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: Risankizumab

Stand: Dezember 2021

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

Risankizumab **[Psoriasis-Arthritis bei Erwachsenen]** **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung nach § 35a SGB V: • Apremilast (Beschluss vom 6. August 2015) • Secukinumab (Beschluss vom 18. Februar 2021) • Ixekizumab (Beschluss vom 16. August 2018) • Tofacitinib (Beschluss vom 21. Februar 2019) • Guselkumab (Beschluss vom 20. Mai 2021) • Upadacitinib (Beschluss vom 15. Juli 2021) Therapiehinweise: - Leflunomid (Beschluss vom 16. August 2007, zuletzt geändert am 15. Mai 2008)
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:	
Risankizumab Skyrizi®	Zugelassenes Anwendungsgebiet Als Monotherapie oder in Kombination mit Methotrexat zur Behandlung erwachsener Patienten mit aktiver Psoriasis-Arthritis, die auf ein oder mehrere krankheitsmodifizierende Antirheumatika (DMARDs) unzureichend angesprochen oder diese nicht vertragen haben.
Klassische synthetische krankheitsmodifizierende Antirheumatika (csDMARD)	
Methotrexat L01BA01 generisch	[…] und der Psoriasis arthropathica. […]
Leflunomid L04AA13 generisch	Leflunomid (medac®) ist ein antirheumatisches Basistherapeutikum („disease modifying antirheumatic drug“ [DMARD]) zur Behandlung von Erwachsenen mit: • aktiver rheumatoider Arthritis. • aktiver Psoriasis-Arthritis (Arthritis psoriatica).
Biologische krankheitsmodifizierende Antirheumatika (bDMARD)	
TNF-alpha-Inhibitoren	
Etanercept L04AB01 Enbrel®	*Psoriasis-Arthritis (Arthritis psoriatica)* Behandlung der aktiven und progressiven Psoriasis-Arthritis bei Erwachsenen, wenn das Ansprechen auf eine vorhergehende Basistherapie unzureichend ist. Enbrel verbessert die körperliche Funktionsfähigkeit bei Patienten mit Psoriasis-Arthritis und reduziert das Fortschreiten der radiologisch nachweisbaren strukturellen Schädigungen der peripheren Gelenke bei Patienten mit polyartikulären symmetrischen Subtypen der Erkrankung. [Stand FI: 11/ 2019]
Infliximab L04AB02	*Psoriasis-Arthritis*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Remicade®/ Inflectra®	Remicade® ist indiziert zur Behandlung der aktiven und fortschreitenden Psoriasis-Arthritis bei erwachsenen Patienten, wenn deren Ansprechen auf eine vorhergehende krankheitsmodifizierende, antirheumatische Arzneimitteltherapie (DMARD-Therapie) unzureichend gewesen ist. Inflectra™ sollte verabreicht werden • in Kombination mit Methotrexat • oder als Monotherapie bei Patienten, die eine Unverträglichkeit gegenüber Methotrexat zeigen oder bei denen Methotrexat kontraindiziert ist. Infliximab verbessert die körperliche Funktionsfähigkeit bei Patienten mit Psoriasis-Arthritis und reduziert die Progressionsrate peripherer Gelenkschaden, wie radiologisch bei Patienten mit polyartikularem symmetrischem Subtyp der Krankheit belegt wurde. [Stand FI: 09/ 2019]
Adalimumab L04AB04 Humira®	*Psoriasis-Arthritis* Humira ist indiziert zur Behandlung der aktiven und progressiven Psoriasis-Arthritis (Arthritis psoriatica) bei Erwachsenen, die nur unzureichend auf eine vorherige Basistherapie angesprochen haben. Humira reduziert das Fortschreiten der radiologisch nachweisbaren strukturellen Schädigungen der peripheren Gelenke bei Patienten mit polyartikularen symmetrischen Subtypen der Erkrankung und verbessert die körperliche Funktionsfähigkeit. [Stand FI: 11/ 2019]
Golimumab L04AB06 Simponi®	*Psoriasis-Arthritis (PsA)* Simponi ist zur Anwendung als Monotherapie oder in Kombination mit MTX zur Behandlung der aktiven und fortschreitenden Psoriasis-Arthritis bei Erwachsenen indiziert, wenn das Ansprechen auf eine vorhergehende Therapie mit krankheitsmodifizierenden Antirheumatika (DMARD) unzureichend gewesen ist. Simponi verringert nachweislich die Progressionsrate der peripheren Gelenkschäden, bestimmt anhand von Röntgenaufnahmen bei Patienten mit polyartikulären symmetrischen Subtypen der Erkrankung und verbessert die körperliche Funktionsfähigkeit. [Stand FI: 04/ 2019]
Certolizumab Pegol L04AB05 Cimzia®	*Psoriasis-Arthritis* Cimzia ist in Kombination mit Methotrexat (MTX) für die Behandlung der aktiven Psoriasis-Arthritis bei Erwachsenen angezeigt, wenn das vorherige Ansprechen auf eine Therapie mit DMARDS ungenügend war. In Fällen von Unverträglichkeit gegenüber Methotrexat oder wenn die Fortsetzung der Behandlung mit Methotrexat ungeeignet ist, kann Cimzia als Monotherapie verabreicht werden. [Stand FI: 06/ 2019]
Interleukin-Inhibitoren	
Ustekinumab L04AC05 Stelara®	*Psoriatische Arthritis (PsA)* STELARA ist allein oder in Kombination mit MTX für die Behandlung der aktiven psoriatischen Arthritis bei erwachsenen Patienten indiziert, wenn das Ansprechen auf eine vorherige nicht-biologische krankheitsmodifizierende antirheumatische (DMARD) Therapie unzureichend gewesen ist. [Stand FI: 02/ 2020]
Ixekizumab L04AC13 Taltz®	Ixekizumab, allein oder in Kombination mit Methotrexat, ist angezeigt für die Behandlung erwachsener Patienten mit aktiver Psoriasis-Arthritis, die unzureichend auf eine oder mehrere krankheitsmodifizierende Antirheumatika (DMARD) angesprochen oder diese nicht vertragen haben. [Stand FI: 05/ 2018]

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Secukinumab L04AC10 Cosentyx®	*Psoriasis-Arthritis (PsA)* Cosentyx, allein oder in Kombination mit Methotrexat (MTX), ist angezeigt für die Behandlung erwachsener Patienten mit aktiver Psoriasis-Arthritis, wenn das Ansprechen auf eine vorhergehende Therapie mit krankheitsmodifizierenden Antirheumatika (DMARD) unzureichend gewesen ist. [Stand FI: Oktober 2019]
Guselkumab L04AC16 Tremfya®	*Psoriasis-Arthritis* Tremfya, als Monotherapie oder in Kombination mit Methotrexat (MTX), ist für die Behandlung der aktiven Psoriasis-Arthritis bei erwachsenen Patienten indiziert, die auf eine vorangegangene krankheitsmodifizierende antirheumatische (disease-modifying antirheumatic drug, DMARD) Therapie unzureichend angesprochen oder diese nicht vertragen haben (siehe Abschnitt 5.1). [Stand FI: 02/2021]
JAK-Inhibitoren	
Tofacitinib L04AA29 XELJANZ®	Tofacitinib ist in Kombination mit MTX indiziert zur Behandlung der aktiven Psoriasis-Arthritis (PsA) bei erwachsenen Patienten, die auf eine vorangegangene krankheitsmodifizierende antirheumatische DMARD-Therapie unzureichend angesprochen oder diese nicht vertragen haben. *<u>Anwendung bei Patienten über 65 Jahre</u>* *Angesichts des erhöhten Risikos für schwere Infektionen, Myokardinfarkt und Malignome im Zusammenhang mit Tofacitinib bei Patienten über 65 Jahre sollte Tofacitinib bei diesen Patienten nur angewendet werden, wenn keine geeigneten Behandlungsalternativen zur Verfügung stehen (siehe weitere Einzelheiten in Abschnitt 4.4 und Abschnitt 5.1).* [Stand FI: 08/ 2021]
Upadacitinib L04AA44 Rinvoq®	*Psoriasis-Arthritis* RINVOQ wird angewendet zur Behandlung der aktiven Psoriasis-Arthritis bei erwachsenen Patienten, die auf ein oder mehrere DMARDs unzureichend angesprochen oder diese nicht vertragen haben. RINVOQ kann als Monotherapie oder in Kombination mit Methotrexat angewendet werden. [Stand FI: 09/2021]
Weitere	
Abatacept L04AA24 Orencia®	*Psoriasis-Arthritis* ORENCIA ist allein oder in Kombination mit Methotrexat (MTX) indiziert zur Behandlung der aktiven Psoriasis-Arthritis (PsA) bei erwachsenen Patienten, die unzureichend auf vorangegangene DMARDs einschließlich Methotrexat ansprachen und für die eine zusätzliche systemische Therapie für psoriatische Hautläsionen nicht notwendig ist. [Stand FI: 12/ 2019]
Apremilast L04AA32 Otezla®	*Psoriasis-Arthritis*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	Otezla allein oder in Kombination mit krankheitsmodifizierenden antirheumatischen Arzneimitteln (DMARDs) ist indiziert zur Behandlung der aktiven Psoriasis-Arthritis (PsA) bei erwachsenen Patienten, die auf eine vorangegangene DMARD-Therapie unzureichend angesprochen oder diese nicht vertragen haben. [Stand FI: 01/ 2020]
Steroidale Antirheumatika (Glucokortikoide)	
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)
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)
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);
Nichtsteroidale Antirheumatika (NSAR oder NSAID)	
z. B. Acemetacin M01AB11 generisch	Acemetacin 60 Heumann zusätzlich bei: – akuten Arthritiden (einschließlich Gichtanfall) – chronischen Arthritiden, insbesondere bei rheumatoider Arthritis (chronische Polyarthritis), (Acemetacin Heumann FI, Stand April 2015)

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2021-B-376z (Risankizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	23. November 2021

Inhaltsverzeichnis

Abkürzungsverzeichnis

ACR	American College of Rheumatolog
AE	Adverse event
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
bDMARD	Biologic DMARD
CDAI	Clinical Disease Activity Index
CTLA	Cytotoxic T-lymphocyte-associated Protein
csDMARD	Conventional synthetic DMARD
CVE	cardiovascular event
DAHTA	Deutsche Agentur für Health Technology Assessment
DAS28	Disease Activity Score 28
DMARD	Disease-modifying antirheumatic drug
DSS	Dactylitis Severity Score
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy–Fatigue
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health Assessment Questionnaire Disability Index
HR	Hazard Ratio
IFPA	Global leader in fighting psoriatic disease
IL	Interleukin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
JAK	Januskinase-Inhibitoren
JAKi	JAK inhibitor
KI	Konfidenzintervall
LEI	Leeds Enthesitis Index
LoE	Level of Evidence
MDA	Minimal disease activity

NMA	Metzwerk Meta-Analyse
MTX	Methotrexat
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NOS	Newcastle-Ottawa scale
NPF	National Psoriasis Foundation
NSAID	Non-steroidal anti-inflammatory drugs
OR	Odds Ratio
PARS	Psoriatic Arthritis Ratingen Score
PASI	Psoriasis Area Severity Index
PDE	Phosphodiesterase
PsA	Psoriasis Arthritis
PsARC	Psoriatic Arthritis Response Criteria
PSORIQOL	Psoriasis Index of Quality of Life
P-Y	Patient years
RoB	Risk of bias
RR	Relatives Risiko
SAE	Serious adverse event
SIGN	Scottish Intercollegiate Guidelines Network
sPGA	Physician's Global Assessment Scale
TNF	Tumor necrosis factor
TRIP	Turn Research into Practice Database
tsDMARD	targeted synthetic DMARDs
vdH-S	van der Heijde-Sharp score
WAEs	Withdrawals due to adverse events
WHO	World Health Organization

1 Indikation

Zur Behandlung der aktiven Psoriasis-Arthritis (PsA) bei erwachsenen Patienten, die unzureichend auf ein oder mehrere krankheitsmodifizierende Antirheumatika (DMARDs) angesprochen oder diese nicht vertragen haben. kann als Monotherapie oder in Kombination mit Methotrexat (MTX) angewendet werden.

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 *Psoriasis Arthritis* 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), MEDLINE (PubMed). Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.startpage.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 28.10.2021 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 526 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 26 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Wildson TD et al., 2019 [24].
Methotrexate for psoriatic arthritis

Fragestellung
To assess the benefits and harms of methotrexate for psoriatic arthritis in adults.

Methodik

Population:

- adults aged 18 years or older with a diagnosis of PsA

Intervention:

- methotrexate (MTX) at any dose and via any formulation (oral or parenteral)

Komparator:

- placebo, other disease-modifying anti-rheumatic drugs (DMARDs) (including bDMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), or other analgesics

  Co-intervention with NSAIDs or other analgesics, provided they were used in all treatment arms were allowed.

Endpunkte:

- Major outcomes: ACR50; PsARC; HAQ score; SF-36; PSORIQOL; DAS28-ESR; CDAI; Psoriatic Arthritis Ratingen Score (PARS); Serious adverse events (SAEs); Withdrawals due to adverse events (WAEs)

Recherche/Suchzeitraum:

- CENTRAL, MEDLINE, EMBASE, the WHO International Clinical Trials Registry Platform, and www.clinicaltrials.gov. From inception to 29 January 2018.

Qualitätsbewertung der Studien:

- Cochran & GRADE Approach

Ergebnisse

Anzahl eingeschlossener Studien:

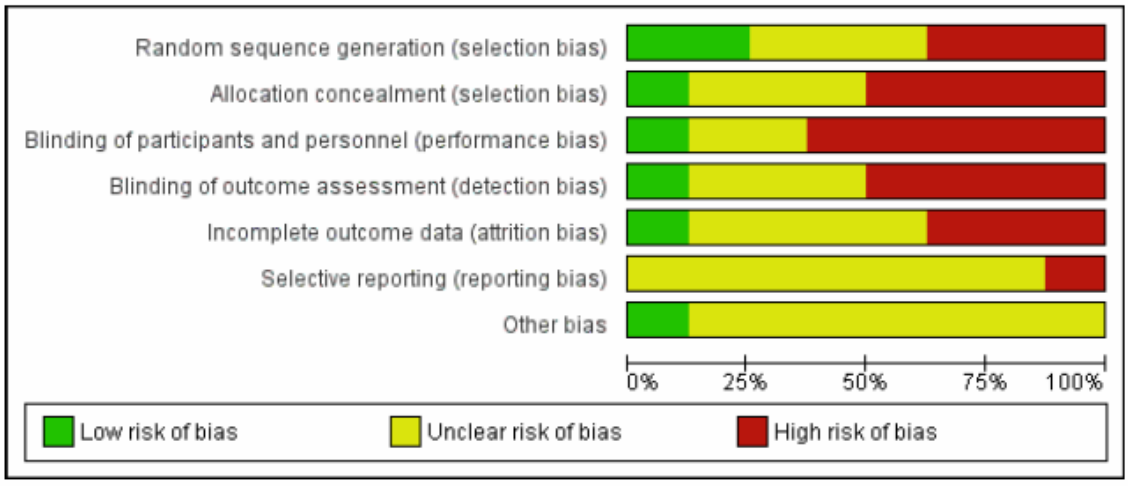
- We included in this review eight RCTs conducted in an outpatient setting, in Italy, the United Kingdom, the United States of America, China, Russia, and Bangladesh.
- Five studies compared methotrexate versus placebo, and four studies compared methotrexate versus other DMARDs.

- The average age of participants varied across studies (26 to 52 years), as did the average duration of psoriatic arthritis (one to nine years).

Qualität der Studien:

- We considered only one study to have low risk of selection and detection bias. The main study informing results of the primary comparison (methotrexate vs placebo up to six months) was at low risk of bias for all domains except attrition bias and reporting bias.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Studienergebnisse:

- Methotrexate versus placebo for up to six months: Low-quality evidence (downgraded due to bias and imprecision) from a single study (221 participants; methotrexate dose 15 mg orally or less per week) informed results for disease response, function, and disease activity.
  - Disease response, measured by the proportion who responded to treatment according to PsARC (response indicates improvement), was 41/109 in the methotrexate group and 24/112 in the placebo group (risk ratio (RR) 1.76, 95% confidence interval (CI) 1.14 to 2.70). This equates to an absolute difference of 16%more responders with methotrexate (4% more to 28% more), and a number needed to treat for an additional beneficial outcome (NNTB) of 6 (95% CI 5 to 25).
  - Mean function, measured by the HAQ (scale 0 to 3; 0 meaning no functional impairment; minimum clinically important difference 0.22), was 1.0 points with placebo and 0.3 points better (95% 0.51 better to 0.09 better) with methotrexate; absolute improvement was 10% (3% better to 17% better), and relative improvement 30% (9% better to 51% better).
  - Mean disease activity as measured by the DAS28-ESR (scale of 0 to 10; lower score means lower disease activity; minimum clinically important difference unknown) was 3.8 points in the methotrexate group and 4.06 points in the placebo group; mean

difference was -0.26 points (95% CI -0.65 to 0.13); absolute improvement was 3% (7% better to 1% worse), and relative improvement 6% (16% better to 3% worse).

- Low-quality evidence (downgraded due to risk of bias and imprecision) from three studies (n = 293) informed our results for serious adverse events and withdrawals due to adverse events. Due to low event rates, we are uncertain if methotrexate results show increased risk of serious adverse events or withdrawals due to adverse events compared to placebo. Results show 1/141 serious adverse events in the methotrexate group and 4/152 in the placebo group: RR 0.26 (95% CI 0.03 to 2.26); absolute difference was 2% fewer events with methotrexate (5% fewer to 1% more). In all, 9/141 withdrawals in the methotrexate group were due to adverse events and 7/152 in the placebo group: RR 1.32 (95% CI 0.51 to 3.42); absolute difference was 1% more withdrawals (4% fewer to 6% more).
- One study measured health-related quality of life but did not report these results. No study measured radiographic progression.

- Methotrexate versus placebo (longer than six months): Only one study with a placebo comparator reported outcomes beyond six months. We extracted data only for WAEs and total AEs.
  - For methotrexate, they reported 12WAEs among 31 participants, and for placebo, 0 WAEs among 41. We calculated the RR for WAEs due to methotrexate of 32.81 (95% CI 2.02 to 533.71; Analysis 3.1), an absolute risk difference of 0.39 (95% CI 0.21 to 0.56), and an NNTH of 3 (95% CI 3 to 5). We judged evidence quality to be very low (downgraded due to risk of bias, indirectness, and imprecision).
  - For methotrexate, 17 of 31 participants experienced AEs, and for placebo, 15 of 41 experienced AEs. We calculated the RR for experiencing an AE from methotrexate of 1.50 (95% 0.90 to 2.51) and an absolute risk difference of 0.18 (95% CI -0.05 to 0.41). We did not calculate an NNTH for this statistically non-significant result. We judged evidence quality to be very low (downgraded due to risk of bias, indirectness, and imprecision).
- Methotrexate versus other DMARDs (up to six months): Three studies with another DMARD comparator reported outcomes up to six months. Not all studies reported all outcomes. *Hinweis FBMed: Keine gepoolten Ergebnisse*

Comparison 5. Methotrexate versus other DMARDs - major outcomes ≤ 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Disease response (ACR50)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Leflunomide (ACR50)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Function (HAQ)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Leflunomide	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Serious adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Leflunomide	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Ciclosporin A	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Withdrawals due to adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Leflunomide	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Ciclosporin A	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 6. Methotrexate versus other DMARDs - minor outcomes ≤ 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Disease response (ACR20)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Leflunomide	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Pain	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Leflunomide	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Skin disease	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Leflunomide	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Ciclosporin A	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Leflunomide	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Patient global assessment of disease activity	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 Leflunomide	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Ciclosporin A	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Physician global assessment of disease activity	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 Leflunomide	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Ciclosporin A	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 Swollen joint count	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.1 Leflunomide	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Ciclosporin A	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 Tender joint count	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
8.1 Leflunomide	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Ciclosporin A	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

- Methotrexate versus other DMARDs (longer than six months): We identified two studies for this category. Studies did not report all outcomes. In the case of Burdeinyi 1992, study authors actually collected data for many of our specified outcomes but did not report them in an extractable way. Study authors could not be contacted or were unable to provide additional information. *Hinweis FBMed: Keine gepoolten Ergebnisse.*

Comparison 7. Methotrexate versus other DMARDs - major outcomes > 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Ciclosporin A	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Withdrawals due to adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Ciclosporin A	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Gold	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Sulfasalazine	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 8. Methotrexate versus other DMARDs - minor outcomes > 6 months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Skin disease	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Ciclosporin A	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Total adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Gold	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Sulfasalazine	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Patient global assessment of disease activity	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Ciclosporin A	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Physician global assessment of disease activity	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 Ciclosporin A	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Swollen joint count	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 Ciclosporin A	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Tender joint count	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 Ciclosporin A	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Anmerkung/Fazit der Autoren

Low-quality evidence suggests that low-dose (15 mg or less) oral methotrexate might be slightly more effective than placebo when taken for six months; however we are uncertain if it is more harmful. Effects of methotrexate on health-related quality of life, radiographic progression, enthesitis, dactylitis, and fatigue; its benefits beyond six months; and effects of higher-dose methotrexate have not been measured or reported in a randomised placebo-controlled trial.

3.2 Systematische Reviews

Maese et al., 2021 [14].

Comparative effectiveness of guselkumab in psoriatic arthritis: results from systematic literature review and network meta-analysis

Fragestellung

The efficacy of the novel interleukin (IL)-23p19 inhibitor guselkumab for psoriatic arthritis (PsA) has recently been demonstrated in two phase 3 trials (DISCOVER-1 & -2) but has not been evaluated vs other targeted therapies for PsA. The objective was to compare guselkumab to targeted therapies for PsA for safety and joint and skin efficacy through network meta-analysis (NMA).

Methodik

Population:

- Active psoriatic arthritis
- ≥18 years of ag

Intervention/Komparator:

- Anti-TNFα agents and their biosimilars: adalimumab, etanercept, infliximab, certolizumab, golimumab
- Anti-IL-12/23 agent: ustekinumab
- Anti-IL-23 agents: guselkumab, tildrakizumab, risankizumab
- Anti-IL-17A agents: brodalumab, ixekizumab, secukinumab, bimekizumab
- Anti PDE-4 agent: apremilas
- JAK inhibitor agent: tofacitinib, upadacitinib
- CTLA-4 agent: abatacep
- DMARDs: methotrexate, azathioprine, ciclosporin/ciclosporin A, leflunomide, sulfasalazine, oral/parenteral gold, 6-mercaptopurine, chloroquine, hydroxychloroquine, D-penicillamine, colchicine, etretinate, photochemotherapy/8-methoxypsoralen, somatostatin, bromocriptine, cimetidine, fumaric acid, 2-chlorodeoxyadenosine, parenteral nitrogen mustard, peptide T, radiation synovectomy with yttrium 90, total lymph node irradiatio
- Placebo

Endpunkte:

- No restriction on outcomes
- Outcomes of interest included American College of Rheumatology (ACR) 20/50/70 response, mean change from baseline in van der Heijde-Sharp (vdH-S) score, Psoriasis Area Severity Index (PASI) 75/90/100 response, as well as adverse events (AEs) and serious adverse events (SAEs).

Recherche/Suchzeitraum:

The search covered multiple databases including EMBASE, MEDLINEVR and Cochrane Central on the OVID platform. The original search was conducted in October 2018 and subsequently updated in January 2020 to expand the comparator scope.

Qualitätsbewertung der Studien:

- The National Institute for Health and Care Excellence (NICE) clinical effectiveness quality assessment checklist was used to appraise the validity of included studies

Ergebnisse

Anzahl eingeschlossener Studien:

- 113 citations reporting on 66 trials were included in the qualitative review.
- Of the 66 trials, 26 (62 citations) were included in the quantitative synthesis (i.e. NMA)
- 13 targeted therapies for PsA

Charakteristika der Population:

Supplementary Table S2: Study and patient characteristics of studies included in NMAs

Author, Publication Date	Trial Name	Primary Timepoint (weeks)	Treatment[a]				Sample Size (N)	Mean Age (years)	Male (%)	Race (% Caucasian)	Body Weight (kg)	Duration of PsA (years)	Prior Biologic Use (%)	No. of swollen joints (mean)	No. of tender joints (mean)	BL PASI Score (mean)	PsO BSA >3% (%)	BL HAQ-DI score
			1	2	3	4												
Nash 2018 (44)	ACTIVE	16	PBO	APR 30 mg	NA	NA	219	49.4	43.9	97.7	91.4	3.8	0.0	9.5	17.8	NR	NR	1.2
Mease 2005 (45)	ADEPT	12	PBO	ADA 40 mg	NA	NA	313	48.9	55.6	95.5	85.7	9.5	0.0	14.3	24.9	7.9	NR	1.0
McInnes 2015 (46)	FUTURE 2	24	PBO	SEC 150 mg	SEC 300 mg	NA	298	47.8	NR	94.0	87.6	NR	35.0	11.7	22.6	13.2	47.7	1.2
Nash 2018 (47)	FUTURE 3	24	PBO	SEC 150 mg	SEC 300 mg	NA	414	49.8	45.2	94.7	85.6	7.5	31.9	10.1	21.6	9.8	45.7	1.2
Kivitz 2019 (48)	FUTURE 4	16	PBO	SEC 150mg w/o LD	SEC 150 mg	NA	341	49.1	41.9	99.7	85.1	6.1	27.0	9.7	20.1	NR	50.1	NR
Mease 2018 (49)	FUTURE 5	16	PBO	SEC 150 mg (w/o LD)	SEC 150 mg	SEC 300 mg	996	48.8	50.2	81.9	83.4	6.6	29.6	11.5	21.0	NR	51.6	1.3
Kavanaugh 2009 (50)	GO-REVEAL	14	PBO	GOL 50 mg	NA	NA	259	46.3	61.0	97.0	84.5	7.4	0.0	13.8	23.1	9.2	72.8	1.0
Kavanaugh 2017 (51)	GO-VIBRANT	14	PBO	GOL 2 mg/kg	NA	NA	480	46.2	51.9	99.6	83.6	5.8	0.0	14.1	25.6	10.0	82.0	1.3
Antoni 2005 (52)	IMPACT 2	14	PBO	IFX 5 mg/kg	NA	NA	200	46.8	61.0	94.5	86.2	8.0	0.0	14.2	24.9	10.8	85.0	1.1
Genovese 2007 (53)	NA	12	PBO	ADA 40 mg	NA	NA	100	49.1	54.0	96.0	90.0	7.4	0.0	18.3	27.3	NR	NR	0.9
Gladman 2017 (54)	OPAL-BEYOND	12	PBO	TOF 5 mg	NA	NA	262	49.3	45.0	91.0	85.0	9.5	100.0	11.3	20.2	NR	63.5	1.3
Mease 2017 (55)	OPAL-BROADEN	12	PBO	TOF 5 mg	ADA 40 mg	NA	318	48.2	49.0	98.0	83.0	6.3	0.0	11.4	19.4	NR	76.3	1.1
Kavanaugh 2014 (56)	PALACE 1	16	PBO	APR 30 mg	NA	NA	336	51.3	48.8	90.8	88.5	7.7	24.4	12.8	23.2	9.2	44.7	1.2
Cutolo 2016 (57)	PALACE 2	16	PBO	APR 30 mg	NA	NA	321	50.8	43.9	96.3	83.8	7.3	14.3	9.8	19.9	8.2	NR	1.2
Edwards 2016 (58)	PALACE 3	16	PBO	APR 30 mg	NA	NA	336	49.7	46.5	96.0	84.1	7.1	27.0	11.3	19.6	7.7	55.5	1.2
Wells 2018 (59)	PALACE 4	16	PBO	APR 30 mg	NA	NA	352	49.5	48.3	98.3	84.1	3.5	0.0	11.1	19.6	6.6	57.4	1.1
McInnes 2013 (60)	PSUMMIT 1	24	PBO	UST 45 mg	UST 90 mg	NA	615	47.7	53.7	96.6	88.4	6.6	0.0	13.5	23.5	11.3	71.5	1.2

Author, Publication Date	Trial Name	Primary Timepoint (weeks)	Treatment[a]				Sample Size (N)	Mean Age (years)	Male (%)	Race (% Caucasian)	Body Weight (kg)	Duration of PsA (years)	Prior Biologic Use (%)	No. of swollen joints (mean)	No. of tender joints (mean)	BL PASI Score (mean)	PsO BSA >3% (%)	BL HAQ-DI score
			1	2	3	4												
Ritchlin 2014 **(61)**	PSUMMIT 2	24	PBO	UST 45 mg	UST 90 mg	NA	312	48.3	47.4	98.4	90.3	8.0	57.7	14.2	25.5	12.2	77.2	1.3
Mease 2013 **(62)**	RAPID-PSA	12	PBO	CZP 200 mg	CZP 400 mg	NA	409	47.5	44.7	97.8	84.4	8.5	19.6	10.6	20.3	NR	61.6	1.3
Mease 2017 **(63)**	SPIRIT-P1	24	PBO	IXE 80 Q2W	IXE 80 Q4W	ADA 40 mg	417	49.5	46.0	94.0	85.6	6.7	0.0	11.0	20.1	6.1	69.5	1.2
Nash 2017 **(64)**	SPIRIT-P2	24	PBO	IXE 80 Q2W	IXE 80 Q4W	NA	363	51.9	46.6	92.0	88.7	10.0	100.0	12.3	23.3	5.9	56.0	1.2
Mease 2019 **(16)**	SPIRIT H2H	24	IXE 80mg Q4W/ Q2W	ADA 40mg	NA	NA	566	47.9	55.0	76.5	83.6	6.3	0.0	10.4	20.2	7.8	100	1.3
Mease 2017 **(65)**	ASTRAEA	24	PBO	ABA 125 mg	NA	NA	424	50.4	45.0	92.6	NR	8.5	61.1	11.6	20.2	7.3	69.3	1.3
Mease 2004 **(66)**	NA	24	PBO	ETN 25 mg	NA	NA	205	47.4	50.9	90.5	NR	9.1	0.0	NR	NR	NR	NR	1.1
Janssen 2019 **(42)**	DISCOVER-1*	24	PBO	GUS 100 mg Q8W	GUS 100 mg Q4W	NA	381	48.4	51.2	91.6	86.0	6.7	31.0	9.9	19.2	8.5	65.4	1.2
Janssen 2019 **(41)**	DISCOVER-2*	24	PBO	GUS 100 mg Q8W	GUS 100 mg Q4W	NA	739	45.7	52.5	98.0	84.3	5.5	0.0	12.3	21.3	9.9	73.5	1.3

[a] Some trials include treatments or dose regimens that are not yet approved for administration in all regions. They have been excluded from this table and from primary analyses.
* Data from the manufacturer-provided clinical study reports were extracted at the time of this review.
ABA: abatacept; ADA: adalimumab; APL: apremilast; BIW: twice weekly; BL: baseline; BSA: body surface area; CERT: certolizumab; ETA: etanercept; GOL: golimumab; GUS: guselkumab; HAQ-DI: Health Assessment Questionnaire Disability Index; INF: infliximab; IXE: ixekizumab; LD: loading dose; NA: not available; N: number; PASI: Psoriasis Area and Severity Index; PBO: placebo; PsA: psoriatic arthritis; PsO: psoriasis; Q2W: every two weeks; Q4W: every four weeks; Q8W: every eight weeks; SEC: secukinumab; TOF: tofacitinib; UST: ustekinumab.

