extrapolated recommendation from category II or III evidence

Levels of agreement: Votes for agreement or disagreement were performed anonymously, by giving a score from 0 (total disagreement) to 10 (total agreement) for each recommendation; the means and SD of scores from the whole group were calculated.

Empfehlungen

Recommendations	LoE	GoR	Levels of Agree-ment
In patients with psoriatic arthritis, non-steroidal anti-inflammatory drugs may be used to relieve musculoskeletal signs and symptoms.	1b	A	9.4±0.9
In patients with active disease (particularly those with many swollen joints, structural damage in the presence of inflammation, high ESR/CRP and/or clinically relevant extraarticular manifestations), treatment with disease-modifying drugs, such as methotrexate, sulfasalazine, leflunomide, should be considered at an early stage.	1b 4	B	9.4±0.7
In patients with active psoriatic arthritis and clinically relevant psoriasis, a disease modifying drug that also improves psoriasis, such as methotrexate, should be preferred.	1b	A	9.1±1.0
Local injections of corticosteroids should be considered as adjunctive therapy in psoriatic arthritis; systemic steroids at the lowest effective dose may be used with caution.	3b 4	C	8.9±1.2
In patients with active arthritis and an inadequate response to at least one synthetic disease-modifying antirheumatic drug, such as methotrexate, therapy with a tumour necrosis factor inhibitor should be commenced.	1b	B	8.9±1.5

In patients with active enthesitis and/or dactylitis and insufficient response to nonsteroidal anti-inflammatory drugs or local steroid injections, tumour necrosis factor inhibitors may be considered.	1b	B	8.5±1.5
In patients with predominantly axial disease that is active and has insufficient response to non-steroidal anti-inflammatory drugs, tumour necrosis factor inhibitors should be considered.	2b	C	9.3±0.9
Tumour necrosis factor inhibitor therapy might exceptionally be considered for a very active patient naive of disease-modifying treatment (particularly those with many swollen joints, structural damage in the presence of inflammation, and/ or clinically relevant extra-articular manifestations, especially extensive skin involvement).	4	D	8.6±1.7
In patients who fail to respond adequately to one tumour necrosis factor inhibitor, switching to another tumour necrosis factor inhibitor agent should be considered.	2b	B	8.9±1.8
When adjusting therapy, factors apart from disease activity, such as comorbidities and safety issues, should be taken into account.	4	D	8.9±1.8

Evidence (based on Ash, 2012)

MTX:

Three RCTs (n=93 patients) comparing methotrexate (MTX) monotherapy versus placebo and seven open or retrospective studies of MTX in PsA were analysed showing efficacy of MTX for the treatment of peripheral arthritis and psoriasis. Data on radiographic progression were not conclusive as it was only analysed in a small case–control study.

Sulfasalazine:

Seven RCTs (n=666 patients) reported comparisons of sulfasalazine (SSZ) monotherapy versus placebo or symptomatic treatment (NSAIDs, analgesics and/or prednisolone ≤5 mg/day). In addition, one open trial and one case–control study were reviewed. SSZ was effective for the treatment of peripheral arthritis and axial manifestations and appeared effective for psoriasis. Two studies reported data on dactylitis with no significant difference found between SSZ and placebo. One study reported on enthesitis, again with no significant benefit of SSZ over placebo. Radiographic progression was not prevented in a small case–control study of 20 SSZ treated patients and 20 matched controls.

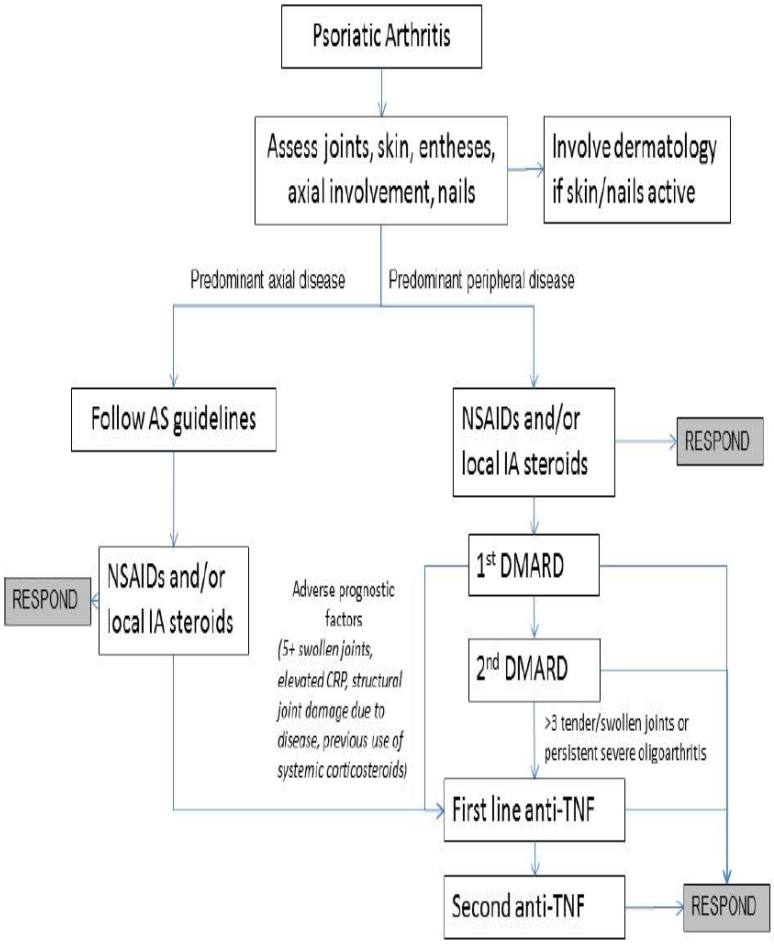
Cyclosporine:

Two RCTs (n=171 patients) reported comparisons of cyclosporine (CsA) monotherapy versus placebo or symptomatic treatment (NSAIDs, analgesics and/or prednisone ≤5 mg/day) and four open trials were reviewed. In a 24-week trial (n=99) assessing CsA monotherapy (3 mg/kg/day) versus symptomatic treatment, CsA appeared effective for the treatment of peripheral arthritis and axial involvement. In a 12-month RCT, patients with active PsA and an incomplete response to MTX were randomized to either CsA or placebo in addition to MTX. The only significant differences between the groups were in synovitis detected by ultrasound and

	psoriasis area and severity index (PASI) score in favour of the MTX/CsA group. There was no direct evidence that CsA reduces the progression of radiographic damage. *Leflunomide* One RCT (n=190 patients) and two open trials of leflunomide in PsA have been conducted. The 24-week RCT comparing leflunomide monotherapy (100 mg/day loading dose for 3 days followed by 20 mg/day orally) versus placebo indicated that leflunomide was clinically effective for the treatment of peripheral arthritis and psoriasis. In an open trial of patients with previous DMARD exposure, 8 of the 12 patients showed at least partial response to leflunomide. *DMARD* Four RCTs and two retrospective studies comparing different DMARDs in PsA were found. One RCT compared CsA (3–5 mg/kg/day) with MTX (7.5–15 mg weekly) in 35 patients. Both were effective at 6 and 12 months for both PsA and skin psoriasis. In a 24-week trial (n=99), CsA monotherapy (3 mg/kg/day) appeared more effective for the treatment of peripheral arthritis and skin than symptomatic treatment and also more effective for the treatment of skin and potentially more effective for peripheral arthritis than SSZ. Two 24-week RCTs compared injectable gold and auranofin, both finding greater efficacy with the injectable preparation. *Biological treatments* 11 RCTs on adalimumab, alefacept, efalizumab, etanercept, golimumab, infliximab and ustekinumab: All studied TNF inhibitors (adalimumab, etanercept, golimumab and infliximab) showed efficacy at 12–16 weeks for PsA Response Criteria (PsARC) response, American College of Rheumatology (ACR) 20, 50 and 70 response criteria and PASI. Efalizumab was not superior to placebo for PsARC or ACR 20, 50 and 70 responses and this drug has now been withdrawn due to concerns of an increased risk of progressive multifocal leukoencephalopathy. Ustekinumab was superior to placebo in achieving ACR 20 and 50 responses. Improvements in Health Assessment Questionnaire were greater with adalimumab, infliximab, ustekinumab and alefacept than placebo at 12 weeks, and with adalimumab, etanercept, golimumab and infliximab at 24 weeks, but not with alefacept at 24 weeks. Radiographic progression as measured by the modified total Sharp or PsA modified van der Heijde Sharp scoring method was lower for patients treated with all studied TNF inhibitors at 12 and/or 6 months compared with placebo. *Is there a different efficacy for biological agents in PsA subtypes of articular involvement (monoarthritis, oligoarthritis, polyarthritis, axial disease, dactylitis, enthesitis)?* No RCTs reported results separately for the different subtypes of PsA. With regard to spinal disease, only one observational study reported on spinal disease associated with PsA, although final results were pooled for patients with and without spinal disease. For dactylitis and enthesitis, six RCTs reported data (between12 and 16 weeks) as secondary end points, showing significant benefits with golimumab, infliximab and ustekinumab. Studies used different outcome measures with only a proportion of patients having documented baseline dactylitis or enthesitis.
Coates LC, et al.	Guideline of British Society for Rheumatology (BSR) and British

2013 [5]. The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics	Health Professionals in Rheumatology (BHPR) Fragestellung: The guidelines cover adult patients with PsA affecting all domains of psoriatic disease. They provide a stepwise management plan giving clear advice on treatment, including inclusion/exclusion criteria for treatment, monitoring requirements and how to quantify response to biologics. They provide evidence-based advice for the use of anti-TNF therapies in difficult situations, including pregnancy and significant comorbidities. A review on the use of conventional DMARDs prior to the use of anti-TNF therapies was not undertaken.
	Methodik Grundlage der Leitlinie – developed by a multidisciplinary working party set up by the British Society for Rheumatology (BSR), including rheumatologists, a dermatologist, specialist nurses and a patient representative. – CoI fully declared – systematic literature search, including electronic bibliographic databases (Medline and Embase) and systematic review databases (Cochrane) up to 1 July 2011. – Consensus agreement: Following evaluation of the literature, draft guidelines were developed by the working party for presentation at the BSR Annual Meeting in 2011 and 2012. Comments from the wider rheumatology community were invited via the BSR website and were incorporated into later drafts. Final draft guidelines were circulated to all members of the working party for a vote on levels of agreement with each recommendation. Voting was performed anonymously, with possible levels of agreement ranging from 0 (total disagreement) to 10 (total agreement). Results of this vote are included with each specific recommendation. LoE: The literature was reviewed and the quality of evidence was graded by the working party according to the Royal College of Physicians' Concise Guidance to Good Practice. GoR: (i) Grade A: meta-analysis of RCTs or an RCT. (ii) Grade B: controlled trial or quasi-experimental study or descriptive study. (iii) Grade C: expert committee recommendation.
	Empfehlungen <u>Peripheral arthritis (polyarticular disease):</u> • Anti-TNF therapy should be considered for those patients with active arthritis (defined as at least three tender and three swollen joints) who have failed treatment with at least two conventional DMARDs*. Anti-TNF therapy may be considered for patients who

	have failed only one DMARD especially where there is evidence of adverse prognostic factors**. (*LoE: Grade A*) • All of the licensed anti-TNF therapies are recommended for use in patients eligible for treatment and choice of therapy should be left to the treating physician after considering concomitant medical problems, patients preference and cost effectiveness. For patients requiring rapid control of skin psoriasis an anti-TNF monoclonal antibody is preferred in accordance with the British Association of Dermatology (BAD) guidelines. (*LoE: Grade A*). <u>Oligoarthritis:</u> • Anti-TNF therapies should be considered in patients with severe persistent oligoarthritis (fewer than three tender/swollen joints), which has a major demonstrable influence on well-being and who have failed treatment with at least two conventional DMARDs and appropriateintra-articular steroids (Grade C) <u>Active axial psoriatic arthritis:</u> • Anti-TNF therapy should be considered for those patients with active axial psoriatic arthritis according to the recommendation of the BSR guidelines for ankylosing spondylitis (LoE: Grade A) ** An adequate therapeutic trial is defined either as failure to tolerate a DMARD or active disease despite treatment of at least 12 weeks at target therapeutic dose of a conventional DMARD e.g. leflunomide, methotrexate, sulfasalazine, ciclosporin* *** adverse prognostic factors defined as 5 or more swollen joints with elevated C-reactive protein (CRP) persisting for more than three months, and/or structural joint damage due to disease, and/or previous use of systemic corticosteroids.* **Alternative biologics in testing/development** A number of new biologic therapies beyond anti-TNF have been tested in PsA more recently. The majority of these are unlikely to replace anti-TNF therapies, as they have not shown responses equivalent to anti-TNF therapies. There is a need for alternative treatments for patients who fail anti-TNF therapies, but to date, none of these drugs has sufficient evidence to support a recommendation for use. […] • Ustekinumab: Provisional evidence therefore suggests that ustekinumab may be moderately effective for PsA. A large phase III programme in PsA is ongoing that is providing further data on its therapeutic utility. • Apremilast: A phase II study of 204 patients found a modest effect in arthritis treatment, with a significant difference in ACR20 for both 20mg bd and 40mg od doses. A significant difference was not seen in ACR70, with very few patients achieving such a marked improvement in disease activity

	
Wendling D, et al. 2014 [27]. Recommendations of the French Society for Rheumatology (SFR) on the everyday management of patients with spondyloarthritis	Guidelines of the French Society for Rheumatology (Société francaise de rhumatologie, [SFR]): Development of practice guidelines for spondyloarthritis spondyloarthritis (including psoriatic arthritis)
	Methodik Grundlage der LL – Update and French adaptation of existing recommendations issued by the ASAS/EULAR and ASAS (Assessment in Spondyloarthritis International Society) – Funding: The French Society for Rheumatology (SFR) participated in organizing the task force meeting and contributed to the publication and translation costs – Systematic literature review: o Search in Medline, Cochrane, Embase: Jan 2010 – Jun 2013; manual search in conference proceedings o level of evidence of each publication was assessed – Presentation of the literature review data, discussion among experts, and development of the practice guidelines during conference of interdisciplinary expert group **LoE/ GoR** The strength of the practice guidelines (based on the level of evidence) and the level of agreement among experts (rated from 0 [strongly disagrees] to 10 [strongly agrees]) are given for each

practice guideline. Strength was graded according to standard practice:

- A: guideline based on level 1 evidence (meta-analysis of RCTs or at least 1 RCT);
- B: guideline based on level 2 evidence (at least 1 non-RCT or quasi-experimental study) or extrapolated from level 1 evidence;
- C: guideline based on level 3 evidence (descriptive study) or extrapolated from level 1 or 2 evidence;
- D: guideline based on level 4 evidence (expert opinion) or extrapolated from level 1, 2, or 3 evidence.

Empfehlungen

…

7.5. Biologic agents

22) TNF alpha antagonist therapy should be offered to patients with persistent disease activity despite conventional treatment, according to the recommendations shown in Fig. 1 (D) (9,8).

All the TNF alpha antagonists available to date for use in spondyloarthritis have been proven effective in various forms of the disease [17,57–59]. TNFalpha antagonist therapy improved the symptoms and signs of spondyloarthritis, quality of life, productivity, and bone mineral density. The safety profile of TNF alpha antagonists in spondyloarthritis is similar to the overall safety profile of these drugs [10,53]. It is worth noting that some patients may experience paradoxical effects [57], defined as the occurrence during TNF alpha antagonist therapy of manifestations that are among the indications for TNF alpha antagonists (e.g., uveitis, psoriasis, or denovo Crohn's disease at a time when the rheumatic manifestations of spondyloarthritis are well controlled by TNF alpha antagonist therapy).

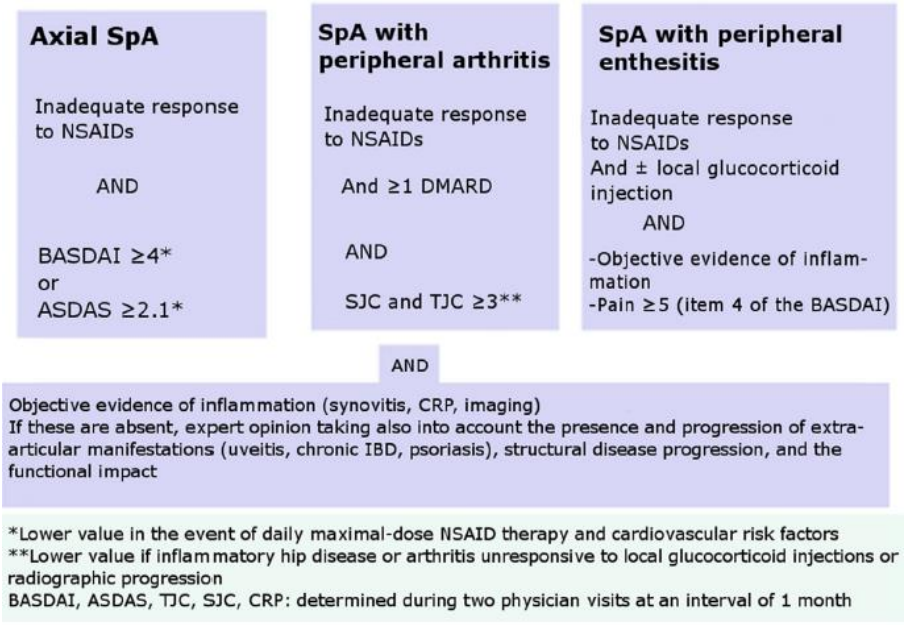


Fig. 1. Indications for TNFα antagonist therapy.

[...]

24) In the event of primary or secondary lack of effectiveness of a TNF alpha antagonist, there is no proof to date that increasing the dosage is beneficial. After reappraising the diagnosis of spondy-

	loarthritis and ruling out a differential diagnosis or complication of the disease, a switch to another TNF alpha antagonist deserves consideration (D) (9,7). Switching to a second TNF alpha antagonist may be beneficial, in particular in the event of escape phenomenon, primary ineffectiveness, or intolerance to a first TNF alpha antagonist (C) (9,7). [...] 26) There is no evidence to support differences across TNF alpha antagonists regarding effectiveness on the axial or peripheral manifestations/enthesitis. In patients with chronic inflammatory bowel disease (IBD), there is a difference in effectiveness on the gastrointestinal manifestations, which should be taken into account. (D) (9.7). 27) There is no evidence to date to support the use of biological agents other than TNF alpha antagonists in patients with axial spondyloarthritis (D) (9,6). In patients who fail treatment with conventional DMARDs and TNFalpha antagonists, no treatment options exist [74]. Abatacept has not been proven effective [75]; rituximab is not effective inpatients having failed TNF alpha antagonist therapy and remains to be evaluated in biotherapy-naive patients with peripheral joint manifestations [76–78]. Retrospective data on IL-6-antagonists are inconclusive [79] and controlled studies show no effect [80].Options currently under investigation for spondyloarthritis and psoriatic arthritis include the anti-IL-17 secukinumab [81,82], the anti-IL-23 ustekinumab [83], and apremilast [84,85]. Ustekinumab(anti-p40 IL-12/23) is licensed for use in patients with psoriatic arthritis and an inadequate response to the conventional treatment. References [6] Baraliakos et al. Update of the literature review on treatment with biologics as a basis for the first update of the ASAS/EULAR management recommendations of ankylosing spondylitis. Rheumatology (Oxford)2012;51:1378–87. [7] Gossec et al. European league against rheuma-tism recommendations for the management of psoriatic arthritis withpharmacological therapies. Ann Rheum Dis 2012;71:4–12. [8] Ash et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis 2012;71:319–26. [9] Pham et al. Recommendations of the French society for rheumatology regarding TNFalpha antagonist therapy in patients with ankylosing spondylitis or psoriatic arthritis: 2007 update. Joint Bone Spine2007;74:638–46. [10] Pham, et al. TNF alpha antagonist therapy and safety monitoring. Joint Bone Spine 2011;78:15–85. [17] Wendling et al. Non-radiographic spondyloarthritis: a theoretical concept or a real entity? Joint Bone Spine 2012;79:531–3. 53] Goeb et al. Conseils d'utilisation des traitements anti-TNF et recommandations nationales de bonne pratique labellisées par la Haute Autorité de santé franc¸ aise. Joint Bone Spine 2013;80:574–81. [57] Machado et al. Treatment of ankylosing spondylitis with TNF blockers: a meta-analysis. Rheumatol Int2013;33:2199–213 [58] Dougados et al. A randomised, multicentre, double-blind, placebo-controlled trial of etanercept in adults with refractory heel enthesitisin spondyloarthritis: the HEEL trial. Ann Rheum Dis 2010;69:1430–5. [59] Dougados et al. Continuous efficacy of etanercept in severe and advanced ankylosing spondylitis: results from a 12-week open-label extension of the SPINE study. Rheumatology (Oxford) 2012;51:1687–96. [74] Wendling . Are there new emerging drugs for ankylosing spondylitis or spondyloarthritis? Expert Opin Emerg Drugs 2013;18:5–7. [75] Song et al. Treatment of active ankylosing spondylitis with abatacept: an open-label, 24-week pilot study. Ann Rheum Dis 2011;70:1108–10.

[76] Song IH, Heldmann F, Rudwaleit M, et al. Different response to rituximab in tumor necrosis factor blocker-naive patients with active ankylosing spondylitis and in patients in whom tumor necrosis factor blockers have failed: a twenty-four-week clinical trial. Arthritis Rheum 2010;62:1290–7.

[77] Song et al. One-year follow-up of ankylosing spondylitis patients responding to rituximab treatment and re-treated in caseof a flare. Ann Rheum Dis 2013;72:305–6.

[78] Wendling D, Dougados M, Berenbaum F, et al. Rituximab treatment for spondy-loarthritis. A nationwide series: data from the AIR registry of the French Societyof Rheumatology. J Rheumatol 2012;39:2327–31.

[79] Lekpa et al. Is IL-6 an appropriate target to treatspondyloarthritis patients refractory to anti-TNF therapy? A multicentre ret-rospective observational study. Arthritis Res Ther 2012;14:R53.

[80] Sieper et al. Assessment of short-termsymptomatic efficacy of tocilizumab in ankylosing spondylitis: results of ran-domised, placebo-controlled trials. Ann Rheum Dis 2013 [Epub ahead of print]

.[81] Baeten et al. Anti-interleukin-17A monoclonal antibodysecukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. Lancet 2013;382:1705–13.

[82] McInnes IB, Sieper J, Braun J, et al. Efficacy and safety of secukinumab, a fullyhuman anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial. Ann Rheum Dis 2013 [Epub aheadof print].

[83] McInnes et al. Efficacy and safety of ustek-inumab in patients with active psoriatic arthritis: 1-year results of the phase3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet2013;382:780–9

.[84] Schett et al. Oral apremilast in the treatment of activepsoriatic arthritis: results of a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum 2012;64:3156–67.

