Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

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

Vorgang: 2023-B-131

Stand: Juni 2023

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
[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 2. Juni 2016) • Ixekizumab (Beschluss vom 16. August 2018) • Tofacitinib (Beschluss vom 21. Februar 2019) • Guselkumab (Beschluss vom 20. Mai 2021) • Upadacitinib (Beschluss vom 15. Juli 2021) • Risankizumab (Beschluss vom 19. Mai 2022) 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:	
	<u>Geplantes Anwendungsgebiet:</u> Behandlung erwachsener Patienten mit aktiver Psoriasis-Arthritis
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.
Infliximab L04AB02 Remicade®/ Inflectra®	*Psoriasis-Arthritis* 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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	• 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.
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.
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.
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.
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.
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.
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.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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).
Risankizumab L04AC18 Skyrizi®	Skyrizi allein oder in Kombination mit Methotrexat (MTX) wird angewendet zur Behandlung erwachsener Patienten mit aktiver Psoriasis-Arthritis, die auf ein oder mehrere krankheitsmodifizierende Antirheumatika (disease-modifying antirheumatic drugs, DMARDs) unzureichend angesprochen oder diese nicht vertragen haben.
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).*
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.
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.
Apremilast L04AA32 Otezla®	*Psoriasis-Arthritis* Otezla allein oder in Kombination mit krankheitsmodifizierenden antirheumatischen Arzneimitteln (DMARDs) ist indiziert zur Behandlung der aktiven Psoriasis-Arthritis (PsA) bei erwachsenen Patienten, die auf eine vorangegangene DMARD-Therapie unzureichend angesprochen oder diese nicht vertragen haben.
Steroidale Antirheumatika (Glucokortikoide)	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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: 2023-B-131

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	13. Juni 2023

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

Behandlung erwachsener Patienten mit aktiver Psoriasis-Arthritis.

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.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 17.05.2023 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 630 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 29 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Sbidian E et al., 2022 [21].

Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

Es liegen weitere SRs zu dieser Fragestellung vor:

- Xie Y et al., 2022 [27].
- Huang X et al., 2022 [10].
- Kang Q et al., 2022 [11].
- Song G et al., 2021 [25].
- Song G et al., 2021 [23].

Fragestellung

To compare the efficacy and safety of non-biological systemic agents, small molecules, and biologics for people with moderate-to-severe psoriasis using a network meta-analysis, and to provide a ranking of these treatments according to their efficacy and safety.

Methodik

Population:

- adults (over 18 years of age) with moderate-to-severe plaque psoriasis (i.e. needed systemic treatment) or psoriatic arthritis whose skin had been clinically diagnosed with moderate-to-severe psoriasis and who were at any stage of treatment.

Intervention:

Systemic treatments included the following:

- Non-biological treatments
  - FAEs
  - Acitretin
  - Ciclosporin
  - Methotrexate
- Small molecules
  - Apremilast
  - Deucravacitinib
- Biologic treatments
  - Anti-TNF alpha
    - Infliximab
    - Etanercept
    - Adalimumab
    - Certolizumab
- Anti-IL12/23
  - Ustekinumab

- Anti-IL17
  - Secukinumab
  - Brodalumab
  - Ixekizumab
  - Bimekizumab
  - Sonelokimab
  - Netakimab
- Anti-IL23
  - Tildrakizumab
  - Guselkumab
  - Risankizumab
- We were interested to compare both the diNerent drugs (n = 20) and the diNerent classes of drugs (n = 6).

Komparator:

- any of the aforementioned systemic treatments; or
- additional treatment not of primary interest but used for the network synthesis, such as topical treatment or phototherapy.
- In multi-arm trials, study groups assessing drugs other than those mentioned above were not eligible. In cases of multi-dose trials, we grouped together all of the different dose groups as a single arm and performed sensitivity analysis at dose level.

Endpunkte:

- Primary outcomes
  - The proportion of participants who achieved clear or almost clear skin, that is, at least PASI 90 at induction phase.
  - The proportion of participants with serious adverse events (SAEs) at induction phase. We used the definition of severe adverse events from the International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, which includes death, lifethreatening events, initial or prolonged hospitalisation, and adverse events requiring intervention to prevent permanent impairment or damage.
- Secondary outcomes
  - Proportion of participants who achieve PASI 75 at induction phase.
  - Proportion of participants who achieve a Physician Global Assessment (PGA) value of 0 or 1 at induction phase.
  - Quality of life measured by a specific scale. Available validatedscales are the Dermatology Life Quality Index (DLQI), Skindex, Psoriasis Disability Index (PDI), or Psoriasis Symptom Inventory (PSI) at induction phase.
  - The proportions of participants with adverse events (AEs) at induction phase ('AE outcome' did not include SAE).
  - Proportion of participants who achieve PASI 75 at 52 weeks.
  - Proportion of participants who achieve PASI 90 at 52 weeks.

Recherche/Suchzeitraum:

- searches of the following databases monthly to October 2021: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase.

Qualitätsbewertung der Studien:

- Cochrane's Risk of bias (RoB) tool

Ergebnisse

Anzahl eingeschlossener Studien:

- This update includes an additional 19 studies, taking the total number of included studies to 167, and randomised participants to 58,912

Charakteristika der Population/Studien:

- The participants were reported to be between 27 and 56.5 years old, with an overall mean age of 44.5; there were more men (39,591) than women (18,814). Age and gender were unreported for, respectively, 1841 and 507 participants (15 and 9 studies).
- The overall mean weight was 85.4 kg (range: 59 to 100.5 kg), and the overall mean Psoriasis Area and Severity Index (PASI) score at baseline was 20.4 (range: 9.5 to 39). The duration of psoriasis was 16.5 years (range 4.5 to 21.5).

Qualität der Studien:

- Onethird of the studies (57/167) had high risk of bias; 23 unclear risk, and most (87) low risk.

Studienergebnisse:

Primary outcomes

1.1 The proportion of participants who achieved clear or almost clear skin, e.g. PASI 90

DIRECT EVIDENCE

- In terms of reaching PASI 90, anti-IL17 treatments (secukinumab, ixekizumab, brodalumab, bimekizumab, and sonelokimab) were more effective than placebo (risk ratio at class level (RR) 27.31, 95% confidence interval (CI) 18.94 to 39.38).
- No significant difference was observed between netakimab and placebo (RR 10.98, 95% CI 0.42 to 288.83). These findings were also confirmed for antiIL23 (guselkumab, tildrakizumab, and risankizumab) (class-level RR 23.15, 95% CI 16.44 to 32.61); anti-IL12/23 (ustekinumab) (RR 18.37, 95% CI 12.56 to 26.85); anti-TNF alpha (infliximab, etanercept, adalimumab, and certolizumab) (class-level RR 13.65, 95% CI 10.71 to 17.40); and small molecules (apremilast, and oral tyrosine kinase 2 (TYK2) inhibitor) (class-level RR 7.56, 95% CI 3.84 to 14.88). Infliximab, adalimumab, and ixekizumab were more effective than methotrexate (respectively: RR 2.86, 95% CI 2.15 to 3.80; RR 3.73, 95% CI 2.25 to 6.19; and RR 2.05, 95% CI 1.43 to 2.94). Secukinumab, ixekizumab, guselkumab, risankizumab, and brodalumab were more effective than FAEs (respectively: RR 8.31, 95% CI 4.23 to 16.35; RR 8.60, 95% CI 3.69 to 20.04; RR 6.02, 95% CI 3.13 to 11.60; RR 8.33, 95% CI 3.87 to 17.95; and RR 3.00, 95% CI 2.04 to 4.42). Ustekinumab, secukinumab, infliximab, ixekizumab, and tildrakizumab were more effective than etanercept. Secukinumab, ixekizumab, brodalumab, risankizumab and bimekizumab were more effective than ustekinumab.
- Guselkumab, risankizumab and bimekizumab were more effective than adalimumab. Secukinumab and ixekizumab were more eNective than guselkumab and bimekizumab was more effective than secukinumab. No significant difference was observed between risankizumab and secukinumab, between sonelokimab and secukinumab, between

certolizumab and etanercept, or between etanercept and apremilast for this outcome (reaching PASI 90).

NETWORK META-ANALYSES

- The PASI 90 outcome was available in 115 trials, involving 48,722 participants (92.7% of the participants in the meta-analysis).
- All of the interventions appeared superior to placebo in terms of reaching PASI 90.
- At class level, anti-IL17 treatment showed a higher proportion of patients reaching PASI 90 compared to all of the interventions, except anti-IL23 (RR 1.14, 95% CI 0.95 to 1.36): versus anti-IL12/23 (RR 1.45, 95% CI 1.23 to 1.71); versus anti-NF alpha (RR 1.95, 95% CI 1.64 to 2.33); versus small molecules (RR 2.96, 95% CI 1.63 to 5.38); versus non-biological systemic agents (RR 5.74, 95% CI 2.40 to 13.73).
- In terms of reaching PASI 90, all of the biologic interventions (anti-IL17, anti-IL12/23, anti-IL23) except anti-TNF alpha, appeared significantly superior to the small molecule class of treatments.
- All of the biologic interventions (anti-IL17, anti-IL12/23, anti-IL23 and anti-TNF alpha) were significantly superior to the non-biological systemic class of treatments for reaching PASI 90.
- Results of comparisons between each of the drugs are available in Figure 7. There was no significant diNerence between infliximab, ixekizumab, bimekizumab, and risankizumab in terms of reaching PASI 90. Bimekizumab, ixekizumab and risankizumab were significantly more likely to reach PASI 90, than other anti-IL17 drugs (secukinumab and brodalumab) and guselkumab.
- Infliximab, bimekizumab, ixekizumab and risankizumab were significantly more likely to reach PASI 90 than ustekinumab, tildrakizumab and the three anti-TNF alpha agents (adalimumab, certolizumab and etanercept). Anti-IL17 drugs (bimekizumab, ixekizumab, secukinumab and brodalumab) and anti-IL23 drugs (risankizumab and guselkumab) except tildrakizumab were significantly more likely to reach PASI 90 than ustekinumab and three anti-TNF alpha agents: adalimumab, certolizumab and etanercept.
- Ustekinumab was superior to certolizumab (RR 1.42, 95% CI 1.06 to 1.91). Adalimumab and ustekinumab were superior to etanercept (RR 1.77, 95% CI 1.58 to 1.99 and RR 1.63, 95% CI 1.43 to 1.86, respectively).
- No significant difference was shown between apremilast and two non-biological drugs: ciclosporin and methotrexate.

1.2 The proportion of participants with serious adverse events

DIRECT EVIDENCE

- We found no significant differences between FAEs, etanercept, adalimumab, certolizumab, ustekinumab, secukinumab, ixekizumab, brodalumab, bimekizumab, netakimab, sonelokimab, guselkumab, tildrakizumab, risankizumab, apremilast, oral tyrosine kinase 2 (TYK2) inhibitor, and placebo in the number of participants with serious adverse events (SAEs).
- The risk of SAEs was significantly lower for participants on methotrexate compared to placebo (RR 0.16, 95% CI 0.03 to 0.88). The risk of SAEs was significantly higher for participants on infliximab compared to methotrexate (RR 2.41, 95% CI 1.04 to 5.59).

- Key messages

- After six months of treatment, medicines called 'biologics' seem to work best to clear patches of psoriasis on the skin.
- Longer studies are needed to assess the benefits and potential harms of longer treatment with medicines that are injected or taken by mouth to treat psoriasis.
- More studies are needed that compare these types of medicines directly against each other.

Anmerkung/Fazit der Autoren

Our review shows that, compared to placebo, the biologics infliximab, bimekizumab, ixekizumab, and risankizumab were the most effective treatments for achieving PASI 90 in people with moderate-to-severe psoriasis on the basis of high-certainty evidence.

This NMA evidence is limited to induction therapy (outcomes measured from 8 to 24 weeks aPer randomisation), and is not sufficient for evaluating longer-term outcomes in this chronic disease. Moreover, we found low numbers of studies for some of the interventions, and the young age (mean 44.5 years) and high level of disease severity (PASI 20.4 at baseline) may not be typical of patients seen in daily clinical practice.

We found no significant difference in the assessed interventions and placebo in terms of SAEs, and the safety evidence for most interventions was low to moderate quality.

More randomised trials directly comparing active agents are needed, and these should include systematic subgroup analyses (sex, age, ethnicity, comorbidities, psoriatic arthritis). To provide long-term information on the safety of treatments included in this review, an evaluation of non-randomised studies and postmarketing reports from regulatory agencies is needed.

- *Editorial note: This is a living systematic review. Living systematic reviews offer a new approach to review updating, in which the review is continually updated, incorporating relevant new evidence as it becomes available. Please refer to the Cochrane Database of Systematic Reviews for the current status of this review.*

3.2 Systematische Reviews

Harkins P et al., 2023 [9].

Are Janus kinase inhibitors safe and effective in treating the key clinical domains of psoriatic arthritis? A systematic review and meta- analysis

Es liegen weitere SRs zu dieser Fragestellung vor:

- Yang F et al. 2023 [29]
- Sarabia S et al. 2022 [20]

Fragestellung

Psoriatic arthritis (PsA), is a complex inflammatory arthropathy with a heterogenous spectrum of disease presentation. Despite the vast therapeutic armamentarium, disease control in a considerable proportion of patients is suboptimal. The aim of this study was to assess the safety and efficacy of Janus kinase inhibitors (JAKi), in the management of key clinical domains of PsA including peripheral arthritis, psoriasis, enthesitis and dactylitis.

Methodik

Population:

- Patients with psoriatic arthritis

Intervention:

- Janus kinase inhibitors

Komparator:

- placebo

Endpunkte:

- this study will assess this outcome via multiple clinical endpoints, reflecting the key domains of the condition, including peripheral arthritis, psoriasis, enthesitis and dactylitis.
- The secondary outcome of this study will assess the safety profile of JAKi relative to placebo in the management of PsA.

Recherche/Suchzeitraum:

- systematic literature search using EMBASE, PubMed and CENTRAL
- from the inception of each database until April 30, 2021

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 5 RCTs were included.
- Patients were randomized to tofacitinib (n = 474), filgotinib (n = 65), upadacitinib (n = 1281) or placebo (n = 937).