Qualität der Studien:

- verall, these assessments found the clinical trials included in NMAs to be of low risk of bias. The allocation concealment, blinding of personnel, and outcome assessment had unclear risk. A high risk of bias was rarely detected in any of the categories for any of the RCTs included in the NMAs

Supplementary Table S3: Risk of bias assessment of studies included in NMAs

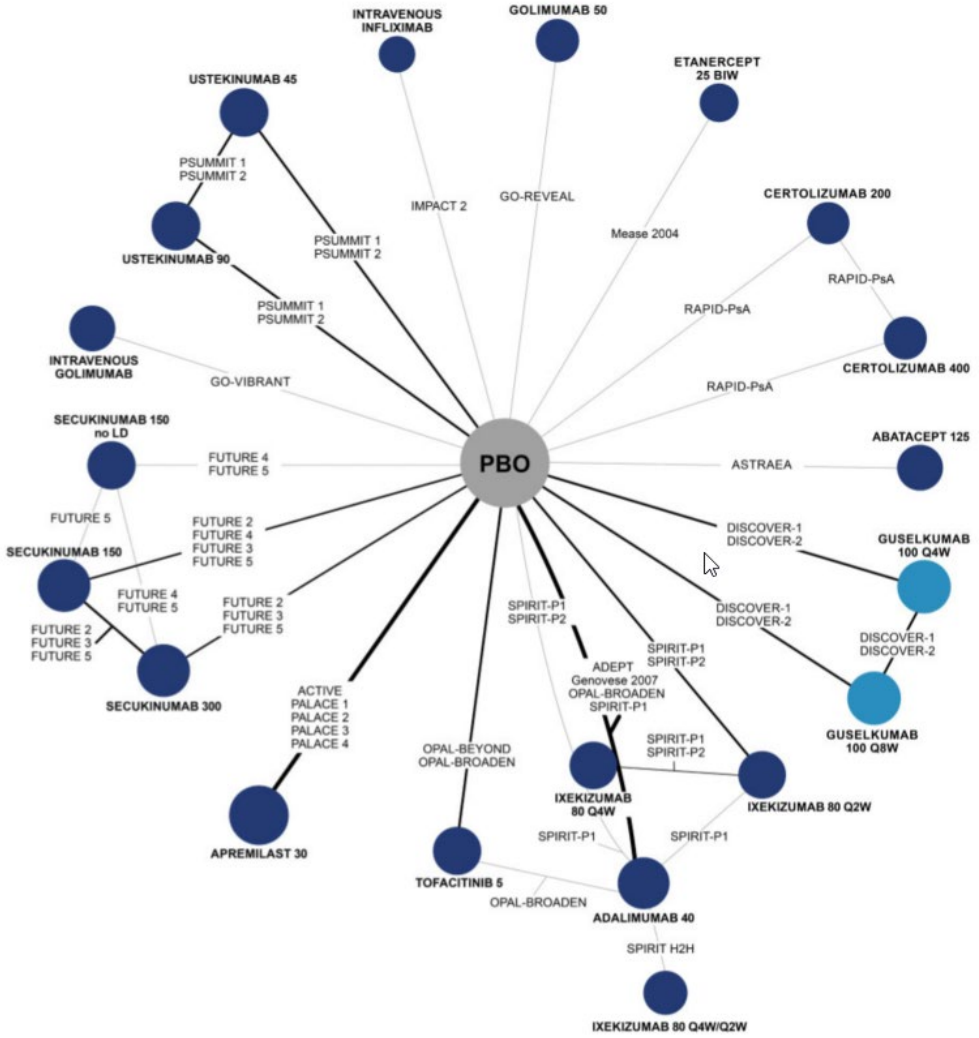
Author, Publication Date	Trial Name	Was randomization carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the participants blind to treatment allocation?	Were the care providers blind to treatment allocation?	Were the outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis?	If so, was this appropriate and were appropriate methods used to account for missing data?
Nash 2018 **(44)**	ACTIVE	Yes	Yes	Yes	Yes	Unclear	Unclear	No	No	Yes	Unclear
Mease 2005 **(45)**	ADEPT	Unclear	Unclear	Yes	Yes	Unclear	Yes	No	No	Yes	Yes
McInnes 2015 **(46)**	FUTURE 2	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Unclear
Nash 2018 **(47)**	FUTURE 3	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No
Kivitz 2019 **(48)**	FUTURE 4	Yes	Yes	Yes	Yes	Yes	Unclear	No	No	Yes	Unclear
Mease 2018 **(49)**	FUTURE 5	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Unclear
Kavanaugh 2009 **(50)**	GO-REVEAL	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Unclear
Kavanaugh 2017 **(51)**	GO-VIBRANT	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Antoni 2005 **(52)**	IMPACT 2	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Genovese 2007 **(53)**	Genovese 2007	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Gladman 2017 **(54)**	OPAL-BEYOND	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Unclear
Mease 2017 **(55)**	OPAL-BROADEN	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Unclear
Kavanaugh 2014 **(56)**	PALACE 1	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Cutolo 2016 **(57)**	PALACE 2	Unclear	Unclear	Yes	Unclear	Yes	Yes	No	No	Yes	Yes
Edwards 2016 **(58)**	PALACE 3	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Wells 2018 **(59)**	PALACE 4	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
McInnes 2013 **(60)**	PSUMMIT 1	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Ritchlin 2014 **(61)**	PSUMMIT 2	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Mease 2013 **(62)**	RAPID-PsA	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Mease 2017 **(63)**	SPIRIT-P1	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Unclear
Nash 2017 **(64)**	SPIRIT-P2	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Unclear
Mease 2019 **(16)**	SPIRIT H2H	Yes	Unclear	Yes	No	No	Yes	No	No	Yes	Unclear
Mease 2017 **(65)**	ASTRAEA	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Unclear
Mease 2004 **(66)**	Mease 2004	Unclear	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes

Note: the DISCOVER-1 and DISCOVER-2 trials have not been included in the risk of bias assessment as they were identified through clinical study reports provided directly by the manufacturer.

Studienergebnisse:

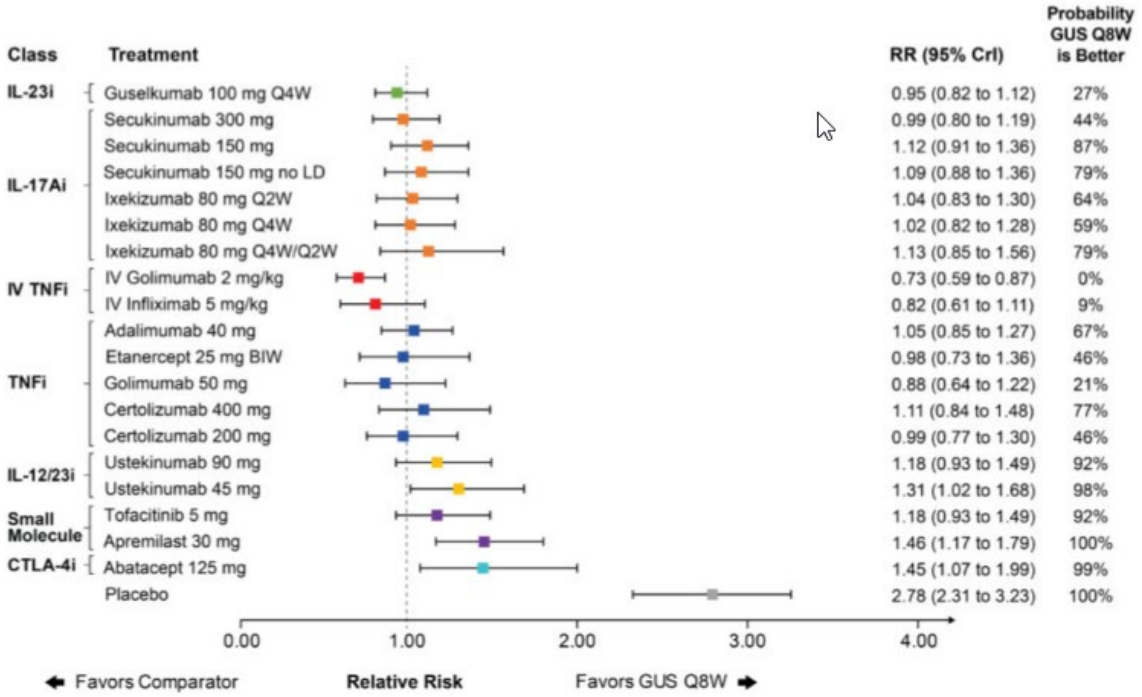
- Network meta-analysis results
  - For ACR 20 response, guselkumab 100mg every 8weeks (Q8W) was comparable to IL-17A inhibitors and subcutaneous tumor necrosis factor (TNF) inhibitors.

FIG. 2 Evidence network for ACR 20



Treatment nodes are sized to reflect the proportionate number of patients randomized to each treatment in the network. Thickness of lines between nodes corresponds to the number of RCTs connecting treatments. BIW: biweekly; LD: loading dose; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks.

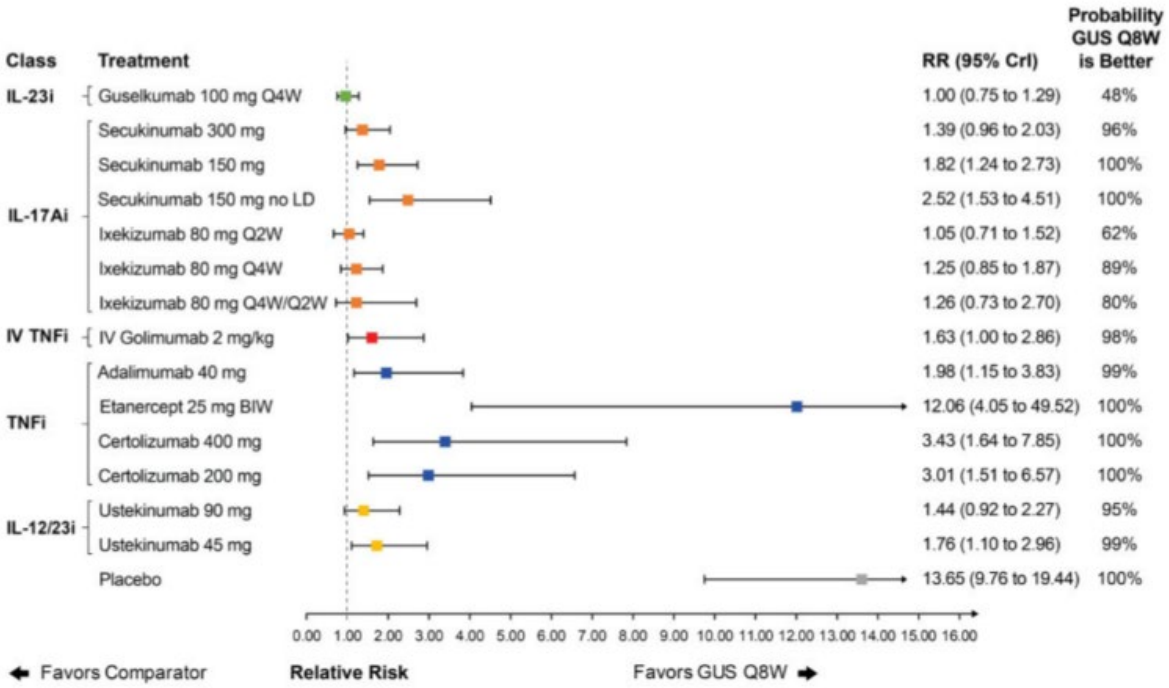
FIG. 3 Forest plot with pairwise comparisons of guselkumab Q8W *vs* all comparators for ACR 20



Comparisons are shown in terms of RRs and 95% CrIs. Treatments are grouped by therapeutic class. The vertical dotted line represents a RR of 1.00. The probability that guselkumab Q8W is better is also shown for each comparator. For the full league table of results, please consult the supplementary appendix, available at *Rheumatology* online. ACR: American College of Rheumatology; BIW: biweekly; CrI: credible interval; CTLA-4i: cytotoxic T-lymphocyte-associated protein 4; GUS: guselkumab; IL-17Ai: interleukin-17A inhibitor; IL-12/23i: interleukin-12/23 inhibitor; IL-23i: interleukin-23 inhibitor; IV: intravenous; LD: loading dose; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; RR: relative risk; TNFi: tumor necrosis factor inhibitor.

- Similar findings were observed for ACR 50 and 70.
- For vdH-S score, guselkumab Q8W was comparable to other agents except intravenous TNF therapies.
- Results for PASI 75 and PASI 90 response suggested guselkumab Q8W was better than most other agents. For PASI 100, guselkumab Q8W was comparable to other active agents.

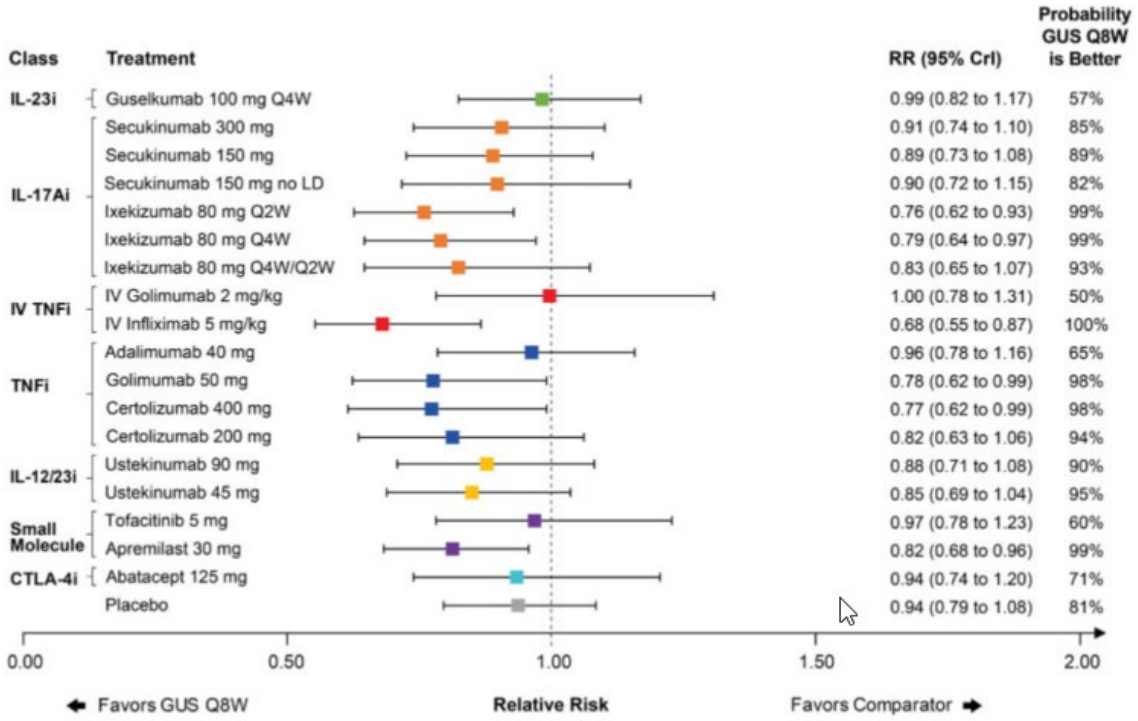
FIG. 5 Forest plot with pairwise comparisons of guselkumab Q8W *vs* all comparators for PASI 90



Comparisons are shown in terms of RRs and 95% CrIs. Treatments are grouped by therapeutic class. The vertical dotted line represents a RR of 1.00. The probability that guselkumab Q8W is better is also shown for each comparator. For the full league table of results, please consult the supplementary appendix, available at *Rheumatology* online. BIW: biweekly; CrI: credible interval; CTLA-4i: cytotoxic T-lymphocyte-associated protein 4; GUS: guselkumab; IL-17Ai: interleukin-17A inhibitor; IL-12/23i: interleukin-12/23 inhibitor; IL-23i: interleukin-23 inhibitor; IV: intravenous; PASI: Psoriasis Area Severity Index; LD: loading dose; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; RR: relative risk; TNFi: tumor necrosis factor inhibitor.

- For AEs and SAEs, guselkumab Q8W ranked highly but comparative conclusions were uncertain.

FIG. 6 Forest plot with pairwise comparisons of guselkumab Q8W *vs* all comparators for AEs



Comparisons are shown in terms of RRs and 95% CrIs. Treatments are grouped by therapeutic class. The vertical dotted line represents a RR of 1.00. The probability that guselkumab Q8W is better is also shown for each comparator. For the full league table of results, please consult the supplementary appendix, available at *Rheumatology* online. AEs: adverse events; CrI: credible interval; CTLA-4i: cytotoxic T-lymphocyte-associated protein 4; GUS: guselkumab; IL-17Ai: interleukin-17A inhibitor; IL-12/23i: interleukin-12/23 inhibitor; IL-23i: interleukin-23 inhibitor; IV: intravenous; LD: loading dose; Q2W: every 2 weeks; Q4W: every 4 weeks: Q8W: every 8 weeks; RR: relative risk; TNFi: tumor necrosis factor inhibitor.

Anmerkung/Fazit der Autoren

In conclusion, analyses suggest that guselkumab has joint efficacy (i.e. ACR and vdH-S score) comparable to IL-17A and subcutneous TNF inhibitors while offering particularly robust efficacy on skin manifestations through the placebo-controlled trial period. Guselkumab ranked highly in analyses of AEs and SAEs, but rarity of events led to significant uncertainty in pairwise comparisons. Overall, guselkumab offers favorable outcomes for patients with PsA by improving both rheumatological and dermatological outcomes coupled with a favorable safety profile.

Kommentare zum Review

- Funding: This work was supported by Janssen Research and Development.

Campanaro et al., 2021 [1].

JAK inhibitors and psoriatic arthritis: A systematic review and meta-analysis

Fragestellung

The aim of our systematic review was to evaluate the efficacy and safety of JAKinhibs for the treatment of patients affected by PsA, in comparison with conventional therapy.

Methodik

Population:

- PsA

Intervention:

- JAKinhibs

Komparator:

- compared to placebo in addition to the standard of care

Endpunkte:

- Efficacy:
  - primary efficacy outcome was the number of patients who achieved the response rate of the American College of Rheumatology 20 score (ACR20)
  - 1) ACR50; 2) ACR70; 3) minimal disease activity (MDA); 4) Psoriasis Area and Severity Index 75 (PASI75); 5) resolution of enthesitis according to the Leeds Enthesitis Index (LEI); 6) resolution of dactylitis according to the Leeds Dactylitis Index (LDI) or the Dactylitis Severity Score (DSS); 7) change from baseline of Health Assessment Questionnaire Disability Index (HAQ-DI); 8) change from baseline of Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F).
- Safety
  - The primary safety outcome was the number of patients who had serious adverse events (SAEs).

Recherche/Suchzeitraum:

- MEDLINE and the EMBASE (up to April 10th, 2021)

Qualitätsbewertung der Studien:

- Cochrane criteria

Ergebnisse

Anzahl eingeschlossener Studien:

- Five RCTs were finally included after the selection process, for a total of 3293 PsA patients

In summary, two were phase III studies on Tofacitinib (OPAL Beyond and OPAL Broaden), one was a phase II study on Filgotinib (EQUATOR) and two were phase III studies on **Upadacitinib (SELECT PsA1 and SELECT PsA2)**.

Charakteristika der Population:

Table 1
Characteristics of patients at baseline: plus–minus values are means ±SD.

	Equator		OPAL Beyond		OPAL Broaden		SELECT-PsA 1		SELECT-PsA 2	
	Filgotinib 200 mg	Placebo	Tofacitinib 5 mg	Placebo	Tofacitinib 5 mg	Placebo	Upadacitinib 15 mg	Placebo	Upadacitinib 15	Placebo
Number of patients	65	66	131	131	107	105	429	423	211	212
Mean age	49.0 ± 12.2	50 ± 10.9	49.5 ± 12.2	49.0 ± 12.6	49.4 ± 12,6	47.7 ± 12.3	51.6 ± 12.2	50.4 ± 12.2	53 ± 12	54.1 ± 11.5
Gender (W/M)	36/29	30/36	64/67	80/51	57/50	56/49	238/191	211/212	113/98	120/92
Mean duration of PsA, (years)	7 ± 6.7	7 ± 6.2	9.6 ± 7.6	9.4 ± 8.1	7.3 ± 8.2	6.4 ± 6.4	6.2 ± 7.4	6.2 ± 7.0	9.6 ± 8.4	11.0 ± 10.3
Swollen-joint count	11.6 ± 5.1	12.7 ± 6.7	12.1 ± 10.6	10.5 ± 9.0	12.9 ± 9.9	11.5 ± 8.8	11.6 ± 9.3	11.0 ± 8.2	11.3 ± 8.2	12.0 ± 8.9
Tender-joint count	18.3 ± 9.2	21.6 ± 13.2	20.5 ± 13.0	19.8 ± 14.9	20.5 ± 12.6	20.6 ± 14.4	20.4 ± 14.7	20.0 ± 14.3	24.9 ± 17.3	25.3 ± 17.6
Mean CRP (mg/L)	13.91 ± 9.8	10.9 ± 17.2	5.7 (0.2–126.0)	4.4 (0.2–164.0)	4.8 (0.2–115.0)	5.0 (0.2–113.0)	Not Reported	Not Reported	11.2 ± 18.5	10.4 ± 18.5
Affected body-surface area ≥ 3%	65%	61%	61%	66%	77%	78%	49.9%	49.9%	61.6%	61.8%
HAQ-DI score	1.43 ± 0.5	1.36 ± 0.6	1.3 ± 0.7	1.3 ± 0.8	1.2 ± 0.6	1.1 ± 0.6	1.2 ± 0.7	1.1 ± 0.6	1.10 ± 0.6	1.23 ± 0.7
Presence of Enthesitis	58%	74%	63%	71%	70%	62%	62.9%	57%	63%	67.9%
Presence of Dactilitys	nr	nr	50%	48%	57%	55%	31.7%	29.8%	26.1%	30.2%
Oral glucocorticoid use on day 1	26%	24%	28%	24%	27%	17%	17%	16.5%	10.4%	11.3%
Concomitant use of CsDMARDs	72%	76%	100%	100%	100%	100%	82.3%	82%	46.4%	47.2%
Concomitant use of Methotrexate	63%	65%	75%	77%	85%	88%	69.7%	69.2%	37.9%	38.7%
Previous use of any bDMARDs	17%	14%	100%	100%	3%	3%	0%	0%	100%	100%

Legend: PsA Psoriatic Arthritis, CRP C-reactive protein, HAQ Health assessment questionnaire, CsDMARDs conventional synthetic disease modifying antirheumatic drugs, bDMARDs biologic disease modifying antirheumatic drugs.

Qualität der Studien:

- All five studies were judged at low risk of bias according to Cochrane criteria (Fig. 2)
- funnel plot analysis does not suggest the presence of publication bias

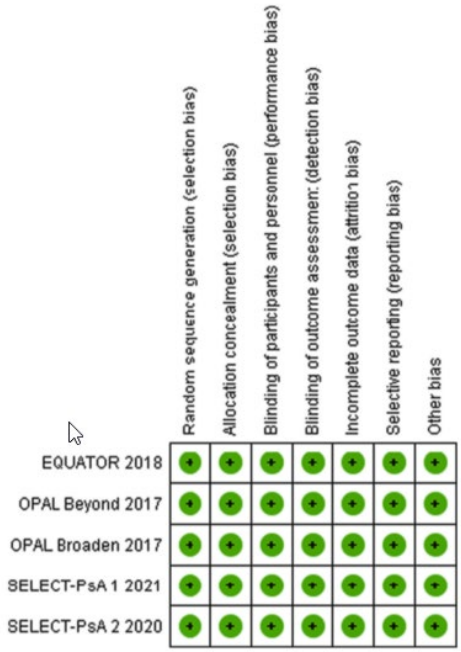


Fig. 2. Risk of bias table.

Studienergebnisse:

- efficacy for arthritis
  - JAKinhibs was significantly associated with a higher response rate compared to placebo (OR 3.78, 95% CI 2.72–5.24, I^2 = 57%, random effect model), as measured by the primary outcome ACR20 (Fig. 3). Among secondary efficacy outcomes,

JAKinhibs also showed a significantly higher ACR50 response rate (OR 4.31, 95% CI 2.89–6.43, I^2 = 52%, random effect model), ACR70 response rate (OR 4.65, 95% CI 2.26–9.57, I^2 = 62%, random effect model) and MDA (OR 4.10, 95% CI 2.34–7.18, I^2 = 68%, random effect model), compared to placebo.

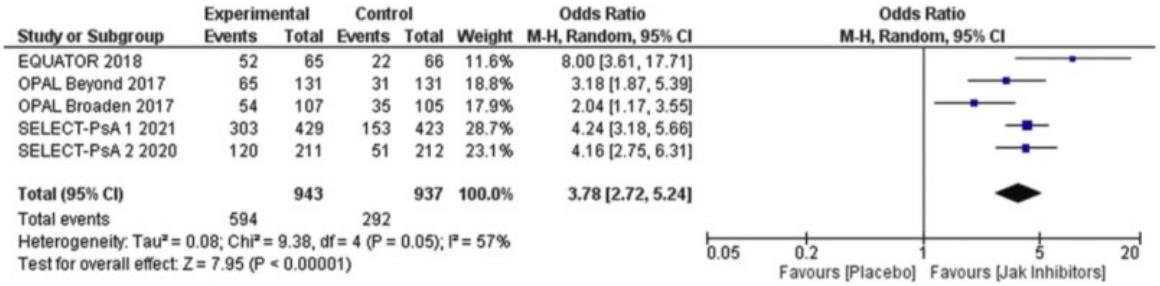


Fig. 3. ACR20 response Filgotinib 200 mg - Tofacitinib 5 mg - Upadacitinib 15 mg.

- Efficacy for other clinical outcomes (cutaneous and entheseal involvement, dactylitis)
  - PASI75 response rate was evaluated only in patients who present at study entry at least 3% of their body surface area affected by psoriasis in all the studies. JAKinhibs showed a higher PASI75 response rate compared to placebo (OR 4.41, 95% CI 2.84–6.84, I^2 = 52%, random effect model) (Fig. 4). […]

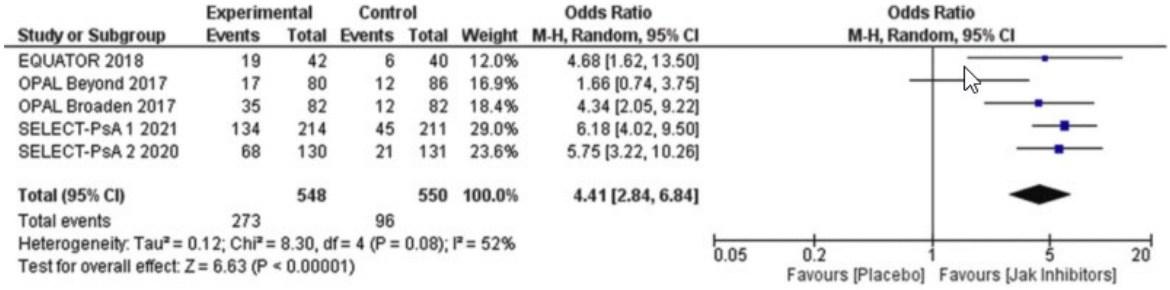


Fig. 4. PASI75 response Filgotinib 200 mg - Tofacitinib 5 mg - Upadacitinib 15 mg.

- Efficacy in patients reported outcomes
  - JAKinhibs were associated with a statistically significant improvement in HAQ-DI (mean difference − 0.25 95% CI -0.29 - -0.20, I^2 = 0%, fixed effect model) and fatigue measured by FACIT-F (mean difference 3.56 95% CI 2.74–4.38, I^2 = 0%, fixed effect model), as compared to placebo.
- Safety outcomes
  - JAKinhibs was associated with a non-statistically significant different risk of SAEs as compared to placebo (OR 1.12, 95% CI 0.14–2.82, I^2 = 46%, random effect model) (Fig. 5). […]

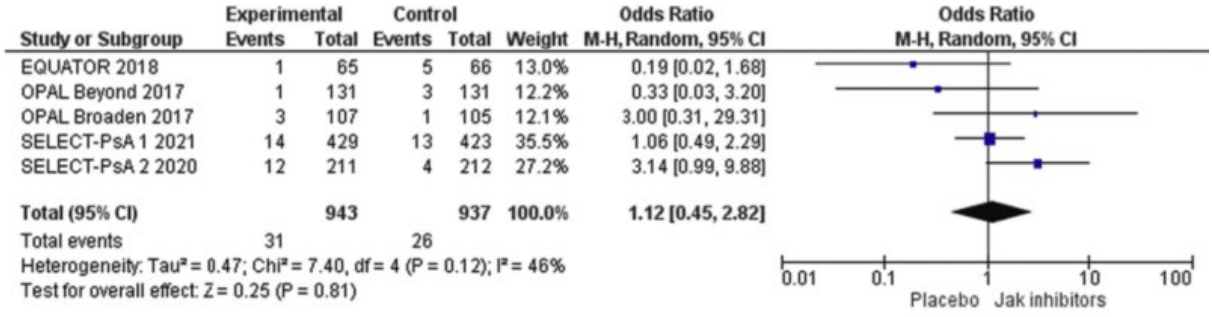


Fig. 5. Serious adverse events Filgotinib 200 mg - Tofacitinib 5 mg - Upadacitinib 15 mg.

Anmerkung/Fazit der Autoren

In conclusion, waiting for long-term safety data and head to head comparative RCTs with bDMARDs, our systematic review and metaanalysis found a statistically significant benefit of JAKinhibs for the treatment of PsA as compared to placebo, in addition to standard of care.

Gao et al., 2021 [7].

Efficacy and safety of IL-17 inhibitors for patients with psoriatic arthritis: a systematic review and meta-analysis

Fragestellung

The efficacy and safety of IL-17 inhibitors for patients with Psoriatic arthritis (PsA) is still a controversial issue. To estimate the efficacy and safety of IL-17 inhibitors in the treatment of PsA, we conducted this systematic review and meta-analysis.

Methodik

Population:

- participants aged 18 years old or older with PsA

Intervention:

- IL-17 inhibitors

Komparator:

- placebo or other active treatments

Endpunkte:

- ACR20, ACR50, ACR70, PASI70, PASI 90 and/ or drug-related adverse events (including serious adverse events, infection, respiratory tract infection, any candida infections, urinary tract infection, hepatic events, allergic reactions or hypersensitivities, injection site reactions, nasopharyngitis, headache, diarrhea, and inflammatory bowel disease)

Recherche/Suchzeitraum:

- MEDLINE (from their earliest records to September 2020), EMBASE (from their earliest records to September 2020), and the Cochrane Library database (from their earliest records to September 2020).

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 studies with 5327 patients

Charakteristika der Population:

Table I. Baseline characteristics of patients in meta-analysis.

	Phase	Age (years)	Male (%)	Weight (kg)	Interventions	Controls	No.of patients	MTX use, %	TNF-α naïve, %	Study Primary outcomes	Secondary outcomes
BE ACTIVE2020	IIb	49.3 ± 12.4	60.0	85.7 ± 18.5	Bimekizuma	Placebo	206	63.6	NA	ACR at week 12	PASI
EXCEED 2020	III	49.0 ± 12.4	51.2	83.8 ± 18.7	Secukinumab	Adalimumab	853	NA	NA	ACR at week 52	PASI
FUTURE 1 2015	III	49 ± 11.7	45.54	82.9 ± 20.5	Secukinumab	Placebo	606	60.7	70.6	ACR at week 24	PASI
FUTURE 2 2015	III	47.9 ± 12.1	46.6	87.1 ± 19.7	Secukinumab	Placebo	397	46.6	65.0	ACR at week 24	PASI
FUTURE 3 2018	III	49.8 ± 12.4	45.2	85.6 ± 19.4	Secukinumab	Placebo	414	47.6	68.1	ACR at week 24	PASI
FUTURE 4 2019	III	49 ± 12.1	41.9	85.1 ± 20.3	Secukinumab	Placebo	341	49.9	76.3	ACR at week 16	PASI
FUTURE 5 2018	III	48.6 ±12.4	50.2	83.4 ± 19.3	Secukinumab	Placebo	996	50.1	70.4	ACR at week 16	PASI
Mease et al.2014	II	52.7 ± 12.4	36.3	90.7 ± 21.3	Brodalumab	Placebo	168	50.0	NA	ACR at week 12	PASI
SPIRIT-P1 2017	III	49.5 ± 11.9	46.0	85.6 ± 20.9	Ixekizumab	Placebo; Adalimumab	417	14.6	54.2	ACR at week 24	PASI
SPIRIT-P2 2017	III	51.9 ± 12.1	46.6	88.6 ± 21.7	Ixekizumab	Placebo	363	NA	41.1	ACR at week 24	PASI
SPIRIT-H2H 2020	IIIb/IV	47.9 ± 12.1	55.1	83.6 ± 19.1	Ixekizumab	Adalimumab	566	NA	59.4	ACR at week 12	NA

- TNF, tumor necrosis factor; MTX, Methotrexate; ACR, American College of Rheumatology; PASI, Psoriasis Area Severity Index; NA, not available.

Qualität der Studien:

- the inherent risks of bias of trials were generally low.
- Statistical testing showed no evidence of publication bias for ACR20 (Begg's test z = 1.58, p = 0.12)

Table III. Inherent risk of bias of included trials.

Trial	Sequence generation	Allocation concealment	Blinding			Incomplete outcome data	Selective outcome reporting	Other source of bias
			Participants	Personnel	Outcome assessors			
BE ACTIVE2020	LOW	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
EXCEED 2020	LOW	LOW	LOW	LOW	LOW	HIHGH	LOW	UNCLEAR
FUTURE 1 2015	LOW	UNCLEAR	LOW	LOW	UNCLEAR	HIGH	UNCLEAR	UNCLEAR
FUTURE 2 2015	LOW	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
FUTURE 3 2018	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW	UNCLEAR
FUTURE 4 2019	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW	UNCLEAR
FUTURE 5 2018	LOW	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
Mease 2014	LOW	UNCLEAR	LOW	LOW	LOW	HIGH	LOW	UNCLEAR
SPIRIT-P1 2017	LOW	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
SPIRIT-P2 2017	LOW	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
SPIRIT-H2H 2020	LOW	LOW	HIGH	HIGH	LOW	LOW	LOW	UNCLEAR

- Assessment of risk bias according to the Cochrane collaboration tool, low risk of bias was represented as "LOW" and high risk was "HIGH".

Studienergebnisse:

- Primary outcomes included the response rates of ACR20, ACR50 and ACR70
  - Our results showed that IL-17 inhibitors were 1.29 times more likely to achieve an ACR20 response (RR 1.29, 95% CI 1.22 to 1.37, p < 0.0001; I2= 93.5%, Figure 2A), 1.44 times for ACR50 response (RR 1.44, 95% CI 1.31 to 1.58, p < 0.0001; I2= 91.6%, Figure 2B) and 1.28 times for ACR70 response (RR 1.28, 95% CI 1.11 to 1.49, p < 0.0001; I2 = 48.4%, Figure 2C) compared with the control group.
  - Compared with TNF inhibitor adalimumab, IL-17 inhibitors did not show the above advantages in ACR20 (RR 1.02, 95% CI 0.95 to 1.09, p = 0.55, Figure 3) and ACR50 (RR 1.09, 95% CI 0.99 to 1.21, p = 0.09, Figure 4) responses, but they were associated with a higher response rate of ACR70 (RR 1.20, 95% CI 1.03 to 1.39, p = 0.02, Figure 5).

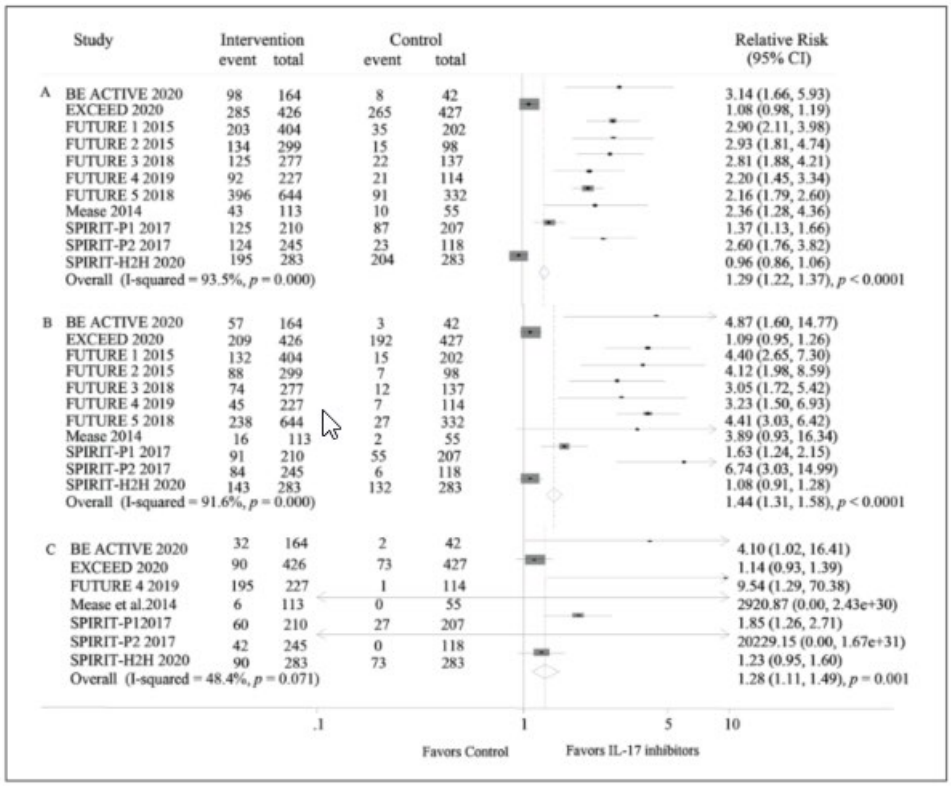


Figure 2. Effects of IL-17 inhibitors compared with placebo or other active control for the responses of ACR20 **(A)**, ACR50 **(B)** and ACR70 **(C)** in patients with psoriatic arthritis.

