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: 2023-B-125-z Bimekizumab

Stand: Juli 2023

| I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA | |
|---|---|
| **Bimekizumab**<br>**[aktive nicht-röntgenologische axiale Spondyloarthritis (nr-axSpA)]**<br><br>**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 | Beschluss über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:<br>• Upadacitinib vom 16. Februar 2023<br>• Secukinumab vom 18. Februar 2021<br>• Ixekizumab vom 21. Januar 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**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet**<br>(Text aus Fachinformation) |
| Zu bewertendes Arzneimittel: | |
| Bimekizumab | Bimzelx wird angewendet zur Behandlung erwachsener Patienten mit aktiver nichtröntgenologischer axialer Spondyloarthritis mit objektiven Anzeichen einer Entzündung, nachgewiesen durch erhöhtes C-reaktives Protein (CRP) und/oder Magnetresonanztomographie (MRT), die auf nicht-steroidale Antirheumatika (NSARs oder non-steroidal anti-inflammatory drugs, NSAIDs) unzureichend angesprochen oder diese nicht vertragen haben. |
| **Biologika** | |
| Adalimumab<br>L04AB04<br>Humira® | *Axiale Spondyloarthritis*<br><br>*Ankylosierende Spondylitis (AS)*<br>Humira wird angewendet zur Behandlung der schweren aktiven ankylosierenden Spondylitis bei Erwachsenen, die nur unzureichend auf eine konventionelle Therapie angesprochen haben.<br><br>*Axiale Spondyloarthritis ohne Röntgennachweis einer AS*<br>Humira wird angewendet 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 (NSAR) angesprochen haben oder bei denen eine Unverträglichkeit gegenüber diesen vorliegt. |
| Certolizumab Pegol<br>L04AB05.<br>Cimzia® | *Axiale Spondyloarthritis*<br>Cimzia ist angezeigt für die Behandlung von erwachsenen Patienten mit schwerer, aktiver axialer Spondyloarthritis, einschließlich:<br><br>*Ankylosierende Spondylitis (AS) (auch radiographische axiale Spondyloarthritis genannt)*<br>Erwachsene mit schwerer, aktiver ankylosierender Spondylitis, die ungenügend auf nichtsteroidale Antiphlogistika (NSARs) angesprochen haben oder die eine Intoleranz gegenüber NSARs besitzen.<br><br>*Axiale Spondyloarthritis ohne Röntgennachweis einer AS (auch nicht-radiographische axiale Spondyloarthritis genannt)* |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| | 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 NSARs angesprochen haben oder die eine Intoleranz gegenüber NSARs besitzen. |
| Etanercept<br>L04AB01<br>Enbrel® | *Axiale Spondyloarthritis*<br><br>*Morbus Bechterew (ankylosierende Spondylitis [AS]):*<br>Behandlung des schweren aktiven Morbus Bechterew bei Erwachsenen, die unzureichend auf eine konventionelle Behandlung angesprochen haben.<br><br>*Nicht-röntgenologische axiale Spondyloarthritis*<br>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. |
| Golimumab<br>L04AB06<br>Simponi® | *Axiale Spondyloarthritis*<br><br>*Ankylosierende Spondylitis (AS)*<br>Simponi ist angezeigt zur Behandlung der schweren, aktiven ankylosierenden Spondylitis bei Erwachsenen, die auf eine konventionelle Therapie unzureichend angesprochen haben.<br><br>*Nicht-röntgenologische axiale Spondyloarthritis (nr-axSpA)*<br>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. |
| Ixekizumab<br>L04AC13 | *Axiale Spondyloarthritis* |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| Taltz® | *Ankylosierende Spondylitis (Röntgenologische axiale Spondyloarthritis)*<br>Taltz ist angezeigt für die Behandlung erwachsener Patienten mit aktiver röntgenologischer axialer Spondyloarthritis, die auf eine konventionelle Therapie unzureichend angesprochen haben.<br><br>*Nicht-röntgenologische axiale Spondyloarthritis*<br>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. |
| Secukinumab<br>L04AC10<br>Cosentyx® | *Axiale Spondyloarthritis (axSpA)*<br><br>*Ankylosierende Spondylitis (AS; Morbus Bechterew, röntgenologische axiale Spondyloarthritis)*<br>Cosentyx ist angezeigt für die Behandlung erwachsener Patienten mit aktiver ankylosierender Spondylitis, die auf eine konventionelle Therapie unzureichend angesprochen haben.<br><br>*Nicht-röntgenologische axiale Spondyloarthritis (nr-axSpA)*<br>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 Magnetresonanztomographie (MRT), bei Erwachsenen, die unzureichend auf nichtsteroidale Antirheumatika (NSAR) angesprochen haben. |
| **JAK-Inhibitoren** | |
| Upadacitinib<br>L04AA44<br>RINVOQ® | *Axiale Spondyloarthritis*<br><br>*Nicht röntgenologische axiale Spondyloarthritis (nr-axSpA)*<br>RINVOQ wird angewendet zur Behandlung der aktiven nicht röntgenologischen axialen Spondyloarthritis bei erwachsenen Patienten mit objektiven Anzeichen einer Entzündung, angezeigt durch erhöhtes C-reaktives Protein (CRP) und/oder Nachweis durch Magnetresonanztomografie (MRT), die unzureichend auf nicht steroidale Antirheumatika (NSAR) angesprochen haben.<br><br>*Ankylosierende Spondylitis (AS, röntgenologische axiale Spondyloarthritis)* |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| | RINVOQ wird angewendet zur Behandlung der aktiven ankylosierenden Spondylitis bei erwachsenen Patienten, die auf eine konventionelle Therapie unzureichend angesprochen haben. |
| **Glucocorticoide** | |
| Prednisolon<br>H02AB06<br>generisch | – andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können:<br>– Spondarthritiden (Spondylitis ankylosans mit Beteiligung peripherer Gelenke (DS: b, c), Arthritis psoriatica (DS: c, d), enteropathische Arthropathie mit hoher Entzündungsaktivität (DS: a)<br>– Reaktive Arthritiden (DS: c)<br>– Arthritis bei Sarkoidose (DS: b initial) |
| Prednison<br>H02AB07<br>generisch | – andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können:<br>– Spondarthritiden (Spondylitis ankylosans mit Beteiligung peripherer Gelenke (DS: b, c), Arthritis psoriatica (DS: c, d), enteropathische Arthropathie mit hoher Entzündungsaktivität (DS: a)<br>– Reaktive Arthritiden (DS: c)<br>– Arthritis bei Sarkoidose (DS: b initial) |
| Triamcinolon<br>H02AB08<br>Volon® | – Andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können:<br>Spondarthritiden (Spondylitis ankylosans mit Beteiligung peripherer Gelenke, Arthritis psoriatica, enteropathische Arthropathie mit hoher Entzündungsaktivität);<br>– Reaktive Arthritiden;<br>– Arthritis bei Sarkoidose; |
| **Nicht-steroidale Antirheumatika (NSAID/ NSAR) z. B.** | |
| Acemetacin | Symptomatische Behandlung von Schmerz und Entzündung bei |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| M01AB11<br>generisch | – akuten Arthritiden (einschließlich Gichtanfall)<br>– chronischen Arthritiden, insbesondere bei rheumatoider Arthritis (chronische Polyarthritis)<br>– Spondylitis ankylosans (Morbus Bechterew) und anderen entzündlich-rheumatischen Wirbelsäulenerkrankungen<br>– Reizzuständen bei Arthrosen und Spondylarthrosen |
| Ibuprofen<br>M01AE01<br>generisch | Symptomatische Behandlung von Schmerz und Entzündung bei<br>– akuten Arthritiden (einschließlich Gichtanfall)<br>– chronischen Arthritiden, insbesondere bei rheumatoider Arthritis (chronische Polyarthritis)<br>– Spondylitis ankylosans (Morbus Bechterew) und anderen entzündlich-rheumatischen Wirbelsäulenerkrankungen<br>– Reizzuständen bei degenerativen Gelenk- und Wirbelsäulenerkrankungen (Arthrosen und Spondylarthrosen) |
| Indometacin<br>M01AB01<br>generisch | Symptomatische Behandlung von Schmerz und Entzündung bei<br>– akuten Arthritiden (einschließlich Gichtanfall)<br>– chronischen Arthritiden, insbesondere bei rheumatoider Arthritis (chronische Polyarthritis)<br>– Spondylitis ankylosans (Morbus Bechterew) und anderen entzündlich-rheumatischen Wirbelsäulenerkrankungen<br>– Reizzuständen bei Arthrosen und Spondylarthrosen |
| Naproxen<br>M01AE02<br>generisch | Symptomatische Behandlung von Schmerz und Entzündung bei<br>– akuten Arthritiden (einschließlich Gichtanfall)<br>– chronischen Arthritiden, insbesondere bei rheumatoider Arthritis (chronische Polyarthritis)<br>– Spondylitis ankylosans (Morbus Bechterew) und anderen entzündlich-rheumatischen Wirbelsäulenerkrankungen<br>– Reizzuständen bei Arthrosen und Spondylarthrosen |

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

## Abteilung Fachberatung Medizin

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

# Vorgang: 2023-B-125-z (Bimekizumab)

| | |
|---|---|
| Auftrag von: | Abt. AM |
| Bearbeitet von: | Abt. FB Med |
| Datum: | 10. Januar 2023 |

# Inhaltsverzeichnis

# Abkürzungsverzeichnis

| | |
|---|---|
| ACR | American College of Rheumatology |
| AS | Ankylosierende Spondylitis |
| ASAS | Assessment of SpondyloArthritis International Society |
| ASDAS | Ankylosing Spondylitis Disease Activity Score |
| ASQoL | Ankylosing Spondylitis Quality of Life |
| AWMF | Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften |
| axSpA | Axiale Spondyloarthritis |
| BASDAI | Bath Ankylosing Spondylitis Disease Activity 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 |
| DGRh | Deutsche Gesellschaft für Rheumatologie e. V. |
| DMARD | Disease-Modifying Antirheumatic Drug |
| ECRI | ECRI Guidelines Trust |
| EMBASE | Excerpta Medica Database |
| EQ-5D | European Quality of Life Five Dimension |
| EULAR | European League Against Rheumatism |
| G-BA | Gemeinsamer Bundesausschuss |
| GIN | Guidelines International Network |
| GoR | Grade of Recommendations |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HLA | Humanes Leukozytenantigen |
| HRQoL | Gesundheitsbezogene Lebensqualität |
| IBD | Inflammatory Bowel Disease |
| IL | Interleukin |
| IL-17A | Interleukin-17A |
| JAK | Januskinase |

| | |
|---|---|
| LoE | Level of Evidence |
| MACE | major cardiovascular event |
| MEDLINE | Medical Literature Analysis and Retrieval System Online |
| MRI | Magnetic Resonance Imaging |
| 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 |
| r-axSpA | radiologische axiale Spondyloarthritis |
| RCT | Randomised Controlled Trial |
| RoB | Risk of Bias |
| SAA | Spondylitis Association of America |
| SER | Spanisch Society of Rheumatology |
| SF-36 | 36-item Short Form Health Survey |
| SGB | Sozialgesetzbuch |
| SIGN | Scottish Intercollegiate Guidelines Network |
| SIJ | Sacroiliac Joint |
| SLR | Systematic Literature Review |
| SPARTAN | Spondyloarthritis Reseach and Treatment Network |
| SSZ | Sulfasalazin |
| TNF | Tumornekrosefaktor |
| TNFi | Tumornekrosefaktor-Inhibitor |
| TRIP | Turn Research into Practice Database |
| tsDMARD | targeted synthetic disease-modifying antirheumatic drugs |
| VAS | Visuelle Analogskala |
| WHO | World Health Organization |