Charakteristika der Population:

TABLE 1 Summary of included studies and baseline patient characteristics

Reference	Trial identifier and study type	Trial duration	Population	Comparator(s); experimental drug(s)	Number of patients, n
Mease 2018[23]	NCT03101670 EQUATOR Phase 2 RCT	16 weeks	cs-DMARD-IR	Placebo Filgotinib 200 mg	66 65
Gladman 2017[27]	NCT01882439 OPAL Beyond Phase 3 RCT	6 months	TNFi-IR	Placebo Tofacitinib 5 mg BD Tofacitinib 10 mg BD	131 131 132
Mease 2017[26]	NCT01877668 OPAL Broaden Phase 3 RCT	12 months	cs-DMARD-IR bDMARD naïve	Placebo Adalimumab 40 mg alt. wks Tofacitinib 5 mg BD Tofacitinib 10 mg BD	105 106 107 104
Mease 2021[25]	NCT03104374 SELECT-PsA 2 Phase 3 RCT	24 weeks	bDMARD-IR	Placebo Upadacitinib 15 mg OD Upadacitinib 30 mg OD	212 211 218
McInnes 2021[24]	NCT03104400 SELECT-PSA1 Phase 3 RCT	24 weeks	cs-DMARD-IR bDMARD naïve	Placebo Adalimumab 40 mg Upadacitinib 15 mg OD Upadacitinib 30 mg OD	423 429 429 423

Reference	Females n (%)	Mean age y (*SD*)	Mean disease duration y (*SD*)	Concomitant MTX n (%)	Concomitant glucocorticoid n (%)
Mease 2018[23]	30 (45) 36 (55)	50 (10.9) 49 (12.2)	7 (6.2) 7 (6.7)	43 (65) 41 (63)	16 (24) 17 (26)
Gladman 2017[27]	80 (61) 64 (49) 74 (56)	49.0 (12.6) 49.5 (12.3) 51.3 (10.9)	9.4 (8.1) 9.6 (7.6) 9.1 (6.8)	101 (77) 98 (75) 91 (69)	31 (24) 37 (28) 25 (19)
Mease 2017[26]	56 (53) 50 (47) 57 (53) 62 (60)	47.7 (12.3) 47.4 (11.3) 49.4 (12.6) 46.9 (12.4)	6.4 (6.4) 5.3 (5.3) 7.3 (8.2) 5.4 (5.8)	92 (88) 79 (75) 91 (85) 92 (88)	18 (17) 23 (22) 29 (27) 11 (11)
Mease 2021[25]	120 (56.6) 113 (53.6) 115 (52.8)	54.1 (11.5) 53.0 (12.0) 53.0 (11.9)	11.0 (10.3) 9.6 (8.4) 9.7 (8.7)	75 (35.4) 74 (35.1) 73 (33.5)	24 (11.3) 22 (10.4) 13 (6.0)
McInnes 2021[24]	211 (49.9) 222 (51.7) 238 (55.5) 236 (55.8)	50.4 (12.2) 51.4 (12) 51.6 (12.2) 49.9 (12.4)	6.2 (7) 5.9 (7.1) 6.2 (7.4) 5.9 (6.4)	267 (63.1) 270 (62.9) 279 (65) 268 (63.4)	70 (16.5) 72 (16.8) 73 (17) 71 (16.8)

Abbreviations: BD, twice daily; bDMARD, biologic disease-modifying antirheumatic agent; csDMARD, conventional synthetic disease-modifying antirheumatic agent; IR, intolerance +/− resistance; MTX, methotrexate; n, number of patients; OD, once daily; *SD*, standard deviation; TNFi, tumor necrosis factor inhibitor.

Qualität der Studien:

- All measures of bias for the included trials were considered to be of low risk, with the exception of the unclear risk of potential reporting bias in 1 study.

Studienergebnisse:

ACR response

- All 5 RCTs23- 27 evaluated the clinical efficacy of JAKi according to ACR 20/50/70 response. Four of the 5 trials24- 27 evaluated response after 12 weeks, and 1 trial23 after 16 weeks.
- The overall result of the pooled analysis demonstrates a statistically significant superiority of JAKi vs placebo in achieving an ACR20 response with up to 16 weeks of treatment (RR 2.10, 95% CI [1.86– 2.37], P < .00001, I2 = 19%).
- Similarly, JAKi demonstrated a superiority in achieving ACR50 (RR 3.43, 95% CI [2.37–4.96], P < .00001, I2 = 66%) and ACR70 (RR 4.57, 95%CI [1.83– 11.44], P = .001, I2 = 82%) response with up to 16 weeks of treatment, vs placebo.

PASI 75 response

- All 5 trials23- 27 evaluated PASI 75 response in those patients suitable for analysis (ie those entering the trial with at least 3% of their body surface area covered by psoriasis). Four trials23- 26 evaluated this response after 16 weeks, and 1 trial27 after 12 weeks.
- JAKi were superior to placebo in achieving a PASI 75 response up to 16 weeks (RR 2.96, 95%CI [2.44– 3.58], P < .00001, I2 = 0%), with 52.3% of those treated with a JAKi, and 17.45% of those treated with placebo achieving PASI 75

Resolution of enthesitis

- Four24- 27 trials evaluated the attainment of a LEI of 0. A total of 1686 patients (JAKi, n = 1143; placebo, n = 543), were included in this analysis. Three trials25- 27 evaluated this clinical endpoint at 12 weeks, and 1 trial24 at 24 weeks. Those treated with JAKi demonstrated a statistically significantly higher attainment of enthesitis resolution, vs those treated with placebo (RR 1.79, 95%CI [1.54– 2.08], P < .00001, I2 = 0%).

Resolution of dactylitis

- Four24- 27 trials evaluated the attainment of a LDI of 0. A total of 931 patients (JAKi, n = 620; placebo, n = 311) were included in this analysis. Three trials25- 27 evaluated this clinical endpoint at 12 weeks, and 1 trial24 at 24 weeks. Those treated with JAKi demonstrated a statistically significant higher attainment of dactylitis resolution, vs those treated with placebo (RR 1.85, 95%CI [1.57– 2.16], P < .00001, I2 = 0%)

Safety

- Safety outcome analyses were performed at 12 weeks in 2 trials,26,27 16 weeks in 1 trial23 and 24 weeks in 2 trials.
- Pooled analysis of all reported adverse events demonstrated that JAKi were associated with a statistically significant higher overall relative risk of adverse events (RR 1.14, 95%CI [1.07– 1.21], P = .0001, I2 = 0%), and serious adverse events (RR 1.67, 95%CI [1.02– 2.74], P = .04, I2 = 2%) vs placebo.
- the pooled relative risk of treatment withdrawal secondary to an adverse event with a JAKi vs placebo was not statistically significant (RR 1.40, 95%CI [0.94– 2.10], P = .10, I2 = 0%)

Referenzen:
23. 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, placebocontrolled, phase 2 trial. Lancet. 2018;392(10162):2367- 2377.
24. McInnes IB, Anderson JK, Magrey M, et al. Trial of upadacitinib and adalimumab for psoriatic arthritis. N Engl J Med. 2021;384(13):1227- 1239.
25. Mease PJ, Lertratanakul A, Anderson JK, et al. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT- PsA 2. Ann Rheum Dis. 2021;80(3):312- 320.
26. Mease P, Hall S, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. N Engl J Med. 2017;377(16):1537- 1550.
27. 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(16):1525- 1536.

Anmerkung/Fazit der Autoren

This pooled analysis demonstrates the efficacy of JAKi in treating key clinical domains of PsA. However, they are associated with an increased risk of adverse events, including infection. Further studies are required to corroborate these findings and further elucidate the safety profile.

Mease PJ et al., 2021 [13].

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

Es liegen weitere SRs zu dieser Fragestellung vor:
- Mease PJ et al., 2023 [14].

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 age

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

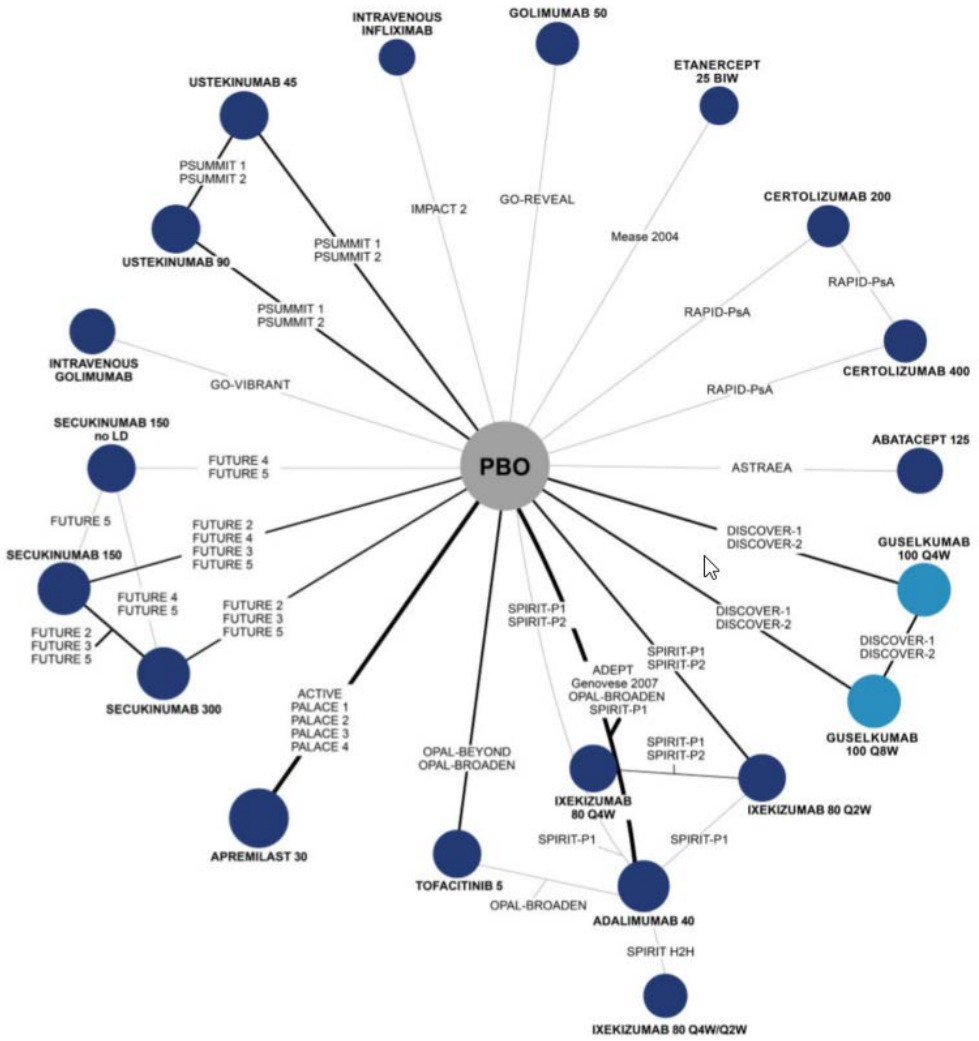
Author, Publication Date	Trial Name	Was randomization carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the participants blind to treatment allocation?	Were the care providers blind 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:

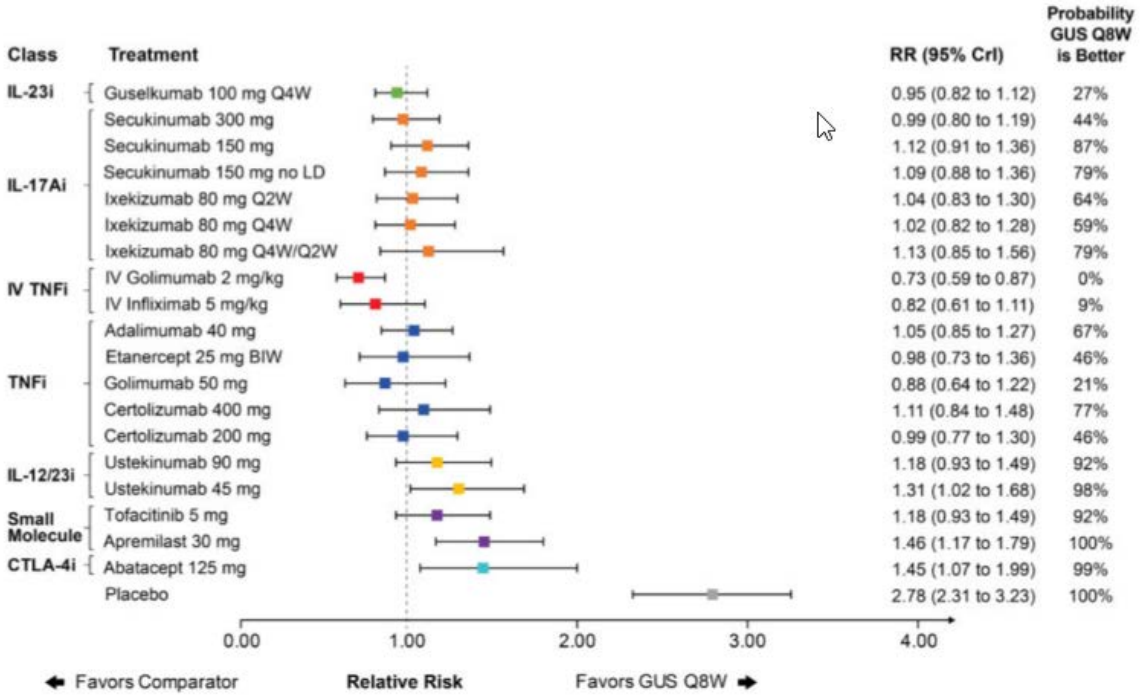
- Network meta-analysis results
  - For ACR 20 response, guselkumab 100mg every 8weeks (Q8W) was comparable to IL-17A inhibitors and subcutaneous tumor necrosis factor (TNF) inhibitors.

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.

