Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: Secukinumab

Stand: Mai 2019

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

Secukinumab [aktive axiale Spondyloarthritis ohne Röntgennachweis einer AS]	
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	Im vorliegenden Anwendungsgebiet liegen keine Beschlüsse über die Nutzenbewertung nach § 35a SGB V vor.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Secukinumab	
Biologika	
Etanercept L04AB01 Enbrel®	*Nicht-röntgenologische axiale Spondyloarthritis* Behandlung Erwachsener mit schwerer nicht-röntgenologischer axialer Spondyloarthritis, mit objektiven, durch erhöhtes C-reaktives Protein (CRP) und/ oder Magnetresonanztomographie (MRT) nachgewiesenen Anzeichen einer Entzündung, die unzureichend auf eine Behandlung mit nichtsteroidalen Antirheumatika (NSARs) angesprochen haben. [Stand: 04/2016]
Adalimumab L04AB04 Humira®	*Axiale Spondyloarthritis ohne Röntgennachweis einer AS* Humira ist indiziert zur Behandlung der schweren axialen Spondyloarthritis ohne Röntgennachweis einer AS, aber mit objektiven Anzeichen der Entzündung durch erhöhtes CRP und/oder MRT, bei Erwachsenen, die nur unzureichend auf nicht steroidale Antirheumatika angesprochen haben oder bei denen eine Unverträglichkeit gegenüber diesen vorliegt. [Stand: 12/2016]
Golimumab L04AB06 Simponi®	*Nicht-röntgenologische axiale Spondyloarthritis (nr-axSpA)* Simponi ist indiziert zur Behandlung Erwachsener mit schwerer, aktiver nicht-röntgenologischer axialer Spondyloarthritis mit objektiven, durch erhöhtes C-reaktives Protein (CRP) und/oder Magnetresonanztomographie (MRT) nachgewiesenen Anzeichen einer Entzündung, die unzureichend auf eine Behandlung mit nichtsteroidalen Antirheumatika (NSARs) angesprochen haben oder bei denen eine Unverträglichkeit gegenüber solchen Substanzen besteht. [Stand: 02/2017]
Certolizumab Pegol L04AB05. Cimzia®	*Axiale Spondyloarthritis ohne Röntgennachweis einer AS* Erwachsene mit schwerer, aktiver axialer Spondyloarthritis ohne Röntgennachweis einer AS, aber mit objektiven Anzeichen der Entzündung, festgestellt durch erhöhtes C-reaktives Protein (CRP) und/oder mittels Magnetresonanztomographie (MRT), die ungenügend auf NSAIDs angesprochen haben oder die eine Intoleranz gegenüber NSAIDs besitzen. [Stand: 01/2017]

II. Zugelassene Arzneimittel im Anwendungsgebiet

Glukokortikoide	
Prednisolon H02AB06 generisch	• andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können: – Spondarthritiden (Spondylitis ankylosans mit Beteiligung peripherer Gelenke (DS b, c), Arthritis psoriatica (DS c, d), enteropathische Arthropathie mit hoher Entzündungsaktivität (DS a) (Prednisolon acis FI, Stand 05/2014)
Prednison H02AB07 generisch	Andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können: – Spondarthritiden (Spondylitis ankylosans mit Beteiligung peripherer Gelenke (DS b, c), Arthritis psoriatica (DS c, d), enteropathische Arthropathie mit hoher Entzündungsaktivität (DS a) (Prednison acis FI, Stand 05/2014)
Triamcinolon H02AB08 Volon®	Andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können: Spondarthritiden (Spondylitis ankylosans mit Beteiligung peripherer Gelenke, Arthritis psoriatica, enteropathische Arthropathie mit hoher Entzündungsaktivität);
Nicht-steroidale Antirheumatika (NSAID/ NSAR) z. B.	
Indometacin M01AB01 generisch	– Spondylitis ankylosans (Morbus Bechterew) und anderen entzündlich-rheumatischen Wirbelsäulenerkrankungen (Indomet-ratiopharm®, FI, Stand 05/2013)
Ibuprofen M01AE01 generisch	Symptomatische Behandlung von Schmerz und Entzündung bei – akuten Arthritiden (einschließlich Gichtanfall) – chronischen Arthritiden, insbesondere bei rheumatoider Arthritis (chronische Polyarthritis) – Spondylitis ankylosans (Morbus Bechterew) und anderen entzündlich-rheumatischen Wirbelsäulenerkrankungen (Ibuprofen AbZ, FI, Stand 01/2014)
Naproxen M01AE02 generisch	Symptomatische Behandlung von Schmerz und Entzündung bei – akuten Arthritiden (einschließlich Gichtanfall); – chronischen Arthritiden, insbesondere rheumatoider Arthritis/chronischer Polyarthritis; – Spondylitis ankylosans (Morbus Bechterew) und anderen entzündlich-rheumatischen Wirbelsäulenerkrankungen; (Naproxen acis.FI, Stand 08/2014)
Acemetacin M01AB11	Symptomatische Behandlung von Schmerz und Entzündung bei – akuten Arthritiden (einschließlich Gichtanfall), – chronischen Arthritiden, insbesondere bei rheumatoider Arthritis (chronische Polyarthritis),

II. Zugelassene Arzneimittel im Anwendungsgebiet	
generisch	– Spondylitis ankylosans (Morbus Bechterew) und anderen entzündlich-rheumatischen Wirbelsäulenerkrankungen, (Acemetacin Heumann, FI, Stand 04/2015)

Quellen: AMIS-Datenbank, Fachinformationen, Lauer-Fischer-Taxe

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2019-B-044 (Secukinumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	28. Februar 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

AGREE	Appraisal of Guidelines for Research & Evaluation
AS	Ankylosierende Spondylitis
ASAS20	Ankylosing Spondylitis Assessment Study group response criteria 20
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
axSpA	Axiale Spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BSR	British Society for Rheumatology
CI	Konfidenzintervall
CoI	Conflict of Interest
CRP	C-reaktives Protein
DMARD	Disease Modifying Antirheumatic Drugs
ETN	Etanercept
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
HR	Hazard Ratio
IBD	Inflammatory Bowel Disease
IL	Interleukin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MRI/MRT	Magnetic Resonance Imaging / Magnetresonanztomographie
MTX	Methotrexat
KI	Konfidenzintervall
LoE	Level of Evidence
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence

nr-axSpA	Nonradiographic axSpA
NSAID	Nichtsteroidale Antirheumatika
NSAR	Nichtsteroidale Antirheumatika
OR	Odds Ratio
PICO	Population Intervention Comparator Outcome
RCT	Randomisierte kontrollierte Studie
RR	Relatives Risiko
SAARD	slow-acting antirheumatic drugs
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematischer Review
TNF	Tumornekrosefaktor
TRIP	Turn Research into Practice Database
VAS	Visuelle Analogskala
WHO	World Health Organization

1 Indikation

zur Behandlung der aktiven nicht-radiografischen axialen Spondyloarthritis mit objektiven Anzeichen der Entzündung, angezeigt durch erhöhtes C-reaktives Protein (CRP) und/oder Nachweis durch Magnetresonanztomografie (MRT), bei Erwachsenen, die nur unzureichend auf nicht-steroidale Antirheumatika (NSAR) angesprochen haben

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *axialer Spondyloarthritis* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 06.09.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 599 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 15 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2016 [3].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 02. Juni 2016 - Secukinumab

Anwendungsgebiet

Ankylosierende Spondylitis (AS; Morbus Bechterew):

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

Zweckmäßige Vergleichstherapie

ein TNF-alpha-Hemmer (Etanercept oder Adalimumab oder Infliximab oder Golimumab) ggf. in Kombination mit Methotrexat

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

3.2 Cochrane Reviews

Es konnten keine relevanten Cochrane Reviews identifiziert werden.

3.3 Systematische Reviews

Ungprasert P et al., 2017 [11].

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

Fragestellung

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

Methodik

Population:

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

Intervention:

- certolizumab and non-TNF inhibitor biologic agents

Komparator:

- TNF inhibitors, placebo

Endpunkt:

- Ankylosing Spondylitis Assessment Study group response criteria 20 (ASAS20)

Recherche/Suchzeitraum:

- Ovid Medline, Ovid CENTRAL, and Ovid EMBASE database from inception to January 2017

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

- 30 trials, 14 trials of older TNF inhibitors (2321 patients), two trials of secukinumab (405 patients), one trial of certolizumab (142 patients), and one trial of tofacitinib (103 patients).

Charakteristika der Population:

- Baseline characteristics of participants were similar across these trials with similar female-to-male ratio, average age, and baseline disease activity as reflected by similar Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). All studies used modified New York criteria to classify participants with AS. The definitions of active AS were consistent across

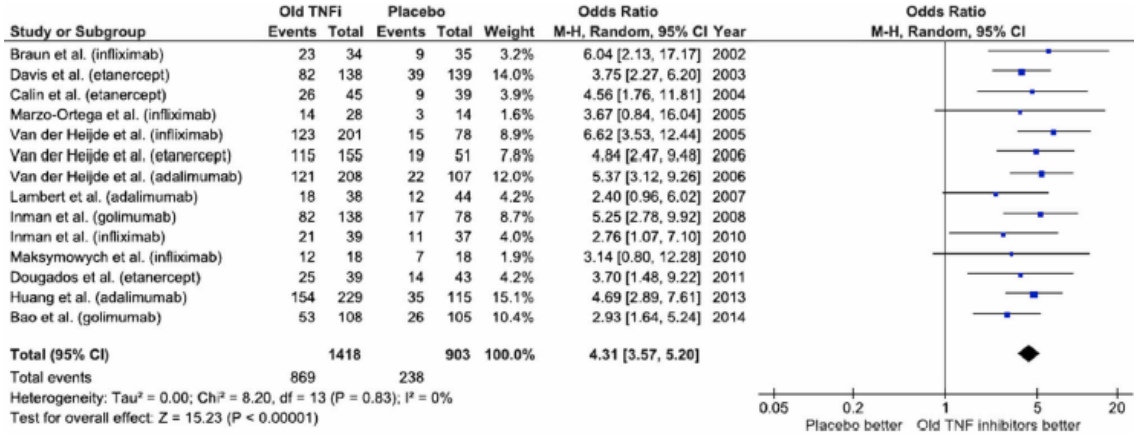
studies (i.e., BASDAI ≥4 and spinal pain VAS ≥ 3 or 4). All studies allowed concomitant use of stable dose of NSAIDs, DMARDs, and steroid at the dose of not more than 10 mg daily of prednisone or equivalent. Nonetheless, the duration of disease varied considerably across the studies, ranging from 1.5 to 18.7 years.

