Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: Tofacitinib

Stand: Mai 2021

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

Tofacitinib
[ankylosierende Spondylitis (AS) (=röntgenologische axiale Spondyloarthritis (r-axSpA))]

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	Beschlüsse zur Nutzenbewertung nach § 35a SGB V - Secukinumab vom 02. Juni 2016 in der Teilindikation (a) AS - Ixekizumab vom 21. Januar 2021 - *Upadacitinib, Beschlussfassung am 25. Juli 2021*
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:	
Tofacitinib Xeljanz®	
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. *Nicht-röntgenologische axiale Spondyloarthritis* Behandlung Erwachsener mit schwerer nicht-röntgenologischer axialer Spondyloarthritis, mit objektiven, durch erhöhtes C-reaktives Protein (CRP) und/ oder Magnetresonanztomographie (MRT) nachgewiesenen Anzeichen einer Entzündung, die unzureichend auf eine Behandlung mit nichtsteroidalen Antirheumatika (NSARs) angesprochen haben. [Stand FI: 04/2016]
Infliximab L04AB02 z.B. Inflectra®	*Ankylosierende Spondylitis* Inflectra ist indiziert zur Behandlung der schwerwiegenden, aktiven ankylosierenden Spondylitis bei erwachsenen Patienten, die auf eine konventionelle Therapie unzureichend angesprochen haben. [Stand FI: 09/2016]
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. *Axiale Spondyloarthritis ohne Röntgennachweis einer AS*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	Humira ist indiziert zur Behandlung der schweren axialen Spondyloarthritis ohne Röntgennachweis einer AS, aber mit objektiven Anzeichen der Entzündung durch erhöhtes CRP und/oder MRT, bei Erwachsenen, die nur unzureichend auf nicht steroidale Antirheumatika angesprochen haben oder bei denen eine Unverträglichkeit gegenüber diesen vorliegt. [Stand FI: 12/2016]
Golimumab L04AB06 Simponi®	*Axiale Spondyloarthritis* *Ankylosierende Spondylitis (AS)* Simponi ist angezeigt zur Behandlung der schweren, aktiven ankylosierenden Spondylitis bei Erwachsenen, die auf eine konventionelle Therapie unzureichend angesprochen haben. *Nicht-röntgenologische axiale Spondyloarthritis (nr-axSpA)* Simponi ist indiziert zur Behandlung Erwachsener mit schwerer, aktiver nicht-röntgenologischer axialer Spondyloarthritis mit objektiven, durch erhöhtes C-reaktives Protein (CRP) und/oder Magnetresonanztomographie (MRT) nachgewiesenen Anzeichen einer Entzündung, die unzureichend auf eine Behandlung mit nichtsteroidalen Antirheumatika (NSARs) angesprochen haben oder bei denen eine Unverträglichkeit gegenüber solchen Substanzen besteht. [Stand FI: 02/2017]
Certolizumab Pegol L04AB05. Cimzia®	*Axiale Spondyloarthritis* Cimzia ist angezeigt für 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. *Axiale Spondyloarthritis ohne Röntgennachweis einer AS* Erwachsene mit schwerer, aktiver axialer Spondyloarthritis ohne Röntgennachweis einer AS, aber mit objektiven Anzeichen der Entzündung, festgestellt durch erhöhtes C-reaktives Protein (CRP) und/oder mittels Magnetresonanztomographie (MRT), die ungenügend auf NSAIDs angesprochen haben oder die eine Intoleranz gegenüber NSAIDs besitzen. [Stand FI: 01/2017]
Secukinumab L04AC10 Cosentyx®	*Ankylosierende Spondylitis (AS; Morbus Bechterew)* Cosentyx ist angezeigt für die Behandlung erwachsener Patienten mit aktiver ankylosierender Spondylitis, die auf eine konventionelle Therapie unzureichend angesprochen haben. *Nicht-röntgenologische axiale Spondyloarthritis*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	Cosentyx ist angezeigt für die Behandlung der aktiven nicht-röntgenologischen axialen Spondyloarthritis mit objektiven Anzeichen der Entzündung, angezeigt durch erhöhtes C-reaktives Protein (CRP) und/oder Nachweis durch Magnetresonanztomografie (MRT), bei Erwachsenen, die unzureichend auf nicht-steroidale Antirheumatika (NSAR) angesprochen haben. [Stand FI: 08/2020]
Ixekizumab L04AC13 Taltz®	*Ankylosierende Spondylitis (Röntgenologische axiale Spondyloarthritis)* Taltz ist angezeigt für die Behandlung erwachsener Patienten mit aktiver röntgenologischer axialer Spondyloarthritis, die auf eine konventionelle Therapie unzureichend angesprochen haben. *Nicht-röntgenologische axiale Spondyloarthritis* Taltz ist angezeigt für die Behandlung erwachsener Patienten mit aktiver nicht-röntgenologischer axialer Spondyloarthritis mit objektiven Anzeichen einer Entzündung, nachgewiesen durch erhöhtes C-reaktives Protein (CRP) und/oder Magnetresonanztomographie (MRT), die unzureichend auf nicht-steroidale Antirheumatika (NSAR) angesprochen haben. [Stand FI: 01/2021]
Upadacitinib L04AA44 Rinvoq®	*Ankylosierende Spondylitis* RINVOQ wird angewendet zur Behandlung der aktiven ankylosierenden Spondylitis bei erwachsenen Patienten, die auf eine konventionelle Therapie unzureichend angesprochen haben. [Stand FI: 01/2021]
Glukokortikoide	
Prednisolon H02AB06 generisch	• andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können: – Spondarthritiden (Spondylitis ankylosans mit Beteiligung peripherer Gelenke (DS b, c), Arthritis psoriatica (DS c, d), enteropathische Arthropathie mit hoher Entzündungsaktivität (DS a) (Prednisolon acis FI, Stand 05/2014)
Prednison H02AB07 generisch	Andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	– Spondarthritiden (Spondylitis ankylosans mit Beteiligung peripherer Gelenke (DS b, c), Arthritis psoriatica (DS c, d), enteropathische Arthropathie mit hoher Entzündungsaktivität (DS a) (Prednison acis FI, Stand 05/2014)
Triamcinolon H02AB08 Volon®	Andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können: Spondarthritiden (Spondylitis ankylosans mit Beteiligung peripherer Gelenke, Arthritis psoriatica, enteropathische Arthropathie mit hoher Entzündungsaktivität);
Nicht-steroidale Antirheumatika (NSAID/ NSAR) z. B.	
Indometacin M01AB01 generisch	– Spondylitis ankylosans (Morbus Bechterew) und anderen entzündlich-rheumatischen Wirbelsäulenerkrankungen (Indomet-ratiopharm® FI, Stand 05/2013)
Ibuprofen M01AE01 generisch	Symptomatische Behandlung von Schmerz und Entzündung bei – akuten Arthritiden (einschließlich Gichtanfall) – chronischen Arthritiden, insbesondere bei rheumatoider Arthritis (chronische Polyarthritis) – Spondylitis ankylosans (Morbus Bechterew) und anderen entzündlich-rheumatischen Wirbelsäulenerkrankungen (Ibuprofen AbZ FI, Stand 01/2014)
Naproxen M01AE02 generisch	Symptomatische Behandlung von Schmerz und Entzündung bei – akuten Arthritiden (einschließlich Gichtanfall); – chronischen Arthritiden, insbesondere rheumatoider Arthritis/chronischer Polyarthritis; – Spondylitis ankylosans (Morbus Bechterew) und anderen entzündlich-rheumatischen Wirbelsäulenerkrankungen; (Naproxen acis FI, Stand 08/2014)
Acemetacin M01AB11 generisch	Symptomatische Behandlung von Schmerz und Entzündung bei – akuten Arthritiden (einschließlich Gichtanfall), – chronischen Arthritiden, insbesondere bei rheumatoider Arthritis (chronische Polyarthritis), – Spondylitis ankylosans (Morbus Bechterew) und anderen entzündlich-rheumatischen Wirbelsäulenerkrankungen, (Acemetacin Heumann FI, Stand 04/2015)
Etoricoxib M01 AH 05 generisch	Etoricoxib Mylan ist angezeigt bei Erwachsenen und Jugendlichen ab 16 Jahren zur Behandlung von Symptomen bei Reizzuständen degenerativer und entzündlicher Gelenkerkrankungen (Arthrose und rheumatoide Arthritis), Spondylitis ankylosans (Morbus Bechterew) sowie von Schmerzen und Entzündungszeichen bei akuter Gichtarthritis. (Stand FI 01/2020)
Celecoxib	Celecoxib Mylan wird angewendet bei Erwachsenen zur Behandlung von Symptomen bei Reizzuständen degenerativer Gelenkerkrankungen

II. Zugelassene Arzneimittel im Anwendungsgebiet	
M01 AH 01 Generisch	(aktivierte Arthrosen), chronischer Polyarthritis (rheumatoide Arthritis) und Spondylitis ankylosans (Morbus Bechterew). (Stand FI 01/2020)

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: Tofacitinib

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	11. Mai 2021

Inhaltsverzeichnis

Abkürzungsverzeichnis

ACR	American College of Rheumatology
ADA	Anti-Drug-Antikörper
AGREE	Appraisal of Guidelines, Research and Evaluation
AM-RL	Arzneimittel-Richtlinie
APR	Apremilast
AS	Ankylosierende Spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
axSpA	Axiale Spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
bDMARD	Biological Disease-Modifying Antirheumatic Drug
BIW	Twice a Week
BT	Biological Therapy
CEBM	Centre for Evidence Based Medicine
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CPG	Clinical Practice Guideline
CRP	C-reaktives Protein
csDMARD	Conventional Synthetic Disease-Modifying Antirheumatic Drug
CT	Computertomographie
DAPSA	Disease Activity in Psoriatic Arthritis Score
DGRh	Deutsche Gesellschaft für Rheumatologie e. V.
DMARD	Disease-Modifying Antirheumatic Drug
DoA	Degree of Agreement
ECRI	ECRI Guidelines Trust
EMBASE	Excerpta Medica Database
EMEUNET	EMering EUlar NETwork
ESR	Erythrozytensedimentationsrate
EULAR	European League Against Rheumatism
G-BA	Gemeinsamer Bundesausschuss
GC	Glucocorticoid

GDG	Guideline Development Group
GIN	Guidelines International Network
GoR	Grade of Recommendations
GP	General Practicioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HLA	Humanes Leukozytenantigen
IBD	Inflammatory Bowel Disease
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IL	Interleukin
IXE	Ixekizumab
LEF	Leflunomid
LoE	Level of Evidence
MC	Multicenter
MEDLINE	Medical Literature Analysis and Retrieval System Online
MDA	Minimal Disease Activity
MRI	Magnetic Resonance Imaging
mSASSS	modified Stoke AS Spine Score
MTX	Methotrexat
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
nr-axSpA	Nicht-radiographische axiale Spondyloarthritis
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSAR	Nichtsteroidales Antirheumatikum
OR	Odds Ratio
OSM	oral small molecule
PAM	Pamidronat
PDE4i	Phosphodiesterase-4-Inhibitor
PRO	Patient-Reported Outcome
QW	Once a Week
RCT	Randomised Controlled Trial
SAA	Spondylitis Association of America
SC	Single center
SEC	Secukinumab
SER	Spanisch Society of Rheumatology
SGB	Sozialgesetzbuch

SIGN	Scottish Intercollegiate Guidelines Network
SIJ	Sacroiliac Joint
SJC	Swollen Joint Count
SLR	Systematic Literature Review
SoR	Strength of recommendation
SPARTAN	Spondyloarthritis Reseach and Treatment Network
SSZ	Sulfasalazin
THL	Thalidomid
TJC	Tender Joint Count
TNF	Tumornekrosefaktor
TNFi	Tumornekrosefaktor-Inhibitor
TOF	Tofacitinib
TRIP	Turn Research into Practice Database
VAS	Visuelle Analogskala
WHO	World Health Organization

1 Indikation

Behandlung von erwachsenen Patientinnen und Patienten mit aktiver ankylosierender Spondylitis, die auf eine konventionelle Therapie unzureichend angesprochen haben.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *ankylosierende Spondylitis* durchgeführt. Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 19.04.2021 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 755 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 17 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA-Beschlüsse / IQWiG-Berichte

G-BA, 2021 [6]

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ixekizumab (neues Anwendungsgebiet: Axiale Spondyloarthritis) vom 21. Januar 2021

Anwendungsgebiet

Axiale Spondyloarthritis

Ankylosierende Spondylitis, röntgenologische axiale Spondyloarthritis

Taltz ist angezeigt für die Behandlung erwachsener Patienten mit aktiver röntgenologischer axialer Spondyloarthritis, die auf eine konventionelle Therapie unzureichend angesprochen haben.

Nicht-röntgenologische axiale Spondyloarthritis

Taltz ist angezeigt für die Behandlung erwachsener Patienten mit aktiver nicht-röntgenologischer axialer Spondyloarthritis mit objektiven Anzeichen einer Entzündung, nachgewiesen durch erhöhtes C-reaktives Protein (CRP) und/oder Magnetresonanztomographie (MRT), die unzureichend auf nicht-steroidale Antirheumatika (NSAR) angesprochen haben

Zweckmäßige Vergleichstherapie

a1) Erwachsene Patienten mit aktiver röntgenologischer axialer Spondyloarthritis, die auf eine konventionelle Therapie unzureichend angesprochen haben

ein TNF-alpha-Inhibitor (Etanercept oder Adalimumab oder Infliximab oder Golimumab oder Certolizumab pegol) oder ein IL17-Inhibitor (Secukinumab)

a2) Erwachsene Patienten mit aktiver röntgenologischer axialer Spondyloarthritis, die auf eine vorhergehende Therapie mit biologischen Antirheumatika (bDMARD) unzureichend angesprochen haben oder bei denen eine Unverträglichkeit gegenüber dieser vorliegt

der Wechsel auf ein anderes biologisches krankheitsmodifizierendes Antirheumatikum: TNF-alpha-Inhibitor (Adalimumab oder Certolizumab pegol oder Etanercept oder Golimumab oder Infliximab) oder IL17-Inhibitor (Secukinumab)

b) Erwachsene Patienten mit aktiver nicht-röntgenologischer axialer Spondyloarthritis mit objektiven Anzeichen einer Entzündung, nachgewiesen durch erhöhtes C-reaktives Protein (CRP) und/oder Magnetresonanztomographie (MRT), die unzureichend auf nicht-steroidale Antirheumatika (NSAR) angesprochen haben

ein TNF-alpha-Inhibitor (Etanercept oder Adalimumab oder Golimumab oder Certolizumab pegol)

Fazit / Ausmaß des Zusatznutzens

a) und b): Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [7].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Secukinumab (neues Anwendungsgebiet) vom 02. Juni 2016

Anwendungsgebiet

Ankylosierende Spondylitis (AS; Morbus Bechterew)

Secukinumab (Cosentyx®) ist angezeigt für die Behandlung erwachsener Patienten mit aktiver ankylosierender Spondylitis, die auf eine konventionelle Therapie unzureichend angesprochen haben.

Zweckmäßige Vergleichstherapie

ein TNF-alpha-Hemmer (Etanercept oder Adalimumab oder Infliximab oder Golimumab)

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

3.2 Cochrane Reviews

Es konnten keine relevanten Cochrane Reviews identifiziert werden.

3.3 Systematische Reviews

Deodhar A et al., 2020 [3].

A systematic review and network meta-analysis of current and investigational treatments for active ankylosing spondylitis.

Fragestellung

To compare the relative efficacy of current and investigational biologic and oral small molecule (OSM) treatments for active ankylosing spondylitis (AS).

Methodik

Population:

adult patients with active AS

Intervention und Komparator:

adalimumab (ADA), apremilast (APR), certolizumab pegol (CZP), etanercept (ETN), filgotinib, infliximab (IFX), ixekizumab, GOL (both IV and subcutaneous (SC) formulations), placebo (PBO), risankizumab, secukinumab (SEC), tofacitinib, and ustekinumab

Endpunkte:

- improvement of ≥ 20% in the Assessment of Spondyloarthritis International Society Criteria (ASAS20),
- change in Bath Ankylosing Spondylitis Functional Index (BASFI), and
- change in C-reactive protein (CRP) at weeks 12 to 16.

Recherche/Suchzeitraum:

- OVID MEDLINE, including Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Embase, and the CENTRAL Database of the Cochrane Library (Wiley version) until November 2018

Qualitätsbewertung der Studien:

Cochrane RoB

NMA-spezifische Angaben:

- Bayesian NMAs were conducted for ASAS20 response, change from baseline in BASFI, and change from baseline in CRP using a random effects (RE) model.
- Under the Cumulative Ranking curve (SUCRA) values, reported as percentages, were calculated to reflect the relative probability of an intervention being among the best options.
- Each NMAwas performed in accordance with the methodology recommended by the National Institute for Health and Care Excellence (NICE).

Ergebnisse

Anzahl eingeschlossener Studien:

30 RCTs included (n=6711 patients)

Charakteristika der Population:

siehe Anhang (Tabelle 1)

- The mean age of patients ranged from 27.4 to 48.0 years and the mean disease duration ranged from 5.2 to 23.0 years. The proportion of male patients ranged from 52.6 to 100% and the proportion of HLA-B27-positive patients ranged from 65.0 to 97.4%.Mean baseline scores for Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ranged from 4.4 to 7.6 cm, for BASFI ranged from 3.2 to 7.4 cm, and for CRP ranged [23] from 6.2 to 32.0 mg/l. Of the 30 studies, 23 allowed concomitant use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), four prohibited concomitant use, and three did not report this information.

Qualität der Studien:

APPENDIX S4. RISK OF BIAS ASSESSMENT

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcomes assessed	Incomplete outcome data	Selective reporting
Deodhar 2018 (GO-ALIVE)*						
Inman 2008*						
Bao 2014*						
Braun 2002						
van der Heijde 2005 (ASSERT)						
van der Heijde 2006 (A)*						
Maksymowych 2008*						
Hu 2012						
Huang 2014						
Landewe 2014*						
Gorman 2002						
Davis 2003						
Calin 2004						
van der Heijde 2006 (B)						
Barkham 2010						
Baeten 2018						
Deodhar 2018 - 3001 (Study 1 - naive to anti-TNF)						
Deodhar 2018 - 3002 (Study 2 - refractory to anti-TNF)						
van der Heijde 2018 (COAST-V)						
Deodhar 2018						
Deodhar 2016 (MEASURE 1)*						
Marzo-Ortega 2017 (MEASURE 2)*						
Pavelka 2017 (MEASURE 3)*						
Kivitiz 2018 (MEASURE 4)						
van der Heijde 2018 (TORTUGA)						
van der Heijde 2017						
Pathan 2012						
Unpublished (NCT01583374)**						

Key: low risk of bias; unclear risk of bias; high risk of bias.

*Crossover was allowed in these studies. However, the results used in this analysis were obtained before crossover and thus were not biased by the study design.

Studienergebnisse:

1) Attainment of ASAS20 response

- n=26 studies included in the comparison of ASAS20 at weeks 12 and 16
- Tofacitinib 5 mg had superior ASAS20 response compared to GOL IV 2 mg/kg and TOF 10 mg, and both TOF 5 mg and GOL IV 2 mg/kg were superior to TOF 2 mg, PBO, RIS 90 mg, SEC SC 75 mg, UST 90 mg, RIS 180 mg, APR 30 mg, and UST 45 mg (Fig. 2).
- Tofacitinib 5 mg and GOL IV 2 mg/kg were of greater or equal efficacy compared to the other treatments. Rankings based on SUCRA values for ASAS20 response were highest for TOF 5 mg (93%), GOL IV 2 mg/kg (90%), and FIL 200 mg (86%).

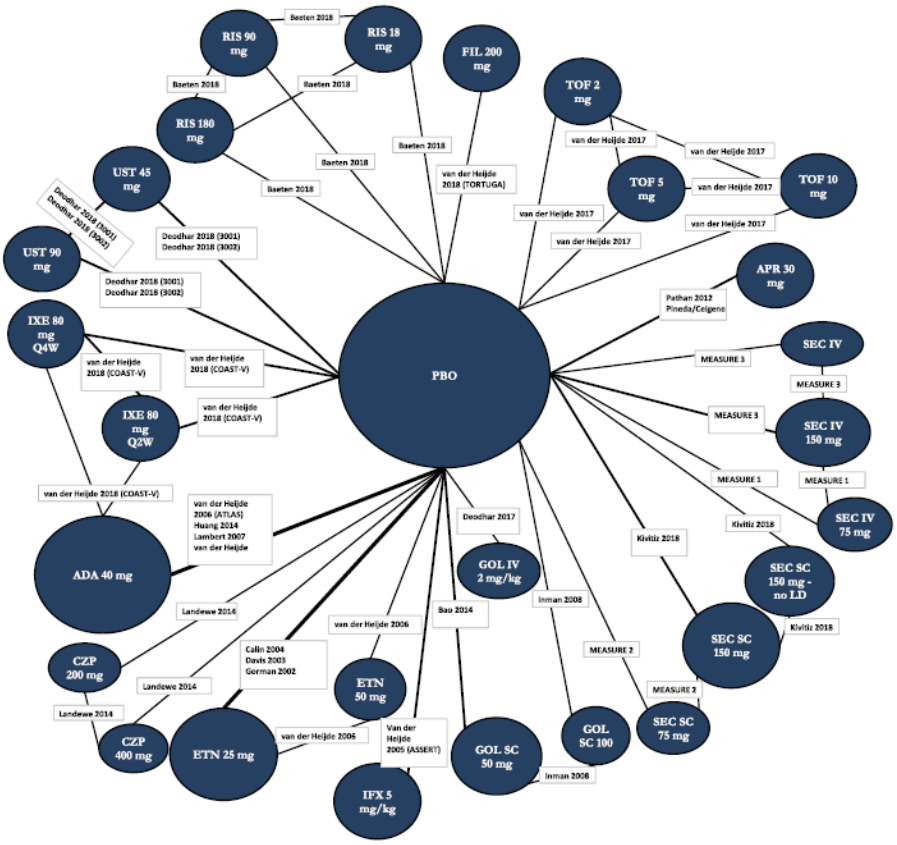


Fig. 1 Evidence network for ASAS20 NMA. Each intervention is represented by a node and randomized comparisons are shown as links between the nodes. The size of each node represents the number of patients randomized to each treatment, and the width of connections is reflective of number of RCTs. Abbreviations: ADA, adalimumab; APR, apremilast; ASAS20, improvement of ≥ 20% in the Assessment of Spondyloarthritis International Society Criteria; CZP, certolizumab pegol; ETN, etanercept; FIL, filgotinib; GOL, golimumab; IFX, infliximab; IV, intravenous; IXE, ixekizumab; LD, loading dose; NMA, network meta-analysis; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; RIS, risankizumab; TOF, tofacitinib; SC, subcutaneous; SEC, secukinumab; UST, ustekinumab