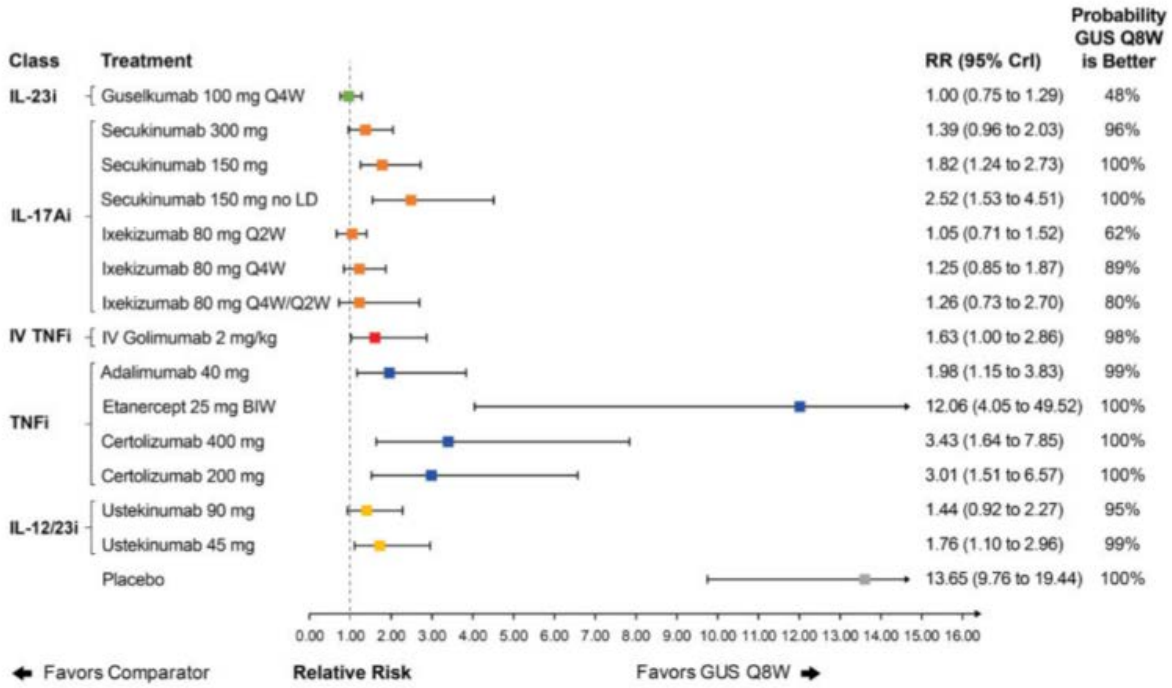
FIG. 3 Forest plot with pairwise comparisons of guselkumab Q8W *vs* all comparators for ACR 20



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.

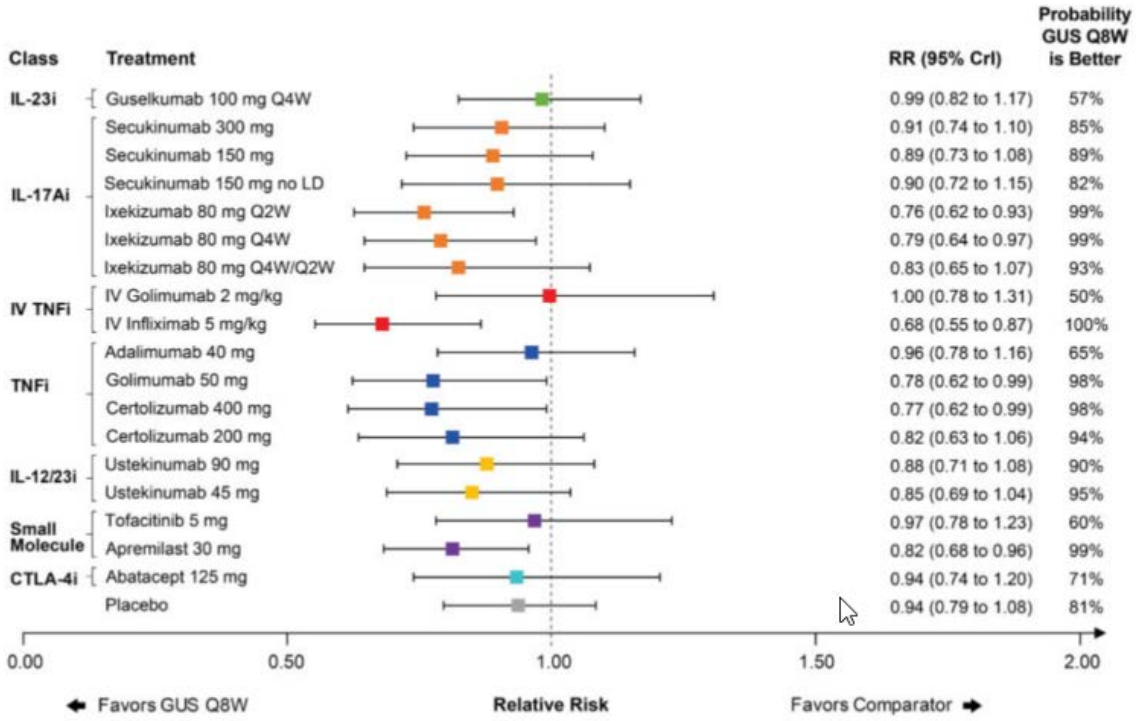
FIG. 5 Forest plot with pairwise comparisons of guselkumab Q8W *vs* all comparators for PASI 90



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 F 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

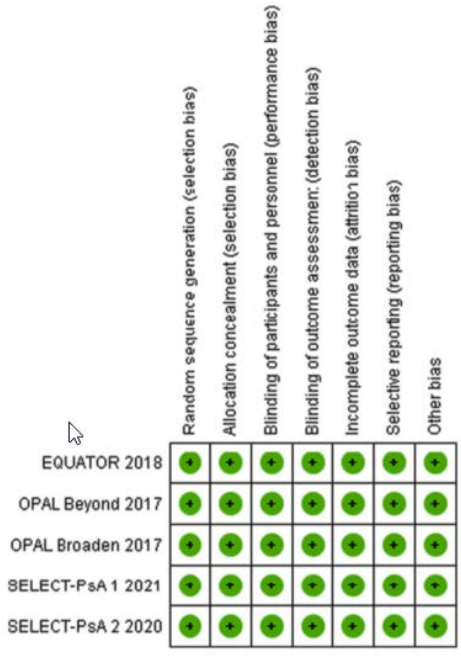


Fig. 2. Risk of bias table.

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.

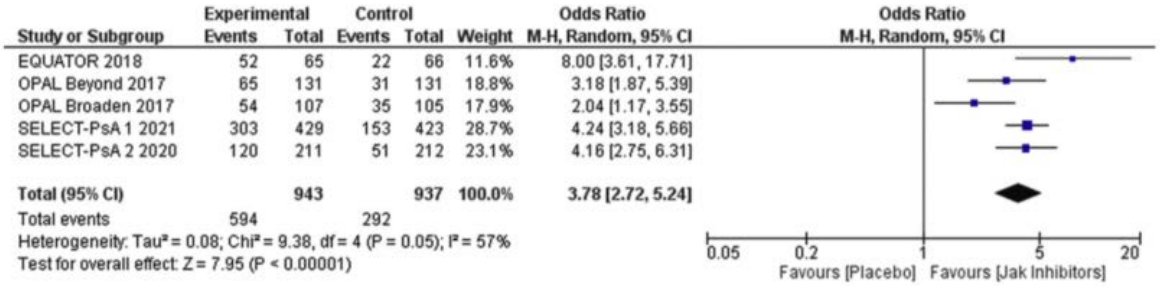


Fig. 3. ACR20 response Filgotinib 200 mg - Tofacitinib 5 mg - Upadacitinib 15 mg.

- 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). […]

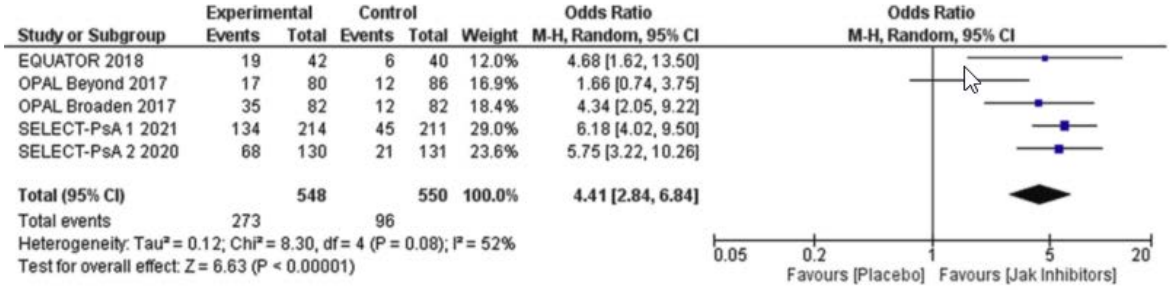


Fig. 4. PASI75 response Filgotinib 200 mg - Tofacitinib 5 mg - Upadacitinib 15 mg.

- 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). […]

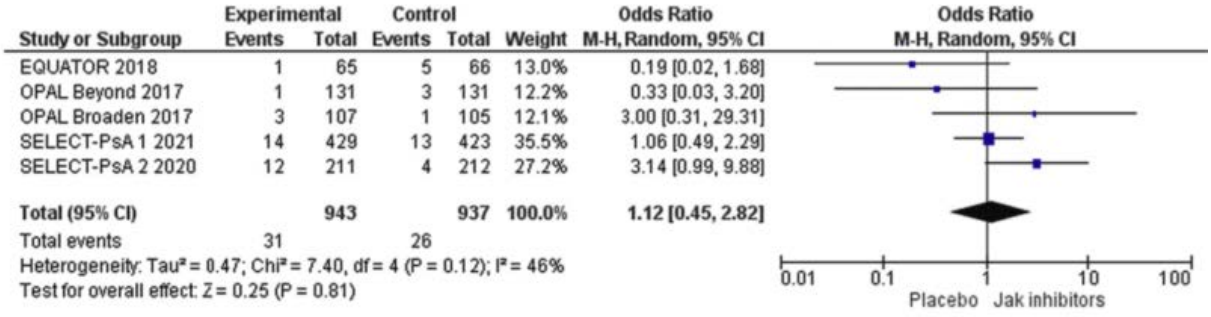


Fig. 5. Serious adverse events Filgotinib 200 mg - Tofacitinib 5 mg - Upadacitinib 15 mg.

  -

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 Q et al., 2021 [6].

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).

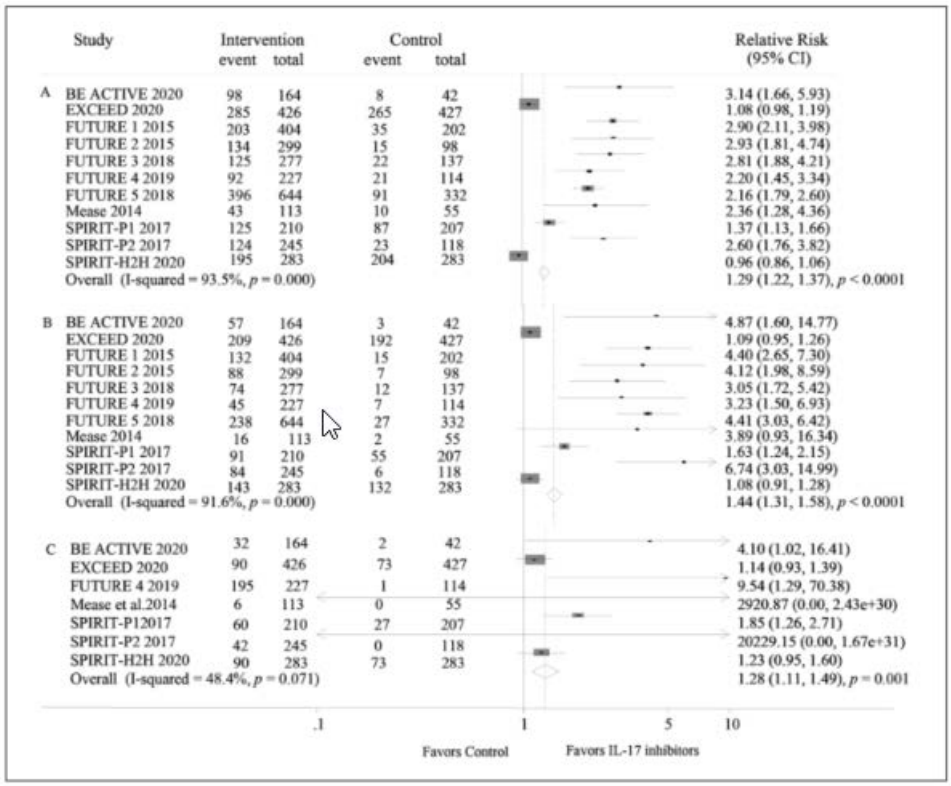


Figure 2. Effects of IL-17 inhibitors compared with placebo or other active control for the responses of ACR20 **(A)**, ACR50 **(B)** and ACR70 **(C)** in patients with psoriatic arthritis.

- 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 [7].