[85] Pathan et al. Efficacy and safety of apremilast, anoral phosphodiesterase 4 inhibitor, in ankylosing spondylitis. Ann Rheum Dis2013;72:1475–80, doi:10.1136/annrheumdis-2012-201915.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NICE, 2010 [19]. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. NICE technology appraisal guidance 199	1.1 Etanercept, infliximab and adalimumab are recommended for the treatment of adults with active and progressive psoriatic arthritis when the following criteria are met. • The person has peripheral arthritis with three or more tender joints and three or more swollen joints, **and** • The psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying antirheumatic drugs (DMARDs), administered either individually or in combination. 1.2 Treatment should normally be started with the least expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules. 1.3 Etanercept, adalimumab or infliximab treatment should be discontinued in people whose psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks. An adequate response is defined as an improvement in at least two of the four PsARC criteria, (one of which has to be joint tenderness or swelling score) with no worsening in any of the four criteria. People whose disease has a Psoriasis Area and Severity Index (PASI) 75 response at 12 weeks but whose PsARC response does not justify continuation of treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response. 1.4 When using the PsARC healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses to components of the PsARC and make any adjustments they consider appropriate. **Evidence** (→ SR: Rodgers et al., 2011**)** The Assessment Group identified six double-blind, placebo controlled, randomised controlled trials (RCTs) in people with psoriatic arthritis for the technologies: two for etanercept, two for infliximab and two for adalimumab.
NICE, 2011 [18]. Golimumab for the treatment of psoriatic arthritis. NICE technology appraisal guidance 220	Golimumab is recommended as an option for the treatment of active and progressive psoriatic arthritis in adults only if: • it is used as described for other tumour necrosis factor (TNF) inhibitor treatments in 'Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis' (NICE technology appraisal guidance 199), and • the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose. When using the Psoriatic Arthritis Response Criteria (PsARC; as set out in NICE technology appraisal guidance 199), healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses to components of the PsARC and make any

	adjustments they consider appropriate.
NICE, 2015 [20]. Ustekinumab for treating active psoriatic arthritis (rapid review of technology appraisal guidance 313). NICE technology appraisal guidance 340	This guidance replaces Ustekinumab for treating active psoriatic arthritis (NICE technology appraisal guidance 313 issued in May 2014). 1.1 Ustekinumab is recommended as an option, alone or in combination with methotrexate, for treating active psoriatic arthritis in adults only when: • treatment with tumour necrosis factor (TNF) alpha inhibitors is contraindicated but would otherwise be considered (as described in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and golimumab for the treatment of psoriatic arthritis) or • the person has had treatment with 1 or more TNF–alpha inhibitors. Ustekinumab is recommended only if the company provides the 90 mg dose of ustekinumab for people who weigh more than 100 kg at the same cost as the 45 mg dose, as agreed in the patient access scheme. 1.2 Ustekinumab treatment should be stopped if the person's psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 24 weeks. An adequate response is defined as an improvement in at least 2 of the 4 criteria (1 of which must be joint tenderness or swelling score), with no worsening in any of the 4 criteria. As recommended in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis, people whose disease has a Psoriasis Area and Severity Index (PASI) 75 response but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response (see NICE technology appraisal guidance on ustekinumab for the treatment of adults with moderate to severe psoriasis). 1.3 When using the Psoriatic Arthritis Response Criteria (PsARC) healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses to components of the PsARC and make any adjustments they consider appropriate. 1.4 People whose treatment with ustekinumab is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue ustekinumab until they and their NHS clinician consider it appropriate to stop. **Consideration of the evidence - clinical effectiveness** …The Committee reviewed the overall clinical effectiveness of ustekinumab. It noted that the evidence for the clinical effectiveness of ustekinumab had been taken from 2 randomised placebo-controlled trials (PSUMMIT 1 and 2), and acknowledged the need for head-to-head studies between ustekinumab and TNF-alpha inhibitors for psoriatic arthritis. The Committee considered that the evidence suggested that ustekinumab is more effective than placebo after 24 weeks of treatment across a number of joint, skin and soft tissue outcomes. It considered that, although the effect is likely to persist for up to 1 year, there is some uncertainty about this because in the trials people switched from placebo to ustekinumab at week 24. The Committee heard from the clinical experts that

	ustekinumab appeared to be effective across a wide range of skin and joint outcomes and also soft tissue conditions associated with psoriatic arthritis. The Committee also noted that the results from the PSUMMIT studies suggested there was no statistically significant difference in the clinical effectiveness of ustekinumab compared with placebo between TNF-alpha inhibitor-naive and TNF-alpha inhibitor-exposed populations for the Psoriatic Arthritis Response Criteria (PsARC) response. The Committee concluded that ustekinumab is clinically effective compared with conventional management, in both TNF-alpha inhibitor-naive and TNF-alpha inhibitor-exposed populations, but acknowledged that there remains some uncertainty about the long-term effects of ustekinumab. … The Committee considered the clinical effectiveness of ustekinumab compared with TNF-alpha inhibitors in the TNF-alpha inhibitor-naïve population. The Committee reviewed the findings of the company's mixed treatment comparison and noted that the analysis explored the 3 outcomes used as clinical effectiveness inputs in the economic model (Psoriasis Area and Severity Index [PASI] 75, PASI 90 and PsARC response rates). It discussed this analysis with the clinical experts, and was aware of the limitations of the mixed treatment comparison. The Committee concluded that ustekinumab appeared to be less effective than TNF-alpha inhibitors for PASI 75, PASI 90 and PsARC response, particularly for the joint outcome. The Committee also considered the clinical effectiveness of ustekinumab compared with TNF-alpha inhibitors in the TNF-alpha inhibitor-exposed population. It was aware that there was limited clinical trial evidence in this setting. It understood from comments received during consultation that there is some evidence for the effectiveness of TNF-alpha inhibitors in the TNF-alpha inhibitor-exposed population, but was aware that there was not enough evidence to compare ustekinumab and TNF-alpha inhibitors. The Committee therefore considered the effectiveness of ustekinumab and TNF-alpha inhibitors compared with conventional management. Although in the PSUMMIT trials there was no difference in clinical effectiveness between TNF-alpha inhibitor-naive and TNF-alpha inhibitor-exposed populations in terms of PsARC response, the Committee heard from the clinical experts that evidence presented at a conference suggested that the effectiveness of ustekinumab measured using the American College of Rheumatology (ACR) criteria may decrease with increasing numbers of prior TNF-alpha inhibitors. The clinical experts noted that the diminishing effectiveness of ustekinumab in TNF-alpha inhibitor-exposed populations is broadly consistent with clinical experience with the TNF-alpha inhibitors, which appear to show diminishing effectiveness as the number of prior therapies increases. The Committee heard from the clinical experts that there is some uncertainty about the size of the diminishing effect. The Committee heard estimates for the response rate with second-line TNF-alpha inhibitors ranging from 20% to 70%. Conversely, the Committee noted comments received during consultation from a company that manufactures a comparator drug (including evidence from a randomized controlled trial of certolizumab pegol and open-label and observation studies of adalimumab) that suggested that the lower estimates in this range may be too low. The Committee also considered whether there may be any variation in clinical effectiveness depending on the reason for withdrawal of the first TNF-alpha inhibitor (for example, initial lack of efficacy, gradual loss of efficacy over time or adverse reactions), but it acknowledged that there was not enough evidence for this aspect to be considered further. The Committee concluded that there is still uncertainty about the relative effectiveness of ustekinumab and TNF-alpha inhibitors in people who have previously had TNF-alpha inhibitors. ...

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 20.07.2015**

#	Suchfrage
1	MeSH descriptor: [Arthritis, Psoriatic] explode all trees
2	(Psoriatic* or psoriasis) and arthritis:ti,ab,kw
3	(Psoriatic* or psoriasis) and arthropath*:ti,ab,kw
4	#1 or #2 or #3
5	#4 from 2010 to 2015

SR, HTAs in Medline (PubMed) am 20.07.2015

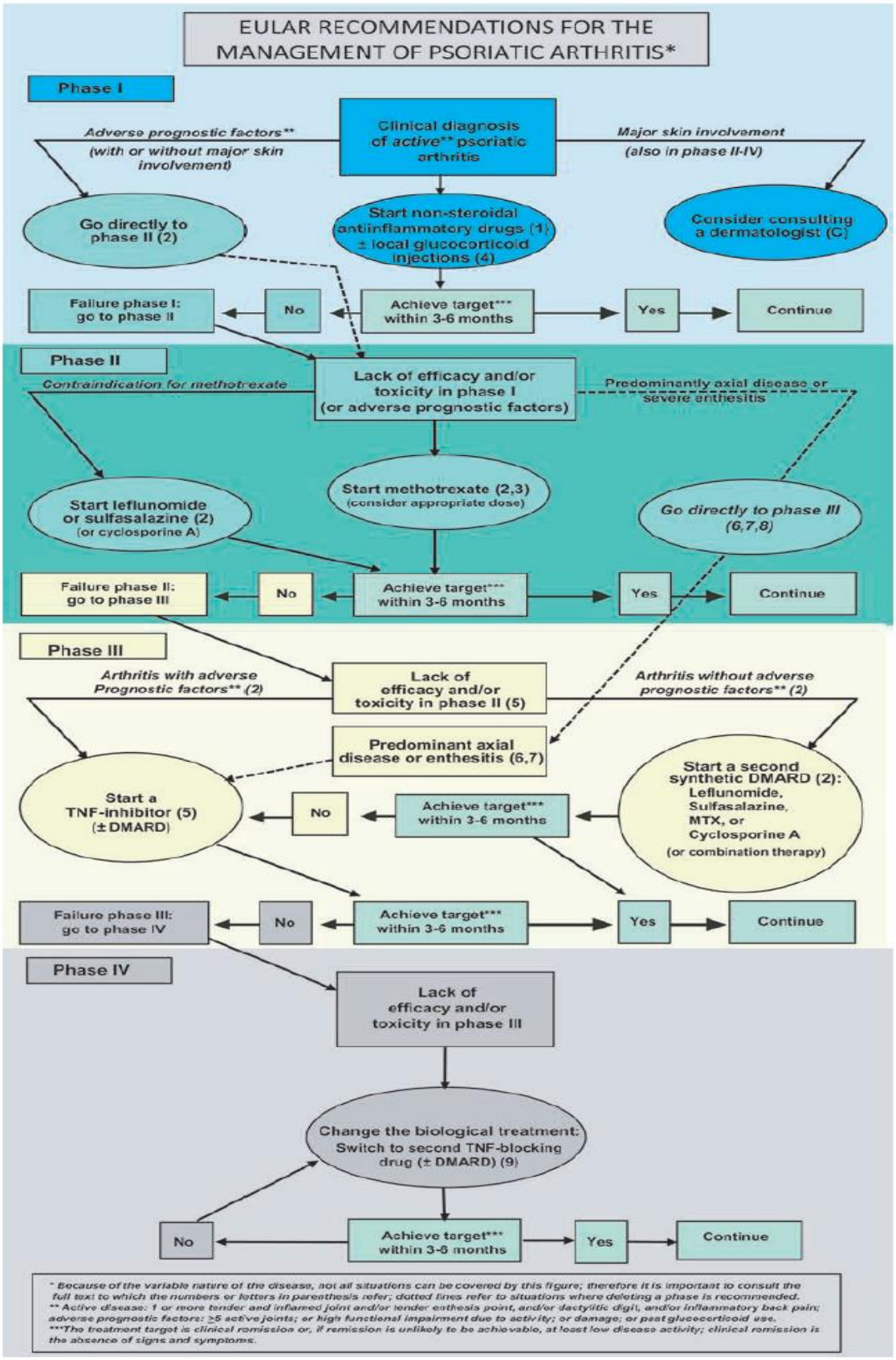
#	Suchfrage
1	Arthritis, Psoriatic[MeSH Terms]
2	(Psoriatic*[Title/Abstract] OR psoriasis[Title/Abstract]) AND arthritis[Title/Abstract]
3	(Psoriatic*[Title/Abstract] OR psoriasis[Title/Abstract]) AND arthropath*[Title/Abstract]
4	#1 OR #2 OR #3
5	(#4) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
6	(#4) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
7	#5 OR #6
8	(#7) AND ("2010/07/01"[PDAT] : "2015/07/20"[PDAT])
9	#8 NOT "The Cochrane database of systematic reviews"[Journal]

Leitlinien in Medline (PubMed) am 20.07.2015

#	Suchfrage
1	Arthritis, Psoriatic[MeSH Terms]
2	(Psoriatic*[Title/Abstract] OR psoriasis[Title/Abstract]) AND arthritis[Title/Abstract]
3	(Psoriatic*[Title/Abstract] OR psoriasis[Title/Abstract]) AND arthropath*[Title/Abstract]
4	#1 OR #2 OR #3
5	((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]
6	#4 AND #5
7	(#6) AND ("2010/07/01"[PDAT] : "2015/07/20"[PDAT])

Anlage

Anlage 1: Therapiealgorithmus EULAR-Leitlinien *Gossec et al. 2012[13]*



Literatur:

1. **Acosta Felquer ML, Coates LC, Soriano ER, Ranza R, Espinoza LR, Helliwell PS, Fitzgerald O, McHugh N, Roussou E, Mease PJ**. Drug therapies for peripheral joint disease in psoriatic arthritis: a systematic review. J Rheumatol 2014; 41 (11): 2277-85.

2. **Agency for Healthcare Research and Quality (AHRQ)**. Drug Therapy for Psoriatic Arthritis in Adults: Update of a 2007 Report (Comparative Effectiveness Review 54). Rockville (USA): AHRQ 2012; http://effectivehealthcare.ahrq.gov/ehc/products/464/1045/CER54_PsoriaticArthritisDrugTherapies_FinalReport_20120601.pdf, Zugriff am 28.07.2015.

3. **Ash Z, Gaujoux-Viala C, Gossec L, Hensor EM, Fitzgerald O, Winthrop K, van der Heijde D, Emery P, Smolen JS, Marzo-Ortega H**. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis 2012; 71 (3): 319-26.

4. **Coates LC, Kavanaugh A, Ritchlin CT**. Systematic review of treatments for psoriatic arthritis: 2014 update for the GRAPPA. J Rheumatol 2014; 41 (11): 2273-6.

5. **Coates LC, Tillett W, Chandler D, Helliwell PS, Korendowych E, Kyle S, McInnes IB, Oliver S, Ormerod A, Smith C, Symmons D, Waldron N, McHugh NJ**. The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics. Rheumatology (Oxford) 2013; 1-17.

6. **Colebatch AN, Marks JL, Edwards CJ**. Safety of non-steroidal anti-inflammatory drugs, including aspirin and paracetamol (acetaminophen) in people receiving methotrexate for inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis). Cochrane Database Syst Rev 2011; (11): CD008872.

7. **Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ**. Methotrexate use and risk of lung disease in psoriasis, psoriatic arthritis, and inflammatory bowel disease: systematic literature review and meta-analysis of randomised controlled trials. BMJ 2015; 350 h1269.

8. **Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ**. Risk of liver injury among methotrexate users: A meta-analysis of randomised controlled trials. Semin Arthritis Rheum 2015.

9. **Dommasch ED, Abuabara K, Shin DB, Nguyen J, Troxel AB, Gelfand JM**. The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials. J Am Acad Dermatol 2011; 64 (6): 1035-50.

10. **Gemeinsamer Bundesausschuss (G-BA)**. Bekanntmachung des Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie/AMR in Anlage 4: Therapiehinweis zu Adalimumab, vom 21. November 2006. Berlin (GER): G-BA 2006; https://www.g-ba.de/downloads/39-261-346/2006-11-21-AMR4-Adalimumab_BAnz.pdf, Zugriff am 17.07.2015.

11. **Gemeinsamer Bundesausschuss (G-BA)**. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie in Anlage 4: Therapiehinweis zu Leflunomid vom 16. August 2007. Berlin (GER): G-BA 2007; https://www.g-ba.de/downloads/40-268-462/2007-08-16-AMR4-Leflunomid_TrG.pdf, Zugriff am 17.07.2015.

12. **Gemeinsamer Bundesausschuss (G-BA)**. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Apremilast, vom 6. August 2015. Berlin (GER): G-BA 2015; https://www.g-ba.de/downloads/40-268-3307/2015-08-06_AM-RL-XII_Apremilast_2015-02-15-D-151_TrG.pdf, Zugriff am 06.08.2015.

13. **Gossec L, Smolen JS, Gaujoux-Viala C, Ash Z, Marzo-Ortega H, van der Heijde D, Fitzgerald O, Aletaha D, Balint P, Boumpas D, Braun J, Breedveld FC, Burmester G, Canete JD, de Wit M, Dagfinrud H, de Vlam K, Dougados M, Helliwell P, Kavanaugh A, Kvien TK, Landewe R, Luger T, Maccarone M, McGonagle D, McHugh N, McInnes IB, Ritchlin C, Sieper J, Tak PP, Valesini G, Vencovsky J, Winthrop KL, Zink A, Emery P**. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. Ann Rheum Dis 2012; 71 (1): 4-12.

14. **Goulabchand R, Mouterde G, Barnetche T, Lukas C, Morel J, Combe B**. Effect of tumour necrosis factor blockers on radiographic progression of psoriatic arthritis: a systematic review and meta-analysis of randomised controlled trials. Ann Rheum Dis 2014; 73 (2): 414-9.

15. **Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)**. Apremilast - Nutzenbewertung gemäß § 35a SGB V: Dossierbewertung (Auftrag A15-09, Version 1.0, Stand: 13.05.2015). Köln (GER): IQWiG 2015; https://www.iqwig.de/download/A15-09_Apremilast_Nutzenbewertung-35a-SGB-V.pdf, Zugriff am 20.07.2015.

16. **Lemos LL, de Oliveira CJ, Almeida AM, Junior HO, Barbosa MM, Kakehasi AM, Acurcio FA**. Treatment of psoriatic arthritis with anti-TNF agents: a systematic review and meta-analysis of efficacy, effectiveness and safety. Rheumatol Int 2014; 34 (10): 1345-60.

17. **Nash P, Lubrano E, Cauli A, Taylor WJ, Olivieri I, Gladman DD**. Updated guidelines for the management of axial disease in psoriatic arthritis. J Rheumatol 2014; 41 (11): 2286-9.

18. **National Institute for Health and Care Excellence**. Golimumab for the treatment of psoriatic arthritis (TA220). London (UK): NICE 2011; http://www.nice.org.uk/guidance/ta220/resources/guidance-golimumab-for-the-treatment-of-psoriatic-arthritis-pdf, Zugriff am 17.07.2015.

19. **National Institute for Health and Care Excellence (NICE)**. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (TA199). London (UK): NICE 2010; http://www.nice.org.uk/guidance/ta199/resources/guidance-etanercept-infliximab-and-adalimumab-for-the-treatment-of-psoriatic-arthritis-pdf, Zugriff am 17.07.2015.

20. **National Institute for Health and Care Excellence (NICE)**. Ustekinumab for treating active psoriatic arthritis (rapid review of technology appraisal guidance 313). London (UK): NICE 2015; http://www.nice.org.uk/guidance/ta340/resources/guidance-ustekinumab-for-treating-active-psoriatic-arthritis-rapid-review-of-technology-appraisal-guidance-313-pdf, Zugriff am 17.07.2015.

21. **Orbai AM, Weitz J, Siegel EL, Siebert S, Savage LJ, Aydin SZ, Luime JJ, Elkayam O, Neerinckx B, Urbancek S, de Vlam K, Ritchlin CT**. Systematic review of treatment effectiveness and outcome measures for enthesitis in psoriatic arthritis. J Rheumatol 2014; 41 (11): 2290-4.

22. **Rodgers M, Epstein D, Bojke L, Yang H, Craig D, Fonseca T, Myers L, Bruce I, Chalmers R, Bujkiewicz S, Lai M, Cooper N, Abrams K, Spiegelhalter D, Sutton A, Sculpher M, Woolacott N**. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess 2011; 15 (10): i-329.

23. **Rose S, Toloza S, Bautista-Molano W, Helliwell PS**. Comprehensive treatment of dactylitis in psoriatic arthritis. J Rheumatol 2014; 41 (11): 2295-300.

24. **Scottish Intercollegiate Guidelines Network (SIGN)**. Diagnosis and management of psoriasis and psoriatic arthritis in adults: A national clinical guideline. Edinburgh (UK): SIGN 2010; (SIGN publication no. 121).http://www.sign.ac.uk/pdf/sign121.pdf, Zugriff 17.07.2015.

25. **Thaler KJ, Gartlehner G, Kien C, Van Noord MG, Thakurta S, Wines RCM, Hansen RA, McDonagh MS**. Drug Class Review: Targeted Immune Modulators: Final Update 3 Report [Internet]. 2012.

26. **Thorlund K, Druyts E, Avina-Zubieta JA, Mills EJ**. Anti-tumor necrosis factor (TNF) drugs for the treatment of psoriatic arthritis: an indirect comparison meta-analysis. Biologics 2012; 6 417-27.

27. **Wendling D, Lukas C, Paccou J, Claudepierre P, Carton L, Combe B, Goupille P, Guillemin F, Hudry C, Miceli-Richard C, Dougados M**. Recommendations of the French Society for Rheumatology (SFR) on the everyday management of patients with spondyloarthritis. Joint Bone Spine 2014; 81 (1): 6-14.

Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: Ankylosierende Spondylitis Secukinumab

Stand: August 2015

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Secukinumab zur Behandlung der aktiven ankylosierenden Spondylitis (Morbus Bechterew)	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*nicht angezeigt*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	*Es liegen keine Beschlüsse vor.*
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Secukinumab L04AC10 Cosentyx®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Ankylosierende Spondylitis Cosentyx ist angezeigt für die Behandlung erwachsener Patienten mit aktiver ankylosierender Spondylitis, die auf eine konventionelle Therapie unzureichend angesprochen haben.
Biologika	
Etanercept L04AB01 Enbrel®	Axiale Spondyloarthritis, Morbus Bechterew (ankylosierende Spondylitis [AS]): Behandlung des schweren aktiven Morbus Bechterew bei Erwachsenen, die unzureichend auf eine konventionelle Behandlung angesprochen haben.
Infliximab L04AB02 Remicade®/ Inflectra®	Ankylosierende Spondylitis Inflectra™ ist indiziert zur Behandlung der schwerwiegenden, aktiven ankylosierenden Spondylitis bei erwachsenen Patienten, die auf eine konventionelle Therapie unzureichend angesprochen haben.
Adalimumab L04AB04 Humira®	Axiale Spondyloarthritis Ankylosierende Spondylitis (AS) Humira ist indiziert zur Behandlung der schweren aktiven ankylosierenden Spondylitis bei Erwachsenen, die nur unzureichend auf eine konventionelle Therapie angesprochen haben.
Golimumab L04AB06 Simponi®	Ankylosierende Spondylitis (AS) Simponi ist angezeigt zur Behandlung der schweren, aktiven ankylosierenden Spondylitis bei Erwachsenen, die auf eine konventionelle Therapie unzureichend angesprochen haben.
Certolizumab Pegol L04AB05. Cimzia ®	*Axiale Spondyloarthritis* Cimzia ist angezeigt fur die Behandlung von erwachsenen Patienten mit schwerer, aktiver axialer Spondyloarthritis, einschlieslich: *Ankylosierende Spondylitis (AS)* Erwachsene mit schwerer, aktiver ankylosierender Spondylitis, die ungenügend auf nichtsteroidale Antiphlogistika (NSAIDs) angesprochen haben oder die eine Intoleranz gegenüber NSAIDs besitzen.

Quellen: AMIS-Datenbank, Fachinformationen

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: Ankylosierende Spondylitis Secukinumab

Auftrag von: Abt. AM

bearbeitet von: Abt. FB Med

Datum: 12.08.2015

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Indikation für die Recherche:

Behandlung erwachsener Patienten mit aktiver ankylosierender Spondylitis (Morbus Bechterew), die auf eine konventionelle Therapie unzureichend angesprochen haben.

Berücksichtigte Wirkstoffe/Therapien:

Übersicht zVT, Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation **„**ankylosierende Spondylitis**“** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 22.07.2015 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), arztbibliothek.de (ÄZQ), AWMF, Clinical Evidence, DAHTA, G-BA, IQWiG, NGC, NICE, TRIP.
Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 372 Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden **88** Quellen eingeschlossen. Insgesamt ergab dies **20** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

AS	ankylosierende Spondylitis / ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
axSpA	axial spondyloarthritis
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
CoI	Conflict of Interest
CRA	Canadian Rheumatology Association
DAHTA	Deutsche Agentur für Health Technology Assessment
ETN	Etanercept
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MRI	magnetic resonance imaging
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
nr-axSpA	nonradiographic axSpA
NSAID	non-steroidal anti-inflammatory drugs
NSAR	nichtsteroidale Antirheumatika
PBO	Placebo
SPARCC	Spondyloarthritis Research Consortium of Canada
TNF	Tumornekrosefaktor
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/ G-BA Beschlüsse

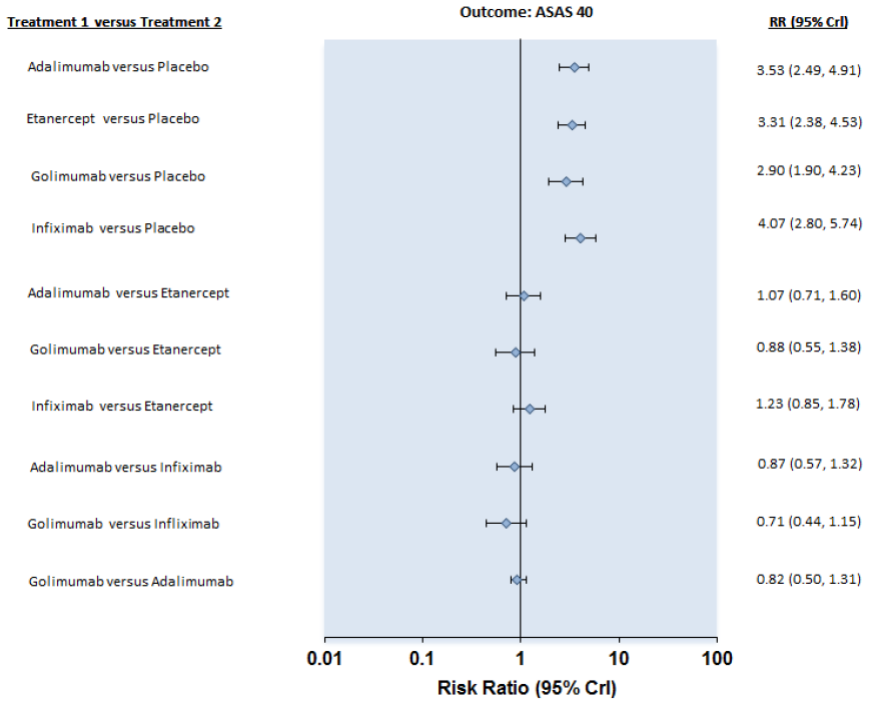
IQWiG Berichte / G-BA Beschlüsse zu möglichen Komparatoren wurden durch die Suche nicht identifiziert.