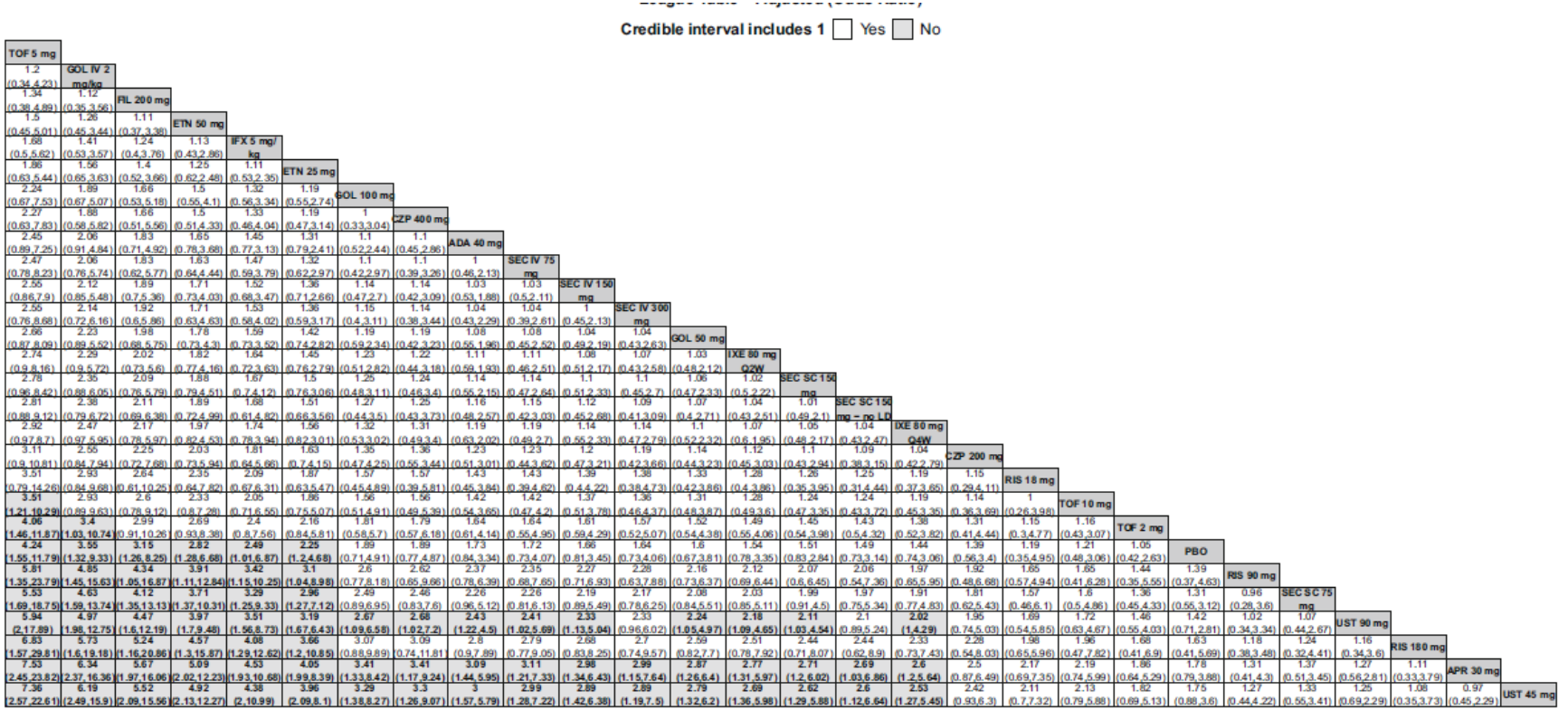


Fig. 2 League table of pairwise comparisons for all treatments in the ASAS20 NMA. Pairwise comparisons are reported as ORs and 95% CrIs. Comparators are ordered from largest (top-left) to smallest (bottom-right) SUCRA values for the ASAS20 NMA. Please refer to Fig. 5 for SUCRA values for each NMA. Superior improvements in ASAS20 are denoted in bold text and light gray cells. Results are shown for the baseline risk-adjusted model for ASAS20. Please refer to Appendix S6 for the model fit statistics. Abbreviations: ADA, adalimumab; APR, apremilast; ASAS20, improvement of ≥20% in the Assessment of Spondyloarthritis International Society Criteria; CrIs, credible intervals; CZP, certolizumab pegol; ETN, etanercept; FIL, filgotinib; GOL, golimumab; IFX, infliximab; IXE, ixekizumab; IV, intravenous; LD, loading dose; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; RIS, risankizumab; SC, subcutaneous; SEC, secukinumab; SUCRA, Surface Under the Cumulative Ranking curve; TOF, tofacitinib; UST, ustekinumab

2) Change from baseline in BASFI

- N= 23 studies included in the comparison of the change from baseline in BASFI at weeks 12 to 16
- Golimumab IV 2 mg/kg was ranked highest among all treatments, followed by IFX 5 mg/kg. Both interventions had superior reductions from baseline for BASFI compared to PBO and UST 45 mg, and IFX 5 mg/kg was also superior to UST 90 mg (Fig. 3).
- SUCRA values for the change from baseline in BASFI were highest for GOL IV 2 mg/kg (81%), IFX 5 mg/kg (80%), and GOL SC 100 mg (69%).

3) Change from baseline in CRP

- N=19 studies included in the comparison of the change from baseline in CRP at weeks 12 to 16
- Infliximab 5 mg/kg was ranked highest among all treatments, followed by GOL IV 2 mg/kg. Infliximab 5 mg/kg showed superior reduction from baseline in CRP compared to UST 90 mg, UST 45 mg, and PBO and GOL IV 2 mg/kg was superior to PBO (Fig. 4).
- SUCRA values for the change in CRP NMA were highest for IFX 5 mg/kg (90%), GOL IV 2 mg/kg (82%), and IXE 80 mg Q4W (76%).

League Table – Unadjusted (Mean Difference)

Credible interval includes 0 ☐ Yes ☐ No

GOL IV 2 mg/kg																				
−0.1 (−1.88,1.73)	IFX 5 mg/kg																			
−0.35 (−2.37,1.59)	−0.26 (−2.01,1.39)	GOL 100 mg																		
−0.4 (−2.44,1.6)	−0.31 (−2.14,1.43)	−0.04 (−2.01,1.91)	SEC SC 150 mg																	
−0.44 (−2.18,1.3)	−0.34 (−1.84,1.08)	−0.08 (−1.47,1.3)	−0.03 (−1.75,1.7)	GOL 50 mg																
−0.43 (−2.67,1.77)	−0.33 (−2.4,1.66)	−0.08 (−2.24,2.08)	−0.05 (−2.21,2.17)	0 (−1.98,1.98)	APR 30 mg															
−0.48 (−2.53,1.56)	−0.39 (−2.19,1.4)	−0.13 (−2.05,1.85)	−0.09 (−2.06,1.91)	−0.05 (−1.77,1.73)	−0.04 (−2.27,2.22)	SEC IV 150 mg														
−0.59 (−2.31,1.17)	−0.49 (−1.95,0.96)	−0.23 (−1.86,1.44)	−0.19 (−1.86,1.54)	−0.15 (−1.53,1.29)	−0.14 (−2.04,1.86)	−0.1 (−1.82,1.63)	IXE 80 mg Q2W													
−0.59 (−2.58,1.44)	−0.5 (−2.26,1.27)	−0.24 (−2.11,1.76)	−0.19 (−2.15,1.83)	−0.16 (−1.85,1.58)	−0.14 (−2.36,2.12)	−0.1 (−1.61,1.42)	−0.01 (−1.73,1.72)	SEC IV 75 mg												
−0.68 (−2.77,1.38)	−0.57 (−2.4,1.21)	−0.31 (−2.28,1.71)	−0.28 (−2.26,1.78)	−0.23 (−2.01,1.56)	−0.24 (−2.49,2.04)	−0.2 (−2.24,1.87)	−0.1 (−1.86,1.64)	−0.09 (−2.14,1.92)	FIL 200 mg											
−0.7 (−2.39,1.01)	−0.59 (−2.05,0.82)	−0.34 (−1.98,1.32)	−0.3 (−1.97,1.43)	−0.26 (−1.61,1.13)	−0.26 (−2.17,1.73)	−0.22 (−1.9,1.48)	−0.11 (−1.25,0.96)	−0.11 (−1.81,1.59)	−0.02 (−1.78,1.73)	IXE 80 mg Q4W										
−0.74 (−2.35,0.82)	−0.64 (−1.99,0.58)	−0.38 (−1.9,1.09)	−0.33 (−1.93,1.24)	−0.31 (−1.52,0.92)	−0.3 (−2.18,1.55)	−0.25 (−1.87,1.32)	−0.15 (−1.3,0.91)	−0.14 (−1.75,1.41)	−0.06 (−1.7,1.53)	−0.05 (−1.16,1.03)	ADA 40 mg									
−0.8 (−2.81,1.27)	−0.68 (−2.53,1.14)	−0.44 (−2.39,1.6)	−0.39 (−2.39,1.7)	−0.36 (−2.11,1.45)	−0.34 (−2.56,1.96)	−0.31 (−2.33,1.75)	−0.2 (−1.95,1.56)	−0.21 (−2.25,1.8)	−0.11 (−2.17,1.98)	−0.09 (−1.81,1.67)	−0.05 (−1.65,1.6)	CZP 400 mg								
−0.88 (−2.99,1.2)	−0.79 (−2.68,1.04)	−0.52 (−2.56,1.49)	−0.48 (−2.58,1.6)	−0.43 (−2.3,1.4)	−0.44 (−2.77,1.83)	−0.39 (−2.55,1.65)	−0.3 (−2.18,1.5)	−0.28 (−2.45,1.74)	−0.21 (−2.36,1.89)	−0.18 (−2.04,1.57)	−0.13 (−1.85,1.57)	−0.09 (−2.26,1.99)	TOF 5 mg							
−0.92 (−2.93,1.16)	−0.8 (−2.64,1.03)	−0.55 (−2.5,1.48)	−0.52 (−2.52,1.57)	−0.47 (−2.18,1.33)	−0.47 (−2.67,1.82)	−0.42 (−2.46,1.63)	−0.32 (−2.11,1.46)	−0.31 (−2.34,1.74)	−0.22 (−2.32,1.89)	−0.21 (−1.95,1.55)	−0.17 (−1.76,1.52)	−0.12 (−1.7,1.56)	−0.03 (−2.09,2.18)	CZP 200 mg						
−0.89 (−2.94,1.1)	−0.81 (−2.6,0.9)	−0.53 (−2.47,1.39)	−0.5 (−2.04,1.02)	−0.47 (−2.17,1.26)	−0.47 (−2.68,1.8)	−0.41 (−2.42,1.56)	−0.31 (−2.07,1.39)	−0.3 (−2.31,1.68)	−0.21 (−2.29,1.76)	−0.19 (−1.92,1.45)	−0.15 (−1.74,1.42)	−0.09 (−2.19,1.9)	−0.03 (−2.09,2.11)	0.01 (−2.06,2.01)	SEC SC 75 mg					
−1.12 (−3.19,0.97)	−1.01 (−2.91,0.83)	−0.77 (−2.74,1.28)	−0.73 (−2.78,1.37)	−0.67 (−2.47,1.14)	−0.68 (−2.92,1.62)	−0.64 (−2.74,1.48)	−0.52 (−2.37,1.27)	−0.52 (−2.61,1.51)	−0.43 (−2.51,1.66)	−0.41 (−2.21,1.38)	−0.38 (−2.02,1.33)	−0.32 (−2.49,1.8)	−0.23 (−1.94,1.53)	−0.2 (−2.36,1.91)	−0.22 (−2.28,1.91)	TOF 10 mg				
−1.27 (−2.82,0.51)	−1.17 (−2.48,0.33)	−0.9 (−2.41,0.85)	−0.87 (−2.4,0.95)	−0.82 (−2.07,0.65)	−0.82 (−2.66,1.19)	−0.78 (−2.37,1.04)	−0.68 (−1.92,0.75)	−0.68 (−2.28,1.09)	−0.58 (−2.24,1.23)	−0.56 (−1.78,0.84)	−0.52 (−1.56,0.72)	−0.48 (−2.15,1.34)	−0.37 (−2.05,1.53)	−0.36 (−1.99,1.46)	−0.37 (−1.93,1.41)	−0.15 (−1.87,1.7)	ETN 25 mg			
−1.38 (−3.5,0.69)	−1.28 (−3.24,0.53)	−1.02 (−3.09,1.01)	−0.97 (−3.15,1.13)	−0.94 (−2.8,0.86)	−0.94 (−3.27,1.38)	−0.9 (−3.02,1.18)	−0.8 (−2.69,0.97)	−0.77 (−2.94,1.23)	−0.7 (−2.9,1.39)	−0.68 (−2.56,1.08)	−0.63 (−2.35,1.06)	−0.59 (−2.82,1.5)	−0.5 (−2.23,1.26)	−0.47 (−2.67,1.57)	−0.48 (−2.6,1.61)	−0.27 (−1.99,1.43)	−0.12 (−2.1,1.55)	TOF 2 mg		
−1.59 (−3.35,0.12)	**−1.5 (−2.99,−0.07)**	−1.25 (−2.91,0.44)	−1.19 (−2.94,0.57)	−1.17 (−2.58,0.26)	−1.16 (−3.16,0.8)	−1.11 (−2.86,0.62)	−1.02 (−2.44,0.38)	−1 (−2.76,0.69)	−0.93 (−2.75,0.84)	−0.9 (−2.28,0.47)	−0.85 (−2.06,0.38)	−0.81 (−2.62,0.97)	−0.73 (−2.53,1.15)	−0.69 (−2.51,1.04)	−0.71 (−2.48,1.06)	−0.48 (−2.3,1.32)	−0.34 (−1.84,0.95)	−0.22 (−2.04,1.63)	UST 90 mg	
−1.75 (−3.5,−0.03)	**−1.65 (−3.17,−0.23)**	−1.39 (−3.09,0.26)	−1.35 (−3.1,0.39)	−1.31 (−2.74,0.11)	−1.32 (−3.28,0.66)	−1.28 (−2.99,0.46)	−1.17 (−2.62,0.21)	−1.16 (−2.9,0.56)	−1.08 (−2.89,0.7)	−1.06 (−2.45,0.32)	−1.01 (−2.22,0.23)	−0.96 (−2.77,0.77)	−0.87 (−2.67,0.98)	−0.84 (−2.67,0.92)	−0.84 (−2.61,0.89)	−0.63 (−2.5,1.18)	−0.5 (−1.98,0.81)	−0.38 (−2.19,1.47)	−0.15 (−1.3,0.97)	UST 45 mg	
−1.9 (−3.34,−0.49)	**−1.8 (−2.9,−0.75)**	**−1.54 (−2.86,−0.22)**	**−1.5 (−2.89,−0.05)**	**−1.46 (−2.46,−0.45)**	−1.46 (−3.15,0.24)	−1.41 (−2.85,0.01)	**−1.31 (−2.3,−0.35)**	−1.31 (−2.74,0.09)	−1.22 (−2.7,0.23)	**−1.2 (−2.17,−0.25)**	**−1.16 (−1.83,−0.44)**	−1.11 (−2.6,0.34)	−1.01 (−2.55,0.54)	−0.98 (−2.48,0.45)	−1 (−2.38,0.41)	−0.78 (−2.34,0.73)	−0.64 (−1.64,0.2)	−0.52 (−2.02,1.07)	−0.3 (−1.31,0.72)	−0.15 (−1.16,0.86)	PBO

Fig. 3 League table with pairwise comparisons for all treatments in the BASFI NMA. Pairwise comparisons are reported as MDs and 95% Crls. Comparators are ordered from largest (top-left) to smallest (bottom-right) SUCRA values for the BASFI NMA. Please refer to Fig. 5 for SUCRA values for each NMA. Superior improvements in BASFI are denoted in bold text and light gray cells. Results are shown for the unadjusted model for BASFI. Please refer to Appendix S6 for the model fit statistics. Abbreviations: ADA, adalimumab; APR, apremilast; BASFI, Bath Ankylosing Spondylitis Functional Index; Crls, credible intervals; CZP, certolizumab pegol; ETN, etanercept; FIL, filgotinib; GOL, golimumab; IV, intravenous; IFX, infliximab; IXE, ixekizumab; MD, mean difference; NMA, network meta-analysis; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous; SEC, secukinumab; SUCRA, Surface Under the Cumulative Ranking curve; TOF, tofacitinib; UST, ustekinumab

League Table – Unadjusted (Mean Difference)

Credible interval includes 0 ☐ Yes ☐ No

IFX 5 mg/kg																	
−0.31 (−1.89,1.19)	**GOL IV 2 mg/kg**																
−0.51 (−1.86,0.83)	−0.2 (−1.49,1.16)	**IXE 80 mg Q4W**															
−0.56 (−1.93,0.79)	−0.25 (−1.58,1.14)	−0.05 (−1.01,0.88)	**IXE 80 mg Q2W**														
−0.6 (−1.85,0.63)	−0.3 (−1.49,0.93)	−0.09 (−1.02,0.79)	−0.04 (−0.96,0.85)	**ADA 40 mg**													
−0.63 (−2.05,0.84)	−0.32 (−1.69,1.17)	−0.12 (−1.31,1.15)	−0.08 (−1.29,1.23)	−0.03 (−1.04,1.13)	**ETN 25 mg**												
−0.95 (−2.55,0.6)	−0.63 (−2.21,0.93)	−0.43 (−1.84,0.91)	−0.39 (−1.79,1)	−0.34 (−1.64,0.92)	−0.32 (−1.84,1.09)	**FIL 200 mg**											
−1.04 (−2.58,0.43)	−0.74 (−2.21,0.8)	−0.54 (−1.86,0.81)	−0.49 (−1.8,0.85)	−0.45 (−1.59,0.78)	−0.41 (−1.87,0.96)	−0.1 (−1.6,1.42)	**GOL 50 mg**										
−1.08 (−2.61,0.42)	−0.77 (−2.25,0.73)	−0.57 (−1.91,0.74)	−0.53 (−1.85,0.78)	−0.49 (−1.65,0.68)	−0.45 (−1.92,0.89)	−0.14 (−1.65,1.44)	−0.04 (−1.53,1.41)	**SEC SC 150 mg – no LD**									
−1.1 (−2.64,0.38)	−0.79 (−2.25,0.72)	−0.59 (−1.91,0.72)	−0.53 (−1.89,0.78)	−0.5 (−1.67,0.69)	−0.47 (−1.95,0.88)	−0.15 (−1.7,1.35)	−0.06 (−1.13,0.99)	−0.01 (−1.47,1.46)	**GOL 100 mg**								
−1.11 (−2.75,0.47)	−0.8 (−2.37,0.83)	−0.6 (−2.07,0.81)	−0.55 (−1.99,0.87)	−0.5 (−1.81,0.77)	−0.49 (−2.07,1)	−0.16 (−1.83,1.49)	−0.06 (−1.64,1.52)	−0.04 (−1.6,1.59)	−0.02 (−1.61,1.57)	**TOF 10 mg**							
−1.21 (−2.82,0.33)	−0.9 (−2.47,0.66)	−0.7 (−2.14,0.67)	−0.65 (−2.08,0.71)	−0.61 (−1.87,0.65)	−0.58 (−2.13,0.84)	−0.26 (−1.9,1.34)	−0.17 (−1.73,1.37)	−0.13 (−1.71,1.41)	−0.11 (−1.66,1.43)	−0.11 (−1.42,1.18)	**TOF 5 mg**						
−1.35 (−3.31,0.56)	−1.04 (−2.95,0.9)	−0.83 (−2.67,0.94)	−0.78 (−2.6,0.99)	−0.74 (−2.44,0.94)	−0.7 (−2.62,1.08)	−0.4 (−2.38,1.6)	−0.29 (−2.23,1.58)	−0.26 (−2.18,1.65)	−0.24 (−2.17,1.65)	−0.24 (−2.24,1.77)	−0.13 (−2.1,1.86)	**SEC IV 75 mg**					
−1.37 (−3.35,0.56)	−1.05 (−2.98,0.87)	−0.86 (−2.66,0.96)	−0.8 (−2.6,0.98)	−0.76 (−2.46,0.96)	−0.75 (−2.65,1.06)	−0.41 (−2.4,1.53)	−0.32 (−2.19,1.6)	−0.26 (−2.21,1.61)	−0.26 (−2.17,1.67)	−0.24 (−2.28,1.77)	−0.14 (−2.09,1.82)	−0.03 (−2.05,2.05)	**SEC IV 150 mg**				
−1.32 (−2.93,0.25)	−1.01 (−2.56,0.59)	−0.81 (−2.25,0.6)	−0.76 (−2.18,0.67)	−0.72 (−2,0.58)	−0.69 (−2.24,0.77)	−0.37 (−2,1.24)	−0.27 (−1.8,1.27)	−0.23 (−1.8,1.33)	−0.22 (−1.75,1.35)	−0.21 (−1.54,1.09)	−0.1 (−1.38,1.15)	0.03 (−1.94,2.03)	0.05 (−1.91,2.02)	**TOF 2 mg**			
−1.33 (−2.8,0.11)	−1.03 (−2.42,0.41)	−0.82 (−2.06,0.36)	−0.77 (−2,0.46)	−0.73 (−1.8,0.36)	−0.7 (−2.08,0.57)	−0.39 (−1.84,1.09)	−0.29 (−1.68,1.12)	−0.25 (−1.31,0.81)	−0.24 (−1.61,1.18)	−0.22 (−1.72,1.31)	−0.12 (−1.58,1.38)	0.01 (−1.88,1.91)	0.04 (−1.8,1.91)	−0.01 (−1.48,1.47)	**SEC SC 150 mg**		
−1.38 (−2.85,−0.05)	−1.07 (−2.47,0.29)	−0.87 (−2.11,0.26)	−0.83 (−2.04,0.31)	−0.78 (−1.82,0.21)	−0.76 (−2.14,0.43)	−0.44 (−1.86,0.94)	−0.33 (−1.75,0.95)	−0.3 (−1.67,1)	−0.29 (−1.69,1.02)	−0.28 (−1.78,1.15)	−0.17 (−1.65,1.22)	−0.05 (−1.91,1.79)	−0.03 (−1.87,1.78)	−0.06 (−1.52,1.36)	−0.05 (−1.34,1.17)	**UST 90 mg**	
−1.45 (−3.22,0.23)	−1.14 (−2.83,0.6)	−0.96 (−2.52,0.6)	−0.89 (−2.45,0.65)	−0.86 (−2.29,0.6)	−0.82 (−2.46,0.76)	−0.5 (−2.26,1.23)	−0.41 (−2.11,1.28)	−0.36 (−2.04,1.34)	−0.35 (−2.04,1.31)	−0.34 (−2.13,1.5)	−0.23 (−2.01,1.55)	−0.1 (−2.2,2.02)	−0.08 (−2.2,2.01)	−0.12 (−1.9,1.63)	−0.11 (−1.69,1.44)	−0.06 (−1.64,1.55)	**SEC SC 75 mg**
−1.6 (−3.03,−0.26)	−1.29 (−2.64,0.11)	−1.09 (−2.3,0.07)	−1.04 (−2.25,0.12)	−1 (−2.03,0.04)	−0.97 (−2.3,0.24)	−0.65 (−2.06,0.76)	−0.55 (−1.93,0.79)	−0.51 (−1.82,0.79)	−0.49 (−1.9,0.85)	−0.49 (−1.97,0.93)	−0.38 (−1.82,1.03)	−0.25 (−2.09,1.57)	−0.24 (−2.06,1.6)	−0.28 (−1.76,1.16)	−0.26 (−1.52,0.95)	−0.21 (−1.18,0.8)	−0.15 (−1.73,1.44)
−1.8 (−2.93,−0.72)	**−1.5 (−2.55,−0.41)**	**−1.29 (−2.11,−0.5)**	**−1.24 (−2.07,−0.45)**	**−1.2 (−1.74,−0.66)**	**−1.17 (−2.16,−0.29)**	−0.86 (−1.98,0.27)	−0.75 (−1.82,0.25)	−0.71 (−1.76,0.31)	−0.71 (−1.75,0.33)	−0.69 (−1.89,0.51)	−0.6 (−1.73,0.56)	−0.47 (−2.05,1.17)	−0.44 (−2.09,1.15)	−0.48 (−1.66,0.67)	−0.47 (−1.42,0.42)	−0.42 (−1.24,0.46)	−0.35 (−1.7,1)

UST 45 mg																		
−0.21 (−1.08,0.66)	**PBO**																	

Fig. 4 League table with pairwise comparisons for all treatments in the CRP NMA. Pairwise comparisons are reported as MDs and 95% CrIs. Comparators are ordered from largest (top-left) to smallest (bottom-right) SUCRA values for the CRP NMA. Please refer to Fig. 5 for SUCRA values for each NMA. Superior improvements in CRP are denoted in bold text and light gray cells. Results are shown for the unadjusted model for CRP. Please refer to Appendix S6 for the model fit statistics. Abbreviations: ADA, adalimumab; CRP, C-reactive protein; CrIs, credible intervals; ETN, etanercept; FIL, filgotinib; GOL, golimumab; IFX, infliximab; IV, intravenous; IXE, ixekizumab; LD, loading dose; MD, mean difference; NMA, network meta-analysis; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; TOF, tofacitinib; SC, subcutaneous; SEC, secukinumab; SUCRA, Surface Under the Cumulative Ranking curve; UST, ustekinumab

Fazit der Autoren

Results of the best-fitting model for each network showed that TOF 5 mg and GOL IV 2 mg/kg were the two top-ranked treatments for ASAS20 response, GOL IV 2 mg/kg and IFX 5 mg/kg were the two top-ranked treatments for change from baseline in BASFI, and IFX 5 mg/kg and GOL IV 2 mg/kg were the two top-ranked treatment for change from baseline in CRP.