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

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

- Wu D et al., 2020 [26]

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

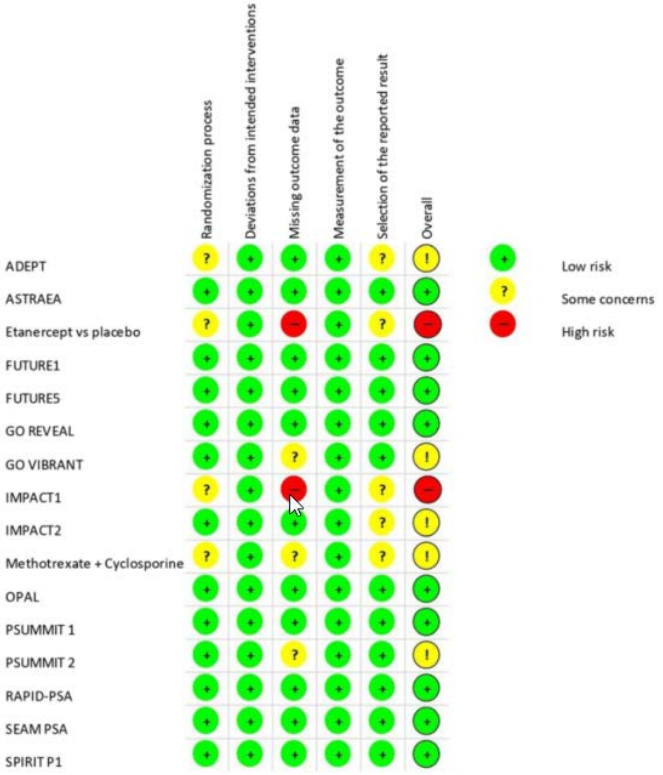
[a] Median (interquartile range)

[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)

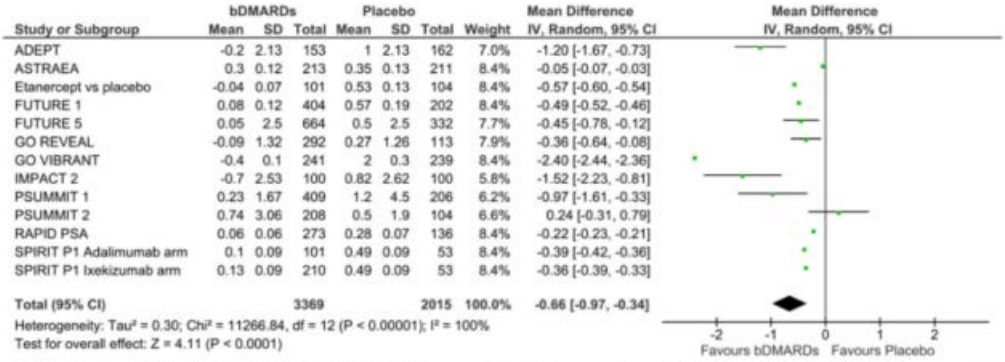


Fig. 3 Mean difference and 95% CIs for the effect of bDMARDs on radiographic progression at 24 weeks of treatment. IV, inverse variance

- 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).

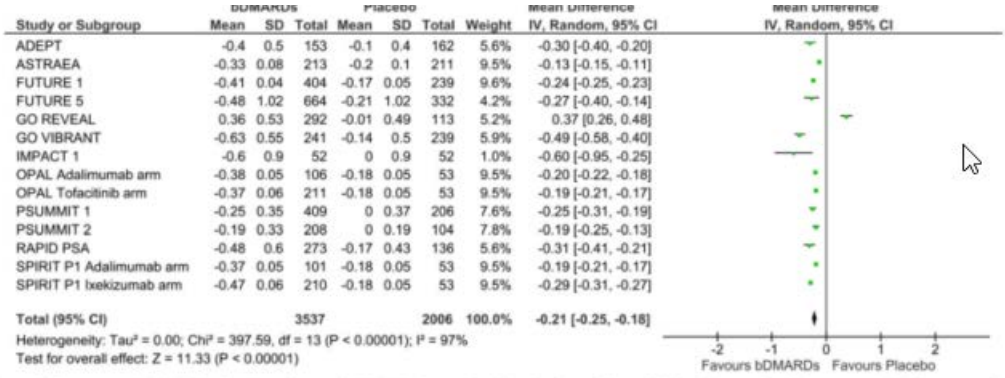


Fig. 4 Mean difference and 95% CIs for the effect of bDMARDs on health-related quality of life at 24 weeks of treatment. IV, inverse variance

- 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.

Xie Y et al., 2021 [28].

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)

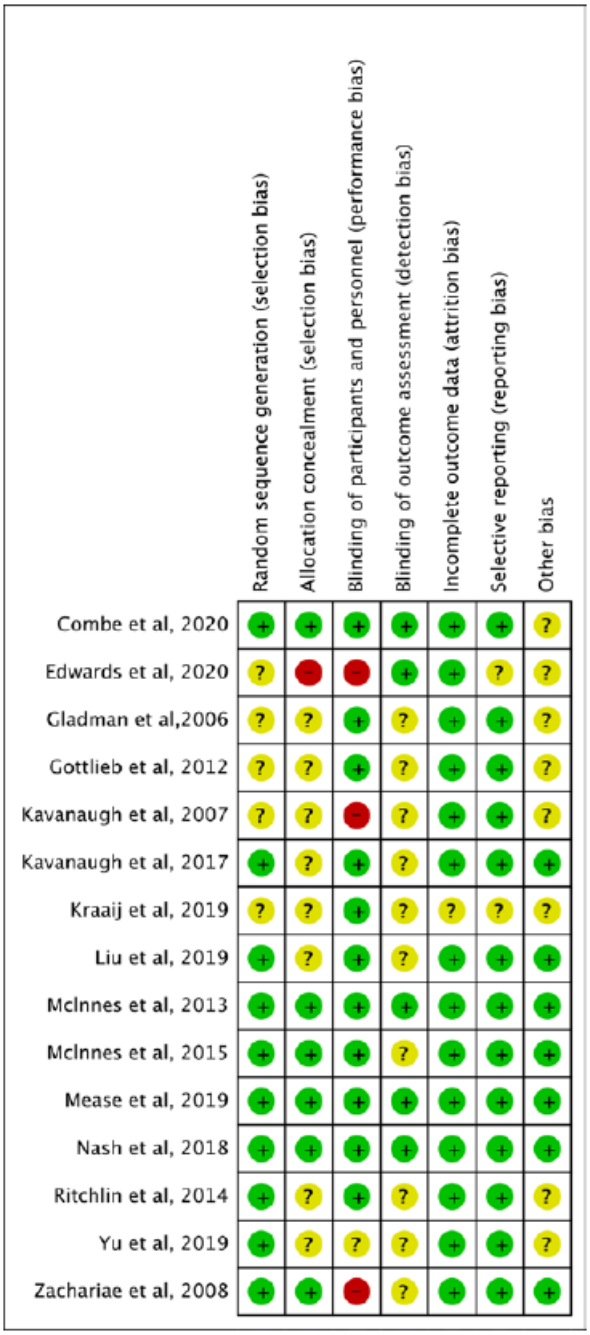
TABLE 1 Characteristics of included studies

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

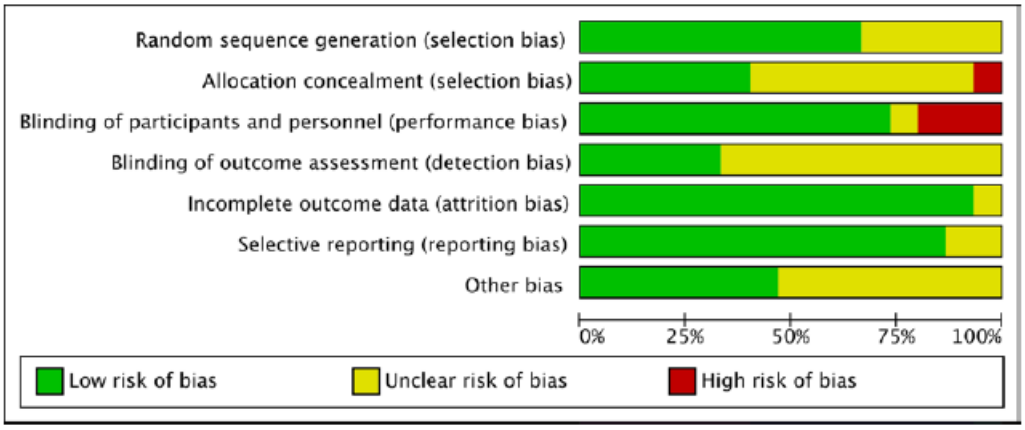
Abbreviations: MTX, methotrexate; rhTNFR-Fc, recombinant human TNF-α receptor II: IgG Fc,fusion protein.

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.

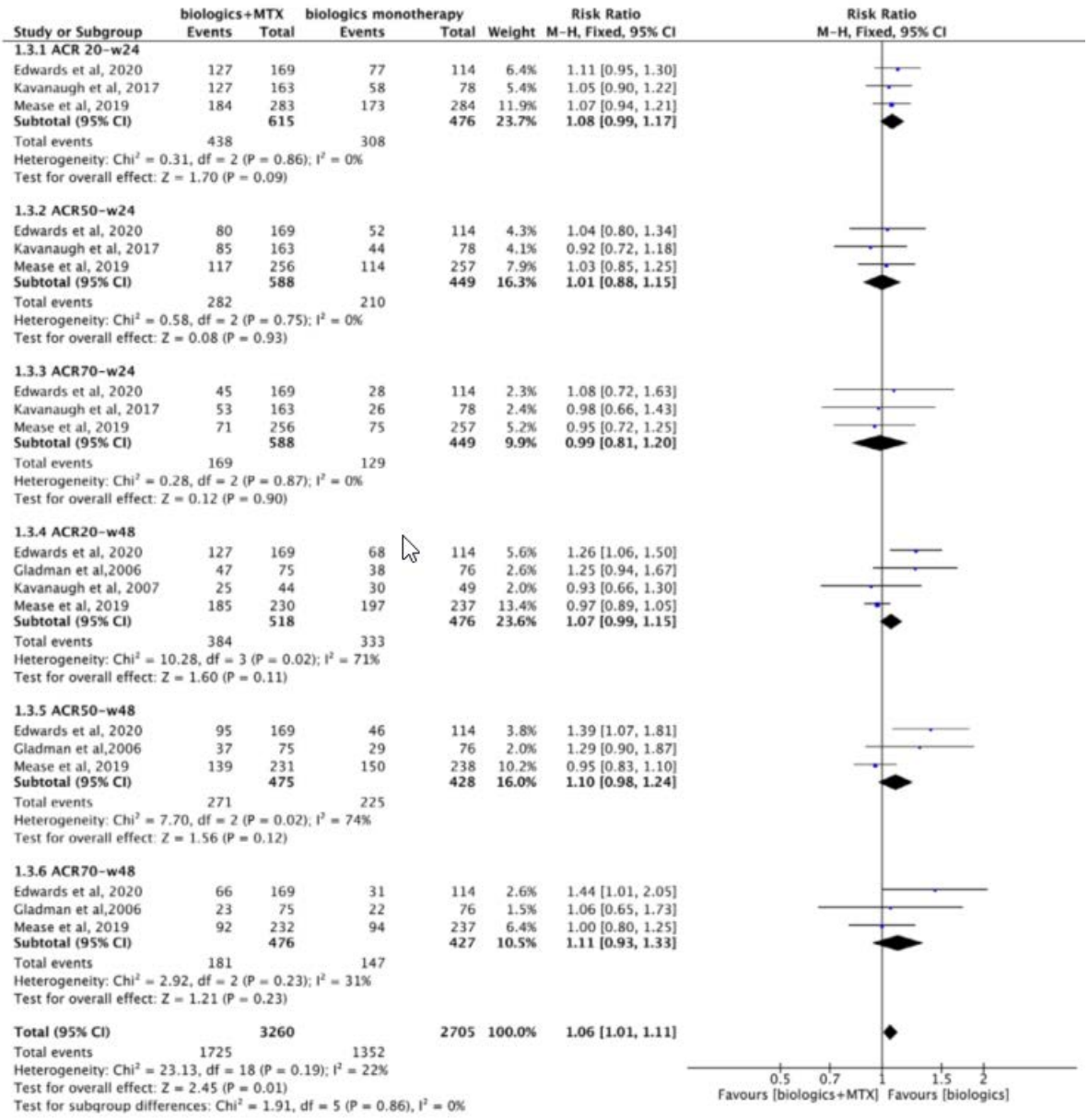


FIGURE 3 The forest plot for clinical efficiency of psoriatic arthritis (TNF inhibitors + MTX vs TNF inhibitors mono), estimated by American College of Rheumatology (ACR) response at week 24 and week 48

- 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).

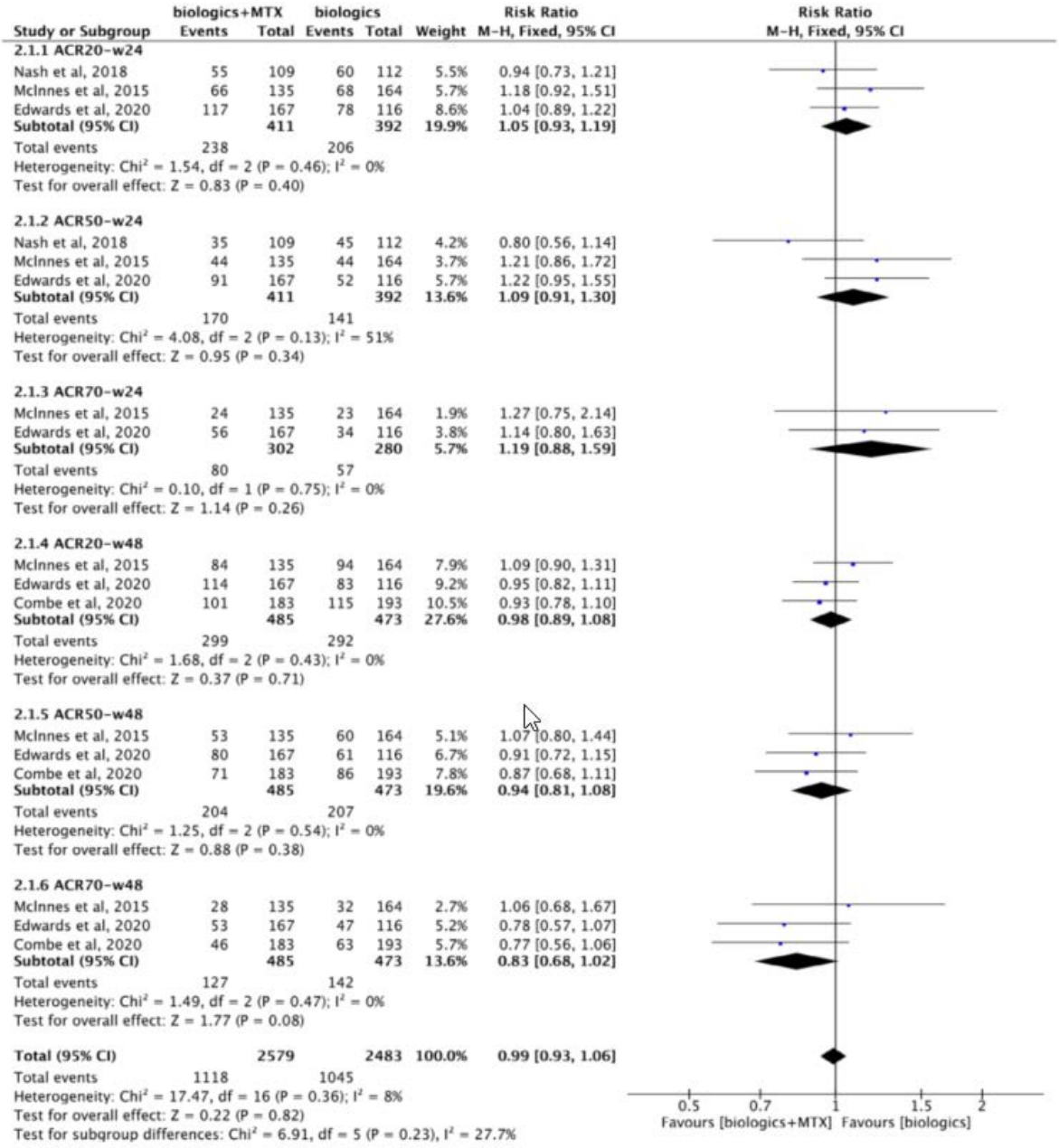


FIGURE 4 The forest plot for clinical efficiency of psoriatic arthritis (IL-17A inhibitors + MTX vs IL-17A inhibitors mono), estimated by American College of Rheumatology (ACR) response at week 24 and week 48

- 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 A et al., 2020 [12].