# 1 Indikation

- Behandlung erwachsener Patienten mit aktiver nichtröntgenologischer axialer Spondyloarthritis mit objektiven Anzeichen einer Entzündung, nachgewiesen durch erhöhtes C-reaktives Protein (CRP) und/oder Magnetresonanztomographie (MRT), die auf nicht-steroidale Antirheumatika (NSARs oder non-steroidal anti-inflammatory drugs, NSAIDs) unzureichend angesprochen oder diese nicht vertragen haben
- Behandlung erwachsener Patienten mit aktiver ankylosierender Spondylitis (AS), die auf eine konventionelle Therapie unzureichend angesprochen oder diese nicht vertragen haben

*Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.*

# 2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation axiale Spondyloarthritis durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.google.com/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 12.12.2022 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 719 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. 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 Referenzen 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 22 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

# 3 Ergebnisse

## 3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

## 3.2 Systematische Reviews

**Webers C et al., 2023 [21].**

Efficacy and safety of biological DMARDs: a systematic literature review informing the 2022 update of the ASAS-EULAR recommendations for the management of axial spondyloarthritis

**Fragestellung**

To update the evidence on efficacy and safety of biological disease-modifying antirheumatic drugs (bDMARDs) in patients with axial spondyloarthritis (axSpA) to inform the 2022 update of the Assessment of SpondyloArthritis international Society/European Alliance of Associations for Rheumatology (ASAS-EULAR) recommendations for the management of axSpA.

**Methodik**

Population:

- adults with a clinical diagnosis of axSpA (r-axSpA or nr-axSpA)

Intervention:

- any bDMARD therapy (bio-originator or biosimilar), including TNFi, IL-17i, interleukin-23 and interleukin-12/23 inhibitors (IL-23i, IL-12/23i), in any formulation and duration

Komparator:

- the same bDMARD in a different dose/regimen, another bDMARD, any non-bDMARD drug treatment, combination of bDMARD with non-bDMARD treatment, placebo or none (for safety only, if population-based incidence rates were reported)

Endpunkte:

- Efficacy
  - ASAS response criteria (ASAS20, ASAS40, ASAS5/6 and partial remission),
  - disease activity (Ankylosing Spondylitis Disease Activity Score [ASDAS]: absolute change, response criteria [clinically important improvement (Δ≥1.1), major improvement (Δ≥2.0)], states [inactive disease (<1.3), low disease activity (<2.1)]; Bath AS Disease Activity Index [BASDAI]: absolute change, response [≥50% improvement]; patient's global assessment of disease activity),
  - day/night pain,
  - spinal mobility (Bath AS Metrology Index [BASMI]; individual spinal mobility measures),
  - physical function (Bath AS Functional Index [BASFI]),
  - peripheral manifestations (enthesitis; swollen/tender joint count),
  - functioning and health (ASAS Health Index [ASAS HI]), radiographic damage (modified Stoke AS Spine Score [mSASSS]; radiographic sacroiliitis according to modified New York criteria),
  - inflammation on MRI (active sacroiliitis according to ASAS/OMERACT definition; Spondyloarthritis Research Consortium of Canada [SPARCC] for sacroiliac joints and spine),
  - work disability and productivity
  - EMMs (psoriasis, acute anterior uveitis [AAU], inflammatory bowel disease [IBD])

- Safety
  - serious adverse events (AEs), withdrawals due to AEs, deaths, infections, malignancies, congestive heart failure, cardiovascular disease, infusion/injection-site reactions, lipid levels, renal function, hepatic effects, hematological abnormalities, gastro-intestinal effects and demyelinating disease

Recherche/Suchzeitraum:

- Medline, Embase, The Cochrane Database of Systematic Reviews, The Cochrane CENTRAL Register of Controlled Trials, Epistemonikos for the period of 1 January 2016 to 31 December 2021

Qualitätsbewertung der Studien:

- RoB 2

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 91 articles and 57 conference abstracts were included
- These included 36 RCTs that were first published after the previous SLR, of which 16 (44%) assessed TNFi (10 originator, 6 biosimilar; including 3 trials on discontinuation and 2 on tapering), 15 (42%) IL-17i (including 1 trial on discontinuation), 4 (11%) IL-12/23i and 1 trial with any bDMARD. From these, 18 trials included patients with r-axSpA (50%), while 7 (19%) and 11 (31%) included patients with nr-axSpA and axSpA (r-axSpA + nr-axSpA), respectively. OLE/LTE results were available for nine RCTs that were already included in the previous SLR. Altogether, 121 records provided data on RCTs and OLE/LTE.

Qualität der Studien:

- Siehe Studienergebnisse

Studienergebnisse:

Efficacy of TNFi

- Four RCTs of originator TNFi versus placebo were included
- Two studies with low RoB confirmed the efficacy of golimumab intravenously in r-axSpA and certolizumab in nr-axSpA (ASAS40 47.6% for golimumab vs 8.7 for placebo (NNT 2.6); 56.6% for certolizumab vs 15.8 for placebo (NNT 2.5)).
- One study of adalimumab in axSpA with a focus on imaging outcomes partially met its primary outcome (whole-body MRI smallest detectable change of ≥2.3 units met (44% vs 13%); SPARCC spine improvement of ≥5 units not met (36% vs 17%) after 6 weeks) and met several secondary outcomes (eg, ASAS40 48% for adalimumab vs 4% for placebo).
- A trial of etanercept versus placebo in patients with 'suspected axSpA' (no objective signs of inflammation required) was negative.
- Only one small study at high risk of bias compared originator TNFi with an active control.
- No RCTs tested the efficacy of TNFi in TNFi-experienced patients or infliximab in nr-axSpA.
- Comparable efficacy and safety of biosimilars and originators was confirmed in four trials of adalimumab, etanercept and infliximab biosimilars.

Efficacy of IL-17i

- In total, 14 placebo-controlled trials assessed the efficacy of IL-17i.
- Patients with r-axSpA on secukinumab showed greater improvement compared to placebo in two phase III trials (ASAS20 58.1–60.5% vs 36.6–36.8%, low/unclear RoB).
- Another phase III trial at low RoB saw numerically higher response rates for secukinumab compared to placebo in patients with r-axSpA, although results were not statistically significant (ASAS20 59.5–61.5% vs 47.0%) For the first time, the efficacy of secukinumab was shown in nr-axSpA, both with loading dose (LD) (ASAS40 41.5% vs 29.2%) and without LD (39.8% vs 19.9%)
- In both r-axSpA and nr-axSpA, response to secukinumab was higher compared to placebo in patients who were TNFi-naïve and in patients with prior inadequate response to TNFi (TNFi-IR), with higher rates in the TNF-naïve (ASAS40 38.8–43.9% vs 28.1–36.8%).
- Three phase III trials assessed the efficacy of ixekizumab, all at low RoB (table 2). In two of these on patients with r-axSpA, one including TNFi-naïve and the other TNFi-IR patients, ixekizumab was superior to placebo after 16 weeks (ASAS40 48–52% vs 18% for TNFi-naïve; 25–31% versus 13% for TNFi-IR).
- Similar results were seen in a trial of patients with nr-axSpA who were TNFi-naïve (ASAS40 35–40% for ixekizumab vs 19% for placebo).

Safety of bDMARDs

- The frequency of serious infections, malignancies and cardiovascular events in RCTs of patients treated with TNFi and IL-17i was low.
- The risk of infections was similar across different TNFi, in two observational studies at high RoB. For malignancies, the risk in TNFi users was not increased compared to non-users in two large Scandinavian registries (incidence rate ratio (IRR) for any malignancy 0.8 (0.6–1.1)) and in one US cohort. Incidence of neuroinflammatory events was higher in TNFi-experienced patients compared to naïve patients (incidence rate 78–88/100 000 person-years (PY) vs 13–50/100 000 PY). Incidence of multiple sclerosis in TNFi (ever) users compared to the general population was increased (IRR 3.9 (1.5–10.4)), although it was unclear whether this was a drug or disease effect. No observational studies on safety of IL-17i were available.

Summary of evidence

- A summary of the level of evidence for all bDMARDs in axSpA is presented in figure 1. This summary is based on evidence included in the current SLR as well as the previous SLR from 2016.9 In addition, a positive RCT of bimekizumab in nr-axSpA that was presented at EULAR 2022 (after conduct of the current SLR), was considered as well.

| Class | Intervention | r-axSpA | nr-axSpA |
|---|---|---|---|
| TNFi | Adalimumab | 1a | 1b |
| | Certolizumab | 1b | 1b |
| | Etanercept | 1a | 1b |
| | Golimumab | 1a | 1b |
| | Infliximab | 1a | NA |
| IL-17i | Secukinumab | 1b | 1b |
| | Ixekizumab | 1b | 1b |
| | Bimekizumab | 1b | * |
| | Brodalumab | 1b† | 1b† |
| | Netakimab | 1b | NA |
| IL-(12/)23i | Ustekinumab | 1b | 1b |
| | Risankizumab | 1b | NA |
| IL-6i | Tocilizumab | 1b | NA |
| | Sarilumab | 1b | NA |
| Other | Abatacept | 4 | NA |
| | Rituximab | 4 | NA |

Supportive Unsupportive No data

**Figure 1** Level of evidence and support for bDMARDs, by axSpA subtype. Colours provide information on whether the available evidence, as included in the current SLR and a previous SLR,[9] supports or does not support the use of each bDMARD in axSpA. The levels of evidence are based on the EULAR standardised operating procedures and the Oxford Centre for Evidence-based Medicine Levels of Evidence. *Judged as 'Supportive' based on a positive RCT presented at EULAR 2022,[79] after conduct of the current SLR. †Formally only tested in axSpA overall, not by subtype. axSpA, axial spondyloarthritis; bDMARDs, biological disease-modifying antirheumatic drugs; IL, interleukin; NA, not available; nr-axSpA, non-radiographic axSpA; RCT, randomised controlled trial; r-axSpA, radiographic axSpA; SLR, systematic literature review; TNFi, tumour necrosis factor inhibitor.