Qualität der Studien:

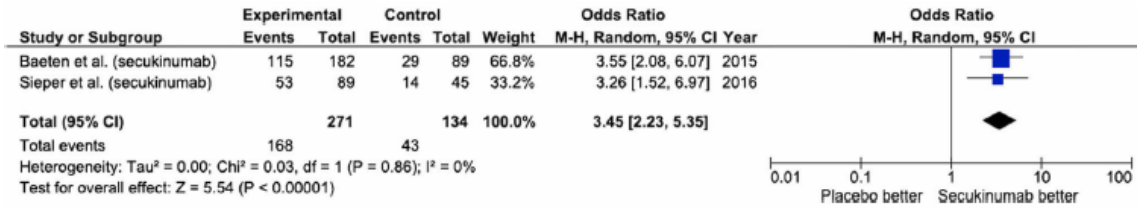
- Risk of bias for individual study was low except for unclear risk of selection bias as most studies did not report the process of randomization in detail (Abbildung 1 im Anhang)

Studienergebnisse:

- 14 trials of older TNF inhibitors were pooled together. The pooled OR of achieving ASAS20 response among older TNF inhibitor-treated patients compared with placebo-treated patients was 4.31 (95% CI, 3.57–5.20). The statistical heterogeneity was low with I2 of 0%.



- Two trials of secukinumab were pooled together. The pooled OR of achieving ASAS20 response among secukinumab-treated patients compared with placebo-treated patients was 3.45 (95% CI, 2.23–5.35). The statistical heterogeneity was low with I2 of 0%.



- Indirect comparison: The four treatments (certolizumab, tofacitinib, older TNF inhibitors and secukinumab) were then compared to each other using placebo as the common comparator. There was no significant difference in any comparisons.

Table 2 Indirect comparison between four treatments

Indirect comparison (ASAS20 response)	OR (95% CI)	*p* value
All older anti-TNF/certolizumab	1.84 (0.86–3.94)	0.12
All older anti-TNF/tofacitinib	1.47 (0.64–3.34)	0.36
All older anti-TNF/secukinumab	1.25 (0.78–2.01)	0.35
Secukinumab/certolizumab	1.47 (0.63–3.43)	0.37
Secukinumab/tofacitinib	1.17 (0.47–2.92)	0.74
Tofacitinib/certolizumab	1.26 (0.42–3.73)	0.68

ASAS Ankylosing Spondylitis Assessment Study, *OR* odds ratio, *CI* confidence interval, *TNF* tumor necrosis factor

Anmerkung/Fazit der Autoren

Older TNF inhibitors, secukinumab, certolizumab, and tofacitinib were compared and their likelihood of achieving ASAS20 response was not significantly different from each other. Thus, from an efficacy standpoint, any one of them could be used as the first line therapy following NSAIDs failure. In conclusion, the current meta-analysis demonstrated that the odds of achieving an ASAS20 response in patients with AS who did not have an adequate response to, or could not tolerate, NSAIDs were not significantly different between older TNF inhibitors, secukinumab, certolizumab, and tofacitinib. However, the interpretation of the results was limited by the small number of included RCTs. Head-to-head RCTs are still required to establish the comparative efficacy.

Kommentare zum Review

Alle Studien erlauben einen begleitenden Einsatz einer konstanten Dosis NSAIDs, DMARDs und Steroiden (nicht höher als 10mg Prednison oder ähnliche). Tofacitinib besitzt in dieser Indikation keine Zulassung

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Chen C et al., 2016 [1].

Comparative Effectiveness of Biologic Therapy Regimens for Ankylosing Spondylitis

Fragestellung

The aim of our study was to assess the comparative efficacy of all available biologic therapy regimens in adults with AS using the technique of network metaanalysis and thus provide meaningful information in the hope of establishing the optimal treatment regimen for the treatment of AS.

Methodik

Population:

- participants aged 18 years or older who had AS defined by 1984 modified New York criteria and had responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs)

Intervention:

- all available biologic agents for AS at present such as anti-TNF-a agent, anti-IL-23 or anti-IL-17 or anti-IL-6 agents or placebo

Komparator:

- Placebo

Endpunkt:

- Proportion of patients achieving 20% improvement in the ASAS Response Criteria (ASAS20) at week 12 or 14

Recherche/Suchzeitraum:

- PubMed, Medline, Embase, Cochrane library, and ClinicalTrials.gov
- Up to June 2015

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Tool for Assessing Risk of Bias
- To appraise the quality of evidences of current direct and network meta-analysis for the primary outcome, we adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 RCTs (13 published, 1 study protocol) (s. Anhang Abbildung 3)

Charakteristika der Population:

- 2672 active AS patients in 14 trials received biologic therapies or placebo
- In general, patients were similar in terms of baseline data such as age, sex, HLA-B27-positive proportion, duration of AS, concomitant drugs, CRP, and BASDAI.
- DMARDs and NSAIDs were permitted to continue in most studies.

Qualität der Studien:

- In general, the studies were considered to be at low risk of bias (s. Anhang Abbildung 2)

Studienergebnisse:

- Two types of meta-analysis were conducted: direct pairwise meta-analyses and random-effect Bayesian network meta-analyses using Markov chain Monte Carlo methods with Aggregate Data Drug Information System (s. Anhang Abbildung 4)
- Compared with placebo, most biologic therapies were associated with significantly higher proportions of patients achieved ASAS20, ASAS40, ASAS5/ 6, ASAS partial remission and BASDAI50, except for secukinumab and tocilizumab. Head-to-head trials, etanercept 50mg QW was comparable to infliximab 5 mg, the effects of etanercept 50 mg QW were substantially equal to that of etanercept 50mg BIW. Direct pairwise meta-analyses were highly heterogeneous in general for all outcomes assessed.
- Network meta-analysis on ASAS20: On comparative effectiveness of all biologic interventions of network meta-analysis, only infliximab 5mg was seen to be superior to tocilizumab (OR, 4.81; 95% CrI, 1.43–17.04). No significant superiority was found among the other regimens. On comparative effectiveness of all biologic interventions of Bayesian network metaanalysis for all the secondary outcomes, no regimen was significantly superior to others, with high degree of imprecision.

Abbildung: Quality of evidence for direct and network metaanalysis for the primary outcome by GRADE