Fan M et al., 2020 [5].

Indirect comparison of NSAIDs for ankylosing spondylitis: Network meta-analysis of randomized, double-blinded, controlled trials.

Fragestellung

to assess the efficacy and safety of NSAIDs in the treatment of AS

Methodik

Population:

patients with active AS

Intervention und Komparator:

Comparisons between different NSAIDs or of an NSAID with placebo

Endpunkte:

- primary efficacy endpoints:
  - mean change in total pain score
  - patients' global assessment of disease activity (PGA)
  - BASFI
- secondary efficacy endpoints:
  - Proportions of patients reaching the Assessment in Ankylosing Spondylitis 20 improvement criteria (ASAS20) defined as an improvement of ≥20% and absolute improvement of ≥10 units (0-100 mm VAS) from baseline in at least 3 of the following 4 domains: PGA, total back pain, BASFI and inflammation/morning stiffness, without any worsening of ≥20% and 10 units in the remaining domain
- Safety endpoints: total AEs, GI events (defined as any abdominal complaints), withdrawals due to AEs, serious AEs during the study

Recherche/Suchzeitraum:

- PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure and WanFang databases up to August 12, 2019

Qualitätsbewertung der Studien:

Cochrane RoB

NMA-spezifische Angaben:

- Indirect comparisons were performed using a random-effects Bayesian network meta-analysis

- For continuous data, the MDs were reported from the median of the posterior distribution with the accompanying 95% credible intervals (CrIs). For dichotomous data, the odds ratios (ORs) with the 95% CrIs were presented.

Ergebnisse

<u>Anzahl eingeschlossener Studien:</u>

N=9 double-blinded RCTs

<u>Charakteristika der Population:</u>

Table I. Major characteristics of the trials included.

First author (year)	Interventions	Study duration (weeks)	Patients		Pain score at baseline (mm)	PGA at baseline (mm)	BASFI at baseline (mm)	(Refs.)
			N (% males)	Age (years)				
Balazcs (2016)	Etoricoxib 60/90 mg/d Naproxen 1,000 mg/d	6	1015 (70.9)	45.2	76.8	NR	NR	(21)
Barkhuizen (2006)	Celecoxib 200/400 mg/d Naproxen 1,000 mg/d Placebo	12	611 (73.8)	44.6	71.9	66.6	52.1	(24)
Dougados (1999)	Meloxicam 15/22.5 mg/d Placebo	6	365 (78.7)	42.0	71.0	NR	NR	(26)
Dougados (2001)	Celecoxib 200 mg/d Placebo	6	156 (70.5)	39.0	70.0	44.5	44.5	(25)
Fatahi (2018)	M2000 1,000 mg/d Naproxen 1,000 mg/d Placebo	12	85 (70.6)	30.5	61.5	62.8	44.3	(27)
Huang (2014)	Celecoxib 200 mg/d Diclofenac 75 mg/d	6	240 (85.8)	29.3	63.4	NR	NR	(18)
Sieper (2008)	Celecoxib 200/400 mg/d Diclofenac 150 mg/d	12	458 (69.2)	44.8	66.0	44.0	44.0	(19)
van der Heijde (2005)	Etoricoxib 90/120 mg/d Naproxen 1,000 mg/d Placebo	6	387 (77.8)	43.6	77.6	55.1	55.1	(20)
Walker (2016)	Celecoxib 200/400 mg/d Diclofenac 150 mg/d	12	330 (72.4)	43.8	65.5	65.4	47.3	(22)

PGA, patient's global assessment of disease activity; BASFI, Bath Ankylosing Spondylitis Functional Index; NR, not reported; M2000, beta-D-mannuronic acid.

Qualität der Studien:

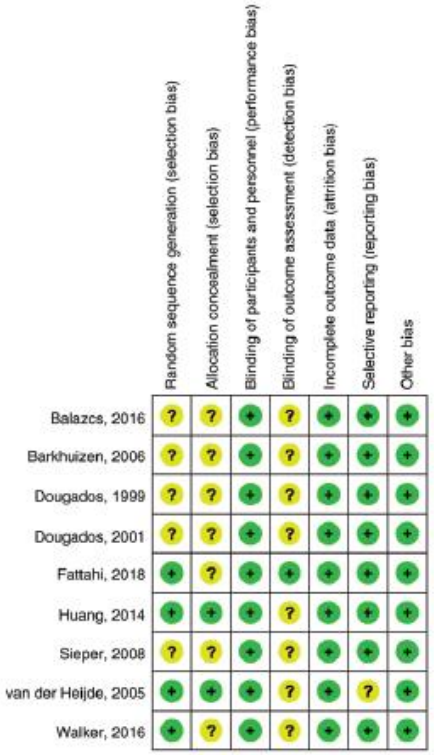


Figure 3. Assessment of the risk of bias for the studies included. Question marks indicate unclear risk of bias and plus symbols indicate low risk of bias.

Studienergebnisse:

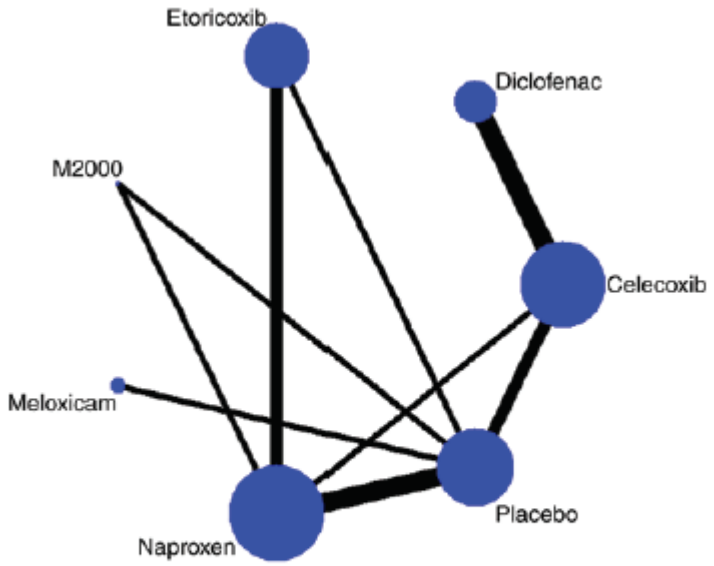


Figure 2. Network diagram of the comparisons in the meta-analysis. The size of the nodes is proportionate to the number of patients randomized to the treatment. The width of the lines is proportionate to the number of direct comparisons between the connected treatments.

Efficacy of NSAIDs

- All of the 9 trials reported the mean change of the pain score (18-22,24-27). A total of 7 trials reported the PGA (19,20,22,24-27), 7 reported the BASFI (18-20,22,24,25,27) and 6 reported the ASAS20 (18-20,22,24,27).
- Etoricoxib was significantly more effective than celecoxib in terms of pain alleviation (MD=-8.39, 95% CrI: -16.55 to -0.79). Analysis of ranking probabilities indicated that etoricoxib had the highest probability of being the best treatment in decreasing pain severity (Pbest, 73.8%)
- Etoricoxib was superior to celecoxib in reducing the PGA score with statistical significance (MD=-9.51, 95% CrI: -17.34 to -1.45).
- However, there were no significant differences among the NSAIDs in decreasing the BASFI.
- All NSAIDs had a significantly higher rate of ASAS20 compared with placebo (ORs between 2.71 and 7.54; Fig. 5B). But celecoxib was significantly less efficacious in reaching ASAS20 than etoricoxib (OR=0.36, 95% CrI: 0.15-0.85).
- The probability analysis suggested that etoricoxib remained the most effective option for the outcomes of PGA, BASFI and ASAS20 (Pbest of 67.2, 76.1 and 71.8%, respectively; Table II).

Safety of NSAIDs

- A total of 8 RCTs reported on the occurrence of total AEs, GI events, withdrawals due to AEs and serious AEs (18-22,24,25,27).
- Furthermore, M2000 was associated with a lower incidence of AEs than celecoxib and diclofenac (OR=0.26, 95% CrI: 0.06-1.00 and OR=0.23, 95% CrI: 0.05-0.99, respectively).
- No significant differences in terms of GI events were determined among the different NSAIDs.

Fazit der Autoren

In summary, NSAIDs are all highly effective and well-tolerated compared to placebo in the treatment of AS. Clinicians should take GI toxicity into account when prescribing NSAIDs.

Kommentare zum Review

- Einschränkungen hinsichtlich der Vergleichbarkeit der Studien durch unterschiedliche Dosierungen und Unterschiede in den Pain Scores, PGA und BASFI zur Baseline

Karmacharya P et al., 2020 [9].

The effect of therapy on radiographic progression in axial spondyloarthritis: a systematic review and meta-analysis.

siehe auch: Arjawat et al. 2020 [1]

Fragestellung

- To investigate effect of therapies on radiographic progression in axial spondyloarthritis (axSpA).

Methodik

Population:

adult patients with axSpA, including AS and nr-axSpA

Intervention und Komparator:

particular treatment vs. no treatment of interest

Endpunkte:

- Primary endpoint: difference in modified Stoke AS Spine Score (mSASSS)
- Secondary endpoint:
  - mSASSS in nr-axSpA,
  - change in number of syndesmophytes,
  - BATH AS Radiology Index (BASRI)-spine,
  - CT score of the facet joints
  - sacroiliac joint radiographic progression in AS and/or nr-axSpA

Recherche/Suchzeitraum:

- Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane un Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. ACR and EULAR abstracts indexed in MEDLINE from inception to January 15, 2019

Qualitätsbewertung der Studien:

- Newcastle Ottawa scale for cohort studies
- RoB 2.0 for RCTs
- Certainty of evidence: GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 24 studies included: 18 studies related to TNFi (N= 4,874), 8 to NSAIDs (N= 2,321), and 1 to secukinumab (N=237). Among these, 3 studies contained data for both NSAIDs and TNFi.

Charakteristika der Population:

Studiencharakteristika siehe Anhang (Tabelle 2)

Qualität der Studien:

RoB Assessment sieht Anhang (Tabelle 3)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNF inhibitors	no TNF inhibitors	Relative (95% CI)	Absolute (95% CI)		
Radiographic progression as defined by mSASSS (follow up: 2 years)												
8	observational studies	serious [a]	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	785	836	-	SMD **0.12 SD lower** (0.25 lower to 0.02 higher)	⨁⨁◯◯ LOW	IMPORTANT
Radiographic progression as defined by mSASSS (follow up: 4 years)												
7	observational studies	serious [a]	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	945	957	-	SMD **0.14 SD lower** (0.32 lower to 0.05 higher)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; SMD: Standardized mean difference

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAIDs	No NSAIDs	Relative (95% CI)	Absolute (95% CI)		
Radiographic progression as defined by mSASSS (follow up: 2 years)												
5	observational studies	serious [a]	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	833	508	-	SMD **0.08 SD lower** (0.32 lower to 0.16 higher)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; SMD: Standardized mean difference

Explanations

a. Observational studies

Studienergebnisse:

Radiographic outcomes – TNFi

- Spinal radiographic progression was not significantly different among the TNFi-treated vs. the biologic-naïve populations at 2 years (mSASSS difference= −0.73, 95% CI −1.52 to 0.12, I2=28%) and at ≥4 years (mSASSS difference= −2.03, 95% CI −4.63 to 0.72, I2=63%).

  However, sensitivity analysis restricted to six studies with low risk of bias (excluding one study[38]) showed a significant difference at ≥4 years (mSASSS difference= −2.17, 95% CI −4.19 to −0.15, I2=49%). [Certainty: low]
- Similarly, there was no difference in the number of syndesmophytes between the TNFi and biologic-naïve groups at 2 years (SMD= −0.04, 95% CI −0.51 to 0.43; change in no. of syndesmophytes= −0.05, 95% CI −0.59 to 0.49, I2=69%) or 8 years of follow-up (SMD= 0.34, 95% CI −0.86 to 1.55; change in number of syndesmophytes= 0.78, 95% CI −3.01 to 4.57, I2=83%).

Radiographic outcomes – NSAIDs

Among 6 studies reporting mSASSS with NSAIDs in AS at 2 years, no significant difference was observed between NSAIDs vs. control group (SMD= −0.08, 95% CI −0.32 to 0.16, mSASSS difference= −0.30, 95% CI =−2.62 to 1.31, I2=71%)

Radiographic outcomes – Secukinumab

The only included study with secukinumab, did not show a significant difference in radiographic progression over 2 years (mean mSASSS difference= −0.34, 95% CI −0.85 to 0.17) [51].

Fazit der Autoren

Although no significant protective effect of TNFi treatment on radiographic progression of AS at the spine at 2 years and 4 years was found in our study, analysis restricted to studies with low risk of bias showed a protective effect at ≥4 years. Therefore, long-term TNFi exposure might have radiographic progression benefit.

Ungprasert P et al., 2017 [15].

Indirect comparisons of the efficacy of biological agents in patients with active ankylosing spondylitis: a systematic review and meta-analysis

Fragestellung

[…] to compare the efficacy of certolizumab and non-TNF inhibitor biologic agents to older TNF inhibitors in patients who are biologic agent-naïve using indirect comparison technique.

Methodik

Population:

patients with active AS who have failed or could not tolerate NSAIDs therapy

Intervention:

certolizumab and non-TNF inhibitor biologic agents

Komparator:

older TNF inhibitors, placebo

Endpunkte:

Ankylosing Spondylitis Assessment Study group response criteria 20 (ASAS20)

ASAS20 response is defined as at least 20% improvement in at least three of four evaluated domains (patient global, pain, function, and inflammation) without worsening of more than 20% of the remaining domain.

Recherche/Suchzeitraum:

- Ovid Medline, Ovid CENTRAL, and Ovid EMBASE database from inception to January 2017
- search in clinicaltrials.gov […] to look for any additional unpublished studies
- the bibliographies of selected review articles and the previous meta-analysis by the Cochrane collaboration were also manually searched

Qualitätsbewertung der Studien:

Risk of bias for individual study was evaluated in six domains including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting.

Ergebnisse

Anzahl eingeschlossener Studien:

18 RCTs met the eligibility criteria, 14 trials of older TNF inhibitors (2321 patients), two trials of secukinumab (405 patients), one trial of certolizumab (142 patients), and one trial of tofacitinib (103 patients).

Charakteristika der Population:

Baseline characteristics of participants were similar across these trials with similar female-to-male ratio, average age, and baseline disease activity as reflected by similar Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). All studies used modified New York criteria to classify participants with AS. The definitions of active AS were consistent across studies (i.e., BASDAI ≥4 and spinal pain VAS ≥ 3 or 4). All studies allowed concomitant use of stable dose of NSAIDs, DMARDs, and steroid at the dose of not more than 10 mg daily of prednisone or equivalent. Nonetheless, the duration of disease varied considerably across the studies, ranging from 1.5 to 18.7 years.

Qualität der Studien:

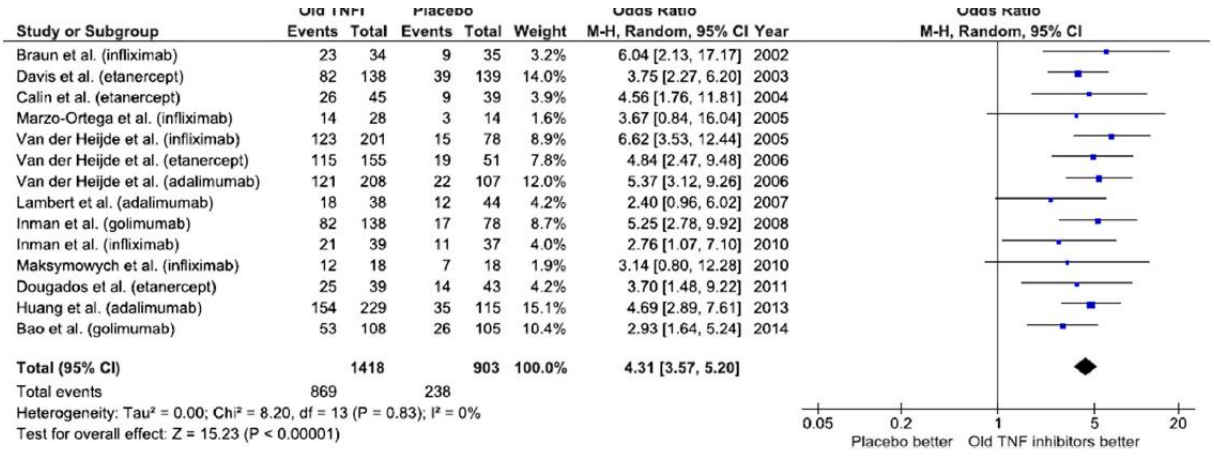
Risk of bias for individual study was low except for unclear risk of selection bias as most studies did not report the process of randomization in detail *(siehe Anhang Abbildung 1)*.

Studienergebnisse:

Direkte Vergleiche

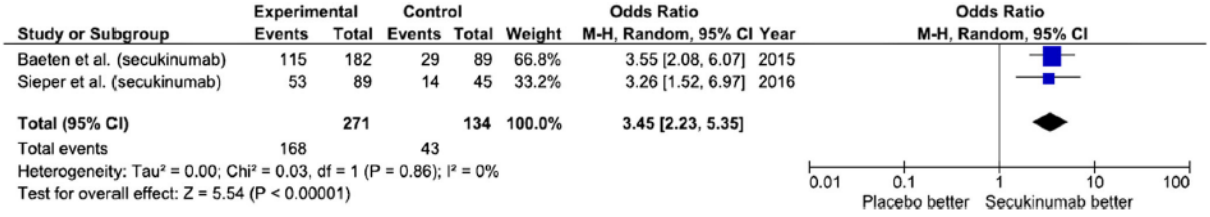
14 trials of older TNF inhibitors were pooled together. The pooled OR of achieving ASAS20 response among older TNF inhibitor-treated patients compared with placebo-treated patients was 4.31 (95% CI, 3.57-5.20). The statistical heterogeneity was low with I^2 of 0%.

Abbildung 1: Forest plot of older TNF inhibitors



The results of two trials of secukinumab were pooled together. The pooled OR of achieving ASAS20 response among secukinumab-treated patients compared with placebo-treated patients was 3.45 (95% CI, 2.23-5.35). The statistical heterogeneity was low with I^2 of 0%.

Abbildung 2: Forest plot of secukinumab



Indirekte Vergleiche

Die Ergebnisse aus den indirekten Vergleichen werden nicht berichtet, da die grundlegenden Annahmen von Netzwerk-Metaanalysen nicht adäquat überprüft wurden.

Fazit der Autoren

In conclusion, the current meta-analysis demonstrated that the odds of achieving an ASAS20 response in patients with AS who did not have an adequate response to, or could not tolerate NSAIDs were not significantly different between older TNF inhibitors [and] secukinumab […]. However, the interpretation of the results was limited by the small number of included RCTs. Head-to-head RCTs are still required to establish the comparative efficacy.

Kommentare zum Review

In allen Studien war eine Begleitmedikation mit einer stabilen Dosis von NSAIDs, DMARDs und Kortikosteroiden (darunter eine Studie zusätzlich mit Methotrexat bis 10 mg pro Woche) erlaubt.

3.4 Leitlinien

Resende GG et al., 2020 [12].
The Brazilian Society of Rheumatology guidelines for axial spondyloarthritis – 2019.

siehe auch Da Gruz Lage et al. für NSAIDs:

Da Cruz Lage R et al. 2021 [2]
Brazilian recommendations for the use of nonsteroidal anti-inflammatory drugs in patients with axial spondyloarthritis.

Zielsetzung/Fragestellung
The purpose of these guidelines is to bring evidencebased information on clinical management of axial SpA patients, including, diagnosis, treatment and prognosis, for rheumatologists, general physicians, allied-specialists (dermatology, ophthalmology and gastroenterology), andother allied-professionals, such as physiotherapists.

Methodik

Grundlage der Leitlinie

Update der früheren LL aus dem Jahr 2013

- Repräsentatives Gremium: unklar
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu
- Regelmäßige Überprüfung der Aktualität geplant in 4 Jahren

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, SciELO/ LILACS, and Cochrane Library, since March 1st, 2012 until December 31, 2018

LoE

- Oxford Centre for Evidence-based Medicine Levels of Evidence of 2001 (siehe Anhang)

GoR

- GRADE
- The degree of expert agreement (inter-rater reliability) was determined by the Delphi method through an online anonymous survey.

Sonstige methodische Hinweise

Methotrexat und Sulfasalazin sind keine für die Indikation axiale Spondyloarthritis zugelassenen Wirkstoffe.