**Anmerkung/Fazit der Autoren**

Bringing the evidence together, this SLR confirms the efficacy and safety of IL-17i in patients with both r-axSpA and nr-axSpA, while IL-23i and IL-12/23i have failed to show relevant benefits in axSpA. TNFi biosimilar-originator equivalence has been confirmed, and spacing seems the preferred method to taper TNFi. Finally, the risk of anterior uveitis seems lowest with monoclonal TNFi compared to other bDMARDs in axSpA. This SLR provides important new insights into the management of patients with bDMARDs, across the entire spectrum of axSpA.

*Kommentare zum Review*

Es liegen weitere SR zu Teil-Fragestellungen mit ähnlichen Schlussfolgerungen vor:

- Azadeh H et al., 2022 [1].

- Hu L et al., 2022 [8].
- He C et al., 2021 [6].
- Man S et al., 2021 [13].
- Wang P et al., 2021 [19].
- Cruz-Machado AR et al, 2020 [2].
- Katsevman GA et al., 2020 [9].
- Kwan YH et al., 2020 [11].
- Sun WT et al., 2020 [17].
- Zhou Y et al., 2020 [22].

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**Ortolan A et al., 2023 [14].**

Efficacy and safety of non-pharmacological and non-biological interventions: a systematic literature review informing the 2022 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis

**Fragestellung**

To update the evidence of non-biological treatments for axial spondyloarthritis (axSpA), as a basis for the 2022 ASAS-EULAR recommendations for the management of axSpA.

**Methodik**

Population:

- adult (≥18 years) axSpA patients

Intervention:

- Any non-pharmacological treatment, including -but not limited to- education, exercise, physiotherapy, surgery, as well as any non-biological pharmacological therapy
- The following pharmacological treatments were considered:
  - csDMARDs: methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, cyclosporine, cyclophosphamide, auranofin, penicillamine or thalidomide
  - non-disease modifying drugs: nonsteroidal anti-inflammatory drugs (NSAIDs), local and systemic glucocorticoids, bisphosphonates, analgesics, opioids, opioid-like drug, neuromodulators (antidepressants, anticonvulsants, and muscle relaxants), or others
  - tsDMARDs: apremilast, tofacitinib, upadacitinib, filgotinib, nilotinib
- All doses, formulations, regimens (e.g., on-demand, continuous) and duration of these therapies, as well as any combination of those were assessed.

Komparator:

- other non-pharmacological treatments, same treatments in different dose or regimens, other non-biological drug treatments (comparators to bDMARDs are included in the SLR about bDMARDs), any combination therapy, or placebo; the absence of a comparator was only accepted for the safety outcome, when incidence rates were described in long term extensions of RCTs.

Endpunkte:

- Efficacy

- ASAS response criteria: ASAS 20, ASAS 40, ASAS 5/6, ASAS partial remission and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50
- Ankylosing Spondylitis Disease Activity Score (ASDAS) response criteria: clinically important improvement (ASDAS-CII), major improvement (ASDAS-MI), low disease activity (ASDAS-LDA), inactive disease (ASDAS-ID)
- disease activity: BASDAI, ASDAS (ASDAS)
- visual analogical scale (VAS) of patient's global assessment
- VAS of diurnal, nocturnal and global pain
- physical function: Bath Ankylosing Spondylitis Functional Index (BASFI)
- spinal mobility: Bath Ankylosing Spondylitis Metrology Index (BASMI) or the individual spinal mobility measures
- enthesitis, swollen joint count, tender joint count (66/68)
- global functioning and health: ASAS health Index (ASAS-HI)
- radiographic damage: modified Stoke Ankylosing Spondylitis Spine Score (mSASSS), radiographic sacroiliitis according to modified New York criteria (mNY)
- inflammation on MRI: presence of active sacroiliitis according to the ASAS/ Outcome Measures in Rheumatology (OMERACT) definition, Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system both for sacroiliac joints and spine;
- extra musculoskeletal manifestations (EMMs) i.e. inflammatory bowel disease, psoriasis and uveitis;
- work disability and work productivity (any instrument)

- Safety
  - number of total and serious adverse events (AE), deaths, withdrawals due to AEs, any infection, serious infections, tuberculosis, opportunistic infections, malignancies, congestive heart failure, cardio-vascular disease, infusion/injection-site reactions, lipid levels, renal function, hepatotoxicity, hematological abnormalities, gastro-intestinal effects, demyelinating disease.

Recherche/Suchzeitraum:

- MEDLINE (Ovid), Cochrane Database of Systematic Reviews CENTRAL, EMBASE (Ovid) and Epistemonikos, including records from 1st January 2016 up to 1st January 2022

Qualitätsbewertung der Studien:

- RoB 2

**Ergebnisse**

Anzahl eingeschlossener Studien:

- Sixty-three publications, including eight qualitative studies, addressed non-pharmacological interventions, namely education, exercise, diet, surgery and others
- Regarding pharmacological, 20 studies were found on non-csDMARDs/non-tsDMARDs: eight on NSAIDs and 12 on other drugs including glucocorticoids and bisphosphonates. Two new RCTs and one strategy trial focused on csDMARDs. Twelve publications, corresponding to six RCTs, studied tsDMARDs in patients with r-axSpA except one, which was conducted in axSpA. Nine publications, of which seven on pharmacological interventions, focused on safety.

Qualität der Studien:

- Siehe Studienergebnisse

Studienergebnisse:

Efficacy of non-pharmacological interventions

- Twenty publications focused on exercise, corresponding to 17 main studies (RCTs or CCTs), and four post-hoc analysis. The type, intensity and duration of exercise were very heterogeneous, ranging from Tai-Chi to high intensity exercise. In addition, some of the programmes were supervised by physiotherapist, while others were not. The ES on disease activity, function and pain were moderate or high (range in RCTs of exercise for ASDAS: 0.29–0.94, BASDAI: 0.14–1.43, BASFI: 0.04–0.92, BASMI: 0.06–1.14). One RCT, at unclear RoB, in axSpA showed that a 3-month high-intensity exercise programme (supervised in two out of three sessions per week) reduced disease activity (primary outcome) (ASDAS 2.6–1.9 in the intervention group vs 2.7–2.6 in controls), and improved function (BASFI 2.9–1.8 vs 3.6–3.2), mobility (BASMI 2.9–2.5 vs 2.6–2.5) and cardiovascular health. Post-hoc analyses of this trial showed also beneficial effects of this programme on fatigue, sleep, mood and general health.

Efficacy of pharmacological interventions: non-tsDMARDs

- Eight studies on NSAIDs were included, of which two non-inferiority RCTs in r-axSpA, one at low and one at unclear RoB. The first study demonstrated non-inferiority of two doses of etoricoxib (60 and 90 mg daily) versus naproxen 1000 mg daily on VAS spinal pain (SMD between etoricoxib 60 mg and 90 mg with naproxen: 0.07 (−0.24, 0.10) and 0.03 (−0.19, 0.26). The second RCT demonstrated the non-inferiority of two doses of celecoxib (400 mg and 200 mg) versus diclofenac 150 mg daily in VAS global pain (SMD not possible to calculate). The other studies were at a high RoB, and did not provide new information about efficacy or safety of NSAIDs.
- One trial examined the efficacy of a short course of oral prednisolone, starting from 60 mg daily, tapered to 10 mg in 6 weeks, then 5 mg for 18 weeks, versus placebo.90 The primary endpoint (BASDAI 50 at week 24) was met, with 12 (37.5%) patients in the prednisolone arm and 3 (9.1%) in the placebo arm reaching this outcome (RR 4.1, 95% CI 1.3 to 13.3). However, other major endpoints such as ASAS 20 and 40 were not met (ASAS 20: 44% vs 24%, RR 1.80, 95% CI 0.90 to 3.70; ASAS 40: 37% vs 15%, RR 2.5, 95% CI 0.98 to 6.20).

Efficacy of pharmacological interventions: tsDMARDs

- Efficacy of four tsDMARDs (apremilast, filgotinib, tofacitinib, upadacitinib) was assessed in r-axSpA in 5 RCTs, all at low RoB.
- Since the 2016 SLR, complete results for the phase-2 tofacitinib RCT became available, and together with the results of the phase-3 RCT, consolidated the evidence for tofacitinib efficacy. Both studies proved superiority of tofacitinib 5 mg two times a day compared with placebo in reaching ASAS 20 (phase 2: RR 2.35, 95% CI 1.25 to 4.41; phase 3: 3.10, 95% CI 1.90 to 5.07).
- Upadacitinib was efficacious in r-axSpA versus placebo, with higher percentages of patients reaching the primary endpoint ASAS 40 (RR 2.02, 95% CI 1.36 to 3.01). Secondary endpoints were also largely met in all these studies.
- Importantly, the large majority of the included patients were bDMARD-naïve, with the exception of the TORTUGA RCT of filgotinib, which included 9.5% of bDMARDs-experienced patients, and of the phase-3 RCT of tofacitinib, in which 23% of patients had previously used bDMARDs. More patients reached ASAS 20 and 40 in the tumor necrosis factor inhibitor (TNFi)-experienced group with tofacitinib compared with

placebo (39% vs 16% and 25% vs 6%); while these figures were somewhat higher in the TNFi-naïve group (ASAS 20: 62% vs 33% ; ASAS40: 45% vs 14%).

Safety: observational studies

- Observational studies focused on NSAIDs, glucocorticoids and csDMARDs and surgery. Most studies used claims databases and were at high RoB.
- One observational study showed a 16% increase in mortality with NSAIDs and a 69% increase with csDMARDs in patients with r-axSpA compared with the general population.
- Another study evaluated the risk of preventable hospitalisation over 9 years and found that the risk was 5% higher for glucocorticoid users than for non-users.
- The risk for hospitalisation was, on the contrary, not different whether patients were treated or not with csDMARDs (eg. HR 0.94; 95% CI 0.43 to 2.06). In another study, patients on csDMARDs had a threefold increase in the risk of infection by herpes zoster compared with non-users.
- Therapy with NSAIDs compared with no use of NSAIDs was associated with a lower risk of cardiovascular disease in patients with r-axSpA.
- The same was observed for sulfasalazine, especially for doses>1 g daily. Recent NSAIDs use in r-axSpA was associated with a higher risk of myocardial infarction than remote use.

Safety: RCTs

- For non-pharmacological interventions, safety was scantly described, but overall, exercise was considered as safe. Even high intensity exercise (eg, where cardiorespiratory and strength exercises were performed) caused, very rarely, only transient pain.
- For NSAIDs, RCTs did not report safety events different from those well-known in the literature.
- In the study on oral prednisolone, no serious AEs occurred over a period of 24 weeks. Usual side-effects of glucocorticoids were observed in a minority of patients (eg. dyspepsia, n=4 vs n=2 patients, or facial puffiness n=9 vs n=2 patients in drug vs placebo arm).
- tsDMARDs were associated with a higher risk of infections than placebo, mostly non-severe infections, in particular herpes zoster, even though not in the first months of treatment (ie. in the placebo-controlled phase of RCTs).
- No major cardiovascular event (MACE) or venous thromboembolism, and only one malignancy (in the upadacitinib RCT, considered to be unrelated with treatment), occurred up to 1 year of observation in phase 3 RCTs of upadacitinib and tofacitinib. Liver enzyme elevation and CPK elevation occurred, but were infrequent.