- Adverse events

Table II. Adverse events reported in the included studies.

Adverse events	Studies reporting	Intervention (n/n)	Control (n/n)	RR (95% CI)	*p* value
Any adverse event	6	1043/1683	650/961	0.98 (0.93,1.04)	0.56
Serious adverse events	8	77/2205	58/1142	0.72 (0.50,1.03)	0.07
Infection	7	734/2241	486/1377	1.05 (0.96,1.15)	0.26
Respiratory tract infection	8	218/2525	131/1380	0.95 (0.77,1.17)	0.61
Any Candida infections	8	53/2883	13/1748	1.99 (1.004,3.81)	**0.04**
Urinary tract infection	4	46/1485	17/685	1.20 (0.69,2.09)	0.52
Hepatic events	3	43/829	23/367	0.80 (0.43,1.32)	0.38
Allergic reactions or hypersensitivities	4	77/1374	80/1035	0.72 (0.52,0.99)	**0.045**
Injection site reactions	6	210/2153	79/1422	1.57 (1.16,2.14)	**0.004**
Nasopharyngitis	7	186/2184	315/1244	1.02 (0.82,1.26)	0.87
Headache	8	136/2848	72/1576	1.13 (0.85,1.50)	0.41
Diarrhea	7	100/2444	73/1374	0.84 (0.62,1.14)	0.27
Inflammatory bowel disease	5	7/2024	0/1322	3.54 (0.62,20,09)	0.15

Anmerkung/Fazit der Autoren

This study provides a clear proof of beneficial effects of IL-17 inhibitors in improving joint disease activity in patients with PsA with an acceptable safety profile. In the presence of relevant skin involvement, IL-17 inhibitors would be preferred over a TNF-α inhibitor adalimumab. More trials that compared IL-17 inhibitors with TNF-α inhibitors are needed to build more evidence for recommending these agents as first-line biologic treatment of active PsA

Garcia-Leal M et al., 2021[8].

Does current evidence on disease-modifying antirheumatic drugs for psoriatic arthritis reinforce an effect on radiographic progression? Results from a systematic review and meta-analysis

Fragestellung

This study aims to estimate the effect of synthetic and biologic disease-modifying antirheumatic drugs (DMARDs) on radiographic progression and quality of life in adult patients with psoriatic arthritis.

Methodik

Population:

- adult patients (≥ 18 years) diagnosed with psoriatic arthritis (as established by the CASPAR criteria)

Intervention:

- synthetic and/or biologic diseasemodifying antirheumatic drugs (DMARDs)

Komparator:

- any different active treatment or placebo

Endpunkte:

- radiographic progression
- quality of life

Recherche/Suchzeitraum:

- MEDLINE, Embase, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials (CCRCT), from each database's inception to May 15, 2020.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool for randomized trials 2.0 (RoB 2.0)

Ergebnisse

Anzahl eingeschlossener Studien:

- 16 trials, comprising 6,833 patients,

Charakteristika der Population:

Table 1 Characteristics of included studies

Author (year)	Acronym	Intervention	Posology	Patients (n)	Age, mean (SD)	% Female	PsA duration, years, mean (SD)	% Baseline MTX use	% Baseline GC use
				Total					
				DMARD	DMARD	DMARD	DMARD	DMARD	DMARD
				Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Mease (2004)	No acronym			205					
		Etanercept	25 mg 2×/week	101	47.6 (ND)	47	9.0 (ND)	42	19
				104	47.3 (ND)	55	9.2 (ND)	41	15
Mease (2005)	ADEPT			315					
		Adalimumab	40 mg/2 weeks	153	48.6 (12.5)	43.7	9.8 (8.3)	51	ND
				162	49.2 (11.1)	45.1	9.2 (8.7)	50	ND
Antoni (2005)	IMPACT 1			104					
		Infliximab	5 mg/kg/8 weeks	52	45.7 (11.1)	42.3	11.7 (9.8)	ND	ND
				52	45.2 (9.7)	42.3	11.0 (6.6)	ND	ND
Antoni (2005)	IMPACT 2			200					
		Infliximab	5 mg/kg/8 weeks	100	47.1 (12.8)	29	8.4 (7.2)	47	15
				100	46.5 (11.3)	49	7.5 (7.8)	45	10
Fraser (2005)	No acronym			72					
		CSA + MTX	2.5 to 4 mg/kg daily	38	46.8 (11.5)	71	3.4 (2.8)	100	5
		MTX		34	47.1 (10.8)	56	3.5 (3.5)	100	0
Kavanaugh (2009)	GO REVEAL			405					
		Golimumab	50 mg/4 weeks	146	45.7 (10.7)	39	7.2 (6.8)	49	13
			100 mg/4 weeks	146	48.2 (10.9)	41	7.7 (7.8)	47	18
			Combined	292					
				113	47.0 (10.6)	39	7.6 (7.9)	48	17
McInnes (2013)	PSUMMIT 1			615					
		Ustekinumab	45 mg/12 weeks	205	48.0 (39.0–55.0)[a]	48.3	3.4 (1.2–9.2)[a]	48	18
			90 mg/12 weeks	204	47.0 (38.5–54.0)[a]	43.1	4.9 (1.7–8.3)[a]	50	14
			Combined	409					
				206	48.0 (38.5–56.0)[a]	47.6	3.6 (1.0–9.7)[a]	47	16
Ritchlin (2014)	PSUMMIT 2			312					
		Ustekinumab	45 mg/12 weeks	103	49.0 (40.0–56.0)[a]	53.4	5.3 (2.3–12.2)[a]	52	20
			90 mg/12 weeks	105	48.0 (41.0–57.0)[a]	53.3	4.5 (1.7–10.3)[a]	50	15
			Combined	208					
				104	48.0 (38.5–56.0)[a]	51	5.5 (2.3–12.2)[a]	47	13

Table 1 (continued)

Author (year)	Acronym	Intervention	Posology	Patients (n)	Age, mean (SD)	% Female	PsA duration, years, mean (SD)	% Baseline MTX use	% Baseline GC use
Mease (2014)	RAPID-PSA			409					
		Certolizumab Pegol	200 mg/2 weeks	138	48.2 (12.3)	53.6	9.6 (8.5)	64	ND
			400 mg/4 weeks	135	47.1 (10.8)	54.1	8.1 (8.3)	65	ND
			Combined	273					
				136	47.3 (11.1)	58.1	7.9 (7.7)	62	ND
Mease (2015)	FUTURE 1			606					
		Secukinumab	150 mg/4 weeks	202	49.6 (11.8)	52.5	ND	60	17
			75 mg/4 weeks	202	48.8 (12.2)	58.4	ND	60	17
			Combined	404					
				202	48.5 (11.2)	52.5	ND	62	13
Kavanaugh (2017)	GO-VIBRANT			480					
		Golimumab	2 mg/kg/8 weeks	241	45.7 (11.3)	46.9	6.2 (6.0)	68	27
				239	46.7 (12.5)	49.4	5.3 (5.9)	73	28
Mease (2017)	SPIRIT P1			417					
		Ixekizumab	80 mg/2 weeks	107	49.8 (12.6)	53.4	7.2 (8.0)	56	ND
			80 mg/4 weeks	103	49.1 (10.1)	57.9	6.2 (6.4)	52	ND
			Combined	210					
		Adalimumab	40 mg/2 weeks	101	48.6 (12.4)	49.5	6.9 (7.5)	53	ND
				106	50.6 (12.3)	54.7	6.3 (6.9)	56	ND
Mease (2017)	OPAL			422					
		Tofacitinib	5 mg 2×/week	107	49.4 (12.6)	53	7.3 (8.2)	85	27
			10 mg 2×/week	104	46.9 (12.4)	60	5.4 (5.8)	88	11
			Combined	211					
		Adalimumab	40 mg/2 weeks	106	47.4 (11.3)	47	5.3 (5.3)	75	22
				105	47.7 (12.3)	53	6.4 (6.4)	88	17
Mease (2017)	ASTRAEA			424					
		Abatacept	125 mg/week	213	51.0 (10.7)	56.8	8.3 (8.1)	61	26
				211	49.8 (11.3)	53.1	8.8 (8.3)	60	24
Mease (2018)	FUTURE 5			996					
		Secukinumab	300 mg with LD/4 weeks	222	48.9 (12.8)	51.4	6.7 (8.3)	51	15
			150 mg with LD/4 weeks	220	48.4 (12.9)	49.5	6.7 (7.1)	49	20
			150 mg without LD/4 weeks	222	48.8 (11.8)	45.9	6.2 (6.1)	54	17
			Combined	664					
				332	49.0 (12.1)	51.5	6.6 (7.6)	48	16
Mease (2019)	SEAM-PSA			851					
		MTX	20 mg/week	284	48.7 (13.1)	56.3	3.6 (6.8)	100	ND
		Etanercept	50 mg/week	284	48.5 (13.5)	46.8	3.1 (6.0)	0	ND
		MTX + etanercept	20 mg MTX/week + 50 mg etanercept/-week	283	48.1 (12.7)	49.1	3.0 (6.0)	100	ND

All studies used a modified total Sharp score, except ‡ that used the Larsen score

CSA, ciclosporin; *GC*, glucocorticoid; *MTX*, methotrexate; *LD*, loading dose; *DMARD*, disease-modifying antirheumatic drug; *SD*, standard deviation; *ND*, no data; *PsA*, psoriatic arthritis

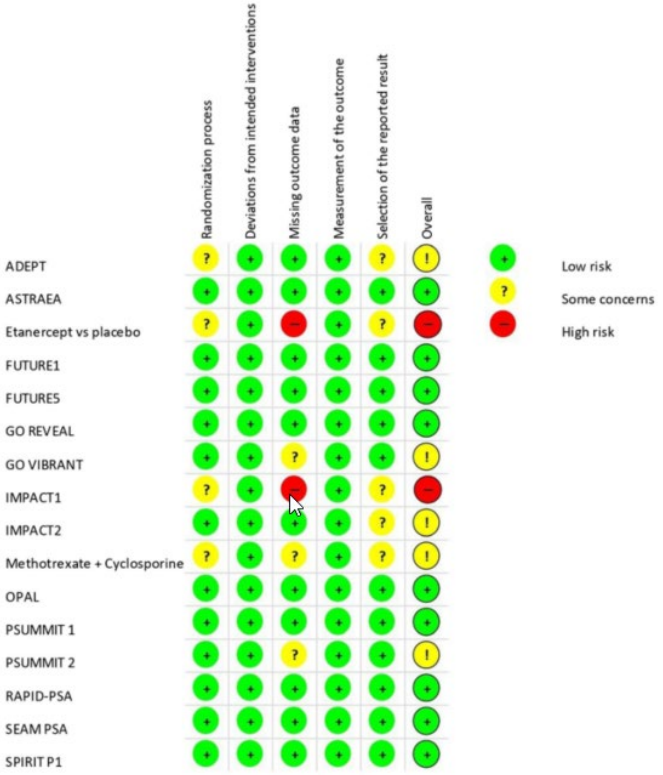
[a] Median (interquartile range)

[b] Data at 48 weeks

[c] Data at 50 weeks

Qualität der Studien:

- Overall risk of bias was rated as moderate, with nine studies considered at low risk [25, 26, 28, 31, 32, 34, 35, 38], five with some concerns [24, 30, 33, 36, 37], and two at high risk [23, 29].



Studienergebnisse:

- In adult patients with psoriatic arthritis, exposure to a biologic agent (regardless of bDMARD class) significantly reduced the radiographic progression of the disease (MD: − 0.66; [95% CI − 0.97 to − 0.34]; P < .00001; I2 = 100%) (Fig. 3) as measured by the van der Heijde-modified total Sharp score (vdH-mTSS)

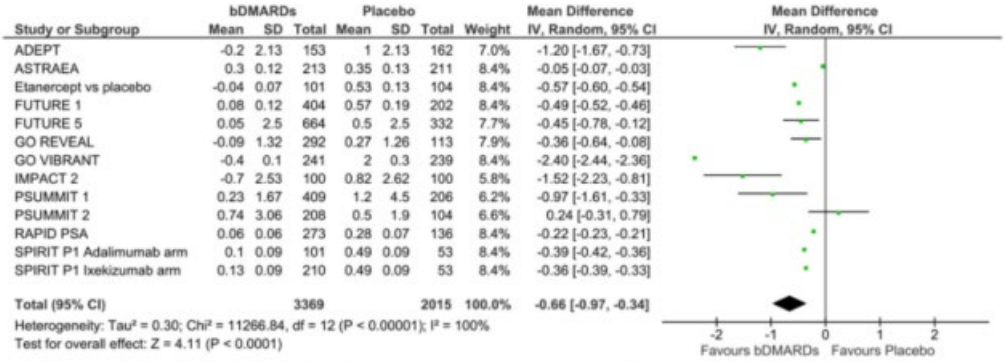


Fig. 3 Mean difference and 95% CIs for the effect of bDMARDs on radiographic progression at 24 weeks of treatment. IV, inverse variance

- Also, improvement in health-related quality of life, reported with the HAQ-DI score was shown in an analysis of twelve studies that measured this outcome (MD: − 0.21; [95% CI − 0.25 to − 0.18]; P <.00001; I2 =97%) (Fig. 4).

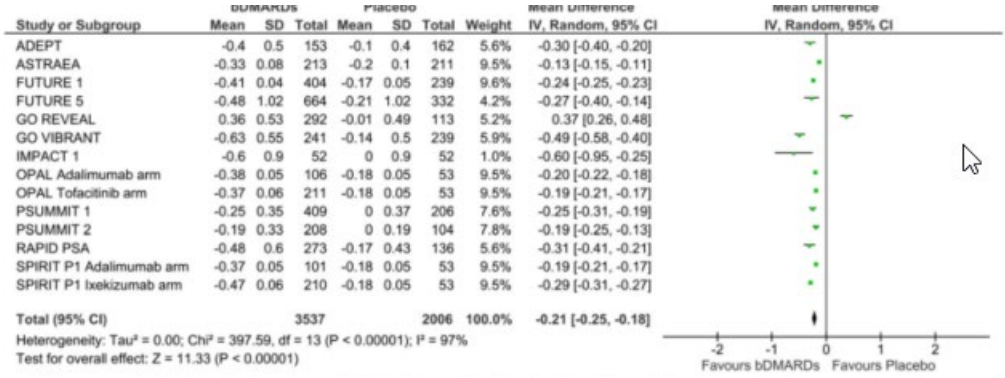


Fig. 4 Mean difference and 95% CIs for the effect of bDMARDs on health-related quality of life at 24 weeks of treatment. IV, inverse variance

- Two trials evaluated radiographic outcomes with csDMARDs. According to one of these studies, the addition of cyclosporine (CSA) to methotrexate (MTX) does not reduce radiographic progression as compared to MTX alone. Similarly, another trial reported significantly less radiological damage with etanercept monotherapy compared to MTX alone (P =0.014).

Anmerkung/Fazit der Autoren

In conclusion, the results of this systematic review and meta-analysis of RCTs suggest a better control of radiological damage with bDMARDs, as compared to placebo, after 24 weeks of treatment. However, the true intervention effect is exceedingly different in the currently best available evidence, in a manner that it cannot be determined with confidence. Further research is required to assess long-term outcomes and to control the heterogeneity between studies by including radiographic progression as a primary outcome in the evaluation of treatments for psoriatic arthritis.

Kommentare zum Review

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Wu et al., 2020 [25]

Xie Y et al., 2021 [27].

Are biologics combined with methotrexate better than biologics monotherapy in psoriasis and psoriatic arthritis: A meta-analysis of randomized controlled trials

Fragestellung

In this meta-analysis, we compared the clinical efficiency and safety profile of biologics plus MTX with biologic monotherapy systemically, trying to elucidate whether biologics plus MTX performs better than biologic monotherapy.

Methodik

Population:

- adult patients (≥18 years old) with psoriasis or PsA

Intervention/Komparator:

- biologics monotherapy or combined with MTX

Endpunkte:

- To assess the efficiency of treatment, Psoriasis Area and Severity Index (PASI) responses (including PASI 50, 75, and 90), and proportion of patients with Physician's Global Assessment Scale (sPGA) scored 0 or 1, were used for psoriasis assessment. The American College of Rheumatology (ACR) 20/50/70 responder indices were used to assess the efficiency for PsA. As for the safety assessment, data related to adverse effects were extracted

Recherche/Suchzeitraum:

- Pubmed, EMBASE, and the Cochrane Library databases was performed from conception through 5 November 2020

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Methods

Ergebnisse

Anzahl eingeschlossener Studien:

- 15 studies13-27 with a total of 4221 patients met the inclusion criteria

Charakteristika der Population:

- 10 studies used TNF inhibitors (4 for etanercept, 3 for adalimumab, and each of the rest 3 for infliximab, golimumab, and Yisaipu, respectively), while four studies used IL-17A inhibitors (3 for ixekizumab and one for secukinumab). Only two studies examined IL-12/23 inhibitors (ustekinumab)

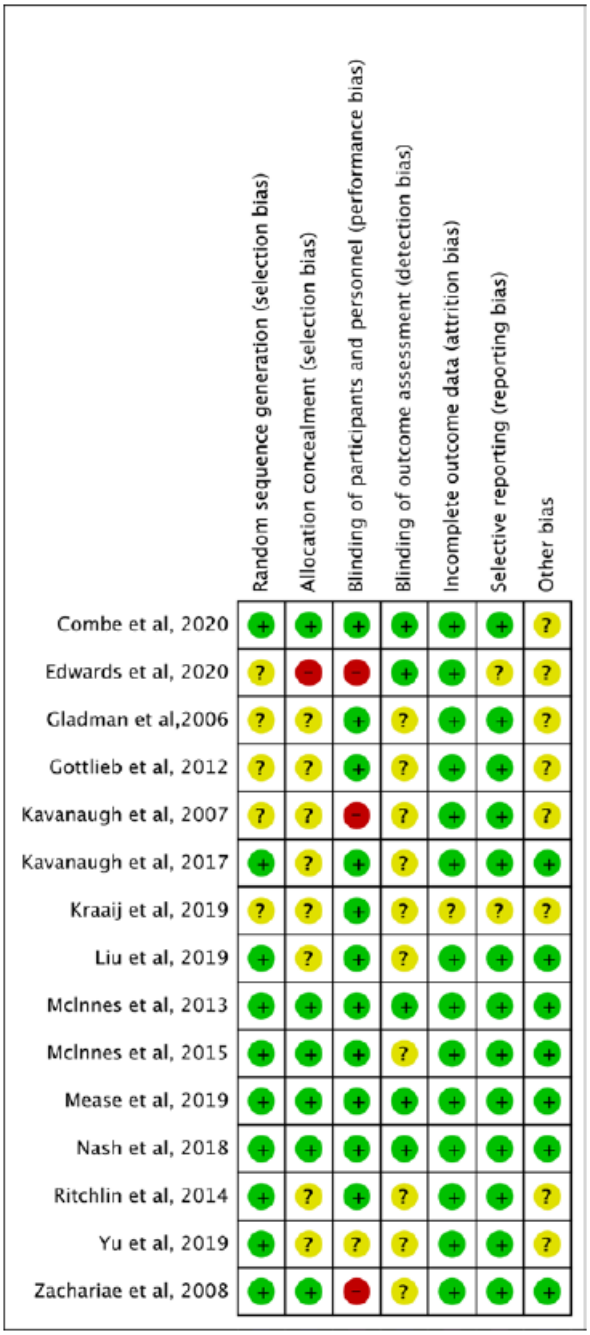
TABLE 1 Characteristics of included studies

References	Country	Age (mean ± SD, years)	Gender (male/female)	Name of biologics	No. of participants	
					Biologics + MTX	Biologics
Combe et al[13]	France	/	/	Ixekizumab	183	193
Edwards et al[14]	Switzerland	48.3 ± 12.3	150/133	Adalimumab	169	114
		47.5 ± 12.0	162/121	Ixekizumab	167	116
Gladman et al[15]	Canada	48.6 ± 12.5	85/66	Adalimumab	75	76
Gottlieb et al, 2012[16]	United States	44.1 ± 13.0	320/158	Etanercept	239	239
Kavanaugh et al[17]	United States	47.1 ± 12.8	71/29	Infliximab	47	53
Kavanaugh et al[18]	United States	45.7 ± 11.3	128/113	Golimumab	163	78
Kraaig et al[19]	Netherlands	/	/	Adalimumab	31	30
Liu et al, 2019[20]	China	43.1 ± 12.4	355/100	rhTNFR-Fc	226	229
McInnes et al[21]	United Kingdom	47.5	222/187	Ustekinumab	200	209
McInnes et al[22]	United Kingdom	47.3 ± 11.9	153/146	Secukinumab	135	164
Mease et al, 2019[23]	United States	48.3 ± 13.1	295/272	Etanercept	283	284
Nash et al, 2018[24]	United States	52.3 ± 12.5	104/117	Ixekizumab	109	112
Ritchlin et al, 2014[25]	United States	48.5	97/111	Ustekinumab	106	102
Yu et al, 2019[26]	China	51.9 ± 14.7	20/10	Etanercept	15	15
Zachariae et al, 2008[27]	Denmark	48.1	43/16	Etanercept	31	28

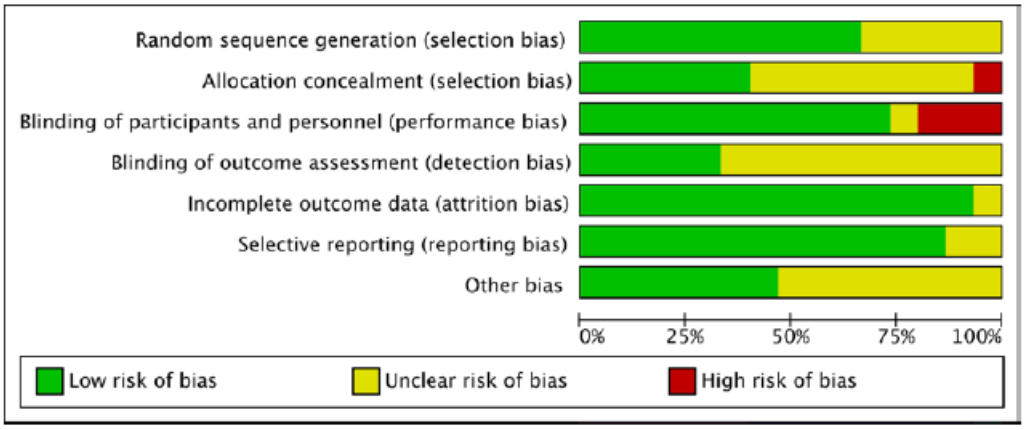
Abbreviations: MTX, methotrexate; rhTNFR-Fc, recombinant human TNF-α receptor II: IgG Fc,fusion protein.

Qualität der Studien:

- of the 15 RCT studies were categorized as low risk of bias, nine studies as unclear, and three as high.



- **Fig.S1** Risk of bias for each included randomized controlled trials



- **Fig.S2** Risk of bias summary of included randomized controlled trials

<u>Studienergebnisse:</u>

FBMed: Es sind nur die Ergebnisse für die PsA dargestellt

- Efficiency
  However, for PsA, with a total of 10 studies reported relevant data, the results were controversial. Five trials examined the efficiency of TNF inhibitors plus MTX compared with TNF inhibitors monotherapy for PsA. And as the results shown in Figure 3, TNF inhibitors plus MTX combination therapy did not lead to any significant higher or lower response rates in ACR20, ACR50, and ACR70, no matter at week 24 (ACR20, RR = 1.08, 95%CI 0.99-1.07, P = .09; ACR50, RR = 1.01, 95%CI 0.88-1.15, P = .93; ACR70, RR = 0.99, 95%CI 0.81-1.20, P = .90) or at week 48 (ACR20, RR = 1.07, 95%CI 0.99-1.15, P = .11; ACR50, RR = 1.10, 95%CI 0.98-1.24, P = .12; ACR70, RR = 1.11, 95%CI 0.93-1.33, P = .23). However, moderate levels of heterogeneities were detected in the results of week 48.

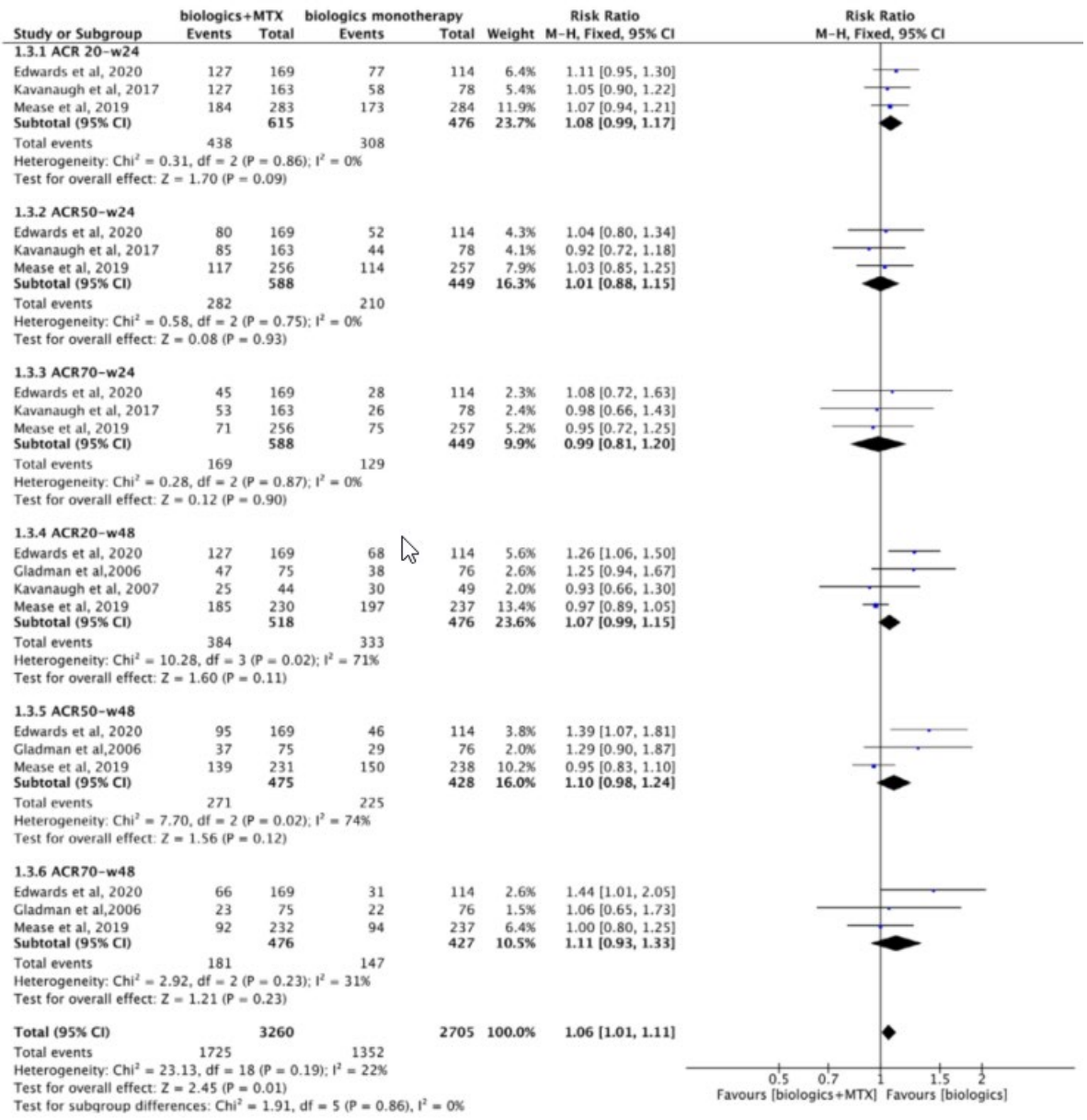


FIGURE 3 The forest plot for clinical efficiency of psoriatic arthritis (TNF inhibitors + MTX vs TNF inhibitors mono), estimated by American College of Rheumatology (ACR) response at week 24 and week 48

- For the comparison of IL-17 inhibitors plus MTX with IL-17inhibitors monotherapy (Figure 4), with four trials involved, the results were similar both at week 24 (ACR20, RR = 1.05, 95%CI 0.93-1.19, P = .40; ACR50, RR = 1.09, 95%CI 0.91-1.30, P =.34; ACR70, RR = 1.19, 95%CI 0.88-1.59, P = .26) and at week 48 (ACR20, RR = 0.98, 95%CI 0.89-1.08, P = .71; ACR50, RR = 0.94, 95%CI 0.81-1.08, P = .38; ACR70, RR = 0.83, 95%CI 0.68-1.02, P = .08). For IL-12/23 inhibitors (Figure 5), only two studies compared the ACR20 response at week 24, and the results still showed no significant difference between the two groups (RR = 0.98, 95%CI 0.82-1.17, P =.83).

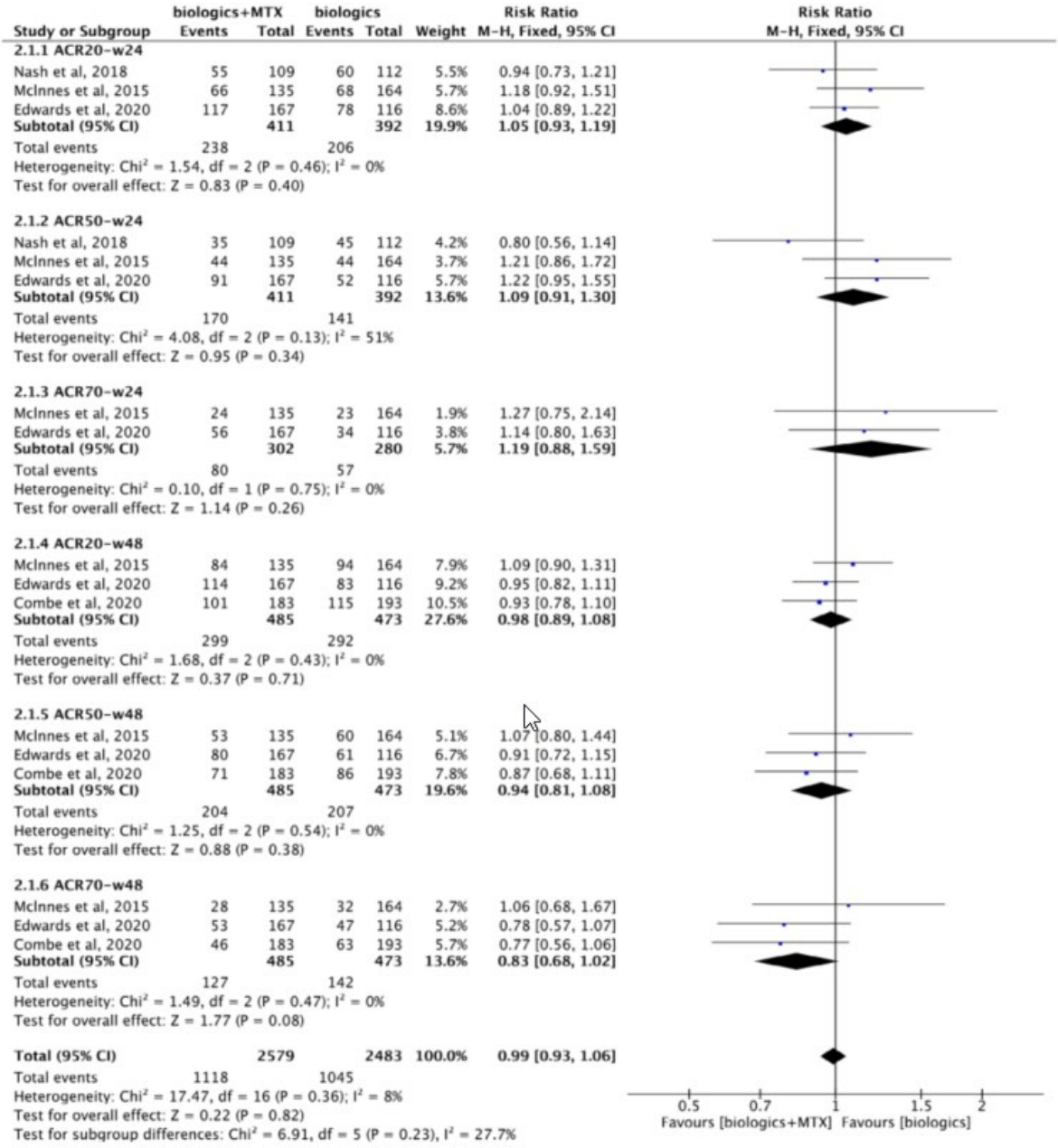


FIGURE 4 The forest plot for clinical efficiency of psoriatic arthritis (IL-17A inhibitors + MTX vs IL-17A inhibitors mono), estimated by American College of Rheumatology (ACR) response at week 24 and week 48

- Safety and tolerability
  - As only one trial involved examined the safety profile of other types of biologics, we only compared the safety profile of TNF inhibitors plus MTX with TNF inhibitors monotherapy
  - The combination group showed a significantly higher incidence rate of total adverse events (RR = 1.21, 95%CI 1.13-1.30). However, a moderate level of heterogeneity was detected (I2 = 66%) for this result. For the incidence of serious adverse events (RR = 0.71, 95%CI 0.42-1.20; P = .20) and drug withdrawals due to adverse effects (RR = 1.12, 95%CI 0.70-1.80; P = .64), there was no significant difference between the two groups

Anmerkung/Fazit der Autoren

In conclusion, this study suggested that biologics plus MTX performed better on improving the clinical efficiency of treating psoriasis when compared with biologic monotherapy, without a difference in tolerability. However, this combination failed to improve the clinical efficiency when treating PsA. More studies are needed to elucidate relevant problems.