Maxwell et al., 2015 [13]. **TNF-alpha inhibitors for ankylosing spondylitis**	1. Fragestellung To assess the benefits and harms of adalimumab, etanercept, golimumab, and infliximab (TNF-alpha inhibitors) in people with ankylosing spondylitis.
	2. Methodik Population Patients meeting the following ankylosing spondylitis classification criteria: 1961 Rome, 1966 New York, or modified 1984 New York; no restrictions regarding age, past or present (co-)medication or ankylosing spondylitis-related comorbidity. Subgroups of patients with ankylosing spondylitis as far as the subgroup was properly randomized and outcome measures were available, specifically for the ankylosing spondylitis subgroup. Intervention / Komparator • Adalimumab versus placebo, other medications, or usual care • Etanercept versus placebo, other medications, or usual care. • Golimumab versus placebo, other medications, or usual care. • Infliximab versus placebo, other medications, or usual care. No restrictions with regard to dose or concomitant treatments in the placebo group (for example, physical exercises, or NSAIDs, or both) Endpunkt 1. ASAS40 2. BASFI (Bath Ankylosing Spondylitis Functional Index) 3. ASAS partial remission 4. Magnetic resonance imaging (MRI) for evidence of inflammation 5. Radiographic progression 6. Withdrawals due to adverse events 7. Serious adverse events Suchzeitraum (Aktualität der Recherche) Cochrane Library (2008, Issue 4) including the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Cochrane Library Health Technology Assessment Database (CLHTA), and NHS Economic Evaluation Database (NHS EED); MEDLINE (1966 to January 26, 2009); EMBASE (1980 to January 26, 2009); CINAHL (1982 to January 26, 2009); ISI Web of Knowledge (1900 to January 2009) for the original search; Update search for all databases in October 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 21 (3308 patients) Qualitätsbewertung der Studien: Cochrane risk of bias tool; 2 additional items: Ascertainment of outcome and definition of adverse outcomes
	3. Ergebnisdarstellung

Legende

95% CI = 95% confidence interval; 95% CrI = 95% credible interval; n/a = not applicable; NNTH = Number needed to treat for harm; RR = risk ratio; OR = odds ratio; SI = sacroiliac joint; SPARCC = Spondyloarthritis Research Consortium of Canada
NNT = not applicable for non-statistically significant results
Note: Results for ASAS40, BASFI, ASAS partial remission, withdrawals due to adverse events, and serious adverse events are based on the mixed treatment comparison analyses. The 'All anti-TNF agents versus placebo' results for withdrawals due to adverse events and serious adverse events are based on standard meta-analyses in Review Manager 5.3.
[1] Assumed risk based on the placebo event rate as calculated in the mixed treatment comparison analysis.
[2] Downgraded for imprecision; fewer events than 300 (a threshold rule-of-thumb) and wide confidence interval.
[3] Downgraded for imprecision: total population is <400.
[4] MRI substudy (N = 60 for placebo and 50 mg golimumab arms) conducted at 10/57 participating sites; N = 216 in full RCT; readers were blinded but concerns regarding only modest level of agreement. Downgraded for concerns regarding missing data (12% did not have baseline and follow-up MRIs and imputed 7% of scores at week 14).
[5] Downgraded for imprecision; total population is <400. MRI data available for 194/201 in infliximab group; 72/78 in placebo group.

ASAS40



BASFI (0 to 10 scale)

Intervention and comparison	Illustrative comparative risks		Relative effect (95% CrI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comment
	Assumed risk with comparator[1]	Corresponding risk with intervention (95% CI or CrI)				
	Placebo	TNF-alpha inhibitor				
Adalimumab versus placebo	The mean BASFI in the control groups was **5 points**	The mean BASFI in the intervention groups was **1.6 lower** (2.2 to 0.9 lower)		786 (4 studies)	⊕⊕⊕⊕ **high**	Absolute increased benefit % = -16% (95% CrI -22% to -9%) ; Relative % change from baseline = -32% (-44% to -18%); NNT to achieve the MCID of 0.7 points = 4 (95% CI 3 to 5)
Etanercept (25 mg twice weekly or 50 mg once weekly) versus placebo	The mean BASFI in the control groups was **5 points**	The mean BASFI in the intervention groups was **1.1 lower** (1.6 to 0.6 lower)		553 (6 studies)	⊕⊕⊕⊕ **high**	Absolute increased benefit % =-11% (95% CrI -16% to -6%) ; Relative % change from baseline = -22% (-32% to -12%); NNT to achieve the MCID of 0.7 points = 4 (4 to 6)

Golimumab versus placebo	The mean BASFI in the control groups was **5 points**	The mean BASFI in the intervention groups was **1.5 lower** (2.3 to 0.7 lower)		429 (2 studies)	⊕⊕⊕⊕ **high**	Absolute increased benefit % =-15% (95% Crl -23% to -7%) Relative % change from baseline = -30% (-46% to -14%) NNT to achieve the MCID of 0.7 points = 4 (3 to 5)
Infliximab versus placebo	The mean BASFI in the control groups was **5 points**	The mean BASFI in the intervention groups was **2.1 lower** (2.7 to 1.4 lower)		348 (2 studies)	⊕⊕⊕⊕ **high**	Absolute increased benefit % = -21% (95% Crl -27% to -14%) Relative % change from baseline = -42% (-54% to -28%) NNT to achieve the MCID of 0.7 points = 2 (2 to 3)

ASAS partial remission

Intervention and comparison	Illustrative comparative risks		Relative effect (95% Crl)	Number of participants (studies)	Quality of the evidence (GRADE)	Comment
	Assumed risk with comparator[1]	Corresponding risk with intervention (95% CI or Crl)				
	Placebo	TNF-alpha inhibitor				
Adalimumab versus placebo	**3 per 100**	**19 per 100** (9 to 38)	**RR 6.28** (3.13 to 12.78)	659 (2 studies)	⊕⊕⊕○ **moderate**[2]	Absolute increased benefit % = 16% (95% Crl 6% to 35%) Relative % change = 528% (95% CI 213% to 1178%) NNT = 7 (95% CI 3 to 16)
Etanercept (25 mg twice weekly or 50 mg once weekly) versus placebo	**3 per 100**	**13 per 100** (7 to 24)	**RR 4.24** (2.31 to 8.09)	785 (3 studies)	⊕⊕⊕○ **moderate**[2]	Absolute increased benefit % = 10% (95% Crl 4% to 21%) Relative % change = 324% (95% CI 131% to 709%); NNT = 11 (95% CI 5 to 26)
Golimumab versus placebo	**3 per 100**	**16 per 100** (6 to 44)	**RR 5.18** (1.90 to 14.79)	216 (1 study)	⊕⊕⊕○ **moderate**[2]	Absolute increased benefit % = 13% (95% Crl 3% to 41%) Relative % change = 418% (95% CI 90% to 1379%); NNT = 8 (95% CI 3 to 38)
Infliximab versus placebo	**3 per 100**	**47 per 100** (16 to 90)	**RR 15.41** (5.09 to 47.98)	348 (2 studies)	⊕⊕⊕○ **moderate**[2]	Absolute increased benefit % = 44% (95% Crl 13% to 87%) Relative % change = 1441% (95% CI 409% to 4698%) NNT = 3 (95% CI 2 to 8)

MRI of spinal inflammation

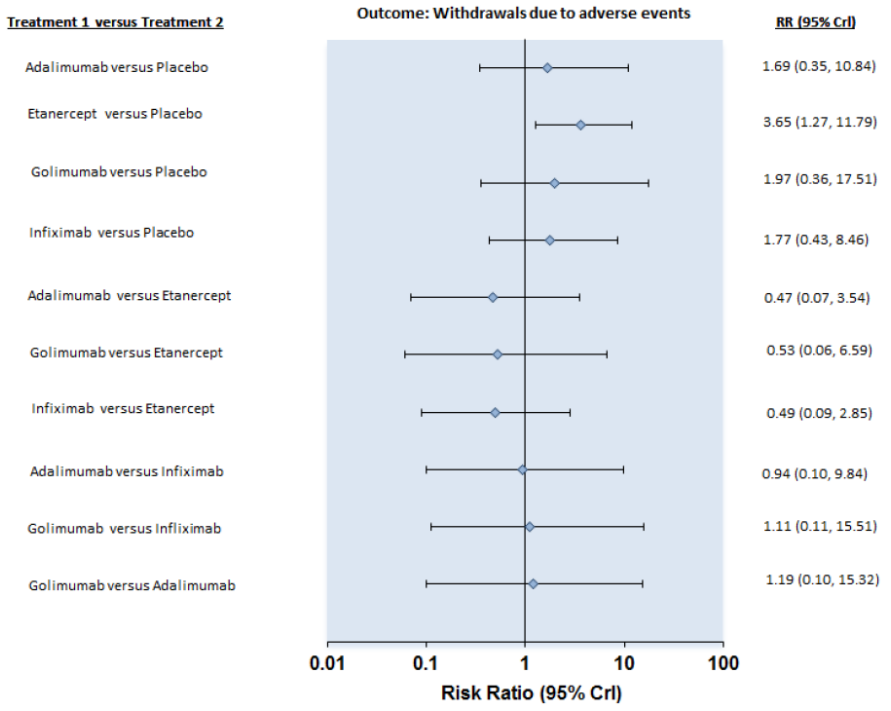
Intervention and comparison	Illustrative comparative risks		Relative effect (95% Crl)	Number of participants (studies)	Quality of the evidence (GRADE)	Comment
	Assumed risk with comparator[1]	Corresponding risk with intervention (95% CI or Crl)				
	Placebo	TNF-alpha inhibitor				
Adalimumab versus placebo Lumbar spine MRI; SPARCC score (0 to 108)	The mean SPARCC score in the control groups was **16.1**	The mean SPARCC score in the intervention groups was **6.5 lower** (13.06 to 0.06 higher)		46 (1 study)	⊕⊕⊕○ **moderate**[3]	Absolute increased benefit % = -6% (95% CI -12% to 0.05%) Relative % change = -33% (95% CI -66% to 0%) NNT = n/a 2nd study with MRI data: Lambert 2007 (N = 82): % change from baseline in SPARCC

						score, week 12 (no variance provided) 1. Spine: Adalimumab group = 53.6% mean decrease Placebo group = 9.4% mean increase Between group: P <0.001 2. Sacroiliac joint, % mean decrease: Adalimumab group = 52.9%, Placebo group = 12.7% Between group: P = 0.017
Etanercept (25 mg twice weekly or 50 mg once weekly) versus placebo	See comment	See comment	Not estimable	0 (0)	See comment	No studies assessed this outcome
Golimumab versus placebo Change from baseline in AS spine MRI activity score (0 to 138; lower means less erosions or edema)	The mean change in the control group was **-2.5 points**	The mean change in the golimumab group was **3.4 points lower (7.7 to 0.90 points lower)**		60 (1 study)	⊕⊕◯◯ **low**[3,4]	Absolute increased benefit % = -2.5% (95% CI -5.6% to -0.7%) Relative % change = -35% (95% CI -80% to 9%) NNT = n/a
Infliximab versus placebo Change from baseline in AS spine MRI activity score (0 to 138; lower means less erosions or edema)	The mean change in the control group was **-0.6 points**	The mean change in the infliximab group was **4.4 points lower (5.6 to 3.3 points lower)**		266 (1 study)	⊕⊕⊕◯ **moderate**[5]	Absolute increased benefit % = -3% (95% CI -4% to -2.4%) Relative % change = -62% (95% CI -79% to -46%) NNT = 3 (95% CI 3 to 5) Inman 2010 assessed MRI in a substudy (N = 26): ' ' when the evaluation was based on the entire spine (23 DVU score), the infliximab group had a mean reduction of 57.2% compared to 3.4% in the placebo group (P <0.001)"

Radiographic progression

Intervention and comparison	Illustrative comparative risks		Relative effect (95% CrI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comment
	Assumed risk with comparator[1]	Corresponding risk with intervention (95% CI or CrI)				
	Placebo	TNF-alpha inhibitor				
Adalimumab versus placebo	See comment	See comment	Not estimable	0 (0)	See comment	No studies assessed this outcome
Etanercept (25 mg twice weekly or 50 mg once weekly) versus placebo	See comment	See comment	Not estimable	0 (0)	See comment	No studies measured this outcome
Golimumab versus placebo	See comment	See comment	Not estimable	0 (0)	See comment	No studies measured this outcome
Infliximab versus placebo	See comment	See comment	Not estimable	0 (0)	See comment	Braun 2002 (N = 60) used the Bath Ankylosing Spondylitis Radiology Index (BASRI) to measure radiographic progression but detailed data was not provided. The results stated the ' ' initial degree of radiological axial changes assessed by the BASRIs was similar in both groups"

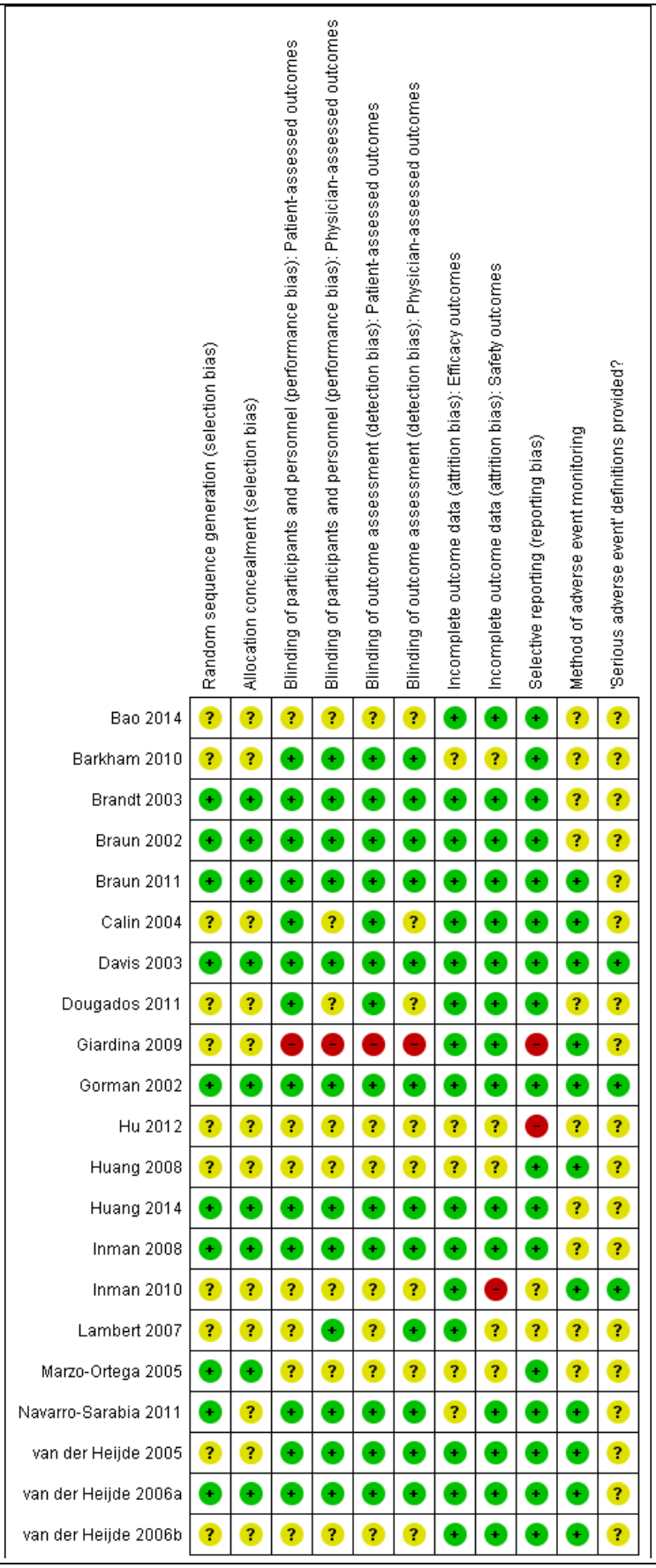
Withdrawals due to adverse events



Serious adverse events

Intervention and comparison	Illustrative comparative risks		Relative effect (95% CrI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comment
	Assumed risk with comparator[1]	Corresponding risk with intervention (95% CI or CrI)				
	Placebo	TNF-alpha inhibitor				
Adalimumab versus placebo	**15 per 1000**	**14 per 1000** (4 to 59)	**RR 0.92** (0.26 to 3.93)	659 (2 studies)	⊕⊕⊕○ **moderate**[2]	Absolute increased harm %= -0.2% (95% CrI -1.1% to 4.4%); Relative % change= -8% (95% CI -74% to 293%); NNT = n/a
Etanercept (25 mg twice weekly or 50 mg once weekly) versus placebo	**15 per 1000**	**25 per 1000** (11 to 56)	**RR 1.69** (0.76 to 3.72)	1061 (8 studies)	⊕⊕⊕○ **moderate**[2]	Absolute increased harm % = 1% (95% CrI -0.4% to 4.1%) Relative % change = 67% (95% CI -27% to 282%) NNT = n/a
Golimumab versus placebo	**15 per 1000**	**10 per 1000** (2 to 50)	**RR 0.69** (0.15 to 3.32)	216 (1 study)	⊕⊕⊕○ **moderate**[2]	Absolute increased harm % = -0.5% (95% CrI -1.3% to 3.5%); Relative % change= -31% (95% CI -85% to 232%); NNT = n/a
Infliximab versus placebo	**15 per 1000**	**38 per 1000** (11 to 166)	**RR 2.53** (0.76 to 11.09)	422 (3 studies)	⊕⊕⊕○ **moderate**[2]	Absolute increased harm % = 2.3% (95% CrI -0.4% to 15.1%) Relative % change = 153% (95% CI -24% to 1009%) NNT = n/a
All anti-TNF agents versus placebo	**15 per 1000**	**22 per 1000** (13 to 36)	**Peto OR 1.45** (0.85 to 2.48)	2408 (15 studies)	⊕⊕⊕○ **moderate**[2]	Absolute increased harm % = 1% (95% CI 0% to 2%) Relative % change = 41% (95% CI -15% to 136%) NNTH = n/a

Critical appraisal



4. Anmerkungen/Fazit der Autoren

There is moderate to high quality evidence that anti-TNF agents improve clinical symptoms in the treatment of ankylosing spondylitis. More participants withdrew due to adverse events when on an anti-TNF agent but we did not find evidence of an

	increase in serious adverse events, though event rates were low and trials had a short duration. The short-term toxicity profile appears acceptable. Based on indirect comparison methodology, we are uncertain whether there are differences between anti-TNF agents in terms of the key benefit or harm outcomes. 5. Hinweise durch FB Med Die verschiedenen Primärstudien haben Patienten mit unterschiedlicher Vor- und Begleitbehandlung eingeschlossen. Declarations of interest: AB: Grants: to department only: Abbvie, Pfizer, Merck, Amgen Travel support to department: Janssen-Cilag; Honorarium: part to department, part personally: Pfizer, UCB, Janssen-Cilag, Abbvie JAS: received research grants from Takeda and Savient and consultant fees from Savient, Takeda, Regeneron and Allergan. JAS is a member of the executive of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 36 companies; a member of the American College of Rheumatology's Guidelines Subcommittee of the Quality of Care Committee; and a member of the Veterans Affairs Rheumatology Field Advisory Committee. PT: grants/honoraria from Bristol Myers, Chiltern International, and UCB.
Kroon et al., 2015 [9]. **Non-steroidal anti-inflammatory drugs (NSAIDs) for axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis)**	1. Fragestellung To assess the benefit and harm of NSAIDs in controlling disease activity, symptoms and radiographic progression in patients with axial spondyloarthritis (axSpA).
	2. Methodik Population Adults aged ≥ 18 years with a clinical diagnosis of axSpA, or patients fulfilling modified New York criteria or ASAS axial SpA criteria, including nr-axSpA and AS. We included both disease subgroups. Intervention / Komparator We included studies that evaluated NSAIDs and all possible variations (dosage, intensity, mode of delivery, duration of delivery, timing of delivery, traditional and COX-2 selective). Comparators were: 1. Placebo; 2. No therapy; 3. Another NSAID; 4. Other pharmacological therapy; 5. Non-pharmacological therapy; 6. Combination therapy; 7. Different doses, modes of delivery, frequency and duration. Endpunkt

Primary outcomes

- Pain (as assessed by the mean change in pain score on a visual analogue scale (VAS) or numerical rating scale (NRS)); back pain was used but if not present in a study, overall pain was used;
- Total number of withdrawals due to adverse events;
- Disease activity as assessed by the mean improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI);
- Physical function as assessed by the mean improvement in Bath Ankylosing Spondylitis Functional Index (BASFI);
- Spinal mobility as assessed by the mean improvement in the Bath Ankylosing Spondylitis Metrology Index (BASMI);
- Radiographic progression as assessed by the mean change in the modified Stoke Ankylosing Spondylitis Spinal Score
- Number of serious adverse events.