**Anmerkung/Fazit der Autoren**

In conclusion, this SLR has consolidated the evidence for non-pharmacological interventions, particularly education and exercise in axSpA, and confirmed the current knowledge about NSAIDs, csDMARDs and other compounds. In addition, it provided new evidence on the use of tsDMARDs, suggesting that treatment options for patients with axSpA are expanding, and highlighting new potential areas of research. The present SLR, together with the SLR on bDMARDs, provided updated information on current treatment options for axSpA.

*Kommentare zum Review*

Es liegen weitere SR zu Teil-Fragestellungen mit ähnlichen Schlussfolgerungen vor:

- Li S et al., 2022 [12].
- Kerschbaumer A et al., 2020 [10].

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**Ho A et al., 2022 [7].**

Impact of biologics on health-related quality of life in patients with Ankylosing spondylitis: A systematic review and meta-analysis of randomized controlled trials

**Fragestellung**

Our study aims to provide a systematic review and meta-analysis to synthesize current evidence of effectiveness of bDMARD therapy on HRQoL outcomes in patients with r-axSpA.

**Methodik**

Population:

- patients with r-axSpA according to the 1984 modified New York diagnostic criteria

Intervention:

- TNF inhibitor or IL-17A antibody agent

Komparator:

- Placebo

Endpunkte:

- HRQoL measures
  - 36-item Short Form Health Survey (SF-36)
  - European Quality of Life Five Dimension (EQ-5D)
  - Ankylosing Spondylitis Quality of Life (ASQoL)

Recherche/Suchzeitraum:

- PubMed, Embase, and Clinicaltrials.gov up to February 2022

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

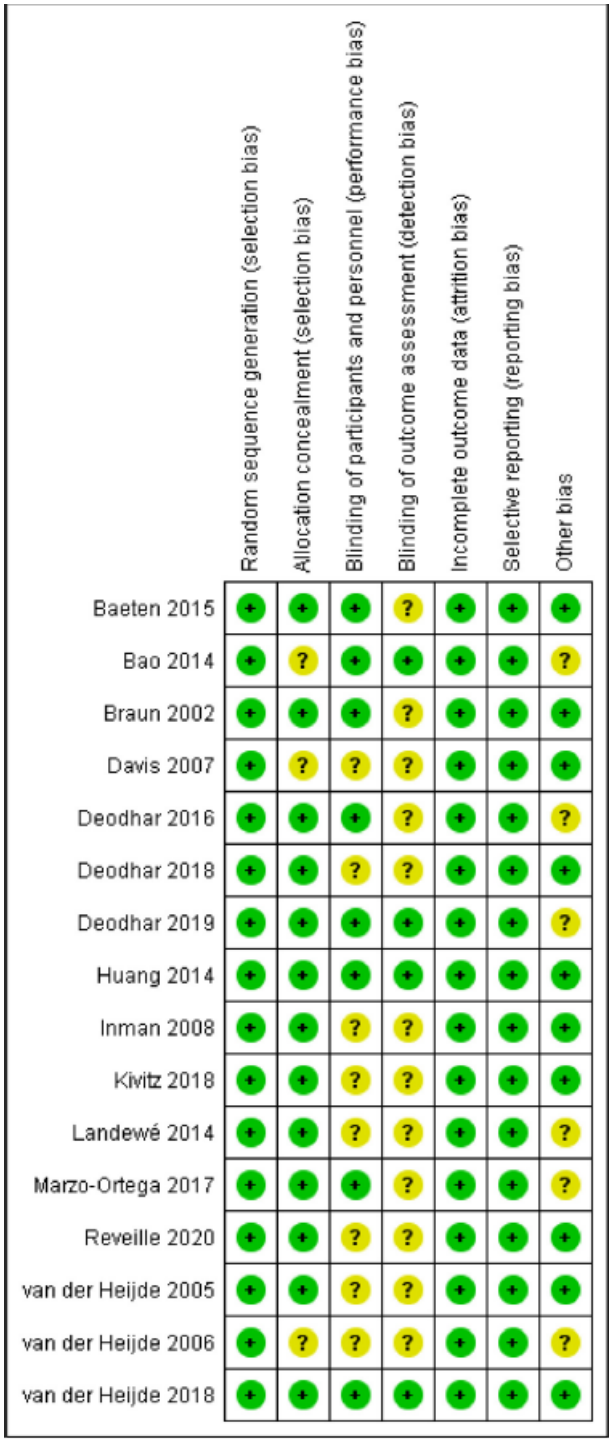
- 16 RCTs (seven studied IL-17A antibody agents vs. placebo, ten studied TNF inhibitors vs placebo, and one studied both)

Charakteristika der Population:

- Sixteen included studies involved 3481 participants, with placebo-controlled and treatment-blinded phases ranging from 12 to 24 weeks.
- Most studies included exclusively or predominantly bDMARD-naïve patients, except COAST-W trial included only patients with prior bDMARD-failure, defined by inadequate response to or intolerance of at most 2 TNF inhibitors before enrollment.

- Majority of participants in the clinical studies (more than 70%) were male with an average age in the late 30s to the early 40s.

Qualität der Studien:




Studienergebnisse:

Health-related quality of life SF-36 physical component score

- Patients in the TNF inhibitor group resulted in better SF-36 PCS score than the control group with pooled mean difference of changes from baseline between the two groups was 4.82 (95% CI: 2.99-6.65, $p < 0.001$). All studies but one showed greater improvement

in SF-36 PCS for the TNF inhibitor group. The heterogeneity was high across the studies ($I^2$ = 85%).

- Similarly, the IL-17A antibody agents yielded better SF-36 PCS than the placebo group. The pooled difference of changes from baseline between the IL-17A antibody group and the placebo group was 3.84 [95% confidence interval (CI): 2.77-4.91], p < 0.001. Each study showed greater improvement in SF-36 PCS for the IL-17A antibody group. The heterogeneity was moderate across the studies ($I^2$ = 48%).
- Overall, receiving a bDMARD, a TNF inhibitor or IL-17A antibody agent, resulted in greater improvement in SF-36 PCS score by 4.39 (95% CI: 3.24-5.54, p < 0.001) compared to the placebo. The overall heterogeneity was high across the studies reporting SF-36 PCS ($I^2$ = 79%).

Health-related quality of life SF-36 mental component score

- Patients in the TNF inhibitor group achieved better SF-36 MCS score than the control group with pooled mean difference of changes from baseline between the two groups was 2.81 (95% CI: 1.35-4.27, p < 0.001). All studies showed greater improvement in SF-36 MCS for the TNF-inhibitor group. The heterogeneity was moderate across the studies ($I^2$ = 66%).
- Similarly, the IL-17A antibody agents yielded better SF-36 MCS than the placebo group. The pooled mean difference of changes from baseline between the IL-17A antibody group and the placebo group was 1.39 (95% CI: 0.01-2.78, p = 0.05). Each study showed greater improvement in SF-36 MCS for the IL-17A antibody group. The heterogeneity was low across the studies ($I^2$ = 21%).
- Overall, receiving a bDMARD, a TNF inhibitor or IL-17A antibody agent, resulted in greater improvement in SF-36 MCS score by 2.37 (95% CI: 1.25-3.49, p < 0.001) compared to the placebo. The overall heterogeneity was moderate across the studies reporting SF- 36 MCS ($I^2$ = 61%).

Health-related quality of life EQ-5D index value

- Three studies reported EQ-5D outcome for bDMARDs vs. placebo. Of these, two studies reported EQ-5D-3L and one study reported EQ-5D-5L. Patients who received a bDMARD, either a TNF inhibitor or IL-17A antibody agent, resulted in a significant improvement in EQ-5D compared to the placebo group with pooled mean difference of changes from baseline between the two groups was 0.11 (95% CI: 0.07-0.14, p < 0.001). The heterogeneity was moderate across the studies reporting EQ-5D outcome ($I^2$ = 34%).

Health-related quality of life ASQoL score

As with other HRQoL outcomes, treatment with a bDMARD, either a TNF inhibitor or IL-17A antibody agent, had a greater improvement in ASQoL scores by -2.45 (95% CI: -3.21 to -1.70, p < 0.001). The heterogeneity was moderate across the studies reporting ASQoL ($I^2$ = 49%).

**Anmerkung/Fazit der Autoren**

Patients with r-axSpA suffered from reduced physical function and quality of life. The use of bDMARD therapy was associated with a significant improvement in HRQoL outcomes in these patients. More research is warranted to further investigate long-term effectiveness of bDMARDs on quality of life in patients with r-axSpA.

## 3.3 Leitlinien

**Ramiro S et al., 2023 [15].**

ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update

**Zielsetzung/Fragestellung**

To update the Assessment of SpondyloArthritis international Society (ASAS)-EULAR recommendations for the management of axial spondyloarthritis (axSpA).

**Methodik**

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz (systematische Review von Webers C et al. [21] und Ortalan et al. [14]);
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: unklar.

Recherche/Suchzeitraum:

- Bis 12/2021 bzw. 01/2022, siehe systematische Reviews von Webers C et al. [21] und Ortalan et al. [14]

LoE

Oxford Center for Evidence Based Medicine 2009

| 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 split-sample§§§ 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" |

Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because:

- ***EITHER*** a single result with a wide Confidence Interval
- ***OR*** a Systematic Review with troublesome heterogeneity.

Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

| | |
|---|---|
| * | By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level. |
| " | Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.) |
| "¡ | See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals. |
| § | Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it. |
| §§ | By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders. |
| §§§ | Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples. |
| "" | An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis. |
| "¡"¡ | Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits. |
| """ | Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study. |
| """" | Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive. |
| ** | Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'. |
| *** | By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors. |
| **** | Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1 – 5 years chronic) |

<u>GoR</u>

Oxford Center for Evidence Based Medicine 2009

| | |
|---|---|
| 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 |

*"Extrapolations" are where data is used in a situation that has potentially clinically important differences than the original study situation.*

<u>Sonstige methodische Hinweise</u>

- Die systematische Suche, Auswahl und Bewertung der Evidenz basiert auf den systematischen Review von Webers C et al. [21] und Ortalan et al. [14]

**Empfehlungen**

<u>Overarching principles</u>

C. The optimal management of patients with axSpA requires a combination of non-pharmacological and pharmacological treatment modalities This OAP applies to several, and likely all, rheumatic and musculoskeletal diseases. Nevertheless, the combination of both treatment modalities is particularly relevant in axSpA and none should be neglected.[14] [19] Non-pharmacological treatment is integral to optimal axSpA management.