Kerschbaumer et al., 2020 [13].

Pharmacological treatment of psoriatic arthritis: a systematic literature research for the 2019 update of the EULAR recommendations for the management of psoriatic arthritis

Fragestellung

To perform an update of a review of the efficacy and safety of disease- modifying antirheumatic drugs (DMaRDs) in psoriatic arthritis (Psa).

Methodik

Population:

- Adult patients (≥18 years) with PsA, classified according to the Classification Criteria for Psoriatic Arthritis (CASPAR) or Moll and Wright criteria.

Intervention:

systemic PsA therapies

- csDMARDs (including methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, chloroquine, injectable gold/gold salts, azathioprine, ciclosporin, penicillamine, cyclophosphamide, mycophenolate, chlorambucil,
- minocycline);
- bDMARDs (anakinra, infliximab, etanercept, adalimumab, rituximab, abatacept, tocilizumab, golimumab, certolizumab- pegol, alefacept, ustekinumab, secukinumab, brodalumab, ixekizumab, guselkumab, clazakizumab and bimekizumab and respective biosimilars);
- targeted synthetic DMARDs (tsDMARDs) (apremilast, tofacitinib, baricitinib, upadacitinib, filgotinib);
- systemic glucocorticoids or NSAIDs; and any combination of these treatments.

Komparator:

- Placebo treatment or any of the agents listed above were eligible as comparator.

Endpunkte:

- Outcomes of interest were signs and symptoms of PsA, defined as composite measures including the American College of Rheumatology (ACR) response criteria, the Disease Activity Index for Psoriatic Arthritis or the minimal disease activity (MDA) state.

Recherche/Suchzeitraum:

- The initial literature search was conducted by a database expert (LF) in Embase, Medline and the Cochrane Library without language restriction. Based on the previous SLR, the search included all studies published between 1 January 2015 and 21 December 2018 (last date searched).

Qualitätsbewertung der Studien:

- Risk of bias (RoB) was assessed using the Cochrane Collaboration's Risk of Bias tool for RCTs, and each study was assigned as having low, unclear or high RoB. Cohort and case–control (ie, safety) studies were assessed using the Newcastle- Ottawa Scale.

Ergebnisse

Anzahl eingeschlossener Studien:

- 56 publications (33 articles on efficacy and 23 on safety) were finally included in this SLR

Table 1 Drugs investigated in PsA randomised controlled trials published in 2015–2018

Therapeutic compound	Articles/ abstracts (n)	Drug target	Population
Biological DMARDs			
Golimumab	1	TNF	csDMARD/NSAID-IR
Etanercept	1		MTX+DMARD-naive
Adalimumab biosimilar (CT-P13)	1		csDMARD-IR
Etanercept biosimilar (CHS-0214)	1		csDMARD-IR
Ixekizumab	10	IL-17A	csDMARD-IR/TNFi-IR
Secukinumab	5		NSAID-IR/mixed csDMARD/TNFi-IR
ABT-122	1	TNF/IL-17A	csDMARD/TNFi-IR
Ustekinumab	1	IL-12/23	Patients with active enthesitis
Risankizumab	1	IL-23–19p	NSAID/csDMARD/ TNFi-IR
Guselkumab	1		csDMARD/TNFi-IR
Clazakizumab	1	IL-6	NSAID/csDMARD-IR
Abatacept	1	CD80/86	csDMARD/TNFi-IR
Targeted synthetic DMARDs			
Apremilast	5	PDE4	csDMARD-IR/TNFi-IR/ csDMARD-naive
Tofacitinib	2	JAK-1/2/3	csDMARD-IR/TNFi-IR
Filgotinib	1	JAK-1	csDMARD-IR

csDMARD, conventional synthetic disease-modifying antirheumatic drug; DMARD, disease-modifying antirheumatic drug; IL, interleukin; IR, insufficient responders; JAK, Janus kinase; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PDE4, phosphodiesterase-4; PsA, psoriatic arthritis; TNF, tumour necrosis factor; TNFi, TNF inhibitor.

Charakteristika der Population:

Table 2 Trials investigating non-TNF biological disease-modifying antirheumatic drugs in PsA

Study	Population	RoB	Treatment	n
IL-17A inhibitors				
Mease *et al* (SPIRIT-P1)[1]	csDMARD-IR	Low	Placebo±csDMARD	106
			IXE 80 mg Q4W±csDMARD	107
			IXE 80 mg Q2W±csDMARD	103
			ADA 40 mg Q2W±csDMARD	101
Nash *et al* (SPIRIT-P2)[2]	TNFi-IR	Low	Placebo±csDMARD	118
			IXE 80 mg Q4W±csDMARD	122
			IXE 80 mg Q2W±csDMARD	123
Nash *et al* (FUTURE-3)[3]	Mixed csDMARD/bDMARD-IR	Low	Placebo±MTX	137
			SEC 300 mg without LD±MTX	139
			SEC 150 mg without LD±MTX	138
Kivitz *et al* (FUTURE-4)[4]	NSAID-IR	Abstract	Placebo±MTX	114
			SEC 150 mg with LD±MTX	114
			SEC 150 mg without LD±MTX	113
Mease *et al* (FUTURE-5)[5]	Mixed	Low	Placebo±MTX	332
			SEC 300 mg with LD±MTX	222
			SEC 150 mg with LD±MTX	220
			SEC 150 mg without LD±MTX	222
IL-23p19 inhibitors				
Deodhar *et al*[6]	Mixed csDMARD/TNFi-IR	Low	Placebo±MTX	49
			GKM 100 mg±MTX	100
Mease *et al* (ACR)[7]	Mixed MTX/TNFi-IR	Abstract	Placebo±MTX	42
			RKM 150 mg Q4W±MTX	42
			RKM 150 mg weeks 0, 4 and 16±MTX	42
			RKM 150 mg weeks 0 and 12±MTX	39
			RKM 75 mg week 0±MTX	20
Other bDMARDs				
Mease *et al*[9]	NSAID/csDMARD-IR	Low	Placebo±MTX	41
			CKM 25 mg±MTX	41
			CKM 100 mg±MTX	42
			CKM 200 mg±MTX	41
Mease *et al* (ASTRAEA)[8]	Mixed csDMARD/TNFi-IR	Low	Placebo±MTX	211
			ABA±MTX	213
Mease *et al*[10]	MTX-IR	Low	Placebo+MTX	24
			ADA 40 mg Q2W+MTX	72
			ABT-122 120 mg Q2W	71
			ABT-122 240 mg Q2W	73

*Week 24.
ABA, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; bDMARD, biological disease-modifying antirheumatic drug; CKM, clazakizumab; csDMARD, conventional synthetic disease-modifying antirheumatic drug; GKM, guselkumab; HAQ-DI, Health Assessment Questionnaire Disability Index; IL, interleukin; IR, insufficient responders; IXE, ixekizumab; LD, loading dose; mTSS, PsA modified total Sharp score; MTX, methotrexate; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; Q2W, every 2 weeks; Q4W, every 4 weeks; Ref, reference arm; RKM, risankizumab; RoB, risk of bias; SEC, secukinumab; TNF, tumour necrosis factor; TNFi, TNF inhibitor.

Qualität der Studien:

- Siehe Table 2 (Charakteristika der Population)

Studienergebnisse:

Efficacy of bDMARDs TNF inhibitors

Two trials investigated the efficacy of TNF inhibition in csDMARD- naive (etanercept) and csDMARD- IR (golimumab). [19 20] The SEAM- PsA study compared etanercept monotherapy or etanercept+MTX combination therapy with MTX monotherapy in csDMARD- naive patients. Etanercept monotherapy as well as combination therapy with MTX were superior to MTX and showed similar efficacy in both treatment groups (ACR20 response at week 24:

50.7% vs 60.9% vs 64% for MTX, etanercept monotherapy and etanercept+MTX combination therapy, respectively); improvement in skin changes, swollen or tender joint counts, and disability according to the HAQ- DI did not differ between the etanercept group and the MTX group. Intravenous golimumab was superior compared with placebo (ACR20 at week 14: 75.1% vs 21.8%).[19] Detailed results are shown in online supplementary tables S3.1 and S3.2. One cohort study (high RoB) investigated the feasibility of switching to a second or third TNFi after insufficient response to a first TNFi. Patients achieved moderate efficacy results in their second, but only weak responses in their third TNFi course. The median drug survival was 64 months (second TNFi) and 14 months (third TNFi).[21]

bDMARDs targeting IL-17A Ten reports of IL- 17A- inhibiting agents (ixekizumab (IXE), secukinumab) were included with low RoB of all primary study reports; secukinumab has already been addressed in the previous SLR.[15] IXE was efficacious in csDMARD- IR as well as TNFi- IR patients. In csDMARD- IR (SPIRIT- P1) better efficacy was seen at week 24 compared with placebo, with numerically similar ACR20, ACR50 and ACR70 rates as adalimumab (ADA) (included as reference arm; study not powered to show noninferiority). Further, structural progression was significantly lower compared with placebo and similar to ADA (table 2); skin responses were also significantly better with IXE than placebo and appeared also better for IXE than ADA.1 [25] Stratification by concomitant DMARD usage revealed similar results regarding clinical signs and symptoms and physical function and a trend towards an advantage of combination therapy as opposed to monotherapy in the Q4W group. Also in TNFi- IR patients (SPIRIT- P2), IXE showed superiority over placebo for IXE every 2 weeks (Q2W) and every 4 weeks (Q4W) at week 24 regarding signs and symptoms, physical disability, skin disease, and extraarticular manifestations (dactylitis, enthesitis) of PsA.2 [26 27] Secukinumab (FUTURE 1–5) continued to show efficacy in reducing signs and symptoms of arthritis as well as skin disease and extra- articular musculoskeletal manifestations(enthesitis, dactylitis) and inhibited radiographic progression when compared with placebo in NSAID- IR, csDMARD- IR and TNF- IR patients.[3–5 28–30]

bDMARDs targeting IL-23-p19 Two trials, investigating molecules targeting the p19 subunit of IL-23, **guselkumab** (low RoB) and risankizumab (conference abstract), were included. Guselkumab was superior compared with placebo in reducing arthritis signs and symptoms, as well as enthesitis and dactylitis.[6] Risankizumab improved arthritis and skin symptoms significantly more than placebo, but there was no clear difference between the different dosing intervals and no significant difference versus placebo in improving dactylitis, enthesitis or physical function.[7 31]

Other bDMARDs In an open- label RCT (high RoB) on patients with primary entheseal disease but unbalanced baseline characteristics, ustekinumab (UST) was reported to be superior to TNFi therapy in resolving enthesitis (Spondyloarthritis Research Consortium of Canada Enthesitis Index, SPARCC=0 at week 24: UST 73.9% vs TNFi 41.7%, p=0.018) and skin disease (PASI100 at week 24: UST 59% vs TNFi 29%, p=0.039). No differences in resolving arthritis disease activity were observed between the groups.[32] A study on abatacept (anti- CD80/86) in patients with PsA with previous IR to csDMARDs or TNFis showed significant but only modest efficacy compared with placebo for musculoskeletal (table 2) and skin manifestations, but was not effective regarding physical function. More patients in the abatacept arm showed radiographic non- progression at week 24 compared with placebo (42.7% vs 32.7%, nominal p=0.034), while the mean change of structural damage appeared similar between the groups (0.30 vs 0.35 at week 24 for abatacept and placebo, respectively).[8] ABT-122 (a dual variable domain immunoglobulin directed against TNF and IL-17) was investigated in a 12- week phase II study in MTX- IR patients. ABT-122 was superior to placebo at both doses (120 mg and 240 mg), showing similar ACR20 responses compared with ADA (table 2); the 240 mg dose showed significantly higher efficacy compared with placebo and ADA in ACR50 and ACR70 responses. PASI75 and

PASI90 responses were similar to ADA and significantly higher in the ABT-122 group compared with placebo.[10] IL-6 inhibition through clazakizumab showed only modest efficacy compared with placebo, with no clear dose response and no difference in skin outcomes in a phase II trial.[9] Detailed results of non- TNFi bDMARDs are shown in table 2.

Efficacy of tsDMARDs:

Three RCTs (all with low RoB) investigated JAKi in PsA (table 3). Tofacitinib was superior to placebo in csDMARD- IR patients and, although not formally tested, exhibited numerically similar results as ADA in OPAL Broaden.[12] OPAL Beyond investigated tofacitinib in TNFi- IR patients and met its co- primary efficacy endpoints (ACR20 and HAQ- DI at week 12) for 5 mg and 10 mg two times per day, compared with placebo (p<0.001). Filgotinib, a selective JAK-1 inhibitor, also significantly reduced signs and symptoms of PsA compared with placebo in a phase II trial.13 Evidence regarding the clinical efficacy of phosphodiesterase-4 (PDE4) inhibition using apremilast (APR) in csDMARD- IR patients was confirmed in two RCTs (one low RoB, one unclear RoB).33 34 Furthermore, APR was effective in reducing signs and symptoms of PsA in patients who were csDMARD- naive (PALACE-4, low RoB)35 or bDMARD- naive (ACTIVE), but the overall response rates were relatively low.36 Detailed results are summarised in table 3 and online supplementary tables S3.1- S3.2.

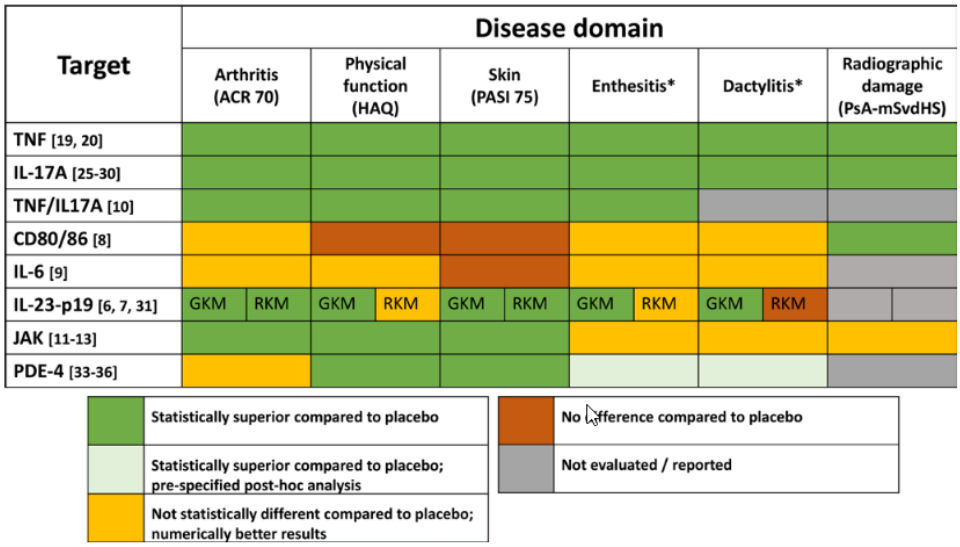


Figure 2 Efficacy results of randomised controlled trials stratified by mode of action and disease domain. Data from previous systematic literature research are also accounted for in this figure. *Different instruments used in studies. ACR, American College of Rheumatology Response; CD, cluster of differentiation; GKM, guselkumab; HAQ, Health Assessment Questionnaire Disability Index; IL, interleukin; JAK, Janus kinases; PASI, Psoriasis Area Severity Index; PDE4, phosphodiesterase-4 inhibitor; PsA-mSvdHS, Psoriatic Arthritis Modified Sharp van der Heijde Score; RKM, risankizumab; TNF, tumour necrosis factor.

6 Deodhar a, Gottlieb aB, Boehncke W- H, et al. efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double- blind, placebo- controlled, phase 2 study. Lancet 2018;391:2213–24.
7 Mease P, Kellner H, Morita a, et al. efficacy and safety results from a phase 2 trial of risankizumab, a selective il- 23p19 inhibitor, in patients with active psoriatic arthritis. Arthritis rheumatol 2017;69.
11 Gladman D, Rigby W, azevedo VF, et al. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TnF inhibitors. N Engl J Med 2017;377:1525–36.

12 Mease P, Hall s, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. N Engl J Med 2017;377:1537–50.
13 Mease P, Coates lC, Helliwell Ps, et al. efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (eQUaTOR): results from a randomised, placebo- controlled, phase 2 trial. Lancet 2018;392:2367–77.
31 Mease PJ, Kellner H, Morita a, et al. efficacy and safety of risankizumab, a selective il- 23p19 inhibitor, in patients with active psoriatic arthritis over 24 weeks: results from a phase 2 trial. Annals of the rheumatic diseases Conference: annual european congress of rheumatology, EULAR 2018 Netherlands 2018;77:200–1.

Anmerkung/Fazit der Autoren

Many drugs in PsA are available and have demonstrated efficacy against placebo. Efficacy varies across PsA manifestations. Safety must also be taken into account.

Kommentare zum Review

This review informed the development of the European League Against Rheumatism 2019 updated PsA management recommendations.

Simons N et al., 2020 [18].

Biological DMARD efficacy in psoriatic arthritis: a systematic literature review and meta-analysis on articular, enthesitis, dactylitis, skin and functional outcomes

Fragestellung

Our purpose is to evaluate the respective efficacy ofTNF inhibitors, IL12/23 inhibitors (ustekinumab), IL17 inhibitors (secukinumab, ixekizumab) and CTLA4Ig (abatacept) on articular, enthesitis, dactylitis, skin and fanctional outcomes in PsA.

Methodik

Population:

- Patients with psoriatic arthritis

Intervention/Komparator:

- one or more marketed bDMARDs versus placebo

Endpunkte:

- ACR20/50/70 and PASI75/90 response rates, enthesitis and dactylitis reduction rates and HAQ-DI mean reductions

Recherche/Suchzeitraum:

- The search was conducted on 15 March 2017 and updated on 5 February 2018.
- It was conducted through the MedLine, Cochrane and Embase databases
- Manual research was also conducted through the 2016 and 2017 ACR and EULAR Congress abstracts.

Qualitätsbewertung der Studien:

- Risk of bias was evaluated using the Cochrane Collaboration's Assessment Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 17 RCTs were analysed (Two RCTs studied etanercept, 2 studied infliximab, 3 studied adalimumab, 2 studied golimumab, 1 studied certolizumab, 2 studied ustekinumab, 2 studied secukinumab, 2 studied ixekizumab and 1 studied abatacept

Charakteristika der Population:

- 4303 patients (bDMARDs: n=2168; placebo: n=2135)
- The mean age at baseline ranged from 43.5 to 52.6 years.
- The percentage of female subjects ranged from 29 to 60%.
- The average duration of the disease ranged from 3.4 to 11.7 years.

Qualität der Studien:

- All of the studies were of good quality, as evaluated per the Cochrane Collaboration's Assessment Tool

Studienergebnisse:

- ACR20/50/70
  - Higher ACR20 response rates were shown for all bDMARDs in comparison to placebo, with RRs (95%CI) ranging from 3.21 (2.52, 4.08) for anti-TNF agents, 2.58 (2.04, 3.27) for anti-IL17 agents, 1.95 (1.52, 2.50) for ustekinumab to 1.77 (1.31, 2.39) for abatacept (Fig. 2).
  - The same trends were observed for ACR50 response rates, with RRs (95%CI) ranging from 6.47 (4.57, 9.17) for anti-TNF agents, 4.22 (2.83, 6.28) for anti-IL17 agents, 2.78 (1.81, 4.27) for ustekinumab to 1.56 (0.99, 2.46) for abatacept (not statistically significant) (Suppl. Fig. 2),
  - ACR70 response rates, with RRs (95%CI) of 8.89 (5.98, 13.21) for anti-TNF agents, 8.84 (3.65, 21.39) for anti-IL17 agents, 3.90 (1.81, 8.39) for ustekinumab and 1.56 (0.82, 2.96) for abatacept (not statistically significant)
- PASI75/90
  - Higher PASI75 response rates were shown for most bDMARDs in comparison to placebo, with RRs (CI95%) ranging from 8.51 (4.56, 15.90) for anti-TNF agents, 5.14 (3.16, 8.36) for anti-IL17 agents, 6.36 (3.49, 11.60) for ustekinumab to 1.62 (0.89, 2.96) for abatacept (not statistically significant) (Fig. 5).
  - PASI90 response rates followed the same trends, with RRs (95%CI) ranging from 8.76 (3.84, 20.01) for anti-TNF agents, 4.95 (2.85, 8.61) for anti-IL17 agents to 11.57 (5.46, 24.52) for ustekinumab (no data available for abatacept)
- HAQ-DI

- Higher HAQ-DI reductions were shown for most bDMARDs compared to placebo, with mean differences (95%CI) of -0.31 (-0.42, -0.20) for anti-TNF agents, -0.26 (-0.33, -0.20) for anti-IL17 agents and -0.13 (-0.25, -0.01) for abatacept (no data available for ustekinumab)

Anmerkung/Fazit der Autoren

All bDMARDs showed higher ACR20 response rates and better HAQ-DI mean reduction compared to placebo. This meta-analysis highlights the variability of bDMARD efficacy on ACR50/70, PASI75/90 and enthesitis or dactylitis response rates. Head-to-head studies are needed to draw definitive conclusions on potential efficacy-related differences between bDMARDs in PsA.

Ruyssen-Witrand A et al., 2020 [17].

Efficacy and safety of biologics in psoriatic arthritis: a systematic literature review and network meta- analysis

Fragestellung

To evaluate the comparative efficacy and safety of approved bDMarDs in patients with Psa.

Methodik

Population:

- patients with psoriatic arthritis (Psa)

Intervention/Komparator:

- abatacept, adalimumab, apremilast, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, secukinumab, tofacitinib and ustekinumab, placebo

Endpunkte:

Efficacy end points:

- ACR response rates (ACR20, ACR50 and ACR70); defined as a minimum of 20%, 50% and 70% improvement from baseline in the ACR score
- PsARC response (defined as improvement from baseline in two of four criteria, one of which must be joint count, without worsening in any measure) and PASI response rates (PASI50, PASI75, PASI90 and PASI100, defined as 50%, 75%, 90% and 100% reduction from baseline in PASI score

Safety end points were evaluated at study end point in the overall population of bDMARD-naïve and bDMARD- experienced patients and included:

- at least one TEAE;
- at least one SAE;
- at least one adverse event leading to discontinuation (DAE) and

- all- cause discontinuation (ie, withdrawal for any reason, including withdrawals from treatment due to lack of efficacy or DAE)

Recherche/Suchzeitraum:

- from 1990 to July 2018) of various databases as well as a review of grey literature.
- The following databases were searched via OVID: EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials and Evidence- Based Medicine Reviews.

Qualitätsbewertung der Studien:

- The validity of each study was assessed using the risk of bias instrument, which is endorsed by the Cochrane Collaboration.
- In addition to the Cochrane risk of bias assessment, the quality of more recent publications identified in updated searches was assessed using the UK National Institute for Health and Care Excellence (NICE) methodology checklist.

Ergebnisse

Anzahl eingeschlossener Studien:

- Of the 50 studies identified in the SLR, 25 were eligible for inclusion in the NMA of the full population (ie, sensitivity analysis and safety analyses) and 22 of these were eligible for inclusion in the base- case NMA of the bDMARD- naïve population.

Charakteristika der Population:

- bDMarD- naïve patients with Psa in terms of american college of rheumatology (acr) criteria, Psoriatic arthritis response criteria (Psarc) and Psoriasis area and severity index (Pasi)

Qualität der Studien:

- the overall quality of the data from the trials included in the NMAs was generally good in terms of randomisation, blinding and intent- to- treat analyses.

Studienergebnisse:

- ACR responses
  - The ACR network for the bDMARD- naïve population included 22 studies and 16 treatment regimens.
  - The ACR network diagram is shown in figure 2A, with lines weighted according to the number of studies included in the respective comparison. With the exception of the two abatacept regimens, all treatments had a statistically greater chance of achieving any ACR score (ACR20, ACR50, ACR70) than placebo (figure 2B). Infliximab was the most effective agent, followed by golimumab and etanercept; these agents were statistically superior to most other treatments, although golimumab and etanercept were not superior to ixekizumab 80 mg every 2 weeks (Q2W).

- Ixekizumab 80 mg Q2W was statistically superior to abatacept subcutaneous (SC), apremilast and both ustekinumab schedules. Ixekizumab 80 mg Q4W was statistically superior to abatacept SC, apremilast and
- ustekinumab 90 mg Q12W. Both schedules of ixekizumab did not significantly differentiate from abatacept intravenous, adalimumab, certolizumab pegol, secukinumab and tofacitinib.

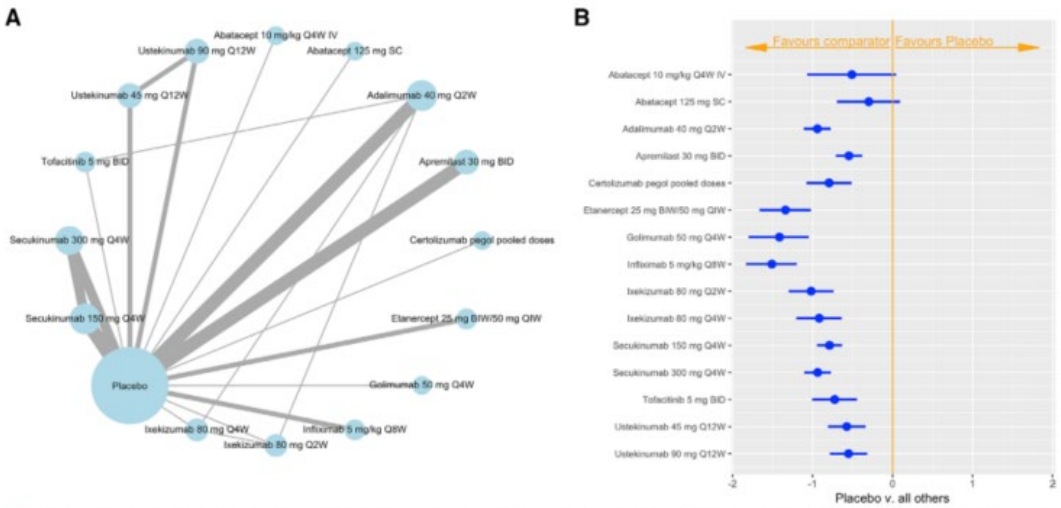


Figure 2 Network diagram (A) and forest plot of treatment differences on the standard normal scale (B) for ACR response at weeks 12–16 among bDMARD-naïve patients with active PsA (placebo as the reference). In the network diagram, line thickness is weighted according to the number of studies included in the respective comparison between treatment regimens or between drug and placebo (indicated by each line connecting circles). Circle size is weighted according to the total number of studies with the treatment regimen or placebo. ACR, American College of Rheumatology; bDMARD, biologic disease-modifying antirheumatic drug; BID, two times per day; BIW, twice weekly; IV, intravenously; PsA, psoriatic arthritis; QxW, every x weeks; SC, subcutaneously.

- PsARC response
  - The PsARC network for the bDMARD- naïve population included 13 studies and 12 treatment regimens, the most frequently studied agent being adalimumab (figure 3A). All treatments had a statistically greater chance of achieving a PsARC response than placebo (figure 3B).
  - The best performing treatments were golimumab, infliximab and etanercept, which were statistically superior to most other agents, including both regimens of ixekizumab. Ixekizumab 80 mg Q2W was statistically superior to tofacitinib. There were no other statistically significant differences between ixekizumab and adalimumab, apremilast, certolizumab pegol and secukinumab.
  - An additional forest plot with ixekizumab 80 mg Q4W as the active reference is provided in online supplementary figure 2.
- PAsI response
  - The PASI network for the bDMARD- naïve population included 17 studies and 14 treatment regimens, the most frequently studied agents being adalimumab, apremilast and secukinumab (figure 4A).

- With the exception of abatacept and etanercept, all treatments had a statistically greater chance of achieving any PASI score (PASI50, PASI75, PASI90 and PASI100) than placebo (figure 4B).
- The greatest benefit was observed for infliximab, but it was not superior to ixekizumab 80 mg Q2W and Q4W, respectively, which was the next best performing therapy.
- The probability of ixekizumab 80 mg Q2W achieving PASI50, PASI75, PASI90 and PASI100 was 88.6%, 73.3%, 54.7% and 38.0%, respectively. Corresponding probabilities for ixekizumab 80 mg Q4W were 87.2%, 70.9%, 52.0% and 35.4%.
- Both schedules of ixekizumab were statistically superior to abatacept, adalimumab, apremilast, certolizumab pegol, etanercept, secukinumab 150 mg, tofacitinib and ustekinumab.

- Adverse events and discontinuation
  - Safety parameters evaluated in the overall population of bDMARD- naïve and bDMARD- experienced patients included TEAEs, SAEs, DAEs and discontinuation for any reason. The TEAE network included five studies and six treatments (both regimens of ixekizumab, adalimumab, certolizumab pegol, infliximab and placebo).
  - No treatment had a statistically higher or lower chance of a TEAE than placebo, and there were no statistically significant differences between any of the active therapies included in this assessment.
  - The SAE network was much larger, including 22 studies and 16 treatments, although the number of SAEs in each study was low, resulting in a high level of uncertainty regarding the estimated treatment effects.
  - No treatment had a statistically higher or lower chance of an SAE than placebo. Ixekizumab 80 mg Q2W had a statistically higher chance of an SAE than golimumab, but there were no other statistical differences between ixekizumab and other therapies.
- sensitivity analysis
  - A sensitivity analysis was conducted for the ACR and PASI networks using efficacy data at week 24 for the overall population of bDMARD- naïve and bDMARD experienced patients.
  - For both of these networks, results of the sensitivity analysis were generally similar to those of the base- case analyses.
  - The ACR responses included 17 studies and 16 treatments.
  - All treatments had a statistically higher chance of achieving any ACR responses than placebo, and the magnitude of benefit was the greatest for infliximab, followed by golimumab. Both regimens of ixekizumab were statistically superior to once- weekly abatacept 125 mg SC and ustekinumab 45 mg Q12W.

- In addition, ixekizumab 80 mg Q4W was statistically better than ustekinumab 90 mg Q12W.
- There were no statistically significant differences between ixekizumab and other treatments.

Anmerkung/Fazit der Autoren

In conclusion, results of this NMA confirm the efficacy and acceptable safety profile of bDMARDs, including ixekizumab, in patients with active PsA. The TNF-α inhibitors infliximab, golimumab and etanercept were the most effective agents for ACR and PsARC responses (ie, joint symptoms), although there were relatively few statistically significant differences between other treatments in these networks. With respect to PASI response (ie, skin symptoms), infliximab and ixekizumab were the best performing therapies. Although the base- case analyses comparing efficacy across three networks (ACR, PsARC and PASI) focused on bDMARD- naïve patients at 12–16 weeks, results of a sensitivity analysis in the overall mixed population of bDMARD- naïve and bDMARDexperienced patients at week 24 were generally similar and support the robustness of the base- case results. Ixekizumab generally performed well in all three networks, particularly for PASI response, for which only infliximab provided a numerically greater magnitude of benefit in the bDMARD- naïve population. The results of this NMA are consistent with the recently completed H2H study comparing ixekizumab with adalimumab.

Kommentare zum Review

- Die für die NMA verwendete Methodik folgte den NICE-Richtlinien.
- Für die Hauptanalyse der klinischen Wirksamkeit konzentrierte sich die Bayes'sche NMA auf bDMARD-naive Patienten und wurde durchgeführt, um die relative Wirksamkeit von in Europa zugelassenen und nach ihren zugelassenen Dosierungsschemata (EU) verabreichten bDMARDs zu vergleichen.

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Qui et al., 2020 [15]

Champs B et al., 2019 [2].

Short-term risk of major adverse cardiovascular events or congestive heart failure in patients with psoriatic arthritis or psoriasis initiating a biological therapy: a meta-analysis of randomized controlled trials

Fragestellung

to investigate the short-term risk of major adverse cardiovascular events (MACEs) or congestive heart failure (CHF) in patients with psoriatic arthritis (PsA) or psoriasis initiating a biological therapy.

Methodik

<u>Population:</u>

- Patients with PsA or psoriasis

Intervention/Komparator:

- anti-tumour necrosis factor (TNF), anti-interleukin (IL)12/23, anti-IL23 and anti-IL17 agents vs. placebo

Endpunkte:

- safety data concerning MACEs (defined as myocardial infarction, stroke or CV death) or CHF (defined as global cardiac failure with signs of right and left cardiac decompensation)

Recherche/Suchzeitraum:

- MEDLINE, Cochrane and EMBASE, from the inception of the database to December 2017

Qualitätsbewertung der Studien:

- Jadad Scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 77 RCTs

Qualität der Studien:

- Jadad Score: Range between 3-5

Studienergebnisse:

- No significant difference was observed in MACE incidences in patients receiving anti-TNF, anti-IL12/23, anti-IL23 or anti-IL17 agents in comparison to the placebo.
- However, 10 MACEs were observed in the anti-IL12/23 group (1150 P-Y) compared with 1 in the placebo group (652 P-Y), with 0.01 −0.00 to 0.02 event/P-Y risk difference, which is not statistically significant.
- This trend was not observed in the anti-IL23 group.
- No significant difference was observed in CHF incidence in patients receiving biological agents in comparison to placebo.

Anmerkung/Fazit der Autoren

Our MA, which is focused on the placebo-controlled phase of RCTs, did not reveal any significant change in the short-term risk of MACEs or CHF in patients with PsA or psoriasis initiating an anti-TNF, anti-IL12/23, anti-IL23 or anti-IL17 agent in comparison to the placebo. Data from the long-term extension phases of these RCTs and from the long-term follow-up of patients with PsA and psoriasis included in biological therapy registries are required to further characterise the long-term impact of biological therapies on the risk of MACEs or CHF.

Song GG et al., 2019 [21].

Comparison of the efficacy and safety of tofacitinib and apremilast in patients with active psoriatic arthritis: a Bayesian network meta-analysis of randomized controlled trials

Fragestellung

to assess the relative efficacy and safety of tofacitinib and apremilast at different doses in patients with active psoriatic arthritis.