	ASAS20		Quality of Evidence	
Biologic Therapy Regimen	**Direct**	**Network**	**Direct**	**Network**
Compare to Placebo				
Adalimumab	2.80 (1.42–5.51)	4.41 (2.65–7.09)	LOW	MODERATE
Etanercept 25 mg BIW	2.09 (1.68–2.60)	3.96 (2.45–6.66)	HIGH	MODERATE
Etanercept 50 mg BIW	NA	3.20 (0.95–11.96)	NA	LOW
Etanercept 50 mg QW	1.99 (1.38–2.88)	4.38 (2.28–8.72)	HIGH	LOW
Golimumab 50 mg	2.73 (1.75–4.24)	3.81 (2.81–6.99)	HIGH	MODERATE
Golimumab 100 mg	2.75 (1.77–4.28)	4.31 (2.17–9.68)	HIGH	MODERATE
Infliximab 3 mg	1.81 (1.02–3.22)	2.58 (0.94–8.88)	HIGH	MODERATE
Infliximab 5 mg	3.23 (2.03–5.16)	7.36 (3.57–16.45)	HIGH	MODERATE
Secukinumab	2.35 (0.37–15.09)	3.34 (0.47–106.63)	MODERATE	VERY LOW
Tocilizumab	1.36 (0.77–2.40)	1.51 (0.51–4.23)	HIGH	MODERATE
Compare to Tocilizumab				
Adalimumab	NA	3.03 (0.92–9.06)	NA	LOW
Etanercept 25 mg BIW	NA	2.64 (0.85–9.92)	NA	LOW
Etanercept 50 mg BIW	NA	2.21 (0.44–10.81)	NA	VERY LOW
Etanercept 50 mg QW	NA	2.91 (0.86–12.68)	NA	VERY LOW
Golimumab 50 mg	NA	2.56 (0.78–7.80)	NA	LOW
Golimumab 100 mg	NA	3.04 (0.82–9.92)	NA	LOW
Infliximab 3 mg	NA	1.62 (0.42–7.93)	NA	LOW
Infliximab 5 mg	NA	4.81 (1.43–17.04)	NA	VERY LOW
Secukinumab	NA	2.15 (0.22–80.94)	NA	VERY LOW
Compare to Secukinumab				
Adalimumab	NA	1.42 (0.04–10.23)	NA	VERY LOW
Etanercept 25 mg BIW	NA	1.22 (0.03–9.17)	NA	LOW
Etanercept 50 mg BIW	NA	0.98 (0.02–10.73)	NA	VERY LOW
Etanercept 50 mg QW	NA	1.34 (0.04–10.58)	NA	VERY LOW
Golimumab 50 mg	NA	1.19 (0.03–8.94)	NA	LOW
Golimumab 100 mg	NA	1.45 (0.03–11.98)	NA	VERY LOW
Infliximab 3 mg	NA	0.85 (0.02–8.02)	NA	LOW
Infliximab 5 mg	NA	2.45 (0.07–18.41)	NA	VERY LOW
Compare to Infliximab 5 mg				
Adalimumab	NA	0.61 (0.23–1.42)	NA	LOW
Etanercept 25 mg BIW	NA	0.55 (0.22–1.19)	NA	LOW
Etanercept 50 mg BIW	NA	0.48 (0.11–1.74)	NA	LOW
Etanercept 50 mg QW	0.79 (0.54–1.16)	0.60 (0.24–1.36)	MODERATE	MODERATE
Golimumab 50 mg	NA	0.54 (0.20–1.28)	NA	LOW
Golimumab 100 mg	NA	0.61 (0.20–1.61)	NA	LOW
Infliximab 3 mg	NA	0.34 (0.10–1.40)	NA	LOW
Compare to Infliximab 3 mg				
Adalimumab	NA	1.73 (0.45–5.09)	NA	LOW
Etanercept 25 mg BIW	NA	1.56 (0.42–4.65)	NA	LOW
Etanercept 50 mg BIW	NA	1.27 (0.22–6.40)	NA	LOW
Etanercept 50 mg QW	NA	1.72 (0.43–5.67)	NA	LOW
Golimumab 50 mg	NA	1.54 (0.39–4.72)	NA	LOW
Golimumab 100 mg	NA	1.76 (0.40–5.90)	NA	LOW
Compare to Golimumab 100 mg				
Adalimumab	NA	1.03 (0.39–2.36)	NA	LOW
Etanercept 25 mg BIW	NA	0.92 (0.34–2.17)	NA	LOW
Etanercept 50 mg BIW	NA	0.77 (0.18–3.19)	NA	LOW
Etanercept 50 mg QW	NA	1.02 (0.33–2.74)	NA	LOW
Golimumab 50 mg	NA	0.89 (0.43–1.77)	NA	MODERATE
Compare to Golimumab 50 mg				
Adalimumab	NA	1.13 (0.52–2.35)	NA	LOW
Etanercept 25 mg BIW	NA	1.00 (0.46–2.24)	NA	LOW
Etanercept 50 mg BIW	NA	0.80 (0.22–3.48)	NA	LOW
Etanercept 50 mg QW	NA	1.10 (0.45–2.74)	NA	LOW
Compare to Etanercept 50mg QW				
Adalimumab	NA	1.03 (0.43–2.26)	NA	LOW
Etanercept 25 mg BIW	NA	0.89 (0.47–1.76)	NA	MODERATE
Etanercept 50 mg BIW	0.94 (0.74–1.19)	0.75 (0.27–2.13)	HIGH	MODERATE
Compare to Etanercept 50 mg BIW				
Adalimumab	NA	1.38 (0.33–4.86)	NA	LOW
Etanercept 25 mg BIW	NA	1.18 (0.34–4.15)	NA	LOW
Compare to Etanercept 25 mg BIW				
Adalimumab	NA	1.14 (0.53–2.16)	NA	LOW

Anmerkung/Fazit der Autoren

Our analysis shows that except for the finding that infliximab 5mg was superior to tocilizumab, no differences between biologic therapies in the treatment of AS could be found. Infliximab 5

mg/kg may be a better biologic therapy regimen for AS, but this interpretation should be accepted very cautiously. Secukinumab also appears promising, though additional data is warranted.

Kommentare zum Review

Die Weiterbehandlung mit DMARDs und NSAIDs war in den meisten Studien erlaubt.

Bei Tocilizumab handelt es sich um ein nicht in dieser Indikation zugelassenes Arzneimittel.

3.4 Leitlinien

Wendling D et al., 2018 [15].

French Society for Rheumatology (SFR)

2018 update of French Society for Rheumatology (SFR) recommendations about the everyday management of patients with spondyloarthritis

Leitlinienorganisation/Fragestellung

To develop practice guidelines for the everyday management of patients with spondyloarthritis (including psoriatic arthritis), by updating previous national and international recommendations, based on a review of recently published data.

Die Leitlinie umfasst Patienten mit Spondyloarthritiden; daher werden nur Empfehlungen zur indikation axSpA extrahiert.

Methodik

Grundlage der Leitlinie

- Update und Adaption der 2013 SFR Empfehlungen
- Einhaltung der Standards aus AGREE II und dem empfohlenen Vorgehen der EULAR
- Einsetzten einer Tast-Force bestehend aus Rheumatologen mit Expertise in der Indikation SpA. Identifikation von neuen Themen und Aktualisierungsbedarf. Entwurf und Umformulierung von Empfehlungen bei einem persönlichen Meeting auf Basis der identifizierten Literatur und der Diskussionen der Expertengruppe.
- Empfehlungen wurden akzeptiert, falls zwei-drittel der Experten diesen zustimmten
- Empfehlungen sind mit Literaturstellen verknüpft

Recherche/Suchzeitraum:

- PubMed-Medline, Cochrane, and Embase databases
- Reference lists of selected articles and proceedings of EULAR and ACR meetings were searched manually
- Update: Articles published between June 17,2013, and May 1, 2017. In addition.

LoE/GoR

- The strength of the practice guidelines (based on the level of evidence) and the level of agreement among experts (rated from 0 [strongly disagrees] to 10 [strongly agrees]) are given for each practice guideline. Strength was graded according to standard practice:
- A: guideline based on level 1 evidence (meta-analysis of randomized controlled trials or at least one randomized controlled trial);
- B: guideline based on level 2 evidence (at least one nonrandomized controlled trial or quasi-experimental study) or extrapolated from level 1 evidence;
- C: guideline based on level 3 evidence (descriptive study) or extrapolated from level 1 or 2 evidence;
- D: guideline based on level 4 evidence (expert opinion) or extrapolated from level 1, 2, or 3 evidence.

Sonstige methodische Hinweise

- Die Angaben zum LoE und GoR sind nicht eindeutig voneinander zu trennen.

Empfehlungen (Grade and Level of agreement)

Empfehlung 8 Analgesics can be use in the event of residual pain despite the use of other treatments (D; 9,58)

Empfehlung 9. In most patients, systemic glucocorticoid therapy is not warranted, particularly for treating axial manifestations (D, B; 9,58)

No recent controlled studies support a beneficial effect of systemic glucocorticoid therapy on the axial manifestations of SpA.

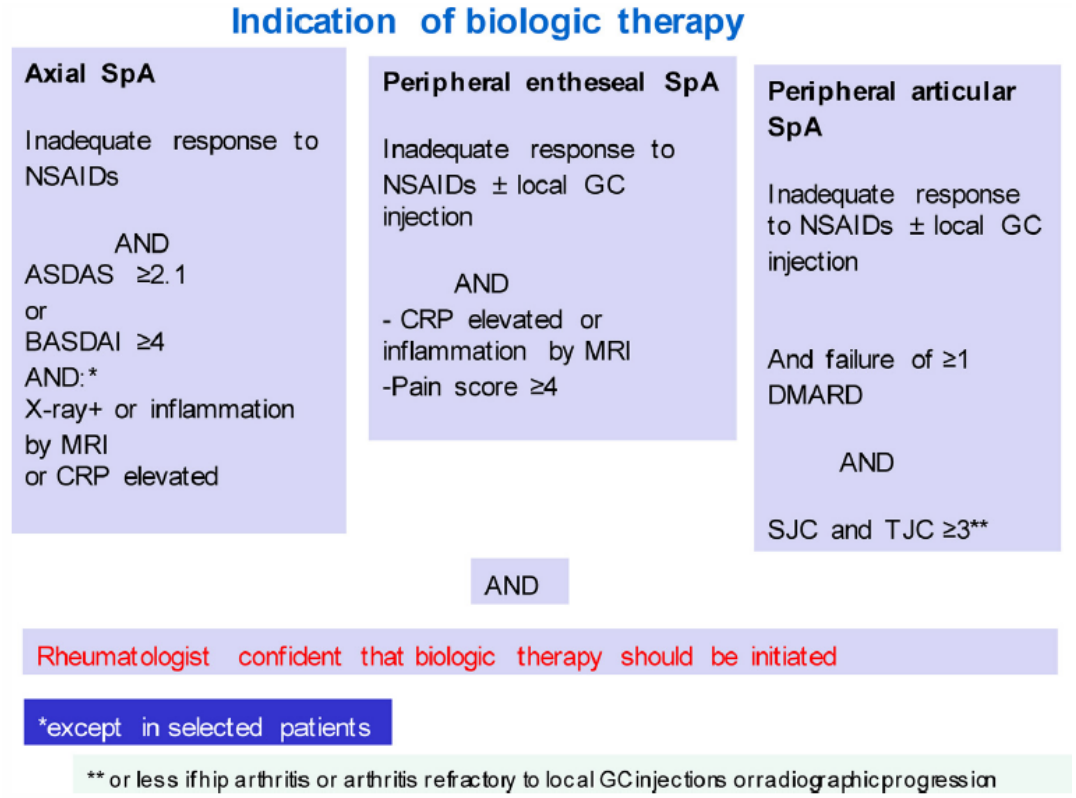
Empfehlung 10. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs including methotrexate, leflunomide, and sulfasalazine) should be considered in patients with peripheral arthritis unresponsive to symptomatic therapy but are not indicated in those with isolated axial or entheseal manifestations (A; 9,41)

In axialSpA, csDMARDs have not been proven effective.