Recommendations

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. (LoE /GoR: 5/D)

This recommendation, driven by expert opinion, remained unchanged, due to the lack of trials on analgesics in axSpA. While short-term use of opioid-(like) drugs may have an acceptable risk–benefit profile, caution is advised for long-term use, which is in general not recommended.[71] The ambivalence about this recommendation with the risk of addiction without proven efficacy in axSpA is also reflected in the lowest LoA among all recommendations (although still high). Given that residual pain is a frequent problem encountered in clinical practice, trials should be conducted to provide the necessary evidence, with the recommendation adapted as appropriate. Approach to pain management can also be guided by specific EULAR recommendations.[72]

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. (LoE /GoR: 2/B [injections], 5/D [long-term systemic GCs])

This recommendation, also unchanged, addresses the use of glucocorticoid injections as an option to treat local inflammation (figure 1). Even though glucocorticoid injections have not been tested on arthritis or enthesitis in patients with axSpA, task force members are of the opinion that they can be efficacious. Local site injections, possibly guided by ultrasound, also refer to injections of the SIJ, which showed improvement in pain, though only tested in very small and old trials.[73 74] Notwithstanding, a definite answer on the efficacy of SIJ injections based on low risk of bias trials is still needed.

Regarding systemic glucocorticoids for purely axial disease, evidence exists on short-term glucocorticoids only. Two studies suggest that short-term high-dose glucocorticoids (50 mg/day or 60 mg/day tapered over 24 weeks) could have a modest effect on signs and symptoms in patients with purely axial disease.[14 75 76] Data on prolonged use of glucocorticoids in axSpA are lacking and, due to their known adverse events, the task force does not support their chronic use for axial disease.

Recommendation 8

Patients with purely axial disease should normally not be treated with csDMARDs; sulfasalazine may be considered in patients with peripheral arthritis. (LoE /GoR: 1a/A [sulfasalazine, methotrexate], 1b/A [leflunomide], 4/A [other csDMARDs], 1a/A [sulfasalazine peripheral disease])

The SLR retrieved no relevant new data on csDMARDs, and therefore this recommendation remained the same.[14] csDMARDs are not recommended for purely axial disease due to their lack of efficacy, which has been shown for sulfasalazine, methotrexate and leflunomide.[77–79] However, methodological shortcomings hamper the interpretation of trials with csDMARDs and, most importantly, there is a dearth of such trials and of relevant outcomes tested. Other treatment options for purely axial disease after failing NSAIDs are bDMARDs or tsDMARDs, which are costly and consequently not always available. Therefore, the task force agreed on emphasising that csDMARDs are normally not used, giving room for their exceptional use, as long as this is aligned with the OAPs, that is, ensuring the 'best care' and in shared decision with the patient. In patients with peripheral arthritis, however, csDMARDs are indicated with sulfasalazine being the preferred option due to its demonstrated efficacy in the subgroup of patients with peripheral arthritis, unlike methotrexate which has not demonstrated efficacy.[77 78]

Recommendation 9

TNFi, IL-17i or JAKi should be considered in patients with persistently high disease activity despite conventional treatments (figure 2); current practice is to start a TNFi or IL-17i. (LoE /GoR: 1a/A)

After failure of conventional therapy, treatment intensification should be considered for patients with persistently high disease activity. Figure 2 summarises the important eligibility criteria of patients to the next step in the treatment algorithm. It has previously been shown that adhering to the ASAS-EULAR recommendations for the initiation and continuation of TNFi leads to better functional outcomes and fewer days of sick leave.[80]

As indicated earlier, the task force considered it important to repeat that the first aspect is a clinical diagnosis of axSpA. The second aspect of the eligibility assessment deals with the presence of criteria that have been either associated with a higher likelihood of response or have been mandated by regulatory authorities. They are listed in decreasing order of the strength of predicting treatment response, namely elevated CRP, followed by presence of inflammation on MRI-SIJ, presence of radiographic sacroiliitis (according to the modified New York grading: grade ≥2 bilaterally or ≥3 unilaterally). Both elevated CRP and presence of MRI-SIJ inflammation should be related to axSpA, meaning that other plausible causes for such abnormalities should be carefully excluded. Elevated CRP has been identified as the strongest predictor of good response to TNFi therapy, both in patients with r-axSpA and nr-axSpA. [81–84] In addition, inflammation on MRI-SIJ appeared to be the second best predictor of response to TNFi therapy, again irrespective of the presence of radiographic sacroiliitis.[84–86] Lastly comes the presence of radiographic sacroiliitis, although not being predictive of response,[7 87] but in order to comply with regulatory approval. When TNFi were historically approved for r-axSpA, no other conditions beyond active disease were mandated. It was only much later, when dealing with the approval of TNFi for nr-axSpA, that these drugs were restricted to patients with either elevated CRP or positive MRI-SIJ, given the higher response in patients with these objective signs of inflammation.[84] However, with increasing knowledge of the predictive response of these factors in r-axSpA, the task force now recommends that CRP and (when available) MRI-SIJ are taken into account when deciding to start a b/tsDMARD, irrespective of the presence of radiographic sacroiliitis.[83–86] Of note, at the time of the formulation of the recommendations, radiographic sacroiliitis was mandatory for infliximab and JAKi, which were only approved for r-axSpA. In the meanwhile, upadacitinib has been approved for nr-axSpA by the European Medicines Agency.[88]

Step 3 in the eligibility assessment refers to the failure of conventional treatment. This means non-pharmacological treatment and the use of at least two NSAIDs, in the maximum dose used in axSpA, over a total period of 4 weeks.[89] In patients with predominantly peripheral manifestations, following recommendations 7 and 8, failure to treatment includes one glucocorticoid injection, if appropriate, and the use of sulfasalazine.

The following step focuses on the level of disease activity. Given the clear advantages of the ASDAS as described in relation to recommendation 2, the task force considers it to be the appropriate disease activity instrument, an observation that has been consolidated over the last decade. The task force therefore decided that high disease activity should be based on the ASDAS ≥2.1 criterion alone. If it is impossible to follow this recommendation, the BASDAI criterion (≥4) can be used as an alternative. There is a high agreement between both criteria but, in case of discordance, the ASDAS selects patients with a higher likelihood of response to treatment.[90–92] In any case, the judgement of high disease activity should not be solely based on a score but complemented by the rheumatologist's opinion, which should favour the start of a b/tsDMARD. Like any therapeutic decision, this should also follow OAP D and be part of shared decision-making with the patient.

In patients with persistently high disease activity despite conventional treatment, as defined above, TNFi, IL-17i or JAKi should be considered (figure 1). All these drug classes have demonstrated efficacy in axSpA trials.[13 14] In the absence of head-to- head trials, it is difficult to prioritise any of them in terms of efficacy on axial disease. In the second part of the recommendation, the focus is placed on current practice, which is to start a TNFi or an IL-17i. This recommendation reflects the longer experience with the use of these drugs, with a larger evidence base, use in patients with multimorbidity (frequently excluded from randomised controlled trials (RCTs)) and more knowledge about drug safety.[13 14 18] This decision is analogous to the previous recommendations, in which 'current practice' at that time was to start with a TNFi, for the exact same reasons, while IL-17i were already available. In addition, as only IL-17A inhibitors have so far been approved, reference to IL-17i is limited to IL-17Ai. Dual inhibition of IL-17A and IL-17F with bimekizumab has been tested in a phase II trial,[93] but more information is needed about its efficacy and safety profile before it can be taken into consideration. For JAKi, at the moment, we only have RCT data, and only in r-axSpA. Data on nr-axSpA are currently underway, but not publicly available at the time of the formulation of the recommendations. Importantly, observational data and experience from daily clinical practice with JAKi in axSpA are missing, thus precluding the consideration of JAKi in 'current practice' part of the recommendation. In the future, observational data and experience with JAKi should help in addressing concerns with regard to safety, such as those identified with tofacitinib in patients with rheumatoid arthritis (RA). Tofacitinib has been associated with a higher risk of major adverse cardiovascular events (number needed to harm (NNH) for 5 mg two times per day tofacitinib of 113 over 5 years) as well as malignancies (NNH 55 over 5 years), when compared with TNFi. The trial was performed in patients with RA who were at least 50 years old and had at least one cardiovascular risk factor, and the risk was higher in patients over 65 years.[94] During drug development, increases in serum lipid levels and the incidence of cancers, including lymphoma, were observed, prompting further investigation.[95 96] In axSpA, such signals have not been described to date.[14 97–99] Possible explanations for this include the younger age of patients with axSpA and their likely lower risk factor profile (including less comorbidities and less use of glucocorticoids), shorter follow-up and efficacy trials not enriched for a high-risk

population.[98 100] It is therefore unclear whether the increased risk of cardiovascular events and malignancies is specific to RA, and whether it will apply to axSpA, as well as whether they are specific to tofacitinib or reflect a JAKi class effect. Until more data become available, the task force recommends being restrictive with starting JAKi in patients above the age of 50 years with one or more additional cardiovascular risk factors and to those above the age of 65 years.

In this entire document, we refer to both original and biosimilar bDMARDs. Currently, biosimilars are available for TNFi. Taking OAPs into account, costs should be considered when choosing a particular drug. Given the similar expected efficacy and safety, cost is potentially an important consideration in choosing between an original and biosimilar bDMARD. This choice is increasingly determined by payers, and based on cost considerations, rather than by rheumatologists or patients. Cost may also drive the choice between an IL-17i and a (biosimilar) TNFi.

Aside from the importance on deciding when a patient is eligible for treatment with b/tsDMARDs, it is important to also decide on whether treatment is efficacious, and therefore appropriate to continue. Figure 3 summarises the criteria for continuation, namely that after at least 12 weeks of treatment, the disease activity has substantially decreased, as assessed by the ASDAS clinical important improvement, that is, improvement in ASDAS ≥1.1, together with the positive opinion from the rheumatologist to continue.[40] As always, the final decision on whether to continue the treatment or not is made as a shared decision with the patient. As for the start of treatment, ASDAS is recommended for the assessment of response to treatment. If not possible to follow this recommendation, BASDAI response (≥2.0) can be used if BASDAI has been used to guide treatment initiation.

### Recommendation 12

### Following a first b/tsDMARD failure, switching to another bDMARD (TNFi or IL-17i) or a JAKi should be considered. (LoE /GoR: 2b/B [TNFi after TNFi failure], 1b/A [IL-17i after TNFi failure], 5/D [all other switches])

The expansion of the treatment armamentarium for axSpA, now with three efficacious b/tsDMARD drug classes, each class with several options, opens more possibilities in the treatment of patients. When one treatment fails and the patient still fulfils the criteria to start a new treatment, a switch should be considered (figure 1). However, the evidence in terms of the efficacy of a given drug (class) after failure of a previous one is very limited. No RCT has been conducted with TNFi in patients failing a first TNFi, that is, TNFi-insufficient responders (TNFi-IR).[13] Observational data suggest that a second TNFi can still be efficacious in TNFi-IR patients, although the level of efficacy may be lower than with the first TNFi.[128] IL-17i have shown to be efficacious in TNFi-IR patients, also with a lower efficacy than in TNFi-naïve patients (direct comparisons only available for secukinumab).[13 129–134] Data on JAKi separately in bDMARD-IR were not available at the time of the formulation of the recommendations. There are no data on the efficacy of TNFi after IL-17i or JAKi failure, neither on IL-17i in the case of JAKi failure nor JAKi in the case of TNFi or IL-17i failure. All these treatment sequences should be formally investigated and are therefore part of the research agenda. In the absence of data showing superiority of switching between different modes of action rather than within the same one, the task force agreed to recommend any switch, keeping all options open, but again taking the precautions for the use of JAKi as described for recommendation 9 (figure 1).