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.

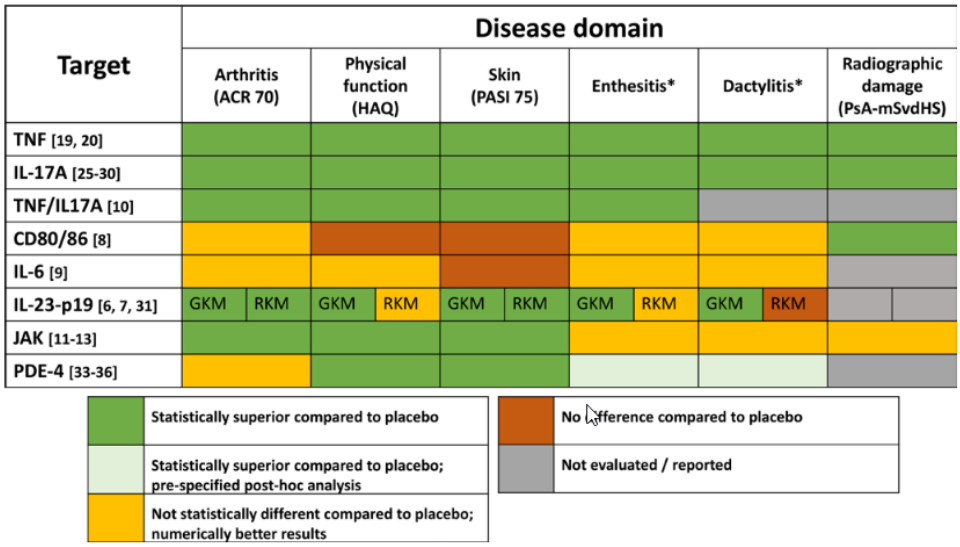


Figure 2 Efficacy results of randomised controlled trials stratified by mode of action and disease domain. Data from previous systematic literature research are also accounted for in this figure. *Different instruments used in studies. ACR, American College of Rheumatology Response; CD, cluster of differentiation; 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.

Ruyssen-Witrand A et al., 2020 [19].

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

Es liegen weitere SRs zu dieser Fragestellung vor:
- Qiu M et al., 2020 [18]

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.

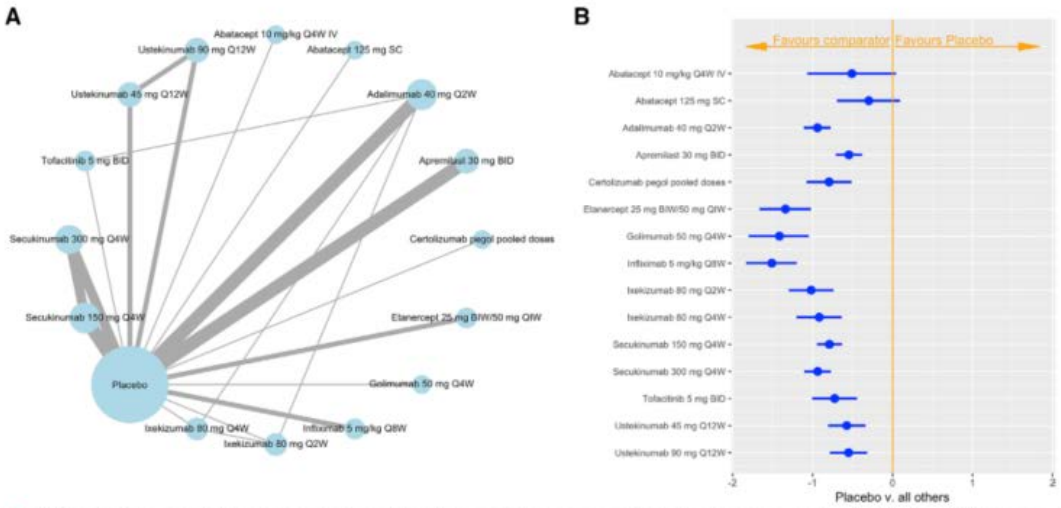


Figure 2 Network diagram (A) and forest plot of treatment differences on the standard normal scale (B) for ACR response at weeks 12–16 among bDMARD-naïve patients with active PsA (placebo as the reference). In the network diagram, line thickness is weighted according to the number of studies included 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:

- Qiu M et al., 2020 [18]

Song GG et al., 2019 [24].

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.

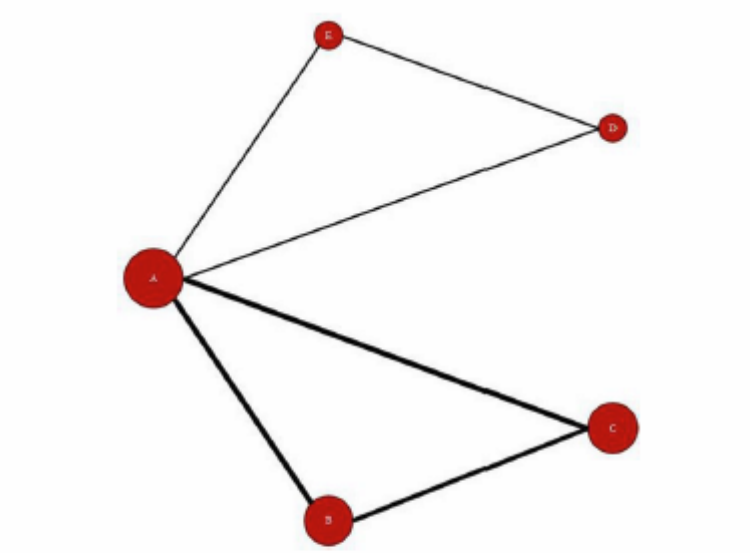


Fig. 1 Evidence network diagram of network meta-analysis comparisons. The width of each edge is proportional to the number of randomized controlled trials comparing each pair of treatments, and the size of each treatment node is proportional to the number of randomized participants (sample size), (A) 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.

3.3 Leitlinien

Nast A et al., 2022 [17]
EUROGUIDERM GUIDELINE FOR THE SYSTEMIC TREATMENT OF PSORIASIS VULGARIS

Siehe auch:

- Empfehlungen der European Dermatology Forum (EDF), European Centre for Guidelines Development, 2021 [5] und Methods & evidence report

Zielsetzung/Fragestellung

- 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)

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.

Recherche/Suchzeitraum:

- Update 2021
- In April 2021, an update of the Cochrane review has been published 33.
- Shortly thereafter an online survey was conducting asking the guideline development group if any updates to the guideline are needed. The group agreed that all chapters were still up to date.

LoE

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

GoR

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 **against** the use of an intervention	'We suggest against . . .'	↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
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.

The recommendations are presented throughout this guideline as displayed below: first the content, then the arrows and colours indicating the direction and the strength of the recommendations, respectively and lastly the rate of expert agreement (consensus strength).

Empfehlungen

3. Guidance for specific clinical and comorbid situations

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

Table 45: Summary of the results for drugs approved for psoriasis of the skin and psoriatic arthritis (Dressler et al [115] updated, see methods report, blue – new data/study in 2021)

	Patients achieving ARC20 after 12-24 weeks			Patients with at least one adverse event		
	RR	95% CI	Certainty Evidence (GRADE)	RR	95% CI	Certainty Evidence (GRADE)
Head-to-head comparisons:						
ADA 40mg EOW (1) vs. SEC 300mg LD then Q4W	0.92	0.82 to 1.02	MODERATE	1.02	0.95 to 1.10	MODERATE
ETA 50mg QW + MTX up to 20mg QW vs. MTX up to 20mg QW	1.28	1.11 to 1.48	LOW	1.01	0.92 to 1.11	MODERATE
INF 5mg/kg w0,2,6,14 + MTX 15mg QW 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 (LD 160mg w0) vs. ADA 40mg EOW (1)	1.08	0.86 to 1.36	VERY LOW	1.02*	0.83 to 1.25	MODERATE
Placebo comparisons:						
ADA 40mg EOW (2) vs. PBO	2.08	1.52-2.86	MODERATE	1.07	0.83 to 1.39	MODERATE
APR 30mg BID	2.01	1.69 to 2.40	MODERATE	1.24	1.12 to 1.36	LOW
CZP 400mg LD then 200mg Q2W	2.71	1.95 to 3.76	MODERATE	1.01*	0.86 to 1.19	MODERATE
CZP 400mg LD then 400mg Q4W (3)	2.36	1.68 to 3.31	MODERATE	1.05*	0.90 to 1.23	MODERATE
ETA 25mg BIW	5.47	3.27 to 9.16	LOW	no data		
GUS 100mg LD then Q8W (4)	2.20	1.75 to 2.78	HIGH	1.02	0.87 to 1.20	MODERATE
INF 5mg/kg w0,2,6,14	4.38	2.24 to 8.56	MODERATE	1.13	0.87 to 1.47	LOW
IXE 80mg Q2W (LD160mg w0)	2.21	1.71 to 2.86	MODERATE	1.39*	1.09 to 1.78	LOW
MTX 7.5mg to 10mg to 15mg	1.82	0.97 to 3.40	LOW	no data		
SEC 300mg + LD vs. PBO	2.69	2.06 to 3.52	HIGH	0.97	0.79 to 1.20	LOW
UST 45mg	1.95	1.52 to 2.50	HIGH	no data		
UST 90mg (5)	2.26	1.80 to 2.82	MODERATE	0.96	0.75 to1.24	VERY LOW

1 - 80mg LD only for pts. with moderate-to-severe PsO
2- no LD of 80mg (this would be the case for PsO)
3- for psoriasis vulgaris, 400mg Q2W can also be considered
4 - For patients at high risk for joint damage according to clinical judgement, a dose of 100 mg every 4 weeks may be considered (SmPC)
5- for Pso patient with >=100kg (dosis not licensed for PsA), 1 study 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.

Referenzen

33. Sbidian E, Chaimani A, Garcia-Doval I *et al.* Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2021.

European Dermatology Forum (EDF), European Centre for Guidelines Development, 2021 und Methods & evidence [5]

Euroguiderm guideline for the systemic treatment of psoriasis vulgaris

Siehe auch:

- Nast A et al., 2021 [15].
- Nast A et al., 2021 [16].

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.

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.

Referenzen aus Leitlinien

17. Nast A, Gisondi P, Ormerod AD et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris--Update 2015--Short version--EDF in cooperation with EADV and IPC. Journal of the European Academy of Dermatology and Venereology : JEADV 2015; 29: 2277-94.Referenzen
18. Nast A, Spuls PI, van der Kraaij G et al. European S3-Guideline on the systemic treatment of psoriasis vulgaris - Update Apremilast and Secukinumab - EDF in cooperation with EADV and IPC. Journal of the European Academy of Dermatology and Venereology: JEADV 2017; 31: 1951-63.
109. Elmamoun M, Chandran V. Role of Methotrexate in the Management of Psoriatic Arthritis. Drugs 2018; 78: 611-9.
110. McInnes IB, Nash P, Ritchlin C et al. Secukinumab for psoriatic arthritis: comparative effectiveness versus licensed biologics/apremilast: a network meta-analysis. Journal of comparative effectiveness research 2018; 7: 1107-23.
111. Mease PJ, Smolen JS, Behrens F et al. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naive patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. Annals of the rheumatic diseases 2020; 79: 123-31.
112. Nash P, McInnes IB, Mease PJ et al. Secukinumab Versus Adalimumab for Psoriatic Arthritis: Comparative Effectiveness up to 48 Weeks Using a Matching-Adjusted Indirect Comparison. Rheumatology and therapy 2018; 5: 99-122.
113. Dressler C, Eisert L, Pham PA, Nast A. Efficacy and safety of systemic treatments in psoriatic arthritis: a systematic review, meta-analysis and GRADE evaluation. Journal of the European Academy of Dermatology and Venereology : JEADV 2019; 33: 1249-60.
114. Murashima A, Watanabe N, Ozawa N, Saito H, Yamaguchi K. Etanercept during pregnancy and lactation in a patient with rheumatoid arthritis: drug levels in maternal serum, cord blood, breast milk and the infant's serum. Annals of the rheumatic diseases 2009; 68: 1793-4.
115. Gossec L, Smolen JS, Gaujoux-Viala C et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. Annals of the rheumatic diseases 2012; 71: 4-12.

Smith CH et al., 2020 [22].