Empfehlungen

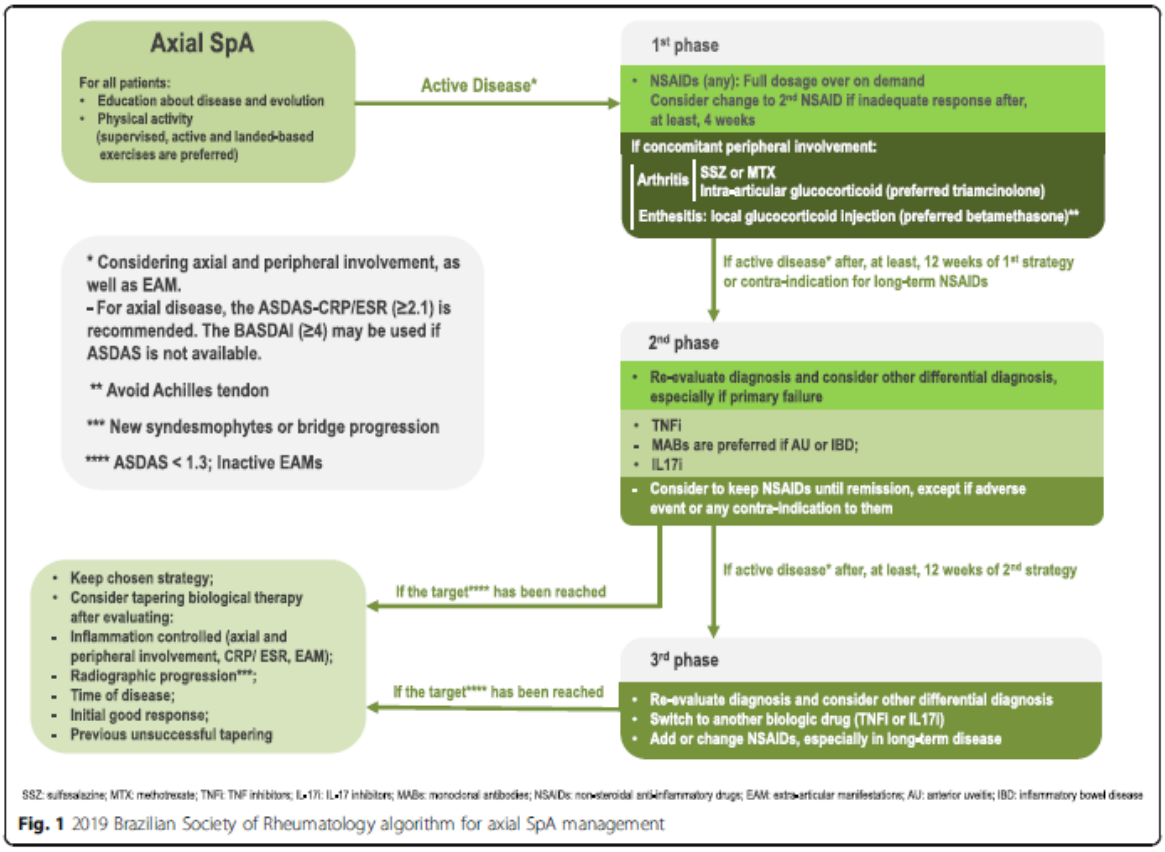


Fig. 1 2019 Brazilian Society of Rheumatology algorithm for axial SpA management

Clinical question 5: What is the evidence for the use of glucocorticoids in patients with axial SpA?

- Long term use of systemic glucocorticoids to treat axial spondyloarthritis is not recommended **(LoE: 5, SoR: D (very weak), DoA: 9.6).**
- Patients with symptomatic peripheral enthesitis can undergo peritendinous glucocorticoid injections. Caution advised because the procedure may increase the risk of rupture, particularly in the Achilles tendon. **(LoE: 2A, SoR: B (moderate); DoA: 9.2)**
- Patients with isolated buttock pain who are unresponsive to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) may experience short-term benefits from an intra-articular injection of triamcinolone acetate in the sacroiliac joints. **(LoE: 2C, SoR: B (moderate), DoA: 8.5)**

Clinical question 6: In which situations is the continuous use of NSAIDs recommended for patients with axial SpA?

- NSAIDs should be indicated as the first-line treatment for active and symptomatic axial SpA. **(LoE: 1A; SoR: A (strong); DoA: 9.8)**
- There is no evidence that a specific NSAID can be considered superior to the other NSAIDs. **(LoE: 1A; SoR: A (strong); DoA: 9.3)**
- Evidence on the effect of NSAIDs on reducing radiographic progression in patients with axial SpA is conflicting. **(LoE: 1B; SoR: B (moderate); DoA: 9.3)**

Weiterführende Empfehlungen in Da Gruz Lage et al. 2021 [2]:

Recommendation 2: In patients with persistent active axSpA, we strongly recommend long-term over short-term use of NSAIDs, because they exhibit sustained symptomatic efficacy. We conditionally recommend that disease activity and adverse events should be regularly monitored, evaluating long-term risks versus benefits. (Quality of Evidence: low, DoA: 9.3)

Recommendation 10: In patients with active axSpA, we conditionally recommend that the choice of specific NSAI D should be based on patient's profile (age, prior toxicity, comorbidities) and on shared decision making. To date, there is no consistent evidence of efficacy and safety differences among the NSAIDs (non-selective or iCOX2) in axSpA. (QoL: low, DoA: 9.6)

R ecommendation 12, 13, 14: In patients with active axSpA, we conditionally recommend to avoid NSAIDs (non-selective or iCOX2) and to start an immunobiologic agent in those with

- current or previous peptic ulcer or gastrointestinal bleeding (Recommendation 12; QoE: low; DoA: 8.9)
- cardiovascular risk factors, mainly in those with previous acute myocardial infarction or stroke, especially if recent (past 12 months). (Recommendation 13; QoE: very low (observational studies), DoA: 8.4)
- increased risk of renal adverse events. (Recommendation 14; QoE: very low (observational studies), DoA: 9.4)

Clinical question 7: What is the evidence for the use of synthetic disease-modifying antirheumatic drugs (methotrexate, sulfasalazine and leflunomide) in patients with axial SpA?

- The use of methotrexate and sulfasalazine is recommended for the treatment of patients with axial SpA when peripheral arthritis is present or in the absence of another pharmacological treatment option due to toxicity, intolerance or contraindications. **(LoE: 2A, SoR: B (moderate); DoA: 8.4)**
- The routine use of methotrexate or sulfasalazine as a co-medication in patients with axial SpA who are using biologics is not recommended. **(LoE: 2B; SoR: B (moderate); DoA: 9.6)**

Clinical question 8: What evidence of efficacy supports indications for the use of biologics in patients with axial SpA?

- Based on the opinion of the rheumatologist, the use of biologics (TNFα inhibitors or interleukin-17 inhibitors) to treat active (BASDAI≥4 or ASDAS≥2.1) and symptomatic axial SpA is recommended when the initial treatment with NSAIDs fails (disease persistence, toxicity or contraindications). **(LoE: 1A, SoR: A (strong); DoA: 8.9)**
- Biologics should be used to treat axial SpA when objective signs of inflammation are detected, such as elevated C-reactive protein (CRP) levels and/or the presence of sacroiliitis on MRI, as these parameters predict the response, particularly in the context of non-radiographic axial SpA. **(LoE: 1B; SoR: A (strong); DoA: 9.6)**
- Anti-TNF inhibitors (adalimumab, etanercept, golimumab and certolizumab pegol) are recommended for the treatment of non-radiographic axial SpA since they had an evidence-based approval. **(LoE: 1B; SoR: A (strong); DoA: 9.7)**

Clinical question 9: Are there any differences regarding efficacy among the biologic agents to treat axial SpA patients?

- The biologics TNFα inhibitors and the IL17A inhibitors exhibit similar effect sizes for controlling inflammatory activity in patients with axial SpA. **(LoE: 1A; SoR: A (strong); DoA: 8.9)**

Clinical question 10: Does the safety of biologics differ in patients with axial SpA?

- The biologics TNFα inhibitors and the IL17A inhibitors have similar effect sizes for the risk of adverse effects and short-term discontinuation. **(LoE: 1A; SoR: A (strong); DoA: 9.1)**

Clinical question 11: Is the use of biological therapy able to reduce structural damage (radiographic progression) in patients with axial SpA?

- The reduction in the progression rate of structural damage (observed on spinal radiographies) in patients with axial SpA can be observed in the long-term use of TNF inhibitors. **(LoE: 2B; SoR: B (moderate); DoA: 8.2)**
- A similar effect on radiographic progression seems to be observed with the continuous use of anti-IL17 (secukinumab) but need to be confirmed in long-term studies. **(LoE: 2C; SoR: B (moderate); DoA: 9.6)**

Clinical question 12: What is the evidence regarding efficacy of biologic agents on extra-articular manifestations in patients with axial SpA?

- In the case of recurrent anterior uveitis or active inflammatory bowel disease in the setting of axial SpA, anti-TNF monoclonal antibodies (infliximab, adalimumab, golimumab, and certolizumab pegol) have shown the best response rates among the biologics. Therefore, it is recommended to choose it, preferably to others**. (LoE: 2A; SoR: B (moderate); DoA: 9.4)**
- Monoclonal anti-TNF inhibitors (infliximab, adalimumab, golimumab, and certolizumab pegol) and ant-IL17 inhibitors have shown be the most effective, among the biologics, for the control of active psoriasis in the setting of axial SpA. Therefore, it is recommended to choose it, preferably to others **(LoE: 2B; SoR: B (moderate); DoA: 9.4)**

Clinical question 13: What is the evidence that supports the switching among biologic agents in patients with axial SpA?

- Patients with axial SpA who fail to show an initial response to a biological therapy (primary treatment failure), loss of efficacy (secondary treatment failure) or adverse effects may switch to another approved biologic, regardless mechanism of action. **(LoE: 2A; SoR: B (moderate); DoA: 9.4)**
- After the first biologic switch, the response rates decrease slightly but remain significant. The little available evidence on the second biologic switch suggest response rates even lower than the second-line treatment. **(LoE: 2A; SoR: B (moderate); DoA: 9.1)**

Clinical question 14: For how long should a biologic be used during the follow-up of a patient with axial SpA?

- In those who have reached the proposed treatment target, for at least 6 months, an attempt may be made to reduce the anti-TNFα dose or increase the interval between doses. Data on other mechanisms of action remains insufficient. However, the risk of long-term radiographic progression should be considered. **(LoE: 1B; SoR: B (moderate); DoA: 8.9)**

Clinical question 15: Is there evidence for the use of biologics and/or target-specific small molecules with other mechanisms of action in patients with axial SpA?

- The use of other biologics and/or target-specific small molecules (abatacept, tocilizumab, rituximab, sarilumab, ustekinumab and apremilast) is not recommended for the treatment of patients with axial SpA. **(LoE: 1B; SoR: A (strong); DoA: 9.5)**
- The Janus kinase (JAK) inhibitors tofacitinib and filgotinib showed promising clinical results in the treatment of ankylosing spondylitis, but more definitive evidence (phase III randomized clinical trials) is still needed prior to their recommendation**. (LoE: 2B; SoR: B (moderate); DoA: 9.1)**

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Deutsche Gesellschaft für Rheumatologie (DGRh), 2019 [4].

S3-Leitlinie Axiale Spondyloarthritis inklusive Morbus Bechterew und Frühformen

Zielsetzung

Das Ziel ist […], die evidenzbasierte Diagnostik und Therapie der axialen SpA darzustellen und damit den Betroffenen die Möglichkeit einer frühzeitigen Diagnosestellung zu eröffnen und die Einleitung einer wissenschaftlich begründeten Therapie zu ermöglichen.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt,
- systematische Suche, Auswahl und Bewertung der Evidenz,
- formale Konsensprozesse und externes Begutachtungsverfahren dargestellt,
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt,
- regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

Es wurde eine systematische Literaturrecherche in Medline (PubMed) und der Cochrane library durchgeführt. Die systematische Recherche nach Studien wurde auf den Zeitraum 01.10.2011-31.08.2017 beschränkt.

LoE

Für die Bewertung der wissenschaftlichen Evidenz wurden die Oxford Kriterien zugrunde gelegt *(siehe Anhang Tabelle 2)*.

GoR

Tabelle 1: Grad der Empfehlung, AB0-Schema

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.

Sonstige methodische Hinweise

Methotrexat und Sulfasalazin sind keine für die Indikation axiale Spondyloarthritis zugelassenen Wirkstoffe.

Empfehlungen

Medikamentöse Therapie

Biologika (Biologic disease-modifying antirheumatic drugs (bDMARDs))

8-15 Eine Therapie mit Biologika soll bei Patienten mit persistierend hoher entzündlicher Krankheitsaktivität und unzureichendem Ansprechen auf eine NSAR-Therapie oder Unverträglichkeit von NSAR begonnen werden. Dabei sind Unterschiede in der Zulassung für TNF- und IL-17-Inhibitoren zu beachten.

(Empfehlungsgrad A, Evidenz 1++)

Die Wirksamkeit und Sicherheit der TNFi ist bei Patienten mit AS sehr gut belegt [247, 253-283, 421]. Patienten mit totaler Ankylose der Wirbelsäule profitieren ebenfalls von einer Therapie mit TNFi [422] [423]. Die Wirksamkeit und Sicherheit einer Gabe von TNFi ist bei Patienten mit nr-axSpA ebenfalls sehr gut belegt. [424, 425] [426, 427]. Die bei nr-axSpA Patienten bestehende geringere Effektstärke im Vergleich zur AS Population wird durch verschiedene Autoren auf eine heterogenere Population der nr-axSpA Patienten und auf geringere Krankheitsschwere in einigen der kontrollierten Studien zurückgeführt [412, 428]. In der Metaanalyse von Callhoff et al. zeigte sich nach Korrektur für das Publikationsjahr (als Proxy für die Krankheitsschwere) jedoch kein Unterschied zwischen der Effektstärke von TNFi bei AS und nr-axSpA [412].

Die klinische Wirksamkeit von TNFi beginnt meist relativ schnell und hält bei einem größeren Teil der Patienten unter fortlaufender Therapie mehrere Jahre an [435], [436], [152], [424], [437], [438], [439], [440], [441], [442], [443], [423], [444], [445], [446], [425], [447], [448], [449], [450], [451], [452], [252, 380, 387, 427, 453-459]. Fast alle kontrollierten Studien sind unter Einschluss von Patienten mit AS durchgeführt worden. Ausnahmen sind die Studie mit Certolizumab [459], die in der Gesamtgruppe axiale SpA durchgeführt wurde, und Adalimumab [427], die in der Indikation nr-axSpA durchgeführt wurden.

8-16 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.

(Empfehlungsgrad B, Evidenz 1)

Diese Empfehlung setzt sich aus Informationen von mehreren Studien zusammen. Sequentielle Studien (lokales Steroid, Sulfasalazintherapie und danach Therapie mit einem TNFi) bei Patienten mit peripherer Arthritis sind nicht durchgeführt worden. Daher wird der -Empfehlungsgrad von „A“ auf „B“ herabgestuft.

8-17 Bei Patienten mit extra-muskuloskelettalen Manifestationen, insbesondere bei Vorliegen einer Uveitis, chronisch-entzündlichen Darmerkrankung oder Psoriasis sollte die unterschiedliche Effektivität der verschiedenen Biologika auf diese Manifestationen beachtet werden.

(Empfehlungsgrad B, Evidenz 1+ / 2b)

8-18 Bei Patienten mit verbleibenden muskuloskelettalen Symptomen unter einer Biologika-Therapie kann eine zusätzliche Therapie mit NSAR erfolgen. *(Statement)*

8-19 Die Wirksamkeit einer Biologika-Therapie soll nach zwölf Wochen überprüft werden.

(Empfehlungsgrad A, Evidenz 1++)

8-20 Bei Patienten, die ein Ansprechen zeigen (BASDAI-Verbesserung um ≥ 2 Punkte (auf einer Skala von 0-10) oder eine Verbesserung im ASDAS um ≥ 1,1) und bei denen eine positive Expertenmeinung für eine Fortführung vorliegt, kann die Therapie fortgeführt werden. Bei Patienten ohne Ansprechen sollte ein Absetzen in Erwägung gezogen werden.

(Empfehlungsgrad B, Evidenz 2b)

8-21 Eine Empfehlung, ob mit einem TNF-Inhibitor oder mit einem IL-17-Inhibitor begonnen werden soll, kann aufgrund der Studiendaten zur Wirksamkeit auf das Achsenskelett und Sicherheit nicht gegeben werden. Für TNF-Inhibitoren bestehen längere Erfahrungen in der klinischen Anwendung. (Statement)

8-22 Bei nicht-ausreichender Wirksamkeit eines Biologikums und bestehender hoher entzündlicher Krankheitsaktivität sollte der Wechsel auf ein weiteres Biologikum erfolgen.

(Empfehlungsgrad B, Evidenz 2)

8-23 Bei Patienten in anhaltender Remission (mind. für sechs Monate) unter einer Biologikagabe kann eine Dosisreduktion bzw. eine Intervallverlängerung und später eventuell auch das Absetzen des Biologikums erwogen werden.

(Empfehlungsgrad B, Evidenz 2)

Basistherapie (Chemisch-synthetische Disease-modifying antirheumatic drugs (csDMARDs))

8-24 Bei Patienten mit axialer SpA und klinisch führender peripherer Arthritis sollte eine Basistherapie mit Sulfasalazin durchgeführt werden (B). Andere Basistherapeutika wie Methotrexat können alternativ eingesetzt werden (Expertenkonsens).

(Empfehlungsgrad B, Evidenz 1)

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.

8-25 Bei Patienten mit AS sollte keine Behandlung der Wirbelsäulensymptomatik mit Methotrexat erfolgen. *(Empfehlungsgrad B, Evidenz 1)*

Herabstufung des Empfehlungsgrad von „A“ auf „B“, da hier eine Extrapolation der Ergebnisse aus der Evidenzebene 1 vorgenommen wurde.

8-26 Es gibt keine ausreichende Evidenz, eine Kombination von TNF-Inhibitoren mit MTX zur Vermeidung von anti-drug-antibodies (ADAs) zu empfehlen. *(Statement)*

Glukokortikoide

8-27 Die systemische Langzeitgabe von Glukokortikoiden wird bei Patienten mit Achsenskelettbeteiligung nicht empfohlen. Für die Wirksamkeit einer kurzfristigen Therapie mit Glukokortikoiden gibt es nur sehr begrenzte Evidenz.

(Empfehlungsgrad 0, Evidenz 4)

Invasive Therapie

Injektionen

8-28 Bei Patienten mit axialer SpA und symptomatischer peripherer Arthritis (Statement) oder Enthesitis kann eine lokale Injektion mit Glukokortikoiden erfolgen.

(Empfehlungsgrad 0, Evidenz 1)

Die Empfehlung bezüglich der Enthesitis basiert auf einer einzigen kontrollierten Studie, in der eine Glukokortikoidinjektion gegenüber einer Injektion mit einem TNFi verglichen wird. Randomisierte Studie mit einem Vergleich Glukokortikoidinjektion versus Plazebo fehlen. Daher wird der Empfehlungsgrad von „A“ auf „0“ herabgestuft.

8-29 Bei Patienten mit axialer SpA und symptomatischer florider Sakroiliitis kann eine Glukokortikoidinjektion in das Sakroiliakal-Gelenk erfolgen.

(Empfehlungsgrad 0, Evidenz 4)

Referenzen:

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Ward MM et al., 2019 [17].

American College of Rheumatology (ACR)

Spondylitis Association of America (SAA)

Spondyloarthritis Research and Treatment Network (SPARTAN)

2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis

Zielsetzung

To update evidence-based recommendations for the treatment of patients with ankylosing spondylitis (AS) and nonradiographic axial spondyloarthritis (SpA).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt,
- systematische Suche, Auswahl und Bewertung der Evidenz,
- formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt,
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt,
- weder Gültigkeit, noch Verfahren zur Überwachung und Aktualisierung beschrieben.

Recherche/Suchzeitraum:

OVID Medline (since 1946), PubMed (since its inception in the mid-1960s), and the Cochrane Library, including Cochrane Central Register of Controlled Trials (CENTRAL), were searched from the beginning of each database through September 9, 2017, and update searches were conducted on February 28, 2018.

LoE

The quality of evidence for each outcome was evaluated by reviewers using GRADE quality assessment criteria. GRADE specifies four categories in which the quality of evidence may be rated: high, moderate, low, and very low.

Tabelle 2: GRADE Working Group grades of evidence definitions

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.

GoR

- A recommendation could be either in favour or against the proposed intervention and either strong or conditional.
- According to GRADE, a recommendation is categorized as strong if the panel is very confident that benefits of an intervention clearly outweigh the harms (or vice versa), that the quality of evidence is high, and that future research will likely not alter the conclusion. Strong recommendations can also be based on less evidence when there is substantial concern for risk of harm.
- Strong recommendations do not imply large clinical benefits from the intervention, but rather confidence in the evidence base.
- A conditional recommendation denotes uncertainty regarding the balance of benefits and harms, such as when the evidence quality is low or very low, or when the decision is sensitive to individual patient preferences, or when costs are expected to impact the decision. Thus, conditional recommendations refer to decisions in which incorporation of patient preferences is a particularly essential element of decision making.
- Judgments are based on the experience of the clinician panel members in shared decision making with their patients, as well as the experience and perspectives of the two patient panel members.
- Following ACR policy, the cost of an intervention was not formally considered in developing recommendations.

Sonstige methodische Hinweise

Methotrexat, Sulfasalazin und Tofacitinib sind keine für die Indikation axiale Spondyloarthritis zugelassenen Wirkstoffe.

Empfehlungen

Recommendations for adults with active AS

Summary of the main recommendations (siehe Anhang Abbildung 8)

We strongly recommend treatment with NSAIDs over no treatment with NSAIDs.

(Level of evidence: Low)

We conditionally recommend continuous treatment with NSAIDs over on-demand treatment with NSAIDs (PICO 1). *(Level of evidence: Low to moderate)*

The efficacy of NSAIDs for symptom improvement in active AS has been established in many controlled trials. Evidence that continuous NSAID use results in slower rates of spinal fusion on radiographs over 2 years compared to on-demand NSAID use is inconsistent, with results of one trial of celecoxib suggesting less progression with continuous use, and one trial of diclofenac indicating no difference in progression (12,13). Despite the uncertainty regarding potential disease-modifying effects, the committee conditionally favored continuous use of NSAIDs in patients with active AS, primarily for controlling disease activity. The decision to use NSAIDs continuously may vary depending on the severity of symptoms, patient preferences, and comorbidities, particularly gastrointestinal and kidney comorbidities, and cardiovascular disease.

We do not recommend any particular NSAID as the preferred choice.

(Level of evidence: Low to moderate)

In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with sulfasalazine, methotrexate, or tofacitinib over no treatment with these medications. Sulfasalazine or methotrexate should be considered only in patients with prominent peripheral arthritis or when TNFi are not available. *(Level of evidence: Low to moderate)*

Treatment with sulfasalazine is recommended primarily for patients with prominent peripheral arthritis and few or no axial symptoms. However, TNFi may provide a better option for these patients. Evidence for the efficacy of sulfasalazine is based on 8 older controlled trials that showed benefit for peripheral arthritis.

Although a recent placebo-controlled trial of sulfasalazine demonstrated improvement in axial symptoms, and modest clinical and imaging responses were seen in a second trial, the preponderance of evidence indicates that sulfasalazine has little benefit for axial symptoms (14,15). Sulfasalazine may have a role in treating patients who have contraindications to TNFi, those who decline treatment with TNFi, or those with limited access to TNFi. Three trials of methotrexate with negative results tested doses of ≤10 mg weekly, and the lack of benefit may reflect the low doses used (16-18). One uncontrolled study of methotrexate 20 mg weekly showed no improvement in axial symptoms, but a decrease in swollen joint count (19). Treatment with methotrexate may be considered for patients with predominately peripheral arthritis, although among nonbiologics, there is more evidence supporting the use of sulfasalazine. A phase II study of tofacitinib showed benefit in both clinical and imaging outcomes of axial disease over 12 weeks (20). Use of tofacitinib could be another option, although the results of phase III trials are not available. Leflunomide, apremilast, thalidomide, and pamidronate are not recommended.