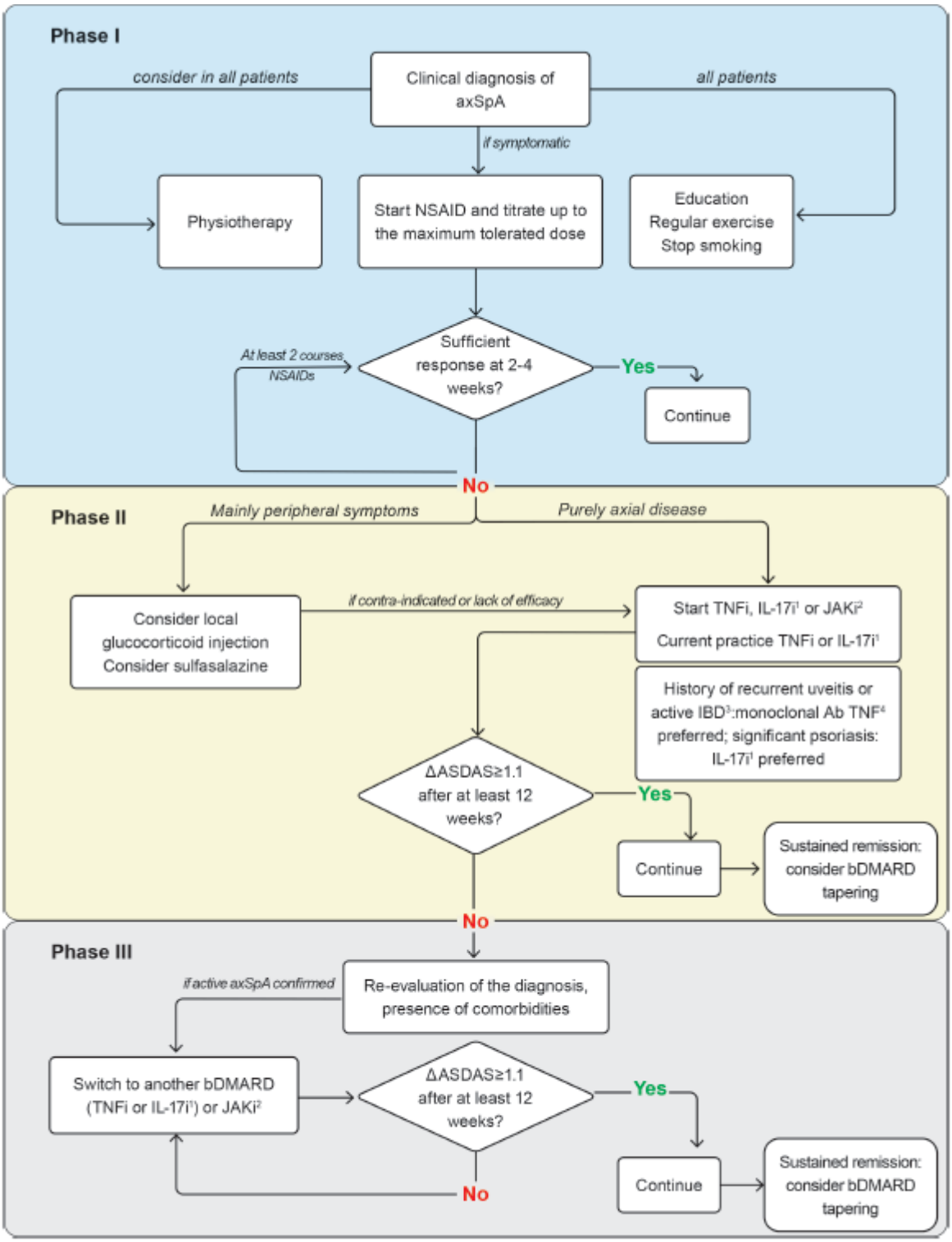



Figure 1 Algorithm based on the ASAS-EULAR recommendations for the management of axial spondyloarthritis (axSpA). Ab, antibody; ASAS, Assessment of SpondyloArthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; bDMARD, biological disease-modifying antirheumatic drug; IBD, inflammatory bowel disease; IL-17i, interleukin-17 inhibitors; JAKi, Janus kinase inhibitors; NSAID, non-steroidal anti-inflammatory drug; TNFi, tumour necrosis factor inhibitors.

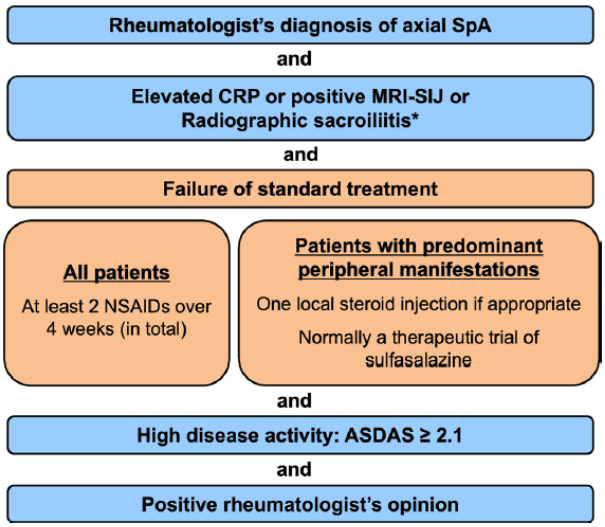



Figure 2 ASAS-EULAR recommendations for the treatment of patients with axial SpA with b/tsDMARDs. *Radiographic sacroiliitis is mandatory for drugs only approved in case of its presence; at the moment of the formulation of the recommendations: infliximab and JAKi. ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; bDMARD, biological disease-modifying antirheumatic drug; CRP, C reactive protein; JAKi, Janus kinase inhibitors; MRI-SIJ, MRI of the sacroiliac joints; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

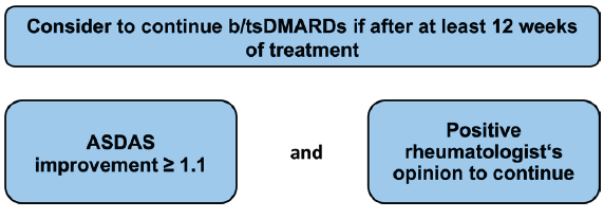



Figure 3 ASAS-EULAR recommendations for the continuation of b/tsDMARDs. ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; bDMARD, biological disease-modifying antirheumatic drug; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

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**Truong SL et al., 2022 [18].**

Australian Consensus Statements for the Assessment and Management of Non-radiographic Axial Spondyloarthritis

**Zielsetzung/Fragestellung**

To update and expand the 2014 consensus statement on the investigation and management of non-radiographic axial spondyloarthritis (nr-axSpA).

**Methodik**

Grundlage der Leitlinie

- Repräsentatives Gremium: unklar (Patienenvertretungen wurden anscheinend als Reviewer, allerdings nicht aktiv in die Entwicklung der Leitlinie eingebunden);
- Interessenkonflikte dargelegt; finanzielle Unabhängigkeit: trifft nicht zu (This work was supported by an unrestricted grants from Novartis, UCB Pharma, Janssen, and Pfizer.);
- 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;

- Regelmäßige Überprüfung der Aktualität gesichert: unklar.

Recherche/Suchzeitraum:

- MEDLINE and Cochrane Library databases from September 1, 2013 until November 1, 2020

LoE / GoR

- GRADE

**Empfehlungen**

EXERCISE AND PHYSIOTHERAPY

Physiotherapy may be useful in the management of nr-axSpA. (LoE /GoR: very low / strong)

Physiotherapy (physical therapy) is a low-risk intervention that addresses multiple causes of back pain, including NSBP, which can occur secondary to, or as a mimic of, nr-axSpA. Evidence for physiotherapy in nr-axSpA is very limited, and was rated very low quality using the GRADE method. We did not identify any standardized program or reproduced results in axSpA.
An observational cohort of 50% nr-axSpA recorded slight improvement in disease activity and mobility outcomes after 6 months of core and spinal exercises and brief exertion compared to baseline, but not compared to controls [90]. A trial of non-controlled physiotherapy in the DESIR cohort of axSpA found a small improvement in BASFI but not other outcome measures [91].
A 2019 Cochrane review of exercise and physiotherapy for AS found that it probably slightly improves function and patient-reported disease activity and may reduce pain, with no evidence it helps fatigue [92].

USE OF CONVENTIONAL MEDICATION/PHARMACOTHERAPY

There is no role for conventional synthetic DMARDs in the management of axial manifestations in nr-axSpA. (LoE /GoR: very low / strong)

There is no evidence base to support the use of conventional synthetic DMARDs to treat axial symptoms in axSpA. A placebo-controlled RCT of sulfasalazine for 230 people with AS found no benefit for axial symptoms, while a small RCT of 67 subjects with AS reported small but significant improvements in outcomes (ASDAS, BASDAI, BASMI) [93, 94]. Multiple observational axSpA and AS studies have not found benefit for axial symptoms [95–97].
Observational data from the control arm of an etanercept AS trial reported the sulfasalazine arm achieving ASAS40 33% and ASAS20 52%, but little improvement in objective measures [98]. As this result occurred in an AS trial with no comparison to placebo to remove confounding disease activity fluctuation, this is very low quality evidence. A 2014 Cochrane review found no significant benefit of SSZ for axial symptoms in AS [99].
A very low quality study of axSpA reported superior TNF inhibitor retention in people taking conventional DMARDs, although the higher rate of peripheral arthritis in the DMARD group confounds this result [100].

Sulfasalazine can be considered for those with peripheral manifestations in nr-axSpA. (LoE /GoR: very low / conditional)

Conventional DMARDs are widely used for peripheral arthritis in nr-axSpA and are presumed to have efficacy based on their use in other forms of SpA.We found no interventional study of nr-axSpA that reports peripheral arthritis as an outcome. An AS RCT reported improvements in patient and physician global assessment on sulfasalazine, and an observational study reported an improvement in peripheral pain score [97, 98]. Neither study found a clinically significant improvement in swollen or tender joint count or CRP. Use of sulfasalazine to treat peripheral arthritis in spondyloarthritis is common but lacks high-quality evidence [101, 102].
We leave our 2014 recommendation unchanged as a low-risk and low-cost initial treatment option for peripheral arthritis.