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		⊖	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
  - o psoriasis disease severity compared with baseline (e.g. PASI baseline to end point score)9
  - o the agreed treatment goal
  - o control of psoriatic arthritis disease activity and/or inflammatory bowel disease (in consultation with a rheumatologist and/or gastroenterologist)
  - o the impact of psoriasis on the person's physical, psychological and social functioning
  - o the benefits vs. the risks of continued treatment
  - o the views of the person undergoing treatment (and their family or carers, where appropriate)
  - o adherence to the treatment.
- R11 (↑↑) Assess whether the minimal response criteria have been met, as defined by
  - o ≥ 50% reduction in baseline disease severity (e.g. PASI 50 response, or percentage BSA where PASI is not applicable) and
  - o 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:
  - o the psoriasis does not achieve the minimum response criteria (primary failure – see R11)

o 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

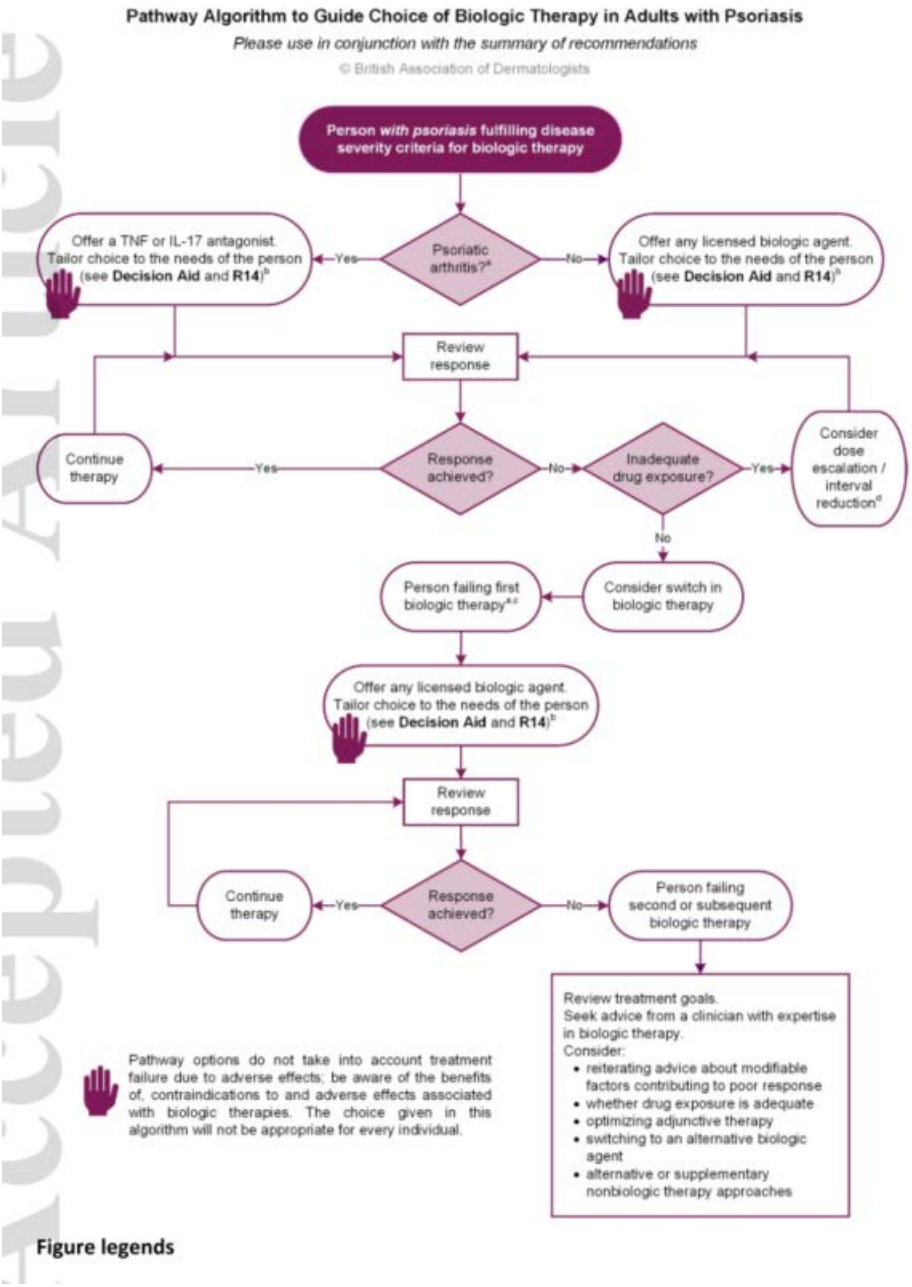
Choice of biologic therapy in adults

- 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:

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



Backgroundinfos aus Leitlinien: siehe Anhang

Gossec L et al., 2012 [8]

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).

LoE

-
-

Table 1 Categories of evidence[9]

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

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

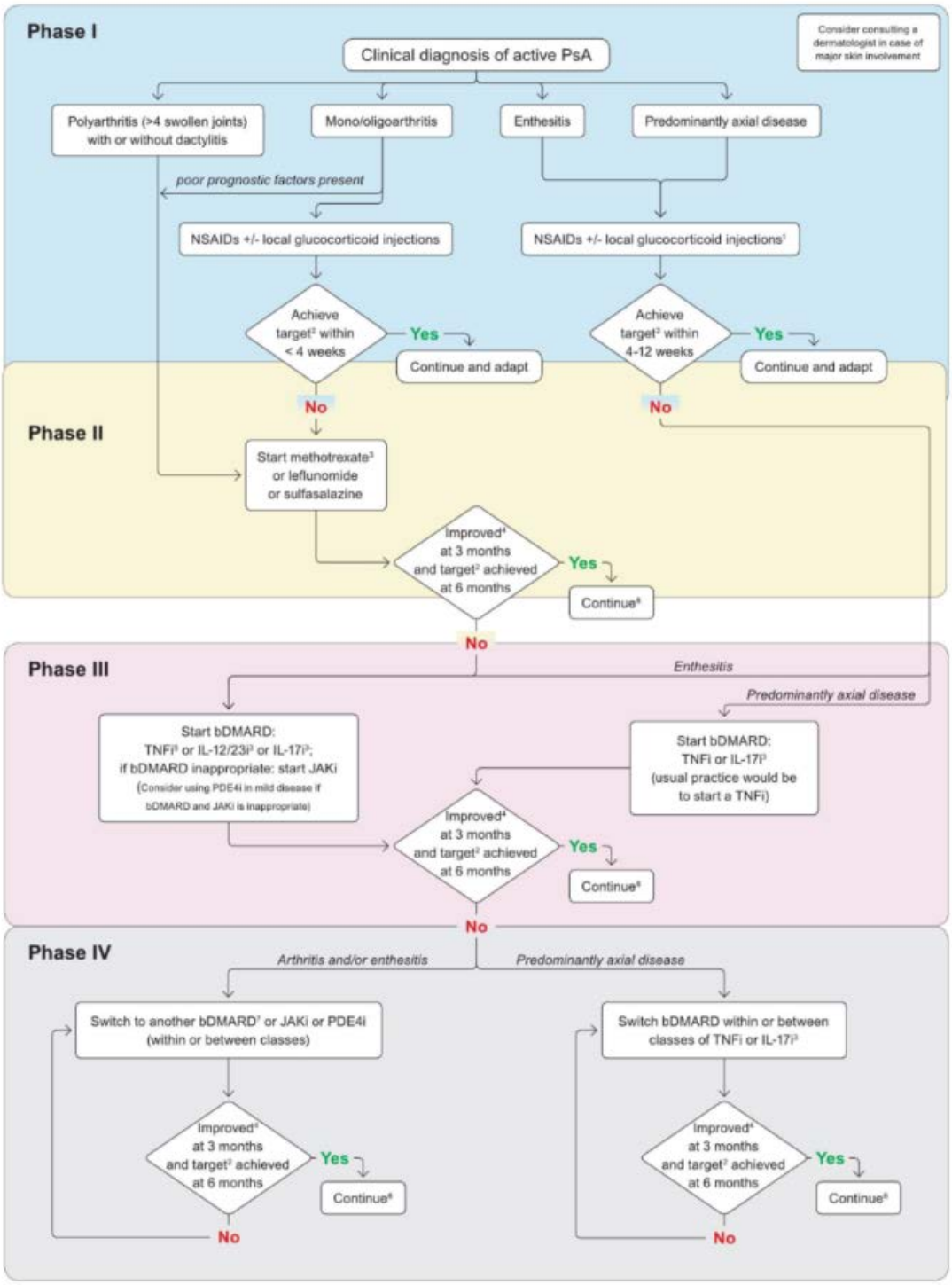
taking this drug and tolerating it well, but the taskforce admitted that to date there is no clear evidence that combination therapy is more efficacious than monotherapy, aside from a slight reduction of immunogenicity that is of doubtful clinical significance.[71] We suggest that MTX dose may be reduced 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

Referenzen aus Leitlinien

1 Kerschbaumer A, Smolen JS, Dougados M, et al. Pharmacological treatment of psoriatic arthritis: a systematic literature research for the 2019 update of the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis 2016.

13 Ritchlin C, Rahman P, Kavanaugh A, et al. Efficacy and safety of the anti- IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non- biological and biological anti- tumour necrosis factor therapy: 6- month and 1- year results of the phase 3, multicentre, double- blind, placebocontrolled, randomised PSUMMIT 2 trial. Ann Rheum Dis 2014;73:990–9.

14 Mease PJ, van der Heijde D, Ritchlin CT, et al. Ixekizumab, an interleukin- 17A specific monoclonal antibody, for the treatment of biologic- naive patients with active psoriatic arthritis: results from the 24- week randomised, double- blind, placebo- controlled and active (adalimumab)- controlled period of the phase III trial SPIRIT- P1. Ann Rheum Dis 2017;76:79–87.
15 Mease P, Hall S, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. N Engl J Med 2017;377:1537–50.
16 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.
40 Heiberg MS, Koldingsnes W, Mikkelsen K, et al. The comparative one- year performance of anti- tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. Arthritis Rheum 2008;59:234–40.
41 Lie E, van der Heijde D, Uhlig T, et al. Effectiveness and retention rates of methotrexate in psoriatic arthritis in comparison with methotrexate- treated patients with rheumatoid arthritis. Ann Rheum Dis 2010;69:671–6.
42 Mease PJ, Gladman DD, Collier DH, et al. Etanercept and methotrexate as monotherapy or in combination for psoriatic arthritis: primary results from a randomized, controlled phase III trial. Arthritis Rheumatol 2019;71:1112–24.
51 Jadon DR, Shaddick G, Tillett W, et al. Psoriatic arthritis mutilans: characteristics and natural radiographic history. J Rheumatol 2015;42:1169–76.
52 El Miedany Y, El Gaafary M, Youssef S, et al. Tailored approach to early psoriatic arthritis patients: clinical and ultrasonographic predictors for structural joint damage. Clin Rheumatol 2015;34:307–13.
53 Geijer M, Lindqvist U, Husmark T, et al. The Swedish early psoriatic arthritis registry 5- year followup: substantial radiographic progression mainly in men with high disease activity and development of Dactylitis. J Rheumatol 2015;42:2110–7.
54 Hellgren K, Dreyer L, Arkema EV, et al. Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: a collaborative study from the ARTIS and DANBIO registers. Ann Rheum Dis 2017;76:105–11.
55 Costa L, Caso F, Del Puente A, et al. Incidence of malignancies in a cohort of psoriatic arthritis patients taking traditional disease modifying antirheumatic drug and tumor necrosis factor inhibitor therapy: an observational study. J Rheumatol 2016;43:2149–54.
56 Nash P, Kirkham B, Okada M, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24- week randomised, double- blind, placebo- controlled period of the SPIRIT- P2 phase 3 trial. The Lancet 2017;389:2317–27.
57 Mease PJ, Smolen JS, Behrens F, et al. A head- to- head comparison of the efficacy and safety of ixekizumab and adalimumab in biological- naïve patients with active psoriatic arthritis: 24- week results of a randomised, open- label, blinded- assessor trial. Ann Rheum Dis 2020;79:123–31.
58 McInnes IB, Kavanaugh A, Gottlieb AB, et al. 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.
59 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.
60 Mease PJ, Kellner H, Morita A, et al. OP0307 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. Ann Rheum Dis 2018;77:200–1.
61 Blauvelt A, Papp KA, Griffiths CEM, et al. Efficacy and safety of guselkumab, an antiinterleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double- blinded, placebo- and active comparator- controlled voyage 1 trial. J Am Acad Dermatol 2017;76:405–17.
62 Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an antiinterleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase III, double- blind, placebo- and active comparatorcontrolled voyage 2 trial. J Am Acad Dermatol 2017;76:418–31.
63 Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate- to- severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double- blind, randomised, placebo-controlled and ustekinumab- controlled phase 3 trials. Lancet 2018;392:650–61.
64 Mease PJ, Kavanaugh A, Reimold A, et al. Secukinumab provides sustained improvements in the signs and symptoms of psoriatic arthritis: final 5- year results from the phase 3 future 1 study. ACR Open Rheumatol 2020;2:18–25.
65 Blauvelt A, Reich K, Tsai T- F, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate- to- severe plaque psoriasis up to 1 year: Results from the CLEAR study. J Am Acad Dermatol 2017;76:e69:60–9.

66 Papp KA, Blauvelt A, Bukhalo M, et al. Risankizumab versus ustekinumab for moderate- to- severe plaque psoriasis. N Engl J Med 2017;376:1551–60.
67 Schreiber S, Colombel J- F, Feagan BG, et al. Incidence rates of inflammatory bowel disease in patients with psoriasis, psoriatic arthritis and ankylosing spondylitis treated with secukinumab: a retrospective analysis of pooled data from 21 clinical trials. Ann Rheum Dis 2019;78:473–9.
68 So A, Inman RD. An overview of biologic disease- modifying antirheumatic drugs in axial spondyloarthritis and psoriatic arthritis. Best Pract Res Clin Rheumatol 2018;32:453–71.
69 Aaltonen K, Heinonen A, Joensuu J, et al. Effectiveness and drug survival of TNFinhibitors in the treatment of psoriatic arthritis: a prospective cohort study. Semin Arthritis Rheum 2017;46:732–9.
70 Behrens F, Cañete JD, Olivieri I, et al. Tumour necrosis factor inhibitor monotherapy vs combination with MTX in the treatment of PSA: a systematic review of the literature. Rheumatology 2015;54:915–26.
71 Zisapel M, Zisman D, Madar- Balakirski N, et al. Prevalence of TNF-α blocker immunogenicity in psoriatic arthritis. J Rheumatol 2015;42:73–8.
72 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.
73 Ema confirms Xeljanz to be used with caution in patients at high risk of blood clots. Available: https://www. ema. europa. eu/ en/ news/ ema- confirms- xeljanz- be- usedcaution- patients- high- risk- blood- clots [Accessed 2 Apr 2020].