Lots of further secondary outcomes

Suchzeitraum (Aktualität der Recherche)

MEDLINE (1946 to June 2014), EMBASE (1980 to June 2014), the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library (Issue 6, 2014)

Anzahl eingeschlossene Studien/Patienten (Gesamt):

31 Studien (Patienten: k. A.)

Qualitätsbewertung der Studien:

Cochrane risk of bias tool

3. Ergebnisdarstellung

Traditional NSAIDs compared with placebo for axSpA (AS and nr-axSpA)

Patient or population: patients with axSpA (AS and nr-axSpA)
Settings: outpatient, hospital
Intervention: traditional NSAID
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Traditional NSAID				
Pain on VAS Scale from 0 to 100 mm (higher is worse) Follow-up: 2 to 6 weeks	The mean pain score in the control group was **61 points**[1]	The mean pain scores in the intervention groups was **16.5 points lower** (12.2 to 20.8 lower)		850 (four studies)	⊕⊕⊕⊕ **high**	Absolute percent difference: **17% lower** (12% to 21% lower) Relative percent change from baseline: **21% lower** (16% to 27% lower)[2] NNT: 4 (3 to 6)[3]
Withdrawals due to adverse events Due to adverse events Follow-up: 2 to 12 weeks	**52 per 1000**[4]	**39 per 1,000** (24 to 63)	**RR 0.75** (0.46 to 1.21)	1165 (five studies)	⊕⊕⊕⊕ **high**	Absolute percent difference: **0% more** (3% less to 2% more) Relative percent difference from baseline: **decrease 25%** (54% decrease to 21% increase)
BASDAI Scale from 0 to 100 (higher is worse) Follow-up: 6 weeks	The mean BASDAI in the control group was **54.7 points**	The mean BASDAI in the intervention group was **17.5 points lower** (11.8 to 23.1 lower)		190 (one study)	⊕⊕⊕○ **moderate**[5]	Absolute percent difference: **18% lower** (12% to 23% lower) Relative percent change from baseline: **28% lower**

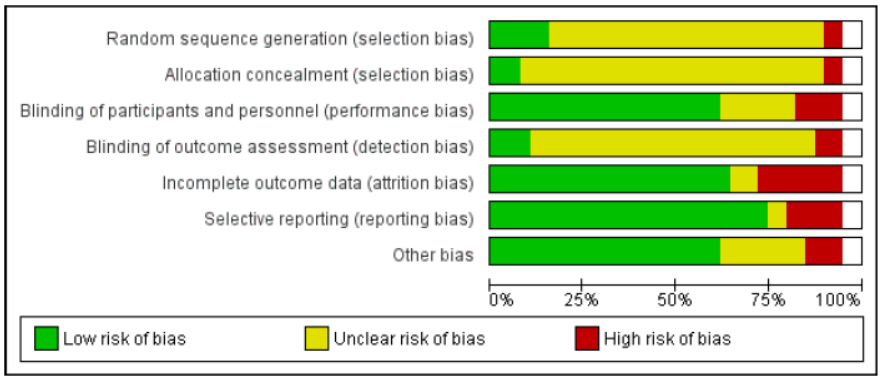
						(19% to 37% lower)[6] NNT: 3 (2 to 4)[7]
BASFI Scale from 0 to 100 (higher is worse) Follow-up: 6 weeks	The mean BASFI in the control groups was **50.0 points**[8]	The mean BASFI in the intervention groups was **9.1 points lower** (5.1 to 13.0 lower)		356 (two studies)	⊕⊕⊕⊕ **high**	Absolute percent difference: **9% lower** (5% to 13% lower) Relative percent change from baseline: **17% lower** (9% to 24% lower)[9] NNT: 5 (3 to 8)[10]
BASMI Scale from 0 to 10 (higher is worse)	See comment	See comment		See comment	See comment	None of the trials included in this comparison reported BASMI
Radiographic progression Mean change in mSASSS. Scale from 0 to 72 (higher is worse)	See comment	See comment		See comment	See comment	None of the trials included in this comparison reported mSASSS
Number of serious adverse events Follow-up: 6 to 12 weeks	**2 per 1000**[11]	**3 per 1,000** (1 to 16)	**RR 1.69** (0.36 to 7.97)	671 (three studies)	⊕⊕⊕◯ **moderate**[12]	Absolute percent difference: **0% more** (1% less to 2% more) Relative percent change from baseline: **increase 69%** (64% decrease to 697% increase)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; RR: risk ratio; NSAID: non-steroidal anti-inflammatory drug; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; VAS: Visual Analogue Scale

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Assumed risk based on mean control group final values taken from Dougados 1994; van der Heijde 2005.
[2] Estimated relative changes based on mean (SD) pain on VAS in placebo group at baseline 77.22 (15.24) from van der Heijde 2005.
[3] Based on MCID of 15 points on a 0 to 100 point scale.
[4] Assumed risk based on the median risk in the control groups.
[5] Downgraded due to potential imprecision due to data available only from a single study (N = 190).
[6] Estimated relative changes based on mean (SD) BASDAI in placebo group at baseline 61.78 (18.70) from van der Heijde 2005.
[7] Based on MCID of 10 points on a 0 to 100 point scale.
[8] Assumed risk based on the control group final values from van der Heijde 2005.
[9] Estimated relative changes based on mean (SD) BASFI in placebo group at baseline 54.12 (26.99) from van der Heijde 2005.
[10] Based on MCID of 10 points on a 0 to 100 point scale.
[11] Assumed risk based on the mean risk in the control groups.
[12] Downgraded due to potential imprecision because the 95% CI includes 'no effect' and the upper confidence limit also crosses 'appreciable harm'.
Since the studies included in the analyses of this comparison were more high quality studies compared to the other included studies in the review, it was decided not to downgrade the evidence for study limitations (as assessed in the risk of bias), as the authors believe this did not importantly affect the quality of the evidence of this comparison.

Critical appraisal



4. Anmerkungen/Fazit der Autoren

   High to moderate quality evidence indicates that both traditional and COX-2 NSAIDs are efficacious for treating axSpA, and moderate to low quality evidence indicates harms may not differ from placebo in the short term. Various NSAIDs are equally effective. Continuous NSAID use may reduce radiographic spinal progression, but this requires confirmation.

5. Hinweise durch FB Med

   Keine einheitliche Angabe zu Vor- oder Begleitbehandlungen;
   Keine Selektion von Patienten mit ankylosierender Spondylitits (Einschlusskriterium: axiale Spondyloarthritis)

Escalas et al., 2010 [5].

Evaluation of the treatment effect of NSAIDs/TNF blockers according to different domains in ankylosing spondylitis: results of a meta-analysis

1. Fragestellung

To assess the treatment effect of NSAIDs and TNF blockers in AS according to different domains of interest.

2. Methodik

Population

Patients with ankylosing spondylitis defined according to the modified New York criteria

Intervention / Komparator

control group receiving placebo and an active group receiving any NSAIDs or TNF blockers

Endpunkt

at least one of the following domains: pain, disease activity, physical function, patient's global assessment, spinal mobility, morning stiffness, fatigue or acute-phase reactants

Suchzeitraum (Aktualität der Recherche)

Medline (from 1966 to October 2009), Embase (from 1990 to November 2009) and the Cochrane central register of controlled trials (Cochrane Library 2009, issue 2)

Anzahl eingeschlossene Studien/Patienten (Gesamt):

13 studies (8 for TNF blockers, 5 for NSAID)

Qualitätsbewertung der Studien:

Jadad score

3. Ergebnisdarstellung

Fig. 2 Efficacy of TNF blockers/NSAIDs in AS for the outcome 'Pain'. ETN: etanercept.

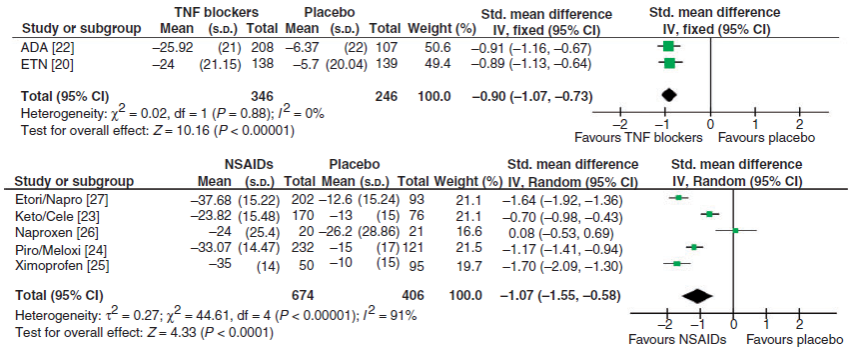
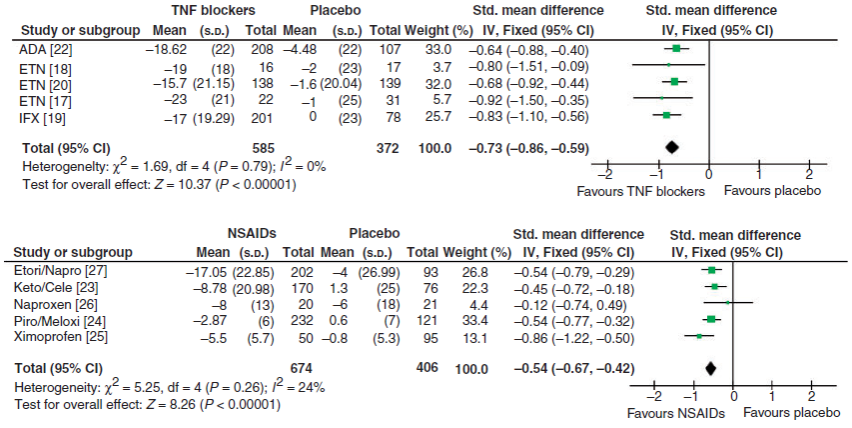


Fig. 3 Efficacy of TNF blockers/NSAIDs in AS for the outcome 'Function'. ETN: etanercept; IFX: infliximab.



Hohe Heterogenität (I^2 = 91%) bei der Analyse von NSAID für das Outcome ‚pain'

Fig. 4 Efficacy of TNF blockers/NSAIDs in AS for the outcome 'Acute-phase reactants'. ETN: etanercept; IFX: infliximab.

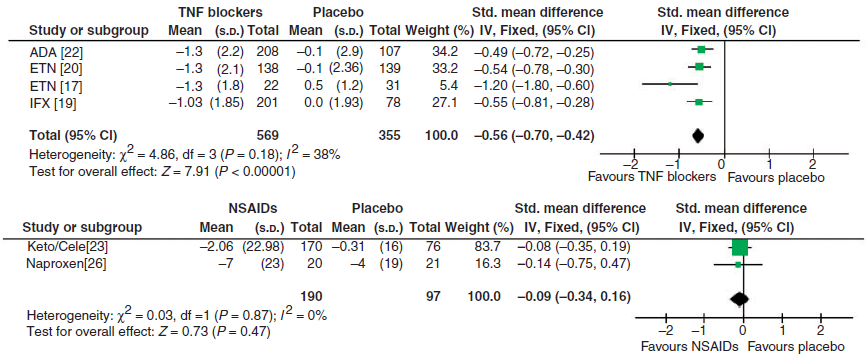


Table 3 Pooled effect sizes of TNF blockers/NSAIDs on each domain

Domains	TNF blockers			NSAIDs		
	No. of studies	No. of patients	Effect size (95% CI)	No. of studies	No. of patients	Effect size (95% CI)
Pain	2	592	−0.9 (−1.07, −0.73)	5	1080	−1.07 (−1.55, −0.58)
Physical function	5	957	−0.73 (−0.86, −0.59)	5	1080	−0.54 (−0.67, −0.42)
Acute-phase reactants	4	924	−0.56 (−0.70, −0.42)	2	287	−0.09 (−0.34, 0.16)
Global assessment	5	837	−1.44 (−1.73, −1.15)	3	894	−0.90 (−1.27, −0.54)
Spinal mobility	5	1266	0.21 (− 0.09, 0.50)	4	785	0.14 (−0.01, 0.29)
Morning stiffness	1	40	−1.04 (−1.70, −0.37)	4	785	−0.44 (−0.72, −0.17)

Critical appraisal

The mean Jadad score was 4.4 (range 3–5) for the TNF blocker studies and 3.8 (range 1–5) for the NSAID studies. Two studies [15, 26] differed from the others by a low methodological quality.

4. Anmerkungen/Fazit der Autoren

This study suggests that the treatment effect of NSAIDs and anti-TNF are both of relevant magnitude considering the main patient-reported outcomes but with a trend in favour of anti-TNF despite the fact that such drugs are given on top of NSAIDs in refractory patients. Moreover, a statistically significant difference was observed for the domain 'acute-phase reactants' confirming the specificity of such drug category.

5. Hinweise durch FB Med

Keine Angabe zu Vor- oder Begleitbehandlungen

Acknowledgements: Abbott France pharmaceutical company provided support by organizing a meta-analysis methods workshop but played no further role in the project.

Disclosure statement: M.D. has acted as a consultant in advisory boards organized by Pfizer, BMS, Abbott, Roche and UCB.

Fouque-Aubert et al., 2010 [7].

Serious infections in patients with ankylosing spondylitis with and without TNF blockers: a

1. Fragestellung

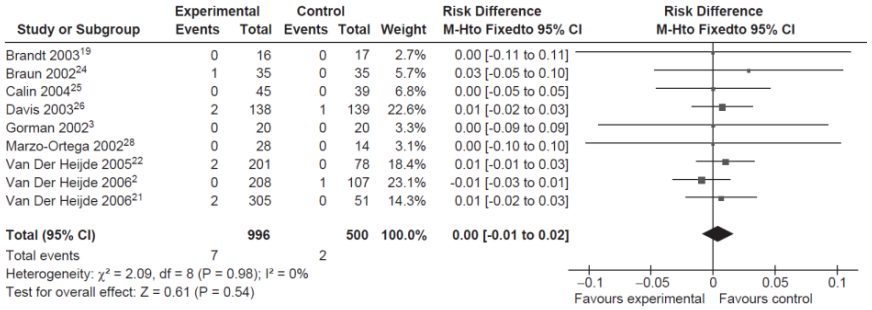
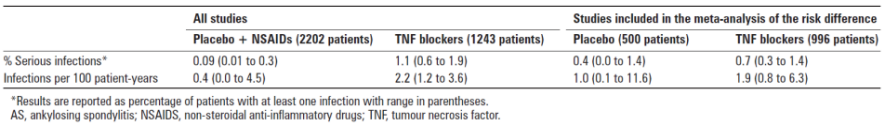
To assess serious infections in patients with AS not exposed and exposed to TNF blockers.

2. Methodik

Population

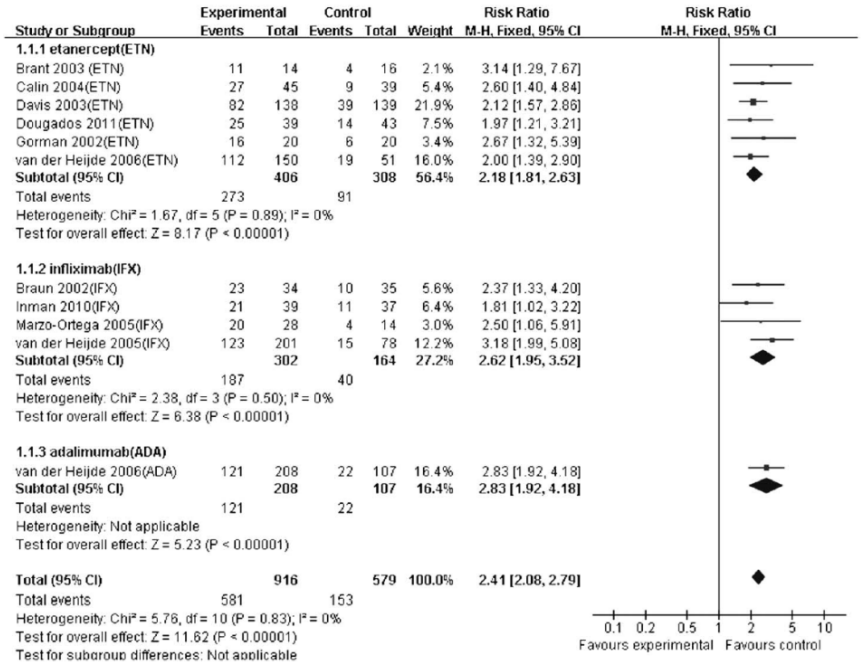
adult populations with AS fulfilling modified New York classification criteria for AS

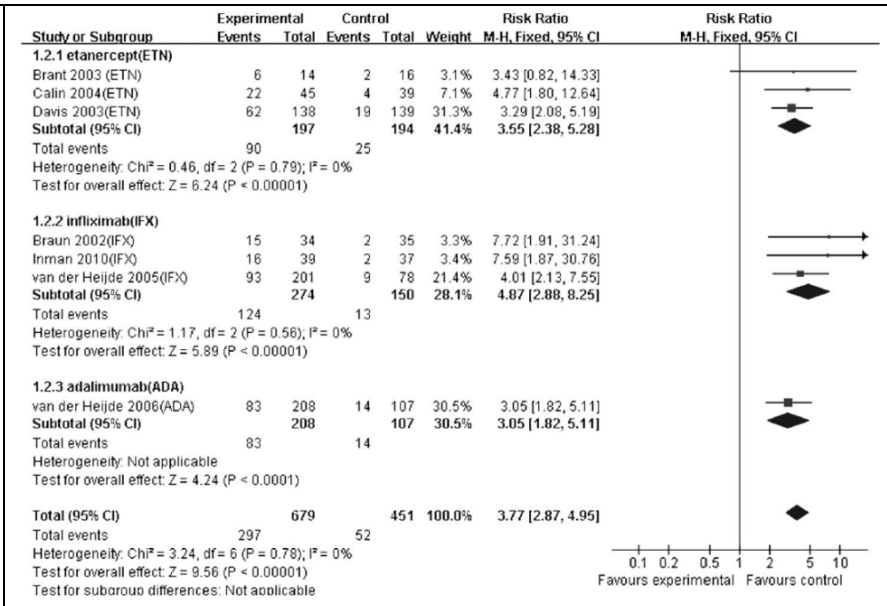
Intervention / Komparator

systematic review and meta-analysis of randomized placebo-controlled trials	NSAIDs or TNF blockers as intervention; placebo or no placebo as control *Endpunkt* serious infections *Suchzeitraum (Aktualität der Recherche)* PubMed (1995 - 9 May 2008) and EMBASE (1995 - 23 March 2007); Cochrane Central Register of Controlled Trials *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 14 trials (3445 patients) *Qualitätsbewertung der Studien:* Jadad Scale
	3. Ergebnisdarstellung Risk of serious infections with tumour necrosis factor blockers versus placebo  Serious infections in patients with AS  *Critical appraisal* The quality of the articles met the required standards (mean Jadad, 3.6 ± 1.0).
	4. Anmerkungen/Fazit der Autoren The absolute risk of serious infections in patients with AS not exposed to TNF blockers is low. The absolute risk of serious infections in patients receiving TNF blockers is higher, but the difference was found to be not significant, possibly through lack of power. Continued monitoring is necessary. 5. Hinweise durch FB Med Keine Angabe zu Vor- oder Begleitbehandlungen
Ren et al., 2013 [14]. **Efficacy of Antitumor Necrosis Factor(a) Agents on Patients With Ankylosing Spondylitis**	1. Fragestellung This study was designed to investigate the efficacy of antitumor necrosis factor (TNF)α agents (etanercept, infliximab, golimumab or adalimumab) in ankylosing spondylitis (AS).
	2. Methodik *Population* patients with AS *Intervention / Komparator* anti-TNFα agents (etanercept, infliximab, golimumab or adalimumab) with placebo

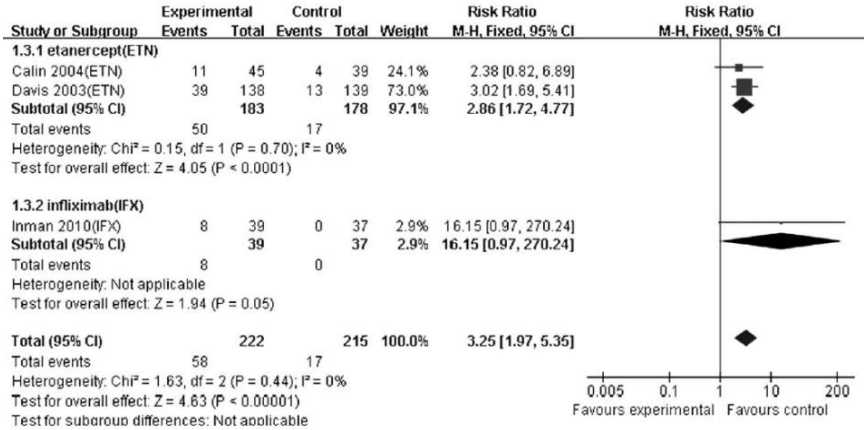
	All studies		Studies included in the meta-analysis of the risk difference	
	Placebo + NSAIDs (2202 patients)	TNF blockers (1243 patients)	Placebo (500 patients)	TNF blockers (996 patients)
% Serious infections*	0.09 (0.01 to 0.3)	1.1 (0.6 to 1.9)	0.4 (0.0 to 1.4)	0.7 (0.3 to 1.4)
Infections per 100 patient-years	0.4 (0.0 to 4.5)	2.2 (1.2 to 3.6)	1.0 (0.1 to 11.6)	1.9 (0.8 to 6.3)

*Results are reported as percentage of patients with at least one infection with range in parentheses.
AS, ankylosing spondylitis; NSAIDS, non-steroidal anti-inflammatory drugs; TNF, tumour necrosis factor.

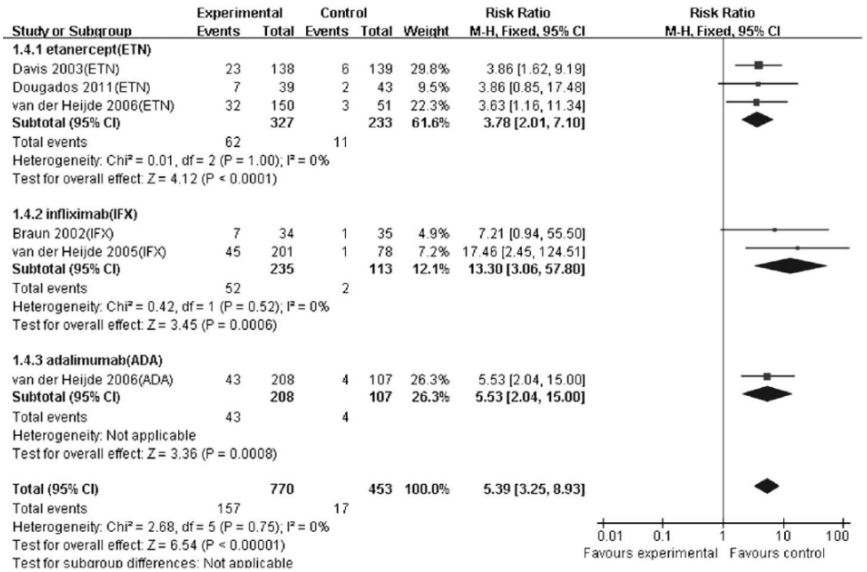
	Endpunkt primary outcome (ASAS 20 responders) secondary outcomes (The ASAS 50/70 responders and partial remission, C reactive protein [CRP] and erythrocyte sedimentation rate [ESR], Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]/Bath Ankylosing Spondylitis Functional Index [BASFI]/total back pain and adverse event) *Suchzeitraum (Aktualität der Recherche)* The Cochrane Central Register of Controlled Trials in the Cochrane Library, MEDLINE, Embase, Science Citation Index Expanded and the meta-register of controlled trials were searched until March 2012 *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 12 trials (1851 patients) *Qualitätsbewertung der Studien:* risk of bias was assessed according to the guidelines of the Cochrane Collaboration and the Cochrane Hepato-Biliary Group Module
	3. Ergebnisdarstellung *Meta-analysis of the rate of the ASAS20 responders*  *Meta-analysis of the rate of the ASAS50 responders*



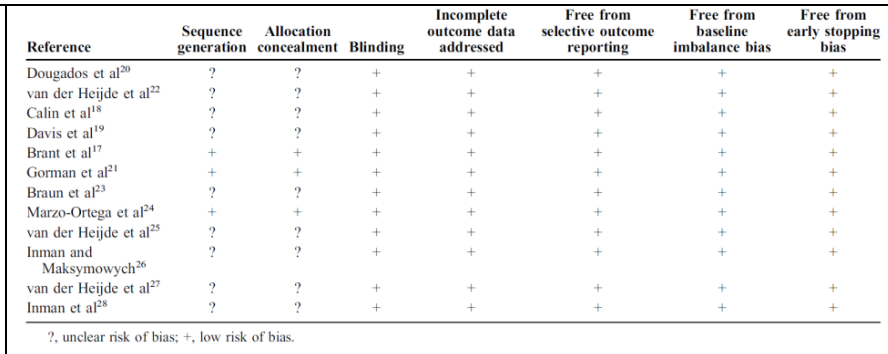
Meta-analysis of the rate of the ASAS70 responders