Sacroiliac corticosteroid injections may have a limited role in the treatment of nr-axSpA. (LoE /GoR: very low / conditional)

Systemic corticosteroids have no definite role in the treatment of nr-axSpA. (LoE /GoR: very low / conditional)

We found no trials that investigate the use of corticosteroids in nr-axSpA. Sacroiliac corticosteroid injections are an established practice in axSpA with little evidence while systemic corticosteroids have inconsistent results.
A single study reports response to corticosteroid injection of the sacroiliac joints for MRI sacroiliitis (52% AS, 48% nr-axSpA) [108]. VAS pain scores halved, which was twice the improvement seen in the active control group of peri-articular injection.
Two small double-blind placebo-controlled RCTs have examined treating axSpA with high-dose oral prednisone. One describes the inconsistent finding of an improvement in BASDAI50 but not ASAS20 or ASAS40 in 32 subjects taking 60 mg prednisone weaned over 18 weeks [109].
The second reports mild-to-moderate improvement in BASDAI (2.4 points) and ASDAS (1.6 points) from 50 mg but not 20 mg prednisone after 2 weeks [110]. A small improvement was seen following intramuscular triamcinolone, where ASDAS fell by 1.4 points in an open, uncontrolled trial of AS and PsA with axial disease [111].
Systemic corticosteroids do not have consistent evidence of benefit. Safer and more efficacious alternatives are available, leaving no clear role in the treatment of axial symptoms. Sacroiliac corticosteroid injections can possibly be considered for acute management of axSpA associated sacroiliitis, however their duration of action is limited.

## USE OF BDMARDS

### TNF and IL-17 inhibitors are efficacious in the treatment of nr-axSpA. (LoE /GoR: high / strong)

The efficacy of TNF inhibitors for the axial symptoms of nr-axSpA has been demonstrated by four large placebo-controlled RCTs of individuals meeting either the clinical or imaging arms of the ASAS classification criteria [112–115]. Trials of anti-TNF in nr-axSpA demonstrated good ASAS40 responses, ranging from 32 to 57%. AxSpA-associated acute anterior uveitis also responded well to certolizumab in a single open-label trial where uveitis flares fell by 87% [116]. Uveitis flares on etanercept are believed to be more common than on other TNF inhibitors [117]. TNF blockade is also recognized to provide significant improvements in enthesitis in AxSpA, with uncommon adverse events such as serious infection or injection site reaction (118). They are also an established treatment for psoriasis and IBD, favoring its use when these comorbidities are present.
The efficacy of IL-17 inhibitors for axial symptoms of nr-axSpA has been demonstrated by two large placebo-controlled RCTs with ASAS40 responses of 35–42% [119, 120]. Their efficacy has not been directly compared to TNF inhibitors in nr-axSpA, while their serious adverse event rate is similar [121]. IL-17 blockade is highly effective for psoriasis and has a small but significant effect on enthesitis in AS, but does not improve IBD and has no evidence for treatment of anterior uveitis [122, 123]. Large trials of the IL-23 inhibitor ustekinumab for nr-axSpA and AS found no benefit compared to placebo [124].
High disease activity is more likely to respond to TNF inhibition. This is most evident when measures of disease activity are combined. ASDAS-CRP, which scores symptoms and CRP, is highly predictive of response to TNF inhibitors in nr-axSpA RCTs, while the value of the symptom-only score BASDAI has mixed results [125–128]. The combination of an ASAS-positive MRI and elevated CRP appears to have some predictive value—two secondary analyses of RCTs observed a modestly higher treatment response [125, 129].
Elevated CRP alone appears to have low-to-moderate predictive value for treatment response, while MRI sacroiliitis alone does not have definite predictive value. In two nr-axSpA RCTs, elevated CRP predicted a two-fold increase in treatment response, whereas another RCT found only a very small difference (OR 1.04) [112, 125, 126]. MRI sacroiliitis at baseline was compared to treatment response in four nraxSpA RCTs. Three found no predictive effect and one a very small effect (OR 1.02) [112, 125, 126, 130].
Other investigations for predictors of TNF inhibitor response, including fibromyalgia, HLA-B27, age, obesity, and smoking have had negative or inconclusive results. Comorbid fibromyalgia does not significantly change the improvement in disease activity scores, although it does increase their baseline values [33, 34]. HLA-B27's predictive value has highly inconsistent reports from three nr-axSpA RCTs and one axSpA RCT [112, 125, 126, 130]. Half found predictive value of moderate size and half found no value.
Age at TNF commencement and gender have wide estimates of effect, ranging from no association to moderate or large effect sizes [112, 125, 126, 130–134]. Two very large longitudinal axSpA cohorts compared smoking to treatment response—one found a large detrimental effect and the other no difference [135, 136]. No interventional studies directly assess whether obesity influences response to TNF inhibitors in nr-axSpA, a phenomenon observed in axSpA and SpA [134, 137]. No difference was observed between the> 70 kg and < 70 kg groups in the ABILITY-1 nr-axSpA RCT [112].

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Referenzen

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**Deutsche Gesellschaft für Rheumatologie (DGRh), 2019 [3,4].**

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. |

**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)*

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**Ward MM et al., 2019 [20].**

*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.

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| 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

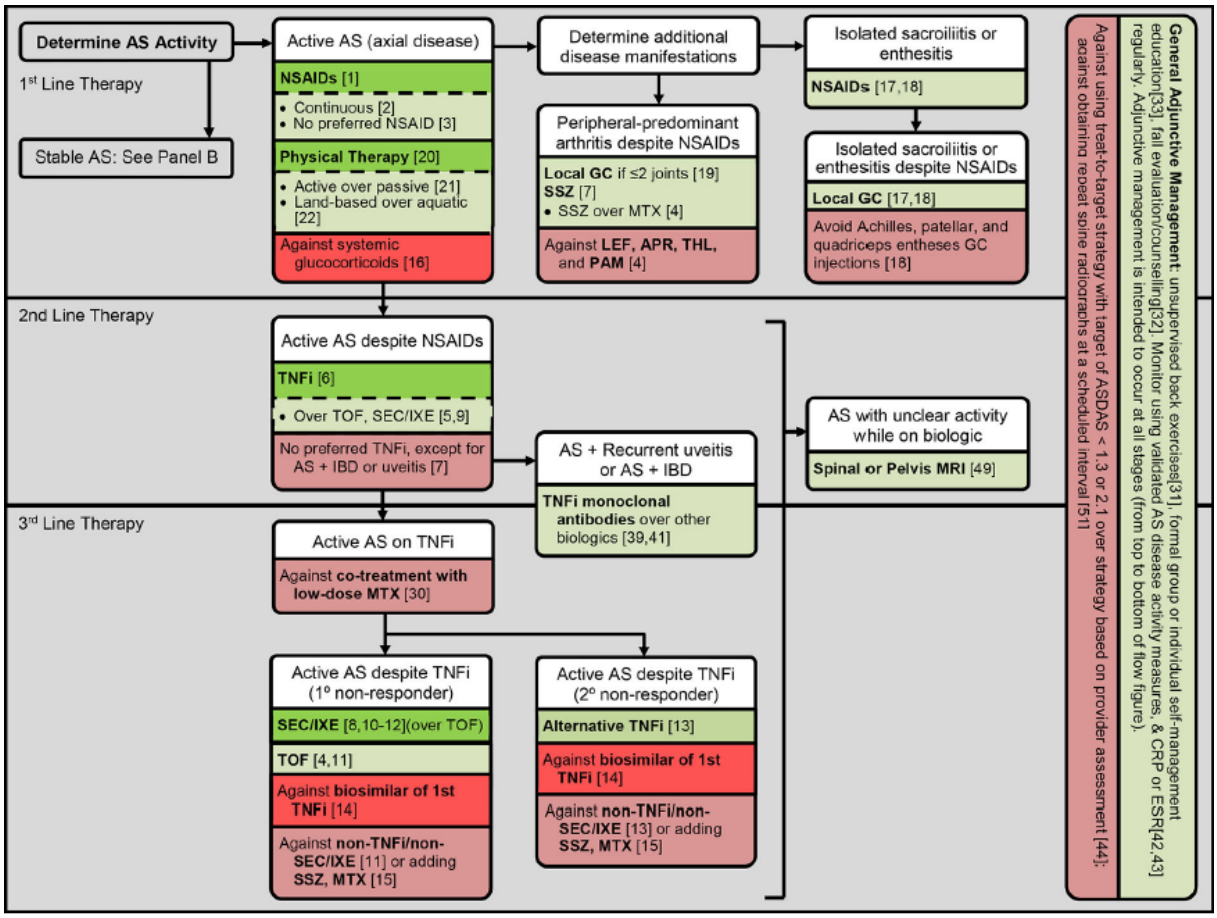
decision. Thus, conditional recommendations refer to decisions in which incorporation of patient preferences is a particularly essential element of decision making.

- 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.

**Empfehlungen**

Recommendations for adults with active AS

*Summary of the main recommendations*




<u>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.</u>
*(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 |
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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.

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**Spanish Society of Rheumatology (SER), 2018 [16].**

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 |

**Empfehlungen**

**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). [5]

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?**

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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# 4 Detaillierte Darstellung der Recherchestrategie

**Cochrane Library - Cochrane Database of Systematic Reviews (Issue 12 of 12, December 2022) am 12.12.2022**

| # | Suchfrage |
|---|---|
| 1 | MeSH descriptor: [Axial Spondyloarthritis] explode all trees |
| 2 | MeSH descriptor: [Spondylarthritis] this term only |
| 3 | (spondyloarthrit* OR spondylarthrit* OR spondyloarthropath* OR spondylarthropath*):ti,ab,kw |
| 4 | (ankylos* OR bechterew* OR bekhterev*):ti,ab,kw |
| 5 | (axSpA OR raxSpA OR nraxSpA OR "axial SpA"):ti,ab,kw |
| 6 | #1 OR #2 OR #3 OR #4 OR #5 |
| 7 | #6 with Cochrane Library publication date from Dec 2017 to present, in Cochrane Reviews |

**Systematic Reviews in PubMed am 12.12.2022**

verwendete Suchfilter:
*Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.*

| # | Suchfrage |
|---|---|
| 1 | Axial Spondyloarthritis[mh] |
| 2 | "Spondylarthritis"[Mesh:NoExp] |
| 3 | spondyloarthrit*[tiab] OR spondylarthrit*[tiab] OR spondyloarthropath*[tiab] OR spondylarthropath*[tiab] |
| 4 | ankylos*[tiab] OR bechterew*[tiab] OR bekhterev*[tiab] |
| 5 | axSpA[tiab] OR raxSpA[tiab] OR nraxSpA[tiab] OR axial SpA[tiab] |
| 6 | #1 OR #2 OR #3 OR #4 OR #5 |
| 7 | (#6) 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] |

| # | Suchfrage |
|---|---|
| | 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 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])))))) |
| 8 | (#7) AND ("2017/12/01"[PDAT] : "3000"[PDAT]) |
| 9 | (#8) NOT "The Cochrane database of systematic reviews"[Journal] |
| 10 | (#9) NOT (retracted publication [pt] OR retraction of publication [pt]) |