In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with tofacitinib. *(Level of evidence: Very low)*

In adults with active AS despite treatment with NSAIDs, we strongly recommend treatment with TNFi over no treatment with TNFi. (Level of evidence: High)

We do not recommend any particular TNFi as the preferred choice. *(Level of evidence: Moderate)*

The efficacy of TNFi in patients with active AS has been demonstrated in 24 randomized controlled trials, most of which were short-term (6 months or shorter) placebo-controlled studies. Improvements were shown in patient-reported outcomes, composite response criteria, and spine and sacroiliac inflammation on magnetic resonance imaging (MRI). The panel judged that the evidence justified a strong recommendation for use of TNFi in

patients whose AS remained active despite treatment with NSAIDs. Indirect comparisons in network meta-analyses of clinical trials have not showed clinically meaningful differences in short-term efficacy among TNFi in the treatment of active AS. Direct comparisons among these medications are limited to a trial of inxliximab versus its biosimilar, and a very small open-label trial of infliximab versus etanercept (22.23). The panel judged that the evidence did not support preference of 1 TNFi over any other for the typical patient.

In adults with active AS despite treatment with NSAIDs, we strongly recommend treatment with secukinumab or ixekizumab over no treatment with secukinumab or ixekizumab.
(Level of evidence: High)

In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with secukinumab or ixekizumab.

(Level of evidence: Very low)

In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with tofacitinib.

(Level of evidence: Very low)

The use of secukinumab and ixekizumab in patients with active AS is supported by data from large placebo-controlled trials. The panel recommended use of TNFi over secukinumab or ixekizumab based on greater experience with TNFi and familiarity with their long-term safety and toxicity. Similarly, the panel judged that TNFi, secukinumab, or ixekizumab should be used over tofacitinib, given the larger evidence base for TNFi, secukinumab, and ixekizumab. In patients with coexisting ulcerative colitis, if treatment with TNFi is not an option, tofacitinib should be considered over secukinumab or ixekizumab. Interleukin-17 (IL-17) inhibitors have not been shown to be efficacious in IBD, although tofacitinib is an approved treatment for ulcerative colitis (26,27).

In adults with active AS despite treatment with NSAIDs and who have contraindications to TNFi, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with sulfasalazine, methotrexate, or tofacitinib. *(Level of evidence: Low)*

No studies have directly compared the risks and benefits of treatment alternatives in patients who have contraindications to treatment with TNFi. The panel favored treatment with secukinumab or ixekizumab over treatment with sulfasalazine or methotrexate based on a higher likelihood of benefit, but this recommendation was conditional on the specific contraindication. If the contraindication to TNFi use was the presence of congestive heart failure or demyelinating disease, secukinumab or ixekizumab was preferred, since these medications have not been shown to worsen these conditions. If the contraindication to TNFi use was tuberculosis, other chronic infection, or a high risk of recurrent infections, sulfasalazine was preferred over secukinumab, izekizumab, and tofacitinib. In these cases, efforts to mitigate the infections should be undertaken so that TNFi might safely be used. Treatment with rituximab, abatacept, ustekinumab, or IL-6 inhibitors is not recommended, even in patients with contraindications to TNFi, due to lack of effectiveness.

In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with a different TNFi in patients with primary nonresponse to TNFi. *(Level of evidence: Very low)*

In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with a different TNFi over treatment with a non-TNFi biologic in patients with secondary nonresponse to TNFi. *(Level of evidence: Very low)*

In adults with active AS despite treatment with the first TNFi used, we strongly recommend against switching to treatment with a biosimilar of the first TNFi.

(Level of evidence: Very low)

In adults with active AS despite treatment with the first TNFi used, we conditionally recommend against the addition of sulfasalazine or methotrexate in favor of treatment with a new biologic. *(Level of evidence: Very low)*

Direct comparisons of treatment strategies for patients who do not have or sustain adequate responses to their first TNFi have not been reported, and the recommendations are based on the panel's consideration of indirect comparisons among the available treatment options. Data from observational studies suggest that 25-40% of patients who switch from one TNFi to another will have a meaningful response (e.g., 50% improvement in Bath AS Disease Activity Index) to the second TNFi (28-30). However, not all patients in these studies switched TNFi because of ineffectiveness. The panel judged that treatment should differ for patients who had a primary nonresponse to TNFi and those with secondary nonresponse to TNFi.

In cases of nonresponse (primary or secondary), the panel recommended against switching to the biosimilar of the first TNFi (e.g., switching from originator infliximab to infliximab-dyyb), as the clinical response would not be expected to be different. The panel also recommended against the addition of sulfasalazine or methotrexate to TNFi in cases of nonresponse to TNFi, judging any benefit would likely be marginal. The addition of sulfasalazine could be considered in the rare patient whose axial symptoms are well-controlled with TNFi but who has active peripheral arthritis.

We strongly recommend against treatment with systemic glucocorticoids.

(Level of evidence: Very low)

In adults with isolated active sacroiliitis despite treatment with NSAIDs, we conditionally recommend treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids. *(Level of evidence: Very low)*

In adults with stable axial disease and active enthesitis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids. Peri-tendon injections of Achilles, patellar, and quadriceps tendons should be avoided. *(Level of evidence: Very low)*

In adults with stable axial disease and active peripheral arthritis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids.

(Level of evidence: Very low)

Recommendations for adults with active or stable AS

In adults receiving treatment with TNFi, we conditionally recommend against co-treatment with low-dose methotrexate. *(Level of evidence: Low)*

In rheumatoid arthritis, the likelihood of TNFi discontinuation is lower among patients who receive co-treatment with methotrexate, perhaps by reducing the development of antidrug antibodies (31). In AS, it is less clear whether the duration of TNFi use, and by inference their effectiveness, is similarly prolonged (32). Data from observational studies are conflicting, although some studies, primarily of infliximab, showed longer TNFi treatment when methotrexate was co-administered. Clinical responses were not greater among patients who received co-treatment with methotrexate. In the absence of convincing evidence of benefit, and due to greater burden for patients, the panel recommended against routine co-administration of methotrexate with TNFi, although its use could be considered in patients treated with infliximab.

Recommendations for adults with active nonradiographic axial SpA

Parallel questions on pharmacologic treatment were investigated for patients with nonradiographic axial SpA. There were no relevant published data for 19 questions. There was high-quality evidence only for the use of TNFi in nonradiographic axial SpA, which was examined in several clinical trials. Low-quality or very low-quality evidence from single studies suggested no differences in outcomes among different TNFi in nonradiographic axial SpA, high likelihood of relapse following discontinuation of TNFi, and no association between co-treatment with nonbiologics and TNFi persistence. Therefore, the recommendations for nonradiographic axial SpA were largely extrapolated from evidence in AS. The recommendations were identical in both patient groups with 1 notable exception: treatment with secukinumab or ixekizumab was strongly recommended over no treatment with secukinumab or ixekizumab in patients with AS, while use of these medications was conditionally recommended in patients with nonradiographic axial SPA, because trials in nonradiographic axial SPA have not been reported. Evidence on tofacitinib in nonradiographic axial SpA has not been reported.

We strongly recommend treatment with NSAIDs over no treatment with NSAIDs. *(Level of evidence: Very low)*

We conditionally recommend continuous treatment with NSAIDs over on-demand treatment with NSAIDs. *(Level of evidence: Very low)*

We do not recommend any particular NSAID as the preferred choice.

(Level of evidence: Very low)

In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with sulfasalazine, methotrexate, or tofacitinib over no treatment with these medications. *(Level of evidence: Very low)*

In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we strongly recommend treatment with TNFi over no treatment with TNFi.

(Level of evidence: High)

We do not recommend any particular TNFi as the preferred choice.

(Level of evidence: Very low)

In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with tofacitinib.

(Level of evidence: Very low)

In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over no treatment with secukinumab or ixekizumab. *(Level of evidence: Very low)*

In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with secukinumab or ixekizumab.

(Level of evidence: Very low)

In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with tofacitinib.

(Level of evidence: Very low)

In adults with active nonradiographic axial SpA despite treatment with NSAIDs and who have contraindications to TNFi, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with sulfasalazine, methotrexate, or tofacitinib.

(Level of evidence: Very low)

In adults with active nonradiographic axial SpA and primary nonresponse to the first TNFi used, we conditionally recommend switching to secukinumab or ixekizumab over switching to a different TNFi. *(Level of evidence: Very low)*

In adults with active nonradiographic axial SpA and secondary nonresponse to the first TNFi used, we conditionally recommend switching to a different TNFi over switching to a non-TNFi biologic. *(Level of evidence: Very low)*

In adults with active nonradiographic axial SpA despite treatment with the first TNFi used, we strongly recommend against switching to the biosimilar of the first TNFi.

(Level of evidence: Very low)

In adults with active nonradiographic axial SpA despite treatment with the first TNFi used, we conditionally recommend against the addition of sulfasalazine or methotrexate in favor of treatment with a different biologic. *(Level of evidence: Very low)*

We strongly recommend against treatment with systemic glucocorticoids.
(Level of evidence: Very low)

In adults with isolated active sacroiliitis despite treatment with NSAIDs, we conditionally recommend treatment with local glucocorticoids over no treatment with local glucocorticoids. *(Level of evidence: Very low)*

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Spanish Society of Rheumatology (SER), 2018 [14].

Clinical practice guideline for the treatment of patients with axial spondyloarthritis and psoriatic arthritis

Zielsetzung

In order to reduce variability in clinical practice and to improve patient care and quality of life for those with axial spondyloarthritis and psoriatic arthritis, the Spanish Society of Rheumatology (SER) has fostered the development of clinical practice guideline (CPG) under the aegis of a multidisciplinary team of professionals involved in the care of such patients.

SER, as sponsor of this guideline, hopes to promote effective, safe, and coordinated decision making on therapeutic interventions for patients suffering from axSpA and PsA.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt,
- systematische Suche, Auswahl und Bewertung der Evidenz,
- Konsensusfindung erwähnt, aber nicht detailliert beschrieben,
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt,
- einzelne Aspekte zum Aktualisierungsverfahren fehlen.

Recherche/Suchzeitraum:

- A literature search was carried out using the MEDLINE database (via PubMed), EMBASE (Elsevier), the Cochrane Library (Wiley Online Library), and Cinahl (EBSCOhost).
- The question regarding physiotherapy was researched in PEDro (Physiotherapy Evidence Database).

- Literature and database searches were limited to those studies published after the creation of ESPOGUIA 2009, i.e., from the beginning of 2008. These searches were completed at the end of 2014.
- [...] if the results proved to be poor or inconsequential, then a supplemental search by hand among the bibliography in the most relevant documents was conducted. Further material was included after consulting with investigators and reviewers. This helped identify those studies published since the initial search until the current guideline were created, 2015.

LoE

The level of scientific evidence was evaluated using a modified version of the Oxford Centre for Evidence-Based Medicine (CEBM) system.

GoR

The strength of each recommendation was evaluated using a modified version of CEBM.

Tabelle 3: Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies or extrapolations from level 1 studies
C	level 4 studies or extrapolations from level 2 or 3 studies
D	level 5 evidence or troublingly inconsistent or inconclusive studies of any level

Sonstige methodische Hinweise

Sulfasalazin und Tocilikumab sind keine für die Indikation axiale Spondyloarthritis zugelassenen Wirkstoffe.

Empfehlungen

In patients with axial spondyloarthritis, does early pharmacological intervention improve functional capacity, structural damage and quality of life?

As soon as axial spondyloarthritis has been diagnosed we recommend commencement of pharmacological treatment. *(Grade D recommendation)*

There is insufficient evidence on the effectiveness of early pharmacological treatment for patients with axial spondyloarthritis (56-61). *(Evidence level 2b, 4)*

In secondary analyses evaluating the effectiveness of early pharmacological treatment in patients with axial spondyloarthritis, those with shorter disease durations responded better to treatment with anti-TNF (57, 62, 63). *(Evidence level 2b, 4)*

In patients with non-radiographic axial spondyloarthritis, what is the effectiveness of different biological therapies compared with placebo or traditional DMARDs? What is the relative effectiveness of the different biological therapies?

Therapy with anti-TNF is recommended as the pharmacological treatment of choice for patients with active* non-radiographic axial spondyloarthritis who are refractory to NSAID.

(Grade A recommendation).

*defined by objective inflammation characteristics (increase in CRP and/or MRI)

Biological therapies with anti-TNF (adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab) have proven effective in treating non-radiographic axial spondyloarthritis (57, 62, 70, 75-78). *(Evidence level 1b)*

Biological agents such as adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab, versus placebo, contribute to (57, 62, 70, 75-78):

- Minimizing inflammatory activity.
- Improving functional capacity. (Evidence level 1b)

The latest SER Consensus also recommends biological therapy commencement in patients with Nr-axSpA when accompanied by high CRP and/or signs of inflammation in MRI (98). [8]

The use of tocilizumab is not recommended in patients with non-radiographic axial spondyloarthritis who are refractory to NSAID and/or treatment with anti-TNF. *(Grade C recommendation)*

In non-radiographic axial spondyloarthritis, the biological agent tocilizumab does not improve clinical or functional parameters that have not previously responded to treatment with anti-TNF (79). *(Evidence level 4)*

In patients with axial spondyloarthritis, what are the prognostic factors regarding response to biological treatment?

Assessment of the predictive factors of response should be considered when indicating biological therapy; however, it is in no way compulsory for treatment application. (*Grade D recommendation)*

Response predictive factors identified include: age, gender, smoking, weight, disease activity (including MRI), functional capacity, disease evolution time and HLA B27 (57, 70, 99-104). *(Evidence level 2b, 3, 4)*

In patients with axial spondyloarthritis, does pharmacological intervention with biological therapy control structural damage progression and axial radiographic lesion?

Predictive factors of structural damage progression should be assessed in the biological therapy indication. *(Grade D recommendation)*

Biological therapy is efficient in reducing vertebral and sacroiliac bone inflammation. Recent data suggest BT is also efficient in reducing radiographic progression in SpA (76, 89, 90, 106-108). *(Evidence level 1b)*

Among the predictive factors of structural damage are: basal radiographic damage, MRI affectation, gender, smoking and disease activity (109-111). *(Evidence level 2b)*

In patients with with axSpA who failed to respond to anti-TNF, would the intervention with another anti-TNF or biological therapy be efficient?

After failure to a first anti-TNF, the patient should be treated with another anti-TNF or anti-IL17A. *(Grade D recommendation)*

Treatment with a second anti-TNF in patients with AS who have failed to a previous anti-TNF is effective in a high percentage of patients (up to 30-50%). However, the clinical response observed is less than that experienced by patients receiving a first anti-TNF (120-125). *(Evidence level 4)*

Evidence evaluating the efficacy of the change to a third anti-TNF in patients with SpA is very limited (120-122). *(Evidence level 4)*

Treatment with Secukinumab in patients with SpA who failed an anti-TNF is efficient in a high percentage of patients (up to 30-50%). The response is lower than observed in patients anti-TNF-naïve (126). *(Evidence level 4)*

In patients with axial spondyloarthritis, is it possible to stop treatment with anti-TNF?

In those patients with axial spondyloarthritis who reach the clinical objective, halting anti-TNF therapy is not recommended. *(Grade C recommendation)*

Discontinuation of anti-TNF therapy in patients with axial spondyloarthritis leads to a breakout within a few months in most cases (129-133). *(Evidence level 4)*

In patients with axial spondyloarthritis, is it possible to reduce the dosage of anti-TNF?

The possibility of reducing the anti-TNF drug dose in patients with axSpA, who have achieved remission or maintain low disease activity, should be considered. *(Grade D recommendation)*

In the event of disease activity increase in patients whose anti-TNF dose was reduced, an increase should be considered returning to previous or standard dosage. *(Grade D recommendation).*

Dose reductions during anti TNF therapy can effectively maintain remission or low disease activity in a great number of patients (>50%) with ankylosing spondylitis (134-141). *(Evidence level 2b, 4)*

There is not enough data to clearly identify which factors predict a good outcome after reducing the dosage of anti TNF in patients suffering axial spondyloarthritis (134-141). *(Evidence level 2b, 4)*

In patients with ankylosing spondylitis, does the use of biological agents, compared with sulfasalazine, reduce the number of uveitis recurrences and does it improve visual prognosis?

The guideline development group believes that in patients with ankylosing spondylitis, the use of anti-TNF, especially monoclonal antibodies, is effective in reducing the number of uveitis recurrences and improving visual prognosis. However, its superiority (or inferiority) in comparison with sulfasalazine cannot be established based on current scientific evidence. *(Grade D recommendation)*

Studies evaluating the effectiveness of biologics, compared with sulfasalazine, in reducing the number of uveitis recurrences and improving visual prognosis in patients with ankylosing spondylitis are scarce. Etanercept has not shown any superiority over the short term. For other anti-TNF drugs, there is no comparative evidence (148). *(Evidence level 1b)*

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National Institute for Health and Care Excellence (NICE), 2017 [10].

Spondyloarthritis in over 16s: diagnosis and management

Zielsetzung

This guideline covers diagnosing and managing spondyloarthritis that is suspected or confirmed in adults who are 16 years or older. It aims to raise awareness of the features of spondyloarthritis and provide clear advice on what action to take when people with signs and symptoms first present in healthcare settings. It also provides advice on the range of treatments available.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt,
- systematische Suche, Auswahl und Bewertung der Evidenz,
- Konsensusfindung erwähnt, aber nicht detailliert beschrieben,
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt,
- regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- The searches were conducted between September 2014 and October 2015.
- The re-run searches took place in March and June 2016 using population only terms.
- Sources searched for the guideline:
  AMED (HDAS)
  CINAHL (HDAS)
  Cochrane Database of Systematic Reviews – CDSR (Wiley)
  Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
  Database of Abstracts of Reviews of Effects – DARE (Wiley)
  Health Technology Assessment Database – HTA (Wiley)
  EMBASE (Ovid), MEDLINE (Ovid)
  MEDLINE In-Process (Ovid)

LoE

- GRADE was used to assess the quality of evidence for the selected outcomes as specified in the "The guidelines manual (2012)".
- Where RCTs are possible, these are initially rated as high quality and the quality of evidence for each outcome was downgraded or not from this initial point.
- If non-RCT evidence was included for intervention-type systematic reviews then these are initially rated as low quality and the quality of the evidence for each outcome was further downgraded or not from this point.

GoR

Interventions that must (or must not) be used

"Must" or "most not" only if there is legal duty to apply the recommendation, occasionally [...] if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions that should (or should not) be used

"Offer" (and similar words such as "refer" or "advise") when [...] confident, that for the majority of patients, an intervention will do more good than harm, and be cost effective. [...] similar forms of words (for example "Do not offer…") when [...] confident that an intervention will not be of benefit for most patients.

Interventions that could be used

"Consider" when [...] confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Empfehlungen

Pharmacological interventions for axial symptoms of spondyloarthritis

13. First-line pharmacological management of axial spondyloarthritis

13.1 Offer NSAIDs at the lowest effective dose to people with pain associated with axial spondyloarthritis,and think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment.

The quality of the evidence was agreed to be moderate. The majority of studies were conducted before 2000 and the quality of reporting of either the methods or the outcomes was poor. However there was no clear evidence of bias in the included studies. The evidence was considered to be directly relevant as the population and the intervention in the included studies met the criteria stated in the review protocol. There was no significant inconsistency between the findings of the network meta-analysis when compared with the results from the pairwise analyses. The quality of the evidence was primarily downgraded as the rescaling of the pain outcome to a 0-100 scale for a number of studies relied on a number of assumptions regarding the original scales (symmetric, unimodal, same distributional shape). Additionally the GDG noted that the wide credible intervals and lack of significant differences between NSAIDs could be attributed to the imputed standard deviations in 9 out of 23 included papers.

Switching or augmenting pharmacological interventions for spondyloarthritis

15. Second-line pharmacological management of axial spondyloarthritis

15.1 If an NSAID taken at the maximum tolerated dose for 2-4 weeks does not provide adequate pain relief, consider switching to another NSAID.

The GDG agreed that the available evidence was limited and of low quality. The GDG noted that all of the identified evidence came from studies of people with psoriatic arthritis. For the purposes of this question, the GDG felt it was appropriate to extrapolate the findings [...].

Biological DMARDs for spondyloarthritis

Recommendations from NICE technology appraisals

17.1. Biological DMARDs – adalimumab, certolizumab pegol, etanercept, golimumab and infliximab for the treatment of ankylosing spondylitis and non-radiographic axial spondyloarthritis.

17.1.1. Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended, within their marketing authorisations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs. Infliximab is recommended only if treatment is started with the least expensive infliximab product. People currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their NHS clinician consider it appropriate to stop.

17.1.2. Adalimumab, certolizumab pegol and etanercept are recommended, within their marketing authorisations, as options for treating severe non-radiographic axial spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.

17.1.3. The choice of treatment should be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available. This may include considering associated conditions such as extra-articular manifestations. If more than 1 treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen.

17.1.4. The response to adalimumab, certolizumab pegol, etanercept, golimumab or infliximab treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response, defined as a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units and a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.

17.1.5. Treatment with another tumour necrosis factor (TNF)-alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response.

17.2. Biological DMARDs-secukinumab for the treatment of ankylosing spondylitis

17.2.1. Secukinumab is recommended, within its marketing authorisation, as an option for treating active ankylosing spondylitis in adults whose disease has responded inadequately to conventional therapy (NSAIDs or TNF-alpha inhibitors). The drug is recommended only if the company provides it with the discount agreed in the patient access scheme.

17.2.2. Assess the response to secukinumab after 16 weeks of treatment and only continue if there is clear evidence of response, defined as a reduction in the BASDAI score to 50% of the pre-treatment value or by 2 or more units and a reduction in the spinal pain VAS by 2 cm or more.

Van der Heijde D et al., 2017 [16].

Assessment of SpondyloArthritis International Society (ASAS)

European League Against Against Rheumatism (EULAR)

2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis

siehe auch: Regel A et al., 2017 [11],
Sepriano A et al., 2017 [13].

Zielsetzung

One aim of this update was to aggregate the existing ASAS-EULAR management recommendations of AS and the ASAS recommendations for the management of axSpA with TNFi into one set of recommendations. The objective of this aggregated set of recommendations is to give guidance on the non-pharmacological and pharmacological management of patients with axSpA.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt,
- Systematische Suche, Auswahl und Bewertung der Evidenz,
- Konsensfindung beschrieben, aber kein formaler Konsensusprozess,
- Empfehlungen mit Graduierung identifizierbar, Verknüpfung mit der Evidenz nur indirekt über den Hintergrundtext zu den Empfehlungen möglich,
- regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

Two fellows under the guidance of the methodologist performed two SLRs: one on non-pharmacological and non-biological pharmacological treatment (AR) and one on biological and targeted synthetic DMARDs (AS). These SLRs focused on the studies published after the locking date of the SLRs for the previous update, that is, 2009 (Regel A et al., 2017 [11], Sepriano A et al., 2017 [13]).

Regel A et al., 2017 [11]

The systematic literature search was performed by using references from MEDLINE, EMBASE and Cochrane CENTRAL databases and as an update of the previous SLR conducted in 2009. The articles included in the present SLR had to be published between 1 January 2009 and 26 February 2016.

Sepriano A et al., 2017 [13]

The following bibliographical databases were searched: MEDLINE, EMBASE and The Cochrane Central Register of Controlled Trials (CENTRAL), from January 2009 until 26 February 2016, without language restrictions.

LoE

Tabelle 4: 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

Tabelle 5: 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

Sonstige methodische Hinweise

Sulfasalazin ist kein für die Indikation axiale Spondyloarthritis zugelassener Wirkstoff.