Methodik

Population:

- active PsA patients

Intervention/Komparator:

- tofacitinib or apremilast with placebo

Endpunkte:

- ACR20 response, ACR50 response, ACR70 response, serious adverse events (SAEs), overall adverse events (AEs), and discontinuation because of AEs

Recherche/Suchzeitraum:

- MEDLINE and EMBASE databases and the Cochrane Controlled Trials Register to identify available articles published prior to October 2018.

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- Eight randomized controlled trials including 3086 patients: ten pairwise comparisons including six direct comparisons of five interventions.

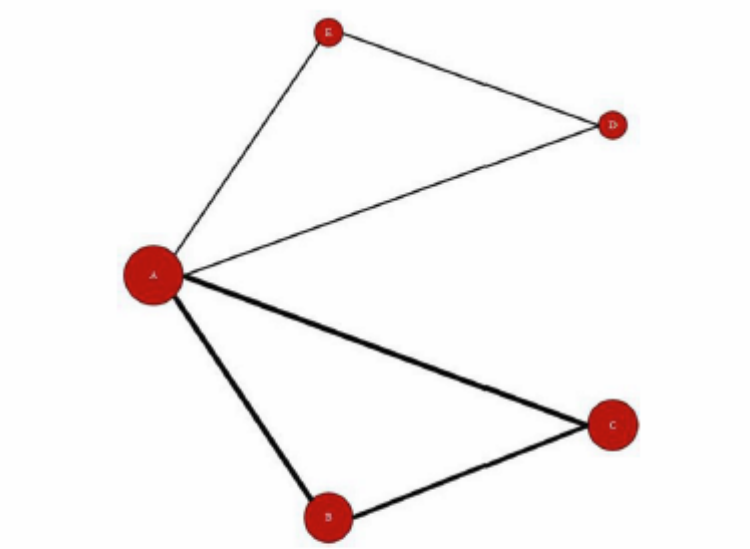


Fig. 1 Evidence network diagram of network meta-analysis comparisons. The width of each edge is proportional to the number of randomized controlled trials comparing each pair of treatments, and the size of each treatment node is proportional to the number of randomized participants (sample size), (A) placebo, (B) apremilast 20 mg, (C) apremilast 30 mg, (D) tofacitinib 5 mg, and (E) tofacitinib 10 mg

Charakteristika der Population:

Table 1 Characteristics of individual studies included in the meta-analysis and systematic review

Study, year	Patient number	Subjects	Doses, twice daily (*n*)	Follow-up time point for evaluation (wk)	Jadad score
Mease et al., 2017 [10]	316	DMARD-IR	Tofacitinib 5 mg (107), tofacitinib 10 mg (104), placebo (105)	12	4
Gladman et al., 2017 [11]	394	TNF-IR	Tofacitinib 5 mg (131), tofacitinib 10 mg (132), placebo (131)	12	4
Nash et al., 2018 [12]	219	DMARD-naive	Apremilast 30 mg (110), placebo (109)	16[a]	3
Wells et al., 2018 [13]	527	DMARD-naive	Apremilast 20 mg (175), apremilast 30 mg (176), placebo (176)	16[a]	3
Cutolo et al., 2016 [14]	484	DMARD/biologic-IR	Apremilast 20 mg (163), apremilast 30 mg (162), placebo (159)	16[a]	4
Edwards et al., 2016 [15]	505	DMARD/biologic-IR	Apremilast 20 mg (169), 30 mg (167), placebo (169)	16[a]	4
Kavanaugh et al., 2014 [16]	504	DMARD/TNF-IR	Apremilast 20 mg (168), apremilast 30 mg (168), placebo (168)	16[a]	3
Schett et al., 2012 [17]	137	DMARD/biologic-IR	Apremilast 20 mg (69), placebo (68)	12[a]	3

DMARD disease-modifying anti-rheumatic drug, *IR* incomplete response, *TNF* tumor necrosis factor

[a]24 wk for safety

Qualität der Studien:

- The Jadad scores of the studies ranged from 3 to 4, indicating a high study quality overall

Studienergebnisse:

- Bayesian network meta-analysis
  - All the interventions achieved a significant American College of Rheumatology 20 response compared with placebo.

- Tofacitinib 10 mg and apremilast 30 mg were among the most effective treatments for active psoriatic arthritis, followed by tofacitinib 5 mg, and apremilast 20 mg.
- The ranking probability based on the surface under the cumulative ranking curve (SUCRA) indicated that tofacitinib 10 mg had the highest probability of being the best treatment in terms of the American College of Rheumatology 20 response rate (SUCRA = 0.785).
- This was followed by apremilast 30 mg (SUCRA = 0.670), tofacitinib 5 mg (SUCRA = 0.596), apremilast 20 mg (SUCRA = 0.448), and placebo (SUCRA = 0.001).

Table 3 Rank probability of the efficacy of tofacitinib and apremilast

Efficacy outcome	Treatment	SUCRA
ACR20	Tofacitinib 10 mg	0.785
	Apremilast 30 mg	0.670
	Tofacitinib 5 mg	0.596
	Apremilast 20 mg	0.448
	Placebo	0.001
ACR50	Apremilast 30 mg	0.719
	Tofacitinib 10 mg	0.683
	Tofacitinib 5 mg	0.654
	Apremilast 20 mg	0.436
	Placebo	0.008
ACR70	Apremilast 30 mg	0.805
	Tofacitinib 5 mg	0.613
	Apremilast 20 mg	0.567
	Tofacitinib 10 mg	0.476
	Placebo	0.039

ACR American College of Rheumatology, *SUCRA* surface under the cumulative ranking curve

- No significant differences in the incidence of serious adverse events after treatment with tofacitinib 10 mg, apremilast 30 mg, tofacitinib 5 mg, apremilast 20 mg, or placebo.

Anmerkung/Fazit der Autoren

We conducted a Bayesian network meta-analysis involving eight RCTs and found that tofacitinib 10 mg and apremilast 30 mg were the most efficacious interventions for patients with active PsA and that neither was associated with a significant risk of SAEs. We need long-term studies to determine the relative efficacy and safety of tofacitinib and apremilast in a large number of patients with active PsA.

Dressler C et al., 2019 [5]

Efficacy and safety of systemic treatments in psoriatic arthritis. A systematic review, meta-analysis and GRADE evaluation.

Fragestellung

The aim of this systematic review was to provide a concise overview of currently available efficacy and safety data of systemic treatments for patients with psoriatic arthritis, conduct a meta-analysis and evaluate the certainty of the evidence.

Methodik

Population:

- diagnosis of PsA, Pso w/ PsA (at least 80% of the included patient population with PsA where no subgroup analysis was conducted)
- adults

Intervention:

- csDMARDs: methotrexate (MTX), sulfasalazine (SSZ), ciclosporin (CSA) or leflunomide (LEF)
- biological (b) DMARDS: adalimumab (ADA), etanercept (ETA), golimumab (GOL), infliximab (INF), ustekinumab (UST), secukinumab (SEC), guselkumab (GUS), ixekizumab (IXE), certolizumab pegol (CZP), including biosimilars for ADA, ETA, GOL and INF
- targeted synthetic (ts) DMARDS: apremilast (APR) or tofacitinib (TOF)

Komparator:

- Comparisons with another included drug and/or placebo

Endpunkte:

- Efficacy outcomes: ACR 20, ACR 50, Health Assessment Questionnaire Disability Index (HAQ-DI), SF-36
- Safety outcomes: proportion of patients with at least one adverse event (AE) and with at least one serious adverse event (SAE)

Recherche/Suchzeitraum:

- MEDLINE Ovid, Embase Ovid, Cochrane Central Register of Controlled Trials [CENTRAL] Wiley
- the literature was searched in March 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- We included 20 trials
- ADA, APR, CZP, ETA, GOL, INF, IXE, LEF, MTX, SEC, SSZ and UST

Charakteristika der Population:

- The inclusion and baseline characteristics of the trials were comparable, although in the trials evaluating more recently developed treatments, patients had higher mean tender joint/swollen joint counts and they were older.
- Table 1 Overview of the included RCTs (bitte online einsehen)

Qualität der Studien:

- Siehe Table 2 (Ergebnisse)

Studienergebnisse:

- The results of the placebo trials evaluating SSZ, LEF, and low dose MTX suggest no difference between the active substance and the placebo even though the magnitude of the effect is in favour of the active substance. Infliximab in combination with MTX appears to be more effective than MTX alone (low quality evidence). No difference was found between IXE and ADA (very low quality evidence). For all other comparisons, the active treatment was always more effective than placebo (high to moderate quality evidence).

Table 2: Quality of evidence for ACR20 (16-24 weeks) and proportion of patients with at least one adverse event (alphabetical order)

Outcome:	Patients achieving ARC20			Patients with at least one adverse event		
Placebo comparisons:	RR	95% CI	Quality of the Evidence (GRADE)	RR	95% CI	Quality of the Evidence (GRADE)
SEC 150mg vs. PBO	3.01	2.29 to 3.97	HIGH	1.07	0.94 to 1.22	HIGH
UST 45mg vs PBO	1.95	1.52 to 2.50	HIGH	n.d.		
UST 90mg vs PBO	2.17	1.71 to 2.76	HIGH	n.d.		
APR 30mg BID vs. PBO	1.98	1.48 to 2.66	MODERATE	1.28	1.13 to 1.44	LOW
ETA 25mg BIW vs. PBO	2.58	1.57 to 4.25	MODERATE	n.d.		
CZP 400mg vs. PBO	2.36	1.68 to 3.31	MODERATE	1.05	0.90 to 1.23	MODERATE
CZP 200mg vs. PBO	2.71	1.95 to 3.76	MODERATE	1.01	0.86 to 1.19	MODERATE
GOL 50mg vs PBO	4.20	2.51 to 7.03	MODERATE	1.14	0.95 to 1.38	LOW
GOL 100mg vs. PBO	4.92	2.96 to 8.17	MODERATE	1.10	0.90 to 1.33	LOW
INF 5mg/kg vs. PBO	4.38	2.24 to 8.56	MODERATE	1.13	0.87 to 1.47	LOW
IXE 80mg Q2W vs. PBO	2.21	1.71 to 2.86	MODERATE	1.39	1.09 to 1.78	LOW
IXE 80mg Q4W vs. PBO	2.25	1.59 to 3.18	MODERATE	1.41	1.10 to 1.79	LOW
SEC 300mg vs. PBO	3.53	2.14 to 5.81	MODERATE	0.96	0.76 to 1.23	MODERATE
ADA 40mg EOW vs. PBO	3.79	2.56 to 5.63	LOW	n.d.		
APR 20mg BID vs PBO	1.89	1.47 to 2.44	LOW	1.29	1.15 to 1.45	MODERATE
LEF 100mg vs. PBO	1.70	0.99 to 2.92	LOW	1.12	0.97 to 1.29	LOW
MTX 7.5mg vs. PBO	1.81	0.97 to 3.40	LOW	n.d.		
SSZ 0.2mg QD vs. PBO	1.29	0.90 to 1.86	VERY LOW	1.29	0.90 to 1.86	VERY LOW
Head-to-head comparisons:						
INF 5mg/kg + MTX vs. MTX 15mg/kg	*1.40*	*1.07 to 1.84*	*VERY LOW*	*1.65*	*1.08 to 2.52*	*VERY LOW*
IXE 80mg Q2W vs. ADA 40mg Q2W	*1.08*	*0.86 to 1.36*	*VERY LOW*	*1.02*	*0.83 to 1.25*	*MODERATE*
LEF 100mg vs. MTX 10mg	*1.01*	*0.84 to 1.21*	*LOW*	*nod*		

CI – confidence interval

n.d. – no data

RR – risk ratio

- Red – difference between treatments

- For the outcome ACR50, the results were very similar. Again, SEC 150mg and both UST dosages were more effective than placebo and the quality of the evidence was rated as high. While more comparisons received a lower quality of the evidence evaluation, most were still rated as moderate or low and each active treatment was more effective than placebo (see online appendix). There was also a difference between INF and MTX versus MTX alone ((RR 1.98 (95 % CI 1.31 to 3.00) low quality evidence) but no difference was seen between IXE and ADA (RR 1.21 (95 % CI 0.88 to 1.66) low quality evidence) or LEF versus MTX (RR 0.96 (95 % CI 0.66 to 1.38) very low quality evidence).
- For the majority of placebo-comparisons, there was no difference when considering the outcome 'patients with at least one adverse event' (see Table 2). There was, however a difference when looking at APR vs. placebo or IXE vs. placebo (all dosages) favouring the placebo group (low quality evidence). There was also a difference between INF + MTX versus MTX alone (very low quality evidence) but no difference was seen between IXE and ADA (moderate quality evidence).[…]
- The outcome HAQ-DI could be assessed for thirteen pair-wise comparisons using GRADE. All active drugs performed better than placebo and the quality of the evidence was mostly rated as low (see online appendix).#
- Similar results were seen for the SF-36 physical capacity (PC) and mental capacity (MC) subscales.

Anmerkung/Fazit der Autoren

The majority of biologics were effective for most outcomes but the certainty varied. Nevertheless, direct comparison between treatment arms from different trials should be avoided. The development and use of core outcome sets[22] may help with direct comparisons in future – still, network meta-analyses or head-to-head trials need to be conducted. Consequently, current treatment algorithms can only be based on very few head-to-head trials and will always have to take real world data and expert experience as well as economic considerations in to account.

Kommentare zum Review

- Der SR war Grundlage zu den Empfehlungen bei PsA der EuroGuiDerm Guiseline [6]

Kawalec P et al., 2018 [12].

Comparative effectiveness of abatacept, apremilast, secukinumab and ustekinumab treatment of psoriatic arthritis: a systematic review and network meta-analysis

Fragestellung

To assess the comparative effectiveness and safety of novel biologic therapies in psoriatic arthritis (PsA) and to establish the position of the non-anti-tumor necrosis factor α (TNF-α) biologic drugs in the treatment regimen of the disease.

Methodik

Population:

- adults with moderate and severe PsA

Intervention:

- abatacept, apremilast, secukinumab, and ustekinumab, and at least one study arm included a licensed dosage of those drug

Komparator:

- another biologic agent or placebo

Endpunkte:

- ACR20, ACR50, PASI75 (efficacy outcomes) and any AEs, SAEs, and withdrawals due to AEs

Recherche/Suchzeitraum:

- from inception to 07/2017

Qualitätsbewertung der Studien:

- The methodological quality of eligible RCTs and the risk of bias within individual studies were assessed using the tool recommended by the Cochrane Collaboration.

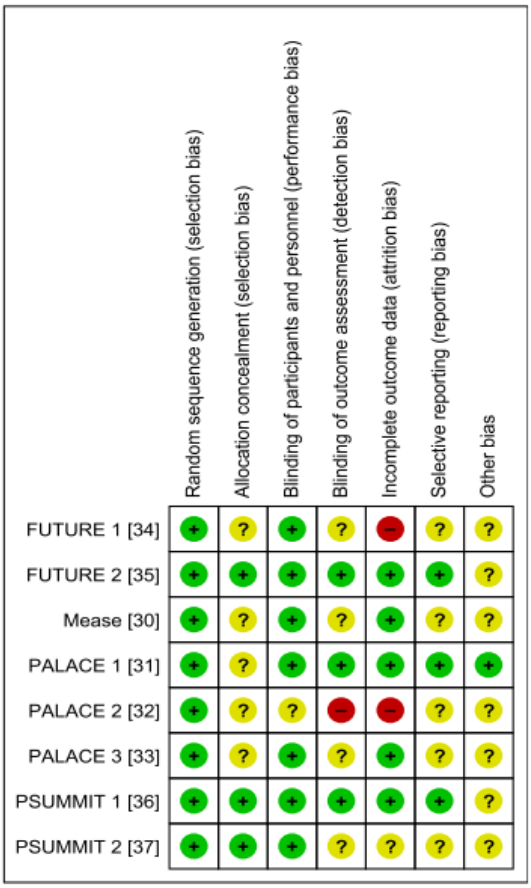
Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs

Qualität der Studien:

- The methodological quality of RCTs in this review was categorized as high, and the risk of bias was assessed as low. The probability of occurrence of bias in most studies and domains was considered low.



- Eight trials were homogeneous enough to perform an NMA for the overall population as well as for the anti-TNF-α- naive subpopulation
- Five studies were appropriate to perform an NMA for the anti-TNF-α-experienced subpopulation
- four studies were appropriate for inadequate response to anti-TNF therapy and/or discontinued treatment due to safety or tolerability issues

<u>Studienergebnisse:</u>

Relative treatment effects

- No significant differences between treatments were revealed with the exception of the following:
  - secukinumab 300 mg increased the ACR20 response rate in the overall population in comparison with apremilast (*P* = 0.020);
  - apremilast reduced the rate of withdrawal due to AEs in comparison with ustekinumab (*P* = 0.002);
  - secukinumab 150 and 300 mg increased the ACR20 response rate in the anti-TNF-α-naive subpopulation in comparison with apremilast and ustekinumab (*P* ranging from 0.004 to 0.024).
  - There was no evidence for the higher efficacy of secukinumab over apremilast and/or ustekinumab in the anti-TNF-α-failure and anti-TNF-α-failure subpopulations

- Compared with placebo, all treatments induced a higher rate of ACR20 and ACR50 responses in the overall population.
- All treatments except abatacept significantly increased the rate of PASI75 response compared with placebo.
- Only apremilast reduced the rate of any AEs and SAEs in comparison with placebo. Ustekinumab was the only treatment which significantly increased the rate of withdrawal due to AEs compared with control.
- Abatacept and apremilast were no better than placebo in inducing ACR20 response among patients from the anti-TNF-α-failure.

Anmerkung/Fazit der Autoren

Our study revealed no significant differences among non-anti-TNF-α biologics in the treatment of PsA in the comparisons performed with regards to the highest efficacy and safety. Both in the overall population and in the analyzed subpopulations, secukinumab 300 mg was ranked the highest for the ACR20 response rate. Secukinumab 300 mg was the safest drug in terms of any AEs, and ustekinumab 90 mg presented the lowest overall risk of SAEs. Head-to-head trials and evaluation of comparative efficacy and safety between non-TNF-α biologics are warranted to inform clinical decision making with a relevant treatment paradigm.

Kommentare zum Review

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Song et al., 2018 [22]

Wu D et al., 2018 [26].

Efficacy and safety of biologics targeting interleukin-6, -12/23 and -17 pathways for peripheral psoriatic arthritis: a network meta-analysis

Fragestellung

To investigate the comparative efficacy, safety and tolerability of IL-6, IL-12/23 and IL-17 inhibitors for patients with active PsA.

Methodik

Population:

- patients with PsA

Intervention:

- IL-6, IL-12/23 and IL-17 inhibitors

Komparator:

- Placebo

Endpunkte:

- 20% or 50% improvement in ACR criteria reported as the primary or major secondary outcome at week 24.

Recherche/Suchzeitraum:

- 12/2016

Qualitätsbewertung der Studien:

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 RCTs /n=2411 participants

Qualität der Studien:

- The risk-of-bias assessment indicated that all included studies were of high quality.

Studienergebnisse:

- Six studies investigating secukinumab, ustekinumab, clazakizumab and ixekizumab were included in the analysis

Meta-analysis of direct treatment effects:

- Pooled effect sizes suggested that all biologics, irrespective of dose, improved ACR20 and ACR50 at week 24 when compared with placebo [ACR20: OR 1.23 (95% CI 0.50, 3.04); ACR50: OR 1.88 (95% CI 0.61, 5.78)]
- no significant difference between secukinumab, clazakizumab and placebo in terms of AEs, SAEs and tolerability.
- Ixekizumab (both 80mg every 2 weeks and 80mg monthly) had more AEs than placebo
- ustekinumab (45mg and 90mg) was even more tolerable than placebo [OR 0.28 (95% CI 0.10, 0.78) and OR 0.32 (95% CI 0.13, 0.83), respectively]

ACR 20 response according to prior anti-TNF exposure:

- Two trials reported the effects of prior anti-TNF exposure on the efficacy of ustekinumab and secukinumab
- Anti-TNF-naıve patients responded significantly better than placebo patients, irrespective of dose
- In contrast, only higher doses of secukinumab and ustekinumab were significantly more effective than placebo in achieving ACR20 in anti-TNF-failure patients

Network meta-analysis of direct comparisons:

- All treatments of ustekinumab, secukinumab and ixekizumab showed significant differences when compared with placebo in both ACR20 and ACR50.

- All these inhibitors were comparable to placebo in terms of safety and tolerability except secukinumab 150mg monthly, which was more tolerable than placebo [OR 0.23 (95% CrI 0.03, 0.83)]

Network meta-analysis of mixed comparisons:

- With regards to the ACR20 response for IL-6, IL-12/23 and IL-17 inhibitors, secukinumab 300mg monthly was more effective than secukinumab 75mg monthly [OR 1.97 (95% CrI 1.02, 3.56)], ustekinumab 45mg every 12 weeks [OR 2.71 (95% CrI 1.20, 5.92)] and clazakizumab 200mg monthly [OR 6.22 (95% CrI 1.77, 20.68)].
- Secukinumab 150mg monthly was more effective than ustekinumab 45mg every 12 weeks [OR 1.89 (95% CrI 1.00, 3.62)] or clazakizumab 200mg monthly [OR 4.28 (95% CrI 1.39, 14.29)].
- Secukinumab 75mg monthly was more effective than ustekinumab 45mg every 12 weeks [OR 3.22 (95% CrI 1.04, 10.90)].
- With regards to the ACR50 response of IL-6, IL-12/23 and IL-17 inhibitors, secukinumab 300mg was more effective than ustekinumab 45mg [OR 2.60 (95% CrI 1.06, 6.36)]

Anmerkung/Fazit der Autoren

In conclusion, secukinumab may be the safest and most efficacious short-term treatment for peripheral PsA among all the new biologics targeting the IL-6, IL-12/23 and IL-17 pathways.

Reygaerts T et al., 2018 [16].

Effect of biologics on fatigue in psoriatic arthritis: a systematic literature review with meta-analysis

Fragestellung

to assess the effect of biological disease modifying antirheumatic drugs and apremilast on fatigue in psoriatic arthritis randomized controlled trials and to compare this effect with the effect in the same trials, on pain, through a systematic literature review and meta-analysis

Methodik

Population:

- Adults with PsA

Intervention/Komparator:

- bDMARD or apremilast with or without a conventional synthetic disease-modifying antirheumatic drug (csDMARD) against placebo with or without the same csDMARD

Endpunkte:

- Fatigue, pain

Recherche/Suchzeitraum:

- up to January 2017 in PubMed, EMBASE and Cochrane databases

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 randomised controlled trials (2341 PsA patients): adalimumab (n = 2), certolizumab pegol (n = 1), secukinumab (n = 2), ustekinumab (n = 1) and apremilast (n = 1), compared to placebo

Charakteristika der Population:

Table 1
Studies and baseline characteristics.

Characteristics	Genovese et al., 2007 [23] M02-570	Gladman et al., 2007 [24] ADEPT	Gladman et al., 2015 [26] RAPID-PSA	Gossec et al., 2015 [27,28] FUTURE2	Strand et al., 2016 [29] FUTURE1	Ritchlin et al., 2014 [30] PSUMMIT2	Strand et al., 2013 [25]
Study drug	Adalimumab	Adalimumab	Certolizumab Pegol	Secukinumab	Secukinumab	Ustekinumab	Apremilast
Study drug dose, mg	40	40	200, 400	75, 150, 300	75, 150	45, 90	20, 40
Number of patients	100	313	409	397	606	312	204
Age, mean ± SD, years	49.1 ± 11.3	48.9 ± 11.1	47.5 ± 11.1	48.0 ± 12.5	49.0 ± 11.2	48.3 ± 13.0	50.6 ± NR
Women (%)	46 (46)	139 (55.3)	226 (55.3)	205 (51.6)	330 (54.5)	164 (52.6)	97 (47.5)
Disease duration, mean ± SD, years	7.4 ± 7.0	9.5 ± 8.7	8.5 ± 7.7	NR	NR	5.1 ± 7.3	7.8 ± NR
SJC, mean ± SD	18.3 ± 12.1	14.3 ± 11.1	10.6 ± 7.6	11.5 ± 10.7	13.4 ± 13.1	11.3 ± 8.2	9.5 ± NR
HAQ-DI score, mean ± SD	0.9 ± 0.7	1.0 ± 0.7	1.3 ± 0.7	1.2 ± 0.7	1.2 ± 0.6	1.3 ± 0.7	1.1 ± NR
PASI score, mean ± SD	NR	7.9 ± 7.2	7.4 ± NR	13.0 ± 8.3	13.8 ± 11.6	8,4 ± 8.5	NR
MTX users (%)	47 (47)	158 (63.6)	260 (63.6)	185 (46.6)	368 (60.7)	155 (49.7)	89 (43.6)
Baseline Fatigue, mean ± SD	32.8 ± 12.3	30.8 ± 12.2	6.1 ± 2.0[a]	28.6 ± 11.6	28.1 ± 11.1	26.2 ± 13.0	29.6 ± 11.8
Baseline Pain VAS (0–100), mean ± SD	46.1 ± 23.5	49.9 ± 21.7	60.3 ± 22.0	57.2 ± 22.1	55.8 ± 21.1	NR	57.5 ± 22.6

SD: Standard deviation of placebo group; SJC: Swollen Joint Count (range: 0–68); *n*: number; mg–milligram; HAQ-DI: Health Assessment Questionnaire-Disability Index (range: 0–3); PASI: Psoriasis Area Severity Index (range: 0–72); MTX: Methotrexate; NR: not reported. All results are weighted means with SD of the placebo group.
[a] VAS: Visual Analog Scale (range: 0–10) was used. Other fatigue results are from Functional Assessment of Chronic Illness Therapy (FACIT) scores (range: 0–52).

Qualität der Studien:

- Jadad score for all studies: 4.7±0.7.

Studienergebnisse:

- In favour for biologics: The pooled standardized mean difference was, for fatigue −0.44 (95% confidence interval: −0.54, −0.35) and for pain, −0.62 (−0.73, −0.52).

Anmerkung/Fazit der Autoren

In conclusion, this review confirmed a significant but small effect of biologics on fatigue at the group level. These results are important to take into account in particular in the context of shared decision-making. Future studies should focus on causal-ity of fatigue in PsA, and other treatment modalities should be explored.

3.3 Leitlinien

European Dermatology Forum (EDF), European Centre for Guidelines Development, 2021 [6] und Methods & evidence report [4]

Euroguiderm guideline for the systemic treatment of psoriasis vulgaris

Zielsetzung/Fragestellung

The overall aim of this guideline is to provide guidance for optimal treatment selection and management in the treatment of adults with moderate to severe plaque type psoriasis. Optimal treatment selection and management are meant to reduce morbidity caused by psoriasis and to improve the health related quality of life of affected individuals.

The objectives of the guideline are to:

- Include new treatments and the evidence that has become available
- Update the recommendations regarding biologic systemic treatment options
- Develop a treatment algorithm including biologic and nonbiologic systemic treatment options
- Provide clear recommendations on how to best monitor and manage patients considering the available treatment options
- Develop several short guidance documents with visual tools for ease of implementation
- Provide guidance on the treatment of special populations and difficult clinical situations (mostly expert consensus)

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium-trifft zu; 23 dermatology experts from 14 countries, two patient representatives nominated by IFPA and the EuroGuiDerm methodologists
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt-trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz-über Updates existierender SRs;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt-trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt-trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert. update of the European Psoriasis Guideline 2015 & 2017-Letztes Update Juni 2021

Recherche/Suchzeitraum:

- Kein Recherchezeitraum angegeben
- The general recommendations developed in this guideline are based on the Cochrane Review published in January 2020 (updated search to January 2019). As this review is a living systematic review updated yearly, new evidence and new results may become available in this rapidly evolving field

LoE

- We utilized the GRADE approach to assess the quality of evidence.

GoR

Wording of recommendations [29-32]

Strength	Wording	Symbols	Implications
Strong recommendation **for** the use of an intervention	'We recommend . . .'	↑↑	We believe that all or almost all informed people would make that choice.Clinicians will have to spend less time on the process of decision-making, and may devote that time to overcome barriers to implementation and adherence. In most clinical situations, the recommendation may be adopted as a policy.
Weak recommendation **for** the use of an intervention	'We suggest . . .'	↑	We believe that most informed people would make that choice, but a substantial number would not. Clinicians and health care providers will need to devote more time on the process of shared decision-making. Policy makers will have to involve many stakeholders and policy making requires substantial debate.
No recommendation with respect to an intervention	'We cannot make a recommendation with respect to . . .'	0	At the moment, a recommendation in favour or against an intervention cannot be made due to certain reasons (e.g. no reliable evidence data available, conflicting outcomes, etc.)
Weak recommendation	'We suggest against . . .'	↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
against the use of an intervention			
Strong recommendation **against** the use of an intervention	'We recommend against . . .'	↓↓	We believe that all or almost all informed people would make a choice against that intervention. This recommendation can be adopted as a policy in most clinical situations.

Sonstige methodische Hinweise

TABLE 8: STRENGTH OF CONSENSUS

100 % consensus	100% agreement	
Strong consensus	Agreement of >95% participants	
Consensus	Agreement of >75-95% participants	
Agreement of the majority	Agreement of >50-75% participants	

- Die Empfehlungen der deutschen S3 Leitline Therapie der Psoriasis vulgaris (nicht in der Synopse enthalten) zur Behandlung der PsA beruhen auf dieser Leitlinie

Empfehlungen

3. Guidance for specific clinical and comorbid situations

3.1. Psoriatic arthritis: How should psoriasis patients with concomitant psoriatic arthritis be managed?

This chapter is based on the previous chapter [17,18]. An existing systematic review and meta-analysis was updated, details of which can be found in the Methods & Evidence report [5].

Results/Answer [109-112]:

We **recommend** interdisciplinary cooperation with a rheumatologist for the confirmation of the diagnosis of psoriatic arthritis and the selection of a suitable treatment whenever needed.	↑↑	STRONG CONSENSUS[1]  EXPERT CONSENSUS

[1] due to personal-financial conflict of interest 4 abstentions

Treatments are usually categorized as NSAIDs (e. g. diclofenac), conventional synthetic disease modifying anti rheumatic drugs (csDMARDs) e. g. MTX, targeted synthetic (ts)DMARDS (e.g. apremilast) and biological (b)DMARDs (e. g. TNF-antagonists).

Head to head trials allowing direct comparison between the different groups or between the individual drugs are extremely rare. Indirect comparisons, e.g. network meta-analyses, are limited by the low number of trials for psoriatic arthritis. See Table 41 for an overview of RCT data on psoriatic arthritis.

Table 41: Summary of the results for drugs approved for psoriasis of the skin and psoriatic arthritis (Dressler et al [113] updated, see methods report)

	Patients achieving ACR20			Patients with at least one adverse event		
	RR	95% CI	Quality of the Evidence (GRADE)	RR	95% CI	Quality of the Evidence (GRADE)
Head-to-head comparisons						
ETA 50mg + MTX vs. MTX 20mg QW	1.28	1.11 to 1.48	LOW	1.01	0.92 to 1.11	MODERATE
INF 5mg/kg W 0, 2, 6, 14 + MTX vs. MTX 15mg QW	1.40	1.07 to 1.84	VERY LOW	1.65	1.08 to 2.52	VERY LOW
IXE 80mg Q2W vs. ADA 40mg Q2W	1.08	0.86 to 1.36	LOW	1.02	0.83 to 1.25	MODERATE
IXE 80mg Q4W vs. ADA 40mg Q2W	0.96	0.86 to 1.06	LOW	1.14	1.01 to 1.28	VERY LOW
Placebo comparisons						
ADA 40mg EOW vs. PBO	3.35	2.24 to 4.99	MODERATE	0.67	0.50 to 0.89	VERY LOW
APR 30mg BID vs. PBO	1.94	1.59 to 2.38	MODERATE	1.24	1.12 to 1.36	LOW
APR 20mg BID vs PBO	1.86	1.49 to 2.31	MODERATE	1.27	1.15 to1.41	LOW

CZP 400mg Q4W vs. PBO	2.36	1.68 to 3.31	MODERATE	1.05	0.90 to 1.23	MODERATE
CZP 200mg Q2W vs. PBO	2.71	1.95 to 3.76	MODERATE	1.01	0.86 to 1.19	MODERATE
ETA 25mg BIW vs. PBO	4.05	2.56 to 6.40	LOW	n.d.		
INF 5mg/kg W 0, 2, 6, 14 vs. PBO	4.38	2.24 to 8.56	MODERATE	1.13	0.87 to 1.47	LOW
IXE 80mg Q2W vs. PBO	2.21	1.71 to 2.86	MODERATE	1.39	1.09 to 1.78	LOW
IXE 80mg Q4W vs. PBO	2.25	1.59 to 3.18	MODERATE	1.41	1.10 to 1.79	LOW
MTX 7.5mg QW vs. PBO	1.82	0.97 to 3.40	LOW	n.d.		
SEC 150mg Q4W vs. PBO	2.44	2.10 to 2.84	HIGH	1.03	0.95 to 1.12	HIGH
SEC 150mg Q4W **+ LD vs. PBO**	2.06	1.70 to 2.49	HIGH	1.01	0.89 to 1.15	MODERATE
SEC 300mg Q4W **+ LD vs. PBO**	2.28	1.87 to 2.80	MODERATE	1.02	0.89 to 1.16	MODERATE
UST 45mg W 0, 4 and Q12W vs PBO	1.95	1.52 to 2.50	HIGH	n.d.		
UST 90mg W 0, 4 and Q12W* **vs PBO**	2.26	1.80 to 2.82	MODERATE	0.96	0.75 to1.24	VERY LOW

*One study (Gottlieb et al. 2009) reported induction dose of QW (weeks 0-3). Abbreviations: ACR20 = 20% improvement in American College of Rheumatology response criteria; RR = risk ratio; 95% CI = 95% confidence interval; ETA = Etanercept; MTX = Methotrexate; mg = milligrams; QW= once a week; INF = Infliximab; kg = kilograms IXE = Ixekizumab; ADA = Adalimumab; Q2W = once every 2 weeks; EOW = every other week; PBO = placebo; APR = Apremilast; BID = twice a day; CZP = Certolizumab Pegol; Q4W = once every 4 weeks; BIW = twice a week; W = week; Sec = Secukinumab; LD = loading dose; UST = Ustekinumab; Q12W = every 12 weeks.