**Leitlinien in PubMed am 12.12.2022**

verwendete Suchfilter:
*Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.*

| # | Suchfrage |
|---|---|
| 1 | Axial Spondyloarthritis[mh] |
| 2 | "Spondylarthritis"[Mesh:NoExp] |
| 3 | spondyloarthrit*[tiab] OR spondylarthrit*[tiab] OR spondyloarthropath*[tiab] OR spondylarthropath*[tiab] |
| 4 | ankylos*[tiab] OR bechterew*[tiab] OR bekhterev*[tiab] |
| 5 | axSpA[tiab] OR raxSpA[tiab] OR nraxSpA[tiab] OR axial SpA[tiab] |
| 6 | #1 OR #2 OR #3 OR #4 OR #5 |
| 7 | (#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti]) |
| 8 | (#7) AND ("2017/12/01"[PDAT] : "3000"[PDAT]) |
| 9 | (#8) NOT (retracted publication [pt] OR retraction of publication [pt]) |

**Iterative Handsuche nach grauer Literatur, abgeschlossen am 12.12.2022**

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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

**Kontaktdaten**

*DGf Rheumatologie, Zustimmung der DGOOC und der Dt. Wirbelsäulengesellschaft*

Indikation gemäß Beratungsantrag

Behandlung erwachsener Patienten mit aktiver nichtröntgenologischer axialer Spondyloarthritis mit objektiven Anzeichen einer Entzündung, nachgewiesen durch erhöhtes C-reaktives Protein (CRP) und/oder Magnetresonanztomographie (MRT), die auf nicht-steroidale Antirheumatika (NSARs oder non-steroidal anti-inflammatory drugs, NSAIDs) unzureichend angesprochen oder diese nicht vertragen haben

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

**Definition einer „aktiven nicht-röntgenologischen axialen Spondyloarthritis“:** Es sei vorausgeschickt, dass die axiale Spondyloarthritis (axSpA) als eine Erkrankung angesehen wird, dass die röntgenologische axSpA (r-axSpA) weitgehend der klassischen Spondylitis ankylosans (AS) entspricht und dass die nicht-röntgenologische Form (nr-axSpA) davon eher formal auf Klassifikationsbasis (Ausmaß der strukturellen Veränderungen in den Sakroiliakalgelenken) unterschieden wird. Es wird vorausgesetzt, dass unter einer aktiven nr-axSpA 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/oder als Compound-Messinstrument (BASDAI Fragen plus CRP/BSG plus Patientenglobalurteil) der Ankylosing Spondylitis Disease Activity Score (ASDAS) verwendet [1,2]

Die Therapie bei Patienten mit nr-axSpA richtet sich nach der Höhe der Krankheitsaktivität. Gemäß der S3-Leitlinie „Axiale Spondyloarthritis inklusive Morbus Bechterew und Frühformen“ gilt der Einsatz von nicht-steroidalen Antirheumatika (NSAR) bei symptomatischen Patienten mit nr-axSpA als Mittel der ersten Wahl (E8-10, LL2019, Empfehlungsgrad A) [3]. Dabei ist in der Regel zur Erlangung einer ausreichenden Symptomkontrolle eine NSAR-Therapie in maximaler Dosierung über einen Zeitraum von mindestens 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 frühere NSAR-Therapie oder Unverträglichkeit von NSAR soll eine Therapie mit Biologika. Anstelle von Biologika wird heute zunehmend der Begriff bDMARD (biologic disease modifying antirheumatic drug) eingesetzt. Im Falle von axSpA geht es vor allem um TNF-Inhibitoren (TNFi) und IL-17-Inhibitoren (IL-17i)(E8-15, LL2019, Empfehlungsgrad A). Diese Empfehlungen finden sich gleichlautend auch in den internationalen ASAS/EULAR Empfehlungen für das Management der axSpA [4] – was nun die nr-axSpA mit einschließt. Mit der Zulassung von Upadacitinib als JAK-Inhibitor (JAKi) für die nr-axSpA ist jetzt ein dritter Wirkmechanismus neben TNFi und IL-17i zugelassen [5]. Die Zulassungsstudie ist kürzlich publiziert worden, die Ergebnisse sind aber aufgrund der Aktualität noch nicht in den Leitlinien berücksichtigt worden. JAKi werden bei nr-axSpA vor allem dann eingesetzt, wenn TNFi und IL17i nicht (mehr) in Frage kommen.

Der Behandlungsstandard in der Behandlung von Erwachsenen mit nr-axSpA, die auf eine vorangegangene NSAR-Therapie nicht ausreichend angesprochen hatten, ist also Grundlage für die Einleitung einer bDMARD-Therapie. Als bDMARDs sind TNFi und IL-17i für Patienten mit axSpA zugelassen. IL-17i sind und TNFi sind bis auf Infliximab (nur für r-axSpA zugelassen) für beide Formen der axSpA zugelassen. Für Patienten mit r-axSpA reicht der Nachweis einer selbstberichteten erhöhten Krankheitsaktivität aus (operationalisiert durch einen BASDAI Schwellenwert von ≥4). Bei nr-axSpA sind neben dem erhöhten

**Kontaktdaten**

*DGf Rheumatologie, Zustimmung der DGOOC und der Dt. Wirbelsäulengesellschaft*

Indikation gemäß Beratungsantrag

Behandlung erwachsener Patienten mit aktiver nichtröntgenologischer axialer Spondyloarthritis mit objektiven Anzeichen einer Entzündung, nachgewiesen durch erhöhtes C-reaktives Protein (CRP) und/oder Magnetresonanztomographie (MRT), die auf nicht-steroidale Antirheumatika (NSARs oder non-steroidal anti-inflammatory drugs, NSAIDs) unzureichend angesprochen oder diese nicht vertragen haben

BASDAI-Wert auch noch der objektive Nachweis von Entzündung (entweder erhöhtes CRP oder Entzündungsnachweis in der MRT der SIG) erforderlich.

**Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „erwachsenen Patienten mit aktiver nicht röntgenologischer axialer Spondyloarthritis mit objektiven Anzeichen einer Entzündung, angezeigt durch erhöhtes C-reaktives Protein (CRP) und/ oder Nachweis durch Magnetresonanztomografie (MRT), die unzureichend auf nicht steroidale Antirheumatika (NSAR) angesprochen haben“ die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

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

Extraartikuläre Manifestationen: Aufgrund der unterschiedlichen Wirksamkeit in Bezug auf extramuskuloskelettale Manifestationen kann bei der klinischen Entscheidungsfindung die Wirksamkeit der Präparate auf eine begleitende Psoriasis, Uveitis oder chronisch entzündliche Darmerkrankung (CED) berücksichtigt werden. So sind IL-17i zwar bei Psoriasis vulgaris sehr gut wirksam, aber nicht bei anteriorer Uveitis und CED [6-8]. Verschiedene TNFi sind für axSpA, Psoriasisarthritis, Psoriasis vulgaris sowie CED und Uveitis zugelassen, was die jeweilige Auswahl potentiell begünstigen kann. In Abhängigkeit von Krankheitsaktivität, bisherigen Therapien und aktueller Krankheitsmanifestation sowie Patientenpräferenz kann Upadacitinib bei Patienten mit nr-axSpA angewendet werden. Die Möglichkeit auf einen dritten Wirkmechanismus zurückgreifen zu können, ist insbesondere vor dem Hintergrund der zum Teil eher mäßigen Retentionsraten für bDMARDs bedeutsam. Außerdem gibt es nicht wenige Patienten, die Probleme mit regelmäßigen Injektionen haben und daher JAKi präferieren würden.

**Entscheidung zwischen TNF- und IL-17-Inhibitoren anhand der Leitlinie**: Eine Empfehlung, ob mit einem TNFi oder mit einem IL-17i begonnen werden soll, kann aufgrund der Studiendaten zur Wirksamkeit auf das Achsenskelett und zur Sicherheit nicht gegeben werden (Empfehlung 8-21, LL2019, Statement). Die Leitlinie stellt aber in dieser Empfehlung auch fest, dass für TNFi längere Erfahrungen in der klinischen Anwendung bestehen. Bei Vorliegen einer ausgedehnten Psoriasis würde man sich aber eher für einen IL-17i entscheiden, bei anteriorer Uveitis eher für einen TNFi (außer Etanercept). Bei CED kommt dagegen ein IL-17i nicht in Frage, sehr wohl aber ein TNFi (außer Etanercept) oder Upadacitinib als JAKi (bei Colitis ulcerosa).

Diese Empfehlung begründet sich darin, dass weder Vergleichsstudien (head-to-head Studie (H2H)) zwischen TNF- und IL-17i noch Strategiestudien bei Patienten mit nr-axSpA vorliegen. Dadurch kann die Effektstärke auf die Reduktion der Krankheitsaktivität nicht vergleichend beurteilt werden.

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

| **Kontaktdaten**<br><br>*DGf Rheumatologie, Zustimmung der DGOOC und der Dt. Wirbelsäulengesellschaft* |
|---|
| Indikation gemäß Beratungsantrag<br><br>Behandlung erwachsener Patienten mit aktiver nichtröntgenologischer axialer Spondyloarthritis mit objektiven Anzeichen einer Entzündung, nachgewiesen durch erhöhtes C-reaktives Protein (CRP) und/oder Magnetresonanztomographie (MRT), die auf nicht-steroidale Antirheumatika (NSARs oder non-steroidal anti-inflammatory drugs, NSAIDs) unzureichend angesprochen oder diese nicht vertragen haben |
| systematischen Reviews und mehreren Registerstudien; kontrollierte Studien fehlen aber [9-13]. Beide Reviews zeigen, dass der Wechsel für einen Teil der Patienten erfolgreich ist, aber mit einem schlechteren Therapieansprechen verknüpft ist. Die Retentionsrate (drug survival) war bei dem 2. TNFi (47-72% über 2 Jahre) bzw. dem 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 ein sekundärer 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 Patienten 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 musste. Daten zur Effektivität einer systematischen Änderung des Wirkprinzips liegen nicht vor.<br><br>**Entscheidung zwischen JAKi und bDMARDs bei nr-axSpA**: Diese Thematik ist bislang aufgrund der Aktualität der Fragestellung in den Leitlinien nicht abgebildet. Es liegen Daten zur randomisiert-kontrollierten Zulassungsstudie SELECT-AXIS Studie 2 vor, die Aussagen zu Biologika-naiven und Biologika-erfahrenen Patienten zulässt. In der Subgruppenanalyse für das Therapieansprechen ASAS40 konnte ein besseres Ansprechen für Upadacitinib gegenüber Placebo in Woche 14 sowohl bei den bDMARD-naiven und den bDMARD-erfahrenen Patienten gezeigt werden. |
| |

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