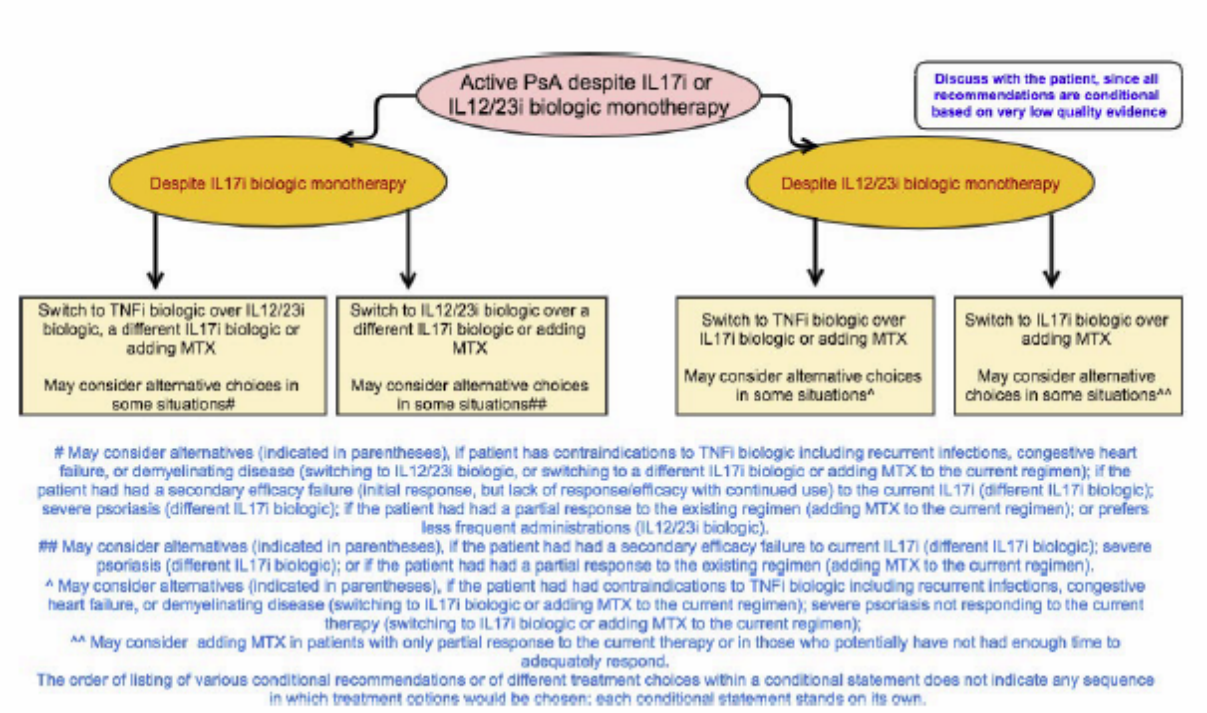


Figure 6. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) despite treatment with interleukin-17 inhibitor (IL-17i) or IL-12/23i biologic monotherapy. All recommendations are conditional based on low- to very-low-quality of evidence. A conditional recommendation means 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., 2022 [4].

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

Siehe auch:

- Coates LC et al., 2021 [2].
- Coates LC et al., 2021 [3].

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; zutreffend
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; zutreffend

  Systematische Suche, Auswahl und Bewertung der Evidenz; searches were initially run in 2019 but were updated in 2020 owing to delays in the recommendation. Additional searches identified evidence published in abstract form at key rheumatology and dermatology conferences (ACR, EULAR and American Academy of Dermatology annual meetings) from 2017 to 2020. Data that had only been published in abstract form at the time the recommendations were created were included so as to provide consideration of the newest data in this fast- evolving discipline, but, as in 2015, it was decided that data derived from abstracts alone should be clearly identified in the recommendations.
- 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, zutreffend
- 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

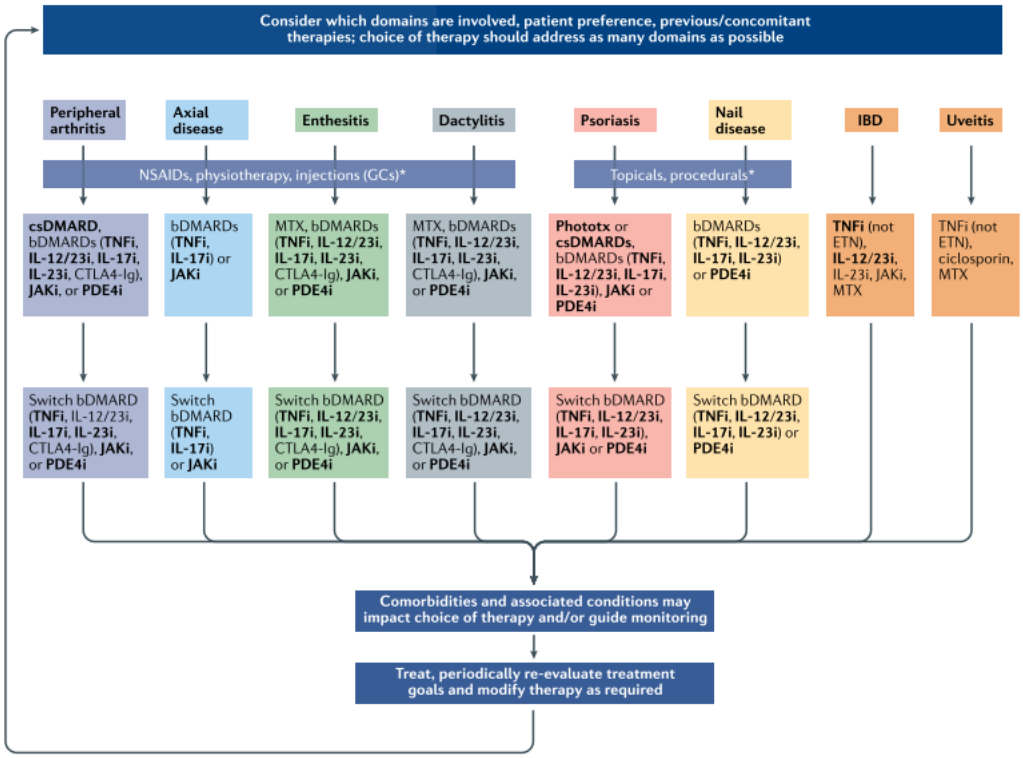


Fig. 2 | **GRAPPA 2021 treatment schema.** The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2021 treatment recommendations for psoriatic arthritis (PsA) use a domain-based approach, but, considering that most patients present with disease in multiple domains, this treatment schema combines the recommendations for each domain to guide therapeutic decisions. Disease activity should be assessed in each of the domains and consideration given to comorbidities, previous therapies and patient preference. Standard 'step-up' approaches, as well as expedited treatment routes, are indicated. Treatment efficacy and tolerability should be re-evaluated periodically and treatment adjusted as appropriate. The order of the products in the boxes is sorted by mechanism of action and does not reflect guidance on relative efficacy or suggested usage. Bold text indicates a strong recommendation, standard text a conditional recommendation. The asterisks indicate a conditional recommendation based on data from abstracts only. bDMARD, biologic DMARD; CTLA4-Ig, CTLA4–immunoglobulin fusion protein; csDMARD, conventional synthetic DMARD; ETN, etanercept; GC, glucocorticoid; IBD, inflammatory bowel disease; JAKi, Janus kinase inhibitor; MTX, methotrexate; PDE4i, phosphodiesterase 4 inhibitor; TNFi, TNF inhibitor.

<u>Peripheral Arthritis</u>

- NSAIDs and intra- articular and oral glucocorticoids are conditionally recommended for relieving symptoms of peripheral arthritis as per the 2015 recommendation, as no new relevant data were identified.
- For treatment- naive patients, there remains a low level of evidence to support the use of csDMARDs for the treatment of peripheral arthritis. However, in view of supportive observational data7–10 and universal accessibility, the use of csDMARDs (methotrexate, sulfasalazine or leflunomide) is strongly recommended.
- In many circumstances, csDMARDs can be used as first- line therapy, with regular assessment of clinical response (every 12–24 weeks) and early escalation of therapy (between 12 and 24 weeks) advised as necessary. It is important to acknowledge that new, high- quality data support the superiority of TNF inhibitors over csDMARDs as first-line therapy, particularly in patients with early disease8–10.
- The decision to use TNF inhibition as first- line therapy should be made as part of a shared decision- making process between the clinician and the patient, with consideration of the risks, benefits and the individual's preference. For all RCTs reviewed for phosphodiesterase 4 inhibitors (PDE4i), TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, IL-23 inhibitors and JAK inhibitors, there were no differences in efficacy for

these treatment options in subgroups of patients with or without concurrent csDMARDs.

- In a large RCT that was adequately powered to compare methotrexate, etanercept and their combination, there was no difference in efficacy between the etanercept monotherapy arm and the etanercept–methotrexate combination arm8.
- These findings support the conclusion that a combination of csDMARDs with bDMARDs might not be necessary to achieve short- term response. With JAK inhibitors, the evidence is scarce but also points in the same direction However, the potential benefit of concomitant therapy with csDMARDs with all bDMARDs is incompletely defined, with conflicting evidence derived largely from uncontrolled studies; further study is indicated to define potential benefits. For patients with an inadequate response to csDMARDs, high- quality evidence supports the use of TNF inhibitors, IL-17 inhibitors, IL-23 inhibitors and JAK inhibitors; and moderate- quality evidence supports IL-12/23 inhibitors or PDE4 inhibitors being superior to placebo. Similar magnitudes of effect sizes for efficacy were observed across RCTs for TNF inhibitors, IL-17 inhibitors, IL-23 inhibitors and JAK inhibitors compared with placebo, whereas effect sizes for PDE4 inhibitors and IL-12/23 inhibitors seemed to be lower (see Supplementary Table 9). These classes of drugs are all strongly recommended on the basis of this evidence. Concerning the choice between different bDMARDs or tsDMARDs, two head- to- head RCTs compared IL-17 inhibition with TNF inhibition11,12, and one compared JAK inhibition with TNF inhibition13.
- These studies were adequately powered to inform a direct comparison between these therapies. On the basis of current evidence, the efficacies of IL-17 inhibitors and TNF inhibitors are comparable for the peripheral arthritis domain in patients with an inadequate response to csDMARDs. Superiority of a JAK inhibitor (given at the higher of two doses) over a TNF inhibitor for some, but not all, peripheral arthritis outcomes was seen in a single RCT13; consistent superiority of JAK inhibitors over other bDMARDs is yet to be shown.
- Based on the evidence, including head- to- head studies, TNF inhibitors, IL-17 inhibitors and JAK inhibitors are equally recommended. There are no current head- to- head studies comparing IL-23 inhibitors with other bDMARDs or JAK inhibitors. Although IL-23 inhibition is still strongly recommended, it might be considered slightly lower in terms of recommendations for use in patients with peripheral arthritis. One small, open- label study comparing IL-12/23 inhibition with TNF inhibition did not show the superiority of IL-12/23 inhibition over TNF inhibition in peripheral joint domains14.
- For patients with previous experience with bDMARDs, TNF inhibitors, IL-17 inhibitors, IL-23 inhibitors and JAK inhibitors are strongly recommended on the basis of moderate- to high- quality evidence. PDE4 inhibition is conditionally recommended. The limitations for these recommendations include the issue that the evidence was derived from patients with PsA who predominantly had polyarthritis, with this evidence then extrapolated to oligoarthritis and other phenotypes. For inadequate responders, there are insufficient data for specific recommendations based on primary versus secondary failure of prior treatment.

<u>Axial disease.</u>

- For patients with axial symptoms who have not responded to treatment with NSAIDs, physiotherapy and/or sacroiliac joint glucocorticoid injections (when appropriate), initiation of a targeted therapy is strongly recommended. TNF inhibition and IL-17 inhibition have demonstrated efficacy in both radiographic and non- radiographic axSpA and were recommended for axial PsA in the previous GRAPPA recommendations2.

- Since the 2015 recommendations2, several phase II, upadacitinib16 and phase II–III RCTs have demonstrated the efficacy of the JAK inhibitors tofacitinib15 and filgotinib17 in ankylosing spondylitis. Data from a . Extrapolating phase III study of tofacitinib in ankylosing spondylitis published in 2021 confirm this efficacy18 from the evidence in axSpA, we recommend these agents for axial PsA as well.
- Only one study was designed specifically to assess axial PsA19. In this phase IIIb RCT, the IL-17 inhibitor secukinumab demonstrated significant improvement in the signs and symptoms of axial disease compared with placebo in patients with PsA who had an inadequate response to NSAIDs; a reduction in MRI scores was also noted As IL-17 inhibitors have shown efficacy and have been approved for use in the treatment of axSpA, these agents are strongly recommended for axial PsA. Although IL-12/23 inhibitors and IL-23 inhibitors have not demonstrated efficacy in ankylosing spondylitis20, post hoc analyses from the trials of ustekinumab and guselkumab in patients who have had axial symptoms suggest that these agents might be effective in axial PsA19,20.
- However, it is also possible that improvement in the outcome measures used (for example, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)) could reflect disease activity in other PsA domains. Because these studies included primarily patients with active PsA, and these agents did not prove effective in axSpA, the evidence is currently too limited and conflicting such that these medications cannot be recommended for axial PsA at this time.