Non-steroidal anti-inflammatory drugs (NSAIDs)

The role of NSAIDs is usually in the relief of symptoms of psoriatic arthritis for patients with mild and non-erosive articular as well as para-articular involvement. Treatment of NSAIDs should be limited to the lowest required dosage for the shortest period as needed [114].

Conventional synthetic DMARDs (e.g. MTX)

We **recommend** starting a conventional synthetic DMARD (MTX) early to prevent progression of disease and erosive destruction of joints for patients with moderate to severe psoriasis and peripheral active joint involvement (PsA) despite the usage of NSAIDs, or glucocorticoid site injections if applicable and/or potential poor prognosis due to polyarthritis, increased inflammatory markers and erosive changes, and extra-articular musculoskeletal manifestations.	↑↑	STRONG CONSENSUS 100 % Agreement EVIDENCE AND EXPERT CONSENSUS TABLE 41

MTX is recommended, taking the label, the efficacy on skin and peripheral joints, the safety profile and the available long-term experience in the treatment of rheumatic joint disorders into to account[114].

We **do not recommend** synthetic monotherapy DMARDs (MTX) for the treatment of axial involvement or enthesitis, as they appear to be not effective in these patients.	↓↓	STRONG CONSENSUS 100 % Agreement EXPERT CONSENSUS

Biological DMARDs

For inadequately responding patients after at least one synthetic DMARD, we **recommend** the use of biological DMARDs as monotherapy or in combination with synthetic DMARDs.	↑↑	STRONG CONSENSUS 100 % Agreement EVIDENCE AND EXPERT CONSENSUS TABLE 41
For the selection of a bDMARD for patients with moderate to severe psoriasis of the skin and active joint involvement (PsA), we **recommend** taking aspects of efficacy with regard to skin and the joints, comorbidity, practicability and safety into account.	↑↑	STRONG CONSENSUS 100 % Agreement EXPERT CONSENSUS

[1] due to personal-financial conflict of interest 4 abstentions

Previously, guidelines have given a preference to TNF alpha antagonists over other bDMARDs. In the guideline group's view, a preference for inhibitors of TNF treatments for PsA is no longer mandatory, since ustekinumab and the IL-17A antibody treatments might be equally effective; however more data are needed for its real-life long term efficacy, safety and co-medication. The treatment with a biological DMARD can be performed in monotherapy or in combination with a conventional synthetic DMARD.

Other treatment options

As apremilast is less efficacious than bDMARDs, it is suggested for patients with psoriatic arthritis and an inadequate response to at least one csDMARD, in whom biological treatments are not appropriate. Local injection of glucocorticoids can be recommended in patients with active mono- or oligoarthritis, dactylitis and in entheseal areas (enthesitis). Systemic usage of glucocorticoids should not be standard for treatment of psoriatic arthritis, but if needed, e. g. during flares, "systemic steroids at the lowest effective dose may be used with caution" [115]. Tapering of glucocorticoids should be done slowly and step-wise when feasible.

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British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020 - a rapid update

Zielsetzung/Fragestellung

The overall aim of the guideline is to provide up-to-date, evidence-based recommendations on the use of biologic therapies targeting TNF (adalimumab, etanercept, certolizumab pegol, infliximab), IL12/23p40 (ustekinumab), IL17A (ixekizumab, secukinumab), IL17RA (brodalumab) and IL23p19 (guselkumab, risankizumab, tildrakizumab) in adults, children and young people for the treatment of psoriasis;

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt; The guideline and supplementary information was made available to the BAD membership, British Society for Paediatric Dermatology, British Dermatological Nursing Group, Primary Care Dermatological Society, British Society for Paediatric and Adolescent Rheumatology, British Society of Rheumatology, Royal College of Obstetrics and Gynaecology, Psoriasis and Psoriatic Arthritis Alliance, Psoriasis Association and relevant pharmaceutical companies (see Appendix M in File S2 for the full list of stakeholders), comments from whom were actively considered by the GDG. The finalized version was peer reviewed by the Clinical Standards Unit of the BAD, made up of the Therapy & Guidelines subcommittee, prior to submission for publication.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- All searches were conducted in PubMed, MEDLINE, EMBASE and Cochrane databases to identify key articles relevant to the questions.
- All searches for this draft version were completed on 7th September 2018 to ensure recommendations remain current to the best available evidence;
- This 2019 guideline updates the previous version.
- An annual literature review is planned for this fast-moving subject and the recommendations updated where necessary, in line with the BAD's recommended guideline development methodology

LoE/GoR:

Table I.3 Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	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	Any estimate of effect is very uncertain

For each comparison, e.g. drug A vs. placebo, the quality of the body of evidence is determined by the majority of the lowest quality rating amongst the ***critical*** outcomes;

Strength	Wording	Symbols	Definition
Strong recommendation *for* the use of an intervention	'Offer' *(or similar, e.g.* *'provide', 'advise', 'screen')*	↑↑	Benefits of the intervention outweigh the risks; most patients would choose the intervention while only a small proportion would not; for clinicians, most of their patients would receive the intervention; for policy makers, it would be a useful performance indicator
Weak recommendation *for* the use of an intervention	'Consider'	↑	Risks and benefits of the intervention are finely balanced; many patients would choose the intervention but many would not; clinicians would need to consider the pros and cons for the patient in the context of the evidence; for policy makers, it would be a poor performance indicator where variability in practice is expected
No recommendation		ɵ	Insufficient evidence to support any recommendation
Strong recommendation *against* the use of an intervention	'Do not offer'	↓↓	Risks of the intervention outweigh the benefits; most patients would *not* choose the intervention while only a small proportion would; for clinicians, most of their patients would *not* receive the intervention

↑

Empfehlungen

Using biologic therapy

- R1 (↑↑) Initiation and supervision of biologic therapy for people with psoriasis should be undertaken by specialist physicians experienced in the diagnosis and treatment of psoriasis. Routine monitoring may be delegated to other healthcare professionals, for

example clinical nurse specialists. Manage psoriatic arthritis and/or multimorbidity in consultation with the relevant healthcare professionals.

- R2 (↑↑) Agree and formalize arrangements for drug administration, monitoring and follow-up between health carers and the person receiving treatment.
- R3 (↑↑) Offer people with psoriasis who are starting biologic therapy the opportunity to participate in long-term safety registries Empfehlung 1 (Empfehlungsgrad)

Criteria for biologic therapy

- R4 (↑↑) Offer biologic therapy to people with psoriasis requiring systemic therapy if methotrexate and ciclosporin have failed, are not tolerated or are contraindicated (see NICE guidelines CG153)7 and the psoriasis has a large impact on physical, psychological or social functioning (for example, Dermatology Life Quality Index (DLQI) or Children's DLQI > 10 or clinically relevant depressive or anxiety symptoms) and one or more of the following disease severity criteria apply:
  - the psoriasis is extensive [defined as body surface area (BSA) > 10% or Psoriasis Area and Severity Index (PASI) ≥ 10]
  - the psoriasis is severe at localized sites and associated with significant functional impairment and/or high levels of distress (for example nail disease or involvement of high-impact and difficult-to-treat sites such as the face, scalp, palms, soles, flexures and genitals).
- R5 (↑) Consider biologic therapy earlier in the treatment pathway (e.g. if methotrexate has failed, is not tolerated or is contraindicated) in people with psoriasis who fulfil the disease severity criteria and who also have active psoriatic arthritis (see the NICE musculoskeletal conditions overview)8 or who have psoriasis that is persistent, i.e. that relapses rapidly (defined as > 50% baseline disease severity within 3 months of completion of any treatment) off a therapy that cannot be continued in the long term

Prescribing biologic therapy

- R6 (↑↑) Be aware of the benefits of, contraindications to and adverse effects associated with biologic therapies and reference the drug-specific SPCs (www.medicines.org.uk/emc).
- R7 (↑↑) Provide high-quality, evidence-based information to people being prescribed biologic therapies. Explain the risks and benefits to people undergoing this treatment (and their families or carers where appropriate), using absolute risks and natural frequencies when possible
- R8 (↑↑) Support and advice should be offered to people with psoriasis (and their families or carers where appropriate) by healthcare professionals who are trained and competent in the use of biologic therapies

Reviewing biologic therapy

- R9 (↑↑) Assess initial response to biologic therapy in people with psoriasis at time points appropriate for the drug in question, and then on a regular basis during therapy (e.g. every 6 months); see File S1: Table S1 – Summary of licensed indications and posology for biologic therapy.
- R10 (↑↑) Review response to biologic therapy by taking into account
  - psoriasis disease severity compared with baseline (e.g. PASI baseline to end point score)9
  - the agreed treatment goal
  - control of psoriatic arthritis disease activity and/or inflammatory bowel disease (in consultation with a rheumatologist and/or gastroenterologist)
  - the impact of psoriasis on the person's physical, psychological and social functioning
  - the benefits vs. the risks of continued treatment
  - the views of the person undergoing treatment (and their family or carers, where appropriate)
  - adherence to the treatment.
- R11 (↑↑) Assess whether the minimal response criteria have been met, as defined by
  - ≥ 50% reduction in baseline disease severity (e.g. PASI 50 response, or percentage BSA where PASI is not applicable) and
  - clinically relevant improvement in physical, psychological or social functioning (e.g. ≥ 4point improvement in DLQI or resolution of low mood)
- R12 (↑) Consider changing to an alternative therapy, including another biologic therapy, if any of the following applies:
  - the psoriasis does not achieve the minimum response criteria (primary failure – see R11)
  - the psoriasis initially responds but subsequently loses this response (secondary failure)

Choice of biologic therapy: general considerations

- R13 (↑↑) Before initiating or making changes to biologic therapy, take into account both psoriasis and psoriatic arthritis and manage treatment in consultation with a rheumatologist or paediatric rheumatologist. Be aware that the presence of and phenotype of psoriatic arthritis (e.g. peripheral vs. axial disease) may influence access to, choice of and dose of biologic therapy. Actively screen for psoriatic arthritis (in people without this diagnosis), using a validated tool, e.g. Psoriasis Epidemiology Screening Tool (PEST), and be aware that the PEST may not detect axial arthritis/inflammatory back pain.
- R14 (↑↑) Tailor the choice of agent to the needs of the person. Take into account the following factors (See File S1: Table S2 – Decision aid):

Psoriasis factors

- the goal of therapy [for example Physician's Global Assessment (PGA) of clear or nearly clear]
- disease phenotype and pattern of activity disease severity and impact
- the presence of psoriatic arthritis (in consultation with an adult or paediatric rheumatologist)
- the outcomes of previous treatments for psoriasis.

Other individual factors

- person's age
- past or current comorbid conditions (e.g. inflammatory bowel disease, heart failure)
- conception plans
- body weight
- the person's views and any stated preference on administration route or frequency
- likelihood of adherence to treatment

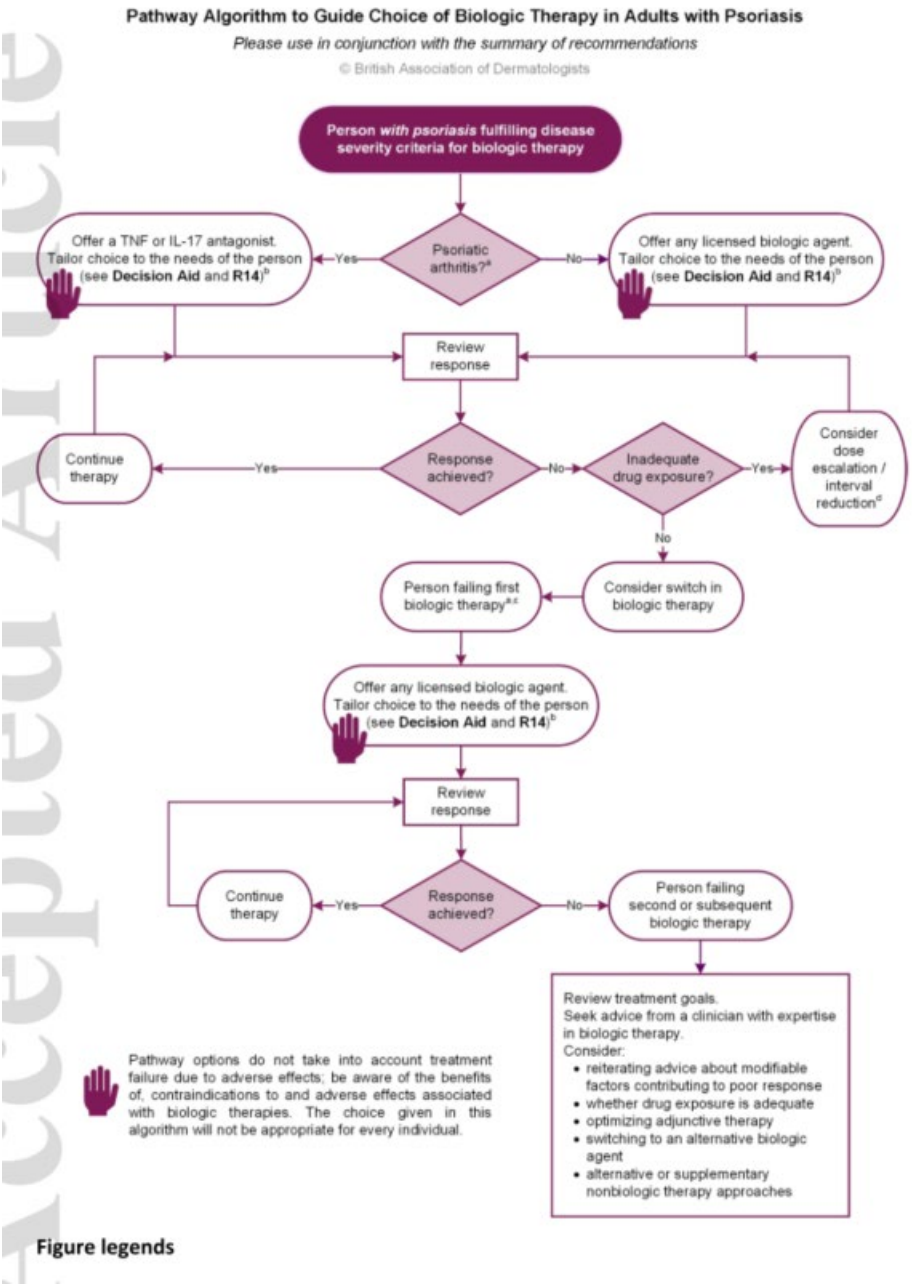
Choice of biologic therapy in adults

- R15 (↑↑) Offer any of the currently licensed biologic therapies as first-line therapy (and with reference to R18 and R19) to adults with psoriasis who fulfil the criteria for biologic therapy (see R4 and R5), using the decision aid (see File S1: Table S2) to inform treatment choice.
- R16 (↑↑) Offer any of the currently licensed biologic therapies (and with reference to R18 and R19) when psoriasis has not responded to a first biologic therapy. Use the decision aid (see File S1: Table S2) and take into account all factors detailed in R14 to select the most appropriate agent.
- R17 (↑↑) Offer a TNF antagonist (and with reference to R18 and R19) or an IL-17 antagonist* as a first-line therapy to adults with psoriasis and who also have psoriatic arthritis, using the decision aid (see File S1: Table S2) to inform treatment choice.10-13 *Please note that brodalumab is not licensed for psoriatic arthritis.
- R18 (↑) Consider etanercept for use in people where a TNF antagonist is indicated and other available biologic agents have failed or cannot be used, or where a short half-life is important.
- R19 (↑↑) Reserve infliximab for use in people with very severe disease, or where other available biologic agents have failed or cannot be used, or where weight-based dosing is a priority.

What to do when a second or subsequent biologic therapy fails in adults

- R21 (↑↑) When a person's psoriasis responds inadequately to a second or subsequent biologic agent, review treatment goals, seek advice from a dermatologist with expertise in biologic therapy and consider any of the following strategies:

- reiterate advice about modifiable factors contributing to poor response such as obesity and poor adherence (intentional or non-intentional)
- consider whether drug exposure is adequate (see R20)
- optimize adjunctive therapy (e.g. switch from oral to subcutaneous methotrexate)
- switch to an alternative biologic agent
- alternative or supplementary nonbiologic therapy approaches (e.g. inpatient topical therapy, phototherapy, or systemic therapies).



Backgroundinfos aus Leitlinien: siehe Anhang

Gossec et al., 2019 [9].

European League Against Rheumatism (EULAR)

EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update

Zielsetzung/Fragestellung

To update the European League Against Rheumatism (EULAR) recommendations for the pharmacological treatment of psoriatic arthritis (PsA) from 2015.

The objective of this taskforce, therefore, was to update the EULAR recommendations for the management of PsA with non- topical, pharmacological therapies.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium; The taskforce consisted of 28 persons from 15 European countries with 15 different healthcare systems: 21 rheumatologists, 2 people affected with PsA, 1 health professional, 1 dermatologist and 3 rheumatology fellows/trainees. The taskforce comprised more than 30% new members compared with 2015.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz; The SLR was performed between October 2018 and May 2019, Where relevant and based on expert opinion, data made available after the end of the SLR were also integrated.
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt; Each recommendation was discussed in detail both in smaller (breakout) groups and in plenary sessions until consensus was reached.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Siehe SR (Kerschbaumer et al. 2020)
- Embase, Medline and the Cochrane Library without language restriction. Based on the previous SLR, the search included all studies published between 1 January 2015 and 21 December 2018 (last date searched).

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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

9 Oxford Centre for Evidence-based Medicine Levels of Evidence. March 2009. http://www.cebm.net/?o=1116

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

- For changes to existing recommendations against which no new evidence has accrued since the last update, a ≥75% vote by the taskforce was mandated in order to prevent new taskforces from reformulating without major reasoning what had previously been developed based on the evidence presented at that point in time. If this majority was not reached, the recommendation was not changed. New recommendations were formulated and then accepted if ≥75% of the members agreed; if this agreement was not reached, the recommendation was reworded and subjected to a renewed vote for which a ≥67% majority was required. If this was not achieved, the wording underwent a next round of discussion and the new phrasing was approved if >50% of the taskforce members voted for it.
- After the face- to- face meeting, the taskforce members were provided with the category of evidence and grade of recommendation for each item, based on the Oxford Evidence Based Medicine categorisation, as per the EULAR procedures.21 22 Then an anonymised, email- based voting on the level of agreement among the taskforce members was performed on a 0–10 scale (with 10 meaning full agreement) allowing calculation of mean levels of agreement.

Empfehlungen

- New recommendation 5, 7, 12
- Modified recommendation 4, 6, 8, 9, 10, 11 from 2015 version

Recommendation

Table 1 2019 EULAR recommendations for the pharmacological management of psoriatic arthritis, with levels of evidence, grade of recommendations and level of agreement

	Overarching principles	Level of agreement, mean (SD)
A	Psoriatic arthritis is a heterogeneous and potentially severe disease, which may require multidisciplinary treatment.	9.9 (0.4)
B	Treatment of psoriatic arthritis patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist, considering efficacy, safety and costs.	9.8 (0.5)
C	Rheumatologists are the specialists who should primarily care for the musculoskeletal manifestations of patients with psoriatic arthritis; in the presence of clinically significant skin involvement, a rheumatologist and a dermatologist should collaborate in diagnosis and management.	9.8 (0.7)
D	The primary goal of treating patients with psoriatic arthritis is to maximise health-related quality of life, through control of symptoms, prevention of structural damage, normalisation of function and social participation; abrogation of inflammation is an important component to achieve these goals.	9.9 (0.4)
E	In managing patients with psoriatic arthritis, consideration should be given to each musculoskeletal manifestation and treatment decisions made accordingly.	9.9 (0.3)
F	When managing patients with psoriatic arthritis, non-musculoskeletal manifestations (skin, eye and gastrointestinal tract) should be taken into account; comorbidities such as metabolic syndrome, cardiovascular disease or depression should also be considered.	9.8 (0.6)

	Recommendations	Level of evidence	Grade of recommendation	Level of agreement, mean (SD)
1	Treatment should be aimed at reaching the target of remission or, alternatively, low disease activity, by regular disease activity assessment and appropriate adjustment of therapy.	1b	A	9.4 (1.0)
2	Non-steroidal anti-inflammatory drugs may be used to relieve musculoskeletal signs and symptoms.	1b	A	9.6 (0.8)
3	Local injections of glucocorticoids should be considered as adjunctive therapy in psoriatic arthritis*; systemic glucocorticoids may be used with caution at the lowest effective dose†.	3b* 4†	C	9.5 (1.1)
4	In patients with polyarthritis, a csDMARD should be initiated* rapidly†, with methotrexate preferred in those with relevant skin involvement*.	1b* 5†	B	9.5 (0.8)
5	In patients with monoarthritis or oligoarthritis, particularly with poor prognostic factors such as structural damage, high erythrocyte sedimentation rate/C reactive protein, dactylitis or nail involvement, a csDMARD should be considered.	4	C	9.3 (1.0)
6	In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a bDMARD should be commenced; when there is relevant skin involvement, an IL-17 inhibitor or IL-12/23 inhibitor may be preferred.	1b	B	9.4 (1.1)
7	In patients with peripheral arthritis and an inadequate response to at least one csDMARD and at least one bDMARD, or when a bDMARD is not appropriate, a JAK inhibitor may be considered.	1b	B	9.2 (1.3)
8	In patients with mild disease* and an inadequate response to at least one csDMARD†, in whom neither a bDMARD nor a JAK inhibitor is appropriate*, a PDE4 inhibitor may be considered.	5* 1b†	B	8.5 (1.9)
9	In patients with unequivocal enthesitis and insufficient response to NSAIDs or local glucocorticoid injections, therapy with a bDMARD should be considered.	1b	B	9.3 (0.9)
10	In patients with predominantly axial disease which is active and has insufficient response to NSAIDs, therapy with a bDMARD should be considered, which according to current practice is a TNF inhibitor; when there is relevant skin involvement, IL-17 inhibitor may be preferred.	1b	B	9.7 (0.6)
11	In patients who fail to respond adequately to, or are intolerant of a bDMARD, switching to another bDMARD or tsDMARD should be considered*, including one switch within a class†.	1b* 4†	C	9.5 (1.2)
12	In patients in sustained remission, cautious tapering of DMARDs may be considered.	4	C	9.5 (0.9)

The level of agreement was computed on a 0–10 scale.
csDMARDs include methotrexate, sulfasalazine or leflunomide; bDMARDs include here TNF inhibitors (both original and biosimilars) and drugs targeting the IL-17 and IL-12/23 pathways.
bDMARDs, biological disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; DMARDs, disease-modifying antirheumatic drugs; EULAR, European League Against Rheumatism; IL, interleukin; JAK, Janus kinase; NSAIDs, non-steroidal anti-inflammatory drugs; PDE4, phosphodiesterase-4; TNF, tumour necrosis factor.

Hintergrundinformation zu Empfehlungen 5,6,7,8

Recommendation 5: In patients with monoarthritis or oligoarthritis, particularly with poor prognostic factors such as structural damage, high erythrocyte sedimentation rate/c reactive protein, dactylitis or nail involvement, a csDMARD should be considered. This recommendation emphasises that patients with oligoarticular disease should (similar to polyarticular patients) receive a csDMARD rapidly in the presence of poor prognostic factors (please see the text of the recommendation). Concerning factors associated with poor prognosis (here defined as radiographic severity), the SLR identified nail involvement in addition to those factors presented in 2011 and 2015, and this element was added accordingly to the phrasing of recommendation 5.[51 52] Dactylitis was previously addressed together with enthesitis (see recommendation 9 in 2015). However, these manifestations have now been separated. The taskforce considered that dactylitis was distinct in terms of physiopathology, diagnosis and prognosis, since it is linked to radiographic changes in PsA, whereas enthesitis is not.[53] Furthermore, although there is a lack of good- quality data, recent studies suggest at least some efficacy of MTX in dactylitis.[41 42] Thus, dactylitis should now be treated similarly to arthritis, and if associated with polyarticular disease it should be treated like polyarthritis. Of note, NSAIDs have not demonstrated efficacy in dactylitis. Given the lack of strong data on oligoarticular PsA, this recommendation was based more on expert opinion than on hard data (level of evidence, 4; grade of recommendation: C).

Recommendation 6: In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a bDMARD should be commenced; when there is relevant skin involvement, an IL-17 inhibitor or IL-12/23 inhibitor may be preferred.

This recommendation addresses patients with peripheral arthritis, after failure or intolerance to at least one csDMARD. In these patients, the taskforce recommends a bDMARD. In some patients, especially those without bad prognostic factors or those with mild disease activity, it may be indicated to rotate to a second csDMARD before starting a bDMARD, as previously outlined in the 2015 recommendations.[12] The taskforce extensively discussed the legitimacy of a bDMARD as first DMARD strategy; the discussion focused on

efficacy and safety, as well as on costs. The taskforce was of the opinion that many patients respond satisfactorily to MTX, while tolerating the drug well. These patients would be subjected to overtreatment if starting a bDMARD immediately rather than waiting for 3 months to determine if a response to MTX has occurred (see recommendations 9 and 10). A good example is revealed in the SEAM- PsA trial. However, if entheseal or axial inflammatory involvement predominates, earlier use of bDMARDs is proposed, since csDMARDs are ineffective in these conditions (please see recommendations 9 and 10). Whereas the 2015 recommendation stated that it was 'usual practice' to start a TNFi in comparison with other bDMARDs, the current update does not distinguish anymore between TNFi, IL-12/23 inhibitor (IL-12/23i) and IL-17 inhibitor (IL- 17i). The SLR reconfirmed the efficacy of TNFi in PsA, and there are now reassuring long- term safety data with these drugs, including data indicating that the incidence of malignancies is not increased.[54 55] Drugs targeting IL-12/23 and IL-17 are also consistently efficacious in comparison with placebo and long- term safety seems favourable.[1] In addition to secukinumab, a second IL- 17i, ixekizumab, has been approved since the 2015 recommendations, showing a similar efficacy and safety profile, which further reassured the taskforce.[14 56] Importantly, a head- to- head trial of ixekizumab versus the TNFi adalimumab showed similar efficacy of ixekizumab and adalimumab for musculoskeletal manifestations.[57]

Of note, efficacy in joints appeared numerically less for the IL-12/23i ustekinumab; however, observational data indicate similar magnitudes of response versus TNFi, and a formal headto- head trial is currently lacking.[13 58] Furthermore, the taskforce noted that recent studies with biologicals targeting the IL-23- p19 subunit (**guselkumab**, risankizumab, tildrakizumab) appear encouraging, and that targeting this pathway has shown excellent efficacy in psoriasis.[59–63] Thus, a suggested order between different targeted pathways is intentionally not given in this recommendation. The total safety picture of these three categories of bDMARDs appeared acceptable in our SLR.[1] The risks of TNFi are well known from large registries for long- term safety including these drugs. IL- 17i may increase the incidence of (mild) localised candidiasis, and monitoring for a possible increased risk of inflammatory bowel disease is still ongoing.[64] In any case, safety must always be considered carefully in every patient; more complete information regarding the safety aspects of bDMARDs is provided in the drugs' package inserts. Taking together data on efficacy and safety, with regard to the treatment of arthritis in PsA, the taskforce found no reason to currently prioritise one of these bDMARDs over another one (as shown also in figure 1); costs should also be taken into account, and these may vary at the country level. In contrast, both IL-12/23i and IL- 17i have shown greater efficacy in skin than TNFi, in head- to- head trials of psoriasis and PsA[62 65 66]; this evidence justifies the second half of the recommendation, which encourages the use of an IL-12/23i or IL- 17i in patients with relevant skin involvement, where 'relevant' is defined (as above) as either extensive or as important to the patient. When choosing a first bDMARD, the differential impact on certain musculoskeletal and non- musculoskeletal manifestations as well as comorbidities such as metabolic syndrome has to be considered. While important skin involvement was already mentioned, IL-12/23 inhibition may not be effective for axial involvement; IL-17 inhibition may not be appropriate for patients with concomitant inflammatory bowel disease for which monoclonal antibodies to TNF and IL-12/23 inhibitors are approved; and in the presence of uveitis, a monoclonal antibody to TNF may be the preferred first and second bDMARD because of respective approval.[67 68] On the other hand, regarding comorbidities, the paucity of relevant data precludes firm recommendations at present; this has been added to the research agenda. The issue of monotherapy with bDMARDs versus combination therapy with a csDMARD was discussed.[69 70] The current recommendation is to continue MTX with a bDMARD (using the latter as an add- on strategy) in patients already

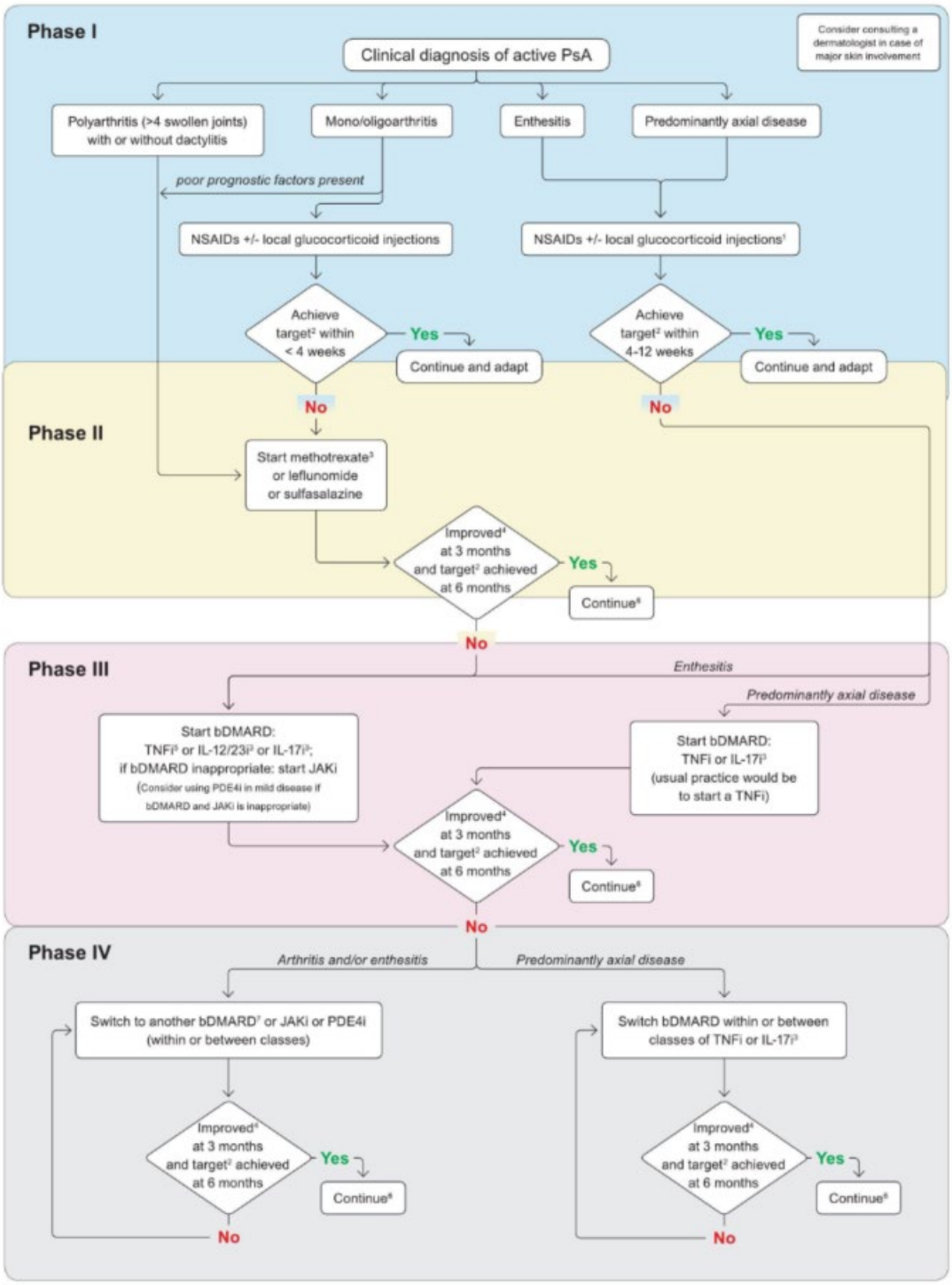
taking this drug and tolerating it well, but the taskforce admitted that to date there is no clear evidence that combination therapy is more efficacious than monotherapy, aside from a slight reduction of immunogenicity that is of doubtful clinical significance.[71] We suggest that MTX dose may be reduced in subjects showing a good biological drug response, especially when there are concerns about MTX toxicity. However, more data are needed and this point was put into the research agenda.

Recommendation 7: In patients with peripheral arthritis and an inadequate response to at least one csDMARD and at least one bDMARD, or when a bDMARD is not appropriate, a JAK inhibitor may be considered.

At this moment, the only JAK inhibitor (JAKi) approved for PsA is tofacitinib. Our SLR indicated tofacitinib may have similar efficacy as the TNFi adalimumab for joint involvement, but numerically lower efficacy in skin psoriasis.[1 15 72] There also appears to be satisfactory efficacy of tofacitinib in TNFi insufficient- responder populations.[1] According to European Medicines Agency approval, tofacitinib must be prescribed with MTX. Safety signals exist for some infections, especially herpes zoster, as well as a recent signal for deep vein thrombosis especially with a high dose of tofacitinib which is not approved for PsA, but also the usual 5 mg twice daily dose particularly in those with cardiovascular risk factors and older patients.[15 72 73] To date, two other JAKis are in development phases for PsA. Filgotinib showed promising efficacy in a phase II trial and **upadacitinib** was approved for use in rheumatoid arthritis shortly after the development of these recommendations, and also showed encouraging results in PsA.[16] *Hinweis der FBMed: die zugrundeliegende Studie 16 untersucht nicht den Einfluss von Upadacitinib sondern Filgotinib.*

Taking these elements into account, as well as the general principle of favouring drugs with robust long- term safety data, the taskforce proposed JAKi either after inadequate response or intolerance to at least one bDMARD, or when a bDMARD is considered not appropriate. 'Not appropriate' means, for example, non- adherence to injections or a strong patient preference for an oral drug (in accordance with the overarching principle A concerning 'shared decision making'). However, the group agreed that normally the step-up approach would be a csDMARD followed by a bDMARD, and subsequently another bDMARD or a JAKi. As new data become available, the current positioning of JAKis may evolve; this will justify an update of the recommendations if appropriate.