Empfehlung 11. In patients with active axial SpA despite NSAID therapy, the use of biologics (antagonists to TNFalpha or IL-17) should be considered (Fig. 1). TNFalpha antagonists are usually chosen. In non radiographic axial SpA with no evidence of inflammation by laboratory tests or MRI, biologics are not indicated, except in highly selected patients (A; 9,41)

Inaxial SpA, TNFalpha antagonists [42,43] and the first biosimilars (ofinfliximab and etanercept) [44] have been unequivocally proveneffective versus a placebo in improving various facets of the disease. Predictors of a response in radiographic and nonradiographic axialSpA have been identified. There is no evidence that one TNFalpha antagonist is superior over the others in improving the axial, peripheral, and/or entheseal manifestations of SpA, although no head-to-head comparisons are available. Thus, there is no hierarchy of TNFalpha antagonists. The extra-rheumatic manifestations (IBD, uveitis) may affect TNFalpha antagonist selection. Thus, etanercept has not been proven effective on uveitis or IBD. In the MEASURE 1 et 2 trials, [45–48], targeting IL-17A with secukinumab was superior over a placebo in patients with ankylosing spondylitis (radiographic axialSpA) who were naive to biologics or had failed TNFalpha antagonist therapy. Head-to-head comparisons with TNFalpha antagonists are not yet available. Given the longer follow-up and greater experience with TNFalpha antagonists, these drugs are usually the first biologics chosen in patients with SpA, in compliance with recommendations by the French transparency committee. Secukinumab has not been proven effective on IBD and is currently indicated only in radio-graphic forms of axial SpA.

No evidence exists to date that routinely adding a conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) to abiologic used to treat axial SpA is beneficial. The therapeutic effects should be evaluated after at least 3 months, using validated tools. A change of treatment shouldbe considered when no significant improvement is apparent after 3 months. When the 6-month goal of clinical remission or low disease activity is not achieved, the treatment must be changed.



Empfehlung 13. When the first biologic fails due to lack of effectiveness or poor tolerance, after an analysis of the reasons of the failure, treatment with a second biologic can be considered (A; 9,66)

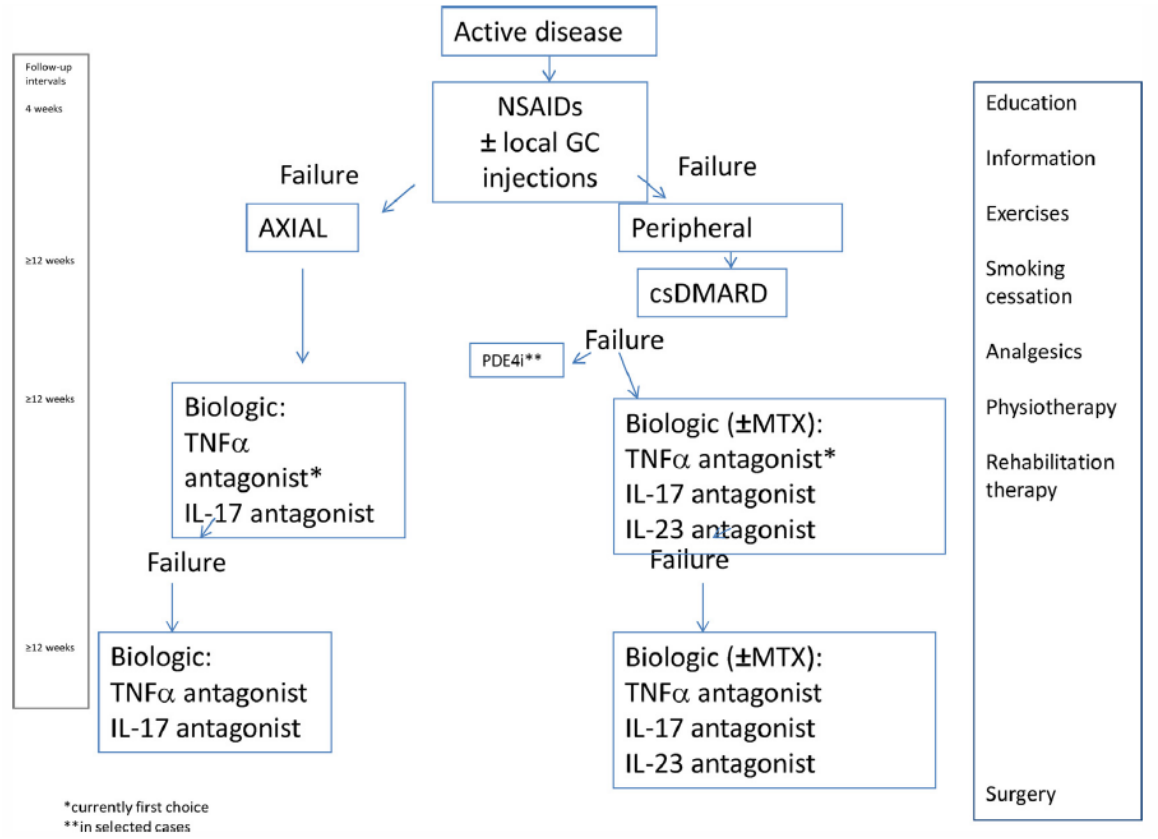
Lackof effectiveness is defined as either failure to achieve the predefined treatment goal (remission or low disease activity, as assessed using validated tools, i.e., the ASDAS, DAPSA, or MDA) or failure to achieve a treatment response (defined in axial SpA as a ≥ 1.1 ASDAS decrease and ≥ 2/10 BASDAI decrease), while taking all the facetsof the disease into account and after 3 to 6 months. In the event of primary or secondary lack of effectiveness of a TNFalpha antagonist, increasing the dosage has not been proven beneficial to date [64]. The switch to a different biologic may be toward a drug of a different class (e.g., TNFalpha antagonist to IL-17 antagonist) or toward a different TNFalpha antagonist. Switching has produced useful results [65].

Empfehlung 14. In patients with a disease remission or low level of activity sustained for at least 6 months during biologic therapy, a gradual increase in the dosing interval or decrease in the drug dosage can be considered (B; 9,75)

The available data suggest that deescalating TNFalpha antagonist therapyis usually feasible in the event of sustained control of disease activity [69]. In most cases, the dosing interval is increased slowly and gradually, because the formulations needed for dosage adjustments are not available for all drugs and, more importantly, because fewer doses translate into a lessened burden on the patient. Abruptly discontinuing the treatment is virtually always followed by a relapse in the short or medium term. Symptom relapses during an attempt to decrease the dosing intervals are easily controlled in most cases by returning to the previous dosing schedule.

No proof exists to date that a similar treatment intensityreduction method is appropriate with biologics other than TNFalpha antagonists.

Abbildung: General outline of the treatment strategy for spondyloarthritis



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Van der Heijde D et al., 2017 [13].

European League Against Rheumatism (EULAR), Assessment of SpondyloArthritis international Society (ASAS)

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

Siehe auch:

Van der Heijde D et al., 2015 [12]; Separino A et al., 2017 [9]; Regel A et al., 2015 [8];

Fragestellung

The 2016 ASAS-EULAR recommendations provide up-to-date guidance on the management of patients with axSpA. One aim of this update was to aggregate the existing ASAS-EULAR management recommendations of AS and the ASAS recommendations for the management of axSpA with TNFi into one set of recommendations.

Methodik

Grundlage der Leitlinie

- Update der Leitlinie von 2006 und 2010
- International, multidisciplinary expert group: When discussing the update of the recommendations, the evidence collected in the previous SRs was also taken into consideration. It was decided that recommendations could only be updated if there was new evidence available that justified such an update according to the task force.
- Durchführung mittels Appraisal of Guidelines for Research & Evaluation II (AGREE II)
- The evidence collected was presented in summary of findings (SoF) tables and included judgements about risk of bias (Cochrane Risk of Bias Tool), which was determined for every study

Recherche/Suchzeitraum:

- system. Literturrecherche (SLR) für nicht-pharmakolog. und nicht biolog-pharmakolog. Behandlungen und für DMARDs (Separino A et al., 2017 [9]; Regel A et al., 2015 [8])
- focused on the studies published after the locking date of the SLRs for the previous update, that is, 2009;
- Angaben Guideline-Update 2010: PubMed, Embase and Cochrane databases for the time period 1 January 2005 to 1 December 2009

LoE

Table 1 Categories of evidence[9]

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

- gemäß Oxford Centre for Evidence-based Medicine Levels of Evidence

GoR

Table 2 Strength of recommendations

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

Sonstige methodische Hinweise

- Empfehlungen sind nicht explizit mit Literaturstellen verknüpft

Empfehlungen (Behandlungsalgorithmus siehe Anhang Abbildung 5)

	Recommendations			
1	The treatment of patients with axSpA should be individualised according to the current signs and symptoms of the disease (axial, peripheral, extra-articular manifestations) and the patient characteristics including comorbidities and psychosocial factors	5	D	9.7 (0.65) 100% ≥8
2	Disease monitoring of patients with axSpA should include patient-reported outcomes, clinical findings, laboratory tests and imaging, all with the appropriate instruments and relevant to the clinical presentation. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity and treatment	5	D	9.6 (0.78) 100% ≥8
3	Treatment should be guided according to a predefined treatment target	5	D	8.9 (1.45) 93% ≥8
4	Patients should be educated* about axSpA and encouraged to exercise* on a regular basis and stop smoking‡; physical therapy† should be considered	2* 5‡ 1a†	B* D‡ A†	9.6 (0.78) 100% ≥8
5	Patients suffering from pain and stiffness should use an NSAID as first-line drug treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs continuous use is preferred if symptomatic otherwise	1a	A	9.4 (0.94) 100% ≥8
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	5	D	8.8 (0.94) 100% ≥8
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‡	2* 5‡	B* D‡	9.4 (0.78) 100% ≥8
8	Patients with purely axial disease should normally not be treated with csDMARDs§; sulfasalazine† may be considered in patients with peripheral arthritis	1a†	A	9.2 (0.78) 100% ≥8
9	bDMARDs should be considered in patients with persistently high disease activity despite conventional treatments (figure 1); current practice is to start with TNFi therapy	1a (TNFi); 1b (IL-17i)	A	9.6 (1.09) 93% ≥8
10	If TNFi therapy fails, switching to another TNFi* or IL-17i** therapy should be considered	2* 1b**	B* A**	9.6 (0.95) 97% ≥8
11	If a patient is in sustained remission, tapering of a bDMARD can be considered	2	B	9.1 (1.57) 97% ≥8
12	Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age; spinal corrective osteotomy in specialised centres may be considered in patients with severe disabling deformity	4	C	9.4 (0.82) 100% ≥8
13	If a significant change in the course of the disease occurs, causes other than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed	5	D	9.9 (0.31) 97% ≥8

§1a (sulfasalazine; methotrexate); 1b (leflunomide); 4 other csDMARDs.
axSpA, axial spondyloarthritis; bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; GoR, grade of recommendation; IL-17i, interleukin-17 inhibitor; LoA, level of agreement; LoE, level of evidence; NSAIDs, non-steroidal anti-inflammatory drugs; TNFi, tumour necrosis factor inhibitor.