Empfehlungen

Behandlungsalgorithmus (siehe Anhang Abbildung 9)

Recommendation 1: The treatment of patients with axSpA should be individualised according to the current signs and symptoms of the disease (axial, peripheral, extra-articular manifestations) and the patient characteristics including comorbidities and psychosocial factors. *(Evidence level: 5; Strength of Recommendation: D; Level of agreement: 9.7)*

Recommendation 5: Patients suffering from pain and stiffness should be use an NSAID as first-line drug treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs continuous use is preferred if symptomatic otherwise.

(Evidence level: 1a; Strength of Recommendation: A; Level of agreement: 9.4)

All task force members were still convinced of the virtues of NSAIDs administered in a full anti-inflammatory dosage. This can be based on the ASAS20 response of >70%, an ASAS40 response in >50% of the patients starting with an NSAID in early disease or 35% of patients in ASAS partial remission (68). Important consideration however needs to be given to the potential side effects of NSAIDs, especially when administered chronically. NSAIDs should therefore only be prescribed if patients are symptomatic. If so, treatment should be advised to the maximum tolerated dose, continuously weighing the risks against the benefits.

Moreover, while there is much discussion on the long-term safety of NSAIDs especially in relatively young patients, data from two studies have suggested that lack of exposure to NSAIDs is associated with an increase in mortality (69, 70).

Recommendation 6: 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.
(Evidence level: 5; Strength of Recommendation: D; Level of agreement: 8.8)

It is formulated as a rather weak recommendation since formal evidence that analgesics are efficacious in axSpA is lacking (not tested). Nevertheless, common sense justifies a statement that analgesics may relieve painful conditions, but only if positively recommended treatments for axSpA, including bDMARDs when indicated, have failed.

Recommendation 7: Glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered. Patients with axial disease should not receive long-term treatment with systemic glucocorticoids.
(Evidence level: 2, 5‡, 1a†; Strength of Recommendation: B*, D‡; Level of agreement: 8.8)*

New data now have suggested that short-term high dose of glucocorticoids (50 mg/day) may have a very modest effect on signs and symptoms in patients with axial disease (79). However, the task force still had the conviction that patients with axial disease should not be treated long-term with systemic glucocorticoids irrespective of the dose.

Recommendation 8: Patients with purely axial disease should normally not be treated with csDMARDs; sulfasalazine may be considered in patients with peripheral arthritis.
(Evidence level: 1a†; Strength of Recommendation: A; Level of agreement: 9.2)

In principle, the task force was of the opinion that patients with purely axial disease should not be treated with csDMARDs. While there is evidence that sulfasalazine, MTX and leflunomide are not efficacious for axial symptoms, there may be exceptional situations in which there is no other pharmacological treatment option left for a particular patient for reasons of toxicity, contraindications or costs (80-82).

Recommendation 9: bDMARDs should be considered in patients with persistently high disease activity despite conventional treatments; current practice is to stark with TNFi therapy.

ß(Evidence level: 1a†; Strength of Recommendation: A; Level of agreement: 9.2)

bDMARDs (in general and not limited anymore to TNFi therapy) should be considered in patients with persistently high disease activity despite conventional treatments. These conventional treatments obviously include non-pharmacological management as well as NSAIDs. And in patients with (mainly) peripheral symptoms, 'conventional management' may also include a local glucocorticoid injection (if considered appropriate) and normally a treatment with sulfasalazine (in case of peripheral arthritis). This recommendation emphasises that a treatment 'should be considered' and the outcome of this process of consideration is dependent on an evaluation of the risks and benefits to be expected.

TNFi therapy is approved in many countries for patients with radiographic axSpA (AS) without further limitations, and in patients with non-radiographic axSpA only if there is an elevated CRP and/or inflammation on MRI. This means that if a patient with axSpA has radiographic sacroiliitis or when this patient has either an elevated CRP or inflammation on MRI, the patient formally complies with the requirements for bDMARD therapy mentioned in the label of the respective drugs. While not brought up as a limitative factor, the task force was of the opinion that many studies have now suggested that also patients with

radiographic axSpA who have an increased CRP have the highest likelihood of treatment success (83, 84).

Currently, only secukinumab is approved, but several other agents are far in their development. To date, only trial data on IL-17i in radiographic axSpA are available and data in patients with non-radiographic axSpA are still lacking. So it is obvious that the body of experience with TNFi in axSpA on efficacy, safety and variety of indications greatly outweighs that with IL-17 pathway inhibition, both in terms of volume and time of follow-up. This is why the task force has decided to recommend TNFi as the first bDMARD, use the wording 'current practice' to justify that choice and implicitly give endorsement to this practice. [...] The choice is very much dependent on local situations, and general recommendations cannot be made, but given the similar expected safety and efficacy with regard to alleviating musculoskeletal symptoms, cost is potentially an important consideration in making a choice between a boDMARD and a bsDMARD.

Recommendation 10: If TNFi therapy fails, switching to another TNFi or an anti-IL-17 therapy should be considered.

(Evidence level: 2,1b**; Strength of Recommendation: B*, A**; Level of agreement: 9.6)*

Data suggest that a second TNFi (after failure of the first TNFi) can still be efficacious, although the level of efficacy may be lower than with the first TNFi (102). IL-17i therapy has proven efficacy in patients who had failed a TNFi but this was also less than in TNFi-naïve patients (26, 27). In patients with a primary nonresponse to the first TNFi, it may be more rational to switch to another class of drugs, that is, an IL-17i. [...] Toxicity to a TNFi may also be a reason to switch directly to an IL-17i. Data proving whether a TNFi is efficacious in patients who have failed IL-17i therapy are still lacking. Therefore, evidence-based guidance cannot be provided, but the task force felt it is reasonable to assume that a TNFi in this situation makes sense.

Recommendation 11: If a patient is in sustained remission, tapering of a bDMARD can be considered.

(Evidence level: 2; Strength of Recommendation: B; Level of agreement: 9.1)

Since the SLRs in 2009 new data have become available that suggest the possibility of successful tapering of bDMARDs and acceptable efficacy after restart (103, 104). However, complete discontinuation of bDMARDs seems to lead to a high percentage of patients that experience flares (105, 106). Given the high costs of long-term bDMARD use, it is considered appropriate to slowly taper bDMARDs in patients who are in sustained remission.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 4 of 12, April 2021) am 19.04.2021

#	Suchfrage
1	[mh Spondylarthritis]
2	((((((spondylarthrit*) OR spondyloarthrit*) OR spondylit*) OR ankylosing) OR bechtere*) OR ankylopoietica):ti,ab,kw
3	#1 OR #2
4	#3 with Cochrane Library publication date from Apr 2016 to present

Systematic Reviews in Medline (PubMed) am 19.04.2021

#	Suchfrage
1	Spondylarthritis[mh]
2	spondylarthrit*[tiab] OR spondyloarthrit*[tiab] OR spondylit*[tiab] OR ankylosing[tiab] OR bechtere*[tiab] OR ankylopoietica[tiab]
3	#1 OR #2
4	(#3) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR

#	Suchfrage
	Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
5	(#4) AND ("2016/04/01"[PDAT] : "3000"[PDAT])
6	(#5) NOT "The Cochrane database of systematic reviews"[Journal]
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 19.04.2021

#	Suchfrage
1	Spondylarthritis[mh]
2	spondylarthrit*[tiab] OR spondyloarthrit*[tiab] OR spondylit*[tiab] OR ankylosing[tiab] OR bechtere*[tiab] OR ankylopoietica[tiab]
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*[ti])
5	(#4) AND ("2016/04/01"[PDAT] : "3000"[PDAT])
6	(#5) NOT (retracted publication [pt] OR retraction of publication [pt])

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Anhang

Tabelle 1: Study characteristics (Deodhar et al. 2020[3])

APPENDIX S1. STUDY AND PATIENT CHARACTERISTICS OF THE INCLUDED STUDIES

Study	Duration used in the NMA (weeks)	Phase	Treatment	n	Age (years)	Male (%)	Race White (%)	HLA-B27 (%)	Disease duration (years)	Baseline BASDAI (cm)	Baseline BASFI (cm)	Baseline CRP (mg/l)	MTX use (%)
TNF Inhibitors													
Deodhar 2018 (GO-ALIVE)(1)	16	III	GOL IV 2 mg/kg	105	38.4 (10.1)	81.9	NR	89.9	5.6 (6.6)	7.0 (1.2)	6.3 (1.9)	20.0 (18.2)	14.3
			PBO	103	39.2 (10.8)	74.8	NR		5.5 (5.9)	7.1 (1.2)	6.1 (2.0)	19.3 (16.7)	20.4
Inman 2008(2)	14	III	GOL SC 50 mg Q4W	138	38.0 (12.6)	73.9	74.6	81.8	11.0 (9.6)	6.6 (1.5)	5.0 (2.6)	11 (15)	21
			GOL SC 100 mg Q4W	140	38.0 (12.6)	70.0	72.9	84.3	11.0 (10.0)	7.0 (1.4)	5.4 (2.9)	9 (15.6)	20
			PBO	78	41.0 (14.1)	70.5	73.1	84.6	16.0 (13.3)	6.6 (1.5)	4.9 (2.4)	11.5 (15.6)	19.2
Bao 2014(3)	16	III	GOL SC 50 mg Q4W	108	30.5 (10.3)	83.3	NR	NR	4.2 (5.22)	6.6 (1.3)	5.0 (2.4)	21 (21)	19.4
			PBO	105	30.6 (8.6)	82.9	NR	NR	3.7 (3.9)	6.5 (1.5)	5.0 (2.4)	19 (20)	21.9
Braun 2002(4)	12	NR	IFX 5 mg/kg	34	40.6 (8.0)	68.0	NR	91.0	16.4 (8.3)	6.5 (1.2)	5.4 (1.8)	24 (21)	Not allowed
			PBO	35	39.0 (9.1)	63.0	NR	88.0	14.9 (9.3)	6.3 (1.4)	5.1 (2.2)	18 (12)	Not allowed
van der Heijde 2005 (ASSERT)(5)	12	III	IFX 5 mg/kg	201	40.0 (11.1)	78.1	98	86.5	7.7 (8.6)	6.6 (1.7)	5.7 (1.9)	15 (19)	Not allowed
			PBO	78	41.0 (9.6)	87.2	97.4	88.5	13.2 (10.5)	6.5 (1.4)	6.0 (2.3)	17 (19)	Not allowed
van der Heijde 2006 (A)(6)	12	III	ADA 40 mg QOW	208	41.7 (11.7)	75.5	NR	78.4	11.3 (10.0)	6.3 (1.7)	5.2 (2.2)	18 (22)	9.6
			PBO	107	43.4 (11.3)	73.8	NR	79.4	10.0 (8.3)	6.3 (1.7)	5.6 (2.2)	22 (29)	7.5
Maksymowych 2008(7)	12	III	ADA 40 mg QOW	38	41.9 (11.1)	76.3	NR	86.8	14.5 (9.0)	6.2 (1.7)	5.3 (2.0)	18 (17)	10.5
			PBO	44	40.0 (10.9)	81.8	NR	81.8	12.1 (8.7)	6.5 (1.6)	5.6 (2.2)	23 (26)	9.1
Hu 2012(8)	12	NR	ADA 40 mg QOW	26	28.2 (6.9)	92.3	NR	96.2	7.4 (5.7)	5.9 (1.4)	3.7 (2.1)	25 (23)	MTX
			PBO	20	27.4 (7.2)	100.0	NR	95.0	7.6 (4.6)	6.2 (1.1)	3.9 (2.0)	32 (29)	MTX
Huang 2014(9)	12	III	ADA 40 mg QOW	229	30.1 (8.7)	80.8	NR	95.6	3.0 (3.8)	6.0 (1.4)	4.3 (2.3)	22 (24)	22.7
			PBO	115	29.6 (7.5)	82.6	NR	94.8	3.0 (3.2)	6.2 (1.4)	4.4 (2.3)	23 (30)	21.7
Landewe	12	III	CZP 200 mg	65	41.0 (10.8)	72.3	NR	81.5	8.8 (5.4)	6.5 (1.7)	5.6 (2.3)	23 (30)	NR

2014(10)¤			Q2W¤											¤
			CZP·400·mg·Q4W¤	56¤	41.9·(11.5)¤	73.2¤	NR¤	78.6¤	8.8·(7.4)[d]¤	6.2·(1.3)¤	5.7·(2.3)¤	21·(22)¤	NR¤	¤
			PBO¤	57¤	41.6·(12.8)¤	71.9¤	NR¤	84.2¤	10.2·(8.4)[d]¤	6.4·(1.9)¤	6.0·(2.0)¤	22·(17)¤	NR¤	¤
Gorman·2002(11)¤	16¤	NR¤	ETN·25·mg·BIW¤	20¤	38.0·(10.0)¤	65.0¤	75¤	95.0¤	15.0·(10.0)¤	N/A¤	4.5·(2.1)¤	20·(18)¤	35·(DMARD)¤	¤
			PBO¤	20¤	39.0·(10.0)¤	90.0¤	70¤	90.0¤	12.0·(9.0)¤	N/A¤	3.2·(2.5)¤	15·(12)¤	40·(DMARD)¤	¤
Davis·2003(12)¤	12¤	II¤	ETN·25·mg·BIW¤	138¤	42.1·(11.5)¤	76.0¤	94¤	84.0¤	10.1·(7.7)[c]¤	5.8·(1.2)¤	5.2·(1.6)¤	19·(17)¤	11¤	¤
			PBO¤	139¤	41.9·(11.8)¤	76.0¤	91¤	84.0¤	10.5·(8.8)[c]¤	6.0·(1.2)¤	5.6·(1.4)¤	20·(17)¤	12¤	¤
Calin·2004(13)¤	12¤	III¤	ETN·25·mg·BIW¤	45¤	45.3·(9.5)¤	80.0¤	93¤	NR¤	15.0·(8.8)¤	6.1·(1.6)[b]¤	6.0·(2.1)[b]¤	19·(16)[b]¤	13¤	¤
			PBO¤	39¤	40.7·(11.4)¤	77.0¤	95¤	NR¤	9.7·(8.2)¤	5.9·(1.3)[b]¤	5.7·(1.6)[b]¤	24·(42)[b]¤	13¤	¤
van·der·Heijde·2006·(B)(14)¤	12¤	III¤	ETN·50·mg·QW¤	155¤	41.5·(11.0)¤	69.7¤	NR¤	NR¤	9.0·(8.7)¤	6.2·(1.7)¤	6.1·(2.0)¤	22·(25)¤	41.9¶ (DMARD)¤	¤
			ETN·25·mg·BIW¤	150¤	39.8·(10.7)¤	76.0¤	NR¤	NR¤	10.0·(9.1)¤	5.9·(1.7)¤	5.8·(2.0)¤	20·(21)¤	36.7·(DMARD)¤	¤
			PBO¤	51¤	40.1·(10.9)¤	78.4¤	NR¤	NR¤	8.5·(6.8)¤	6.1·(1.4)¤	6.0·(1.9)¤	22·(23)¤	33.3·(DMARD)¤	¤
Barkham·2010(15)¤	12¤	NR¤	ETN·25·mg·BIW¤	20¤	40.8·(9.7)¤	75.0¤	NR¤	NR¤	11.0·(7.2)¤	6.0·(1.7)¤	5.6·(2.0)¤	N/A¤	MTX¤	¤
			PBO¤	20¤	39.4·(10.1)¤	85.0¤	NR¤	NR¤	20.0·(4.9)¤	5.5·(1.7)¤	5.3·(1.8)¤	N/A¤	MTX¤	¤
IL-12/23· Inhibitors¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤
Deodhar·2018·-·3001·(Study·1·-·naive·to·anti-TNF)(16)¤	16¤	III¤	UST·45·mg¤	116¤	39.2·(10.5)¤	80.2¤	72.4¤	95.7¤	6.3·(7.05)[c]¤	7.4·(1.3)¤	6.8·(1.9)¤	21.0·(22.1)¤	25¤	¤
			UST·90·mg¤	114¤	39.5·(11.3)¤	87.7¤	71.9¤	96.5¤	6.3·(6.45)[c]¤	7.3·(1.3)¤	7.0·(1.6)¤	25.0·(31.1)¤	19¤	¤
			PBO¤	116¤	38.3·(11.4)¤	87.1¤	74.1¤	97.4¤	6.6·(6.99)[c]¤	7.4·(1.4)¤	6.6·(2.2)¤	21.0·(20.8)¤	24¤	¤
Deodhar·2018·-·3002·(Study·2·-·refractory·to·anti-TNF)(16)¤	16¤	III¤	UST·45·mg¤	106¤	41.4·(11.3)¤	83.0¤	79.2¤	89.6¤	9.1·(7.94)[c]¤	7.6·(1.4)¤	6.9·(2.0)¤	26.0·(27.0)¤	28¤	¤
			UST·90·mg¤	105¤	41.5·(11.0)¤	87.6¤	80¤	93.3¤	9.6·(8.09)[c]¤	7.5·(1.3)¤	6.9·(1.7)¤	25.0·(25.0)¤	36¤	¤
			PBO¤	104¤	40.8·(11.7)¤	76.9¤	78.8¤	92.3¤	7.8·(6.73)[c]¤	7.5·(1.3)¤	7.2·(1.6)¤	28.0·(31.8)¤	25¤	¤
IL-23·Inhibitors¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤
Baeten·2018(17)¤	12¤	II¤	RIS·18·mg¤	40¤	38.0·(11.1)¤	70.0¤	NR¤	75.0¤	7.4·(8.2)¤	6.4·(1.4)¤	NR¤	NR¤	20·(DMARD)¤	¤
			RIS·90·mg¤	39¤	39.5·(10.8)¤	77.0¤	NR¤	77.0¤	6.6·(8.8)¤	5.8·(1.6)¤	NR¤	NR¤	20.5·(DMARD)¤	¤
			RIS·180·mg¤	40¤	40.6·(11.9)¤	75.0¤	NR¤	85.0¤	10.2·(9.5)¤	6.1·(2.2)¤	NR¤	NR¤	50·(DMARD)¤	¤
			PBO¤	40¤	37.6·(11.0)¤	63.0¤	NR¤	65.0¤	8.1·(8.2)¤	6.3·(1.5)¤	NR¤	NR¤	50·	¤

													(DMARD)¤
IL-17A· Inhibitors¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤
van·der·Heijde· 2018·(COAST-V)(18)¤	16¤	III¤	ADA·40·mg· Q2W¤	90¤	41.8·(11.4)¤	81.0¤	63¤	91.0¤	7.5·(7.5)¤	6.7·(1.5)¤	6.1·(2.1)¤	12.5·(17.6)¤	9¤
			IXE·Q2W¤	83¤	41.3·(11.2)¤	77.0¤	62.6¤	90.0¤	8.2·(9.0)¤	6.7·(1.6)¤	6.3·(2.1)¤	13.4·(15.3)¤	5¤
			IXE·Q4W¤	81¤	41.0·(12.1)¤	84.0¤	64.2¤	93.0¤	8.3·(9.6)¤	6.8·(1.3)¤	6.1·(1.8)¤	12.2·(13.3)¤	11¤
			PBO¤	87¤	42.7·(12.0)¤	83.0¤	68.7¤	89.0¤	6.8·(7.6)¤	6.8·(1.2)¤	6.4·(1.9)¤	16.0·(21.0)¤	9¤
Deodhar·2018(19)¤	16¤	III¤	IXE·Q2W¤	98¤	44.2·(10.8)¤	76.5¤	79.6¤	NR¤	11.7·(8.8)¤	7.5·(1.3)¤	7.4·(1.4)¤	16.9·(19.8)¤	9.2¤
			IXE·Q4W¤	114¤	47.4·(13.4)¤	79.8¤	80.5¤	NR¤	10.1·(7.8)¤	7.5·(1.3)¤	7.4·(1.8)¤	20.2·(34.3)¤	10.5¤
			PBO¤	104¤	46.6·(12.7)¤	83.7¤	81.7¤	NR¤	13.0·(10.5)¤	7.3·(1.3)¤	7.0·(1.7)¤	16.0·(22.3)¤	19.2¤
Deodhar·2016· (MEASURE· 1)(20)¤	16¤	III¤	SEC·IV·75·mg¤	124¤	42.3·(13.2)¤	71.0¤	61.3¤	79.8¤	7.9·(9.7)[c]¤	6.0·(1.4)¤	5.4·(2.2)¤	NR¤	NR¤
			SEC·IV·150·mg¤	125¤	40.1·(11.6)¤	67.2¤	55.2¤	68.8¤	6.5·(6.9)[c]¤	6.3·(1.6)¤	5.6·(2.2)¤	NR¤	NR¤
			PBO¤	122¤	43.1·(12.4)¤	69.7¤	66.4¤	73.8¤	8.3·(8.9)[c]¤	6.5·(1.5)¤	5.8·(2.0)¤	NR¤	NR¤
Marzo-Ortega· 2017·(MEASURE· 2)(21)¤	16¤	III¤	SEC·SC·75·mg¤	73¤	44.4·(13.1)¤	69.9¤	NR¤	72.6¤	5.3·(7.4)[c]¤	6.6·(1.3)¤	NR¤	5.7·(0.5-86.2)[b]¤	MTX¤
			SEC·SC·150·mg¤	72¤	41.9·(12.5)¤	63.9¤	NR¤	79.2¤	7.0·(8.2)[c]¤	6.6·(1.5)¤	NR¤	7.5·(0.4-237.0)[b]¤	MTX¤
			PBO¤	74¤	43.6·(13.2)¤	75.7¤	NR¤	78.4¤	6.4·(8.9)[c]¤	6.8·(1.3)¤	NR¤	8.3·(0.5-84.6)[b]¤	MTX¤
Pavelka·2017· (MEASURE· 3)(22)¤	16¤	III¤	SEC·IV·150·mg¤	74¤	42.9·(11.1)¤	62.2¤	73¤	70.3¤	6.0·(7.2)[c]¤	7.0·(1.4)¤	NR¤	21.1·(0.4-111.3)[b]¤	13.5¤
			SEC·IV·300mg¤	76¤	42.1·(11.8)¤	65.8¤	68.4¤	73.7¤	5.3·(7.3)[c]¤	7.0·(1.4)¤	NR¤	13.3·(0.2-65.1)[b]¤	17.1¤
			PBO¤	76¤	42.7·(11.4)¤	52.6¤	76.3¤	69.7¤	5.2·(6.4)[c]¤	6.9·(1.3)¤	NR¤	20.0·(0.2-112.5)[b]¤	7.9¤
Kivitiz·2018· (MEASURE· 4)(23)¤	16¤	III¤	SEC·150·mg¤	116¤	44.5·(11.6)¤	69.8¤	97.4¤	86.2¤	8.4·(10.84)[c]¤	7.0·(1.2)¤	NR¤	6.25·(0.4-123.0)[b]¤	9.5¤
			SEC·150·mg·-·no·loading·dose¤	117¤	41.2·(11.1)¤	70.9¤	100¤	84.6¤	6.5·(7.55)[c]¤	7.0·(1.3)¤	NR¤	6.20·(0.3-120.9)[b]¤	9.4¤
			PBO¤	117¤	43.4·(12.5)¤	65.0¤	97.4¤	79.5¤	7.1·(9.23)[c]¤	7.1·(1.3)¤	NR¤	5.40·(0.3-129.3)[b]¤	8.5¤
JAK·Inhibitors¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤	¤
van·der·Heijde· 2018· (TORTUGA)(24)¤	12¤	II¤	FIL°200·mg¤	58¤	41.0·(11.6)¤	78.0¤	NR¤	88.0¤	6.0·(5.5)¤	6.9·(1.2)¤	7.0·(1.5)¤	19.6·(13.3)¤	16¤
			PBO¤	58¤	42.0·(9.0)¤	71.0¤	NR¤	88.0¤	8.0·(7.6)¤	7.0·(1.3)¤	6.9·(1.6)¤	21.2·(23.0)¤	7¤
van·der·Heijde· 2017(25)¤	12¤	II¤	TOF·10·mg·BID¤	52¤	41.6·(12.2)¤	73.1¤	NR¤	94.2¤	NR¤	6.9·(1.7)¤	5.7·(2.4)¤	NR¤	30.8·(csDMARD)¤

			TOF 5 mg BID	52	41.2 (10.3)	75.0	NR	84.6	NR	6.5 (1.9)	5.8 (2.2)	NR	30.8 (csDMARD)
			TOF 2 mg BID	52	41.8 (12.3)	65.4	NR	84.6	NR	7.0 (1.7)	5.5 (1.9)	NR	44.2 (csDMARD)
			PBO	51	41.9 (12.9)	62.7	NR	86.3	NR	6.3 (1.9)	5.7 (2.3)	NR	27.5 (csDMARD)
PDE4 Inhibitors													
Pathan 2012 (26)	12	II	APR 30 mg BID	17	44.9 (11.1)	NR	NR	NR	20.9 (12.3)	4.8 (2.2)	4.6 (2.4)	11.4 (12.1)	Not allowed
			PBO	19	39.2 (13.3)	NR	NR	NR	18.4 (10.2)	4.4 (1.8)	3.5 (2.2)	6.2 (2.6)	Not allowed
Unpublished (NCT01583374) (27)	16	III	APR 20 mg	163	45.2 (11.9)	74.2	94.5	NR	11.1 (11.5)	NR	NR	NR	NR
			APR 30 mg	163	44.8 (11.8)	65.6	96.9	NR	10.3 (9.9)	NR	NR	NR	NR
			PBO	164	44.0 (12.9)	75.6	96.3	NR	10.4 (10.4)	NR	NR	NR	NR

Note: Values are mean (SD) unless otherwise specified

[a] Data extracted from Wang et al. [4]

[b] Studies reported hsCRP median (min-max)

[c] Studies labelled disease duration using synonyms such as Time Since Diagnosis of AS, AS Diagnosis, Duration of AS, and Duration of Disease Since Axial Spondyloarthritis diagnosis

[d] Based on Symptom Duration

Abbreviations: ADA = adalimumab; APR = apremilast; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BID = twice a day; BIW = biweekly; CRP = C-reactive protein; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CZP = certolizumab pegol; DMARD = disease-modifying antirheumatic drugs; ETN = etanercept; FIL = filgotinib; GOL = golimumab; HLA-B27 = human leukocyte antigen B27; hs-CRP = highly sensitive C-reactive protein; IFX = infliximab; IL = interleukin; IV = intravenous; IXE = ixekizumab; JAK = Janus Kinase; MTX = methotrexate; NMA = network meta-analysis; NR = not reported; PBO = placebo; PDE = phosphodiesterase; QW = once per week; QOW = every other week; Q2W = every 2 weeks; Q4W = every 4 weeks; RIS = risankizumab; SEC = secukinumab; SC = subcutaneous; TNF = tumor necrosis factor; TOF = tofacitinib; UST = ustekinumab.

Baseline characteristics of the included studies

Author, Year	Study Design	Follow-up duration (years)	AS/ AxSpA characteristics	Treatment				Control			
				Drug	N	Disease duration, yrs (SD)	Baseline mSASSS (SD)	Drug	N	Disease duration, yrs (SD)	Baseline mSASSS (SD)
TNFi											
Baraliakos 2005 [42]	Open label extension of RCT	2	Active AS	Infliximab 5 mg/kg IV every 6 wk	41	15.5 (7.5)	12.1 (16.9)	No TNFi, GESPIC historical cohort	41	5.5 (2.25)	5.9 (13.4)
Baraliakos 2007 [22]	Open label extension of RCT	4	Active AS (same cohort as 2005 study)	Infliximab 5 mg/kg IV every 6 wk	33	19.0 (23.4)	11.6 (15.3)	No TNFi, OASIS historical cohort	132	11.7 (9.3)	12.7 (17.4)
van der Heijde (I) 2008 [24]	Open label extension of 24 week RCT	2 (96 wk)	Active AS (ASSERT cohort)	Infliximab 5 mg/kg IV every 6 wk after loading dose	201	10.2 (8.7)	17.7 (17.9)	No TNFi, OASIS historical cohort-matched	70	9.9 (8.8)	17.5 (19.1)
van der Heijde (E) 2008 [23]	Open label extension of 24 week RCT	2 (96 wk)	AS	Etanercept 25 mg SC twice a wk	257	10 (8.5)	14 (17.6)	No TNFi, OASIS historical cohort (meeting RCT entry criteria)	76	12 (9.8)	19 (20.8)
van der Heijde 2009 [21]	Open label extension of 24 week RCT	2	AS (Canadian [M03–606] study and the ATLAS study group	Adalimumab 40 mg SC every other week	307	19.8 (19.3)	19.8 (19.3)	No TNFi, OASIS historical cohort (eligible patients)	77	11.3 (8.7)	15.8 (17.6)
Pedersen 2011 [45]	Cohort study	2	AS	Infliximab 3 or 5 mg/kg (11), etanercept 25 mg twice a wk (10), adalimumab 40 mg every other wk (2)	23	18.2 (11.4)	14.5 916.1)	No TNFi, standard therapy	27	15 (10)	10.0 (12.1)
Haroon 2013 [27]	Cohort, prospective	1.5 to 9	AS	TNFi- type and dose not specified	201	-	-	No TNFi	133	-	-
Kang 2013 [46]	Cohort study	2	AS	Infliximab, etanercept or adalimumab	26	9.5 (5.1)	4.0 (6.6)	No TNFi (NSAID and/or MTX or SSZ)	37	8.0 (4.5)	3.7 (6.8)

Author, Year	Study Design	Follow-up duration (years)	AS/ AxSpA characteristics	Treatment				Control			
				Drug	N	Disease duration, yrs (SD)	Baseline mSASSS (SD)	Drug	N	Disease duration, yrs (SD)	Baseline mSASSS (SD)
Min 2014 [38]	Cohort, retrospective, single-center	8	AS	TNFi- type and dose not specified	14	-	-	Continuous NSAIDs	12	-	-
Braun 2014 [35]	Phase 3, multicentric, randomized, placebo-controlled, double- blind, placebo crossover	2 (104 wk)	Active AS (GO-RAISE trial)	Golimumab 50 or 100 mg every 4 wk	233	7.25 (35.59)	12.64 (17.71)	Placebo, crossover to golimumab 50 mg at wk 16 or 24	66	5.20 (45.94)	16.1 (18.7)
		4	Active AS (GO-RAISE trial)	Golimumab 50 or 100 mg every 4 wk	233	7.25 (35.59)	12.64 (17.71)	Placebo, crossover to golimumab 50 mg at wk 16 or 24	66	5.20 (45.94)	16.1 (18.7)
Baraliakos 2014 [43]	Open label extension of RCT	8	AS (DIKAS)	Infliximab 5 mg/kg IV every 6 wk	22	15.8 (8.5)	13.2 (17.6)- adjusted to 13.8 for comparison	No TNFi, Herne historical cohort	34	20.7 (5.7)	14.2 (13.8)- adjusted to 13.8 for comparison
Chung 2015 [47]	Clinical trial	4 (42– 66 mo)	AS	TNFi- type and dose not specified	25	4.15 (4.02)	-	No TNFi	25	2.13 (1.73)	-
Minhas 2016 [25]	Cohort, prospective	≥2, up to >10 (Median= 3)	AS (PSOAS cohort)	TNFi (>50% of FU)- type and dose not specified	630 (total)	-	-	No TNFi (<50% of FU period)	630 (total)	-	-
Kim 2016 [48]	Cohort, prospective	5	AS (OKSAR cohort)	TNFi- type and dose not specified	269	11.33 (7.51)	18.87 (17.96)	TNF naïve	341	8.04 (6.57)	15.68 (15.49)
Dougados 2018 [41]	Open label extension of RCT	2	Nr-axSpA (EMBARK trial)	Etanercept 25 mg SC twice a wk	162	2.4 (1.8)	Baseline total SIJ score- 1.5 (1.2)	No biologics, Contemporary DESIR cohort	193	1.70 (1.0)	Baseline SIJ score= 1.9 (1.6)
Molnar 2018 [34]	Cohort study	10 (2 year radiographic interval progression)	AS (patients fulfilling modified NY criteria for AS from SCQM AxSpA cohort)	Any TNFi before radiographic interval, NSAIDs	163	13.8 (9.7)	6.6 (12.5)	No TNFi before radiographic interval	269	-	-
Gensler 2018 [26]	Cohort, prospective	2, 4	AS (PSOAS cohort)	TNFi- type and dose not specified	239	16.8 (12.5)	14.2 (19.6)	No TNFi	280	16.8 (12.5)	14.2 (19.6)
Park 2019 [44]	Cohort study, single center	4	Early AS (<10 year symptom duration)	TNFi- type and dose not specified	135	2.7 (2.6)	6.2 (9.9)	NSAIDs, Control group from different institution	80	0.7 (1.8)	7.3 (10.8)

Author, Year	Study Design	Follow-up duration (years)	AS/ AxSpA characteristics	Treatment				Control			
				Drug	N	Disease duration, yrs (SD)	Baseline mSASSS (SD)	Drug	N	Disease duration, yrs (SD)	Baseline mSASSS (SD)
								(same location-Seoul)			
NSAIDs											
Wanders 2005 [37]	RCT, open label, radiographs blinded	2	AS patients	Continuous NSAIDs (started on celecoxib 200 mg bid but allowed to increase or change NSAID)	76	13 (10.2)	7.9 (14.7)	On-demand NSAIDs (celecoxib or another NSAID)	74	10.2 (9.3)	9.3 (15.2)
Poddubnyy 2012 [49]	Cohort study	2	AxSpA (GESPIC)	High NSAID intake (NSAID intake ≥50)	43	-	-	Low NSAID intake (NSAID index <50)	121	-	-
			AS		24	5.5 (2.7)	6.7 (7.7)		64	5.0 (2.9)	5.7 (11.6)
			Nr-AxSpA		19	3.7 (2.1)	1.6 (4.0)		57	3.0 (2.2)	2.6 (4.8)
Gensler 2018 [26]	Cohort, prospective	2,4	AS (PSOAS cohort)	NSAIDs	343	16.8 (12.5)	14.2 (19.6)	No NSAIDs	176	16.8 (12.5)	14.2 (19.6)
Schiotis 2013 [50]	Cohort study	3	AS (REGISPONSER), BASRI spine ≥12 excluded	Continuous NSAIDs	81	25.32 (9.38)	BASRI spine- 7.23 (3.34)	On-demand NSAIDs	37	25.54 (12.3)	BASRI-spine= 6.69 (3.4)
Minhas 2016 [25]	Cohort, prospective	>2, up to >10 (Median= 3)	AS (PSOAS cohort)	NSAID index>50	total in both groups=630	-	-	-	total in both groups=630	-	-
Sieper 2016 [36]	RCT, open label, radiographs blinded	2	AS (ENRADAS)	Continuous Diclofenac 150 mg /day (or equivalent dose if could not tolerate)	85	12.2 (10.3)	11.3 (14.9)	On-demand NSAIDs	82	15.2 (12.4)	14.0 (16.8)
Molnar 2018 [34]	Cohort study	10 (2 year radiographic interval progression)	AS (patients fulfilling modified NY criteria for AS from SCQM AxSpA cohort)	NSAIDs	286	13.8 (9.7)	6.6 (12.5)	no NSAIDs	55	-	-
Rumyantseva 2018 [39]	Cohort study	2	Early AxSpA	Continuous NSAIDs	35	24.1 (15.4)	SIJ score-3.67 (0.74)	On-demand NSAIDs	33	24.1 (15.4)	3 (1.48)

Author, Year	Study Design	Follow-up duration (years)	AS/ AxSpA characteristics	Treatment				Control			
				Drug	N	Disease duration, yrs (SD)	Baseline mSASSS (SD)	Drug	N	Disease duration, yrs (SD)	Baseline mSASSS (SD)
Secukinumab											
Braun 2018 [51]	Retrospective analysis of RCT	2	AS (MEASURE 1)	Secukinumab 150 mg or 75 mg IV every 4 wk	168	-	9.55 (14.14)	Biologic-naïve (on NSAIDs only), ENRADAS	69	-	9.95 (13.76)

AS- ankylosing spondylitis (defined as meeting modified New York criteria), axSpA- axial spondyloarthritis, nr- non-radiographic, N- number of participants, wk-week, SD- standard deviation, mSASSS- modified Stoke AS Spine Score, TNFi- tumor necrosis factor alpha, NSAIDs- non-steroidal anti-inflammatory drugs, BASRI(Bath AS Radiology Index), SIJ- sacroiliac joint, OASIS -Outcome Assessment in Ankylosing Spondylitis, ASSERT-Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy, ATLAS- Adalimumab Trial Evaluating Long-term Efficacy and Safety for Ankylosing Spondylitis, SCQM- Swiss Clinical Quality Management, GESPIC- early German AS cohort, DIKAS- Seutsche Infliximab Kohorte fur AS, GO-RAISE- golimumab in ankylosing spondylitis, PSOAS- Prospective Study of Outcomes in Ankylosing Spondylitis, GLAS- Groningen Leeuwarden AS, ENRADAS- Effects of NSAIDs on Radiographic Damage in Ankylosing Spondylitis, DESIR- French Cohort of Undifferentiated Spondyloarthritis, REGISPONSER- Spanish National Registry of Spondyloarthropathies.

Tabelle 3: RoB Assessment (Karmacharya et al. 2020[9])

Author, Year	Selection				Comparability		Outcome			Overall quality of study
	Representativeness of the exposed cases	Representativeness of the non-exposed group	Ascertainment of exposure	Determination that outcome not present initially	Study controls for age, sex	Study controls for other factors	Assessment of outcome	Long enough follow-up	Adequacy of follow-up	
TNFi										
Baraliakos 2005	yes	no	yes	yes	yes	yes	yes	yes	yes	Good
Baraliakos 2007	yes	no	yes	yes	yes	no	yes	yes	yes	Good
van der Heijde (E) 2008	yes	no	yes	yes	yes	no	yes	yes	yes	Good
van der Heijde (I) 2008	yes	no	yes	yes	yes	yes	yes	yes	yes	Good
van der Heijde 2009	yes	no	yes	yes	yes	no	yes	yes	yes	Good
Pedersen 2011	yes	yes	yes	yes	yes	no	yes	yes	yes	Good
Haroon 2013	yes	yes	yes	yes	yes	yes (propensity matched)	yes	yes	yes	Good
Kang 2013	yes	yes	yes	yes	yes	yes	yes	yes	yes	Good
Baraliakos 2014	yes	no	yes	yes	yes	yes	yes	yes	yes	Good
Min 2014	yes	yes	yes	yes	no mention	no mention	yes	yes	yes	Poor

Chung·2015·¤	yes¤	yes¤	yes¤	yes¤	yes¤	no¤	yes¤	yes¤	yes¤	Good¤
Kim·2016¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes·(propensity·matched)¤	yes¤	yes¤	yes¤	Good¤
Minhas·2016¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	Good¤
Molnar·2018¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	Good¤
Dougados·2018¤	yes¤	no¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	Good¤
Gensler·2018¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	Good¤
Park·2019¤	yes¤	no·-·separate·cohort·used¤	yes¤	yes¤	yes¤	yes·(propensity·matched)¤	yes¤	yes¤	yes¤	Good¤
NSAIDs¤										
Poddubnyy·2012¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	Good¤
Haroon·2013¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	Good¤
Schiotis·2013·abs¤	yes¤	yes¤	yes¤	yes¤	yes¤	no¤	yes¤	yes¤	yes¤	Good¤
Minhas·2016¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	Good¤
Molnar·2018¤	yes¤	yes¤	no¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	Good¤
Rumyantseva·2018¤	yes¤	yes¤	yes¤	yes¤	no¤	no¤	yes¤	yes¤	yes¤	Poor¤
Secukinumab¤										
braun·2018¤	yes¤	no¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	yes¤	Good¤

Study/year	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
TNF inhibitor						
Braun 2014	low	some concerns	some concerns (missing data at wk 208 extrapolated)	low	low	low
NSAID						
Wanders 2005	low	high	some concerns	low	low	high
Sieper 2016	low	high	some concerns	low	low	high

Supplementary File 2A. Risk of bias of the included studies i) New-Castle Ottawa scale for observational cohort studies, and ii) Revised Cochrane risk-of-bias tool (RoB 2.0) for randomized controlled trials.

Abbildung 1: Qualitätsbewertung der eingeschlossenen Studien (Ungprasert P et al., 2017 [15])

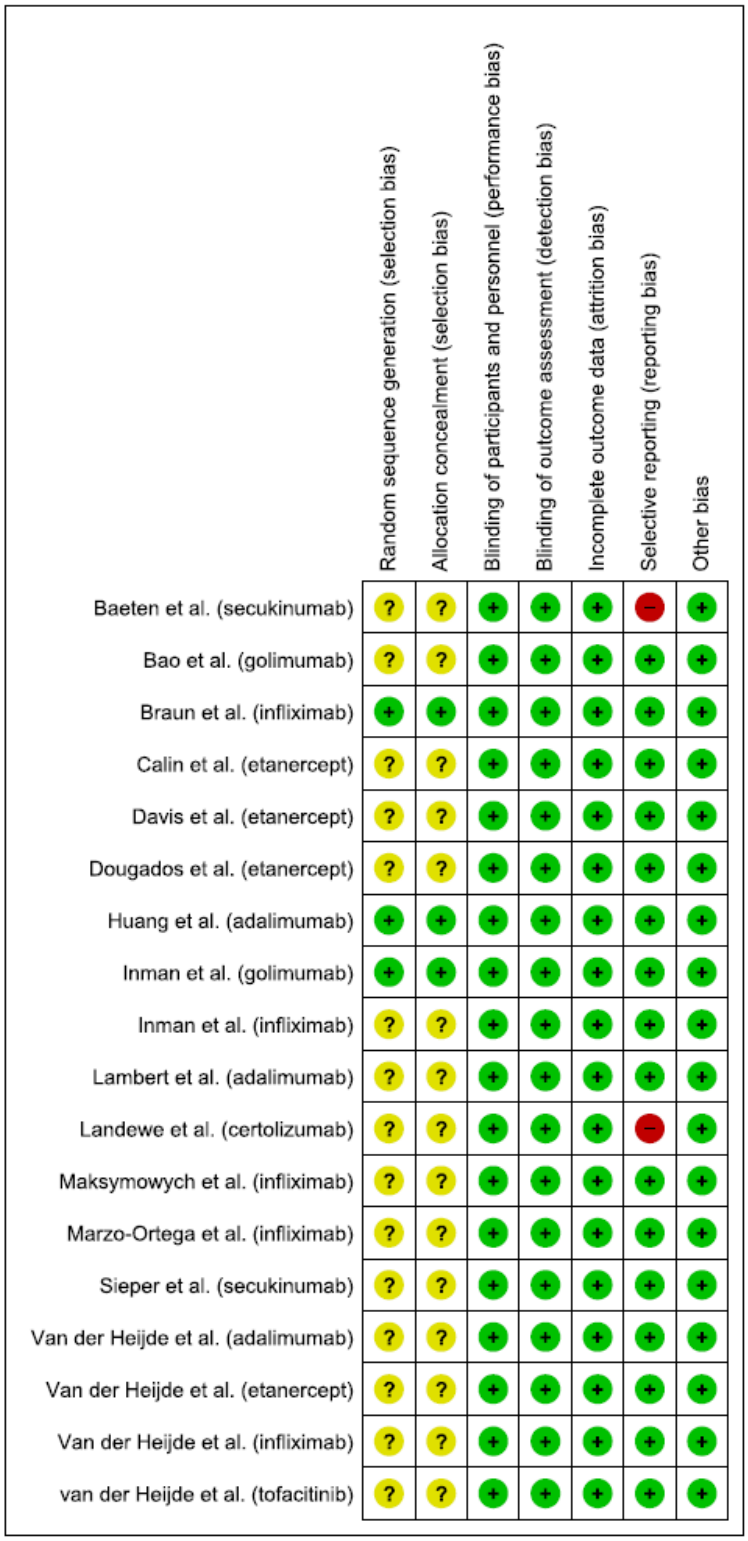


Tabelle 4 Oxford Centre for Evidence-based Medicine Levels of Evidence (Resende et al., 2020 [12])

Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with > 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case series	Absolute SpPins and SnNouts††	All or none case series	Absolute better-value or worse-value analyses††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level > 2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level 2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§§ only	Exploratory** cohort study with good††† reference standards; CDR† after derivation, or validated only on splits-ample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case series (and poor quality cohort and case control studies§§)	Case series (and poor quality prognostic cohort studies***)	Case control study, poor or non-independent reference standard	Case series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Tabelle 5: Oxford Klassifikation (Stand 2009) (Deutsche Gesellschaft für Rheumatologie, 2019)

Evidenzgrad	Therapie/Prävention/ Ätiologie/Schaden	Prognose	Diagnose	Differentialdiagnose/Symptom Prävalenz
1a	Systematischer Review von RCTs (mit Homogenität der Studienergebnisse)	Systematischer Review von Kohortenstudien mit Validierung in verschiedenen Populationen (mit Homogenität der Studienergebnisse	Systematischer Review von diagnostischen Studien mit Evidenzgrad 1; Klinische Entscheidungsregeln von 1b-Studien aus verschiedenen klinischen Zentren (mit Homogenität der Studienergebnisse)	Systematischer Review von prospektiven Kohortenstudien (mit Homogenität der Studienergebnisse)
1b	Individuelle RCTs (mit kleinem Konfidenzintervall)	Individuelle prospektive Kohorten-studien mit ≥ 80% Follow-up; Klinische Entscheidungsregeln, die in nur einer Population validiert wurden	Validierende Kohortenstudie mit guten Referenzstandards; Klinische Entscheidungsregeln, die nur innerhalb eines Zentrums evaluiert wurden	Prospektive Kohortenstudien mit gutem Follow-up
1c	Alles oder Nichts	Alles oder Nichts Fallserien	Absolute SpPins und SnNouts*	Alles oder Nichts Fallserien
2a	Systematischer Review von Kohortenstudien (mit Homogenität der Studienergebnisse)	Systematischer Review von retrospektiven Kohortenstudien oder unbehandelten Kontrollgruppen aus RTCs (mit Homogenität der Studien-ergebnisse)	Systematischer Review von diagnostischen Studien mit einem Evidenzgrad > 2 (mit Homogenität der Studienergebnisse)	Systematischer Review von 2b und besseren Studien (mit Homogenität der Studienergebnisse)
2b	Einzelne Kohortenstudien (einschließlich RCTs mit niedriger Studienqualität, z. B. < 80 % Follow-up)	Retrospektive Kohortenstudie oder Follow-up von unbehandelten Patienten einer RCT, Ableitung von klinischen Entscheidungsregeln oder Validierung nur aufgrund von „Split-Sample“	Explorative Kohortenstudie mit guten Referenzstandards; Klinische Entscheidungsregeln unter Ableitung oder Validierung aus „Split-Sample“ oder Datenbanken	Retrospektive Kohortenstudien mit schlechtem Follow-up
2c	„Outcomes“ Forschung, Ökologische Studien	„Outcomes“ Forschung		Ökologische Studien
3a	Systematischer Review von Fall-Kontrollstudien (mit Homogenität der Studienergebnisse)		Systematischer Review von 3b und besseren Studien (mit Homogenität der Studienergebnisse)	Systematischer Review von 3b und besseren Studien (mit Homogenität der Studienergebnisse)
3b	Einzelne Fall-Kontrollstudien		Nicht-konsekutive Studien oder ohne konsistente Anwendung eines Referenzstandards	Nicht-konsekutive Kohortenstudien oder sehr limitierte Population
4	Fallserien (und Kohorten und Fall-Kontrollstudien von schlechter Studienqualität)	Fallserien (und prognostische Kohortenstudien von schlechter Studienqualität)	Fall-Kontrollstudie mit schlechtem oder nicht-unabhängigem Referenzstandard	Fall-Serien oder abgelöste Referenzstandards
5	Expertenmeinung ohne explizite kritische Bewertung oder basierend auf Physiologie oder Laborergebnissen	Expertenmeinung ohne explizite kritische Bewertung oder basierend auf Physiologie oder Laborergebnissen	Expertenmeinung ohne explizite kritische Bewertung oder basierend auf Physiologie oder Laborergebnissen	Expertenmeinung ohne explizite kritische Bewertung, oder basierend auf Physiologie oder Laborergebnissen
*__SpPins__ die Spezifität ist so hoch, dass ein positives Ergebnis die Diagnose bestätigt, __SnNouts__ die Sensitivität ist so hoch, dass ein negatives Ergebnis die Diagnose ausschließt.				