Recommendation 8: In patients with mild disease and an inadequate response to at least one csDMARD, in whom neither a bDMARD nor a JAK inhibitor is appropriate, a PDE4 inhibitor may be considered. Similar to the 2015 update, this recommendation reserves a special place for apremilast: it should be used only when csDMARD therapy has failed and bDMARDs and JAKi are not appropriate; however, the taskforce considered that the value of apremilast may be found in treating patients with relatively mild disease or those in whom other agents are contraindicated, such as in patients with chronic infections. Mild disease is defined here as only few joints (four or less, thus oligoarticular disease), lower disease activity by composite scores and/or limited skin involvement. The reason for proposing the use of apremilast primarily for mild disease is that profound responses, such as Amercian College of Rheumatology 70% (ACR70), are rarely seen in clinical trials with apremilast and are sometimes not different from placebo.[11 74–77] Moreover, radiographic data providing the disease- modifying potential of the drug are still lacking for apremilast, and therefore this drug may not be appropriate for patients with poor prognostic factors. A randomised controlled trial with apremilast in oligoarticular disease is currently under way.[78] The level of agreement with this recommendation was lower than for the others, suggesting diverse expert views on the place of this drug.



1. No glucocorticoids for axial disease.
2. The target is remission or low disease activity (especially with long standing disease) in accordance with the treat-to-target recommendations.
3. Preferred in the presence of relevant skin involvement, however in case of concomitant inflammatory bowel disease or uveitis, an anti-TNF antibody would be preferred.
4. Improvement means at least 50% reduction in disease activity.
5. As add-on to methotrexate.
6. Consider cautious tapering in sustained remission.
7. Including abatacept.
8. For definition of individual items see text. Phase I: recommendations 1, 2, 3, 4, 5; Phase II: recommendations 1, 3, 4, 5, 12; Phase III: recommendations 6, 8, 9, 10, 12; Phase IV: recommendations 7, 11,12

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American College of Rheumatology/National Psoriasis Foundation

Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis

Leitlinienorganisation/Fragestellung

To develop an evidence-based guideline for the pharmacologic and nonpharmacologic treatment of psoriatic arthritis (PsA), as a collaboration between the American College of Rheumatology (ACR) and the National Psoriasis Foundation (NPF).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt; a voting panel, including rheumatologists, dermatologists, other health professionals, and patients, achieved consensus on the direction and the strength of the recommendations
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology was used to rate the quality of the evidence & Cochrane risk of bias tool
- Regelmäßige Überprüfung der Aktualität gesichert; A Literature Review Team performed a systematic literature review (through November 15, 2016 & conducted updated searches on May 2, 2017 and again on March 8, 2018) to summarize evidence supporting the benefits and harms of available pharmacologic and non-pharmacologic therapies for PsA.

- Identification of critical outcomes in PsA and clinically relevant PICO (population/intervention/comparator/ outcomes) questions.

Recommendations for pharmacologic interventions

Active PsA in treatment-naive patients:

Note: All recommendations for treatment-naive patients with active PsA are conditional based on low- to very-low quality evidence.

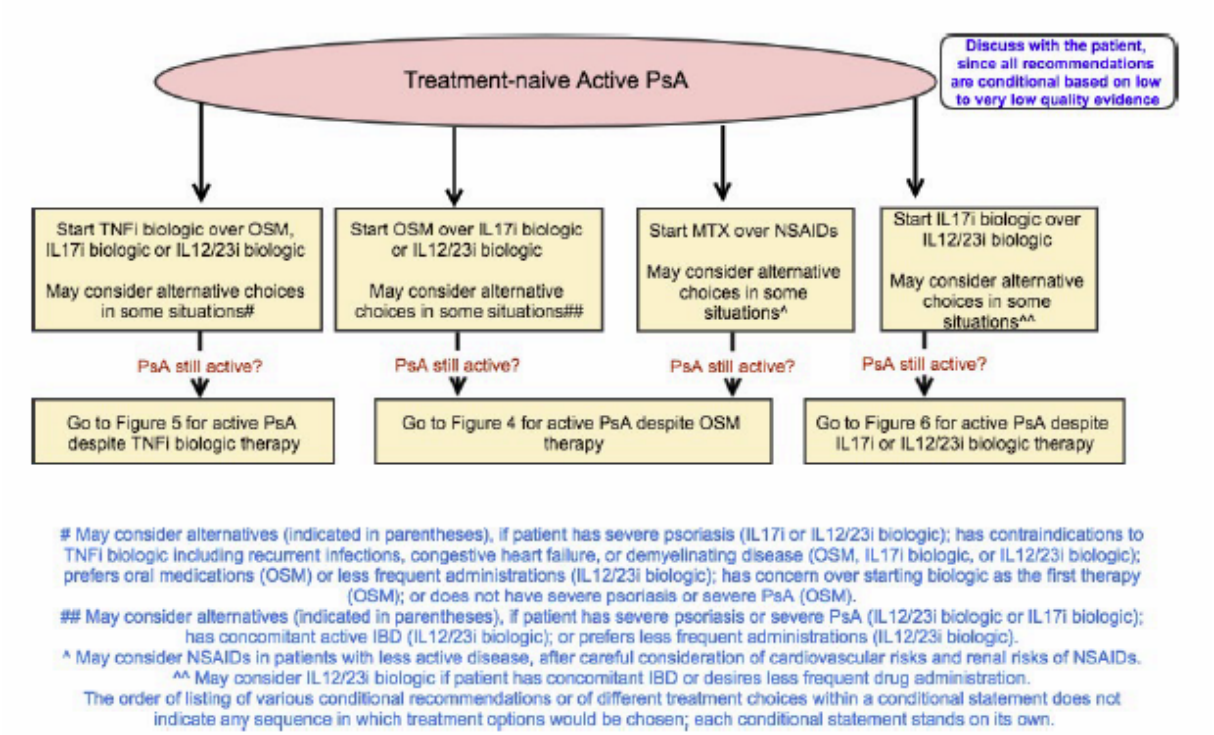
	Level of evidence (evidence [refs.] reviewed)†
In OSM- and other treatment–naive patients with active PsA,	
1. **Treat with a TNFi biologic over an OSM** (MTX, SSZ, LEF, CSA, or APR) (PICO 10a–e) **Conditional recommendation** based on low-quality evidence; may consider an OSM if the patient does not have severe PsA,‡ does not have severe psoriasis,§ prefers oral therapy, has concern over starting a biologic as the first therapy, or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Low (53–66)
2. **Treat with a TNFi biologic over an IL-17i biologic** (PICO 14) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-17i biologic if the patient has severe psoriasis or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
3. **Treat with a TNFi biologic over an IL-12/23i biologic** (PICO 13) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-12/23i biologic if the patient has severe psoriasis, prefers less frequent drug administration, or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
4. **Treat with an OSM over an IL-17i biologic** (PICO 12) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-17i biologic if the patient has severe psoriasis and/or severe PsA.	Very low
5. **Treat with an OSM over an IL-12/23i biologic** (PICO 11) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-12/23i biologic if the patient has concomitant IBD and/or severe psoriasis and/or severe PsA or prefers less frequent drug administration.	Very low
6. **Treat with MTX over NSAIDs** (PICO 9) **Conditional recommendation** based on very-low-quality evidence; may consider NSAIDs before starting MTX in patients with less active disease, after careful consideration of cardiovascular risks and renal risks of NSAIDs.	Very low (67)
7. **Treat with an IL-17i biologic over an IL-12/23i biologic** (PICO 15) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-12/23i biologic if the patient has concomitant IBD or prefers less frequent drug administration.	Very low

* Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD). Oral small molecules (OSMs) are defined as methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), cyclosporine (CSA), or apremilast (APR) and *do not* include tofacitinib, which was handled separately since its efficacy/safety profile is much different from that of other OSMs listed above. OSM- and other treatment-naive is defined as naive to treatment with OSMs, tumor necrosis factor inhibitors (TNFi,) interleukin-17 inhibitors (IL-17i), and IL-12/23i; patients may have received nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids, and/or other pharmacologic and nonpharmacologic interventions.

† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.

‡ Because there are currently no widely agreed-upon definitions of disease severity, PsA severity should be established by the health care provider and patient on a case-by-case basis. For the purposes of these recommendations, severity is considered a broader concept than disease activity in that it encompasses the level of disease activity at a given time point, as well as the presence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of ≥1 of the following: a poor prognostic factor (erosive disease, elevated levels of inflammation markers such as C-reactive protein or erythrocyte sedimentation rate attributable to PsA), long-term damage that interferes with function (e.g., joint deformities, vision loss), highly active disease that causes major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease.

§ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.



May consider alternatives (indicated in parentheses), if patient has severe psoriasis (IL17i or IL12/23i biologic); has contraindications to TNFi biologic including recurrent infections, congestive heart failure, or demyelinating disease (OSM, IL17i biologic, or IL12/23i biologic); prefers oral medications (OSM) or less frequent administrations (IL12/23i biologic); has concern over starting biologic as the first therapy (OSM); or does not have severe psoriasis or severe PsA (OSM).
May consider alternatives (indicated in parentheses), if patient has severe psoriasis or severe PsA (IL12/23i biologic or IL17i biologic); has concomitant active IBD (IL12/23i biologic); or prefers less frequent administrations (IL12/23i biologic).
^ May consider NSAIDs in patients with less active disease, after careful consideration of cardiovascular risks and renal risks of NSAIDs.
^^ May consider IL12/23i biologic if patient has concomitant IBD or desires less frequent drug administration.
The order of listing of various conditional recommendations or of different treatment choices within a conditional statement does not indicate any sequence in which treatment options would be chosen; each conditional statement stands on its own.

Figure 3. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) who are treatment-naive (no exposure to oral small molecules [OSMs] or other treatments). All recommendations are conditional based on low- to very-low-quality evidence. A conditional recommendation means that the panel believed the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. Due to the complexity of management of active PsA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show only the key recommendations. For a complete list of recommendations, please refer to the Results section of the text. For the level of evidence supporting each recommendation, see Table 1 and the related section in the Results. This figure is derived from recommendations based on PICO (population/intervention/comparator/outcomes) questions that are based on the common clinical situations. Active PsA was defined as symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining health care provider to be due to PsA based on the presence of at least 1 of the following: actively inflamed joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and/or extraarticular manifestations such as uveitis or inflammatory bowel disease (IBD). TNFi = tumor necrosis factor inhibitor; IL-17i = interleukin-17 inhibitor; MTX = methotrexate; NSAIDs = nonsteroidal antiinflammatory drugs.

Active PsA despite treatment with an OSM

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA despite treatment with an OSM,	
1. **Switch to a TNFi biologic over a different OSM** (PICO 23) **Conditional recommendation** based on moderate-quality evidence; may consider switching to a different OSM if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, if the patient prefers an oral versus parenteral therapy, or in patients without evidence of severe PsA‡ or severe psoriasis.§	Moderate (62–66, 69–86)
2. **Switch to a TNFi biologic over an IL-17i biologic** (PICO 17) **Conditional recommendation** based on moderate-quality evidence; may consider an IL-17i if the patient has severe psoriasis and/or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, and/or a family history of demyelinating disease such as multiple sclerosis.	Moderate (62–66, 72–78, 87–97)
3. **Switch to a TNFi biologic over an IL-12/23i biologic** (PICO 16) **Conditional recommendation** based on moderate-quality evidence; may consider an IL-12/23i if the patient has severe psoriasis and/or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers less frequent drug administration.	Moderate (62–66, 72–78, 97–102)
4. **Switch to a TNFi biologic over abatacept** (PICO 67) **Conditional recommendation** based on low-quality evidence; may consider abatacept if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Low (62–66, 72–78, 103, 104)
5. **Switch to a TNFi biologic over tofacitinib** (PICO 76) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers oral medication.	Low (62–66, 72–78, 105)
6. **Switch to an IL-17i over a different OSM** (PICO 25) **Conditional recommendation** based on low-quality evidence; may consider switching to a different OSM if the patient prefers an oral versus parenteral therapy or in patients without evidence of severe PsA or severe psoriasis.	Low (79–87, 89–95)
7. **Switch to an IL-17i biologic over an IL-12/23i biologic** (PICO 18) **Conditional recommendation** based on moderate-quality evidence; may consider an IL-12/23i biologic if the patient has concomitant IBD or prefers less frequent drug administration.	Moderate (87, 89–95, 98–100, 106, 107)
8. **Switch to an IL-17i biologic over abatacept** (PICO 69) **Conditional recommendation** based on low-quality evidence; may consider abatacept in patients with recurrent or serious infections.	Low (89–95, 103, 104)
9. **Switch to an IL-17i biologic over tofacitinib** (PICO 78) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy or has a history of recurrent *Candida* infections.	Low (89–95, 105)
10. **Switch to an IL-12/23i biologic over a different OSM** (PICO 24) **Conditional recommendation** based on low-quality evidence; may consider switching to a different OSM if the patient prefers an oral versus parenteral therapy or in patients without evidence of severe PsA or severe psoriasis.	Low (79–86, 98–100)
11. **Switch to an IL-12/23i biologic over abatacept** (PICO 68) **Conditional recommendation** based on low-quality evidence; may consider abatacept in patients with recurrent or serious infections.	Low (98–100, 103, 104)

	Level of evidence (evidence [refs.] reviewed)†
12. **Switch to an IL-12/23i biologic over tofacitinib** (PICO 77) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy.	Low (98–100, 105)
13. **Add apremilast to current OSM therapy over switching to apremilast** (PICO 22b) **Conditional recommendation** based on low-quality evidence; may consider switching to apremilast if the patient has intolerable side effects with the current OSM.	Low (83, 84, 108)
14. **Switch to another OSM (except apremilast) over adding another OSM (except apremilast) to current treatment** (PICO 22a) **Conditional recommendation** based on low-quality evidence; may consider adding another OSM (except apremilast) to current treatment if the patient has demonstrated partial response to the current OSM.	Low (83, 84, 108)
15. **Switch to a TNFi biologic monotherapy over MTX and a TNFi biologic combination therapy** (PICO 19) **Conditional recommendation** based on low-quality evidence; may consider MTX and TNFi biologic combination therapy if the patient has severe skin manifestations, has had a partial response to current MTX therapy, has concomitant uveitis (since uveitis may respond to MTX therapy), and if the current TNFi biologic is infliximab or adalimumab.	Low (109–111)
16. **Switch to an IL-17i biologic monotherapy over MTX and an IL-17i biologic combination therapy** (PICO 21) **Conditional recommendation** based on very-low-quality evidence; may consider MTX and an IL-17i biologic combination therapy if the patient has severe skin manifestations, has had a partial response to current MTX therapy, or has concomitant uveitis (since uveitis may respond to MTX therapy).	Very low
17. **Switch to an IL-12/23i biologic monotherapy over MTX and an IL-12/23i biologic combination therapy** (PICO 20) **Conditional recommendation** based on very-low-quality evidence; may consider MTX and an IL-12/23i biologic combination therapy if the patient has severe skin manifestations, has had a partial response to current MTX therapy, or has concomitant uveitis (since uveitis may respond to MTX therapy).	Very low

* Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD). Oral small molecules (OSMs) are defined as methotrexate (MTX), sulfasalazine, leflunomide, cyclosporine, or apremilast and *do not* include tofacitinib, which was handled separately since its efficacy/safety profile is much different from that of other OSMs listed above. TNFi = tumor necrosis factor inhibitor; IL-17i = interleukin-17 inhibitor.

† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.

‡ Because there are currently no widely agreed-upon definitions of disease severity, PsA severity should be established by the health care provider and patient on a case-by-case basis. For the purposes of these recommendations, severity is considered a broader concept than disease activity in that it encompasses the level of disease activity at a given time point, as well as the presence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of ≥1 of the following: a poor prognostic factor (erosive disease, elevated levels of inflammation markers such as C-reactive protein or erythrocyte sedimentation rate attributable to PsA), long-term damage that interferes with function (e.g., joint deformities, vision loss), highly active disease that causes major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease.

§ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

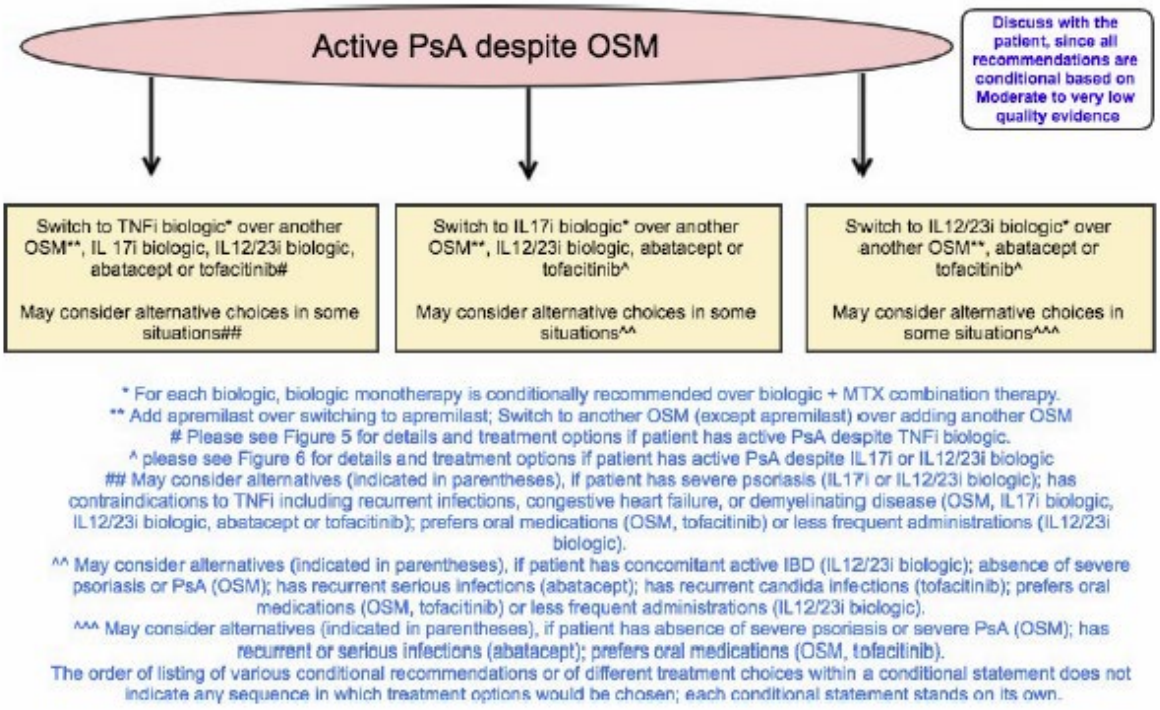


Figure 4. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) despite treatment with oral small molecules (OSMs). All recommendations are conditional based on low- to very-low-quality evidence. A conditional recommendation means that the panel believed the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. Due to the complexity of management of active PsA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show only the key recommendations. For a complete list of recommendations, please refer to the Results section of the text. For the level of evidence supporting each recommendation, see Table 2 and the related section in the Results. TNFi = tumor necrosis factor inhibitor; IL-17i = interleukin-17 inhibitor; MTX = methotrexate.

Active PsA despite treatment with a TNFi biologic agent as monotherapy or in combination therapy

	Level of evidence (evidence [refs.] reviewed)†
In adult patients with active PsA despite treatment with a TNFi biologic monotherapy,	
1. **Switch to a different TNFi biologic over switching to an IL-17i biologic** (PICO 28) **Conditional recommendation** based on low-quality evidence; may consider an IL-17i if the patient had a primary TNFi biologic efficacy failure or a TNFi biologic–associated serious adverse event or severe psoriasis.‡	Low (72, 73, 90–93, 95)
2. **Switch to a different TNFi biologic over switching to an IL-12/23i biologic** (PICO 27) **Conditional recommendation** based on low-quality evidence; may consider an IL-12/23i if the patient had a primary TNFi biologic efficacy failure or a TNFi biologic–associated serious adverse effect or prefers less frequent drug administration.	Low (72, 73, 99, 100)
3. **Switch to a different TNFi biologic over switching to abatacept** (PICO 70) **Conditional recommendation** based on low-quality evidence; may consider abatacept if the patient had a primary TNFi biologic efficacy failure or TNFi biologic–associated serious adverse effect.	Low (72, 73, 103, 104)
4. **Switch to a different TNFi biologic over switching to tofacitinib** (PICO 73) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy or had a primary TNFi biologic efficacy failure or a TNFi biologic–associated serious adverse effect.	Low (62–66, 72–78, 105)
5. **Switch to a different TNFi biologic (with or without MTX) over adding MTX to the same TNFi biologic monotherapy** (PICO 26 and 26A) **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX when patients have demonstrated partial response to the current TNFi biologic therapy, especially if the TNFi biologic is a monoclonal antibody.	Very low
6. **Switch to an IL-17i biologic over switching to an IL-12/23i biologic** (PICO 29) **Conditional recommendation** based on low-quality evidence; may consider an IL-12/23i if the patient has IBD or if the patient prefers less frequent drug administration.	Low (90–93, 95, 99, 100)
7. **Switch to an IL-17i biologic over abatacept** (PICO 72) **Conditional recommendation** based on low-quality evidence; may consider abatacept if the patient prefers IV dosing or in patients with recurrent or serious infections.	Low (90–93, 95, 103, 104, 112)
8. **Switch to an IL-17i biologic over tofacitinib** (PICO 75) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy or in patients with concomitant IBD or a history of recurrent *Candida* infections.	Low (90–93, 105)
9. **Switch to an IL-12/23i biologic over abatacept** (PICO 71) **Conditional recommendation** based on of low-quality evidence; may consider abatacept if the patient prefers IV dosing or in patients with recurrent or serious infections.	Low (99, 100, 103, 104)
10. **Switch to an IL-12/23i biologic over tofacitinib** (PICO 74) **Conditional recommendation** based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy.	Low (98–100, 105)
11. **Switch to a different TNFi biologic monotherapy over switching to a different TNFi biologic and MTX combination therapy** (PICO 30) **Conditional recommendation** based on very-low-quality evidence; may consider switching to a TNFi biologic and MTX combination therapy if the current TNFi biologic is infliximab.	Very low
12. **Switch to an IL-17i biologic monotherapy over switching to an IL-17i biologic and MTX combination therapy** (PICO 32) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-17i biologic and MTX combination therapy in patients with concomitant uveitis, as uveitis may respond to MTX therapy.	Very low

	Level of evidence (evidence [refs.] reviewed)†
13. **Switch to an IL-12/23i biologic monotherapy over switching to an IL-12/23i biologic and MTX combination therapy** (PICO 31) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-12/23i biologic and MTX combination therapy if the patient has severe psoriasis.	Very low
In adult patients with active PsA despite treatment with a TNFi biologic and MTX combination therapy,	
14. **Switch to a different TNFi biologic + MTX over switching to a different TNFi biologic monotherapy** (PICO 33) **Conditional recommendation** based on very-low-quality evidence; may consider switching to a different TNFi biologic monotherapy if the patient has demonstrated MTX-associated adverse events, prefers to receive fewer medications, or perceives MTX as a burden.	Very low
15. **Switch to an IL-17i biologic monotherapy over an IL-17i biologic and MTX combination therapy** (PICO 35) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-17i biologic and MTX combination therapy if the patient had had a partial response to the existing regimen or in patients with concomitant uveitis, as uveitis may respond to MTX therapy. Continuing MTX during the transition to an IL-17i biologic was discussed as potentially beneficial to allow the new therapy time to work.	Very low
16. **Switch to IL-12/23i biologic monotherapy over IL-12/23i biologic and MTX combination therapy** (PICO 34) **Conditional recommendation** based on very-low-quality evidence; may consider switching to an IL-12/23i biologic and MTX combination therapy if the patient had had a partial response to the existing regimen or in patients with concomitant uveitis, as uveitis may respond to MTX therapy. Continuing MTX during the transition to an IL-12/23i biologic was discussed as potentially beneficial to allow the new therapy time to work.	Very low

* Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD). TNFi = tumor necrosis factor inhibitor; MTX = methotrexate; IL-17i = interleukin-17 inhibitor; IV = intravenous.
† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.
ǂ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

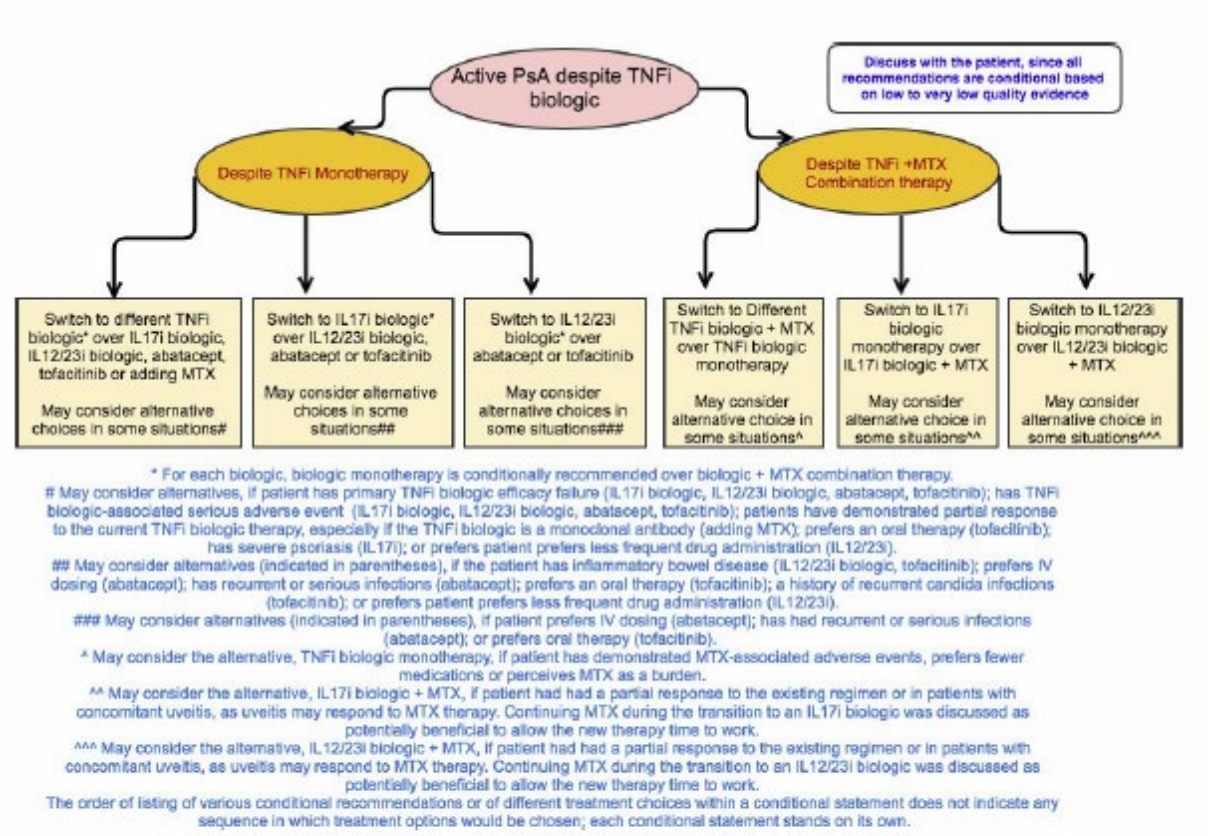


Figure 5. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) despite treatment with a tumor necrosis factor inhibitor (TNFi) as monotherapy or as combination therapy with methotrexate (MTX). All recommendations are conditional based on low- to very-low-quality evidence. A conditional recommendation means that the panel believed the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. Due to the complexity of management of active PsA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show only the key recommendations. For a complete list of recommendations, please refer to the Results section of the text. For the level of evidence supporting each recommendation, see Table 3 and the related section in the Results. IL-17i = interleukin-17 inhibitor; IV = intravenous.

Active PsA despite treatment with an IL-17i biologic agent as monotherapy / Active PsA despite treatment with an IL-12/ 23i biologic agent as monotherapy

	Level of evidence†
In adult patients with active PsA despite treatment with an IL-17i biologic monotherapy,	
1. **Switch to a TNFi biologic over switching to an IL-12/23i biologic** (PICO 39) **Conditional recommendation** based on very-low-quality-evidence; may consider switching to IL- 12/23i if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers less frequent drug administration.	Very low
2. **Switch to a TNFi biologic over switching to a different IL-17i biologic** (PICO 42) **Conditional recommendation** based on very-low-quality evidence; may consider switching to a different IL-17i if the patient had had a secondary efficacy failure to current IL-17i, or severe psoriasis, or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
3. **Switch to a TNFi biologic over adding MTX to an IL-17i biologic** (PICO 41) **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX to an IL-17i if the patient had had a partial response to the existing regimen or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
4. **Switch to an IL-12/23i biologic over switching to a different IL-17i biologic** (PICO 43) **Conditional recommendation** based on very-low-quality evidence; may consider switching to a different IL-17i if the patient had had a secondary efficacy failure to current IL-17i or severe psoriasis,‡ or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
5. **Switch to an IL-12/23i biologic over adding MTX to an IL-17i biologic** (PICO 40) **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX to an IL-17i if the patient had had a partial response to the existing regimen.	Very low
In adult patients with active PsA despite treatment with an IL-12/23i biologic monotherapy,	
6. **Switch to a TNFi biologic over switching to an IL-17i biologic** (PICO 38) **Conditional recommendation** based on very-low-quality evidence; may consider an IL-17i if the patient has severe psoriasis or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
7. **Switch to a TNFi biologic over adding MTX to an IL-12/23i biologic** (PICO 36) **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX in patients in whom the severe psoriasis is not responding to the current therapy, or if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.	Very low
8. **Switch to an IL-17i biologic over adding MTX to an IL-12/23i biologic** (PICO 37). **Conditional recommendation** based on very-low-quality evidence; may consider adding MTX in patients with only partial response to the current therapy or in those who potentially have not had enough time to adequately respond.	Very low

* Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease. IL-17i = interleukin-17 inhibitor; TNFi = tumor necrosis factor inhibitor; MTX = methotrexate.

† When there were no published studies—as was the case with all of the recommendations presented in this table—we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.

‡ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.

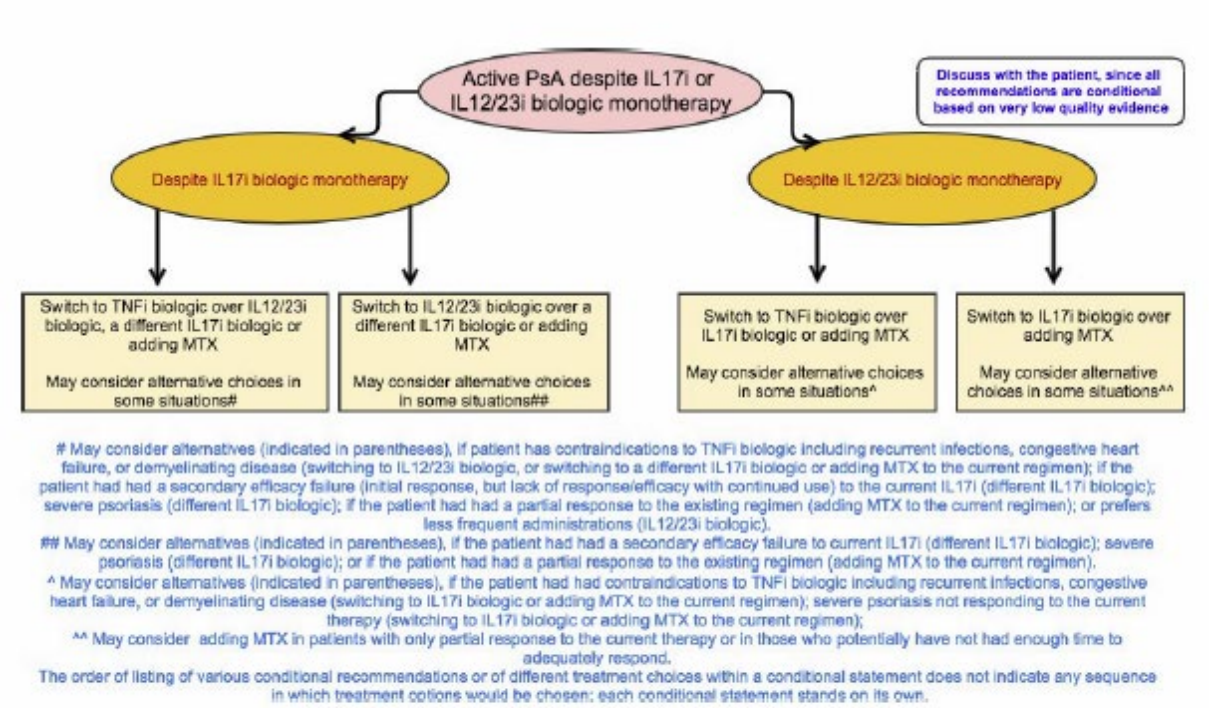


Figure 6. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) despite treatment with interleukin-17 inhibitor (IL-17i) or IL-12/23i biologic monotherapy. All recommendations are conditional based on low- to very-low-quality of evidence. A conditional recommendation means that the panel believed the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. Due to the complexity of management of active PsA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show only the key recommendations. For a complete list of recommendations, please refer to the Results section of the text. For the level of evidence supporting each recommendation, see Table 4 and the related section in the Results. TNFi = tumor necrosis factor inhibitor; MTX = methotrexate.

Coates LC et al., 2016 [3].

Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)

Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 treatment recommendations for psoriatic arthritis

Leitlinienorganisation/Fragestellung

To update the 2009 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations for the spectrum of manifestations affecting patients with psoriatic arthritis (PsA).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz; systematic literature review of the PsA treatment literature was conducted: Coates et al., 2014 [4]; further literature update and review of abstracts presented at the annual meetings of the American College of Rheumatology (November 2014) and the American Academy of Dermatology (March 2015).

- Formale Konsensusprozesse und externes Begutachtungsverfahren unklar; recommendations were critically reviewed and edited via in-person discussion and online survey.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was applied
- Regelmäßige Überprüfung der Aktualität gesichert.
- GRAPPA rheumatologists, dermatologists, and PsA patients drafted recommendations

Sonstige methodische Hinweise

- Bewertung der internen Validität der Einzelstudien unklar
- Z.T. keine eindeutige Zuordnung der zugrundeliegenden Evidenz zu den Empfehlungen
- Der Ausblick einer überarbeiteten Version ist veröffentlicht jedoch steht die Veröffentlichung der aktualisierten und vollumfänglichen Leitlinie noch aus.