Recommendation 1: The treatment of patients with axSpA should be individualised according to the current signs and symptoms of the disease (axial, peripheral, extra-articular manifestations) and the patient characteristics including comorbidities and psychosocial factors. (LoE 5 und GoR: D)

Recommendation 5: Patients suffering from pain and stiffness should use an NSAID as first-line drug treatment up to the maximum dose, taking risks and benefits into account. For patients

who respond well to NSAIDs continuous use is preferred if symptomatic otherwise (LoE 1a; GoR: A)

- Important consideration however needs to be given to the potential side effects of NSAIDs, especially when administered chronically. NSAIDs should therefore only be prescribed if patients are symptomatic. (68-70)

Recommendation 6: Analgesics, such as paracetamol and opioid-(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated and/or poorly tolerated. (LoE 5; GoR: D)

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 2*, 5+; GoR B*, D+)

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

Recommendation 8: Patients with purely axial disease should normally not be treated with csDMARDs; sulfasalazine+ may be considered in patients with peripheral arthritis. (LoE 1a+; GoR A)

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

Recommendation 9: bDMARDs should be considered in patients with persistently high disease activity despite conventional treatments (figure 1); current practice is to start with TNFi therapy (LoE 1a (TNFi), 1b (IL-17i); GoR A)

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

TNFi therapy is approved in many countries for patients with radiographic axSpA (AS) without further limitations, and in patients with non-radiographic axSpA only if there is an elevated CRP and/or inflammation on MRI. This means that if a patient with axSpA has radiographic sacroiliitis or when this patient has either an elevated CRP or inflammation on MRI, the patient formally complies with the requirements for bDMARD therapy mentioned in the label of the respective drugs. While not brought up as a limitative factor, the task force was of the opinion that many studies have now suggested that also patients with radiographic axSpA who have an increased CRP have the highest likelihood of treatment success. (83, 84)

Currently, only secukinumab is approved, but several other agents are far in their development. To date, only trial data on IL-17i in radiographic axSpA are available and data in patients with

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

Recommendation 10: If TNFi therapy fails, switching to another TNFi* or an anti-IL-17 **therapy should be considered (LoE 2*, 1b**; GoR B*, A**)

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

Empfehlung 11 (LoE 2; GoR B)

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

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National Institute for Health and Care Excellence, 2017 [6].

NICE

Spondyloarthritis in Over 16s: Diagnosis and Management

Fragestellung

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

Methodik

Grundlage der Leitlinie

- Manual für die Entwicklung von NICE Guidelines[1]
- The processes and methods are based on internationally accepted criteria of quality, as detailed in the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument, and primary methodological research and evaluation undertaken by the NICE teams
- developed by independent and unbiased Committees of experts

Recherche/Suchzeitraum:

- Systematische Literaturrecherche bis November 2015

LoE/GoR

- Nicht angegeben

Sonstige methodische Hinweise

- In Bezug auf die Evidenzgrundlage vergleiche die HTAs von NICE im Kapitel ergänzende Dokumente

1.4 Pharmacological management of spondyloarthritis

NSAIDs

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

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

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

1.4.3 Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended, within their marketing authorisations, as options for treating severe active

[1] https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview#information-about-this-manual

ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.

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

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

Referenz:
Nice 2016. TNFalpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis.

Biological DMARDs – secukinumab for the treatment of ankylosing spondylitis

1.4.9 Secukinumab is recommended, within its marketing authorisation, as an option for treating active ankylosing spondylitis in adults whose disease has responded inadequately to conventional therapy (NSAIDs or TNF-alpha inhibitors).

Referenz:
Nice 2016. Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors Referenzen aus Leitlinien

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Ward MM et al., 2015 [14].

SPARTAN, ACR, SAA

American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis

Fragestellung

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

This project was developed by members of the Spondyloarthritis Research and Treatment Network (SPARTAN), a group of North American rheumatologists with special interest in SpA, in response to a request for proposals from the American College of Rheumatology (ACR) and with support from the Spondylitis Association of America (SAA), a patient advocacy organization

Methodik

Grundlage der Leitlinie

- Interdisziplinäre LL
- guideline development and quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method
- Die den Empfehlungen zugrundeliegenden Studien sind in Anhang der Leitlinie mit ihrer Qualitätsbewertung aufgeführt.
- Ableitung von Empfehlungen aus der Qualiät der Evidenz und Effekten nach GRADE
- Anonyme Abstimmung der Empfehlungen beim Meeting der „Voting Group“ bis mindestens 80% der Mitglieder einer Empfehlung zustimmten.

Recherche/Suchzeitraum:

- systematic literature research, search conducted in OVID Medline (1946–2014), PubMed (1966–2014), and the Cochrane Library

LoE

- High quality: Further research is very unlikely to change our confidence in the estimate of effect; quality is rated 4 out of 4, represented as: ⊕⊕⊕⊕
- Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; quality is rated 3 out of 4, represented as: ⊕⊕⊕O
- 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; quality is rated 2 out of 4, represented as: ⊕⊕OO
- Very low quality: We are very uncertain about the estimate; quality is rated 1 out of 4, represented as: ⊕OOO

GoR

Table 2. Strength of recommendations in GRADE*

Strength	Interpretation	Implications for clinicians	Implications for policymakers
Strongly in favor	Almost all informed patients would choose to receive the intervention	Should be accepted by most patients to whom it is offered	Should be adopted as policy
Conditionally in favor	Most informed patients would choose the intervention, but a sizable minority would not	Large role for education and shared decision-making	Requires stakeholder engagement and discussion
Conditionally against	Most informed patients would not choose the intervention, but a small minority would	Large role for education and shared decision-making	Requires stakeholder engagement and discussion
Strongly against	Most patients should not receive the intervention	Should not be offered to patients	Should be adopted as policy

* GRADE = Grading of Recommendations, Assessment, Development and Evaluation.

In adults with active AS despite treatment with NSAIDs

In adults with active AS despite treatment with NSAIDs, we conditionally recommend against treatment with SAARDs (slow-acting antirheumatic drugs) (PICO 7; very low- to moderate-quality evidence, depending on the drug; vote 90% agreement).

We strongly recommend treatment with TNFi over no treatment with TNFi (PICO 6; moderate-quality evidence; vote 80% agreement).

We do not recommend any particular TNFi as the preferred choice, except for patients with concomitant inflammatory bowel disease or recurrent iritis (PICO 5; moderate-quality evidence; conditional recommendation; vote 100% agreement).

In adults with active AS despite treatment with NSAIDs and who have contraindications to TNFi, we conditionally recommend treatment with a SAARD over treatment with a non-TNFi biologic agent (PICO 8; very low to lowquality evidence, depending on the drug; vote 100% agreement).

In adults with active AS despite treatment with the first TNFi used:

We conditionally recommend treatment with a different TNFi over adding a SAARD (PICO 9; very low-quality evidence; vote 100% agreement).

We conditionally recommend treatment with a different TNFi over treatment with a non-TNFi biologic agent (PICO 10; very low-quality evidence; vote 90% agreement).

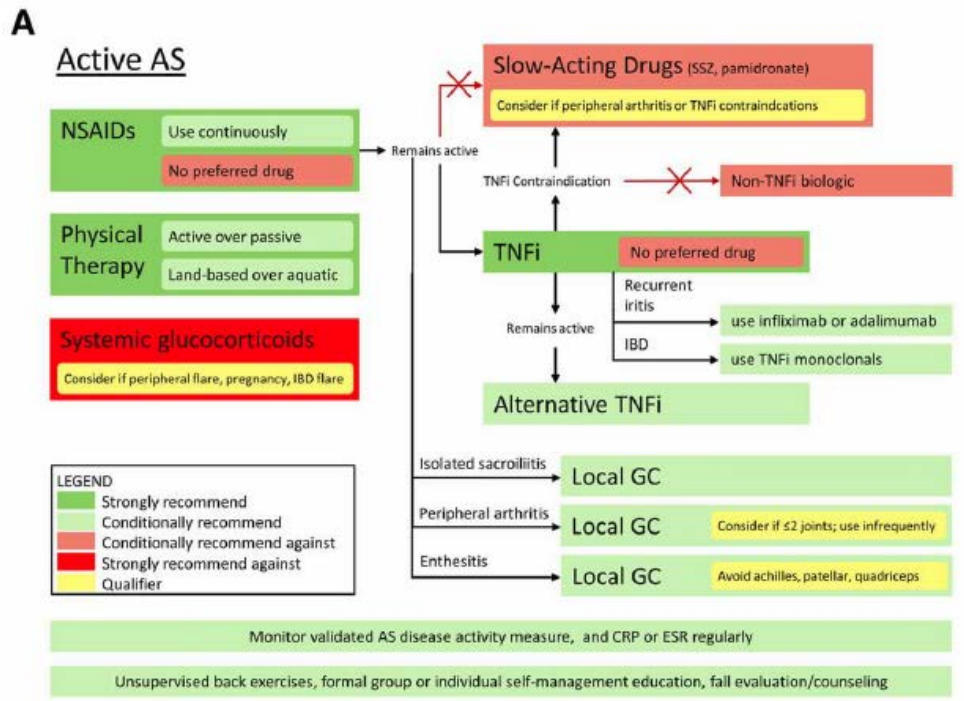
In adults with active AS, we strongly recommend against treatment with systemic glucocorticoids (PICO 4; very low-quality evidence; vote 100% agreement).