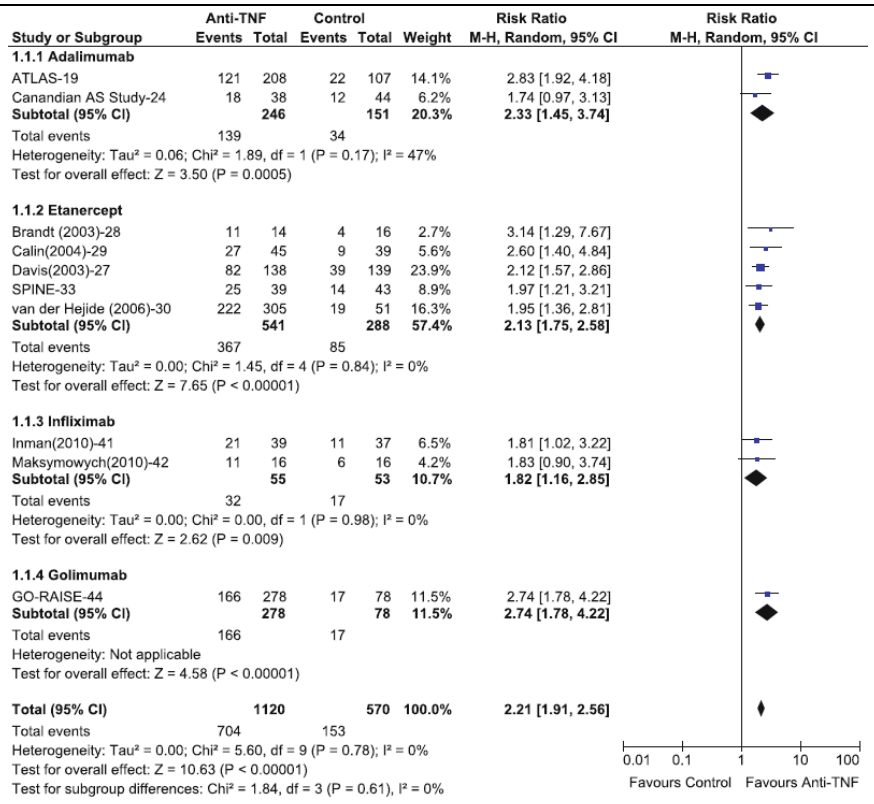


Meta-analysis of the rate of patients with partial remission



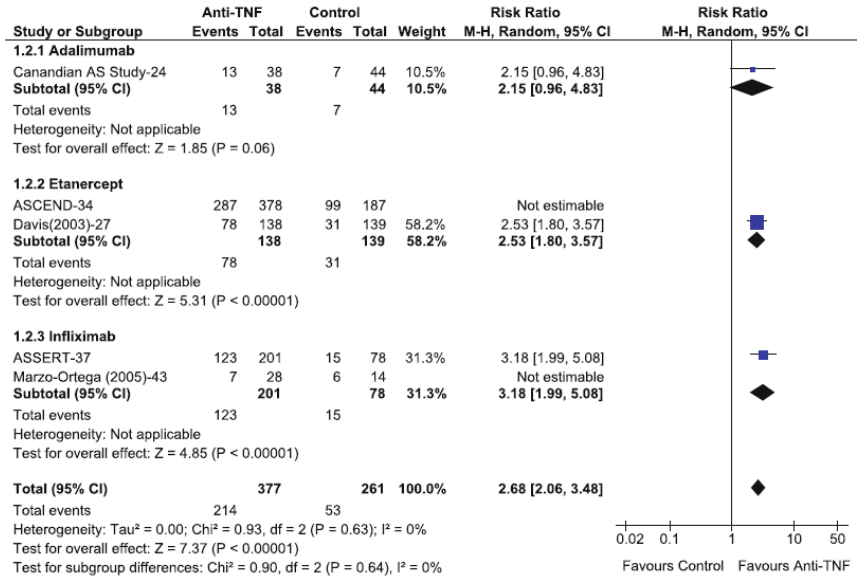
Critical appraisal

	 ?, unclear risk of bias; +, low risk of bias.
	4. Anmerkungen/Fazit der Autoren Anti-TNFα agents is an effective and well-tolerated treatment for reducing clinical symptoms of AS. 5. Hinweise durch FB Med Keine Angabe zu Vor- oder Begleitbehandlungen Die X-Achsen der Metaanalysen sind nicht korrekt benannt. Bei allen Metaanalysen führt die Intervention zu besseren Outcomes als die Kontrolle.
Machado et al., 2013 [12]. **Treatment of ankylosing spondylitis with TNF blockers: a meta-analysis**	1. Fragestellung To evaluate the efficacy and safety of the anti-TNF agents infliximab, etanercept, adalimumab, golimumab, and certolizumab for the treatment of ankylosing spondylitis.
	2. Methodik *Population* adult patients diagnosed with active AS, as defined by the modified New York criteria *Intervention / Komparator* studies comparing treatment with infliximab, etanercept, adalimumab, golimumab, and certolizumab either alone or in combination with other medications, against control groups. *Endpunkt* primary outcome was the ASAS 20 response secondary outcomes were the ASAS 40 response, the ASAS 5/6 response, partial remission according to ASAS criteria, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the BASDAI 50 response, the Bath Ankylosing Spondylitis Functional Index (BASFI), the Bath Ankylosing Spondylitis Metrology Index (BASMI), withdraws and safety outcomes *Suchzeitraum (Aktualität der Recherche)* EMBASE, MEDLINE, Cochrane Controlled Trials Register, and LILACS (September/2012) *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 27 Artikel (Patienten: k. A.) *Qualitätsbewertung der Studien:* modified Jadad scale (score ranging from 0 to 6)
	3. Ergebnisdarstellung Meta-analysis of ASAS 20 responses after 12 weeks of follow-up



Meta-analysis of ASAS 20 responses after 24 weeks of follow-up

The ASCEND and Marzo-Ortega et al. studies have been excluded from the meta-analysis because of the statistical heterogeneity



Meta-analysis of efficacy outcomes after 12/14 and 24 weeks

Outcome	Studies	Participants	Relative risk (CI 95 %)[a]	I^2 (%)[b]	p value[c]
Up to 12/14 weeks[d]					
ASAS 40 response	5 [19, 30, 33, 41, 42]	861	2.77 (2.05; 3.75)	0	0.45
ASAS 5/6 response	4 [19, 30, 33, 41]	829	3.52 (2.17; 5.71)	36	0.20
Partial remission	4 [19, 28, 30, 33]	783	4.79 (2.46; 9.34)	0	0.92
Up to 24 weeks					
ASAS 40 response	3 [19, 37, 40, 44]	629	3.32 (2.44; 4.51)	0	0.92
ASAS 5/6 response	3 [19, 37, 40]	627	4.25 (2.80; 6.46)	0	0.50
Partial remission	4 [19, 27, 37, 40]	905	4.43 (2.62; 7.49)	0	0.51

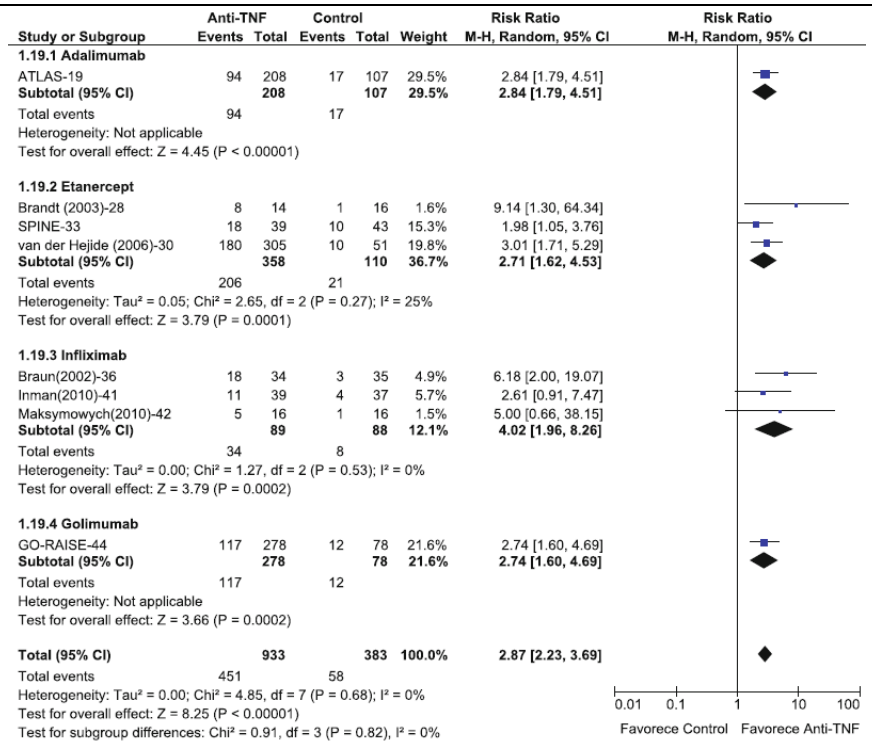
[a] CI 95 %: 95 % confidence interval

[b] A value of $I^2 > 40$ % indicates statistical heterogeneity between the studies

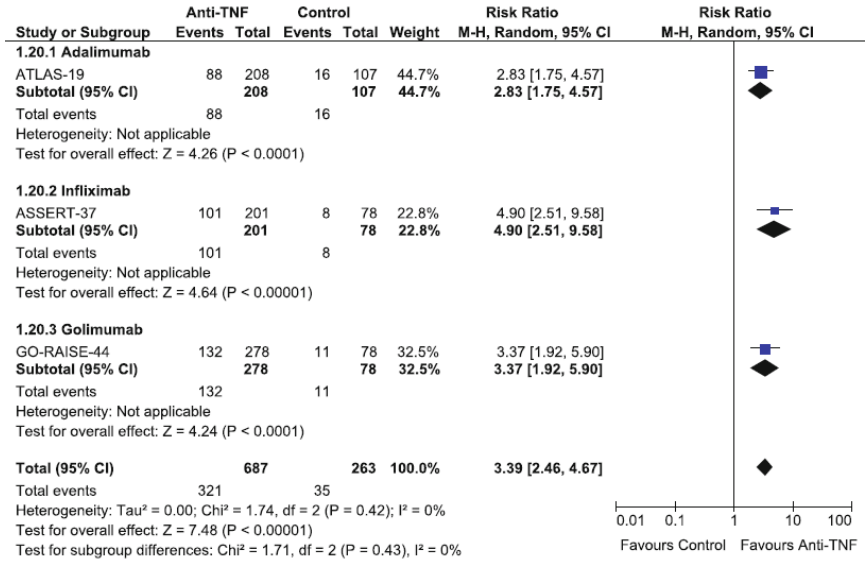
[c] A value of $p < 0.10$ from the chi-square test indicates statistical heterogeneity between the studies

[d] Meta-analysis with the GO-RAISE study [44] after 14 weeks

Meta-analysis of BASDAI 50 responses after 12/14 weeks of follow-up



Meta-analysis of BASDAI 50 responses after 24 weeks of follow-up



Meta-analysis of BASDAI, BASFI, and BSAMI outcomes after 12 and 24/30 weeks

Outcome	Studies	Participants	Mean difference (CI 95 %)[a]	I^2 (%)[b]	p value[c]
Up to 12 weeks					
BASDAI	4 [19, 32, 33, 42]	469	−1.64 (−2.06; −1.22)	0	0.69
BASFI	3 [19, 32, 33]	437	−1.39 (−1.59; −1.19)	0	0.85
BASMI	3 [19, 33, 41]	473	−0.53 (−0.72; −0.35)	9	0.32
Up to 24/30 weeks[d]					
BASDAI	4 [19, 37, 40, 43]	676	−1.79 (−2.27; −1.31)	0	0.49
BASFI	2 [19, 40]	355	−1.52 (−1.72; −1.31)	0	0.32
BASMI	1 [19]	82	−0.60 (−0.87; −0.33)	NA	NA

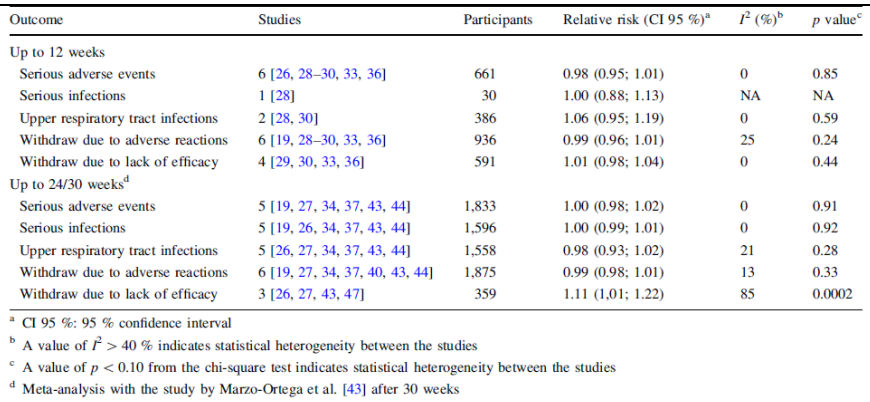
[a] CI 95 %: 95 % confidence interval

[b] A value of $I^2 > 40$ % indicates statistical heterogeneity between the studies

[c] A value of $p < 0.10$ from the chi-square test indicates statistical heterogeneity between the studies

[d] Meta-analysis with the study by Marzo-Ortega et al. [43] after 30 weeks

Meta-analysis of safety outcomes and withdraw after 12 and 24/30 weeks

	 Outcome | Studies | Participants | Relative risk (CI 95 %)[a] | I^2 (%)[b] | p value[c] Up to 12 weeks Serious adverse events | 6 [26, 28–30, 33, 36] | 661 | 0.98 (0.95; 1.01) | 0 | 0.85 Serious infections | 1 [28] | 30 | 1.00 (0.88; 1.13) | NA | NA Upper respiratory tract infections | 2 [28, 30] | 386 | 1.06 (0.95; 1.19) | 0 | 0.59 Withdraw due to adverse reactions | 6 [19, 28–30, 33, 36] | 936 | 0.99 (0.96; 1.01) | 25 | 0.24 Withdraw due to lack of efficacy | 4 [29, 30, 33, 36] | 591 | 1.01 (0.98; 1.04) | 0 | 0.44 Up to 24/30 weeks[d] Serious adverse events | 5 [19, 27, 34, 37, 43, 44] | 1,833 | 1.00 (0.98; 1.02) | 0 | 0.91 Serious infections | 5 [19, 26, 34, 37, 43, 44] | 1,596 | 1.00 (0.99; 1.01) | 0 | 0.92 Upper respiratory tract infections | 5 [26, 27, 34, 37, 43, 44] | 1,558 | 0.98 (0.93; 1.02) | 21 | 0.28 Withdraw due to adverse reactions | 6 [19, 27, 34, 37, 40, 43, 44] | 1,875 | 0.99 (0.98; 1.01) | 13 | 0.33 Withdraw due to lack of efficacy | 3 [26, 27, 43, 47] | 359 | 1.11 (1,01; 1.22) | 85 | 0.0002 [a] CI 95 %: 95 % confidence interval [b] A value of $I^2 > 40$ % indicates statistical heterogeneity between the studies [c] A value of $p < 0.10$ from the chi-square test indicates statistical heterogeneity between the studies [d] Meta-analysis with the study by Marzo-Ortega et al. [43] after 30 weeks Hohe Heterogenität für den Endpunkt “withdraw due to lack of efficacy” (I^2 = 85%) *Critical appraisal* The average modified Jadad score was 5.0, with the majority of studies having high-quality scores (i.e., 5 or 6).
	4. Anmerkungen/Fazit der Autoren The results of this systematic review and meta-analysis indicate significant positive benefits for the anti-TNF agents infliximab, etanercept, adalimumab, and golimumab for the treatment of AS with respect to several metrics, including the ASAS response, disease activity, physical function, vertebral mobility after 12 and 30 weeks of treatment compared with control treatments. The incidence of adverse events was not significantly different between the groups. Any conclusion about certolizumab could not be done because the search did not retrieve RCT with only AS patients. 5. Hinweise durch FB Med Innerhalb der Primärstudien waren verschiedene Begleitmedikationen erlaubt; keine Angabe zur Vorbehandlung; Conflict of interest: Adriana Maria Kakehasi claims to have received an educational grant from Abbott
Li et al., 2013 [10]. Etanercept in the treatment of ankylosing spondylitis: a meta-analysis of randomized, double-blind, placebo controlled clinical trials, and the comparison of the Caucasian and Chinese population	1. Fragestellung This article intends to focus on the present evidence for etanercept’s application for AS, analyzing its efficacy and safety in clinical practice, and to compare its outcome between the Caucasian and the Chinese population.
	2. Methodik *Population* Participants were patients diagnosed as AS *Intervention / Komparator* The interventions were taking etanercept or placebo as treatment *Endpunkt* efficacy and safety *Suchzeitraum (Aktualität der Recherche)* PubMed, EMBASE, COCHRANE library, EBSCO, Biosis

Previews, and OVID. The reviewed Chinese databases included CNKI and WanFang (articles published between January 1966 and October 2011)

Anzahl eingeschlossene Studien/Patienten (Gesamt):

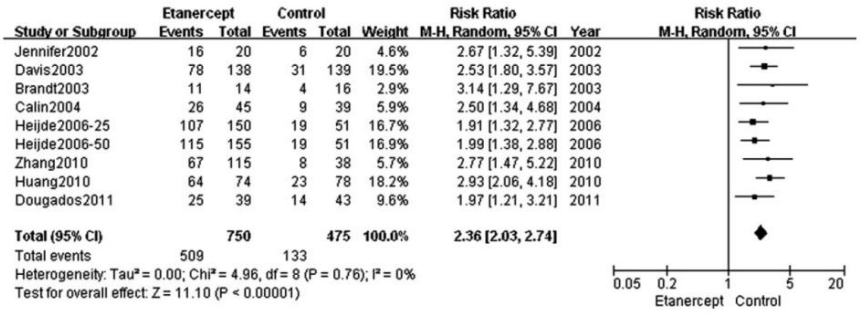
14 studies (1570 patients)

Qualitätsbewertung der Studien:

Methodology assessment of Jadad scale should be no less than three

3. Ergebnisdarstellung

ASAS20



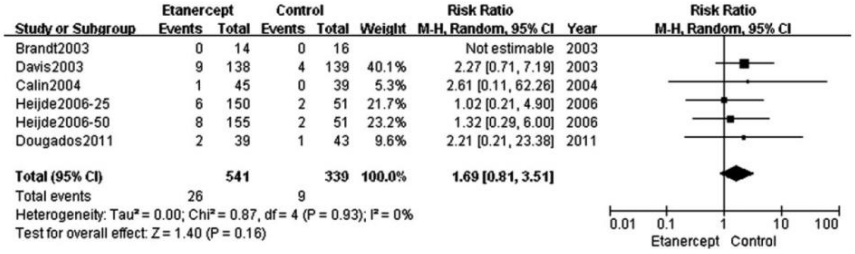
Disease activity controlling

Outcomes	Heterogeneity				Test for overall effect	
	χ^2	*P*	I^2 (%)	Z	*P*	RR (95 % CI)
ASAS20	4.96	0.76	0	11.10	<0.00001	2.36 (2.03, 2.74)
ASAS40	5.42	0.25	26	6.05	<0.00001	2.81 (2.01, 3.92)
ASAS5/6	7.91	0.10	49	5.39	<0.00001	3.28 (2.13, 5.05)
Partial remission	0.57	0.97	0	5.33	<0.00001	4.31 (2.52, 7.37)
BASFI	345.71	<0.00001	98	2.98	0.003	−1.85 (−3.06, −0.63)
BASDI	421.85	<0.00001	99	2.76	0.006	−2.75 (−4.71, −0.80)
BASMI	0.00	0.95	0	2.88	0.004	−0.56 (−0.94, −0.18)
Patient's global assessment	363.74	<0.00001	99	2.65	0.008	−2.56 (−4.45, −0.67)

Symptoms relieving

Outcomes	Heterogeneity				Test for overall effect	
	χ^2	*P*	I^2 (%)	Z	*P*	RR (95 % CI)
Total back pain	357.37	<0.00001	99	2.23	0.03	−2.22 (−4.18, −0.27)
Nocturnal pain	0.53	0.77	0	5.77	<0.00001	−1.30 (−1.74, −0.86)
Chest expansion	249.25	<0.00001	99	0.94	0.35	1.07 (−1.16, 3.30)
Morning stiffness	1.42	0.70	0	4.41	<0.0001	−0.62 (−0.90, −0.34)
Tender joint score	1.88	0.17	47	1.45	0.15	−0.45 (−1.07, 0.16)
Swollen join score	2.81	0.42	0	1.57	0.12	−0.22 (−0.49, 0.05)
Occiput-to-wall	66.35	<0.00001	97	1.43	0.15	−1.27 (−3.01, 0.47)

Serious adverse events



Critical appraisal

	Studies / Jadad scale: Randomization / Double blinding / Withdrawals and dropouts / Total score Gorman (2002) [29] 1 1 1 3 Brandt et al. [14] 2 2 1 5 Davis et al. [18] 1 2 1 4 Calin et al. [30] 1 2 1 4 Wanders et al. [35] 1 1 1 3 Maksymowych (2005) [34] 1 1 1 3 Heijde et al. [32] 1 1 1 3 Wang et al. [36] 1 1 1 3 Zhang et al. [37] 2 2 1 5 Zhang et al. [38] 1 2 1 4 Barkham et al. [21] 1 2 1 4 Huang et al. [33] 2 2 1 5 Zhang [39] 1 2 1 4 Dougados et al. [31] 1 1 1 3
	4. Anmerkungen/Fazit der Autoren According to our review, it is likely that etanercept did have the ability to control the disease activity, reflected by ASAS20, ASAS40, ASAS5/6, partial remission, BASFI, BASDI, BASMI, and patient's global assessment of the disease. 5. Hinweise durch FB Med Keine Angabe zu Vor- oder Begleitbehandlungen; Die Angabe des Effektmaßes ist für einige Outcomes nicht korrekt. Relative risk wurde nur für dichotome Outcomes verwendet, für kontinuierliche Outcomes wurde die standard mean difference verwendet.
Liu et al., 2014 [11]. Etanercept in the treatment of ankylosing spondylitis: A systematic review and meta-analysis	1. Fragestellung The present meta‐analysis evaluated randomised controlled trials (RCTs) to compare the effects of ETN (Etanercept) and a PBO (Placebo) or sulfasalazine (SSZ) in patients with AS.
	2. Methodik *Population* Patients diagnosed as exhibiting AS according to the modified New York criteria *Intervention / Komparator* For the types of interventions, treatment with ETN alone in RCTs was considered. The control groups consisted of treatments with a Placebo or SSZ. *Endpunkt* Primary outcome was ASAS20 Secondary outcomes comprised the ASAS 50, ASAS 70, Bath AS Disease Activity Index (BASDAI), BASDAI 50, Bath AS Functional Index (BASFI), ASAS partial remission (ASAS PR), and levels of ESR and C‐reactive protein. Spinal mobility, assessed by the Schober's test (ST) and the occiput‐to‐wall (OW) distance, was also considered to be a secondary outcome. *Suchzeitraum (Aktualität der Recherche)* PubMed, Embase, the Cochrane Library and ClinicalTrials.gov. In addition, Chinese databases were searched, including the China National Knowledge Infrastructure, VIP, Chinese Biomedical Literature and WanFang Databases, and the Chinese Clinical Trial Register. All the databases were searched from the available date of inception to the latest issue (2013)

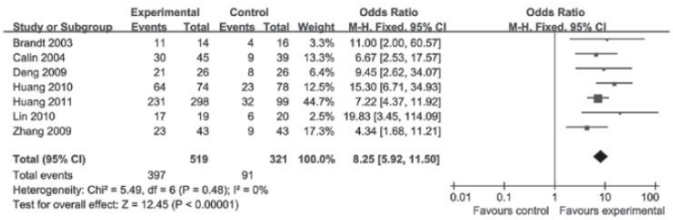
Anzahl eingeschlossene Studien/Patienten (Gesamt):
15 studies (2194 patients)
Qualitätsbewertung der Studien:
Jadad scale

3. Ergebnisdarstellung

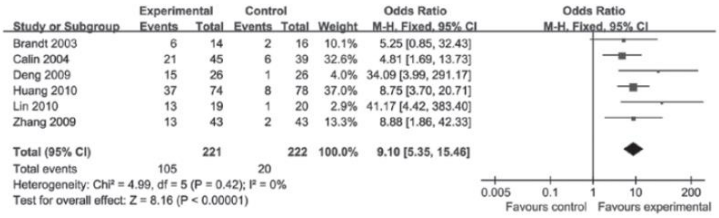
Forest plots of etanercept treatment compared with a placebo in terms of: (A) ASAS 20, (B) ASAS 50, (C) ASAS 70, (D) ASAS partial remission (E) BASDAI and (F) BASDAI 50.

BASDAI, Bath ankylosing spondylitis disease activity index; ASAS, assessments in ankylosing spondylitis; CI, confidence interval; SD standard deviation

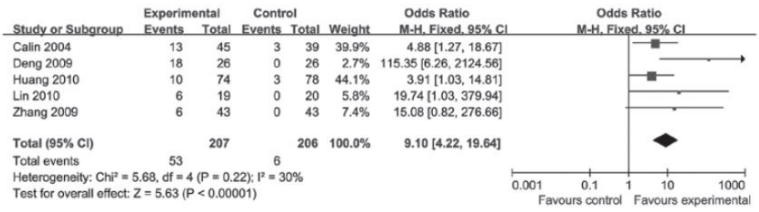
A



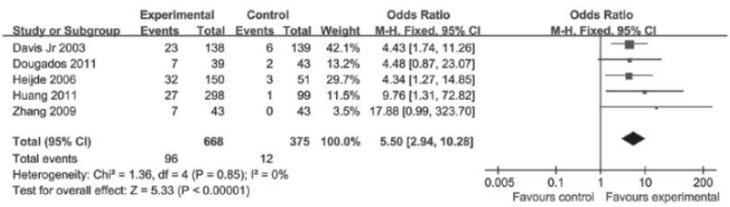
B



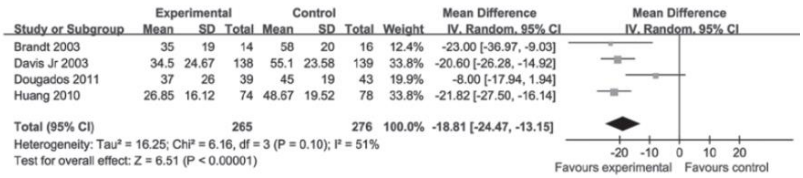
C



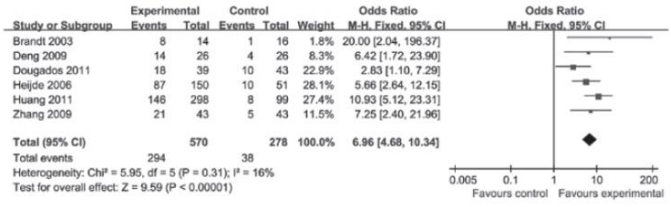
D



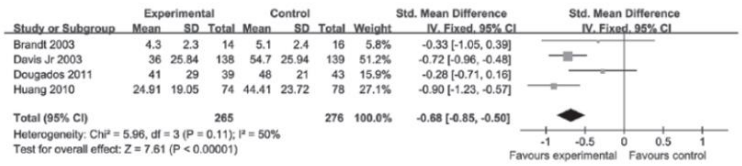
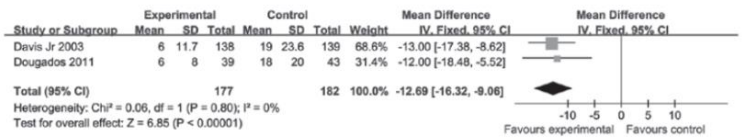
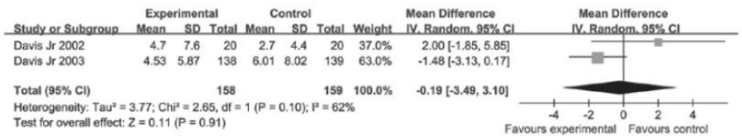
E

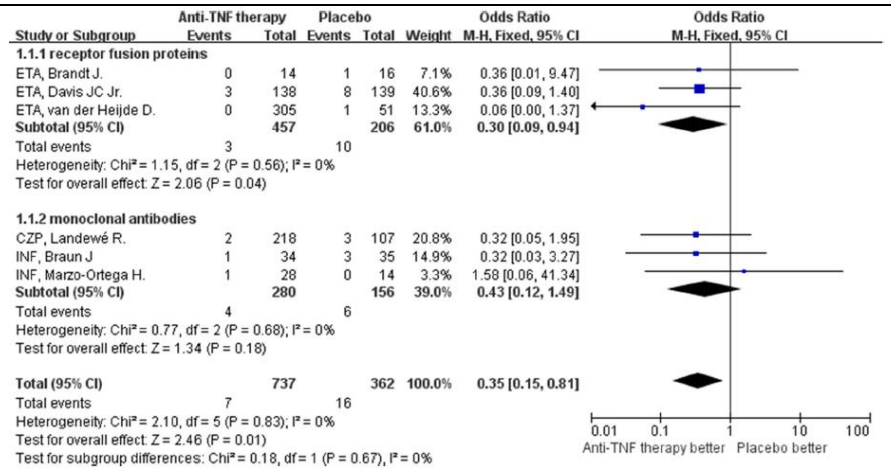
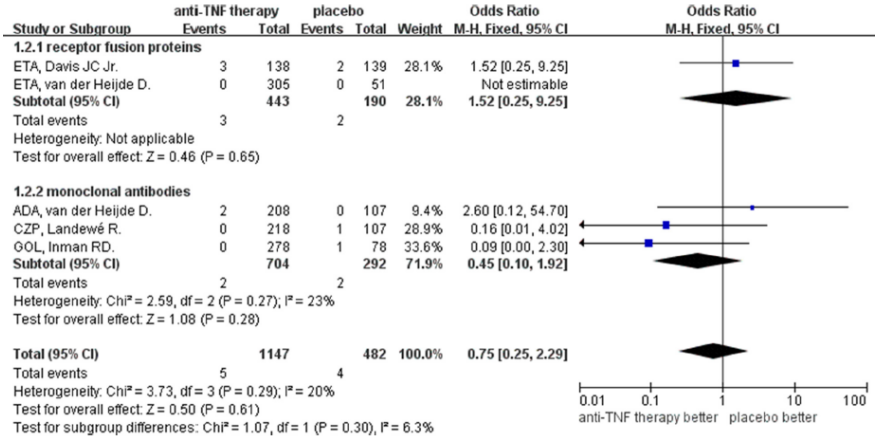


F



Forest plots of etanercept treatment compared with a placebo in terms of: (G) Bath ankylosing spondylitis functional index, (H) C-reactive protein and (I) occiput-to-wall. CI, confidence interval; SD standard deviation

	G  H  I  Hohe Heterogenität für den Endpunkt “occiput-to-wall” *Critical appraisal* Approximately three-quarters of included trials were moderate quality (Jadad score ≥3), whereas four of the Chinese trials were of low quality (Jadad score <3) due to unclear randomisation, deficient allocation concealment, inadequate blinding, and undisclosed withdrawal and dropouts.
	4. Anmerkungen/Fazit der Autoren This meta‑analysis shows that ETN monotherapy is effective in improving physical function and reducing disease activity in patients with AS. 5. Hinweise durch FB Med Keine Angabe zu Vor- oder Begleitbehandlungen
Wu et al., 2015 [20]. Efficacy of anti–tumor necrosis factor therapy for extra-articular manifestations in patients with ankylosing spondylitis: a meta–analysis	1. Fragestellung We performed a meta–analysis of randomized clinical trials (RCTs) to provide an up–to–date and comprehensive picture of the clinical efficacy of anti–TNF therapy for the most common extra–articular manifestations (EAMs) in patients with AS—uveitis, inflammatory bowel disease (IBD) and psoriasis.
	2. Methodik *Population* patients with AS *Intervention / Komparator* TNF inhibitor versus placebo treatment *Endpunkt* uveitis, inflammatory bowel disease and psoriasis *Suchzeitraum (Aktualität der Recherche)* MEDLINE, EMBASE and the Cochrane Library (before 2014) *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 8 studies (1,770 patients) *Qualitätsbewertung der Studien:* modified Jadad criteria with an 8-item scale
	3. Ergebnisdarstellung Meta-analysis of uveitis between anti-TNF therapy and placebo for ankylosing spondylitis

	 Meta-analysis of inflammatory bowel disease between anti-TNF therapy and placebo for ankylosing spondylitis  *Critical appraisal* Overall, included studies were of adequate methodological quality (mean modified Jadad score 6.875 for included studies, and all 8 studies had a score ≥6)
	4. Anmerkungen/Fazit der Autoren The results indicate significant positive benefits of anti-TNF agents to treat uveitis in these patients. For IBD treatment outcomes, the anti- TNF therapy group and the placebo group did not significantly differ. 5. Hinweise durch FB Med Innerhalb der Primärstudien waren verschiedene Begleitmedikationen erlaubt; keine Angabe zur Vorbehandlung
Shu et al., 2013 [16]. Indirect comparison of anti-TNF-α agents for active ankylosing spondylitis: mixed treatment comparison of randomised controlled trials	1. Fragestellung We aimed to identify different anti-TNF-α agents for ankylosing spondylitis (AS) assessed in randomised controlled trials (RCTs) and to compare them within a single evidence synthesis framework.
	2. Methodik *Population* patients suffering from ankylosing spondylitis *Intervention / Komparator* Adalimumab, etanercept, infliximab, and golimumab

Endpunkt

the main outcome measure was the percentages of patients achieving the Assessments in Ankylosing Spondylitis 20% response (ASAS20) at weeks 12

Suchzeitraum (Aktualität der Recherche)

PubMed (1980 to the present), Embase (1980 to the present) and Cochrane databases; last search was run on November 2012

Anzahl eingeschlossene Studien/Patienten (Gesamt):

14 Studien (Patienten: k. A.)

Qualitätsbewertung der Studien:

Adequacy of randomisation and concealment of allocation, blinding of patients, health care providers, data collectors, and outcome assessors; and extent of loss to follow-up

3. Ergebnisdarstellung

The direct and indirect comparisons of all treatments, using etanercept 20 mg twice a week and placebo as reference treatments, respectively

Comparisons	25 mg twice a week etanercept OR (95%CI)	Comparisons	Placebo OR (95%CI)
25 mg twice a week etanercept		*placebo*	
Placebo	0.21 (0.13, 0.31)	25 mg twice a week etanercept	5.05 (3.28, 7.91)
50 mg etanercept once a week	1.22 (0.63, 1.99)	50 mg etanercept once a week	5.98 (3.62, 9.29)
50 mg etanercept twice a week	1.06 (0.28, 2.70)	50 mg etanercept twice a week	5.31 (1.54, 13.04)
50 mg golimumab	1.25 (0.40, 2.91)	50 mg golimumab	5.94 (2.29, 12.66)
100 mg golimumab	1.29 (0.41, 3.07)	100 mg golimumab	6.09 (2.32, 12.95)
5 mg/kg infliximab	1.38 (0.58, 2.73)	5 mg/kg infliximab	6.53 (3.35, 11.61)
3 mg/kg infliximab	0.69 (0.18, 1.89)	3 mg/kg infliximab	3.31 (0.95, 8.68)
40 mg adalimumab	1.25 (0.44, 2.76)	40 mg adalimumab	5.92 (2.51, 12.23)
Placebo		*25 mg twice a week etanercept*	
50 mg etanercept once a week	5.94 (3.55, 9.27)	50 mg etanercept once a week	1.23 (0.64, 2.00)
50 mg etanercept twice a week	5.20 (1.49, 13.25)	50 mg etanercept twice a week	1.09 (0.29, 2.68)
50 mg golimumab	6.04 (2.29, 13.04)	50 mg golimumab	1.24 (0.40, 2.80)
100 mg golimumab	6.22 (2.34, 13.6)	100 mg golimumab	1.27 (0.41, 2.86)
5 mg/kg infliximab	6.65 (3.36, 11.97)	5 mg/kg infliximab	1.35 (0.58, 2.67)
3 mg/kg infliximab	3.33 (0.96, 8.72)	3 mg/kg infliximab	0.69 (0.18, 1.89)
40 mg adalimumab	6.03 (2.52, 12.56)	40 mg adalimumab	1.23 (0.44, 2.69)
50 mg etanercept once a week		*50 mg etanercept once a week*	
50 mg etanercept twice a week	0.88 (0.29, 2.05)	50 mg etanercept twice a week	0.89 (0.29, 2.03)
50 mg golimumab	1.08 (0.36, 2.63)	50 mg golimumab	1.06 (0.35, 2.48)
100 mg golimumab	1.13 (0.36, 2.72)	100 mg golimumab	1.08 (0.36, 2.56)
5 mg/kg infliximab	1.19 (0.50, 2.45)	5 mg/kg infliximab	1.16 (0.50, 2.33)
3 mg/kg infliximab	0.60 (0.15, 1.69)	3 mg/kg infliximab	0.59 (0.15, 1.64)
40 mg adalimumab	1.09 (0.38, 2.54)	40 mg adalimumab	1.05 (0.38, 2.42)
50 mg etanercept twice a week		*50 mg etanercept twice a week*	
50 mg golimumab	1.62 (0.30, 5.25)	50 mg golimumab	1.54 (0.28, 4.65)
100 mg golimumab	1.67 (0.31, 5.38)	100 mg golimumab	1.57 (0.30, 4.75)
5 mg/kg infliximab	1.77 (0.40, 3.17)	5 mg/kg infliximab	1.68 (0.40, 4.72)
3 mg/kg infliximab	0.90 (0.14, 3.17)	3 mg/kg infliximab	0.86 (0.14, 3.02)
40 mg adalimumab	1.63 (0.32, 4.917)	40 mg adalimumab	1.53 (0.32, 4.70)
50 mg golimumab		*50 mg golimumab*	
100 mg golimumab	1.13 (0.48, 2.19)	100 mg golimumab	1.10 (0.48, 2.16)
5 mg/kg infliximab	1.37 (0.40, 3.43)	5 mg/kg infliximab	1.34 (0.41, 3.33)
3 mg/kg infliximab	0.69 (0.13, 2.24)	3 mg/kg infliximab	0.69 (0.13, 2.15)
40 mg adalimumab	1.25 (0.32, 3.31)	40 mg adalimumab	1.22 (0.33, 3.27)
100 mg golimumab		*100 mg golimumab*	
5 mg/kg infliximab	1.32 (0.38, 3.35)	5 mg/kg infliximab	1.31 (0.39, 3.29)
3 mg/kg infliximab	0.66 (0.12, 2.15)	3 mg/kg infliximab	068 (0.13, 2.12)
40 mg adalimumab	1.20 (0.30, 3.24)	40 mg adalimumab	1.20 (0.32, 3.23)
5 mg/kg infliximab		*5 mg/kg infliximab*	
3 mg/kg infliximab	0.56 (0.13, 1.62)	3 mg/kg infliximab	0.57 (0.13, 1.63)
40 mg adalimumab	1.01 (0.32, 2.47)	40 mg adalimumab	1.01 (0.33, 2.46)
3 mg/kg infliximab		*3 mg/kg infliximab*	
40 mg adalimumab	2.55 (0.51, 7.56)	40 mg adalimumab	2.48 (0.51, 7.36)

Critical appraisal

All of included trials was considered to be of high methodological quality, except one (20). All trials were randomized adequately, and most trials were double blinding designed.

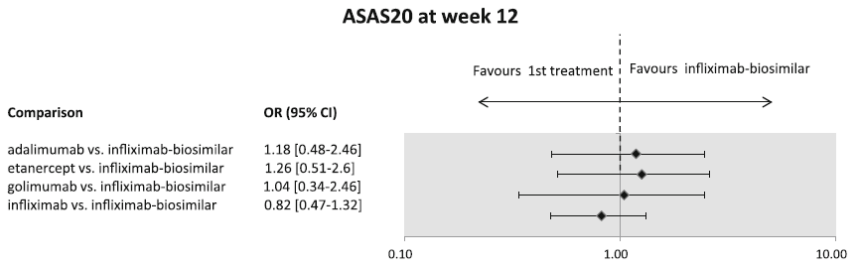
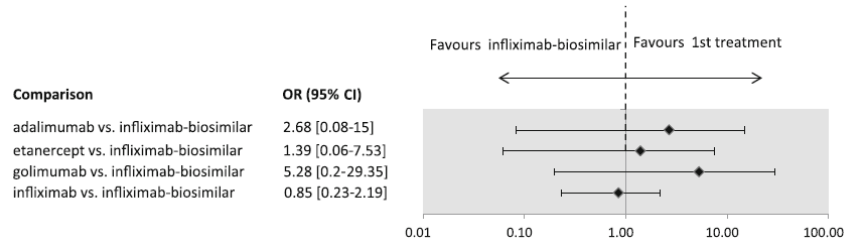
4. Anmerkungen/Fazit der Autoren

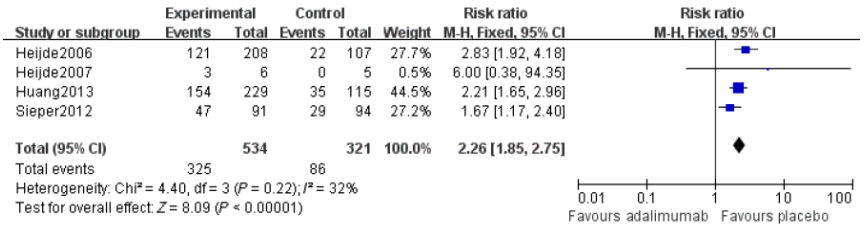
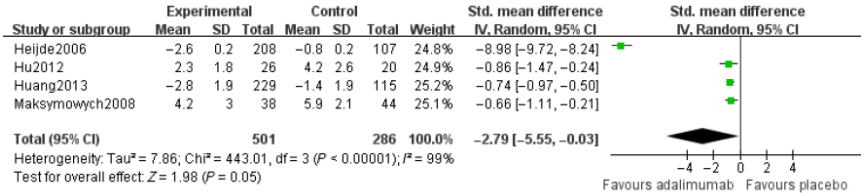
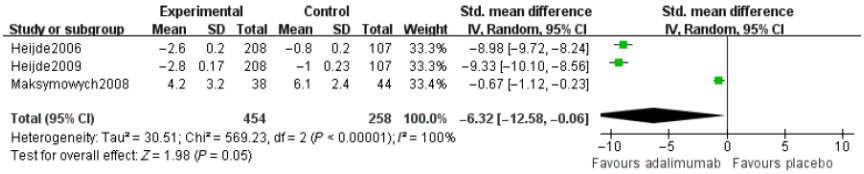
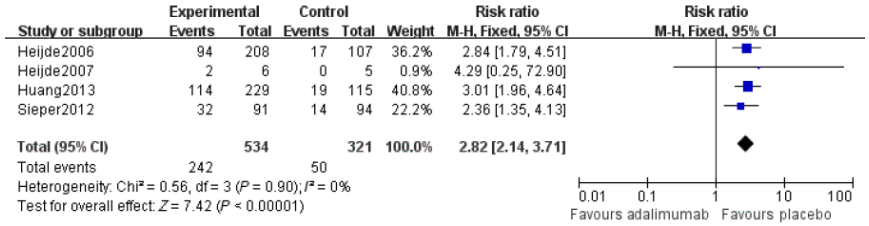
Generally, our present study suggested that compared with placebo, all anti-TNF agents were effective in the management of acute ankylosing spondylitis refractory to NSAIDs in the

<table>
<tr><td></td><td>aspects of clinical response index ASAS20, and 5 mg/kg Infliximab at 0, 2, 6 weeks maybe was the most effective.
5. Hinweise durch FB Med
Keine Angabe zur Begleitbehandlung; in den Einschlusskriterien ist keine Vorbehandlung definiert, aber auf Basis der Conclusion ist anzunehmen, dass Patienten, die zuvor NSAID erhalten haben, eingeschlossen wurden.</td></tr>
<tr><td rowspan="3">Baji et al., 2014 [1].

Comparative efficacy and safety of biosimilar infliximab and other biological treatments in ankylosing spondylitis: systematic literature review and meta-analysis</td><td>1. Fragestellung
To compare the efficacy and safety of infliximab-biosimilar with other biological drugs for the treatment of active ankylosing spondylitis (AS).</td></tr>
<tr><td>2. Methodik

Population
AS patients (≥ 18 years), diagnosed based on the modified New York criteria
Intervention / Komparator
adalimumab, etanercept, golimumab and infliximab are considered as comparators of infliximab-biosimilar
Endpunkt
ASAS20 response at weeks 12 and 24; occurrence of serious adverse events at week 24
Suchzeitraum (Aktualität der Recherche)
Medline and Cochrane Library; We carried out the search for the period between November 1, 2005 and August 20, 2013. To identify RCTs from earlier years, we relied on the systematic review of McLeod et al. [8] published in 2007, which assessed the comparative clinical effectiveness of adalimumab, etanercept and infliximab for the treatment of AS.
Anzahl eingeschlossene Studien/Patienten (Gesamt):
13 Studien (Patienten: k. A.)
Qualitätsbewertung der Studien:
JADAD-score</td></tr>
<tr><td>3. Ergebnisdarstellung
Efficacy of infliximab-biosimilar and other biologicals compared to placebo in AS, results of mixed treatment comparison
<table><tr><th>Substance</th><th>ASAS20 at week 12, OR (95 % CI)</th><th>ASAS20 at week 24, OR (95 % CI)</th><th>Serious adverse events OR (95 % CI)</th></tr><tr><td>Adalimumab</td><td>4.65 (3.29–6.43)</td><td>4.81 (2.67–8.18)</td><td>1.57 (0.27–5.72)</td></tr><tr><td>Etanercept</td><td>4.35 (3.09–5.96)</td><td>4.76 (2.73–7.81)</td><td>2.36 (0.64–6.58)</td></tr><tr><td>Golimumab</td><td>5.7 (2.88–10.44)</td><td>4.53 (2.32–8.22)</td><td>0.69 (0.14–2.1)</td></tr><tr><td>Infliximab</td><td>6.74 (3.81–11.3)</td><td>7.2 (3.68–13.19)</td><td>2.71 (0.35–12.03)</td></tr><tr><td>Infliximab-biosimilar[a]</td><td>6.39 (2.75–12.78)</td><td>6.25 (2.55–13.14)</td><td>2.31 (0.17–11.43)</td></tr></table>Efficacy of infliximab-biosimilar compared to other biologicals in AS, results of mixed treatment comparison (ASAS20 response at weeks 12 and 24).</td></tr>
</table>

	  The safety of infliximab-biosimilar compared to other biologicals in AS: serious adverse events  *Critical appraisal* All studies scored 4 or 5 points on the Jadad-scale
	4. Anmerkungen/Fazit der Autoren The results have proven the similar efficacy and safety profile of infliximab-biosimilar treatment compared to other biologicals. 5. Hinweise durch FB Med Keine Aussage zu Vorbehandlung Acknowledgments: The study was supported by an unrestricted grant from EGIS Pharmaceuticals and the Center for Public Affairs Studies Foundation.
Wang et al., 2014 [18]. Randomized, placebo controlled and double-blind trials of efficacy and safety of adalimumab for treating ankylosing spondylitis: a meta-analysis	1. Fragestellung The current meta-analysis and systematic review will assess the efficacy and safety of adalimumab treatment, relative to a placebo, in adult patients with AS.
	2. Methodik *Population* adult patients experiencing AS *Intervention / Komparator* adalimumab group versus a placebo group *Endpunkt* primary outcomes evaluated in the present review were the ASAS20 response, BASDAI, BASDAI50 response, and HRQoL. We extracted data collected at week 12 and week 24 endpoint; Secondary outcomes were data about safety, including any

	adverse events (AEs), serious adverse events, infection, drug discontinuation and injection-site reaction *Suchzeitraum (Aktualität der Recherche)* Keine Angabe zum Suchzeitraum; PubMed, EMBASE, Web of Science, and the Cochrane Library databases *Anzahl eingeschlossene Studien/Patienten (Gesamt):* 8 studies (993 patients) *Qualitätsbewertung der Studien:* Jadad composite scale
	3. Ergebnisdarstellung Meta-analysis of ASAS20 response criteria at week 12 in patients with ankylosing spondylitis randomized to receive adalimumab  Meta-analysis of BASDAI at week 12 in patients with ankylosing spondylitis randomized to receive adalimumab  Meta-analysis of BASDAI at week 24 in patients with ankylosing spondylitis randomized to receive adalimumab  Meta-analysis of BASDAI50 at week 12 in patients with ankylosing spondylitis randomized to receive adalimumab  HRQoL Three studies reported the SF-36 PCS, two studies reported the SF-36 MCS at week 12 endpoint, and two studies reported the ASQoL at week 24 visit. The meta-analysis results showed that the difference in SF-36 PCS, SF-36 MCS and ASQoL were significant (SMD 5.27, 95% CI 0.40 to 10.94; SMD 0.39, 95% CI

	0.23–0.56; SMD 6.92, 95% CI 7.75 to 6.09, respectively). Summary of adverse events (AEs) Outcome | Studies | Adalimumab events/total | Placebo events/total | Heterogeneity (P, I^2) | Statistical method | Effect estimate | P-value Any AEs | 3 | 292/528 | 147/316 | 0.16, 46% | Risk Ratio (M-H, Fixed, 95% CI) | 1.23 (1.07, 1.41) | 0.003 Serious AEs | 3 | 10/528 | 5/316 | 0.57, 0% | Risk Ratio (M-H, Fixed, 95% CI) | 1.03 (0.26, 4.03) | 0.69 Infection | 3 | 119/528 | 63/316 | 0.43, 0% | Risk Ratio (M-H, Fixed, 95% CI) | 1.22 (0.98, 1.60) | 0.16 Drug discontinuation | 2 | 6/320 | 1/209 | 0.68, 0% | Risk Ratio (M-H, Fixed, 95% CI) | 3.06 (0.48, 19.41) | 0.23 Injection-site reaction | 2 | 48/437 | 5/222 | 0.50, 0% | Risk Ratio (M-H, Fixed, 95% CI) | 4.88 (1.97, 12.09) | 0.0006 M-H, Mantel–Haenszel. *Critical appraisal* Seven studies scored 5 points and one study scored 4 points on the Jadad scale
	4. Anmerkungen/Fazit der Autoren This meta-analysis has not shown an increased risk of infection or risk of serious AEs in patients with active AS treated with adalimumab therapy, and adalimumab treatment can significantly improve patient disease status and physical function. 5. Hinweise durch FB Med Keine Aussage zu Vor- und Begleitbehandlung; kein Suchzeitraum angegeben; Für die Outcomes ‚ASAS20' und ‚BASDAI50' sind die Erläuterungen zu den X-Achsen nicht korrekt. In beiden Fällen zeigt sich ein Vorteil für Adalimumab.

Leitlinien

Deutsche Gesellschaft für Rheumatologie, 2013 [4]. **AWMF-Leitlinie** Axiale Spondyloarthritis inklusive Morbus Bechterew und Frühformen	10) Welche medikamentöse Therapie sollte zu welchem Zeitpunkt bei Patienten mit axialer SpA eingesetzt werden und für wie lange? 11) Nach welchem Zeitraum sollte bei den verschiedenen Medikamenten ein Therapieerfolg evaluiert werden? Population • Axiale Spondyloarthritis inklusive AS Intervention • NSAR • COX-2 Hemmer • Analgetika • Glukokortikoide (lokal, systemisch) • Basistherapie („DMARDs") (Sulfasalazin, Methotrexat) • TNF-Blocker • Biologika andere als TNF-Blocker • Biphosphonate Kontrolle • Behandlung (Verum), kontinuierlich/ bei Bedarf • Keine Behandlung Outcome

	• ASAS-20 response • ASAS Remission • ASDAS, BASDAI • Schmerzen • Funktionsfähigkeit (inkl. Steifheit, BASFI, BASMI) • Lebensqualität • Knochenneubildung (Ankylose) • mSASSS, Berlin Score • Enthesitis Score • CED Schub/Uveitis Rezidiv, Verschlechterung Psoriasis • Arbeitsfähigkeit / Erwerbsfähigkeit *Die Leitlinie umfasst Patienten mit axialer Spondyloarthritis; daher sind nicht alle Empfehlungen speziell auf Patienten mit AS ausgerichtet*
	Methodik *S3-Leitlinie* Grundlage der Leitlinie – Systematische Leitliniensuche und –adaptation; Interdisziplinäre Leitliniengruppe: Experten aus den beteiligten Fachgesellschaften; Empfehlungen im formalisierten Konsensusprozess (zweiteiliger Nominaler Gruppenprozess) verabschiedet; CoI wurde abgefragt und bei vorhandenem CoI waren die entsprechenden Mandatsträger nicht stimmberechtigt – Die letzte inhaltliche Überarbeitung fand am 27.11.2013 statt. Die nächste Aktualisierung ist für das Jahr 2018 geplant Suchzeitraum: • Leitlinienrecherche 2001 bis 2011 • systematische Literaturrecherche in PubMed, PEDro und der Cochrane library (Suchzeitraum 30.09.2006 bis 39.09.2011; Nachrecherche bis zum 31.07.2012) – Weitere Kriterien für die Qualität einer LL: • Empfehlungen sind mit Literaturstellen verknüpft LoE

Grad	Studien zu Therapie/ Prävention / Ätiologie
1++	Qualitativ hochstehende systematische Übersichtsarbeiten/Metaanalysen von randomisierten kontrollierten Studien (RCTs) oder RCTs mit sehr geringem Bias-Risiko.
1+	Gut durchgeführte systematische Übersichtsarbeiten/Metaanalysen von RCTs oder RCTs mit geringem Bias-Risiko.
1	Systematische Übersichtsarbeiten/Metaanalysen von RCTs oder RCTs mit hohem Bias-Risiko.
2++	Qualitativ hochstehende systematische Übersichten über Fall-Kontroll- oder Kohorten-Studien. Qualitativ hochstehende Fall-Kontroll- oder Kohorten-Studien mit sehr niedrigem Störgrößen- (Confounder) oder Bias-Risiko und hoher Wahrscheinlichkeit für ursächliche Zusammenhänge.
2+	Gut durchgeführte Fall-Kontroll- oder Kohorten-Studien mit niedrigem Störgrößen-(Confounder) oder Bias-Risiko und mäßigem Risiko nicht ursächlicher Zusammenhänge.
2-	Fall-Kontroll- oder Kohorten-Studien mit hohem Störgrößen-(Confounder) oder Bias-Risiko und hohem Risiko nicht ursächlicher Zusammenhänge.
3	Nicht analytische Studien, z.B. Fallstudien, Fallserien.
4	Expertenmeinung.

GoR

A	„Soll"-Empfehlung: Zumindest eine randomisierte, kontrollierte Studie von insgesamt guter Qualität und Konsistenz, die sich direkt auf die jeweilige Empfehlung bezieht und nicht extrapoliert wurde (Evidenzebenen Ia und Ib).
B	„Sollte"-Empfehlung: Gut durchgeführte klinische Studien, aber keine randomisierten klinischen Studien, mit direktem Bezug zur Empfehlung (Evidenzebenen II und III) oder Extrapolation von Evidenzebene I, falls der Bezug zur spezifischen Fragestellung fehlt.
0	„Kann"-Empfehlung: Bericht von Expertenkreisen oder Expertenmeinungen und/oder klinische Erfahrung anerkannter Autoritäten (Evidenzebene IV) oder Extrapolation von Evidenzebene IIa, IIb oder III. Diese Einstufung zeigt an, dass direkt anwendbare klinische Studien von guter Qualität nicht vorhanden oder nicht verfügbar sind.
KKP	(Klinischer Konsenspunkt) „Standard in der Behandlung": Empfohlen als gute klinische Praxis im Konsens und aufgrund der klinischen Erfahrung der Mitglieder der Leitliniengruppe als ein Standard der Behandlung, bei dem keine experimentelle wissenschaftliche Erforschung möglich oder angestrebt ist.

Freitext/Empfehlungen/Hinweise

8.8) Nicht-steroidale Antirheumatika (NSAR) inklusive Coxibe sollen bei symptomatischen Patienten mit axialer SpA als Mittel der ersten Wahl eingesetzt werden. (A; 1+)

8.9) Die Dosierung und Dauer der nicht-steroidalen Antirheumatika (NSAR) inklusive Coxibe richtet sich nach der Intensität der Beschwerden des Patienten. (0; 4)

8.10) Die Effektivität einer Therapie mit nicht-steroidalen Antirheumatika (NSAR) einschließlich Coxiben kann nach 2 – 4 Wochen beurteilt werden (Statement). Wenn ein NSAR einschließlich Coxib nicht gewirkt hat, sollte innerhalb von 2-4 Wochen ein zweites NSAR versucht werden. (B; 1+)

8.11) Eine kontinuierliche Therapie mit nicht-steroidalen Antirheumatika (NSAR) einschließlich Coxiben hat mögliche Vorteile vor allem bei Patienten mit persistierend aktiver symptomatischer Erkrankung. Hierzu gehören auch mittelfristig günstige Einflüsse auf die Röntgenprogression. (Statement)

8.12) Aufgrund des Sicherheitsprofils der NSAR-Präparate sollte die Dosierung und Fortdauer der Therapie fortwährend überprüft werden. (KKP)

8.13) Eine Therapie mit TNF-Blocker soll bei Patienten mit persistierend aktiver axialer SpA einschließlich AS und unzureichendem Ansprechen auf eine NSAR-Therapie begonnen

werden. (A; 1++)

8.14) Bei Patienten mit axialer SpA und symptomatischer peripherer Arthritis sollte eine TNF-Blocker Therapie versucht werden, wenn der Patient auf mindestens eine lokale Steroidinjektion ungenügend angesprochen hat, und ein angemessener Behandlungsversuch mit einem Basistherapeutikum, bevorzugt Sulfasalazin, keine Wirkung gezeigt hat. (B; 1)

8.15) Bei Patienten mit extra-muskuloskeletalen Manifestationen, insbesondere bei Vorliegen einer chronisch entzündlichen Darmerkrankung oder Uveitis, sollte die unterschiedliche Effektivität der verschiedenen TNF-Blocker auf diese Manifestationen beachtet werden. (B; 1+ / 2b)

8.16) Bei Patienten mit verbleibenden muskuloskeletalen Symptomen unter einer TNF-Blocker-Therapie kann eine zusätzliche Therapie mit NSAR erfolgen. (KKP)

Tabelle 10: ASAS Empfehlungen zur Anwendung von TNF-Blocker bei Patienten mit axialer Spondyloarthritis, update 2010

Auswahl der Patienten	Empfehlung
Diagnose	Patienten, die die modifizierten New-York-Kriterien oder die ASAS-Klassifikationskriterien für die axiale SpA erfüllen
Aktive Erkrankung	• Aktive Erkrankung über einen Zeitraum von >4 Wochen • BASDAI ≥ 4 (0-10)++ und • eine positive Expertenmeinung §
Therapieversagen	**Alle Patienten** sollten einen angemessenen Therapieversuch mit mindestens zwei NSAR durchlaufen haben. Ein angemessener Therapieversuch ist definiert als eine Behandlung mit **mindestens zwei NSAR über einen Zeitraum von 4 Wochen insgesamt** in der maximal empfohlenen oder verträglichen Dosis - es sei denn, es liegt eine Kontraindikation vor.
	Bei Patienten mit vorwiegend axialer Manifestation ist eine Vorbehandlung mit Basistherapeutika nicht erforderlich.
	Patienten mit symptomatischer peripherer Arthritis sollten auf mindestens eine lokale Steroidinjektion ungenügend angesprochen haben, sofern angebracht, und in der Regel einen angemessenen Behandlungsversuch mit einem Basistherapeutikum, bevorzugt Sulfasalazin, durchlaufen haben.
	Patienten mit symptomatischer Enthesitis müssen auf eine angemessene lokale Behandlung nicht angesprochen haben.
Beurteilung de Erkrankung	ASAS-Core Set# für die tägliche Praxis und BASDAI
Beurteilung des Ansprechens	
- Kriterien bezüglich des Ansprechens	50%ige Veränderung des BASDAI oder absolute Veränderung um 2 Punkte (auf einer Skala von 0-10) und positive Expertenmeinung für eine Fortführung
- Zeitpunkt der Beurteilung	Nach mindestens 12 Wochen

++BASDAI bewertet auf einer Skala (VAS oder NRS) von 0-10.

§ Bei einem Experten handelt es sich um einen Arzt, in der Regel einen Rheumatologen, mit Spezialisierung im Bereich entzündlicher Rückenschmerzen und der Anwendung von Biologika. Experten sollten lokal festgelegt werden. Eine Expertenmeinung sollte klinische Merkmale (Anamnese und Untersuchung) sowie entweder die Konzentration von Akut-Phase-Proteinen im Serum oder Befunde bildgebender Verfahren, wie Röntgenaufnahmen, die ein schnelles Fortschreiten nachweisen, oder MRT-Aufnahmen, die auf eine Entzündung hinweisen, berücksichtigen.
# ASAS Core Set für die tägliche Praxis [318]: körperliche Funktionsfähigkeit (BASFI); Schmerzen (VAS/NRS, letzte Woche, Wirbelsäule während der Nacht, infolge der AS und VAS/NRS, letzte Woche, Wirbelsäule infolge der AS); Wirbelsäulenbeweglichkeit (Thoraxexkursion, modifizierter Schober, Occiput-Wand-Abstand, zervikale Rotation und (laterale lumbale Flexion oder BASMI); Allgemeines Patientenurteil (VAS/NRS, letzte Woche); Steifigkeit (VAS/NRS Dauer der Morgensteifigkeit der Wirbelsäule, letzte Woche); Periphere Gelenke und Sehnen (Anzahl der geschwollenen Gelenke [44 Gelenke], validierter Enthesitis-Score, zum Beispiel Maastricht-, Berlin- oder San Fransisco); Entzündungsparameter (bevorzugt CRP); Ermüdbarkeit (VAS/NRS)

8.17) Die Wirksamkeit einer TNF-Blocker-Therapie soll nach 12 Wochen überprüft werden (A). Die Fortführung der Behandlung kann erfolgen, wenn eine relative 50%ige Verbesserung des BASDAI oder eine absolute Verbesserung um 2 Punkte (auf einer Skala von 0-10) und eine positive Expertenmeinung für eine Fortführung vorliegen (KKP). (A; 1++)

	8.18) Bei nicht-ausreichender Wirksamkeit einer TNF-Blocker-Therapie kann der Wechsel auf einen zweiten TNF-Blocker erfolgen, insbesondere bei Wirkverlust. (0; 4) 8.19) Bei Patienten mit axialer SpA und peripherer Arthritis sollte eine Basistherapie mit Sulfasalazin durchgeführt werden (B). Andere Basistherapeutika wie Methotrexat können alternativ eingesetzt werden (KKP). (B; 1) Kommentar zu 8-19: Diese Empfehlung basiert auf einer Cochrane Analyse, die einen geringen Effekt der Sulfasalazin Behandlung bei Patienten mit peripherer Arthritis diskutiert hat. Daher wird der Empfehlungsgrad von „A“ auf „B“ herabgestuft. 8.20) Bei Patienten mit AS sollte keine Behandlung der Wirbelsäulensymptomatik mit Methotrexat erfolgen. (B; 1) Kommentar zu 8-20: Herabstufung des Empfehlungsgrad von „A“ auf „B“, da hier eine Extrapolation der Ergebnis aus der Evidenzebene 1 vorgenommen wurde. 8.21) Die systemische Langzeitgabe von Kortikosteroiden wird bei Patienten mit Achsenskelettbeteiligung nicht empfohlen. Für die Wirksamkeit einer kurzfristigen Therapie mit Kortikosteroiden gibt es keine ausreichende Evidenz. (0; 4) 8.22) Bei Patienten mit axialer SpA und symptomatischer peripherer Arthritis (KKP) oder Enthesitis kann eine lokale Injektion mit Glukokortikoiden erfolgen. (0; 1) Kommentar zu 8-22: Die Empfehlung bezüglich der Enthesitis basiert auf einer einzigen kontrollierten Studie, in der eine Glukokortikoidinjektion gegenüber einer Injektion mit einem TNF-Blocker verglichen wird. Randomisierte Studie mit einem Vergleich Glukokortikoidinjektion versus Plazebo fehlen. Daher wird der Empfehlungsgrad von „A“ auf „0“ herabgestuft. 8.23) Bei Patienten mit axialer SpA und symptomatischer florider Sakroiliitis kann eine Glukokortikoidinjektion in das Sakroiliakal-Gelenk erfolgen. (0; 4)
Espoguia Group, 2010 [6]. Clinical Guidelines for patients with espondyloarthritis	– The Spanish Society of Rheumatology (Spanish acronym, SER), a non-profit organization, has sponsored this clinical practice guideline (CPG). – The objective of this GPC is to reduce the variability in the management of spondyloarthritis (SpA), improving the quality of care by offering physicians who treat these patients practical recommendations adapted to their setting and based on the best, most up-to-date available evidence on the comprehensive management of SpA. *Die Leitlinie umfasst Patienten mit Spondyloarthritiden; daher sind nicht alle Empfehlungen speziell auf Patienten mit AS ausgerichtet*
	Methodik Grundlage der Leitlinie The methodology used to produce ESPOGUIA includes nominal groups of experts (multidisciplinary expert panel), Delphi surveys and systematic review of the literature (carried out by members of the SER Working Group on Evidence-Based Rheumatology). The guideline was developed taking into consideration at all times the AGREE instrument for the evaluation of GPCs, as a guide for the quality of ESPOGUIA itself. – Financing This GPC, sponsored by the Spanish Society of Rheumatology,

was financed by Abbott.

- Suchzeitraum
  The literature review was carried out in 2008 in the following databases:
  • MEDLINE
  • Embase
  • Cochrane Central
- Weitere Kriterien für die Qualität einer LL:
  - Empfehlungen sind mit Literaturstellen verknüpft

LoE / GoR

GoR	LoE	Therapy/Prevention, Aetiology/Harm
A	1a	SR (with homogeneity*) of RCTs
	1b	Individual RCT (with narrow Confidence Interval‡)
	1c	All or none§
B	2a	SR (with homogeneity*) of cohort studies
	2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
	2c	"Outcomes" Research; Ecological studies
	3a	SR (with homogeneity*) of case-control studies
	3b	Individual Case-Control Study
C	4	Case-series (and poor quality cohort and case-control studies§§)
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category.)
‡	See note #2 for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when <u>all</u> patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but <u>none</u> now die on it.
§§	By poor quality <u>cohort</u> study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality <u>case-control</u> study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.

Freitext/Empfehlungen/Hinweise

[LoE, GoR, Level of agreement among the experts about each recommendation]

General considerations
Recommendation 46. SpA treatment should be adjusted to the clinical manifestations of the disease, severity of the symptoms, other clinical findings, and prognostic factors, as well as general patient characteristics (age, sex, comorbidity, etc.), preferences and

	expectations [5, D, 92.9%]. Recommendation 47. Optimal management of SpA patients requires a combination of pharmacological and non-pharmacological treatments which should be started as early as possible [5, D, 92.9%]. **Analgesics** Recommendation 49. Analgesics like paracetamol or opiates can be offered to patients with SpA whose pain is not controlled with NSAIDs, or when NSAIDs are contraindicated or poorly tolerated [5, D, 87.1%]. **Nonsteroidal anti-inflammatory drugs** Recommendation 50. The NSAIDs are recommended (unless contraindicated) as first-line treatment for the control of pain and stiffness and to improve function in patients with SpA [1b, A, 94.3%]. Once the therapeutic goal is achieved, the minimum effective dose should be maintained [5, D, 94.3%]. Before considering an NSAID to be ineffective, it should have been administered for at least 2-4 weeks at the maximum recommended or tolerated doses [4, C, 94.3%]. **Glucocorticoids** Recommendation 51. Local GC infiltrations are recommended in SpA patients refractory to NSAIDs [1c, A, 90%]. The use of systemic GCs is recommended only in exceptional situations of major inflammation [2b, B, 90%]. **Disease-modifying antirheumatic drugs** Recommendation 52. In SpA patients who are refractory to NSAIDs, the use of DMARDs should be evaluated [1a, A, 84.3%]. **Sulfasalazine** Recommendation 53. Routine use of sulfasalazine is not recommended for treatment of axial symptoms in SpA [1a, A, 85.7%], but it is indicated in cases of peripheral involvement [1a, A, 85.7%] and for other extra-articular manifestations like uveitis [2c, B, 85.7%] and IBD [1a, A, 85.7%]. **Methotrexate** Recommendation 54. The use of MTX should be evaluated individually in patients with AS, uSpA or ReA (especially peripheral forms and enthesitis) who are refractory to all available treatments with proven efficacy [5, D, 78.6%]. MTX should be assessed for routine use in PsA [2a, B, 78.6%] and in extra-articular manifestations like uveitis [2c, B, 78.6%] and IBD [1a, A, 78.6%]. **Leflunomide** Recommendation 55. The use of LEF should be evaluated individually in patients with AS, uSpA and ReA (especially in peripheral forms and enthesitis), and extra-articular manifestations refractory to all available treatments with proven efficacy [5, D, 77.1%]. LEF should be assessed for routine use in PsA for peripheral arthritis and dactylitis [1b, A, 77.1%], and enthesitis [5, D, 77.1%]. **Cyclosporin A** Recommendation 56. The use of CsA should be evaluated individually in patients with AS, uSpA and ReA (especially in peripheral forms and enthesitis), refractory to all available treatments with proven effectiveness [5, D, 55,7%]. Its use should be assessed in

	extraarticular manifestations [2b, B] and in PsA for peripheral arthritis and dactylitis [2b, B, 55,7%], and enthesitis [5, D, 55,7%]. **Other DMARDs** Recommendation 57. SpA patients who are clinically active and in whom other treatments have failed or are not possible should be evaluated individually for possible use of AZA, gold salts, cyclophosphamide or d-penicillamine provided that the potential benefit is considered to outweigh the possible adverse events [5, D, 48.5%]. **Bisphosphonates** Recommendation 58. Pamidronate may be offered in selected cases to SpA patients who are refractory to conventional treatments and in whom initiation of anti-TNF therapy is contraindicated [5, D, 58.6%]. **Thalidomide** Recommendation 59. SpA patients with particularly severe axial involvement and who are refractory to all therapies with proven efficacy should be evaluated individually for possible use of thalidomide, with special attention to its toxicity profile [5, D, 58.6%]. **Treatment changes and evaluation** Recommendation 60. Whenever the therapeutic goal is not attained, the patient's treatment should be reevaluated [5, D, 74,3%]. Recommendation 61. The recommended variables for evaluation of treatment response in SpA are the BASDAI, PtGA, nocturnal spinal pain, arthritis/enthesitis, DAS-28, and acute phase reactants (APRs) [5, D, 87.1%]. **Patients without previous treatment** Recommendation 62. In SpA, it is recommended that pharmacological treatment be evaluated at 3-4 months [5, D, 85.7%]. Recommendation 63. In patients with predominantly axial SpA, anti-TNF-α agents should be used if, after 3 months of NSAID treatment, the BASDAI remains ≥4, together with at least one of the following criteria: a) PtGA ≥4; b) nocturnal pain ≥4; c) elevated APR. In any case, the opinion of a rheumatologist or physician expert in SpA is essential [5, D, 87.1%]. Recommendation 64. For peripheral forms of SpA, the anti-TNF-α are indicated if, despite treatment with at least two NSAIDs, SSZ (AS and PsA), or other DMARDs (PsA) and local treatments, arthritis or enthesitis persist for more than 3-4 months, in addition to PtGA ≥ 4 and/or elevated ESR/CRP and, for pure polyarticular arthritis, if the patient's DAS-28 is ≥ 3.2 [5, D, 85.7%]. Recommendation 65. In SpA, certain conditions such as monoarthritis, enthesitis or some extra-articular manifestations refractory to conventional treatment which have a pronounced functional or other type of impact on the patient, must be considered as treatment failure [5, D, 87,1%]. **Patients with previous treatment** Recommendation 66. In SpA patients who are considered not to have been treated correctly, treatment should be restarted or completed

	correctly before an anti-TNF-α is indicated [5, D, 87.1%]. Recommendation 67. In patients with SpA who responded to a DMARD that was subsequently withdrawn, in case of a new flare-up, the same DMARD should be prescribed before indicating an anti-TNF-α [5, D, 81.4%]. **Evaluation of response to TNFa antagonist agents** Recommendation 68. A patient with SpA and axial involvement will be considered to respond to anti-TNF-α if, after 3-4 months of treatment, disease remission is achieved or there is a 50% relative decrease on the BASDAI (or an absolute reduction of 2 points with respect to previous values) in at least one of the following: PtGA, nocturnal axial pain (if both were >4 before treatment), or reduction in ESR and/or CRP (if they were previously elevated) [5, D, 88.6%]. Recommendation 69. SpA patients with axial involvement who have not responded to one anti-TNF-α can switch to a second anti-TNF-α [5, D, 88.6%]. Recommendation 70. In SpA patients with axial involvement, if the response achieved with the second anti-TNF-α is <50% but >20% on the BASDAI and the PtGA, since the most effective therapeutic options currently available will have been used, treatment with the biological agent that the clinician considers of choice should be maintained unless one of the nonbiological treatments previously used would have been more effective, in which case consideration should be given to reinstating that treatment [5, D, 87.1%]. Recommendation 71. In SpA patients with axial involvement, if the response achieved with the second anti-TNF-α is <20% on the BASDAI and PtGA, the anti-TNF-α should be withdrawn if deemed advisable by the physician [5, D, 88.3%]. Recommendation 72. SpA patients with peripheral polyarticular involvement who are taking an anti-TNF-α agent should achieve clinical remission (DAS28 <2.6) or at least reduce inflammatory activity to DAS28 <3.2. When this is not achieved, a DAS reduction of 1.2 (from the previous level) would be accepted as sufficient to maintain treatment with the anti-TNF-α that the clinician considers to be of choice, unless one of the non-biological treatments previously used would have been more effective, in which case its reinstatement should be considered [5, D, 80%].
Rohekar et al., 2015 [15]. **Canadian Rheumatology Association** 2014 Update of the Canadian Rheumatology Association/ Spondyloarthritis Research Consortium of	*These recommendations apply to both axial and peripheral SpA. Included in axSpA is ankylosing spondylitis (AS) as well as nr-axSpA* Methodik Grundlage der Leitlinie – The 2014 Update on the CRA/SPARCC Treatment Recommendations for the Management of Spondyloarthritis was undertaken using a systemic approach with broad stakeholder input. The CRA/SPARCC Treatment Recommendations working group was composed of the SPARCC executive committee, rheumatologist leaders from SPARCC collaborating sites, Canadian rheumatologists from across the country with a special interest in SpA (representing both community and academic