Empfehlungen

Peripheral Arthritis

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are conditionally recommended for use in peripheral arthritis to improve symptoms of the disease, but with caution due to their potential adverse effects.
- Corticosteroids are conditionally recommended for peripheral arthritis, to be administered either systemically or intraarticularly, at the smallest dosages required for efficacy (usually ,7.5 mg/day) and for short periods, to minimize adverse effects, including psoriasis flare, after withdrawal of the treatment.
- In DMARD-naive patients, both DMARDs (MTX, leflunomide, and SSZ; cyclosporine is not recommended due to scant evidence of its efficacy and its toxicity profile) and TNFi are strongly recommended for treatment.
- In many instances, DMARDs may be used first, but consideration should be given to early escalation of therapy, particularly in patients with poor prognostic factors (e.g., increased levels of inflammatory markers, high counts of joints with active disease). Despite the lack of evidence from randomized controlled trials (RCTs), DMARDs are recommended based on data from observational studies, their low costs and universal access, and the lack of evidence that a short time delay in the introduction of more effective therapies would impact long-term function and quality of life.
- no definitive evidence to date on the benefit of concomitant DMARDs with biologic therapies. In the TNFi RCTs, similar efficacy results were commonly seen with or without MTX. However, registry data suggest that effect of the monoclonal antibodies, particularly infliximab, persists longer with concomitant DMARD treatment.

- no definitive evidence to date on the benefit of concomitant DMARDs with biologic therapies. In the TNFi RCTs, similar efficacy results were commonly seen with or without MTX. However, registry data suggest that effect of the monoclonal antibodies, particularly infliximab, persists longer with concomitant DMARD treatment (13).

13. Acosta Felquer ML, Coates LC, Soriano ER, Ranza R, Espinoza LR, Helliwell PS, et al. Drug therapies for peripheral joint disease in psoriatic arthritis: a systematic review. J Rheumatol 2014;41:2277–85.

Axial disease.

- The treatment recommendations for axial disease are derived from diagnostic criteria, screening, monitoring, and response to therapy in ankylosing spondylitis (AS) since these data are not available for axial PsA. For patients with axial symptoms that have not responded to NSAIDs, physiotherapy, and sacroiliac joint injections (when appropriate), initiation of TNFi is recommended;
- DMARDs are not effective for treatment of diseases in this domain. There is no available evidence on the efficacy of SSZ in axial disease within AS or PsA (29). NSAIDs are conditionally recommended, usually as an adjunct to further therapy, for patients with an inadequate response to TNFi.
- Formal published data on switching agents for axial disease are not available but observational data support switching as in the other domains, leading to a conditional recommendation in the case of inadequate response to TNFi treatment. Clinical trial data sowing efficacy of secukinumab (phase III trial) (30) and ustekinumab (openlabel proof-of-concept trial with 20 patients) (31) in AS have been published, but these agents are currently not approved for AS or axial PsA.

29. Chen J, Lin S, Liu C. Sulfasalazine for ankylosing spondylitis. Cochrane Database Syst Rev 2014;11:CD004800.
30. Baeten D, Baraliakos X, Braun J, Sieper J, Emery P, van der Heijde D, et al. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. Lancet 2013;382:1705–13.
31. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al, on behalf of the PSUMMIT 1 Study Group. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet 2013;382:780–9.

Enthesitis.

- NSAIDs are the first-line agents for treatment of enthesitis, based on expert opinion; however data from RCTs are lacking (32). Physiotherapy is also often prescribed, although formal studies of efficacy have not been published. In one study with defined enthesitis end points and placebo controls, SSZ was not effective (33), and no published data support the efficacy of other DMARDs in placebo-controlled studies (15,32). There is high-quality evidence of the effectiveness of TNFi and ustekinumab (15). Data on the efficacy of PDE-4i (34) and secukinumab (35) for enthesitis in PsA are published in abstract form only. Formal data on treatment switching are not available.

15. Orbai AM, Weitz J, Siegel EL, Siebert S, Savage LJ, Aydin SZ, et al, the GRAPPA Enthesitis Working Group. Systematic review of treatment effectiveness and outcome measures for enthesitis in psoriatic arthritis. J Rheumatol 2014;41:2290–4.

32. Sakkas LI, Alexiou I, Simopoulou T, Vlychou M. Enthesitis in psoriatic arthritis. Semin Arthritis Rheum 2013;43:325–34.
33. Clegg DO, Reda DJ, Mejias E, Cannon GW, Weisman MH, Taylor T, et al Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis: a Department of Veterans Affairs CooperativeStudy. Arthritis Rheum 1996;39:2013–20.
35. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A

Dactylitis.

- In contrast to enthesitis, DMARDs were recommended as first-line treatment of dactylitis, based on limited studies for this indication. Corticosteroid injections should also be considered, although no formal studies of this intervention have been published.
- There are efficacy data for biologic agents (TNFi or ustekinumab), but data on treatment switching are not available. Published abstracts show efficacy of both PDE-4i (34) and secukinumab (35) in dactylitis, but again, data on switching agents are not available.

34. Gladman DD, Mease PJ, Kavanaugh A, Adebajo AO, Gomez- Reino JJ, Wollenhaupt J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, is associated with long-term (52-week) improvements in enthesitis and dactylitis in patients with psoriatic arthritis: pooled results from three phase 3, randomized, controlled trials [abstract]. Arthritis Rheum 2013;65 Suppl:S347.
35. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A

Skin disease

- Topical agents are generally the first-line treatment of psoriasis, particularly milder disease, followed by phototherapy and DMARDs. Treatment may be initiated with topical agents in combination with phototherapy or DMARDs in patients with widespread disease. For patients who do not respond to these therapies, biologic agents are recommended. Biologic agents may be first-line therapy, with or without topical treatments and DMARDs, in certain patients. Switching from one DMARD to another, from a DMARD to a biologic treatment, or from one biologic treatment to another can be done.

Nail disease.

- Recommendations for the treatment of nail disease in PsA rely on data from studies in skin psoriasis; there are relatively few studies, some of which had methodologic issues affecting their interpretation (11,18). The best data were obtained in studies of biologic agents, particularly TNFi, and these agents would certainly be recommended for PsA patients with moderate-to-severe nail involvement. High-quality data on alternative biologic treatments, including ustekinumab and IL-17 inhibitors, have also been published (36,37), and these agents could be considered alternative biologic therapies to TNFi.
- Efficacy of PDE-4i in the treatment of nail disease in psoriasis has been reported in multiple abstracts describing RCTs (38,39), but no published article was available at the time of the literature review.

11. Cassell S, Kavanaugh AF. Therapies for psoriatic nail disease: a systematic review. J Rheumatol 2006;33:1452–6.

18. Armstrong AW, Tuong W, Love TJ, Carneiro S, Grynszpan R, Lee SS, et al. Treatments for nail psoriasis: a systematic review by the GRAPPA Nail Psoriasis Work Group. J Rheumatol 2014; 41:2306–14.
36. Rich P, Bourcier M, Sofen H, Fakharzadeh S, Wasfi Y, Wang Y, et al. Ustekinumab improves nail disease in patients with moderate-to-severe psoriasis: results from PHOENIX 1. Br J Dermatol 2014;170:398–407.
37. Paul C, Reich K, Gottlieb AB, Mrowietz U, Philipp S, Nakayama J, et al. Secukinumab improves hand, foot and nail lesions in moderate-to-severe plaque psoriasis: subanalysis of a randomized, double-blind, placebo-controlled, regimen-finding phase 2 trial. J Eur Acad Dermatol Venereol 2014;28:1670–5.
38. Gooderham M, Crowley J, Wasel N, Weisman J, Tyrings S, Hu CC, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with nail, scalp and palmoplantar psoriasis: 52-week results from the ESTEEM 2 study [abstract]. J Invest Dermatol 2015;135:S31.
39. Crowley J, Gooderham M, Wasel N, Weisman J, Tyring S, Hu CC, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with nail, scalp and palmoplantar psoriasis: 52-week results from the ESTEEM 2 study [abstract]. J Am Acad Dermatol 2015;72:AB226.

Spanish Society of Rheumatology, 2018 [23].

Spanish Society of Rheumatology (SER)

Clinical practice guideline for the treatment of patients with axial spondyloarthritis and psoriatic arthritis; Update 2015

Leitlinienorganisation/Fragestellung

Provide guidance to rheumatologists on treatment recommendations based on the available scientific evidence; specifically, therapeutic interventions for the management of adult patients suffering from axSpA and PsA. In those situations, where sufficient evidence is lacking, recommendations are based on the consensus of the members who participated in the guideline development group.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium; A 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. All participants are mentioned in the authorship and collaborations subsection.
- 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;
- Regelmäßige Überprüfung der Aktualität gesichert.

Sonstige methodische Hinweise

- Updating the former Espoguía was deemed necessary due to the time elapsed since its last publication and because of new findings and advances. The former guideline have been partially updated and are hereby replaced with the new CPG. Delimitation in the scope and objectives of the CPG was consensually determined, drawing upon the clinical experience and information provided by the participating health professionals.

- A literature search was carried out using the MEDLINE database (via PubMed), EMBASE (Elsevier), the Cochrane Library (Wiley Online Library), and Cinahl (EBSCOhost) revision was completed in 2016.
- subsequently panelists identified some studies which had been published in 2017 and were included in the evidence corpus.
- 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. From the selected studies, the most significant data referring to methodology, outcomes, and quality were extracted and entered in evidence tables.
- The level of scientific evidence was evaluated using a modified version of the Oxford Centre for Evidence-Based Medicine (CEBM) system.
- After the considered review, recommendations were formulated. These formulations were based on the 'formal evaluation' or 'reasoned judgement' after previously summarizing the best available evidence for each clinical question. The strength of each recommendation was evaluated using a modified version of CEBM. Recommendations that proved controversial or that lacked sufficient evidence were submitted to the development group consensus.

Empfehlungen

Treatment of Psoriatic Arthritis (PsA)

2017	Early pharmacological intervention with conventional synthetic DMARDs (csDMARDs) is recommended in patients with PsA, chiefly in those with bad basal prognosis factors, to improve signs and symptoms, functional capacity and quality of life (Grade D recommendation).
	Biologic monotherapies have proven more effective than csDMARDs or a placebo in treating patients with psoriatic arthritis in its different manifestations: peripheral, axial, enthesitis, dactylitis, and uveitis (Grade D recommendation).
2017	Use of biological therapy is recommended for patients with peripheral PsA refractory to at least one csDMARD (Grade A recommendation).
2017	Patients with predominantly ax-PsA refractory to NSAIDs, use of biological therapy (i-TNF or anti-IL17A) is recommended (Grade D recommendation).
	Traditional csDMARDs (methotrexate, leflunomide, sulfasalazine) are recommended as first line treatment for active peripheral psoriatic arthritis (Grade C recommendation).
	Among them, methotrexate is considered first choice treatment due to its effects on arthritis and psoriasis (Grade D recommendation).
	These drugs should not be used to treat symptoms of axial disease. There is no evidence supporting their use against enthesitis. There are questions about their effectiveness against dactylitis (Grade C recommendation).
2017	The use of Apremilast is recommended in treating peripheral arthritis after failure or intolerance to csDMARD, when it is deemed more convenient than BT given the patient profile (Grade C recommendation).
2017	The use of biological therapy or tsDMARD (Apremilast) is recommended in patients with PsA and enthesitis refractory to NSAID and local treatment (Grade C recommendation).
2017	The use of biological therapy or tsDMARD (Apremilast) is recommended in patients with PsA and dactylitis refractory to NSAID and local treatment with corticoid infiltrations (Grade C recommendation).
2017	Use of biological therapy is recommended in both monotherapy and combined with csDMARD, for all peripheral manifestations of PsA. Combined therapy with MTX may increase survival of the TNFi monoclonal drugs, particularly the chimeric ones (Grade C recommendation).
2017	Switching to another biological therapy albeit another i-TNF or a drug with a different action mechanism like i-IL12/23 or anti-IL17A or tsDMARD (Apremilast), is recommended in patients with peripheral PsA and an i-TNF failure (Grade B recommendation).
2017	CVD risk profile should be considered both in assessing and treating these patients (Grade D recommendation).
	It is recommended that dermatologists and rheumatologists work closely together in order to gain optimal control over the psoriatic disease (Grade D recommendation).
	This type of consultation is recommended whenever a multidisciplinary approach can be arranged atthe health center of reference (Grade D recommendation).

Holroyd CR et al., 2019 [10].

The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis

Siehe auch: Holroyd, CR et al., 2019 [11]

Zielsetzung/Fragestellung

The purpose of this guideline is to provide evidence-based recommendations for the safe use of biologic therapies in adults (aged >18 years).

Although the majority of published safety data still concern the use of first-generation anti-TNF agents in RA, this guideline has been expanded from the previous to cover the safety aspects of all biologic therapies (approved by the National Institute for Health and Care Excellence (NICE) as of June 2016; Table 1) for the treatment of RA, PsA and axial spondyloarthritis (SpA) including AS [referred to as inflammatory arthritis (IA) henceforth]. Therapies approved by NICE after June 2016, such as secukinumab, sarilumab and the Janus kinase inhibitors, are not included.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium; The Guideline Working group (GWG) was composed of rheumatology consultants from various clinical backgrounds, rheumatology specialty trainees, rheumatology nurse specialists and a patient representative. All members contributed to the development of key questions on which to base the search strategy, guideline content, recommendations and strength of agreement (SOA).
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz; This guideline has been developed in line with BSR's guideline protocol. A comprehensive literature search was undertaken by two reviewers, using MEDLINE, Cochrane, PubMed and EMBASE databases with specific search terms
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; The GRADE method was used to assess the quality of evidence and the strength of recommendation
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- All searches were performed up to the end of June 2016. Abstracts from BSR, EULAR and ACR annual conferences up to and including EULAR 2016 were also included.

LoE/ GoR:

- Using the GRADE approach, the quality of evidence was determined as either high (A), moderate (B) or low/very low (C) reflecting the confidence in the estimates of benefits or harm.

- High quality (A): typically generated from well-conducted meta-analyses, randomized controlled trials (RCTs) or other overwhelming evidence (such as large, well-executed observational studies with a low risk of bias). Further research is very unlikely to change confidence in the estimate of effect.
- Moderate quality (B): usually from randomized controlled trails or observational studies with important limitations. Further research is likely to have an important impact on and may change the estimate of effect.
- Low quality (C): usually from observational studies, or randomized controlled trials with major limitations. Further research is very likely to have an important impact on the confidence in the effect estimate and is likely to change the estimate. Very low quality evidence is usually derived from observational studies with serious limitations or from non-systematic observations (such as case reports and case series).

Empfehlungen: For patients receiving biologic therapy

Empfehlung 1 (grade 2C, SOA 94%)

For patients receiving biologic therapy Monitoring on treatment

(i) All patients should be reviewed for drug safety in a specialist department at least every 6 months. High risk patients (e.g. those at high risk of TB) should be reviewed every 3 months (grade 2C, SOA 94%).

(ii) Patients prescribed a biologic (other than TCZ) without concomitant csDMARD (or with csDMARDs that do not require blood test monitoring), should have monitoring blood tests (FBC, creatinine/calculated GFR, ALT and/or AST and albumin every 3–6 months (grade 2C, SOA 97%).

(iii) Patients receiving csDMARD may require more regular laboratory monitoring (as per BSR/BHPR non-biologic DMARD guidelines, 2017) (grade 2B, SOA 96%).

(iv) Patients receiving RTX should have serum immunoglobulins (especially IgG and IgM) checked prior to each cycle of RTX. Clinicians and patients should be aware that the risk of infection increases as serum IgG levels fall below normal (grade 2A, SOA 99%).

(v) Patients receiving i.v. or s.c. TCZ, with or without MTX, should have laboratory monitoring every 4 weeks for neutrophils and ALT/AST (grade 2B). Blood tests should ideally be in the week before i.v. TCZ, and in the 3 days before every fourth s.c. injection. Any decision to halt treatment should be made in accordance with the guidance in the TCZ SPC (grade 2C, SOA 96%).

(vi) Patients receiving TCZ should have their serum lipids checked at 3 months, and be treated appropriately if abnormal; they may be checked again thereafter at physician's discretion (grade 2A, SOA 99%).

Backgroundinfos aus Leitlinien: There is no evidence on the optimal monitoring requirements for patients receiving biologics. However, in view of the aforementioned potential risks associated with these treatments, and the NICE requirements to ensure a satisfactory clinical response to treatment, we suggest that patients are reviewed at least every 6months by a rheumatology specialist. Higher risk patients may require more frequent review, as supported by NICE guidance. The 2011 NICE guideline cg117 [76] and the 2005 BTS guideline [208] recommend that high-risk TB patients should be monitored every 3 months (with a CXR and sputum cultures, if respiratory symptoms develop).

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2021) am 25.10.2021

#	Suchfrage
1	[mh "Arthritis, Psoriatic"]
2	(psoria* NEAR/3 (arthriti* OR arthropath*)):ti,ab,kw
3	{OR #1-#2}
4	#3 with Cochrane Library publication date from Oct 2016 to present

Systematic Reviews in Medline (PubMed) am 25.10.2021

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

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

#	Suchfrage
	(((((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 ("2016/10/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
6	(#5) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 25.10.2021

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

#	Suchfrage
1	Arthritis, Psoriatic[mh]
2	psoria*[tiab] AND (arthriti*[tiab] OR arthropath*[tiab])
3	#1 OR #2
4	(#3) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
5	(((#4) AND ("2016/10/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
6	(#5) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 25.10.2021

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- ECRI Guidelines Trust (ECRI)
- 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

2021-B-376-z

Kontaktdaten

DGRh

Indikation

treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Alone or in combination with methotrexate (MTX)

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

Bei der PsA handelt es sich um eine Erkrankung, die sich durch ihre sehr heterogenen klinischen Ausprägungen und durch ihre unterschiedlichen Symptome auszeichnet, die die Krankheitslast der Patienten definieren. Im Wesentlichen handelt es sich um die klassische (periphere) Arthritis im Sinne einer (intrakapsulären) Synovialitis, die Enthesitis, die Daktylitis und die axiale Manifestation (Spondyloarthritis) als muskuloskelettale Manifestationen (MSK), sowie um die Psoriasis der Haut und Nägel als Manifestationen der psoriatischen Erkrankung selbst und ggf. um begleitende extra-muskuloskelettaler Manifestationen bzw. assoziierte Erkrankungen (z.B. Uveitis, chronisch-entzündliche Darmerkrankung). Diese können in unterschiedlicher Ausprägung in einem von PsA-betroffenen Individuum auftreten.

Nachdem die zugelassenen und verfügbaren medikamentösen Therapien nicht in gleicher Weise alle diese möglichen Manifestationen adressieren und zum Teil hinreichende Evidenzen zur Beurteilung der Effektivität nicht für (alle) Manifestationen vorhanden sind, ist ein klassischer Therapiealgorithmus im Sinne einer allgemeingültigen Definition einer Erstlinien-, Zweitlinien-,… X-Linientherapie für diese Erkrankung als Ganzes so ungeeignet.

Die geeignete evidenzbasierte Therapie der „aktiven PsA“ nach einer (konventionellen synthetischen: cs) DMARD-Therapie (DMARD-IR: *inadequate response*) unterschiedet sich daher in Abhängigkeit von der klinischen Ausprägung der Erkrankung und dem Vorliegen und Ausmaß von Funktionsverlust von Gelenken in Folge von Strukturschäden, sowie von den (teils mit der PsA assoziierten) Begleiterkrankungen, aber auch von der individuellen Patientenpräferenz. Zusätzlich muss in den Fällen, in denen auf das zuvor eingesetzte csDMARD eine unzureichende Wirkung aufgetreten war, unterschieden werden, ob diese Therapie (z.B. wegen Teilansprechen) beibehalten werden kann und soll, oder nicht.

Die nachfolgenden Ausführungen beziehen auch Patienten mit ein, bei denen wegen Kontraindikationen oder anderer Gründe eine csDMARD-Therapie nicht geeignet ist.

Zunächst kommen prinzipiell bei (cs)DMARD-IR Patienten alle die medikamentösen Therapien in Frage, die in klinischen Studien für PsA mindestens eine Wirksamkeit überlegen zu Placebo zeigen konnten. Bei Patienten mit PsA muss dieses Kriterium zunächst und als Mindestanforderung für die Behandlung der *peripheren* Arthritis erfüllt sein, da dies die häufigste Manifestationsform darstellt und auch stets der primäre Endpunkt der entsprechenden Zulassungsstudien reflektiert.

Bei den folgenden Therapien ist dies der Fall:

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treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Alone or in combination with methotrexate (MTX)

csDMARDs: Sulfasalazin (SSZ), Leflunomid (LEF), Cyclosporin A (CSA). Bei Methotrexat (MTX) liegt keine adäquate placebo-kontollierte Studie vor, die die Wirksamkeit sicher beweist. Dadurch, dass diese Substanz in RCTs teils als Kontrollarm eingesetzt und auch viele Beobachtungsdaten aus bereits jahrzehntelangem Einsatz im Versorgungsalltag vorliegen, kann eine Wirksamkeit bei peripherer Arthritis hinreichend sicher angenommen werden.

bDMARDs: Infliximab (IFX), Adalimumab (ADA), Etanercept (ETA), Golimumab (GOL), Certolizumab pegol (CZP), Ustekinumab (UST), Secukinumab (SEC), Abatacept (ABA), Ixekizumab (IXE), Guselkumab (GUS)

tsDMARDs: Apremilast (APR), Tofacitinib (TOFA), Upadacitinib (UPA).

csDMARDs bei Patienten nach DMARD-IR:

Es liegen keine Daten aus RCTs vor, die primär untersuchten, ob csDMARDs nach einer vorausgegangenen (cs)DMARD-Therapie wirksam sind. Allenfalls können aus Baseline-Charakteristika von Studien Hinweise gewonnen werden, ob in Studien, die die Wirksamkeit eines csDMARD geprüft haben, auch Patienten mit csDMARD Vortherapie erlaubt waren und auch bezüglich des Ansprechens als Subgruppe ausgewertet wurden. Eine aktuelle Studie, die einen MTX Arm einbezog, ist die SEAM-Studie, die MTX, ETA und MTX+ETA vergleicht. Die RESPOND-Studie untersuchte MTX vs. MTX +IFX. In beiden Studien waren im MTX-Arm 13-15% der Patienten mit einem csDMARD vortherapiert. Ob in dieser Gruppe alleine ein hinreichendes Ansprechen gezeigt werden konnte, ist nicht belegt. Für SSZ und CSA liegen keine Daten vor, die hinreichend sicher zeigen, dass die jeweilige Therapie nach einer anderen (cs)DMARD-Therapie wirksam ist. In der Leflunomid-Zulassungsstudie wird berichtet, dass ca. 60% der in den Leflunomid-Arm eingeschlossenen Patienten eine Vortherapie mit csDMARDs (im wesentlichen MTX) hatten und diese Tatsache keinen Unterschied bezüglich des Ansprechens (auf die Arthritis) ausmachte. Insgesamt muss die Wirkstärke der Substanz als moderat betrachtet werden, bei den Vortherapien ist insbesondere unklar, ob diese wegen unzureichendem Ansprechen oder anderer Gründe beendet worden war. Eine csDMARD-Therapie nach einer b- oder tsDMARD Vortherapie wurde nicht geprüft. Bei allgemein geringerer Wirkstärke des csDMARDs kommt diese Therapieoption nach b/ts-DMARD-IR allenfalls in Ausnahmesituationen in Frage. Basierend auf der sehr geringen Datenlage kommt allenfalls LEF nach MTX bei dominant/ausschließlich peripherer Arthritis in Frage. Hinreichende Daten jenseits der peripheren Arthritis nach csDMARD-IR liegen darüber hinaus nicht vor, bei einer Spondyloarthritis sind csDMARDs (auch als Erstlinientherapie) sicher unwirksam. Daten zur Kombination, also einer Zugabe eine csDMARDs zu einer unzureichenden csDMARD-Therapie liegen nicht vor. Daten, die eine Verhinderung von chondralen und/oder ossären Strukturschäden und nachfolgendem Funktionsverlust der Gelenke verhindern, liegen nicht vor.

csDMARDs stellen daher nach DMARD-IR keinen evidenzbasierten Behandlungsstandard dar.

bDMARDs bei Patienten nach DMARD-IR
TNF-Inhibitoren:

Kontaktdaten

DGRh

Indikation

treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Alone or in combination with methotrexate (MTX)

In den ersten Studien zu TNFi zur Therapie der PsA wurden sowohl Patienten nach NSAID als auch nach (cs)DMARD-IR eingeschlossen. In diesen Studien konnte die Wirksamkeit dieses Therapieprinzips nach csDMARD-IR sicher gezeigt werden. Dies gilt im Wesentlichen für alle muskuloskelettalen Manifestationen (inkl. Daten zur Inhibition struktureller Knorpel/Knochenschäden) und die kutanen Psoriasis-Manifestationen. In späteren Phase III – Studien und Beobachtungsstudien konnte ebenfalls gezeigt werden, dass diese Behandlung auch nach einer vorausgegangenen bDMARD-Therapie (im Wesentlichen einer TNFi Therapie) wirksam ist. Inwieweit eine TNFi-Therapie nach Versagen einer anti-IL17- oder einer anti-IL12/23 bzw. anti-IL23 oder Abatacept-Therapie wirksam ist, oder auch nach einer tsDMARD-Therapie, ist in RCT nicht gezeigt. TNF-Inhibitoren sind wirksam mit, oder ohne Beibehaltung einer vorbestehenden csDMARD-Therapie. Hinreichend robuste Hinweise, dass die Hinzunahme u./o. Beibehaltung von MTX (oder einem anderen csDMARD) einen positiven Einfluss auf die MSK-Manifestationen zeigt, bestehen nicht. Zu beachten ist, dass der Effekt des Rezeptor-Fusionsproteins Etanercept auf die kutane Manifestation geringer ausfällt als bei den monoklonalen Antikörpern gegen TNF.

TNF-Inhibitoren stellen daher nach csDMARD-IR und eingeschränkt auch nach einer TNFi-DMARD-IR einen evidenzbasierten Behandlungsstandard dar, wenn die Wirkstärke auf die kutane Psoriasis (geringe bis mäßige Aktivität) ausreichend erscheint.

bDMARDs bei Patienten nach DMARD-IR,
IL-12/23-Inhibition (Ustekinumab) und IL-23 Inhibition (Guselkumab):

In den beiden Zulassungsstudien von UST wurden zum eine Patienten nach csDMARD-Therapie eingeschlossen, in der Psummit-2 Studie wurden explizit auch jenen, mit einer TNFi-Vortherapie eingeschlossen. In beiden Studien zeigte UST seine gegenüber Placebo signifikante Wirkung im Bereich der MSK-Manifestationen (inkl. Daten zur Inhibition struktureller Knorpel/Knochenschäden) wie auch bei der Psoriasis der Haut. Auch in den Zulassungsstudien zu GUS (Discover) konnte dies gezeigt werden. In Studien zur Psoriasis alleine wurde die Überlegenheit von UST bzw. GUS gegenüber TNFi gezeigt. In einer offenen randomisierten Studie zur zeigte sich auch eine Überlegenheit von UST in der Therapie der Enthesitis gegenüber TNFi. UST bzw. GUS sind wirksam mit, oder ohne Beibehaltung einer csDMARD-Therapie. In ersten Indirekten Vergleichen erscheint die Therapie mit GUS bezüglich der Wirkstärke bei Arthritis jene des UST überlegen. Die Wirksamkeit bezügliche diese Wirkprinzips bei spondloarthritischen (axialen) Manifestationen der PsA ist aktuell Ziel weitere Untersuchungen, da Studien zur ankylosierenden Spondylitis negative ausgefallen waren für das IL (12)/23-Wirkprinzip.

UST bzw. GUS stellen daher nach csDMARD-IR und eingeschränkt auch nach TNFi-DMARD-IR einen evidenzbasierten Behandlungsstandard dar, insbesondere wenn die Wirkstärke auf die kutane Psoriasis geboten erscheint.

bDMARDs bei Patienten nach DMARD-IR,
CTLA4Ig (Abatacept):

Kontaktdaten

DGRh

Indikation

treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Alone or in combination with methotrexate (MTX)

In der Phase III Zulassungsstudie waren sowohl Patienten nach csDMARD-IR alleine, oder auch nach (zusätzlich) vorausgegangener TNFi-Therapie (60%) (nicht zwingend „IR“) eingeschlossen. Sowohl in der DMARD-IR, als auch in der TNFi vortherapierten Gruppe zeigte sich ein gegenüber Placebo signifikanter Effekt bei der Therapie der peripheren Arthritis (inkl. Daten zur Inhibition struktureller Knorpel/Knochenschäden). Therapieeffekte auf Daktylitis und Enthesitis zeigten sich nur numerisch zum Vorteil für ABA, ein klinisch bedeutsamer Effekt der kutanen Manifestation zeigt sich nicht. ABA ist wirksam mit, oder ohne Beibehaltung einer csDMARD-Therapie

Abatacept stellt daher nach csDMARD-IR und eingeschränkt auch nach TNFi-DMARD-IR einen evidenzbasierten Behandlungsstandard nur für die peripherer Arthritis dar, insbesondere wenn keine Systemtherapie der kutanen Psoriasis geboten ist.

bDMARDs bei Patienten nach DMARD-IR,
IL-17-Inhibition (Secukinumab, Ixekizumab):

In den Zulassungsstudien sowohl für SEC (Future-Studien), als auch für IXE (SPIRIT) wurden sowohl Patienten nach csDMARD-IR als auch nach bDMARD (TNFi)-Vortherapie eingeschlossen. In diesen Studien konnten für beide Substanzen in sehr großen RCTs die Wirksamkeit der Substanzen bei den MSK-Manifestationen der PsA gezeigt werden (inkl. Daten zur Inhibition struktureller Knorpel/Knochenschäden). Für beide Substanzen ist darüber hinaus auch in dermatologischen Studien die Überlegenheit bezüglich der Therapie der Psoriasis gegenüber TNFi bewiesen worden. Besonders für IXE ist eine explizite Studie zum Nachweis der Wirksamkeit nach TNFi-IR durchgeführt worden. IL-17 Inhibitoren sind wirksam mit, oder ohne Beibehaltung einer csDMARD-Therapie. Kürzlich wurden Head-to-head Studien zu beiden Substanzen publiziert, die die mindestens gleichwertige Wirksamkeit der Substanzen gegenüber ADA bei der peripheren Arthritis zeigten und die Überlegenheit bei den kutanen Manifestationen in PsA-Kollektiven bestätigten. In der IXE H2H zeigte sich auch eine Überlegenheit im Erreichen der sogenannten „minimalen Krankheitsaktivität“ (MDA) und zu einem Zeitpunkt auch im Auflösen der Enthesitis, wenn eine umfangreiche Untersuchung der Sehnenansatzstellen erfolgt.

SEC und IXE stellen daher nach csDMARD-IR und (eingeschränkt für SEC, sicher bewiesen für IXE) auch nach TNFi-DMARD-IR einen evidenzbasierten Behandlungsstandard dar, insbesondere wenn die Wirkstärke auf die kutane Psoriasis geboten erscheint.

tsDMARDs bei Patienten nach DMARD-IR,
PDE-4-Inhibition (Apremilast):
APR hat in einem umfangreichen Studienprogramm die Wirksamkeit nach DMARD-Therapie gezeigt. In der PALACE 3 Studie mussten alle Patienten für den Studieneinschluss mindestens eine cs- oder bDMARD Vortherapie erhalten haben. 26% hatten eine bDMARD Vortherapie, wovon 8 % unzureichend auf selbige angesprochen hatten. Beschrieben ist, dass die Überlegenheit vs. Placebo unabhängig von der

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DGRh

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treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Alone or in combination with methotrexate (MTX)

Begleittherapie (verschiedene csDMARDs waren als Kombinationspartner erlaubt) und auch von der Vortherapie ist. Die Wirksamkeit auf Enthesitis/Daktylitis ist ebenso beschrieben wie auch die Wirksamkeit auf die Psoriasis der Haut. Daten zur Inhibition struktureller Knorpel/Knochenschäden liegen nicht vor. APR ist wirksam mit, oder ohne Beibehaltung einer csDMARD-Therapie

APR stellt daher alleine nach csDMARD-IR und auch nach einer TNFi-DMARD-IR einen evidenzbasierten Behandlungsstandard dar, wenn die Wirkstärke ausreichend erscheint.

tsDMARDs bei Patienten nach DMARD-IR,
JAK-Inhibition (Tofacitinib, Upadacitinib):
TOFA und UPA sind zugelassen zur Behandlung der PsA und zeigten in RCTs ihre Wirksamkeit bezüglich der peripheren Gelenkbeteiligung, aber auch bezüglich anderer MSK Manifestationen bei Patienten mit csDMARD-IR aber auch für TOFA in einer hierfür designten Studie nach TNF-Inhibitor-IR. Bezüglich der kutanen Psoriasis liegt die Effektgröße im Bereich von Adalimumab (für TOFA nicht gepowert für direkten Vergleich, für UPA in einer Head-to-Head Studie gezeigt). Die Therapie von TOFA kann laut Zulassung derzeit nur in Kombination mit MTX eingesetzt werden. UPA kann auch in Monotherapie zum Einsatz kommen.

UPA und TOFA stellen daher nach csDMARD-IR und auch nach einer TNFi-DMARD-IR einen evidenzbasierten Behandlungsstandard dar, wenn die Wirkstärke auf die kutane Psoriasis (geringe bis mäßige Aktivität) ausreichend und ggf. eine Kombination mit MTX (bei Tofacitinib) sinnvoll und möglich erscheint.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung der „active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs)**“, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

- Periphere Arthritis alleine: TNFi, IL17i, IL12/23i, IL23i, ABA, JAKi
- mit axialer Manifestation (Spondyloarthritis): TNFi, IL17i, JAKi
- mit mittelschwerer bis schwere Psoriasis: TNFi, IL17i, IL12/23i, IL23i
- mit assoziierter CED: TNFi, IL12/23i, IL23i, JAKi
- mit assoziierter Uveitis: TNFi (plus MTX)

Quellenverzeichnis:

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