Recommendations for the treatment of patients with nonradiographic axial SpA

Because nonradiographic axial SpA has only recently been defined, the literature on treatment of this condition is limited. Therefore, the panel relied on the AS literature as the basis for most recommendations. These recommendations were the same as for AS, with the exception of the PICO question on use of TNFi. This question also had the highest level of evidence among those for nonradiographic axial SpA.

In adults with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over no treatment with TNFi (PICO 38; moderate-quality evidence; vote 90% agreement)

Abbildung: Summary of the main recommendations fort he treatment of patients with active AS (A)



Hamilton L et al., 2017 [4].

British Society for Rheumatology und British Health Professionals in Rheumatology

Titel der Leitlinie

Leitlinienorganisation/Fragestellung

These guidelines provide evidence-based guidance for UK clinicians prescribing biologics for adult patients with axSpA. This includes the criteria for starting treatment, the choice of drug and assessing response to treatment.

Methodik

Grundlage der Leitlinie

- Update einer BSR Guideline zur Verschreibung von TNF-alpha Blockern bei Erwachsenen mit AS
- Formierung einer „working party“ durch die BSR mit Rheumatologen, Gesundheitsexperten, einem Allgemeinarzt, einem Patientenvertreter und einem vertreter der National Ankylosing Spondylitis Society
- Evidenzgrundlage: qualitativ hochwertige Metaanalysen, SR und RCTs; kontrollierte Observationsstudien falls keine anderen Daten oder für Sicherheitsanalysen
- Entwicklung von Empfehlungen auf Basis des SR durch die „working party“, die dann von den Mitgliedern nach ihrem Grad der Zustimmung von 0-10 anonym bewertet wurden
- Kommentierung der Leitlinie auf dem jährlichen Meeting der BSR
- Der Literaturreview sollte bereits 2017 updated werden, wozu jedoch keine Informationen vorliegen

Recherche/Suchzeitraum:

- Medline, Embase und Cochrane Library bis 30. Juni 2014

LoE

1 ++ High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias

1- Meta-analyses, systematic reviews or RCTs with a high risk of bias

2 ++ High-quality systematic reviews of case-control or cohort studies; High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+ Well-conducted case_control or cohort studies with a low risk of confounding or bias and a moderate possibility that the relationship is causal

2- Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3 Non-analytic studies (e.g. case reports, case series)

4 Expert opinion

GoR

A Directly based on level 1 evidence

B Level 2 evidence or extrapolation from level 1

C Level 3 evidence or extrapolation from level 1 or 2

D Level 4 evidence or extrapolation from level 2 or 3

Sonstige methodische Hinweise

- Die Leitlinie wurde bereits 2015 konsentiert, jedoch erst 2017 publiziert. Die Evidenz zu Secukinumab war zu diesem Zeitpunkt noch relativ limitiert, weshalb dieser Wirkstoff noch nicht in den Empfehlungen existiert

Recommendations for treatment eligibility

(i) Anti-TNF therapy is effective at reducing disease activity and spinal pain in axSpA [level of evidence (LOE) 1+; strength of recommendation A; consensus score 9.6].

(ii) Currently there is insufficient evidence to recommend the use of other biologic agents in axSpA (LOE 1+; strength of recommendation B; consensus score 9.3).

(iii) Patients should be considered for anti-TNF therapy if they have active axSpA (LOE 1+; strength of recommendation B; consensus score 9.6).

(iv) Active disease is defined as a BASDAI and spinal pain VAS 54 despite standard therapy (LOE 1+; strength of recommendation B; consensus score 8.5).

(v) The BASDAI should be measured on two occasions at least 4 weeks apart (LOE 2+; strength of recommendation C; consensus score 7.2).

(vi) Patients with active disease who do not meet modified New York criteria for AS should also have had a positive MRI and/or elevated CRP (LOE 1+; strength of recommendation B; consensus score 9.3).

Recommendation for choice of drug

(i) Extra-articular manifestations and patient choice should be considered when selecting an anti-TNF agent (LOE 4; strength of recommendation D; consensus score 8.9).

Switching drugs

(i) In the event of anti-TNF failure due to inefficacy or adverse event, an alternative anti-TNF agent should be offered if clinically appropriate (LOE 2+; strength of recommendation C; consensus score 9.7).

Recommendations for withdrawal of therapy

(i) In the absence of an initial clinical response by 6 months, or failure to maintain response at two consecutive assessments at least 4 weeks apart, withdrawal of that anti-TNF agent should be considered (LOE 4; strength of recommendation D; consensus score 9.4).

(ii) There is no evidence to support the withdrawal of anti-TNF therapy in treatment responders (LOE 2+; strength of recommendation B; consensus score 9).

Spanish Society of Rheumatology, 2015 [10].

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

Leitlinienorganisation/Fragestellung

Clinical Practise Guideline Spanish Society of Rheumatology (SER), ESPOGUIA development group. This guideline focus on the care of those patients affected by axial spondyloarthritis (axSpA) or psoriatic arthritis (PsA).

Die Leitlinie umfasst Patienten mit axialer Spondyloarthritis; daher sind Empfehlungen nicht speziell auf Patienten mit AS ausgerichtet

Methodik

Grundlage der Leitlinie

- Update der LL von 2010; weiteres Update in vier Jahren vorgesehen
- multi-disciplinary work group was set up consisting of professionals involved in medical care, technical experts from the Research Unit (RU) of SER, and patient representatives
- A critical reading of the studies was conducted using the critical SIGN (Scottish Intercollegiate Guidelines Network) reading templates, and their internal and external validity measures were assessed.

Recherche/Suchzeitraum:

- literature search was carried out using the MEDLINE database (via PubMed), EMBASE (Elsevier), the Cochrane Library (Wiley Online Library), and Cinahl (EBSCOhost).
- Suchzeitraum: 2008-2014

LoE

- modified version of the Oxford Centre for Evidence-Based Medicine (CEBM) system

GoR

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

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

Treatment of Axial Spondyloarthritis (axSpA)

In patients with active axial spondyloarthritis (axSpA), it is recommended that pharmacological treatment begin as soon as possible. (Grade D recommendation).

There is insufficient evidence on the effectiveness of early pharmacological treatment for patients with axial spondyloarthritis. 2b, 4

In secondary analyses evaluating the effectiveness of early pharmacological treatment in patients with axial spondyloarthritis, those with shorter disease durations responded better to treatment with anti-TNF. 2b, 4

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).

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).

- Biologic therapies with anti-TNF (adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab) have proven effective in treating non-radiographic axial spondyloarthritis. 1b
- Biologic agents such as adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab, versus placebo, contribute to:
  - Minimizing inflammatory activity.
  - Improving functional capacity. 1b
- In non-radiographic axial spondyloarthritis, the biologic agent tocilizumab does not improve clinical or functional parameters that have not previously responded to treatment with anti-TNF. 4

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. 4

In those patients with ankylosing spondylitis who reach the clinical objective following administration of standard dosage anti-TNF, the possibility of reducing the dosage should be assessed. (Grade C 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
- 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. 2b, 4

Deutsche Gesellschaft für Rheumatologie (DGRh), 2013 [2].

Axiale Spondyloarthritis inklusive Morbus Bechterew und Frühformen; S3-Leitlinie

Leitlinienorganisation/Fragestellung

S3-Leitlinie der Deutschen Gesellschaft für Rheumatologie (DGRh) in Kooperation mit der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) „Axiale Spondyloarthritis

inklusive Morbus Bechterew und Frühformen“

Methodik

Grundlage der Leitlinie

- Systematische Leitliniensuche und –adaptation; Interdisziplinäre Leitliniengruppe: Experten aus den beteiligten
- Fachgesellschaften; Empfehlungen im formalisierten Konsensusprozess (zweiteiliger Nominaler Gruppenprozess) verabschiedet; CoI wurde abgefragt und bei vorhandenem CoI waren die entsprechenden Mandatsträger nicht stimmberechtigt
- Die letzte inhaltliche Überarbeitung fand am 27.11.2013 statt.

- Bei Therapiestudien wurden Studien mit dem Endpunkt klinische Verbesserung (z.B. ASAS-20), Verbesserung der körperlichen Funktionsfähigkeit (z.B. BASFI), radiologische Veränderungen (z.B. mSASSS) und Sicherheitsdaten (z.B. Abbrecher) berücksichtigt
- Weitere Kriterien für die Qualität einer LL: Empfehlungen sind mit Literaturstellen verknüpft
- Abstimmung mittels Delphi-Verfahren

Recherche/Suchzeitraum:

- Systematische Literaturrecherche in PubMed, PEDro und der Cochrane library. Beschränkung auf 30.09.2006 bis 30.09.2011 (Nachrecherche bis zum 31.07.2012). Da durch die Quell-Leitlinien (Recherche 2001-2011) der Zeitraum vor September 2006 bereits systematisch erfasst worden ist, wurde er nicht erneut in die systematische Suche miteinbezogen.

LoE

Tabelle 11: Kriterien des Scottish Intercollegiate Guidelines Network (SIGN)

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

GoR

Tabelle 14: Grad der Empfehlung, ABO-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.
KKP	(Klinischer Konsenspunkt) „Standard in der Behandlung": Empfohlen als gute klinische Praxis im Konsens und aufgrund der klinischen Erfahrung der Mitglieder der Leitliniengruppe als ein Standard der Behandlung, bei dem keine experimentelle wissenschaftliche Erforschung möglich oder angestrebt ist.