Canada Treatment Recommendations for the Management of Spondyloarthritis. Part II: Specific Management Recommendations Methodik siehe: Part I: principles of the management of spondyloarthritis in Canada + Supplements	centers), epidemiologists/health services researchers, members of the CRA Executive and Therapeutics Committee, and a patient representative from the Canadian Spondylitis Association. Pharmaceutical or industry representatives were not involved in the development of the 2014 Update in any way. – Update der älteren Version von 2007 – Suchzeitraum: MEDLINE (OVID) and Pubmed (completed in April 2013) – Weitere Kriterien für die Qualität einer LL: • Empfehlungen sind mit Literaturstellen verknüpft LoE / GoR LOE I: Metaanalysis, systematic reviews of RCT, or an individual RCT II: Metaanalysis, systematic reviews of observational studies (cohort/case control studies), or individual observational studies, OR RCT subgroup/posthoc analysis III: Nonanalytic studies (case reports, case series) IV: Expert opinion NR: Recommendation is not linked to evidence SOR A: Strong recommendation: • Direct level 1 evidence B: Moderate recommendation: • Direct level 2 or extrapolated level 1 evidence C: Weak recommendation: • Direct level 3 or extrapolated level 2 evidence D: Consensus recommendation: • Expert opinion based on very little evidence LOE: level of evidence; SOR: strength of recommendation; RCT: randomized controlled trial; NR: not reported. Expert Opinion (EO) was evaluated on a 5-point Likert scale ranging from “disagree completely” to “agree completely”.
	Freitext/Empfehlungen/Hinweise **NSAID and analgesics** 3. NSAID are recommended as first-line drug treatment for symptomatic patients with axSpA. A sufficient trial of therapy is defined as at least 2 NSAID, each administered over a minimum 2-week period at the maximum tolerated dosage, unless contraindicated. (LoE: I; SoR: A; EO: 4.9) 4. The decision to use NSAID should be made after considering the patient’s cardiovascular risk factors. NSAID with the best cardiovascular safety profile should be preferred. (LoE: I; SoR: A; EO: 4.9) 5. When there is no therapeutic advantage, selective COX-2 inhibitor therapy should be used in patients at increased risk for GI adverse events. In patients at risk who respond best to a traditional NSAID, a gastroprotective agent can be used. (LoE: I; SoR: A; EO: 4.7) 6. Patients on longterm, regular NSAID therapy should be regularly monitored for changes in GI, cardiovascular, and renal status. (LoE: I; SoR: B; EO: 4.7) 7. If NSAID are insufficient or contraindicated, alternative pain control strategies (i.e., acetaminophen, opioids) should be considered. It should be noted that non-NSAID analgesics do not control inflammation. (LoE: IV; SoR: D; EO: 4.9) **Corticosteroids** 8. Corticosteroid injections at local sites of inflammation (i.e., SI joints, peripheral joints, and entheses) may be considered. (LoE: I [SI joints], II [PsA joints], IV [all other sites]; SoR: A [SI joints], B [PsA joints], D [all other sites]; EO: 4.7)

	9. Short courses of systemic corticosteroids may be considered for specific manifestations. The sustained use of systemic steroids is not recommended or supported. (LoE: I (AS); SoR: A (AS); EO: 4.7) **DMARD** 10. There is no evidence for the efficacy of DMARD, including SSZ and MTX, for the treatment of axSpA. (LoE: I; SoR: A; EO: 4.8) **Antibiotics** 13. A trial of rifampin plus either doxycycline or azithromycin may be tried for 6 mos in cases of proven post-Chlamydia chronic reactive arthritis. There is no evidence of efficacy for antibiotics in axSpA. (LoE: IV; SoR: D; EO: 4.5) **TNFi** 14. TNFi should be given only under supervision by a rheumatologist to patients with persistently high disease activity, despite other therapy. Routine laboratory screening (complete blood count, liver and renal function) as well as screening for Hepatitis B and C (and HIV in high risk patients) should be performed prior to initiation. Screening for latent TB infection should be performed prior to initiation. Baseline ANA may be considered. CRA recommendations for prevention of TB should be followed. Seasonal vaccination for influenza is recommended for patients before or during treatment with TNFi. Hepatitis B vaccine should be considered in high-risk groups in patients determined to be nonimmune to HBV. H. zoster vaccine should be considered in patients aged 60 yrs or older. (LoE: IV; SoR: D; EO: 4.9) 15. There is no evidence to support the obligatory use of DMARD before, or concomitant with, TNFi in patients with axSpA. (LoE: I; SoR: A; EO: 4.8) 16. For patients with predominantly axSpA, TNFi should be offered to those with persistent symptoms after a trial of NSAID therapy as defined above and evidence of active disease as defined by at least 2 of the following: • BASDAI > 4 • Elevated CRP or ESR • Inflammatory lesions in the SI joints and/or spine on MRI (LoE: I [TNFi efficacy], IV [active disease definition]; SoR: A [TNFi efficacy], IV [active disease definition]; EO: 4.2) 18. For patients with refractory enthesitis or dactylitis, TNFi should be offered to those with persistent inflammation. (LoE: I [enthesitis], II [dactylitis]; SoR: A [enthesitis], B [dactylitis]; EO: 4.5) 19. Several TNFi are available for the treatment of SpA, including infliximab, etanercept, adalimumab, golimumab, and certolizumab.

	The choice of TNFi should be determined by consultation between the physician and patient. Dosing and monitoring of these drugs should be tailored to the individual patient and follow usual standard of care. (LoE: I; SoR: B; EO: 5.0) 20. Maintenance on TNFi should be based on attainment of clinical response 16 weeks after initiating treatment. In axSpA, a clinical response is defined as either an absolute reduction of the BASDAI by 2 (0–10 scale) or a relative reduction of 50%. In peripheral SpA, a clinical response is defined as a reduction in active joint count by 30%. (LoE: IV; SoR: D; EO: 4.7) 21. The choice of TNFi should incorporate the presence or absence of extraarticular manifestations. When possible, the chosen TNFi should treat both SpA and the particular extrarticular manifestations effectively. (LoE: I; SoR: A; EO: 4.9) 22. Combination of MTX and TNFi does not influence clinical efficacy, though in peripheral SpA it may be associated with prolonged drug response. (LoE: II; SoR: B; EO: 4.5) 23. Nonresponders to TNFi may benefit from switching to another TNFi. (LoE: II; SoR: B; EO: 4.9) **Other biologic agents** 24. Rituximab may be considered for the treatment of axSpA for patients in whom TNFi are contraindicated. (LoE: II; SoR: B; EO: 4.2) 25. Ustekinumab may be considered for the treatment of patients with SpA with concomitant moderate to severe cutaneous psoriasis. (LoE: I; SoR: A; EO: 4.8) 26. There is currently no evidence for the use of other biologic agents in SpA, including TCZ, and anakinra. (LoE: II [ABA], I [TCZ], II [anakinra]; SoR: B [ABA], A [TCZ], B [anakinra]; EO: 4.9)
Braun et al., 2011 [3]. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis Siehe auch: Kiltz et al., 2013 [8]. Empfehlungen für	The recommendations were to apply to all patients fulfilling the modified New York criteria for AS, independent of extra-articular manifestations. Patients of all ages, including paediatric patients, were included, and all pharmacological and non-pharmacological interventions for AS were taken into account.
	Methodik Grundlage der Leitlinie – International, multidisciplinary expert group; discussion of former recommendations on the basis of new systematic reviews; The experts met on 15/26 February 2010 in Zurich. During the meeting, the data from the SLR dating from the previous search in 2005 until December 2009 were presented to the international experts. Each bullet point was discussed in detail until consensus was

die Behandlung der ankylosierenden Spondylitis gemäß ASAS/EULAR	reached as to whether rewording was necessary. New recommendations were considered if this was proposed by a member of the panel. – Als Evidenzgrundlage wurden 2 systematische Reviews durchgeführt (Baraliakos et al., 2012 [2], van den Berg et al., 2012 [17]) – Update der Leitlinie von 2006 – Suchzeitraum (Aktualität der Recherche): PubMed, Embase and Cochrane databases for the time period 1 January 2005 (which represents the date after the end of the last systematic literature review on this topic) to 1 December 2009 (for treatment with biologics); PubMed, EMBASE, PEDro and Cochrane between 1 January 2005, which is the end date of the last literature search, and 1 December 2009 (for non-pharmacological treatment and non-biologic drugs) – Weitere Kriterien für die Qualität einer LL: • Empfehlungen sind nicht explizit mit Literaturstellen verknüpft LoE / GoR Im vorliegenden Update der Leitlinie wurden keine LoE / GoR angegeben. Scoring on an 11-point numerical rating scale for the strength of recommendation was done by email by each expert for each bullet point after the meeting.
	Freitext/Empfehlungen/Hinweise **General treatment** The treatment of patients with AS should be individualized according to: • The current manifestations of the disease (axial, peripheral, entheseal, extra-articular symptoms and signs) • The level of current symptoms, clinical findings and prognostic indicators • The general clinical status (age, gender, comorbidities, concomitant medications, psychosocial factors). *Strength of recommendation: 9.5±0.1.* **Non-steroidal anti-inflammatory drugs** • Non-steroidal anti-inflammatory drugs (NSAID), including Coxibs, are recommended as first-line drug treatment for AS patients with pain and stiffness. • Continuous treatment with NSAID is preferred for patients with persistently active, symptomatic disease. • Cardiovascular, gastrointestinal and renal risks should be taken into account when prescribing NSAID. *Strength of recommendation: 9.3±0.3.* **Analgesics** • Analgesics, such as paracetamol and opioid-(like) drugs, might be considered for residual pain after previously recommended

	treatments have failed, are contraindicated, and/or poorly tolerated. *Strength of recommendation: 8.0±0.5.* **Glucocorticoids** • Glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered. • The use of systemic glucocorticoids for axial disease is not supported by evidence. *Strength of recommendation: 8.9±0.4.* **Disease modifying antirheumatic drugs** • There is no evidence for the efficacy of disease-modifying antirheumatic drugs (DMARD), including sulfasalazine and methotrexate, for the treatment of axial disease. • Sulfasalazine may be considered in patients with peripheral arthritis. *Strength of recommendation: 9.4±0.2.* **Anti-TNF therapy** • Anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments according to the ASAS recommendations. • There is no evidence to support the obligatory use of DMARD before or concomitant with anti-TNF therapy in patients with axial disease. • There is no evidence to support a difference in efficacy of the various TNF inhibitors on the axial and articular/entheseal disease manifestations; but in the presence of IBD a difference in gastrointestinal efficacy needs to be taken into account. • Switching to a second TNF blocker might be beneficial especially in patients with loss of response. • There is no evidence to support the use of biological agents other than TNF inhibitors in AS. *Strength of recommendation: 9.4±0.2.*
Wendling et al., 2014 [19]. Recommendations of the French Society for Rheumatology (SFR) on the every day management of patients with spondyloarthritis	To develop practice guidelines for the everyday management of patients with spondyloarthritis (including psoriatic arthritis), by updating previous national and international recommendations, based on a review of recently published data. *Die Leitlinie umfasst Patienten mit Spondyloarthritiden; daher sind nicht alle Empfehlungen speziell auf Patienten mit AS ausgerichtet*
	Methodik Grundlage der Leitlinie – A physical meeting was held for presentation of the literature review data, discussion among experts, and development of the practice guidelines. Subsequently, the practice guidelines were reviewed by the same experts for validation and rating of the level of agreement, from which the grade of each practice guideline was determined. Finally, the practice guidelines were submitted to a group of reviewers designated by the task force and described below. The final version was modified based on the comments by both groups. – Suchzeitraum:

	based on an update and French adaptation of existing recommendations issued by the ASAS/EULAR and ASAS (Referenzen Braun und van der Heijde); Articles published between January 1, 2010, and June 17, 2013, were retrieved using appropriate key terms to search PubMed-Medline, Cochrane, and Embase. – Weitere Kriterien für die Qualität einer LL: • Empfehlungen sind mit Literaturstellen verknüpft LoE / GoR The strength of the practice guidelines (based on the level of evidence) and the level of agreement among experts (rated from 0 [strongly disagrees] to 10 [strongly agrees]) are given for each practice guideline. Strength was graded according to standard practice: •A: guideline based on level 1 evidence (meta-analysis of randomized controlled trials or at least one randomized controlled trial); •B: guideline based on level 2 evidence (at least one nonrandomized controlled trial or quasi-experimental study) or extrapolated from level 1 evidence; •C: guideline based on level 3 evidence (descriptive study) or extrapolated from level 1 or 2 evidence; •D: guideline based on level 4 evidence (expert opinion) or extrapolated from level 1, 2, or 3 evidence.
	Freitext/Empfehlungen/Hinweise **Treatment with conventional medications** 15) In the absence of contraindications, NSAIDs constitute the first-line pharmacological treatment of symptomatic spondyloarthritis (A) (10). 16) The NSAID regimen should be tailored to each individual patient, and the lowest dosage and duration ensuring symptom control should be used. When selecting the NSAID, the risks of adverse cardiovascular, gastrointestinal, and renal effects should be among the factors taken into consideration (C) (9,7). 17) Analgesics can be used in patients with residual pain despite NSAID therapy and in patients with failure of, contraindications to, or intolerance to NSAIDs (D) (9,8). 18) Local glucocorticoid injections at symptomatic sites (most notably sites of arthritis or enthesitis) can be considered (D) (9,8). 19) In general, systemic glucocorticoid therapy is not warranted for treating the axial manifestations of spondyloarthritis (D) (9,7). 20) To date, there is no indication for conventional disease-modifying antirheumatic drugs ([DMARDs], methotrexate, leflunomide, and sulfasalazine) to treat isolated axial manifestations or enthesitis (C) (9,3).

21) The use of conventional DMARDs (methotrexate, leflunomide,and sulfasalazine) can be considered in patients with peripheralarthritis that fails to respond to symptomatic therapy (D) (9,8).

Biologic agents

22) TNFα antagonist therapy should be offered to patients withpersistent disease activity despite conventional treatment, according to the recommendations shown in Fig. 1 (D) (9,8).

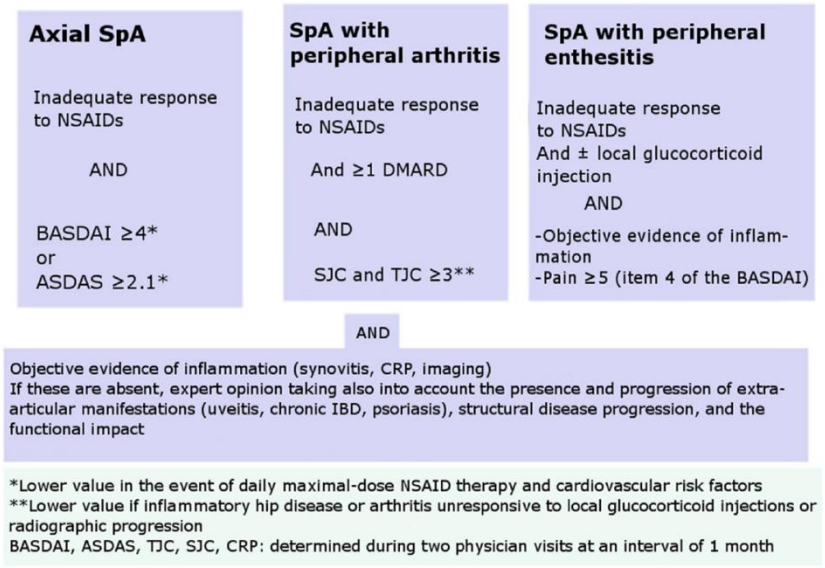


Fig. 1. Indications for TNFα antagonist therapy.

23) The response to TNFα antagonist therapy should be evaluated after at least 3 months, using objective measures of disease activity (D) (9,1).

24) In the event of primary or secondary lack of effectiveness of a TNFα antagonist, there is no proof to date that increasing the dosage is beneficial. After reappraising the diagnosis of spondyloarthritis and ruling out a differential diagnosis or complication of the disease, a switch to another TNFα antagonist deserves consideration (D) (9,7). Switching to a second TNFα antagonist may be beneficial, in particular in the event of escape phenomenon, primary ineffectiveness, or intolerance to a first TNFα antagonist (C) (9,7).

25) In the event of a disease remission or low level of activity sustained for at least 3 to 6 months under TNFα antagonist therapy, a gradual increase in the dosing interval or decrease in the drug dosage can be considered (C) (9,6).

26) There is no evidence to support differences across TNFα antagonists regarding effectiveness on the axial or peripheral manifestations/enthesitis. In patients with chronic inflammatory bowel disease (IBD), there is a difference in effectiveness on the gastrointestinal manifestations, which should be taken into account. (D) (9.7).

27) There is no evidence to date to support the use of biological agents other than TNFα antagonists in patients with axial spondyloarthritis (D) (9,6).

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren wurden durch die Suche nicht identifiziert.

Primärstudien

Da ausreichend Information aus aggregierter Evidenz vorliegt, wurde eine Suche nach Primärstudien nicht in Auftrag gegeben.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 21.07.2015**

#	Suchfrage
1	MeSH descriptor: [Spondylitis, Ankylosing] explode all trees
2	ankylosing spondylitis:ti,ab,kw
3	bechtere*:ti,ab,kw
4	#1 or #2 or #3
5	#4 from 2010 to 2015

SR, HTAs in Medline (PubMed) am 22.07.2015

#	Suchfrage
1	Spondylitis, Ankylosing[MeSH]
2	(ankylosing[Title/Abstract]) AND spondylitis[Title/Abstract]
3	bechtere*[Title/Abstract]
4	#1 OR #2 OR #3
5	(#4) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
6	(#4) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
7	#5 OR #6
8	(#7) AND ("2010/07/01"[PDAT] : "2015/07/22"[PDAT])

Leitlinien in Medline (PubMed) am 22.07.2015

#	Suchfrage
1	Spondylarthritis[MesH]
2	((spondylarthrit*[Title/Abstract]) OR spondyloarthrit*[Title/Abstract]) OR ((ankylosing[Title/Abstract]) AND spondylitis[Title/Abstract])
3	#1 OR #2
4	(#3) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title/Abstract])
5	(#4) AND ("2010/07/01"[PDAT] : "2015/07/22"[PDAT])

Literatur:

1. **Baji P, Pentek M, Szanto S, Geher P, Gulacsi L, Balogh O, Brodszky V**. Comparative efficacy and safety of biosimilar infliximab and other biological treatments in ankylosing spondylitis: systematic literature review and meta-analysis. Eur J Health Econ 2014; 15 (Suppl 1): S45-S52.

2. **Baraliakos X, van den Berg R, Braun J, van der Heijde D**. Update of the literature review on treatment with biologics as a basis for the first update of the ASAS/EULAR management recommendations of ankylosing spondylitis. Rheumatology (Oxford) 2012; 51 (8): 1378-87.

3. **Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, Dagfinrud H, Dijkmans B, Dougados M, Emery P, Geher P, Hammoudeh M, Inman RD, Jongkees M, Khan MA, Kiltz U, Kvien T, Leirisalo-Repo M, Maksymowych WP, Olivieri I, Pavelka K, Sieper J, Stanislawska-Biernat E, Wendling D, Ozgocmen S, van DC, van RB, van der Heijde D**. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis 2011; 70 (6): 896-904.

4. **Deutsche Gesellschaft für Rheumatologie**. Axiale Spondyloarthritis inklusive Morbus Bechterew und Frühformen. S3-Leitlinie (Stand: 11/2013). Düsseldorf (GER): Arbeitsgemeinschaft der WissenschaftlichenMedizinischen Fachgesellschaften e V (AWMF) 2013; (Registernummer 060-03).http://www.awmf.org/leitlinien/detail/ll/060-003.html, Zugriff am 21.07.2015.

5. **Escalas C, Trijau S, Dougados M**. Evaluation of the treatment effect of NSAIDs/TNF blockers according to different domains in ankylosing spondylitis: results of a meta-analysis. Rheumatology (Oxford) 2010; 49 (7): 1317-25.

6. **Espoguia Group, Spanish Society of Rheumatology (SER), Research Unit (RI) of the SER, Abbott**. Espoguia. Clinical guidelines for patients with spondyloarthritis. Madrid (ESP): Spanish Society of Rheumatology 2010; http://www.ser.es/practicaClinica/espoguia/anexos/Espoguia-ENG.pdf, Zugriff am 22.07.2015.

7. **Fouque-Aubert A, Jette-Paulin L, Combescure C, Basch A, Tebib J, Gossec L**. Serious infections in patients with ankylosing spondylitis with and without TNF blockers: a systematic review and meta-analysis of randomised placebo-controlled trials. Ann Rheum Dis 2010; 69 (10): 1756-61.

8. **Kiltz U, Sieper J, Braun J**. Empfehlungen fur die Behandlung der ankylosierenden Spondylitis gemass ASAS/EULAR : evaluation der Updates von 2010 im deutschsprachigen Raum. Z Rheumatol 2013; 72 (1): 71-80.

9. **Kroon Féline PB, van der Burg Lennart RA, Ramiro S, Landewé Robert BM, Buchbinder R, Falzon L, van der Heijde D**. Non-steroidal anti-inflammatory drugs (NSAIDs) for axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis). Cochrane Database of Systematic Reviews 2015; (7): CD010952.

10. **Li ZH, Zhang Y, Wang J, Shi ZJ**. Etanercept in the treatment of ankylosing spondylitis: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials, and the comparison of the Caucasian and Chinese population. Eur J Orthop Surg Traumatol 2013; 23 (5): 497-506.

11. **Liu YF, Dong H, Tu SH, Zheng CH, Liu PL, Hu YH**. Etanercept in the treatment of ankylosing spondylitis: A systematic review and meta-analysis. Exp Ther Med 2014; 8 (5): 1585-92.

12. **Machado MA, Barbosa MM, Almeida AM, de Araujo VE, Kakehasi AM, Andrade EI, Cherchiglia ML, Acurcio FA**. Treatment of ankylosing spondylitis with TNF blockers: a meta-analysis. Rheumatol Int 2013; 33 (9): 2199-213.

13. **Maxwell LJ, Zochling J, Boonen A, Singh JA, Veras Mirella MS, Tanjong GE, Benkhalti JM, Tugwell P, Wells GA**. TNF-alpha inhibitors for ankylosing spondylitis. Cochrane Database of Systematic Reviews 2015; (4): CD005468.

14. **Ren L, Li J, Luo R, Tang R, Zhu S, Wan L**. Efficacy of antitumor necrosis factor(alpha) agents on patients with ankylosing spondylitis. Am J Med Sci 2013; 346 (6): 455-61.

15. **Rohekar S, Chan J, Tse SM, Haroon N, Chandran V, Bessette L, Mosher D, Flanagan C, Keen KJ, Adams K, Mallinson M, Thorne C, Rahman P, Gladman DD, Inman RD**. 2014 Update of the Canadian Rheumatology Association/spondyloarthritis research consortium of Canada treatment recommendations for the management of spondyloarthritis. Part I: principles of the management of spondyloarthritis in Canada. J Rheumatol 2015; 42 (4): 654-64.

16. **Shu T, Chen GH, Rong L, Feng F, Yang B, Chen R, Wang J**. Indirect comparison of anti-TNF-alpha agents for active ankylosing spondylitis: mixed treatment comparison of randomized controlled trials. Clin Exp Rheumatol 2013; 31 (5): 717-22.

17. **van den Berg R, Baraliakos X, Braun J, van der Heijde D**. First update of the current evidence for the management of ankylosing spondylitis with non-pharmacological treatment and non-biologic drugs: a systematic literature review for the ASAS/EULAR management recommendations in ankylosing spondylitis. Rheumatology (Oxford) 2012; 51 (8): 1388-96.

18. **Wang H, Zuo D, Sun M, Hua Y, Cai Z**. Randomized, placebo controlled and double-blind trials of efficacy and safety of adalimumab for treating ankylosing spondylitis: a meta-analysis. Int J Rheum Dis 2014; 17 (2): 142-8.

19. **Wendling D, Lukas C, Paccou J, Claudepierre P, Carton L, Combe B, Goupille P, Guillemin F, Hudry C, Miceli-Richard C, Dougados M**. Recommendations of the French Society for Rheumatology (SFR) on the everyday management of patients with spondyloarthritis. Joint Bone Spine 2014; 81 (1): 6-14.

20. **Wu D, Guo YY, Xu NN, Zhao S, Hou LX, Jiao T, Zhang N**. Efficacy of anti-tumor necrosis factor therapy for extra-articular manifestations in patients with ankylosing spondylitis: a meta-analysis. BMC Musculoskelet Disord 2015; 16 19.