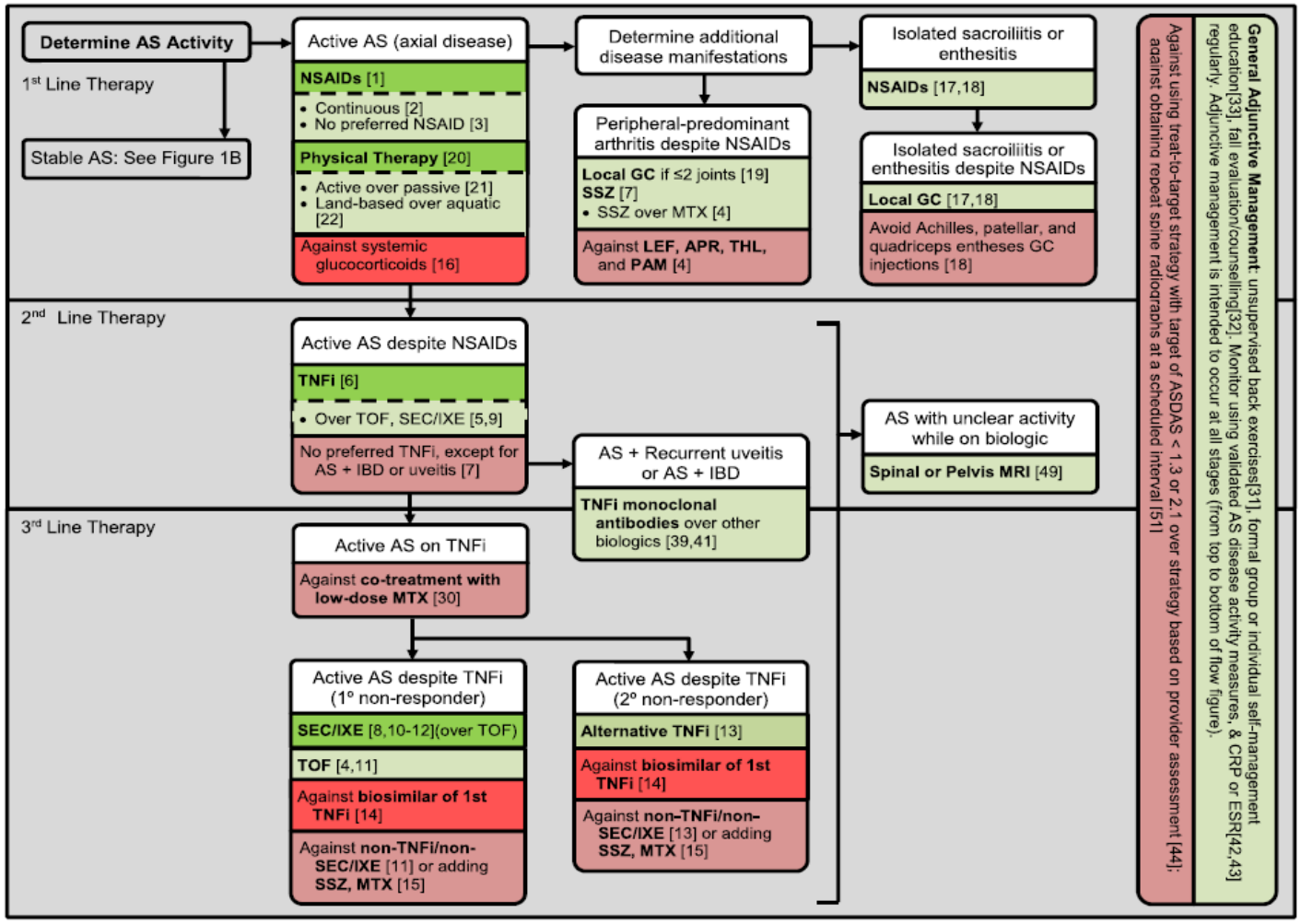
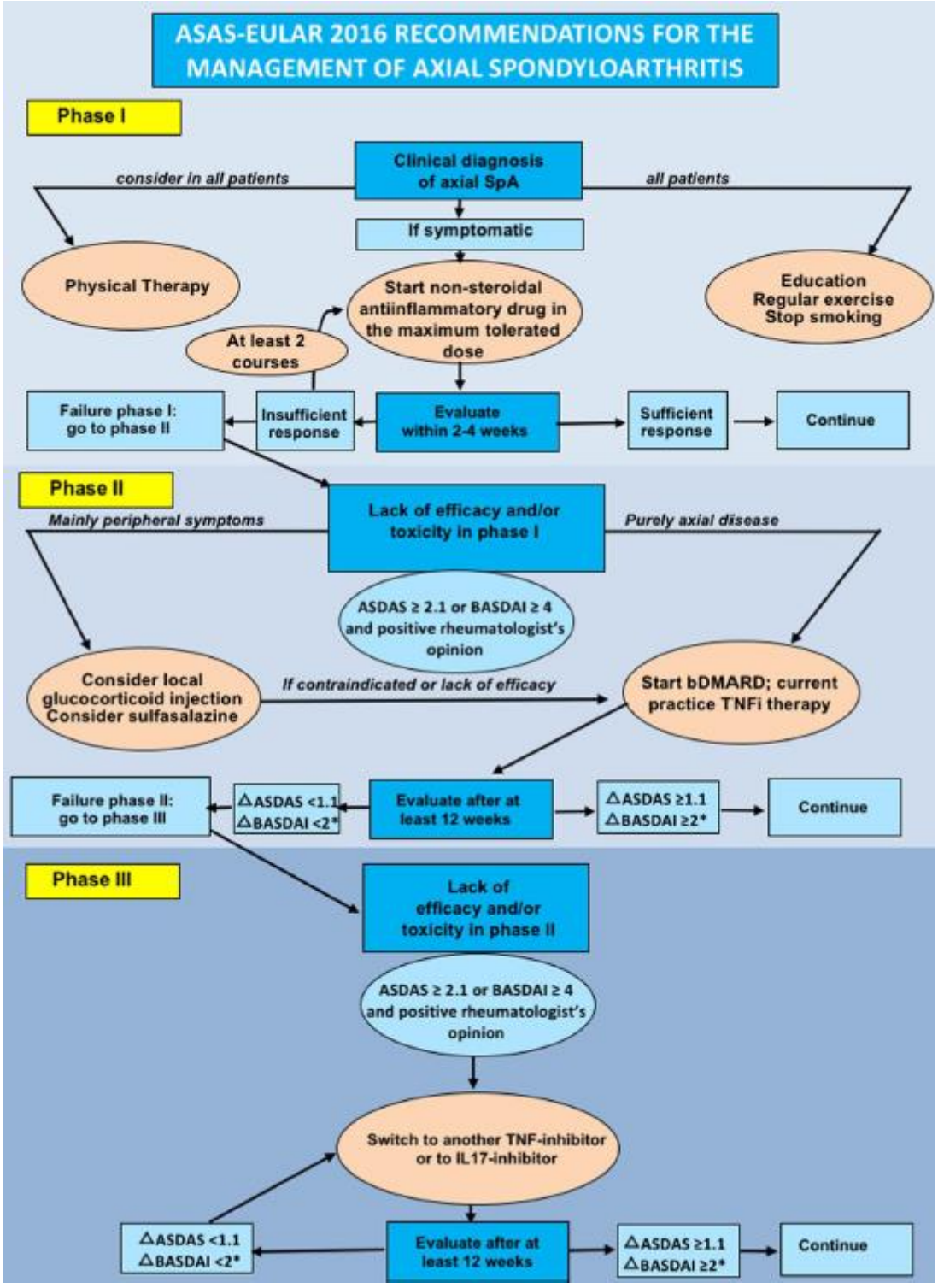


Abbildung 2:Summary of the main recommendations for the treatment of patients with active ankylosing spondylitis (Ward MM et al., 2019 [17])

Abbildung 3: Algorithm based on the ASAS-EULAR recommendations for the management of axial spondyloarthritis (Van der Heijde D et al., 2017 [16])



Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Kontaktdaten

DGf Rheumatologie (DGRh), Deutsche Wirbelsäulengesellschaft (DWG), DGf Orthopädie und Unfallchirurgie (DGOU)

Indikation gemäß Beratungsantrag

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Definition einer „aktiven axialen Spondyloarthritis“: Es wird vorausgesetzt, dass unter einer aktiven axSpA Erkrankung eine Erkrankung mit hoher Krankheitsaktivität verstanden wird. Eine hohe Krankheitsaktivität wird sowohl durch Patientenselbstauskunft als auch durch den Nachweis objektiver Entzündungszeichen (CRP oder Bildgebung wie MRT) nachgewiesen. Zur Erfassung der selbstberichteten Krankheitsaktivität wird der Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) und als Compound-Messinstrument (BASDAI Fragen plus CRP/BSG plus Patientenglobalurteil) der Ankylosing Spondylitis Disease Activity Score (ASDAS) verwendet (1)

Die Therapie bei Patienten mit axSpA richtet sich nach der Höhe der Krankheitsaktivität und nach dem Ausmaß der Funktionseinschränkungen. Wie grundsätzlich sonst auch ist immer eine differenzialdiagnostische Abklärung von Rückenschmerzen erforderlich, so dass als Standard im Management der Erkrankung zunächst die differenzialdiagnostische Einordnung von Rückenschmerzen (u.a. Degeneration, Fraktur, Fibromyalgie) vor Beginn und Änderung einer Therapie erfolgen muss. Bei symptomatischen Patienten kommt gemäß der S3-Leitlinie „Axiale Spondyloarthritis inklusive Morbus Bechterew und Frühformen“ der Einsatz von nicht-steroidalen Antirheumatika (NSAR) bei symptomatischen Patienten mit axialer SpA als Mittel der ersten Wahl in Frage (E8-10, LL2019, Empfehlungsgrad A) (2). Dabei ist in der Regel zur Erlangung von Symptomkontrolle die Therapie in maximaler Dosierung über einen Zeitraum von 4 Wochen erforderlich. Wenn das erste NSAR innerhalb von 2 Wochen nicht zu einer Reduktion der Krankheitsaktivität geführt hat, sollte ein zweites NSAR für weitere 2-4 Wochen verordnet werden (E8-13, LL2019, Empfehlungsgrad B). Bei Patienten mit persistierend hoher entzündlicher Krankheitsaktivität und unzureichendem Ansprechen auf eine vorangegangene NSAR-Therapie oder Unverträglichkeit von NSAR soll eine Therapie mit Biologika begonnen werden (E8-15, LL2019, Empfehlungsgrad A). Diese Empfehlungen finden sich gleichlautend auch in den internationalen ASAS/EULAR Empfehlungen für das Management der axSpA (3).

Der Behandlungsstandard in der Behandlung von Erwachsenen mit axialen Spondyloarthritis, die auf eine vorangegangene NSAR-Therapie nicht ausreichend angesprochen haben, ist also die Einleitung einer Biologika Therapie. Als Biologika sind TNF Inhibitoren und IL-17 Inhibitoren für Patienten mit axSpA zugelassen. IL-17 Inhibitoren sind für beide Formen der axialen SpA zugelassen und TNF Inhibitoren sind bis auf Infliximab (nur r-axSpA) für beide Formen der axialen SpA zugelassen. Für Patienten mit r-axSpA reicht der Nachweis der selbstberichteten Krankheitsaktivität aus (operationalisiert durch einen BASDAI Schwellenwert von ≥4), bei der nr-axSpA sind neben dem erhöhten BASDAI Wert auch noch der objektive

Nachweis von Entzündung (entweder CRP oder Nachweis einer Entzündung in dem MRT der SIG) notwendig.

Mit der Zulassung von Upadacitinib für die r-axSpA ist jetzt ein dritter Wirkmechanismus neben TNF Inhibitoren und IL-17 Inhibitoren zugelassen. Die Zulassungsstudie ist publiziert, die Ergebnisse sind aufgrund der Aktualität noch nicht in der Leitlinie enthalten und es zählt aktuell nicht zum Behandlungsstandard (4).

Was wird in der Indikation unter einer konventionellen Therapie verstanden?

Bitte begründen Sie Ihre Ausführungen.

(hier ergänzen – sofern verfügbar – auf welcher (Daten-)Grundlage basiert die Einschätzung; ggf. beifügen der zitierten Quellen)

Unter einer konventionellen Therapie wird sowohl eine nicht-medikamentöse Therapie als auch eine Therapie mit einem NSAR verstanden. Allerdings ist zu betonen, dass der Begriff „konventionelle Therapie" in der S3-Leitlinie „Axiale Spondyloarthritis inklusive Morbus Bechterew und Frühformen" nicht verwendet wird, da er für die Beschreibung der Therapie der axSpA im deutschen Sprachraum nicht häufig eingesetzt wird. Er findet sich jedoch im englischsprachigen Schrifttum häufig als „conventional therapy".

Nicht-medikamentöse Therapie: Das optimale Management für Patienten mit axialer SpA sollte eine Kombination aus nicht-pharmakologischen und pharmakologischen Maßnahmen beinhalten (E8-1, LL2019, Empfehlungsgrad B). Allerdings muss festgestellt werden, dass die Studienlage zu Bewegungstherapien bei axSpA Patienten, methodisch bedingt, eher spärlich ist und qualitativ nicht mit interventionellen Studien zur Überprüfung der Wirksamkeit bei einer medikamentösen Therapie verglichen werden kann.

Körperliche Aktivität stellt neben der gewöhnlich parallellaufenden medikamentösen Therapie eine wesentliche Säule im Behandlungskonzept der axialen SpA dar. Ziele der Bewegungstherapie sind nicht nur der Erhalt der körperlichen Beweglichkeit und die Verminderung der Steifheit, sondern auch die Schmerzreduktion, eine verbesserte Haltung, Koordination, Sturzprophylaxe und der Erhalt der funktionalen Gesundheit. Die körperliche Aktivität sollte sich auf die Bereiche kardiorespiratorisches Training, Widerstandsübungen, Dehnungen und Stabilisationsübungen erstrecken. Nicht-medikamentöse Therapieoptionen existieren für folgende Methoden: Bewegungstherapien (angeleitete Einzelkrankengymnastik, Eigenübungsprogramm im Rahmen der häuslichen Bewegungstherapie, angeleitete Gruppentherapien und eine Kombination, Balneotherapie als auch Übungen im Trockenen), manuelle Therapie. Hyperthermie/Kältetherapie, Elektrotherapie und ggf. Ergotherapie.

Bewegungsübungen, die zu Hause durchgeführt werden, sind zwar effektiv, aber allein nicht immer ausreichend. Angeleitete Bewegungstherapien (als Trocken- oder Wasserübungen), individuell oder als Gruppe, sollten zusätzlich zum häuslichen Bewegungsprogramm verordnet werden (E8-6, LL2019, Empfehlungsgrad B). Die Leitlinie empfiehlt, dass Bewegungstherapien zusätzlich zur medikamentösen Therapie (B) bzw. interventionellen Therapien (Expertenkonsens) erfolgen sollten, da sie zu einer weiteren Verbesserung der Beweglichkeit und der Funktionsfähigkeit im Alltag führen (E8-7, LL2019, Empfehlungsgrad B). Manuelle Therapie (Mobilisation) kann durchgeführt werden, um eine Verbesserung der Wirbelsäulen-beweglichkeit und eine verbesserte Körperhaltung zu erreichen. Manipulationen an der Wirbelsäule sollten nicht durchgeführt werden (E8-8 und 8-9, LL2019, Empfehlungsgrad B).

NSAR: Wie in Antwort 1 bereits dargestellt, ist bei symptomatischen Patienten mit axSpA der Einsatz von NSAR Mittel der ersten Wahl (E8-10, LL2019, Empfehlungsgrad A). Dabei richtet sich die Dosierung und Therapiedauer der NSAR inklusive Coxibe nach der Intensität der Beschwerden des Patienten (E8-11, LL2019, Statement). Eine kontinuierliche Therapie mit NSAR ist indiziert, solange diese für eine gute Symptomkontrolle erforderlich ist ((E8-14, LL2019, Statement).

Lokale Injektionstherapie

Die lokale Applikation von Glukokortikoiden in periphere Gelenke, Sehnenansatzbereiche, der Wirbelsäule und Sakroiliakal-Gelenke ist eine Möglichkeit zur symptomatischen Therapie. Ziel ist die Verbesserung der Mobilität, der Schmerzreduktion und somit der Lebensqualität. In den Empfehlungen der Leitlinie kann als Therapieoption die Injektion in diesen Arealen durchgeführt werden (E8-28, E8-29 LL2019).

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „aktiven ankylosierenden Spondylitis bei erwachsenen Patienten, die auf eine konventionelle Therapie unzureichend angesprochen haben**", die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Bitte begründen Sie Ihre Ausführungen

(hier ergänzen – sofern verfügbar – auf welcher (Daten-)Grundlage basiert die Einschätzung; ggf. beifügen der zitierten Quellen)

Bei Patienten mit axialer SpA, die auf NSAR nicht ausreichend gut angesprochen haben, und bei denen eine Biologika Therapie indiziert ist, richtet sich der behandelnde Arzt nach dem Schweregrad der Erkrankung (r-axSpA oder nr-axSpA) und nach dem Ausmaß extraartikulärer Manifestationen.

-Schweregrad: Sowohl TNF Inhibitoren als auch IL-17 Inhibitoren sind für beide Formen der axSpA zugelassen, Upadacitinib im Moment nur für die r-axSpA.

- Extraartikulärer Manifestationen: Aufgrund der unterschiedlichen Wirksamkeit in Bezug auf extraskelettale Manifestationen kann in der klinischen Entscheidungsfindung die Wirksamkeit auf eine begleitende Psoriasis oder Uveitis bzw. CED berücksichtigt werden. IL-17 Inhibitoren haben eine exzellente Wirksamkeit in Bezug auf eine Psoriasis vulgaris, aber keine Wirksamkeit in Bezug auf eine akute anteriore Uveitis oder eine CED (5-7). Verschiedene TNF Inhibitoren sind für die axiale SpA, Psoriasisarthritis und einer Psoriasis vulgaris sowie CED und Uveitis zugelassen. Die Daten für Upadacitinib hinsichtlich extraartikulärer Manifestationen ist nicht so ausgereift, dass hier eine belastbare Zusammenfassung gegeben werden kann.

Entscheidung zwischen TNF und IL-17 Inhibitoren anhand der Leitlinie: Eine Empfehlung, ob mit einem TNF-Inhibitor oder mit einem IL-17-Inhibitor begonnen werden soll, kann aufgrund der Studiendaten zur Wirksamkeit auf das Achsenskelett und Sicherheit nicht gegeben werden (Empfehlung 8-21, LL2019, Statement). Die Leitlinie stellt aber in dieser Empfehlung auch fest, dass für TNF-Inhibitoren längere Erfahrungen in der klinischen Anwendung bestehen.

Diese Empfehlung begründet sich darin, dass weder Vergleichsstudien (head-to-head Studie (H2H)) zwischen TNF-Inhibitoren und IL-17-Inhibitoren noch Strategiestudien bei Patienten mit axialer SpA vorliegen. Dadurch kann die Effektstärke auf die Reduktion der Krankheitsaktivität nicht vergleichend beurteilt werden. Zur Beurteilung einer unterschiedlich starken Hemmung der radiologischen Progression im Vergleich zwischen Adalimumab (als TNF Inhibitor) und Secukinumab (als IL-17 Inhibitor) wird aktuell eine H2H-Studie durchgeführt (Studienprotokoll (8)).

Die o.g. Kriterien beziehen sich überwiegend auf die Ersteinstellung eines Biologikums. Die Leitlinie stellt fest, dass bei nicht-ausreichender Wirksamkeit eines Biologikums und bestehender hoher entzündlicher Krankheitsaktivität der Wechsel auf ein weiteres Biologikum erfolgen sollte (E 8-22, LL2019, Empfehlungsgrad B)). Die Datenlage zu Therapiewechsel bei bDMARD Therapie ist spärlich und bezieht sich überwiegend auf TNFi Daten. Der Wechsel von einem TNFi zu einem anderen ist möglich, ist aber mit

einem schlechteren Therapieansprechen verknüpft. Diese Aussage basiert auf drei systematischen Reviews und mehreren Registerstudien; kontrollierte Studien fehlen (9-13). Beide Reviews zeigen, dass der Wechsel für einen Teil der Patienten erfolgreich ist, aber mit einem schlechteren Therapieansprechen verknüpft ist. Drug survival war bei dem 2. TNFi (47-72% über 2 Jahre) oder 3. TNFi (49% über 2 Jahre) niedriger als beim ersten TNFi. In der dänischen Kohorte mussten 30% der Patienten auf einen zweiten TNFi umgestellt werden, wobei der Hauptgrund für die Umstellung der sekundäre Wirkverlust war (10). Von den umgestellten Patienten erreichten immer noch 52% der Patienten eine klinische Remission, Daten der Schweizer Kohorte legen nahe, dass das mittlere Therapiedauer bei Pateinten mit Wechsel auf einen zweiten TNFi bei primärer Wirkungslosigkeit deutlich kürzer ist als bei einem sekundären Wirkverlust (mittlere Therapiedauer mit einem zweiten TNFi: 1.06 Jahre (95 %CI, 0.75 – 1.96) nach primären Versagen versus 3.76 Jahre (95 %CI 3.12 – 4.28) nach sekundärem Versagen (11). In einer prospektiven longitudinalen Kohorte aus Schweden mit 514 AS Patienten wechselten 77 Patienten auf einen zweiten TNFi, entweder wegen Wirkverlust oder wegen Nebenwirkungen (9). Die Krankheitsaktivität konnte zwar für einige Patienten gesenkt werden, die Krankheitsaktivität war aber höher als in der Patientengruppe, die keinen Wechsel der Medikation durchführen mussten. Daten zur Effektivität einer Änderung des Wirkprinzips liegen nicht vor.

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