Sonstige methodische Hinweise

- Die nächste Aktualisierung ist für das Jahr 2018 geplant

Tumornekrosefaktor-Blocker (TNF-Blocker)

8-13 Eine Therapie mit TNF-Blocker soll bei Patienten mit persistierend aktiver axialer SpA einschließlich AS und unzureichendem Ansprechen auf eine NSAR-Therapie begonnen werden. (LoE 1++; GoR A)

Die Wirksamkeit und Sicherheit der TNF-Blocker ist bei Patienten mit AS sehr gut belegt [247, 253-283]. Patienten mit totaler Ankylose der Wirbelsäule profitieren ebenfalls von der Therapie mit Adalimumab oder Etanercept [268] [269]. Einige wenige Studien zeigen, dass die Behandlung mit TNF-Blocker bei Patienten mit nr-axSpA ebenfalls effektiv und wirksam ist [270, 271] [272], [273].

Klinisches Bild: Die klinische Wirksamkeit von TNF-Blocker beginnt relativ schnell und hält bei einem größeren Teil der Patienten unter fortlaufender Therapie mehrere Jahre an [274], [275], [276], [270], [277], [278], [279], ([280], [281], [282], [283], [269], [284], [285], [286], [271], [287], [288], [289], [290], [291], [292], [293], [294]. Für Adalimumab liegen Daten über 3 Jahre, für Etanercept über 5 Jahre, für Golimumab über 2 Jahre und für Infliximab über 8 Jahre vor [276], [282], [292].

8-14 Bei Patienten mit axialer SpA und symptomatischer peripherer Arthritis sollte eine TNF-Blocker Therapie versucht werden, wenn der Patient auf mindestens eine lokale Steroidinjektion ungenügend angesprochen hat, und ein angemessener Behandlungsversuch mit einem Basistherapeutikum, bevorzugt Sulfasalazin, keine Wirkung gezeigt hat. (LoE 1; GoR B)

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

8-15 Bei Patienten mit extra-muskuloskeletalen Manifestationen, insbesondere bei Vorliegen einer chronisch entzündlichen Darmerkrankung oder Uveitis, sollte die unterschiedliche Effektivität der verschiedenen TNF-Blocker auf diese Manifestationen beachtet werden. (LoE 1+/2b; GoR B)

8-16 Bei Patienten mit verbleibenden muskuloskeletalen Symptomen unter einer TNF-Blocker-Therapie kann eine zusätzliche Therapie mit NSAR erfolgen. (KKP)

8-17 Die Wirksamkeit einer TNF-Blocker-Therapie soll nach 12 Wochen überprüft werden (A). Die Fortführung der Behandlung kann erfolgen, wenn eine relative 50%ige Verbesserung des BASDAI oder eine absolute Verbesserung um 2 Punkte (auf einer Skala von 0-10) und eine positive Expertenmeinung für eine Fortführung vorliegen (KKP). (LoE 1++; GoR A)

Wechsel von einem TNF-Blocker zu einem anderen TNF-Blocker

8-18 Bei nicht-ausreichender Wirksamkeit einer TNF-Blocker- Therapie kann der Wechsel auf einen zweiten TNF-Blocker erfolgen, insbesondere bei Wirkverlust. (LoE 4; GoR 0)

Basistherapie

8-20 Bei Patienten mit AS sollte keine Behandlung der Wirbelsäulensymptomatik mit Methotrexat erfolgen. (LoE 1; GoR B)

Kommentar zu 8-20: Herabstufung des Empfehlungsgrad von „A“ auf „B“, da hier eine Extrapolation der Ergebnisse aus der Evidenzebene 1 vorgenommen wurde.

Glukokortikoide:

8-21 Die systemische Langzeitgabe von Kortikosteroiden wird bei Patienten mit Achsenskelettbeteiligung nicht empfohlen. Für die Wirksamkeit einer kurzfristigen Therapie mit Kortikosteroiden gibt es keine ausreichende Evidenz. (LoE 4; GoR 0)

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3.5. Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

National Institute for Health and Care Excellence et al., 2016 [7].

TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis

1 Recommendations

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

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

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

1.4 The response to adalimumab, certolizumab pegol, etanercept, golimumab or infliximab treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response, defined as:

- a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units and
- a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.

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

National Institute for Health and Care Excellence et al., 2016 [5].

TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis

1 Recommendations

1.1 Secukinumab is recommended, within its marketing authorisation, as an option for treating active ankylosing spondylitis in adults whose disease has responded inadequately to

conventional therapy (non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors). The drug is recommended only if the company provides it with the discount agreed in the patient access scheme.

1.2 Assess the response to secukinumab after 16 weeks of treatment and only continue if there is clear evidence of response, defined as:

- a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units and
- a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 9 of 12, September 2018) am 05.09.2018

#	Suchfrage
1	[mh Spondylarthritis]
2	spondylarthrit*:ti,ab,kw or spondyloarthrit*:ti,ab,kw or spondylit*:ti,ab,kw or ankylosing:ti,ab,kw kw or bechtere*:ti,ab,kw or ankylopoietica:ti,ab,kw
3	#1 or #2
4	#3 with Cochrane Library publication date from Sep 2013 to Dec 2018

Systematic Reviews in Medline (PubMed) am 05.09.2018

#	Suchfrage
1	Spondylarthritis[mh]
2	spondylarthrit*[tiab] OR spondyloarthrit*[tiab] OR spondylit*[tiab] OR ankylosing[tiab] OR bechtere*[tiab] OR ankylopoietica[tiab]
3	#1 OR #2
4	(#3) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR 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]))))
5	((#4) AND ("2013/09/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 05.09.2018

#	Suchfrage
1	Spondylarthritis[mh]
2	spondylarthrit*[tiab] OR spondyloarthrit*[tiab] OR spondylit*[tiab] OR ankylosing[tiab] OR bechtere*[tiab] OR ankylopoietica[tiab]
3	#1 OR #2
4	(#4) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[ti] OR recommendation*[ti]) NOT (letter[ptyp] OR comment[ptyp])))
5	(((#4) AND ("2013/09/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]))

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Anhang

Abbildung 1: Qualitätsbewertung der Studien von *Ungprasert et al. (2017)*

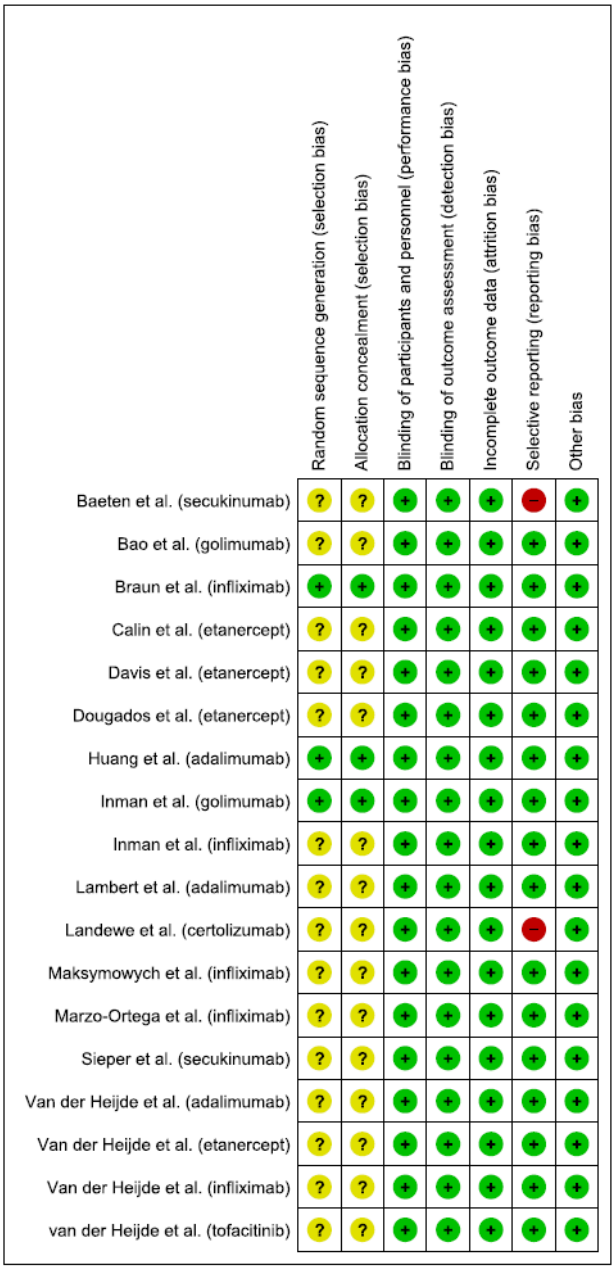

Abbildung 2: Qualitätsbewertung der Studien *von Chen et al. (2016)*

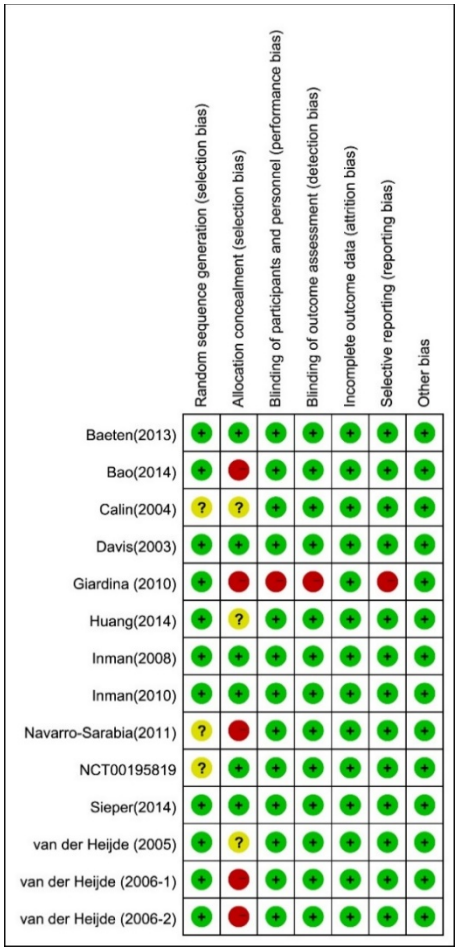

Abbildung 3: Baseline Charakteristika der Studien von Chen et al. (2016)

TABLE 1. Baseline Characteristics of Studies Included in the Network Meta-Analysis

Study, Year/NCT ID	Study Design	Number of Patients	HLA-B27 Positive, n (%)	Male, n (%)	Average Age(Yr)	Duration of AS (Yr)	Extra-articular manifestations, n (%)	Concomitant DMARDs, n (%)	Concomitant corticosteroids, n (%)	Concomitant NSAIDs, n (%)	CRP, mg/l	BASDAI (0–10cm)	Comparison (s)
Davis, 2003[31]	International MC	277	217 (78.3)	210 (75.8)	42.0	10.3	13 (4.7)	87 (31.4)	38 (13.7)	254 (91.7)	19.5	5.9	Etanercept 25 mg BIW vs. placebo
Calin, 2004[32]	European MC	84	NA	66 (78.6)	43.2	NA	NA	32 (38.1)	13 (15.5)	73 (86.9)	NA	6,0	Etanercept 25 mg BIW vs. placebo
van der Heijde, 2005[33]	International MC	279	242 (86.7)	225 (80.6)	40	8.8	137 (49.1)	NA	NA	NA	15.6	6.6	Infliximab 5mg/kg vs. placebo
van der Heijde, 2006-1[34]	International MC	315	248 (78.7)	236 (74.9)	42.3	10.9	145 (46.0)	62 (19.7)	31 (9.8)	250 (79.4)	19.4	6.3	Adalimumab vs. placebo
van der Heijde, 2006-2[35]	European MC	356	NA	262 (73.4)	40.6	9.3	66 (18.5)	137 (38.5)	44 (12.4)	291 (81.7)	20.1	6.1	Etanercept 50 mg QW vs. etanercept; 25 mg BIW vs. placebo
Inman, 2008[42]	International MC	356	296 (83.1)	255 (71.6)	38.7	12.1	163 (45.8)	171 (48.0)	57 (16.0)	319 (89.6)	10.3	6.8	Golimumab 50 mg vs. golimumab 100 mg vs. placebo
Giardina, 2010[36]	Italian SC	50	47 (94.0)	39 (78.0)	32.2	15.6	NA	NA	NA	NA	24.0	6.6	Etanercept 50 mg QW vs. infliximab 5mg/kg
Inman, 2010[37]	Canadian MC	76	55 (72.4)	61 (80.3)	41.1	11.4	38 (50.0)	NA	NA	NA	17.7	NA	infliximab 3mg/kg vs. placebo
Navarro-Sarabia, 2011[38]	Spanish MC	108	88 (81.5)	86 (79.6)	41.4	13.1	NA	31 (28.7)	11 (10.2)	93 (86.1)	19.0	6.3	Etanercept 50 mg BIW vs. etanercept 50 mg QW
Baeten, 2013[39]	European MC	30	21 (70.0)	19 (63.3)	41.9	10.1	19 (63.3)	11 (38.0)	3 (10.0)	28 (97.0)	13.3	7.1	Secukinumab vs. placebo
Sieper, 2014[41]	International MC	102	88 (86.3)	76 (74.5)	42.2	6.5	NA	NA	NA	NA	16.5	6.7	Tocilizumab vs. placebo
Huang, 2014[18]	Chinese MC	344	328 (95.3)	280 (81.4)	29.9	7.9	12 (3.5)	204 (59.3)	13 (3.8)	272 (79.1)	22.6	6.1	Adalimumab vs. placebo
Bao, 2014[40]	Chinese MC	213	200 (93.9)	177 (83.1)	30.5	7.1	NA	156 (73.2)	10 (4.7)	148 (69.5)	19.7	6.5	Golimumab 50 mg vs. placebo
NCT00195819	Canadian MC	82	69 (84.1)	65 (79.3)	40.9	13.2	NA	NA	NA	NA	NA	NA	Adalimumab vs. placebo

Abbildung 4: Network of all eligible comparisons for the primary outcome of biologic therapies in patients with AS von Chen et al. (2016)

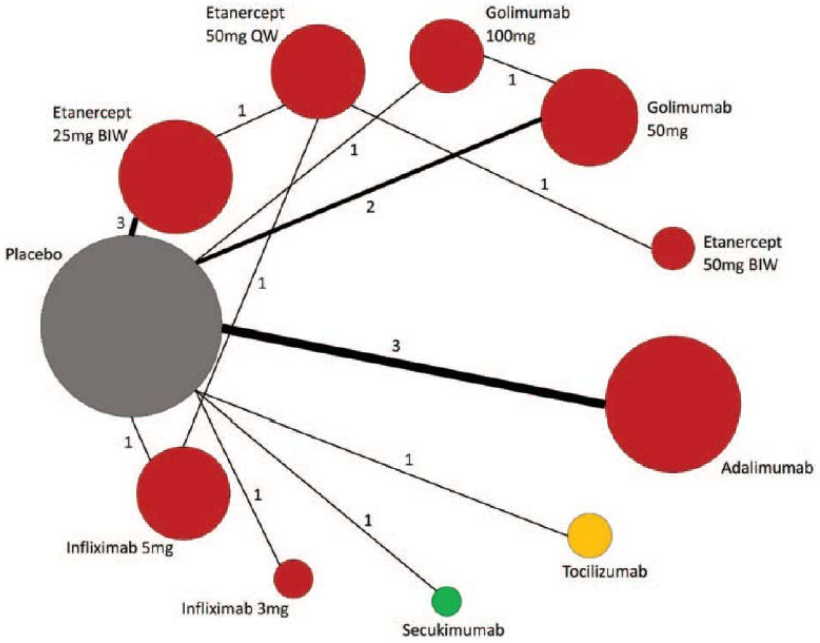

Abbildung 5: Behandlungsalgorithmus der ASAS-EULAR Empfehlungen für die axSpA

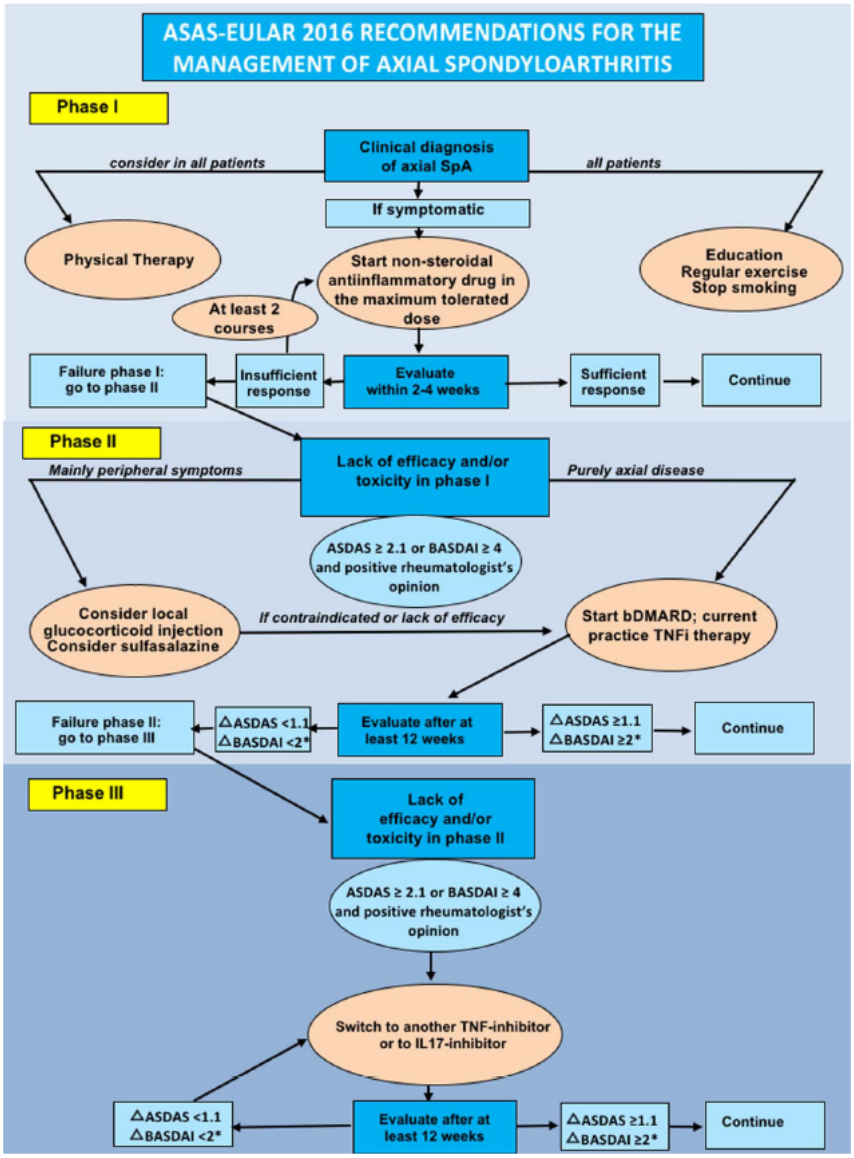

Figure 3 Algorithm based on the ASAS-EULAR recommendations for the management of axial spondyloarthritis. ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease-modifying antirheumatic drug; TNFi, tumor necrosis factor inhibitor; IL17-inhibitor, interleukin-17 inhibitor. *Either BASDAI or ASDAS, but the same outcome per patient.