<u>Enthesitis.</u>

- Classes of advanced therapies found to be effective and thus strongly recommended as treatment options for active enthesitis in patients with PsA include TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, IL-23 inhibitors, JAK inhibitors and PDE4 inhibitors. Despite novel information about the comparative efficacy of different classes of medications emerging from head- to- head studies, including comparisons of IL-17 inhibitors with TNF inhibitors11,12 , methotrexate with TNF inhibitors8,9, and IL-12/23 inhibitors with TNF inhibitors14, none of the evaluated classes of medications was found to have clear and consistent superiority over the other. Therefore, none of the medication classes detailed above was prioritized for the treatment of enthesitis in the recommendations. Methotrexate received a conditional recommendation for the treatment of active enthesitis. This is a change from previous guidelines, in which methotrexate was not recommended owing to a lack of evidence1,2.
- The change was made on the basis of expert opinion and data emerging from the SEAM-PsA trial, which suggested efficacy of methotrexate for enthesitis that was similar to that observed for etanercept8 . It should be noted that the SEAM- PsA trial did not include a placebo arm, so the evidence is limited and therefore the recommendation is conditional.
- The use of NSAIDs, local glucocorticoid injections and physiotherapy was conditionally recommended, despite the lack of high- quality studies that investigated their efficacy for enthesitis in PsA or SpA. These modes of treatment, which are commonly used as first- line therapies for enthesitis, provide a relatively safe and affordable option, especially for localized enthesitis

<u>Dactylitis</u>

- Meaningful advances have been made in the treatment of dactylitis since the last GRAPPA recommendations2.

- In the SEAM- PsA RCT8 , no statistically significant difference was found between methotrexate monotherapy, etanercept monotherapy and methotrexate–etanercept combination therapy, neither in the change from baseline in the Leeds Dactylitis Index (LDI) nor in the proportion of patients achieving complete resolution of dactylitis. However, no definite conclusion regarding effect size could be drawn owing to the lack of a placebo control group.
- The therapeutic armamentarium for dactyli, ixekizumab24 and brodalumab25 tis has increased considerably. The IL-17 inhibitors secukinumab21–23 demonstrated superior efficacy compared with placebo for improving dactylitis signs and symptoms in RCTs; another IL-17 inhibitor, bimekizumab, is being studied. In RCTs the IL-23 inhibitors guselkumab and risankizumab were found to be effective for dactylitis as assessed by the proportion of patients with total resolution of dactylitis at week 24 (refs26,27); another IL-23 inhibitor, tildrakizumab, decreased mean LDI at week 52 compared with baseline in a phase II trial28 . The T cell modulator abatacept (CTLA4- Ig) numerically improved the proportion of patients achieving resolution of dactylitis at week 24 compared with placebo29.
- Head- to- head trials comparing TNF inhibitors and IL-17 inhibitors11,12 assessed the proportion of patients achieving resolution of dactylitis at week 24 and did not find a statistically significant difference between the two classes of biologic agents.
- Dactylitis- related outcomes were assessed as secondary outcomes in trials of JAK inhibitors, and these drugs were considered statistically superior to placebo in most of these studies13,30,31.
- In a head- to- head trial comparing JAK inhibition with TNF inhibition, the improvements in dactylitis disease activity of upadacitinib and adalimumab at week 24 were similar13.
- Considering the evidence, the group made a conditional recommendation for the use of methotrexate and against the use of other csDMARDs in the treatment of dactylitis. The use of NSAIDs and local glucocorticoid injections was also conditionally recommended for the treatment of dactylitis. A strong recommendation was established for the use of TNF inhibitors, IL-12/23 inhibitors, IL-23 inhibitors, IL-17 inhibitors, JAK inhibitors and PDE4 inhibitors, and a conditional recommendation was established for the use of CTLA4- Ig in the treatment of dactylitis in PsA.

<u>Skin disease</u>

- The evidence reviewed for the update of the recommendations for the treatment of skin psoriasis was limited to that presented in RCTs for PsA and interpreted in the context of the large body of psoriasis literature and previous GRAPPA recommendations. Topical agents are strongly recommended as first- line treatment for patients with limited body surface area involvement.
- For patients with more widespread psoriasis or psoriasis unresponsive to topicals, phototherapy, oral therapies (methotrexate, ciclosporin, PDE4 inhibitors and JAK inhibitors) and bDMARDs (TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors and IL-23 inhibitors) are strongly recommended. Phototherapy is efficacious for psoriasis affecting the trunk and extremities. Acitretin, an oral retinoid, is conditionally recommended for psoriasis in patients with PsA owing to its limited efficacy as monotherapy for plaque psoriasis and scarce evidence from the PsA population; however, this agent can be efficacious for pustular psoriasis.
- Strong recommendations were made for TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors and IL-23 inhibitors; newer mode of action drugs (inhibitors of IL-17, IL-12/23 and IL-23) show higher efficacy for skin involvement than TNF inhibitors in studies of psoriasis and/or PsA. The selection of one drug over another should be influenced by

the results of head- to- head studies in psoriasis populations, the presence of comorbidities, and disease activity in other PsA domains.

- It should be noted that some csDMARDS (leflunomide and sulfasalazine) have limited evidence for efficacy in skin disease and were graded in the context of other available therapies as having limited evidence for cutaneous psoriasis. CTLA4- Ig (abatacept) also has limited evidence for efficacy in skin disease.

Nail disease

- As with psoriatic skin disease, the evidence reviewed for the update of the treatment of nail psoriasis was limited to that presented in RCTs for PsA and interpreted in the context of the large body of psoriasis literature and previous GRAPPA recommendations.
- As in the previous recommendations2 , strong recommendations were made for bDMARDs given the rigorous evidence from RCTs. bDMARDs, including TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors and IL-23 inhibitors, are strongly recommended for the treatment of psoriatic nail disease; the selection of one of these agents over another should be informed by head- to- head studies in psoriasis, comorbidities and activity in other PsA domains.
- Conditional recommendations were made for a number of topical and/or local therapies as well as systemic medications. Topical therapies that can be considered include calcipotriol and glucocorticoid preparations, topical tacrolimus, topical ciclosporin, intralesional glucocorticoids and pulsed dye laser.
- Systemic medications that should also be considered are ciclosporin, methotrexate, acitretin, JAK inhibitors and PDE4 inhibitors. In many cases, evidence specifically for nail psoriasis remains insufficient. Agents with limited evidence preventing recommendations include topical glucocorticoids, topical tazarotene, dimethyl fumarates/fumaric acid esters, phototherapy and alitretinoin

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 05 of 12, May 2023) am 15.05.2023

#	Suchfrage
1	[mh "Arthritis, Psoriatic"]
2	(psoria* NEAR/3 (arthriti* OR arthropath*)):ti,ab,kw
3	#1 OR #2
4	#3 with Cochrane Library publication date from May 2018 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 15.05.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	Arthritis, Psoriatic[mh]
2	psoria*[tiab] AND (arthriti*[tiab] OR arthropath*[tiab])
3	#1 OR #2
4	(#3) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
5	(#4) AND ("2018/05/01"[PDAT] : "3000"[PDAT])

#	Suchfrage
6	(#5) NOT "The Cochrane database of systematic reviews"[Journal]
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in Medline (PubMed) am 15.05.2023

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*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
5	(#4) AND ("2018/05/01"[PDAT] : "3000"[PDAT])
6	(#5) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 17.05.2023

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

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

Referenzen

1. **Campanaro F, Batticciotto A, Zaffaroni A, Cappelli A, Donadini MP, Squizzato A.** JAK inhibitors and psoriatic arthritis: a systematic review and meta-analysis. Autoimmun Rev 2021;20(10):102902.
2. **Coates LC, Corp N, van der Windt DA, O'Sullivan D, Soriano ER, Kavanaugh A.** GRAPPA treatment recommendations: 2021 update. J Rheumatol 2022;49(6 Suppl 1):52-54.
3. **Coates LC, Corp N, van der Windt DA, Soriano ER, Kavanaugh A.** GRAPPA treatment recommendations: an update from the 2020 GRAPPA annual meeting. J Rheumatol Suppl 2021;97:65-66.
4. **Coates LC, Soriano ER, Corp N, Bertheussen H, Callis Duffin K, Campanholo CB, et al.** Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. Nat Rev Rheumatol 2022;18(8):465-479.
5. **Dressler C, Avila Valle G, Jacubzyk R, Nast A.** EuroGuiDerm guideline on the systemic treatment of psoriasis vulgaris - methods and evidence report [online]. Zürich (SUI): European Dermatology Forum; 2021. [Zugriff: 16.05.2023]. URL: https://www.guidelines.edf.one//uploads/attachments/cl2effhcu01qmjujnfbc971nm-a-methods-report-oct-2021.pdf.
6. **Gao Q, Zhao YX, Wang XJ, Shi J, Wang HM.** Efficacy and safety of IL-17 inhibitors for patients with psoriatic arthritis: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 2021;25(7):2958-2970.
7. **Garcia-Leal M, Reyes-Soto MA, Hernandez-Galarza I, Alvarez-Villalobos NA, Galarza-Delgado DA, Flores-Alvarado DE.** 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. Clin Rheumatol 2021;40(9):3499-3510.
8. **Gossec L, Baraliakos X, Kerschbaumer A, de Wit M, McInnes I, Dougados M, et al.** EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis 2020;79(6):700-712.
9. **Harkins P, Burke E, Swales C, Silman A, Conway R.** Are janus kinase inhibitors safe and effective in treating the key clinical domains of psoriatic arthritis? A systematic review and meta-analysis. Int J Rheum Dis 2023;26(1):31-42.
10. **Huang X, Shentu H, He Y, Lai H, Xu C, Chen M, et al.** Efficacy and safety of IL-23 inhibitors in the treatment of psoriatic arthritis: a meta-analysis based on randomized controlled trials. Immunol Res 2023 [Online ahead of print].
11. **Kang Q, Chen JS, Yang H.** Efficacy and safety profile of phosphodiesterase 4 inhibitor in the treatment of psoriasis: a systematic review and meta-analysis of randomized controlled trials. Front Immunol 2022;13:1021537.
12. **Kerschbaumer A, Smolen JS, Dougados M, de Wit M, Primdahl J, McInnes I, et al.** Pharmacological treatment of psoriatic arthritis: a systematic literature research for the 2019 update of the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis 2020;79(6):778-786.
13. **Mease PJ, McInnes IB, Tam LS, Eaton K, Peterson S, Schubert A, et al.** Comparative effectiveness of guselkumab in psoriatic arthritis: results from systematic literature review and network meta-analysis. Rheumatology (Oxford) 2021;60(5):2109-2121.

14. **Mease PJ, McInnes IB, Tam LS, Rajalingam R, Peterson S, Hassan F, et al.** Comparative effectiveness of guselkumab in psoriatic arthritis: updates to a systematic literature review and network meta-analysis. Rheumatology (Oxford) 2023;62(4):1417-1425.

15. **Nast A, Altenburg A, Augustin M, Boehncke WH, Härle P, Klaus J, et al.** German S3-guideline on the treatment of psoriasis vulgaris, adapted from EuroGuiDerm - part 1: treatment goals and treatment recommendations. J Dtsch Dermatol Ges 2021;19(6):934-150.

16. **Nast A, Altenburg A, Augustin M, Boehncke WH, Härle P, Klaus J, et al.** German S3-guideline on the treatment of psoriasis vulgaris, adapted from EuroGuiDerm - part 2: treatment monitoring and specific clinical or comorbid situations. J Dtsch Dermatol Ges 2021;19(7):1092-1115.

17. **Nast A, Smith C, Spuls PI, Avila Valle G, Bata-Csörgö Z, Bogdanov I, et al.** EuroGuiDerm guideline for the systemic treatment of psoriasis vulgaris [online]. Zürich (SUI): European Dermatology Forum; 2022. [Zugriff: 16.05.2023]. URL: https://www.guidelines.edf.one//uploads/attachments/cl27nt7yb001q90jnmykcah83-euroguiderm-pso-gl-feb-2022.pdf.

18. **Qiu M, Xu Z, Gao W, Xiong M, Wen X, Zhu W, et al.** Fourteen small molecule and biological agents for psoriatic arthritis: a network meta-analysis of randomized controlled trials. Medicine (Baltimore) 2020;99(31):e21447.

19. **Ruyssen-Witrand A, Perry R, Watkins C, Braileanu G, Kumar G, Kiri S, et al.** Efficacy and safety of biologics in psoriatic arthritis: a systematic literature review and network meta-analysis. RMD Open 2020;6(1):e001117.

20. **Sarabia S, Ranjith B, Koppikar S, Wijeratne DT.** Efficacy and safety of JAK inhibitors in the treatment of psoriasis and psoriatic arthritis: a systematic review and meta-analysis. BMC Rheumatol 2022;6(1):71.

21. **Sbidian E, Chaimani A, Garcia-Doval I, Doney L, Dressler C, Hua C, et al.** Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database of Systematic Reviews [online]. 2022(5):Cd011535. URL: http://dx.doi.org/10.1002/14651858.CD011535.pub5.

22. **Smith CH, Yiu ZZN, Bale T, Burden AD, Coates LC, Edwards W, et al.** British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020: a rapid update. Br J Dermatol 2020;183(4):628-637.

23. **Song GG, Lee YH.** Comparative efficacy and safety of secukinumab, ixekizumab, and tofacitinib in patients with active psoriatic arthritis showing insufficient response to tumor necrosis factor inhibitors. Int J Clin Pharmacol Ther 2021;59(7):511-518.

24. **Song GG, Lee YH.** 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. Clin Drug Investig 2019;39(5):421-428.

25. **Song GG, Lee YH.** Relative efficacy and safety of secukinumab and guselkumab for the treatment of active psoriatic arthritis: a network meta-analysis. Int J Clin Pharmacol Ther 2021;59(6):433-441.

26. **Wu D, Li C, Zhang S, Wong P, Cao Y, Griffith JF, et al.** Effect of biologics on radiographic progression of peripheral joint in patients with psoriatic arthritis: meta-analysis. Rheumatology (Oxford) 2020;59(11):3172-3180.

27. **Xie Y, Liu Y.** Does previous use of tumour necrosis inhibitors change the therapeutic effect of interleukin (IL)-17 or IL-12/23 inhibitors on psoriasis and psoriatic arthritis? Results of a systematic review. Clin Exp Dermatol 2022;47(9):1627-1635.

28. **Xie Y, Liu Y, Liu Y.** Are biologics combined with methotrexate better than biologics monotherapy in psoriasis and psoriatic arthritis: a meta-analysis of randomized controlled trials. Dermatol Ther 2021;34(3):e14926.

29. **Yang F, Lu C, Wang Y, Liu H, Leng X, Zeng X.** Efficacy and safety of janus kinase inhibitors in patients with psoriasis and psoriatic arthritis: a systematic review and meta-analysis. Clin Rheumatol 2023;42(6):1593-1605.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Gemeinsamer Bundesausschuss

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

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO