Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2020-B-079 Upadacitinib

Stand: Juni 2020

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

Zur Behandlung erwachsener Patienten mit aktiver Psoriasis-Arthritis

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 02. Juni 2016) • Ixekizumab (Beschluss vom 16. August 2018) • Tofacitinib (Beschluss vom 21. Februar 2019) 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:	
Upadacitinib Rinvoq®	<u>Geplantes Anwendungsgebiet lau Beratungsanforderung</u> RINVOQ ist indiziert zur Behandlung der aktiven Psoriasis-Arthritis (PsA) bei erwachsenen Patienten, die unzureichend auf ein oder mehrere krankheitsmodifizierende Antirheumatika (DMARDs) angesprochen oder diese nicht vertragen haben. RINVOQ kann als Monotherapie oder in Kombination mit nicht-biologischen DMARDs angewendet werden.
Klassische synthetische krankheitsmodifizierende Antirheumatika (csDMARD)	
Methotrexat L01BA01 generisch	[…] und der Psoriasis arthropathica. […]
Leflunomid L04AA13 generisch	Leflunomid (medac®) ist ein antirheumatisches Basistherapeutikum („disease modifying antirheumatic drug“ [DMARD]) zur Behandlung von Erwachsenen mit: • aktiver rheumatoider Arthritis. • aktiver Psoriasis-Arthritis (Arthritis psoriatica).
Biologische krankheitsmodifizierende Antirheumatika (bDMARD)	
TNF-alpha-Inhibitoren	
Etanercept L04AB01 Enbrel®	*Psoriasis-Arthritis (Arthritis psoriatica)* Behandlung der aktiven und progressiven Psoriasis-Arthritis bei Erwachsenen, wenn das Ansprechen auf eine vorhergehende Basistherapie unzureichend ist. Enbrel verbessert die körperliche Funktionsfähigkeit bei Patienten mit Psoriasis-Arthritis und reduziert das Fortschreiten der radiologisch nachweisbaren strukturellen Schädigungen der peripheren Gelenke bei Patienten mit polyartikulären symmetrischen Subtypen der Erkrankung. [Stand FI: 11/ 2019]
Infliximab L04AB02 Remicade®/	*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.

II. Zugelassene Arzneimittel im Anwendungsgebiet

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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	unzureichend gewesen ist. [Stand FI: Oktober 2019]
Weitere	
Abatacept L04AA24 Orencia®	*Psoriasis-Arthritis* ORENCIA ist allein oder in Kombination mit Methotrexat (MTX) indiziert zur Behandlung der aktiven Psoriasis-Arthritis (PsA) bei erwachsenen Patienten, die unzureichend auf vorangegangene DMARDs einschließlich Methotrexat ansprachen und für die eine zusätzliche systemische Therapie für psoriatische Hautläsionen nicht notwendig ist. [Stand FI: 12/ 2019]
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. [Stand FI: 01/ 2020]
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. [Stand FI: 01/ 2020]
Steroidale Antirheumatika (Glucokortikoide)	
Prednisolon H02AB06 generisch	• andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können: – Spondarthritiden (Spondylitis ankylosans mit Beteiligung peripherer Gelenke (DS b, c), Arthritis psoriatica (DS c, d), enteropathische Arthropathie mit hoher Entzündungsaktivität (DS a)
Prednison H02AB07 generisch	Andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können: – Spondarthritiden (Spondylitis ankylosans mit Beteiligung peripherer Gelenke (DS b, c), Arthritis psoriatica (DS c, d), enteropathische Arthropathie mit hoher Entzündungsaktivität (DS a)
Triamcinolon H02AB08 Volon®	Andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können: Spondarthritiden (Spondylitis ankylosans mit Beteiligung peripherer Gelenke, Arthritis psoriatica, enteropathische Arthropathie mit hoher Entzündungsaktivität);
Nichtsteroidale Antirheumatika (NSAR oder NSAID)	
z. B. Acemetacin	Acemetacin 60 Heumann zusätzlich bei:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
M01AB11 generisch	– akuten Arthritiden (einschließlich Gichtanfall) – chronischen Arthritiden, insbesondere bei rheumatoider Arthritis (chronische Polyarthritis), (Acemetacin Heumann FI, Stand April 2015)

Quellen: AmAnDa-Datenbank, Fachinformationen, Lauer-Fischer-Taxe®

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2020-B-079 (Upadacitinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	7. Mai 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

ACR	American College of Rheumatolog
AE	Adverse event
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CDAI	Clinical Disease Activity Index
CVE	cardiovascular event
DAHTA	Deutsche Agentur für Health Technology Assessment
DAS28	Disease Activity Score 28
DMARD	Disease-modifying antirheumatic drug
EULAR	European League Against Rheumatism
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
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
NSAID	Non-steroidal anti-inflammatory drugs
OR	Odds Ratio
PARS	Psoriatic Arthritis Ratingen Score
PsA	Psoriasis Arthritis
PsARC	Psoriatic Arthritis Response Criteria
PSORIQOL	Psoriasis Index of Quality of Life

P-Y	Patient years
RR	Relatives Risiko
SAE	Serious adverse event
SIGN	Scottish Intercollegiate Guidelines Network
TNF	Tumor necrosis factor
TRIP	Turn Research into Practice Database
WAEs	Withdrawals due to adverse events
WHO	World Health Organization

1 Indikation

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

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Psoriasis-Arthritis* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 14.04.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 473 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 29 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2015 [8].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 06. August 2015 – Apremilast

Anwendungsgebiet

(…) 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.

Zweckmäßige Vergleichstherapie

Die zweckmäßige Vergleichstherapie für die Behandlung der aktiven Psoriasis-Arthritis bei erwachsenen Patienten, die auf eine vorangegangene DMARD-Therapie unzureichend angesprochen oder diese nicht vertragen haben, ist:

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

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [7].

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

Anwendungsgebiet

(…) Psoriasis-Arthritis (PsA): Secukinumab (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.

Vergleichstherapie

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

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

G-BA, 2018 [9].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. August 2018 - Ixekizumab (neues Anwendungsgebiet: Psoriasis-Arthritis)

Anwendungsgebiet

Taltz, 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.

Vergleichstherapie

- Erwachsene Patienten mit aktiver Psoriasis-Arthritis, die für eine andere klassische DMARD-Therapie außer Methotrexat infrage kommen: Leflunomid
- Erwachsene Patienten mit aktiver Psoriasis-Arthritis, die bDMARD-naiv sind und für die eine erstmalige Therapie mit bDMARDs angezeigt ist: ein TNF-alpha-Hemmer (Adalimumab oder Certolizumab Pegol oder Etanercept oder Golimumab oder Infliximab) ggf. in Kombination mit Methotrexat
- Erwachsene Patienten mit aktiver Psoriasis-Arthritis, die unzureichend auf eine vorhergehende Therapie mit krankheitsmodifizierenden biologischen Antirheumatika (bDMARDs) angesprochen oder diese nicht vertragen haben: der Wechsel auf ein anderes biologisches krankheitsmodifizierendes Antirheumatikum (Adalimumab oder Certolizumab Pegol oder Etanercept oder Golimumab oder Infliximab oder Secukinumab oder Ustekinumab) ggf. in Kombination mit Methotrexat

Fazit / Ausmaß des Zusatznutzens / Ergebnis

- Erwachsene Patienten mit aktiver Psoriasis-Arthritis, die für eine andere klassische DMARD-Therapie außer Methotrexat infrage kommen: Ein Zusatznutzen ist nicht belegt.
- Erwachsene Patienten mit aktiver Psoriasis-Arthritis, die bDMARD-naiv sind und für die eine erstmalige Therapie mit bDMARDs angezeigt ist:
  - Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Adalimumab: Anhaltspunkt für einen geringen Zusatznutzen.
- Erwachsene Patienten mit aktiver Psoriasis-Arthritis, die unzureichend auf eine vorhergehende Therapie mit krankheitsmodifizierenden biologischen Antirheumatika (bDMARDs) angesprochen oder diese nicht vertragen haben: Ein Zusatznutzen ist nicht belegt.

G-BA, 2019 [10].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V –Tofacitinib (neues Anwendungsgebiet: Psoriasis-Arthritis) vom 21. Februar 2019

Anwendungsgebiet

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.

Vergleichstherapie

- Erwachsene Patienten mit aktiver Psoriasis-Arthritis, die auf eine vorangegangene krankheitsmodifizierende antirheumatische (DMARD-) Therapie unzureichend angesprochen oder diese nicht vertragen haben.
  - ein TNF-alpha-Antagonist (Adalimumab oder Certolizumab Pegol oder Etanercept oder Golimumab oder Infliximab) ggf. in Kombination mit Methotrexat
- Erwachsene Patienten mit aktiver Psoriasis-Arthritis, die unzureichend auf eine vorhergehende Therapie mit krankheitsmodifizierenden biologischen Antirheumatika (bDMARD) angesprochen oder diese nicht vertragen haben.
  - der Wechsel auf ein anderes biologisches krankheitsmodifizierendes Antirheumatikum (Adalimumab oder Certolizumab Pegol oder Etanercept oder Golimumab oder Infliximab oder Secukinumab oder Ustekinumab) ggf. in Kombination mit Methotrexat

Fazit / Ausmaß des Zusatznutzens / Ergebnis

- Erwachsene Patienten mit aktiver Psoriasis-Arthritis, die auf eine vorangegangene krankheitsmodifizierende antirheumatische (DMARD-) Therapie unzureichend angesprochen oder diese nicht vertragen haben.
  - Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Tofacitinib in Kombination mit Methotrexat gegenüber Adalimumab in Kombination mit Methotrexat: Anhaltspunkt für einen geringen Zusatznutzen.
- Erwachsene Patienten mit aktiver Psoriasis-Arthritis, die unzureichend auf eine vorhergehende Therapie mit krankheitsmodifizierenden biologischen Antirheumatika (bDMARD) angesprochen oder diese nicht vertragen haben.
  - Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Tofacitinib in Kombination mit Methotrexat gegenüber der zweckmäßigen Vergleichstherapie: Ein Zusatznutzen ist nicht belegt.

G-BA, 2007 [6].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie in Anlage 4: Therapiehinweis zu Leflunomid vom 16. August 2007

- Leflunomid (Arava®): Empfehlungen zur wirtschaftlichen Verordnungsweise; Beschluss vom: 16.08.2007 / 15.05.2008; In Kraft getreten am: 21.12.2007 / 03.09.2008
- Indikation: Leflunomid ist ein antirheumatisches Basistherapeutikum. Es ist zugelassen zur Behandlung Erwachsener mit aktiver rheumatoider Arthritis und aktiver Psoriasis-Arthritis.
  - Psoriasis-Arthritis: Die Wirkung aller bisher untersuchten DMARDs bei der Psoriasis-Arthritis wird generell als gering bis mittelmäßig eingeschätzt. Im Gegensatz zur rheumatoiden Arthritis konnte für kein DMARD in dieser Indikation eine Verzögerung der Progression von Gelenkdestruktionen belegt werden. Es existieren bisher keine

vergleichenden Studien von Leflunomid mit anderen Basistherapeutika zur Wirksamkeit bei Psoriasis-Arthritis.

- Patienten mit Psoriasis-Arthritis, die gleichzeitig systemisch behandlungsbedürftige Hautläsionen aufweisen, sollten primär mit MTX oder Ciclosporin behandelt werden, da bei diesen Substanzen eine gute Wirksamkeit nicht nur bezüglich der dermatologischen Symptome, sondern auch bezüglich der arthritischen Symptome belegt ist. Bei der kleinen Gruppe von Patienten mit Psoriasis-Arthritis ohne wesentliche dermatologische Symptomatik kommt, sofern eine Therapie mit NSAR nicht ausreichend ist, unter Berücksichtigung des Zulassungsstatus der Einsatz von Leflunomid oder MTX in Betracht.

3.2 Cochrane Reviews

Wildson TD et al., 2019 [27].

Methotrexate for psoriatic arthritis

Fragestellung

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

Methodik

Population:

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

Intervention:

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

Komparator:

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

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

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Cochran & GRADE Approach

Ergebnisse

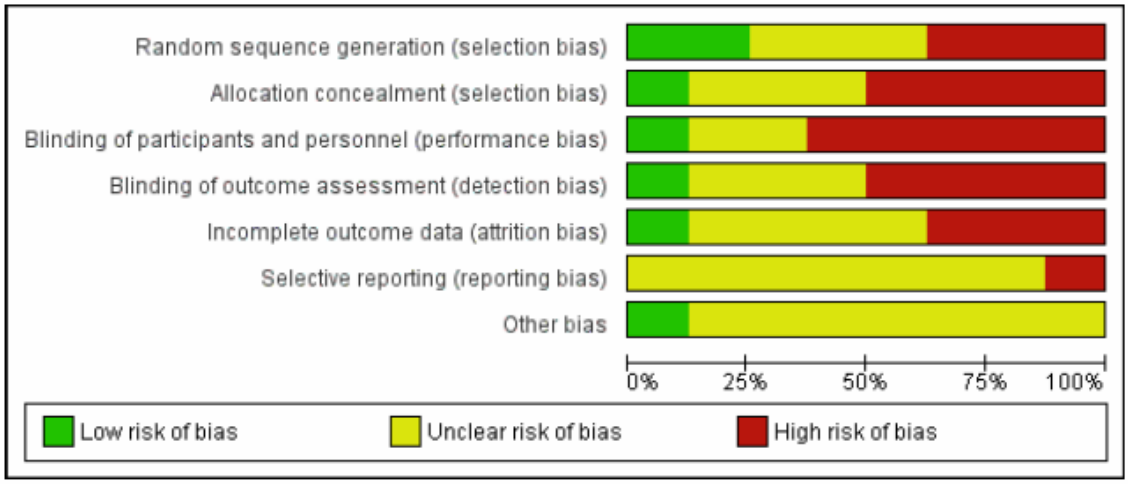
Anzahl eingeschlossener Studien:

- We included in this review eight RCTs conducted in an outpatient setting, in Italy, the United Kingdom, the United States of America, China, Russia, and Bangladesh.
- Five studies compared methotrexate versus placebo, and four studies compared methotrexate versus other DMARDs.
- The average age of participants varied across studies (26 to 52 years), as did the average duration of psoriatic arthritis (one to nine years).

Qualität der Studien:

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

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



Studienergebnisse:

- Methotrexate versus placebo for up to six months: Low-quality evidence (downgraded due to bias and imprecision) from a single study (221 participants; methotrexate dose 15 mg orally or less per week) informed results for disease response, function, and disease activity.
  - Disease response, measured by the proportion who responded to treatment according to PsARC (response indicates improvement), was 41/109 in the methotrexate group and 24/112 in the placebo group (risk ratio (RR) 1.76, 95% confidence interval (CI) 1.14 to 2.70). This equates to an absolute difference of 16%more responders with methotrexate (4% more to 28% more), and a number needed to treat for an additional beneficial outcome (NNTB) of 6 (95% CI 5 to 25).
  - Mean function, measured by the HAQ (scale 0 to 3; 0 meaning no functional impairment; minimum clinically important difference 0.22), was 1.0 points with placebo and 0.3 points better (95% 0.51 better to 0.09 better) with methotrexate; absolute improvement was 10% (3% better to 17% better), and relative improvement 30% (9% better to 51% better).
  - Mean disease activity as measured by the DAS28-ESR (scale of 0 to 10; lower score means lower disease activity; minimum clinically important difference unknown) was 3.8 points in the methotrexate group and 4.06 points in the placebo group; mean difference was -0.26 points (95% CI -0.65 to 0.13); absolute improvement was 3% (7% better to 1% worse), and relative improvement 6% (16% better to 3% worse).
  - Low-quality evidence (downgraded due to risk of bias and imprecision) from three studies (n = 293) informed our results for serious adverse events and withdrawals due to adverse events. Due to low event rates, we are uncertain if methotrexate results show increased risk of serious adverse events or withdrawals due to adverse events compared to placebo. Results show 1/141 serious adverse events in the methotrexate group and 4/152 in the placebo group: RR 0.26 (95% CI 0.03 to 2.26); absolute difference was 2% fewer events

with methotrexate (5% fewer to 1% more). In all, 9/141 withdrawals in the methotrexate group were due to adverse events and 7/152 in the placebo group: RR 1.32 (95% CI 0.51 to 3.42); absolute difference was 1% more withdrawals (4% fewer to 6% more).

- One study measured health-related quality of life but did not report these results. No study measured radiographic progression.

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

- Methotrexate versus other DMARDs (up to six months): Three studies with another DMARD comparator reported outcomes up to six months. Not all studies reported all outcomes. *Hinweis FBMed: Keine gepoolten Ergebnisse*

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

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

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

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

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

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

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

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

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

Anmerkung/Fazit der Autoren

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

3.3 Systematische Reviews

Kawalec P et al., 2018 [14].

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

Fragestellung

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

Methodik

Population:

- adults with moderate and severe PsA

Intervention:

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

Komparator:

- another biologic agent or placebo

Endpunkte:

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

Recherche/Suchzeitraum:

- from inception to 07/2017

Qualitätsbewertung der Studien:

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

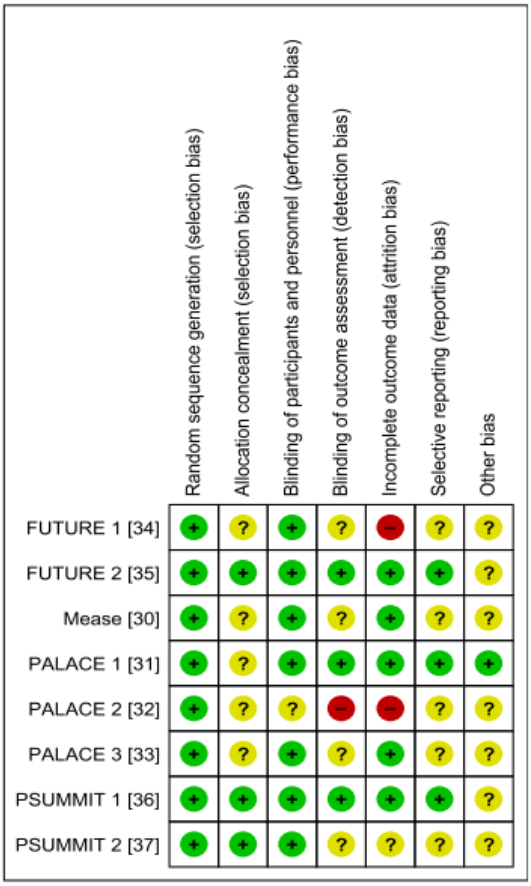
Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs

Qualität der Studien:

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



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

Studienergebnisse:

Relative treatment effects

- No significant differences between treatments were revealed with the exception of the following:
  - secukinumab 300 mg increased the ACR20 response rate in the overall population in comparison with apremilast (*P* = 0.020);
  - apremilast reduced the rate of withdrawal due to AEs in comparison with ustekinumab (*P* = 0.002);
  - secukinumab 150 and 300 mg increased the ACR20 response rate in the anti-TNF-α-naive subpopulation in comparison with apremilast and ustekinumab (*P* ranging from 0.004 to 0.024).
  - There was no evidence for the higher efficacy of secukinumab over apremilast and/or ustekinumab in the anti-TNF-α-failure and anti-TNF-α-failure subpopulations
  - Compared with placebo, all treatments induced a higher rate of ACR20 and ACR50 responses in the overall population.

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

Anmerkung/Fazit der Autoren

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

Song GG et al., 2018 [22].

Relative efficacy and safety of apremilast, secukinumab, and ustekinumab for the treatment of psoriatic arthritis

Fragestellung

To assess the relative efficacy and safety of apremilast, secukinumab, and ustekinumabat different doses in patients with active psoriatic arthritis (PsA).

Methodik

Population:

- patients with active PsA

Intervention:

- apremilast, secukinumab, and ustekinumab

Komparator:

- placebo

Endpunkte:

- clinical efficacy with ACR20 and safety

Recherche/Suchzeitraum:

- 01/2017

Qualitätsbewertung der Studien:

- Jadad score

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs/3289 patients

Qualität der Studien:

- Jadad scores of the studies were 3–4, which indicated a high quality study.

Studienergebnisse:

- Network meta-analysis of the efficacy of apremilast, secukinumab and ustekinumab in RCTs:
  - Secukinumab 150mg, secukinumab 75mg, ustekinumab 90mg, apremilast 30mg, apremilast 20mg, and ustekinumab 45mg were also more efficacious than placebo
  - no significant difference in the efficacy among the eight interventions.
- Network meta-analysis of the safety of apremilast, secukinumab, and ustekinumab in RCTs:
  - The number of serious adverse events did not differsignificantly among the apremilast, secukinumab, ustekinumab, and placebo groups

Anmerkung/Fazit der Autoren

All drug treatments were more efficacious than placebo; however, there were no significant differences in the efficacy and safety between the drugs at the different doses.

Druyts E et al., 2017 [5].

Treatment modifying factors of biologics for psoriatic arthritis: a systematic review and Bayesian meta-regression

Fragestellung

The aim of this study was to explore factors that modify treatment effects of non-conventional biologics versus placebo in patients with psoriatic arthritis.

Methodik

Population:

- patients with psoriatic arthritis

Intervention:

- The following treatments as monotherapy or in combination with a conventional disease-modifying anti-rheumatic drugs (DMARDs*) were considered eligible:
  - Etanercept
  - Infliximab
  - Adalimumab
  - Golimumab
  - Certolizumab
  - Tocilizumab
  - Anakinra
  - Abatacept

- Rituximab
- Ustekinumab
- Secukinumab

Komparator:

- The following comparisons as monotherapy or in combination with a conventional DMARD were considered eligible:
  - Placebo or no treatment
  - Any of the above mentioned interventions

Endpunkte:

- The following outcomes at 12 and 24 weeks (continuous, categorical or both) were considered:

  Efficacy
  - 20% improvement in the American College of Rheumatology response criteria (ACR 20 response)
  - 50% improvement in the American College of Rheumatology response criteria (ACR 50 response)
  - 75% improvement in the Psoriasis Area and Severity Index (PASI 75 response)

  Quality of Life
  - SF-36 Physical Component Summary (PCS)
  - SF-36 Mental Component Summary (MCS)

Recherche/Suchzeitraum:

- from inception to 10/2014

Qualitätsbewertung der Studien:

- Cochrane risk-of-bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 12

Qualität der Studien:

- The risk-of-bias assessment indicated that most included studies had a low risk of bias.

Studienergebnisse:

- ACR 20:
  - treatment effects for ACR 20 response at 12 weeks were significantly lower in trials enrolling older versus younger patients (OR=0.48)
  - Furthermore, treatment effects for ACR 20 at 12 weeks were significantly higher in trials with longer versus shorter psoriasis disease durations (OR=2.94).
  - At 24 weeks, trials with longer versus shorter PsA duration showed significantly higher treatment effects for ACR 20 response (OR=1.88)

- ACR 50:
  - treatment effects at 12 weeks that were significantly greater in trials with a larger versus smaller proportion of males (OR=2.27),
  - significantly smaller in trials with higher versus lower proportions of prior anti-TNF use (OR=0.28) and in trials published more recently versus earlier (OR=0.37)
- PASI 75:
  - treatment effects for PASI 75 were significantly higher in trials with higher versus lower proportions of male patients (OR=2.56 at 24 weeks), and in trials with patients with higher versus lower swollen joint counts and higher versus lower tender joint counts (OR=8.33 at 12 weeks; OR=14.44 at 24 weeks)
  - trials with a high versus low proportion of prior anti-TNF use showed significantly smaller treatment effects (OR=0.41 at 24 weeks)
- SF-36 PCS:
  - treatment effects for SF-36 PCS scores at 24 weeks were significantly higher in trials with patients with a longer versus shorter psoriasis disease duration (OR=2.95) and longer versus shorter PsA disease duration (OR=4.76), and in trials published in an earlier versus later year (OR=4.19)
- SF-36 MCS:
  - The exploratory analyses suggested that age and proportion of Caucasian patients were associated with treatment effects for SF-36 MCS scores
  - However, in the meta-regression analysis, there were no significant associations observed

Anmerkung/Fazit der Autoren

Our analyses show that differences in baseline characteristics may explain some of the differences in response to biologics versus placebo across different trials. Accounting for these factors in future studies will likely be important.

Wu D et al., 2018 [28].

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

Fragestellung

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

Methodik

Population:

- patients with PsA

Intervention:

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

Komparator:

- Placebo

Endpunkte:

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

Recherche/Suchzeitraum:

- 12/2016

Qualitätsbewertung der Studien:

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 RCTs /n=2411 participants

Qualität der Studien:

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

Studienergebnisse:

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

Meta-analysis of direct treatment effects:

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

ACR 20 response according to prior anti-TNF exposure:

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

Network meta-analysis of direct comparisons:

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

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

Network meta-analysis of mixed comparisons:

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

Anmerkung/Fazit der Autoren

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

Ramiro S et al., 2016 [15].

Pharmacological treatment of psoriatic arthritis: a systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis

Fragestellung

To update the evidence on efficacy and safety of pharmacological agents for the management of patients with PsA through a systematic literature review with meta-analysis if possible to inform the task force on the update of the EULAR recommendations for the management of PsA.

Methodik

Population:

- adults with PsA

Intervention/Komparator:

- biological DMARD, (bDMARD)
- synthetic DMARD (sDMARD: conventional (csDMARD) and targeted (tsDMARD)
- 10 systemic glucocorticoids; non-steroidal anti-inflammatory drugs (NSAIDs)
- or any combination of them

Endpunkte:

- efficacy (e.g. ACR; PASI, radiographic progression), safety (e.g. withdrawals due to AEs)

Recherche/Suchzeitraum:

- 2010 – 12/2014

Qualitätsbewertung der Studien:

- Cochrane Approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 17

Charakteristika der Population & Qualität der Studien:

- In total, 15 papers and 2 abstracts focused on tumour necrosis factor inhibitors (TNFis), mainly the ones for which no data were previously available in PsA8—golimumab and certolizumab pegol
- one study on the combination of infliximab with MTX versus MTX in MTX-naïve patients,28 one post hoc analysis with adalimumab and one study compared two etanercept regimens.
- A substantial part of the new evidence (6 papers and 10 abstracts) addressed the new compounds: UST (bDMARD anti-IL-12/23), SEC (bDMARD, anti-IL-17A) and APR (tsDMARD, inhibitor of phosphodiesterase 4).
- No studies were found on biosimilars, glucocorticoids or NSAIDs

Table 1 Characteristics of the RCTs of pharmacological drugs in PsA published in 2010–2015†

Drug and trial acronym	Number of publications (abstracts)	Interventions compared	Type of patients included	Timing of primary end point	Primary end point	Risk of bias assessment
MTX (MIPA)[14]	1 (0)	MTX 15 m/week, PBO	DMARD or NSAIDs failure, but MTX naive	24W	PsARC	Low
MTX vs Ciclosporine[15]	1 (0)	ETA+MTX, ETA+CYC	DMARD failure	24W	NA	Unclear
Leflunomide[16]	1 (0)	LEF, MTX	NA	24W	PsARC	High
Golimumab (GO-REVEAL)[17–21]	5 (0)	GOL 100 mg, GOL 50 mg, PBO	DMARD or NSAIDs failure	14W+24W (coprimary end point)	ACR20+change in radiographic score	Low
Certolizumab pegol (RAPID-PsA)[22–27]	4 (2)	CZP 400 mg, CZP 200 mg, PBO	DMARD or TNFi failure	12W	ACR20	Low
Infliximab (RESPOND)[28]	1 (0)	IFX 5 mg/kg+MTX 15 mg, MTX 15mg	DMARD or NSAIDs failure, but MTX naive	16W	ACR20	High
Adalimumab (ADEPT)[29]	1 (0)	ADA 40 mg, PBO	NSAIDs failure	12W+24W (coprimary end point)	ACR20+change in radiographic score	Unclear
Etanercept (PRESTA)[30 31 32 33]	4 (0)	ETA 50 mg 2×week, ETA 50 mg 1×week	DMARD or NSAIDs failure	12W	Physician's global assessment of psoriasis	Low

Studienergebnisse:

- Tumour necrosis factor inhibitors
  - no trial comparing the start of a TNFi as monotherapy versus the start of a TNFi with MTX.
  - comparing the combination of infliximab and MTX with MTX did not provide useful information (1 Studie → Respond)
  - Efficacy of tumour necrosis factor inhibitors (including golimumab and certolizumab pegol) was confirmed

  - The Psoriasis Randomized Etanercept Study in Subjects with Psoriatic Arthritis (PRESTA) trial,30–33 comparing two regimens of etanercept (50 mg twice a week vs 50 mg once a week) revealed no differences in joint responses (similar ACR responses), nor in the effect on the entheses, dactylitis or on functional disability, but a higher skin response for the higher dose (PASI75 of 55% for etanercept twice a week vs 36% for etanercept once a week).
- Drugs with new modes of action: ustekinumab, secukinumab and apremilast: All were placebo-compared trials

Efficacy - Risk Ratios versus Placebo:

Treatment arm vs PBO	ACR20 RR (95% CI)	ACR50 RR (95% CI)	ACR70 RR (95% CI)	PAIS75 RR (95% CI)	PASI90 RR (95% CI)
UST 90mg	2.17 (1.71; 2.76)	3.25 (2.14; 4.95)	4.63 (2.18; 9.82)	6.94 (3.79; 12.72)	11.85 (3.80; 36.93)
UST 45mg	1.95 (1.52; 2.50)	2.78 (1.81; 4.27)	3.90 (1.81; 8.39)	6.39 (3.46; 11.78)	8.00 (2.51; 25.51)
SEC 300mg	3.31 (2.04; 5.36)	4.90 (2.29; 10.50)	19.60 (2.68; 143.23)	3.90 (1.90; 7.98)	5.24 (1.96; 14.04)
SEC 150mg	5.82 (1.56; 21.71)	4.74 (3.08; 7.29)	11.14 (4.52; 27.44)	4.76 (1.92; 11.78)	6.62 (1.88; 23.30)
SEC 75mg	4.47 (0.66; 30.26)	3.59 (2.30; 5.61)	7.94 (3.18; 19.83)	3.75 (0.82; 17.06)	4.26 (0.40; 45.59)
APR 30mg	1.98 (1.64; 2.38)	NA	NA	NA	NA
APR 20mg	1.70 (1.40; 2.06)	NA	NA	NA	NA

* Time point of the primary endpoint: for UST and SEC 24 weeks, for APR 16 weeks

Safety

Ustekinumab

- No differences in withdrawals due to AEs or serious infections with UST compared with PBO.

Secukinumab

- no differences in withdrawals due to AEs or SAEs in SEC compared with PBO.
- some cases of candidiasis with SEC (2% in FUTURE-1 and 5% in FUTURE-2, both with SEC 150 mg), though not leading to more withdrawals, and no case was observed with PBO.

Apremilast

- numerically slightly more withdrawals due to AEs (e.g., 7.1% with APR30 mg, 6% with APR20 mg vs 4.8% PBO in PALACE-1), but there were no differences in SAEs.
- Up to 19% of the patients on APR developed diarrhea, which occurred early after treatment start and was usually self-limited.
- For the three new compounds, no signals on higher malignancy rates compared with PBO were identified.

Anmerkung/Fazit der Autoren

UST, SEC and APR are new drugs with efficacy demonstrated for the treatment of PsA. No major safety signals arise, but long-term studies are needed. This review informed about the European League Against Rheumatism recommendations for management of PsA.

Kommentare zum Review

- Unterschiedliche Vortherapien

Ungprasert P et al., 2016 [24].

Indirect comparisons of the efficacy of biological agents in patients with psoriatic arthritis with an inadequate response to traditional disease-modifying anti-rheumatic drugs or to non-steroidal anti-inflammatory drugs: a meta-analysis

Fragestellung

assessing the comparative efficacy of these agents in patients who had persistently active disease despite traditional non-steroidal anti-inflammatory drugs (NSAIDs)/ disease-Modifying anti-rheumatic drugs (DMARDs), or who could not tolerate NSAIDs/DMARDs.

Methodik

Population:

- patients with active PsA despite of DMARDs/NSAIDs or could not tolerate DMARDs/NSAIDs

Intervention:

- targeted therapies

Komparator:

- Placebo

Endpunkte:

- ACR20

Recherche/Suchzeitraum:

- up to 11/2014

Qualitätsbewertung der Studien:

- modified Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 12

Charakteristika der Population:

- Biological DMARD vs placebo:
  - Infliximab: 2 studies
  - Adalimumab: 2 studies
  - Etanercept:2 studies
  - Golimumab 1 study
  - Certolizumab: 1 study
  - Ustekinumab:2 studies
  - Apremilast: 1 study
  - Secukinumab: 1 study

Qualität der Studien:

- All studies with Jadad score ≥3
- Substantial heterogeneity between all bDMARDs with respect to ACR20 (I^2= 72%)

Studienergebnisse:

Direct comparison:

- Superiority of biologics compared to placebo based on ACR20
  - o all anti-TNF apha (7 studies): RR 4,4 (95% CI 3,4; 5,5); low heterogeneity between all anti-TNF apha studies
  - o ustekinumab 45mg (2 studies): RR 1,9 (95% CI 1,4; 2,7);I^2=0% ustekinumab 90mg (studies): RR 2,1 (95% CI 1,6; 2,7);I^2=0%
  - o secukinumab / apremilast: RR not stated

ACR20 response rates with active drug and placebo

ACR20 response rates for both arms of all included trials

Study	Arms	ACR20 response rate, number of patients (%)		
		Achieved	Not achieved	Total
Mease et al. [27]	Etanercept	22 (73.3)	8 (26.7)	30
	Placebo	4 (13.3)	26 (86.7)	30
Mease et al. [28]	Etanercept	60 (59.4)	51 (40.6)	101
	Placebo	15 (14.4)	89 (85.6)	104
Antoni et al. [23] (IMPACT 1)	Infliximab	34 (65.4)	18 (34.6)	52
	Placebo	5 (9.6)	47 (90.4)	52
Antoni et al. [24] (IMPACT 2)	Infliximab	58 (58.0)	42 (42.0)	100
	Placebo	11 (11.0)	89 (89.0)	100
Mease et al. [25] (ADEPT)	Adalimumab	88 (58.3)	63 (41.7)	151
	Placebo	23 (14.2)	139 (85.8)	162
Genovese et al. [26]	Adalimumab	20 (39.2)	31 (60.8)	51
	Placebo	8 (16.3)	41 (83.7)	49
Kavanaugh et al. [29] (GO-REVEAL)	Golimumab	140 (47.9)	152 (52.1)	292
	Placebo	10 (8.8)	103 (91.2)	113
Mease et al. [30] (RAPID-PsA)	Certolizumab	120 (54.8)	99 (45.2)	219
	Placebo	30 (27.8)	80 (72.7)	110
McInnes et al. [31] (PSUMMIT 1)	Ustekinumab 45 mg	87 (42.4)	118 (57.6)	205
	Ustekinumab 90 mg	101 (49.5)	103 (50.5)	204
	Placebo	47 (22.8)	159 (77.2)	206
Richlin et al. [32] (PSUMMIT 2)	Ustekinumab 45 mg	23 (53.5)	20 (46.5)	43
	Ustekinumab 90 mg	26 (55.3)	21 (44.7)	47
	Placebo	12 (28.6)	30 (71.4)	42
Kavanaugh et al. [33] (PALACE 1)	Apremilast 20 mg	39 (31.2)	86 (68.8)	125
	Apremilast 30 mg	52 (43.3)	68 (56.7)	120
	Placebo	28 (27.7)	90 (72.3)	118
McInnes et al. (FUTURE 2) [34]	Secukinumab 75 mg	24 (36.9)	41 (63.1)	65
	Secukinumab 150 mg	40 (63.5)	23 (36.5)	63
	Secukinumab 300 mg	39 (58.2)	28 (41.8)	67
	Placebo	10 (15.9)	53 (84.1)	63

Indirect comparison:

- older TNF inhibitors had a statistically significantly higher chance of achieving ACR20 response compared with apremilast 20mg, apremilast 30mg,ustekinumab 45mg,ustekinumab 90mg,and certolizumab
- Secukinumab superior to apremilast and ustekinumab 45 mg

Indirect comparison	ACR20 response rate	
	RR (95% CI)	*p* Value
All older anti-TNF/Certolizumab	2.20 (1.48–3.26)	<0.001
All older anti-TNF/Apremilast 20 mg	3.36 (2.10–5.38)	<0.001
All older anti-TNF/Apremilast 30 mg	2.42 (1.55–3.77)	<0.001
All older anti-TNF/Utsekinumab 45 mg	2.38 (1.68–3.35)	<0.001
All older anti-TNF/Utsekinumab 90 mg	2.08 (1.48–2.93)	<0.001
All older anti-TNF/Secukinumab 75 mg	1.90 (0.95–3.78)	0.07
All older anti-TNF/Secukinumab 150 mg	1.10 (0.58–2.09)	0.33
All older anti-TNF/Secukinumab 300 mg	1.21 (0.63–2.29)	0.57
Certolizumab/Apremilast 20 mg	1.53 (0.88–1.53)	0.13
Certolizumab/Apremilast 30 mg	1.10 (0.66–1.82)	0.71
Certolizumab/Utsekinumab 45 mg	1.08 (0.71–1.64)	0.72
Certolizumab/Utsekinumab 90 mg	0.95 (0.63–1.44)	0.81
Certolizumab/Secukinumab 75 mg	0.86 (0.42–1.79)	0.68
Certolizumab/Secukinumab 150 mg	0.50 (0.25–1.00)	0.05
Certolizumab/Secukinumab 300 mg	0.55 (0.28–1.09)	0.08
Apremilast 20 mg/Utsekinumab 45 mg	0.71 (0.43–1.16)	0.18
Apremilast 20 mg/Utsekinumab 90 mg	0.62 (0.38–1.02)	0.06
Apremilast 20 mg/Secukinumab 75 mg	0.57 (0.26–1.22)	0.16
Apremilast 20 mg/Secukinumab 150 mg	0.33 (0.16–0.68)	0.003
Apremilast 20 mg/Secukinumab 300 mg	0.36 (0.17–0.75)	0.008
Apremilast 30 mg/Utsekinumab 45 mg	0.98 (0.62–1.56)	0.93
Apremilast 30 mg/Utsekinumab 90 mg	0.86 (0.54–1.37)	0.53
Apremilast 30 mg/Secukinumab 75 mg	0.79 (0.37–1.67)	0.55
Apremilast 30 mg/Secukinumab 150 mg	0.46 (0.23–0.93)	0.03
Apremilast 30 mg/Secukinumab 300 mg	0.50 (0.25–1.00)	0.05
Utsekinumab 45 mg/Secukinumab 75 mg	0.80 (0.40–1.61)	0.53
Utsekinumab 45 mg/Secukinumab 150 mg	0.47 (0.24–0.91)	0.03
Utsekinumab 45 mg/Secukinumab 300 mg	0.50 (0.26–0.98)	0.04
Utsekinumab 90 mg/Secukinumab 75 mg	0.91 (0.45–1.83)	0.79
Utsekinumab 90 mg/Secukinumab 150 mg	0.53 (0.28–1.02)	0.06
Utsekinumab 90 mg/Secukinumab 300 mg	0.58 (0.30–1.11)	0.11

Anmerkung/Fazit der Autoren

Our study demonstrated that patients with PsA who did not have an adequate response from or could not tolerate DMARDs/ NSAIDs had a higher probability of achieving the ACR20 response with older TNF inhibitors (etanercept, infliximab, adalimumab,and golimumab) and secukinumab at the dose of 150 mg and 300 mg weekly, compared with apremilast, certolizumab, and ustekinumab. However, this analysis has some limitations. Therefore, head-to-head comparisons are required to confirm these findings. Physician should take this data in conjunction with other factors such as patients' comorbidities, safety profile of each medication, mode of administration, and patient's preference into account when considering a biologic agent for an individual patient.

Kommentare zum Review

- Bewertung der Homogenität der Studienergebnisse anhand der I^2-Statistik, Metaanalyse mittels Random effects model
- Indirekter Vergleich nach Bucher und Song

- Kein Einschluss direkter Vergleiche der Medikamente; indirekte Vergleiche beruhen nur auf Placebo-kontrollierten Studien; zentrale Annahme der Konsistenz der Ergebnisse aus direkten und indirekter Evidenz kann dadurch nicht beurteilt werden
- zentrale Annahme der Ähnlichkeit anhand der Studiencharakteristika untersucht: vergleichbare Baselinecharakteristika der Patienten mit Ausnahme der Vortherapien (vorangegangene TNF Inhibitortherapie in 1 der 2 Ustekinumab- und in der Sekukinumab-Studie mgl.)
- Placebo (=Brückenkomparator) zwischen den Studien aufgrund der verschiedenen Applikationsschemata der aktiven Medikamente unterschiedlich (Infusion / SC / oral; unterschiedliche Häufigkeit der Anwendung)
- Outcome beschränkt sich auf ACR20 an Woche 12-24, keine anderen Endpunkte betrachtet

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Wang J et al., 2016 [26].

A systematic review on the efficacy and safety of Infliximab in patients with psoriasis

Fragestellung

Our study will analyze the applications of randomized and controlled clinical trials of infliximab in the treatment of psoriasis by meta-analysis in order to evaluate the efficacy and safety of infliximab for the treatment of psoriasis.

Methodik

Population:

- Psoriasis patients

Intervention:

- infliximab

Komparator:

- placebo or methotrexate

Endpunkte:

- Psoriasis Area and Severity Index (PASI) score before and after treatment. The observed Total Efficiency, TE= (cure + markedly effective) /total number of cases £ 100%. Adverse events were also observed during treatment.

Recherche/Suchzeitraum:

- bis 2014

Qualitätsbewertung der Studien:

- Quality analysis was carried out using the method described in Juni10 et al. Four quality evaluation criteria were used for the assessment of randomized controlled trials: 1. Did the trial use the correct randomized method? 2. Is concealment of allocation assessed and is the method correct? 3. Was the blind method used in the trial? 4. Does the trial have withdrawals or dropouts? Does the trial have the intention to treat analysis if follow ups or drop outs occur? If all 4 evaluation criteria are met then there is a low risk of bias.

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 (davon 5 articles regarding the treatment of psoriasis arthritis (PsA) by infliximab)

Charakteristika der Population & Qualität der Studien:

Research	Methods	Allocation concealment	Participants	Interventions	Outcome measures	Jadad scale
A Karanaugh[18]	Random Double-blinded	A	100 patients in infliximab 5 mg/kg, 100 patients in placebo	24 weeks infliximab 5 mg/kg and placebo	ACR 20 efficiency	4
Antoni C[19]	Random Double-blinded	A	100 patients in infliximab 5 mg/kg, 100 patients in placebo	14 weeks infliximab 5 mg/kg and placebo	ACR 20 efficiency	4
Asta Baranauskaite[20]	Open-label, Random	B	51 patients in infliximab+ methotrexate 5 mg/kg, 48 patients in methotrexate	16 weeks infliximab 5 mg/kg and placebo	ACR 20 efficiency	2
Christian E. Antoni[21]	Random Double-blinded	A	52 patients in infliximab 5 mg/kg, 52 patients in placebo	16 weeks infliximab 5 mg/kg and placebo	ACR 20 efficiency	4
LAURAC COATES[22]	Random Double-blinded	A	31 patients in infliximab 5 mg/kg,	16 weeks infliximab 5 mg/kg and	ACR 20 efficiency	4

Studienergebnisse:

- *Hinweis: berichtet werden ausschließlich die Ergebnisse zu: 5 articles regarding the treatment of psoriasis arthritis (PsA) by infliximab)*
- The efficacy of infliximab (5mg/ kg) and placebo in the controlled treatment of psoriasis arthritis (PsA).
- The 5 research studies had clinical homogeneity and statistical homogeneity (x2=8.28, p=0.08).
- The results of meta-analysis showed that statistically significant differences in efficacy were found for the infliximab (5 mg/kg) group compared with the control group, which received placebo in treatment of psoriasis arthritis (PsA) [OR8.36, 95% CI (5.63, 12.40)].

Anmerkung/Fazit der Autoren

In conclusion, infliximab treatment is well tolerated and leads to significant associated with symptom relief in psoriasis patients.

Conway R et al., 2015 [4].

Risk of liver injury among methotrexate users: a meta-analysis of randomized controlled trials

Fragestellung

To evaluate the relative risk and severity of liver disease among patients treated with methotrexate.

Methodik

Population:

- Adults with rheumatoid arthritis, psoriasis, psoriatic arthritis or inflammatory bowel disease

Intervention:

- MTX

Komparator:

- No MTX

Endpunkte:

- Liver adverse events

Recherche/Suchzeitraum:

- April 2014

Qualitätsbewertung der Studien:

- Cochrane Approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 32 including 1 RCT on PsA

Qualität der Studien:

- low risk of bias in the included studies

Studienergebnisse:

- 1 RCT on PsA (Kingsleyetal. [21]): MTX vs placebo (n=221), study duration 24 w
- Increased risk of total liver AE with MTX: RR 6.17 (95%CI 1.41-26.9)

Anmerkung/Fazit der Autoren

Our study found an increased risk of elevated transaminases but not liver failure, cirrhosis or death with MTX compared to other agents. We were unable to assess long-term liver toxicity due to the short duration of included clinical trials.

Conway R et al., 2015 [3].

Methotrexate use und risk of lung disease in psoriasis, psoriatic arthritis, and inflammatory bowel disease: systematic literature review and meta-analysis of randomized controlled trials

Fragestellung

To evaluate the relative risk of pulmonary disease among patients with psoriasis, psoriatic arthritis, and inflammatory bowel disease treated with methotrexate.

Methodik

Population:

- Adults with rheumatoid arthritis, psoriasis, psoriatic arthritis or inflammatory bowel disease

Intervention:

- MTX

Komparator:

- Not MTX

Endpunkte:

- respiratory adverse events

Recherche/Suchzeitraum:

- Jan 2014

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 RCTs including 1 RCT on PsA

Qualität der Studien:

- low risk of bias in the included studies

Studienergebnisse:

- 1 RCT on PsA: MTX vs placebo (n=221), study duration 24 w:
- No increased risk of total adverse respiratory events with MTX (RR 1.27 [95%CI 0.81-2.01])

Anmerkung/Fazit der Autoren

Findings suggested that there was no increased risk of lung disease in methotrexate treated patients with non-malignant inflammatory diseases. Given the limitations of the study, however, we cannot exclude a small but clinically important risk.

Yang ZS et al., 2016 [29].

The effect of TNF inhibitors on cardiovascular events in psoriasis and psoriatic arthritis: an updated meta-analysis.

Fragestellung

to evaluate the effect of TNF inhibitors on adverse cardiovascular events (CVEs) in Pso with or without PsA

Methodik

Population:

- participants with Pso with or without PsA

Intervention:

- TNF inhibitor treatment

Komparator:

- Siehe Ergebnisteil

Endpunkte:

- Major adverse cardiovascular events (CVEs, the composite rate of mortality, myocardial infarction, and stroke)

Recherche/Suchzeitraum:

- systematic searches of MEDLINE, EMBASE, Wanfang database, Cochrane Database, and Google scholar through December 31, 2015

Qualitätsbewertung der Studien:

- The Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement was followed. Methodological quality of observational studies was assessed by the Newcastle-Ottawa scale (NOS)

Ergebnisse

Anzahl eingeschlossener Studien:

- Five studies (49,795 patients)
- The TNF inhibitors used were adalimumab, etanercept, golimumab, and infliximab

Qualität der Studien:

- One study has been scored NOS <6 stars and considered as low quality. Meanwhile, the others had been awarded ≥6 stars and qualified as high quality

Studienergebnisse:

- Overall, compared with topical/photo treatment, TNF inhibitors were associated with a significant lower risk of CVE (RR, 0.58; 95 % CI, 0.43 to 0.77; P < 0.001; I2 = 66.2 %).
- Additionally, compared with methotrexate (MTX) treatment, risk of CVE was also markedly decreased in the TNF inhibitor group (RR, 0.67; 95%CI, 0.52 to 0.88; P = 0.003; I2 = 9.3 %).
- TNF inhibitors were linked to reduced incidence of myocardial infarction compared with topical/photo or MTX treatment (RR, 0.73; 95 % CI, 0.59 to 0.90; P = 0.003; I2 = 56.2 % and RR, 0.65; 95 % CI, 0.48 to 0.89; P = 0.007; I2 = 0.0 %, respectively).
- subgroup analysis for different treatment regimens (TNF inhibitor vs topical/photo therapy, TNF inhibitor vs MTX) did not show any significant difference between groups with regard to CVE and myocardial infarction

Anmerkung/Fazit der Autoren

Given existing data, TNF inhibitors are associated with reductions in cardiovascular events in patients with psoriasis and/or psoriatic arthritis. Therefore, TNF inhibitors could provide cardio protective effect and may be especially useful in population at increased risk for cardiovascular events. Randomized clinical trials will need to be conducted to evaluate whether TNF inhibitors truly result in reduction of cardiac and cerebrovascular events. Efforts are necessary to decide if patients with moderate to severe psoriasis with or without psoriatic arthritis should be targeted for more intense goals for lipid control, as has been recommended for rheumatoid arthritis.

Kommentare zum Review

- all studies included are low-quality observational clinical trial, which could increase the risk of heterogeneity
- cardiovascular events, are used in combination with TNF inhibitors in some studies and could also increase the risk of heterogeneity.

- most studies did not provide data on potentially significant confounding factors, including the coexistence of diabetes, dyslipidemia, and blood pressure

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Ungprasert P et al., 2016 [25].

Indirect comparisons of the efficacy of subsequent biological agents in patients with psoriatic arthritis with an inadequate response to tumor necrosis factor inhibitors: a meta-analysis.

Fragestellung

to compare the efficacy of non-TNF biologic agents in patients who previously failed or could not tolerate TNF inhibitors using the indirect comparison technique.

Methodik

Population:

- patients with active PsA despite of DMARDs/NSAIDs or could not tolerate DMARDs/NSAIDs

Intervention:

- non-TNF inhibitor biologic agents

Komparator:

- placebo

Endpunkte:

- American College of Rheumatology 20 (ACR20) response rates were reported as the primary or major secondary outcome

Recherche/Suchzeitraum:

- Medline, Cochrane Central, and EMBASE from inception to September 2015

Qualitätsbewertung der Studien:

- modified Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- Five RCTs of four non-TNF inhibitor biologic agents, including abatacept, secukinumab, ustekinumab, and apremilast, with 675 participants

Qualität der Studien:

- All included trials were of high quality

Studienergebnisse:

- no significant difference in any comparisons, with the p values ranging from 0.14 to 0.98. Our study demonstrates that the likelihood of achieving the ACR20 response in patients with TNF inhibitor experience is not significantly different between the four non-TNF biologic agents.

Anmerkung/Fazit der Autoren

In conclusion, our study demonstrated that the odds of achieving an ACR20 response in patients with PsA who did not have an adequate response to or could not tolerate TNF inhibitors were not significantly different between four non-TNF inhibitor biologic agents. However, this interpretation of this analysis was limited by the small sample sizes. Head-to-head comparisons are still required to confirm the comparative efficacy.

Kommentare zum Review

- small sample sizes

Champs B et al., 2019 [1].

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

Fragestellung

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

Methodik

Population:

- Patients with PsA or psoriasis

Intervention/Komparator:

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

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Jadad Scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 77 RCTs

Qualität der Studien:

- Jadad Score: Range between 3-5

Studienergebnisse:

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

Anmerkung/Fazit der Autoren

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

Reygaerts T et al., 2018 [16].

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

Fragestellung

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

Methodik

Population:

- Adults with PsA

Intervention/Komparator:

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

Endpunkte:

- Fatigue, pain

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

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

Charakteristika der Population:

Table 1
Studies and baseline characteristics.

Characteristics	Genovese et al., 2007 [23] M02-570	Gladman et al., 2007 [24] ADEPT	Gladman et al., 2015 [26] RAPID-PSA	Gossec et al., 2015 [27,28] FUTURE2	Strand et al., 2016 [29] FUTURE1	Ritchlin et al., 2014 [30] PSUMMIT2	Strand et al., 2013 [25]
Study drug	Adalimumab	Adalimumab	Certolizumab Pegol	Secukinumab	Secukinumab	Ustekinumab	Apremilast
Study drug dose, mg	40	40	200, 400	75, 150, 300	75, 150	45, 90	20, 40
Number of patients	100	313	409	397	606	312	204
Age, mean ± SD, years	49.1 ± 11.3	48.9 ± 11.1	47.5 ± 11.1	48.0 ± 12.5	49.0 ± 11.2	48.3 ± 13.0	50.6 ± NR
Women (%)	46 (46)	139 (55.3)	226 (55.3)	205 (51.6)	330 (54.5)	164 (52.6)	97 (47.5)
Disease duration, mean ± SD, years	7.4 ± 7.0	9.5 ± 8.7	8.5 ± 7.7	NR	NR	5.1 ± 7.3	7.8 ± NR
SJC, mean ± SD	18.3 ± 12.1	14.3 ± 11.1	10.6 ± 7.6	11.5 ± 10.7	13.4 ± 13.1	11.3 ± 8.2	9.5 ± NR
HAQ-DI score, mean ± SD	0.9 ± 0.7	1.0 ± 0.7	1.3 ± 0.7	1.2 ± 0.7	1.2 ± 0.6	1.3 ± 0.7	1.1 ± NR
PASI score, mean ± SD	NR	7.9 ± 7.2	7.4 ± NR	13.0 ± 8.3	13.8 ± 11.6	8.4 ± 8.5	NR
MTX users (%)	47 (47)	158 (63.6)	260 (63.6)	185 (46.6)	368 (60.7)	155 (49.7)	89 (43.6)
Baseline Fatigue, mean ± SD	32.8 ± 12.3	30.8 ± 12.2	6.1 ± 2.0[a]	28.6 ± 11.6	28.1 ± 11.1	26.2 ± 13.0	29.6 ± 11.8
Baseline Pain VAS (0–100), mean ± SD	46.1 ± 23.5	49.9 ± 21.7	60.3 ± 22.0	57.2 ± 22.1	55.8 ± 21.1	NR	57.5 ± 22.6

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

Qualität der Studien:

- Jadad score for all studies: 4.7±0.7.

Studienergebnisse:

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

Anmerkung/Fazit der Autoren

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

Song GG et al., 2019 [21].

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

Fragestellung

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

Methodik

Population:

- active PsA patients

Intervention/Komparator:

- tofacitinib or apremilast with placebo

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

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

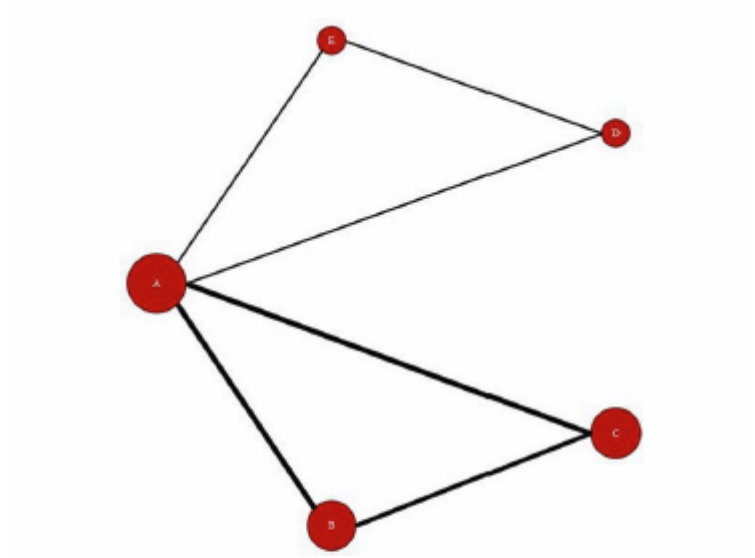


Fig. 1 Evidence network diagram of network meta-analysis comparisons. The width of each edge is proportional to the number of randomized controlled trials comparing each pair of treatments, and the size of each treatment node is proportional to the number of randomized participants (sample size), (A)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

Charakteristika der Population:

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

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

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

[a]24 wk for safety

Qualität der Studien:

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

Studienergebnisse:

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

Table 3 Rank probability of the efficacy of tofacitinib and apremilast

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

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

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

Anmerkung/Fazit der Autoren

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

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

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

Fragestellung

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

Methodik

Population:

- patients with psoriatic arthritis (Psa)

Intervention/Komparator:

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

Endpunkte:

Efficacy end points:

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

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

- at least one TEAE;
- at least one SAE;
- at least one adverse event leading to discontinuation (DAE) and
- all- cause discontinuation (ie, withdrawal for any reason, including withdrawals from treatment due to lack of efficacy or DAE)

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

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

Charakteristika der Population:

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

Qualität der Studien:

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

Studienergebnisse:

- ACR responses
  - The ACR network for the bDMARD- naïve population included 22 studies and 16 treatment regimens.
  - The ACR network diagram is shown in figure 2A, with lines weighted according to the number of studies included in the respective comparison. With the exception of the two abatacept regimens, all treatments had a statistically greater chance of achieving any ACR score (ACR20, ACR50, ACR70) than placebo (figure 2B). Infliximab was the most effective agent, followed by golimumab and etanercept; these agents were statistically superior to most other treatments, although golimumab and etanercept were not superior to ixekizumab 80 mg every 2 weeks (Q2W).
  - Ixekizumab 80 mg Q2W was statistically superior to abatacept subcutaneous (SC), apremilast and both ustekinumab schedules. Ixekizumab 80 mg Q4W was statistically superior to abatacept SC, apremilast and
  - ustekinumab 90 mg Q12W. Both schedules of ixekizumab did not significantly differentiate from abatacept intravenous, adalimumab, certolizumab pegol, secukinumab and tofacitinib.

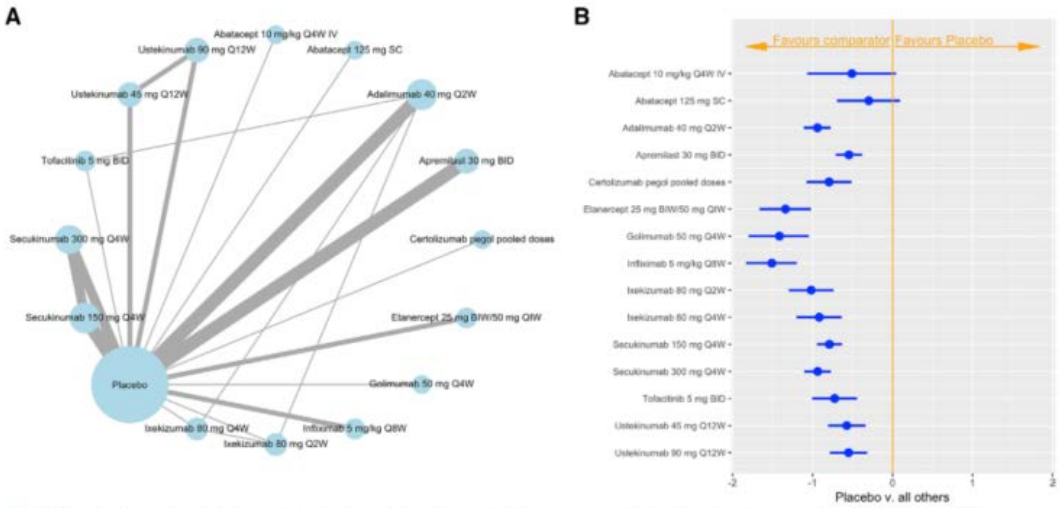


Figure 2 Network diagram (A) and forest plot of treatment differences on the standard normal scale (B) for ACR response at weeks 12–16 among bDMARD-naïve patients with active PsA (placebo as the reference). In the network diagram, line thickness is weighted according to the number of studies included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

- PsARC response
  - The PsARC network for the bDMARD- naïve population included 13 studies and 12 treatment regimens, the most frequently studied agent being adalimumab (figure 3A). All treatments had a statistically greater chance of achieving a PsARC response than placebo (figure 3B).
  - The best performing treatments were golimumab, infliximab and etanercept, which were statistically superior to most other agents, including both regimens of ixekizumab. Ixekizumab 80 mg Q2W was statistically superior to tofacitinib. There were no other statistically significant differences between ixekizumab and adalimumab, apremilast, certolizumab pegol and secukinumab.
  - An additional forest plot with ixekizumab 80 mg Q4W as the active reference is provided in online supplementary figure 2.
- PAsI response
  - The PASI network for the bDMARD- naïve population included 17 studies and 14 treatment regimens, the most frequently studied agents being adalimumab, apremilast and secukinumab (figure 4A).
  - With the exception of abatacept and etanercept, all treatments had a statistically greater chance of achieving any PASI score (PASI50, PASI75, PASI90 and PASI100) than placebo (figure 4B).
  - The greatest benefit was observed for infliximab, but it was not superior to ixekizumab 80 mg Q2W and Q4W, respectively, which was the next best performing therapy.
  - The probability of ixekizumab 80 mg Q2W achieving PASI50, PASI75, PASI90 and PASI100 was 88.6%, 73.3%, 54.7% and 38.0%, respectively. Corresponding probabilities for ixekizumab 80 mg Q4W were 87.2%, 70.9%, 52.0% and 35.4%.

- Both schedules of ixekizumab were statistically superior to abatacept, adalimumab, apremilast, certolizumab pegol, etanercept, secukinumab 150 mg, tofacitinib and ustekinumab.

- Adverse events and discontinuation
  - Safety parameters evaluated in the overall population of bDMARD- naïve and bDMARD-experienced patients included TEAEs, SAEs, DAEs and discontinuation for any reason. The TEAE network included five studies and six treatments (both regimens of ixekizumab, adalimumab, certolizumab pegol, infliximab and placebo).
  - No treatment had a statistically higher or lower chance of a TEAE than placebo, and there were no statistically significant differences between any of the active therapies included in this assessment.
  - The SAE network was much larger, including 22 studies and 16 treatments, although the number of SAEs in each study was low, resulting in a high level of uncertainty regarding the estimated treatment effects.
  - No treatment had a statistically higher or lower chance of an SAE than placebo. Ixekizumab 80 mg Q2W had a statistically higher chance of an SAE than golimumab, but there were no other statistical differences between ixekizumab and other therapies.
- sensitivity analysis
  - A sensitivity analysis was conducted for the ACR and PASI networks using efficacy data at week 24 for the overall population of bDMARD- naïve and bDMARD experienced patients.
  - For both of these networks, results of the sensitivity analysis were generally similar to those of the base- case analyses.
  - The ACR responses included 17 studies and 16 treatments.
  - All treatments had a statistically higher chance of achieving any ACR responses than placebo, and the magnitude of benefit was the greatest for infliximab, followed by golimumab. Both regimens of ixekizumab were statistically superior to once- weekly abatacept 125 mg SC and ustekinumab 45 mg Q12W.
  - In addition, ixekizumab 80 mg Q4W was statistically better than ustekinumab 90 mg Q12W.
  - There were no statistically significant differences between ixekizumab and other treatments.

Anmerkung/Fazit der Autoren

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

numerically greater magnitude of benefit in the bDMARD- naïve population. The results of this NMA are consistent with the recently completed H2H study comparing ixekizumab with adalimumab.

Kommentare zum Review

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

Simons N et al., 2020 [18].

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

Fragestellung

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

Methodik

Population:

- Patients with psoriatic arthritis

Intervention/Komparator:

- one or more marketed bDMARDs versus placebo

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

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

Charakteristika der Population:

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

Qualität der Studien:

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

Studienergebnisse:

- ACR20/50/70
  - Higher ACR20 response rates were shown for all bDMARDs in comparison to placebo, with RRs (95%CI) ranging from 3.21 (2.52, 4.08) for anti-TNF agents, 2.58 (2.04, 3.27) for anti-IL17 agents, 1.95 (1.52, 2.50) for ustekinumab to 1.77 (1.31, 2.39) for abatacept (Fig. 2).
  - The same trends were observed for ACR50 response rates, with RRs (95%CI) ranging from 6.47 (4.57, 9.17) for anti-TNF agents, 4.22 (2.83, 6.28) for anti-IL17 agents, 2.78 (1.81, 4.27) for ustekinumab to 1.56 (0.99, 2.46) for abatacept (not statistically significant) (Suppl. Fig. 2),
  - ACR70 response rates, with RRs (95%CI) of 8.89 (5.98, 13.21) for anti-TNF agents, 8.84 (3.65, 21.39) for anti-IL17 agents, 3.90 (1.81, 8.39) for ustekinumab and 1.56 (0.82, 2.96) for abatacept (not statistically significant)
- PASI75/90
  - Higher PASI75 response rates were shown for most bDMARDs in comparison to placebo, with RRs (CI95%) ranging from 8.51 (4.56, 15.90) for anti-TNF agents, 5.14 (3.16, 8.36) for anti-IL17 agents, 6.36 (3.49, 11.60) for ustekinumab to 1.62 (0.89, 2.96) for abatacept (not statistically significant) (Fig. 5).
  - PASI90 response rates followed the same trends, with RRs (95%CI) ranging from 8.76 (3.84, 20.01) for anti-TNF agents, 4.95 (2.85, 8.61) for anti-IL17 agents to 11.57 (5.46, 24.52) for ustekinumab (no data available for abatacept)
- HAQ-DI
  - Higher HAQ-DI reductions were shown for most bDMARDs compared to placebo, with mean differences (95%CI) of -0.31 (-0.42, -0.20) for anti-TNF agents, -0.26 (-0.33, -0.20) for anti-IL17 agents and -0.13 (-0.25, -0.01) for abatacept (no data available for ustekinumab)

Anmerkung/Fazit der Autoren

All bDMARDs showed higher ACR20 response rates and better HAQ-DI mean reduction compared to placebo.

This meta-analysis highlights the variability of bDMARD efficacy on ACR50/70, PASI75/90 and enthesitis or dactylitis response rates. Head-to-head studies are needed to draw definitive conclusions on potential efficacy-related differences between bDMARDs in PsA.

3.4 Leitlinien

Gossec L et al., 2016 [11].

European League Against Rheumatism (EULAR)

European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update.

Leitlinienorganisation/Fragestellung

Since the publication of the European League Against Rheumatism recommendations for the pharmacological treatment of psoriatic arthritis (PsA) in 2012, new evidence and new therapeutic agents have emerged. The objective was to update these recommendations.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium; Task Force: 34 persons from 14 European countries: 27 rheumatologists, 3 people affected with PsA, 2 health professionals, 1 dermatologist and 1 rheumatologist)
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz; Systemtic literature search: 2010 -06/2014 + 01/2015 siehe Ramiro et al. 2016 [21]), Suchzeitraum vor 2010 (LL-Version 2012): Ash et al. 2012 [2])
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt; After the final meeting, an anonymised email-based voting on the level of agreement was performed, using a 0–10 scale with a vote of 0 meaning total disagreement with a particular recommendation and 10 meaning total agreement with it. The means and SDs of scores from the whole group were calculated. The Task Force members were provided with the category of evidence and grade of recommendation for each item
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; Each recommendation from 2012 as well as those that were newly developed based on the SR were discussed in detail and, where necessary, modified until acceptable to the Task Force; at each step, a 67% majority was required for approval or rejection of a particular recommendation. If a clear-cut approval or rejection was not obtained, the wording was amended until it met the predetermined level of approval
- Regelmäßige Überprüfung der Aktualität gesichert.

LoE

- Oxford Levels of Evidence

GoR:

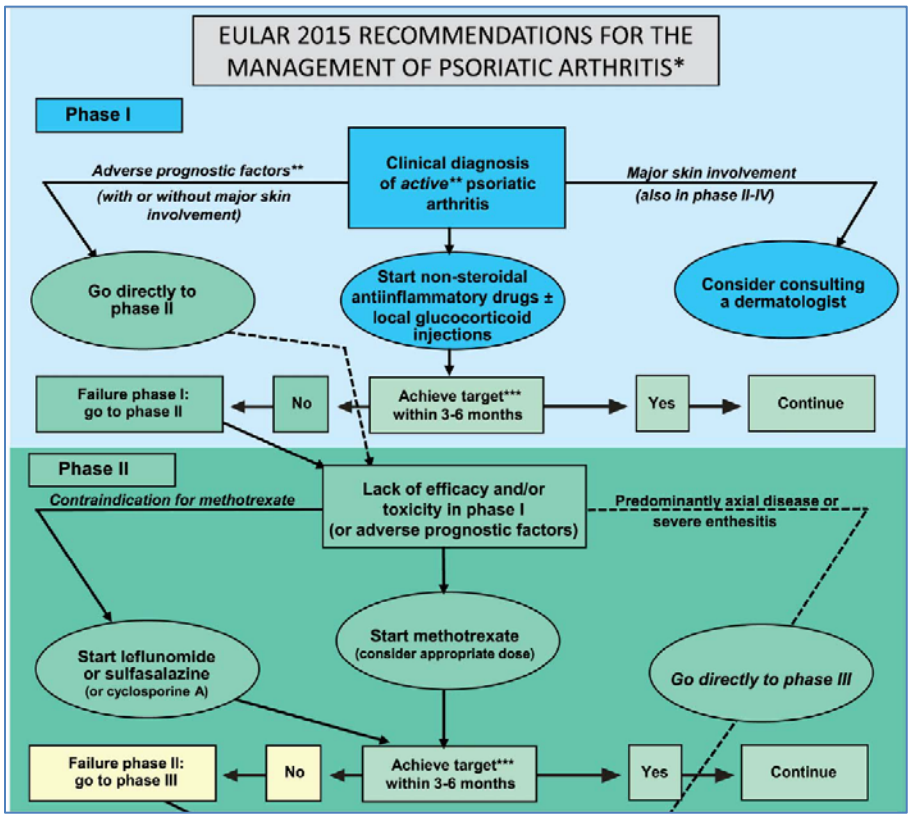
- verwendetes System nicht beschrieben, Empfehlungen wurden mit A bis C klassifiziert

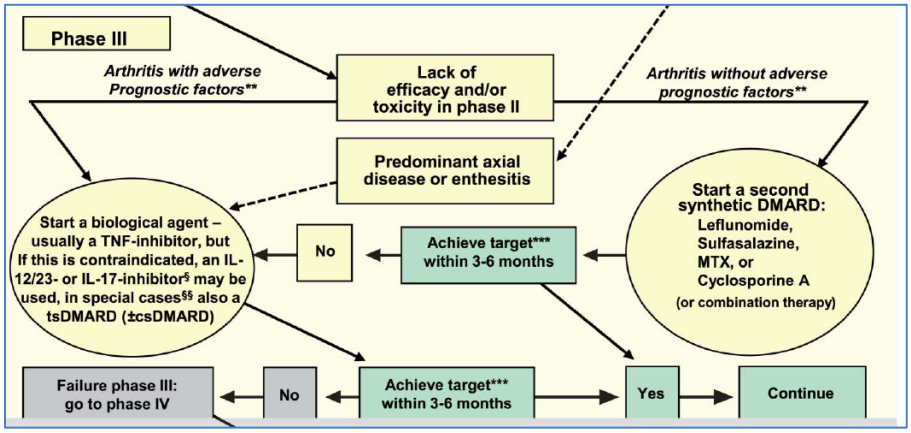
Sonstige methodische Hinweise

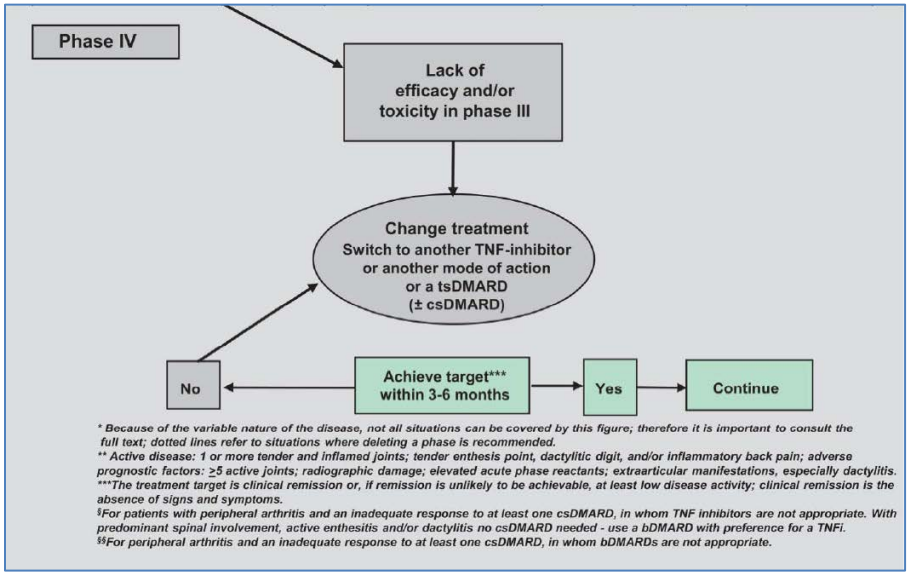
- Keine eindeutige Zuordnung der zugrundeliegenden Evidenz zu den Empfehlungen

Empfehlungen

- Treatment should be aimed at reaching the target of remission or, alternatively, minimal/low disease activity, by regular monitoring and appropriate adjustment of therapy (1b; A)
- In patients with PsA, NSAIDs may be used to relieve musculoskeletal signs and symptoms (1b; A)
- In patients with peripheral arthritis, particularly in those with many swollen joints, structural damage in the presence of inflammation, high ESR/CRP and/or clinically relevant extra-articular manifestationsa, csDMARDs should be consideredb at an early stagea, with methotrexate preferred in those with relevant skin involvementb (a: 3; B/ b:1b; B)
- Local injections of glucocorticoids should be considered as adjunctive therapy in PsA[a]; systemic glucocorticoids may be used with caution at the lowest effective dose[b] (a: 3b; C/ b: 4; C)
- In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a bDMARD, usually a TNF inhibitor, should be commenced. (1b; B)
- In patients with peripheral arthritis and an inadequate response to at least one csDMARD, in whom TNF inhibitors are not appropriate, bDMARD targeting IL12/23 or IL 17 pathways may be considered. (1b; B)
- In patients with peripheral arthritis and an inadequate response to at least one csDMARD, in whom bDMARDs are not appropriate, a targeted synthetic DMARD such as a PDE4-inhibitor may be considered. (1b; B)
- In patients with active enthesitis and/or dactylitis and insufficient response to NSAIDs or local glucocorticoid injections, therapy with a bDMARD should be considered, which according to current practice is a TNF inhibitor. (1b; B)
- In patients with predominantly axial disease that is active and has insufficient response to NSAIDs, therapy with a bDMARD should be considered, which according to current practice is a TNF inhibitor. (1b; B)
- In patients who fail to respond adequately to a bDMARD, switching to another bDMARD should be considered, including switching between TNF inhibitors. (1b; B)


EULAR 2015 RECOMMENDATIONS FOR THE MANAGEMENT OF PSORIATIC ARTHRITIS*
Phase I
Clinical diagnosis of active** psoriatic arthritis
Adverse prognostic factors** (with or without major skin involvement)
Major skin involvement (also in phase II-IV)
Go directly to phase II
Start non-steroidal antiinflammatory drugs ± local glucocorticoid injections
Consider consulting a dermatologist
Failure phase I: go to phase II
No
Achieve target*** within 3-6 months
Yes
Continue
Phase II
Contraindication for methotrexate
Lack of efficacy and/or toxicity in phase I (or adverse prognostic factors)
Predominantly axial disease or severe enthesitis
Start leflunomide or sulfasalazine (or cyclosporine A)
Start methotrexate (consider appropriate dose)
Go directly to phase III
Failure phase II: go to phase III
No
Achieve target*** within 3-6 months
Yes
Continue


Phase III
Arthritis with adverse Prognostic factors**
Lack of efficacy and/or toxicity in phase II
Arthritis without adverse prognostic factors**
Predominant axial disease or enthesitis
Start a biological agent – usually a TNF-inhibitor, but If this is contraindicated, an IL-12/23- or IL-17-inhibitor§ may be used, in special cases§§ also a tsDMARD (±csDMARD)
No
Achieve target*** within 3-6 months
Start a second synthetic DMARD: Leflunomide, Sulfasalazine, MTX, or Cyclosporine A (or combination therapy)
Failure phase III: go to phase IV
No
Achieve target*** within 3-6 months
Yes
Continue



Coates LC et al., 2016 [2].

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

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

Leitlinienorganisation/Fragestellung

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

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz; systematic literature review of the PsA treatment literature was conducted: Coates et al., 2014 [4]; further literature update and review of abstracts presented at the annual meetings of the American College of Rheumatology (November 2014) and the American Academy of Dermatology (March 2015).
- Formale Konsensusprozesse und externes Begutachtungsverfahren unklar; recommendations were critically reviewed and edited via in-person discussion and online survey.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was applied
- Regelmäßige Überprüfung der Aktualität gesichert.
- GRAPPA rheumatologists, dermatologists, and PsA patients drafted recommendations

Sonstige methodische Hinweise

- Bewertung der internen Validität der Einzelstudien unklar
- Z.T. keine eindeutige Zuordnung der zugrundeliegenden Evidenz zu den Empfehlungen

Empfehlungen

Peripheral Arthritis

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are conditionally recommended for use in peripheral arthritis to improve symptoms of the disease, but with caution due to their potential adverse effects.
- Corticosteroids are conditionally recommended for peripheral arthritis, to be administered either systemically or intraarticularly, at the smallest dosages required for efficacy (usually ,7.5 mg/day) and for short periods, to minimize adverse effects, including psoriasis flare, after withdrawal of the treatment.
- In DMARD-naive patients, both DMARDs (MTX, leflunomide, and SSZ; cyclosporine is not recommended due to scant evidence of its efficacy and its toxicity profile) and TNFi are strongly recommended for treatment.
- In many instances, DMARDs may be used first, but consideration should be given to early escalation of therapy, particularly in patients with poor prognostic factors (e.g., increased levels of inflammatory markers, high counts of joints with active disease). Despite the lack of evidence from randomized controlled trials (RCTs), DMARDs are recommended based on data from observational studies, their low costs and universal access, and the lack of evidence that a short time delay in the introduction of more effective therapies would impact long-term function and quality of life.
- no definitive evidence to date on the benefit of concomitant DMARDs with biologic therapies. In the TNFi RCTs, similar efficacy results were commonly seen with or without MTX. However, registry data suggest that effect of the monoclonal antibodies, particularly infliximab, persists longer with concomitant DMARD treatment.
- no definitive evidence to date on the benefit of concomitant DMARDs with biologic therapies. In the TNFi RCTs, similar efficacy results were commonly seen with or without MTX. However, registry data suggest that effect of the monoclonal antibodies, particularly infliximab, persists longer with concomitant DMARD treatment (13).

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

Axial disease.

- The treatment recommendations for axial disease are derived from diagnostic criteria, screening, monitoring, and response to therapy in ankylosing spondylitis (AS) since these data are not available for axial PsA. For patients with axial symptoms that have not responded to NSAIDs, physiotherapy, and sacroiliac joint injections (when appropriate), initiation of TNFi is recommended;
- DMARDs are not effective for treatment of diseases in this domain. There is no available evidence on the efficacy of SSZ in axial disease within AS or PsA (29). NSAIDs are conditionally recommended, usually as an adjunct to further therapy, for patients with an inadequate response to TNFi.

- Formal published data on switching agents for axial disease are not available but observational data support switching as in the other domains, leading to a conditional recommendation in the case of inadequate response to TNFi treatment. Clinical trial data sowing efficacy of secukinumab (phase III trial) (30) and ustekinumab (openlabel proof-of-concept trial with 20 patients) (31) in AS have been published, but these agents are currently not approved for AS or axial PsA.

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

Enthesitis.

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

15. Orbai AM, Weitz J, Siegel EL, Siebert S, Savage LJ, Aydin SZ, et al, the GRAPPA Enthesitis Working Group. Systematic review of treatment effectiveness and outcome measures for enthesitis in psoriatic arthritis. J Rheumatol 2014;41:2290–4.
32. Sakkas LI, Alexiou I, Simopoulou T, Vlychou M. Enthesitis in psoriatic arthritis. Semin Arthritis Rheum 2013;43:325–34.
33. Clegg DO, Reda DJ, Mejias E, Cannon GW, Weisman MH, Taylor T, et al Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis: a Department of Veterans Affairs CooperativeStudy. Arthritis Rheum 1996;39:2013–20.
35. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A

Dactylitis.

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

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

Skin disease

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

Nail disease.

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

11. Cassell S, Kavanaugh AF. Therapies for psoriatic nail disease: a systematic review. J Rheumatol 2006;33:1452–6.
18. Armstrong AW, Tuong W, Love TJ, Carneiro S, Grynszpan R, Lee SS, et al. Treatments for nail psoriasis: a systematic review by the GRAPPA Nail Psoriasis Work Group. J Rheumatol 2014; 41:2306–14.
36. Rich P, Bourcier M, Sofen H, Fakharzadeh S, Wasfi Y, Wang Y, et al. Ustekinumab improves nail disease in patients with moderate-to-severe psoriasis: results from PHOENIX 1. Br J Dermatol 2014;170:398–407.
37. Paul C, Reich K, Gottlieb AB, Mrowietz U, Philipp S, Nakayama J, et al. Secukinumab improves hand, foot and nail lesions in moderate-to-severe plaque psoriasis: subanalysis of a randomized, double-blind, placebo-controlled, regimen-finding phase 2 trial. J Eur Acad Dermatol Venereol 2014;28:1670–5.
38. Gooderham M, Crowley J, Wasel N, Weisman J, Tyrings S, Hu CC, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with nail, scalp and palmoplantar psoriasis: 52-week results from the ESTEEM 2 study [abstract]. J Invest Dermatol 2015;135:S31.
39. Crowley J, Gooderham M, Wasel N, Weisman J, Tyring S, Hu CC, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with nail, scalp and palmoplantar psoriasis: 52-week results from the ESTEEM 2 study [abstract]. J Am Acad Dermatol 2015;72:AB226.

Spanish Society of Rheumatology, 2018 [23].

Spanish Society of Rheumatology (SER)

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

Leitlinienorganisation/Fragestellung

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

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium; A multi-disciplinary work group was set up consisting of professionals involved in medical care, technical experts from the Research Unit (RU) of SER, and patient representatives. All participants are mentioned in the authorship and collaborations subsection.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;

- Regelmäßige Überprüfung der Aktualität gesichert.

Sonstige methodische Hinweise

- Updating the former Espoguía was deemed necessary due to the time elapsed since its last publication and because of new findings and advances. The former guideline have been partially updated and are hereby replaced with the new CPG. Delimitation in the scope and objectives of the CPG was consensually determined, drawing upon the clinical experience and information provided by the participating health professionals.
- A literature search was carried out using the MEDLINE database (via PubMed), EMBASE (Elsevier), the Cochrane Library (Wiley Online Library), and Cinahl (EBSCOhost) revision was completed in 2016.
- subsequently panelists identified some studies which had been published in 2017 and were included in the evidence corpus.
- A critical reading of the studies was conducted using the critical SIGN (Scottish Intercollegiate Guidelines Network) reading templates, and their internal and external validity measures were assessed. From the selected studies, the most significant data referring to methodology, outcomes, and quality were extracted and entered in evidence tables.
- The level of scientific evidence was evaluated using a modified version of the Oxford Centre for Evidence-Based Medicine (CEBM) system.
- After the considered review, recommendations were formulated. These formulations were based on the ‘formal evaluation’ or ‘reasoned judgement’ after previously summarizing the best available evidence for each clinical question. The strength of each recommendation was evaluated using a modified version of CEBM. Recommendations that proved controversial or that lacked sufficient evidence were submitted to the development group consensus.

Empfehlungen

Treatment of Psoriatic Arthritis (PsA)

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

Singh JA et al., 2019 [19].

American College of Rheumatology/National Psoriasis Foundation

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

Leitlinienorganisation/Fragestellung

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

Methodik

Grundlage der Leitlinie

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

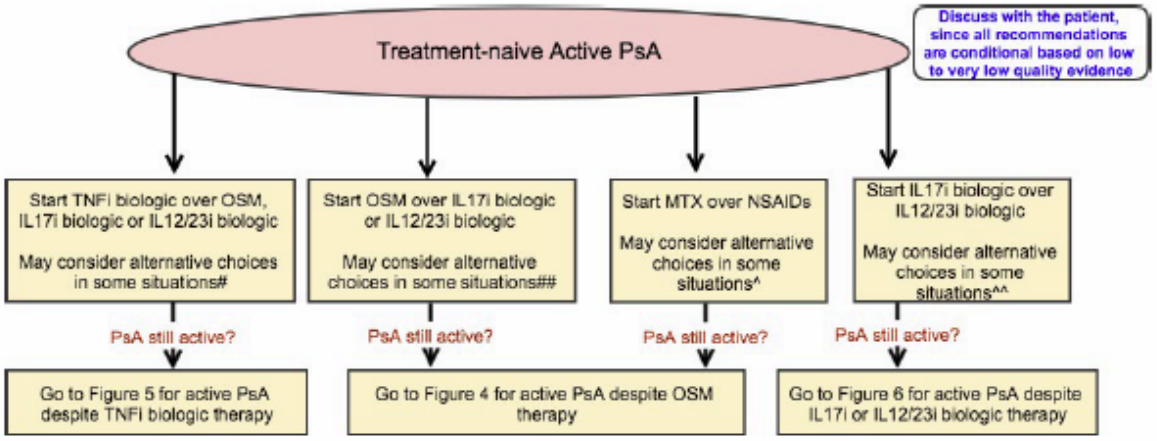
Recommendations for pharmacologic interventions

Active PsA in treatment-naive patients:

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

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

* Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD). Oral small molecules (OSMs) are defined as methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), cyclosporine (CSA), or apremilast (APR) and *do not* include tofacitinib, which was handled separately since its efficacy/safety profile is much different from that of other OSMs listed above. OSM- and other treatment–naive is defined as naive to treatment with OSMs, tumor necrosis factor inhibitors (TNFi,) interleukin-17 inhibitors (IL-17i), and IL-12/23i; patients may have received nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids, and/or other pharmacologic and nonpharmacologic interventions.
† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.
‡ Because there are currently no widely agreed-upon definitions of disease severity, PsA severity should be established by the health care provider and patient on a case-by-case basis. For the purposes of these recommendations, severity is considered a broader concept than disease activity in that it encompasses the level of disease activity at a given time point, as well as the presence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of ≥1 of the following: a poor prognostic factor (erosive disease, elevated levels of inflammation markers such as C-reactive protein or erythrocyte sedimentation rate attributable to PsA), long-term damage that interferes with function (e.g., joint deformities, vision loss), highly active disease that causes major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease.
§ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.



May consider alternatives (indicated in parentheses), if patient has severe psoriasis (IL17i or IL12/23i biologic); has contraindications to TNFi biologic including recurrent infections, congestive heart failure, or demyelinating disease (OSM, IL17i biologic, or IL12/23i biologic); prefers oral medications (OSM) or less frequent administrations (IL12/23i biologic); has concern over starting biologic as the first therapy (OSM); or does not have severe psoriasis or severe PsA (OSM).

May consider alternatives (indicated in parentheses), if patient has severe psoriasis or severe PsA (IL12/23i biologic or IL17i biologic); has concomitant active IBD (IL12/23i biologic); or prefers less frequent administrations (IL12/23i biologic).

^ May consider NSAIDs in patients with less active disease, after careful consideration of cardiovascular risks and renal risks of NSAIDs.

^^ May consider IL12/23i biologic if patient has concomitant IBD or desires less frequent drug administration.

The order of listing of various conditional recommendations or of different treatment choices within a conditional statement does not indicate any sequence in which treatment options would be chosen; each conditional statement stands on its own.

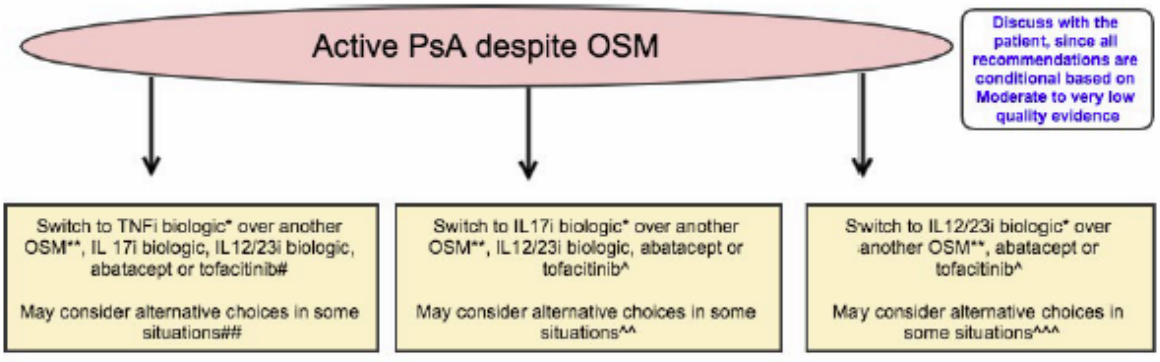
Figure 3. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) who are treatment-naive (no exposure to oral small molecules [OSMs] or other treatments). All recommendations are conditional based on low- to very-low-quality evidence. A conditional recommendation means that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

Active PsA despite treatment with an OSM

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

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

* Active psoriatic arthritis (PsA) is defined as disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be *due to PsA* based on ≥1 of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease (IBD). Oral small molecules (OSMs) are defined as methotrexate (MTX), sulfasalazine, leflunomide, cyclosporine, or apremilast and *do not* include tofacitinib, which was handled separately since its efficacy/safety profile is much different from that of other OSMs listed above. TNFi = tumor necrosis factor inhibitor; IL-17i = interleukin-17 inhibitor.
† When there were no published studies, we relied on the clinical experience of the panelists, which was designated very-low-quality evidence.
‡ Because there are currently no widely agreed-upon definitions of disease severity, PsA severity should be established by the health care provider and patient on a case-by-case basis. For the purposes of these recommendations, severity is considered a broader concept than disease activity in that it encompasses the level of disease activity at a given time point, as well as the presence of poor prognostic factors and long-term damage. Examples of severe PsA disease include the presence of ≥1 of the following: a poor prognostic factor (erosive disease, elevated levels of inflammation markers such as C-reactive protein or erythrocyte sedimentation rate attributable to PsA), long-term damage that interferes with function (e.g., joint deformities, vision loss), highly active disease that causes major impairment in quality of life (i.e., active psoriatic inflammatory disease at many sites [including dactylitis, enthesitis] or function-limiting inflammatory disease at few sites), and rapidly progressive disease.
§ Because there are currently no widely agreed-upon definitions of disease severity, psoriasis severity should be established by the health care provider and patient on a case-by-case basis. In clinical trials, severe psoriasis has been defined as a Psoriasis Area and Severity Index (PASI) score (25) of ≥12 and a body surface area score of ≥10. In clinical practice, however, the PASI tool is not standardly utilized given its cumbersome nature. In 2007, the National Psoriasis Foundation published an expert consensus statement, which defined moderate-to-severe disease as a body surface area of ≥5% (68). In cases in which the involvement is in critical areas, such as the face, hands or feet, nails, intertriginous areas, scalp, or where the burden of the disease causes significant disability or impairment of physical or mental functioning, the disease can be severe despite the lower amount of surface area of skin involved. The need to factor in the unique circumstances of the individual patient is of critical importance, but this threshold provides some guidance in the care of patients.



* For each biologic, biologic monotherapy is conditionally recommended over biologic + MTX combination therapy.
** Add apremilast over switching to apremilast; Switch to another OSM (except apremilast) over adding another OSM
# Please see Figure 5 for details and treatment options if patient has active PsA despite TNFi biologic.
^ please see Figure 6 for details and treatment options if patient has active PsA despite IL17i or IL12/23i biologic
May consider alternatives (indicated in parentheses), if patient has severe psoriasis (IL17i or IL12/23i biologic); has contraindications to TNFi including recurrent infections, congestive heart failure, or demyelinating disease (OSM, IL17i biologic, IL12/23i biologic, abatacept or tofacitinib); prefers oral medications (OSM, tofacitinib) or less frequent administrations (IL12/23i biologic).
^^ May consider alternatives (indicated in parentheses), if patient has concomitant active IBD (IL12/23i biologic); absence of severe psoriasis or PsA (OSM); has recurrent serious infections (abatacept); has recurrent candida infections (tofacitinib); prefers oral medications (OSM, tofacitinib) or less frequent administrations (IL12/23i biologic).
^^^ May consider alternatives (indicated in parentheses), if patient has absence of severe psoriasis or severe PsA (OSM); has recurrent or serious infections (abatacept); prefers oral medications (OSM, tofacitinib).
The order of listing of various conditional recommendations or of different treatment choices within a conditional statement does not indicate any sequence in which treatment options would be chosen; each conditional statement stands on its own.

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

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

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

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

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

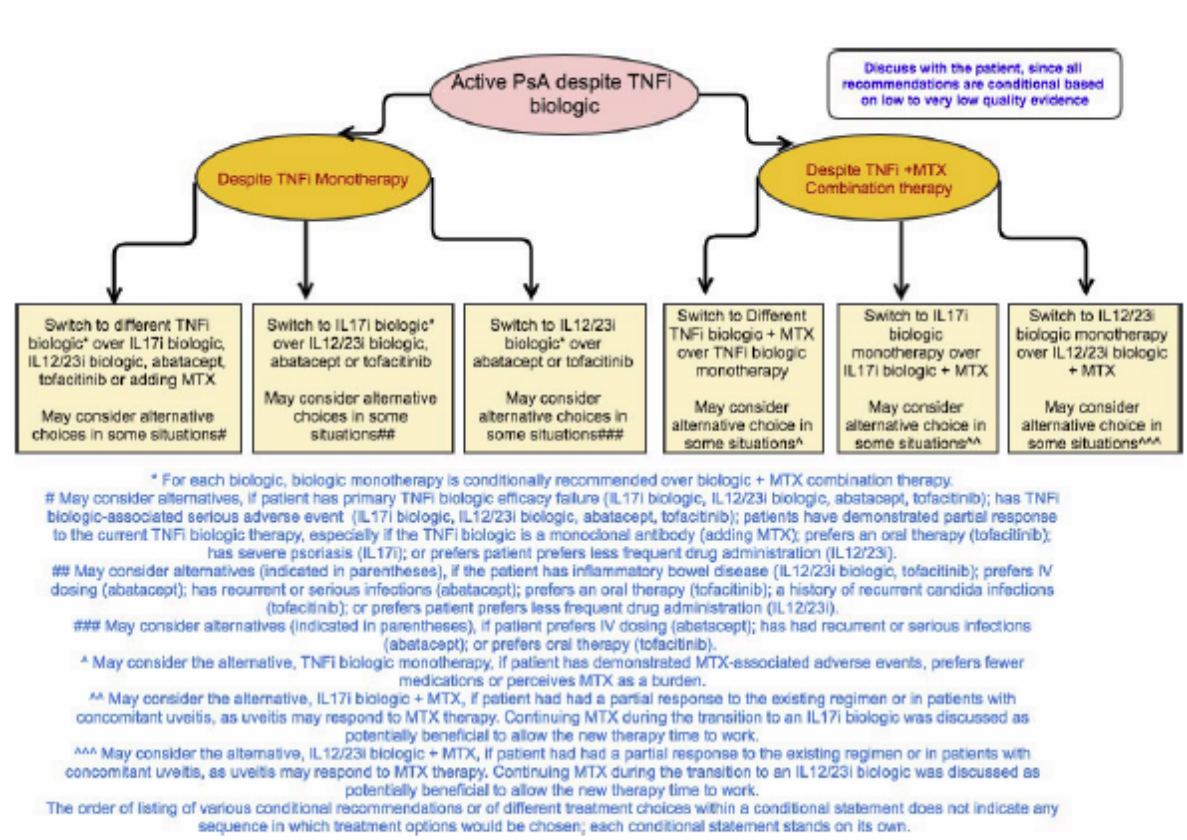


Figure 5. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) despite treatment with a tumor necrosis factor inhibitor (TNFi) as monotherapy or as combination therapy with methotrexate (MTX). All recommendations are conditional based on low- to very-low-quality evidence.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

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

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

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

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

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

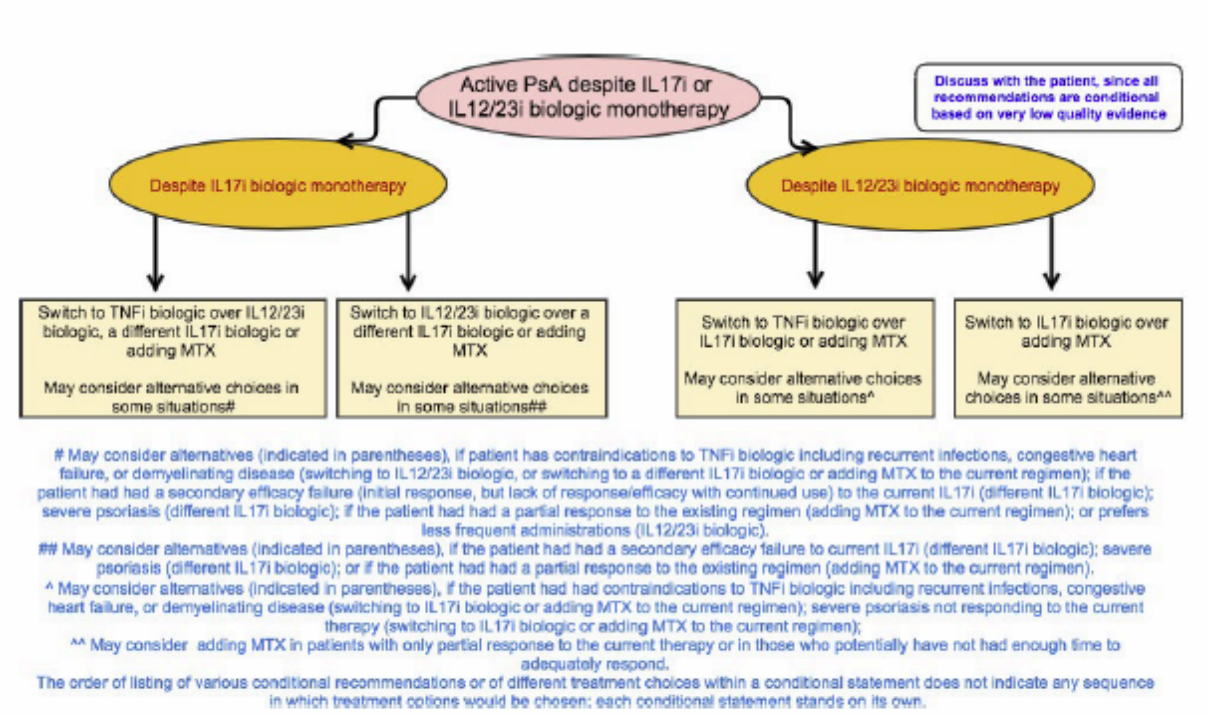


Figure 6. Recommendations for the treatment of patients with active psoriatic arthritis (PsA) despite treatment with interleukin-17 inhibitor (IL-17i) or IL-12/23i biologic monotherapy. All recommendations are conditional based on low- to very-low-quality of evidence. A conditional recommendation means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

Holroyd CR et al., 2019 [12].

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

Siehe auch: Holroyd, CR et al., 2019 [13]

Zielsetzung/Fragestellung

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

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

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium; The Guideline Working group (GWG) was composed of rheumatology consultants from various clinical backgrounds, rheumatology specialty

trainees, rheumatology nurse specialists and a patient representative. All members contributed to the development of key questions on which to base the search strategy, guideline content, recommendations and strength of agreement (SOA).

- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz; This guideline has been developed in line with BSR's guideline protocol. A comprehensive literature search was undertaken by two reviewers, using MEDLINE, Cochrane, PubMed and EMBASE databases with specific search terms
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; The GRADE method was used to assess the quality of evidence and the strength of recommendation
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

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

LoE/ GoR:

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

Empfehlungen: For patients receiving biologic therapy

Empfehlung 1 (grade 2C, SOA 94%)

For patients receiving biologic therapy Monitoring on treatment

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

(ii) Patients prescribed a biologic (other than TCZ) without concomitant csDMARD (or with csDMARDs that do not require blood test monitoring), should have monitoring blood

tests (FBC, creatinine/calculated GFR, ALT and/or AST and albumin every 3–6 months (grade 2C, SOA 97%).

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

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

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

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

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

Smith CH et al., 2020 [20].

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	'Offer' *(or similar, e.g.*	↑↑	Benefits of the intervention outweigh the risks; most patients would choose the intervention while

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

↑

Empfehlungen

Using biologic therapy

- R1 (↑↑) Initiation and supervision of biologic therapy for people with psoriasis should be undertaken by specialist physicians experienced in the diagnosis and treatment of psoriasis. Routine monitoring may be delegated to other healthcare professionals, for example clinical nurse specialists. Manage psoriatic arthritis and/or multimorbidity in consultation with the relevant healthcare professionals.
- R2 (↑↑) Agree and formalize arrangements for drug administration, monitoring and follow-up between health carers and the person receiving treatment.
- R3 (↑↑) Offer people with psoriasis who are starting biologic therapy the opportunity to participate in long-term safety registries Empfehlung 1 (Empfehlungsgrad)

Criteria for biologic therapy

- R4 (↑↑) Offer biologic therapy to people with psoriasis requiring systemic therapy if methotrexate and ciclosporin have failed, are not tolerated or are contraindicated (see NICE guidelines CG153)7 and the psoriasis has a large impact on physical, psychological or social functioning (for example, Dermatology Life Quality Index (DLQI) or Children's DLQI > 10 or clinically relevant depressive or anxiety symptoms) and one or more of the following disease severity criteria apply:

  - the psoriasis is extensive [defined as body surface area (BSA) > 10% or Psoriasis Area and Severity Index (PASI) ≥ 10]
  - the psoriasis is severe at localized sites and associated with significant functional impairment and/or high levels of distress (for example nail disease or involvement of high-impact and difficult-to-treat sites such as the face, scalp, palms, soles, flexures and genitals).
- R5 (↑) Consider biologic therapy earlier in the treatment pathway (e.g. if methotrexate has failed, is not tolerated or is contraindicated) in people with psoriasis who fulfil the disease severity criteria and who also have active psoriatic arthritis (see the NICE musculoskeletal conditions overview)8 or who have psoriasis that is persistent, i.e. that relapses rapidly (defined as > 50% baseline disease severity within 3 months of completion of any treatment) off a therapy that cannot be continued in the long term

Prescribing biologic therapy

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

Reviewing biologic therapy

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

- R12 (↑) Consider changing to an alternative therapy, including another biologic therapy, if any of the following applies:
  - the psoriasis does not achieve the minimum response criteria (primary failure – see R11)
  - the psoriasis initially responds but subsequently loses this response (secondary failure)

Choice of biologic therapy: general considerations

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

Psoriasis factors

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

Other individual factors

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

Choice of biologic therapy in adults

- R15 (↑↑) Offer any of the currently licensed biologic therapies as first-line therapy (and with reference to R18 and R19) to adults with psoriasis who fulfil the criteria for biologic therapy (see R4 and R5), using the decision aid (see File S1: Table S2) to inform treatment choice.
- R16 (↑↑) Offer any of the currently licensed biologic therapies (and with reference to R18 and R19) when psoriasis has not responded to a first biologic therapy. Use the decision aid (see File S1: Table S2) and take into account all factors detailed in R14 to select the most appropriate agent.
- R17 (↑↑) Offer a TNF antagonist (and with reference to R18 and R19) or an IL-17 antagonist* as a first-line therapy to adults with psoriasis and who also have psoriatic arthritis, using the decision aid (see File S1: Table S2) to inform treatment choice.10-13 *Please note that brodalumab is not licensed for psoriatic arthritis.

- R18 (↑) Consider etanercept for use in people where a TNF antagonist is indicated and other available biologic agents have failed or cannot be used, or where a short half-life is important.
- R19 (↑↑) Reserve infliximab for use in people with very severe disease, or where other available biologic agents have failed or cannot be used, or where weight-based dosing is a priority.

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

- R21 (↑↑) When a person's psoriasis responds inadequately to a second or subsequent biologic agent, review treatment goals, seek advice from a dermatologist with expertise in biologic therapy and consider any of the following strategies:
  - reiterate advice about modifiable factors contributing to poor response such as obesity and poor adherence (intentional or non-intentional)
  - consider whether drug exposure is adequate (see R20)
  - optimize adjunctive therapy (e.g. switch from oral to subcutaneous methotrexate)
  - switch to an alternative biologic agent
  - alternative or supplementary nonbiologic therapy approaches (e.g. inpatient topical therapy, phototherapy, or systemic therapies).

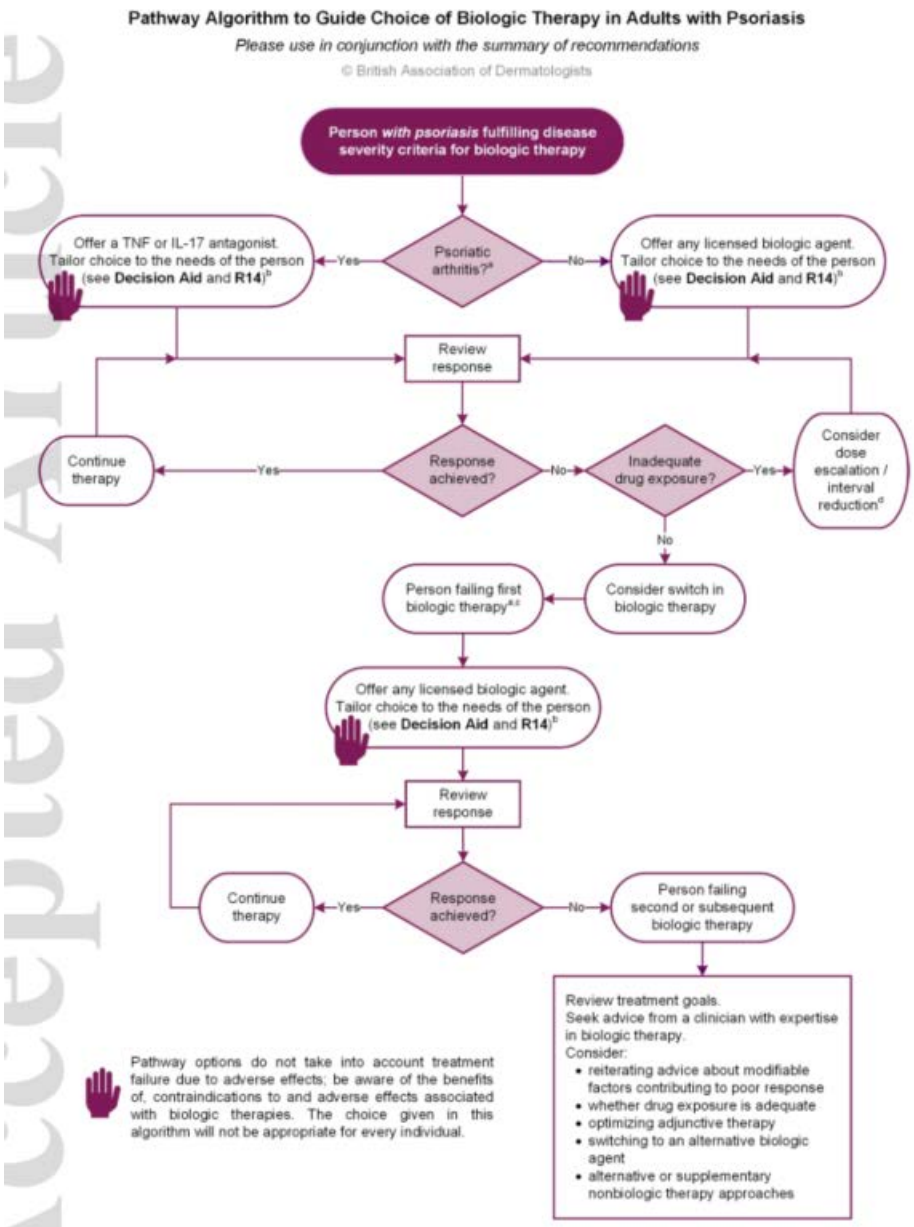


Figure legends

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Backgroundinfos aus Leitlinien: siehe Anhang

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 4 of 12, April 2020) am 08.04.2020

#	Suchfrage
1	MeSH descriptor: [Arthritis, Psoriatic] explode all trees
2	(psoria* NEAR/3 (arthriti* OR arthropath*)):ti,ab,kw
3	#1 OR #2
4	#3 with Cochrane Library publication date from Apr 2015 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 08.04.2020

#	Suchfrage
1	Arthritis, Psoriatic[mh]
2	psoria*[tiab] AND (arthriti*[tiab] OR arthropath*[tiab])
3	#1 OR #2
4	(#3) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
5	(#4) AND ("2015/04/01"[PDAT] : "3000"[PDAT])
6	(#5) NOT "The Cochrane database of systematic reviews"[Journal]
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 08.04.2020

#	Suchfrage
1	Arthritis, Psoriatic[mh]
2	psoria*[tiab] AND (arthriti*[tiab] OR arthropath*[tiab])
3	#1 OR #2
4	(#3) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
5	(#4) AND ("2015/04/01"[PDAT] : "3000"[PDAT])
6	(#5) NOT (retracted publication [pt] OR retraction of publication [pt])

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Anhang

Smith CH et al., 2020 [20].

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

Abbildung 1: TABLE S2: DECISION AID – BIOLOGIC THERAPY FOR PSORIASIS

TABLE S2: DECISION AID – BIOLOGIC THERAPY FOR PSORIASIS

This is a decision aid to help clinicians and patients decide their treatment choice and not a comprehensive data source or replacement for the individual drug Summary of Product Characteristics. Please use in conjunction with the published guidelines, pathway algorithm and discussions in the online supporting information document.

	How do I take it?		How effective is it?		How common are the side effects?		Is there anything else to consider?	
Questions you might want to ask	How often do I need to inject the treatment?*	For how long has this treatment been around?†	Roughly what proportion of people becomes clear or nearly clear (PASI90) after 3-4 months?‡	What is the likelihood of staying on this treatment past 1 year?§	Roughly what proportion of people stops their treatment in the first 3-4 months due to unwanted effects?‡	Roughly what proportion of people gets a serious infection in the first 3-4 months?**	What are *some* of the conditions that would make your doctor hesitant about giving you the treatment?††	What if I have psoriatic arthritis?
TNF								
Adalimumab	1 injection under the skin, every other week	Since 2008	41%	77-81% chance[1]	2%	< 1%	Moderate or severe heart failure, multiple sclerosis (or other conditions affecting the nerves)	Recommended treatment for psoriatic arthritis
Certolizumab pegol	1 or 2 injections under the skin, every 2 weeks	Since 2019	41-48%	Not known at present	2%	< 1%	Moderate or severe heart failure, multiple sclerosis (or other conditions affecting the nerves)	Recommended treatment for psoriatic arthritis
Etanercept	1 injection under the skin, once or twice a week	Since 2004	23%	67-73% chance[1]	2%	< 1%	Moderate or severe heart failure, multiple sclerosis (or other conditions affecting the nerves)	Recommended treatment for psoriatic arthritis
Infliximab	1 injection in the vein,‡‡ every 8 weeks	Since 2006	53%	54-74% chance[1]	5%	Not known at present	Moderate or severe heart failure, multiple sclerosis (or other conditions affecting the nerves)	Recommended treatment for psoriatic arthritis
IL12/23								
Ustekinumab	1 injection under the skin, every 12 weeks	Since 2009	46%	86-92% chance[1]	1%	< 1%	No particular condition	Recommended treatment for psoriatic arthritis only when TNF inhibitors have failed
IL17								
Brodalumab	1 injection under the skin, every 2 weeks	Since 2018	73%	Not known at present	2%	< 1%	Inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), recurrent candida infection (i.e. thrush)	This treatment is not licensed§§ for psoriatic arthritis

* Only licensed maintenance doses are featured; see File S1: Table S1 for information on initiation dosing schedules
† First approval of the drug for moderate to severe plaque psoriasis
‡ The evidence is drawn from clinical trials including a mixed biologic-naïve and experienced population; figures quoted are based on results from network meta-analyses of licensed biologic doses
§ The evidence is drawn from a real-world UK biologic-naïve population; it may not apply to biologic choice for subsequent lines of treatment
** The evidence is drawn from clinical trials including a mixed biologic-naïve and experienced population; figures quoted are based on Peto odds ratio analyses of all biologic doses
†† Please refer to individual drugs' summary of product characteristics for a more comprehensive list (www.medicines.org.uk)
‡‡ Requires attendance to hospital
§§ A treatment that is not licensed for a particular condition means it has not been awarded a Market Authorisation from the U.K. Medicines Healthcare Products Regulatory Agency (MHRA) for that condition. Once awarded, the licensed treatment can be marketed and sold in the U.K.

6

TABLE S2: DECISION AID – BIOLOGIC THERAPY FOR PSORIASIS

This is a decision aid to help clinicians and patients decide their treatment choice and not a comprehensive data source or replacement for the individual drug Summary of Product Characteristics. Please use in conjunction with the published guidelines, pathway algorithm and discussions in the online supporting information document.

	How do I take it?		How effective is it?		How common are the side effects?		Is there anything else to consider?	
Questions you might want to ask	How often do I need to inject the treatment?*	For how long has this treatment been around?†	Roughly what proportion of people becomes clear or nearly clear (PASI90) after 3-4 months?‡	What is the likelihood of staying on this treatment past 1 year?§	Roughly what proportion of people stops their treatment in the first 3-4 months due to unwanted effects?‡	Roughly what proportion of people gets a serious infection in the first 3-4 months?**	What are *some* of the conditions that would make your doctor hesitant about giving you the treatment?††	What if I have psoriatic arthritis?
Ixekizumab	1 injection under the skin, every 4 weeks	Since 2016	72%	Not known at present	3%	< 1%	Inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), recurrent candida infection (i.e. thrush)	Recommended treatment for psoriatic arthritis
Secukinumab	2 injections under the skin, every month	Since 2015	60%	Not known at present	2%	< 1%	Inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), recurrent candida infection (i.e. thrush)	Recommended treatment for psoriatic arthritis
IL23								
Guselkumab	1 injection under the skin, every 8 weeks	Since 2018	68%	Not known at present	2%	< 1%	No particular condition	This treatment is not licensed§§ for psoriatic arthritis
Risankizumab	2 injections under the skin, every 12 weeks	Since 2019	74%	Not known at present	1%	< 1%	No particular condition	This treatment is not licensed§§ for psoriatic arthritis
Tildrakizumab	1 or 2 injections under the skin, every 12 weeks	Since 2019	39%	Not known at present	2%	< 1%	No particular condition	This treatment is not licensed§§ for psoriatic arthritis
Placebo								
No active treatment	Does not apply	Does not apply	2%	Does not apply	2%	< 1%	Does not apply	Does not apply

NICE eligibility criteria, infliximab: PASI ≥20, DLQI >18; other biologic therapies: PASI ≥10, DLQI >10

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

2020-B-079

Kontaktdaten

Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 11.05.2020

Indikation gemäß Beratungsantrag

Was ist der Behandlungsstandard in der Behandlung der „aktiven Psoriasis-Arthritis (PsA) bei erwachsenen Patienten, die unzureichend auf ein oder mehrere krankheitsmodifizierende Antirheumatika (DMARDs) angesprochen oder diese nicht vertragen haben“?

Gegen die verschiedenen Manifestationen der aktiven PsA (periphere und axiale Arthritis, Enthesitis, Daktylitis, Haut- und Nagelbeteiligung, sowie extraartikuläre Uveitis und entzündliche Darmerkrankung (IBD)) sind konventionelle DMARDs (cDMARDs) (Methotrexat (MTX), Sulfasalazin (SSZ), Leflunomid (LEF), Ciclosporin A (CSA)) nur wenig effektiv. Allenfalls zeigen MTX und Apremilast bei der peripheren Arthritis eine marginale Wirksamkeit bewirken jedoch keine Hemmung der radiologischen Progression. Den Behandlungsstandard bilden seit 2011 (1) aufgrund mehrerer Phase-III-Studien Tumornekrosefaktor alpha (TNFα)-Inhibitoren (Adalimumab, Infliximab, Golimumab, Certolizumab, Etanercept), sie wirken nicht nur günstig auf die peripheren und axialen Arthritis-Manifestationen, sondern helfen auch gegen Daktylitis, Enthesitis, Uveitis, Haut- und Nagelbeteiligung und verlangsamen die radiologische Progression der PsA (2). Die Ansprechraten gemessen im ACR20 liegen bei 40–65 % nach 12–52 Wochen (3;4). Weitere effektive Therapieoptionen stehen mit IL-12/IL-23-Inhibitoren, IL-17-Inhibitoren, CTLA-Ig (Abatacept) und dem Jak-Inhibitor Tofacitinib zur Verfügung ((4), Tab. 1). Entsprechend ergeben sich viele Optionen bei Erstmanifestation, cDMARD-resistenten und TNFα- resistenten PsA Verläufen. Leider werden in der kürzlich erschienen Guideline des ACR nur 6 % der möglichen Therapieentscheidungen als überzeugend („strong“) und 94 % nur als eingeschränkt („conditional“) empfehlenswert bewertet. Der Diskussionsbedarf bei der aktiven und therapierefraktären PsA wird durch unterschiedliche Krankheitsverläufe und Komorbiditäten noch erhöht. Zudem gibt es keine validierten, PsA-spezifischen Aktivitätskriterien, sondern man greift bei peripherem Gelenkbefall auf die Rheumatoide Arthritis-spezifischen ACR20-/50-/70-Kriterien, bei axialem Befall, auf SPA-Kriterien und bei Hautbefall auf den PASI 75/100 zurück. Letztendlich ist der Schweregrad einer PsA fallspezifisch und prognoseabhängig zu beurteilen; er wird bestimmt von Ausdehnung, Erosivität, Destruktivität und Funktionseinschränkung des Gelenkbefalls, den Entzündungswerten, Daktylitis, Enthesitis, Haut- und Nagelbefall.

Neben Gewichtsreduktion, körperlicher Aktivität, physikalischer Therapie und Einstellung von Rauchen, haben NSAIDs und lokale Steroidinjektionen einen festen Stellenwert in der PsA-Therapie. In den spezifischen Therapie-Algorhythmen folgen nach cDMARDs (MTX, LEF, SSZ, CSA, Apremilast) und 1–2 Versuchen mit TNFα-Inhibitoren, IL-12/IL-23-Inhibitoren oder IL-17-Inhibitoren. Da letztere eine sehr gute Wirkung auf die Hautpsoriasis zeigen, werden bei PsA mit starkem Hautbefall IL-17-Inhibitoren durchaus auch vor TNF-Inhibitoren eingesetzt; andererseits sind IL-17-Inhibitoren bei anamnestischen Hinweisen auf entzündliche Darmerkrankungen eher kontraindiziert. TNFα-Inhibitoren wiederum sind kontraindiziert bei Herzinsuffizienz (> NYHA II), schweren Infekten, chronischen Lungenkrankheiten (COPD), und Hinweisen für demyelinisierende ZNS-Erkrankungen. Hier kommt Abatacept als Zweitlinientherapie In Betracht oder der Jak-1-Inhibitor Tofacitinib.

Kontaktdaten

Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 11.05.2020

Indikation gemäß Beratungsantrag

Non-pharmacologic therapies	• physical therapy, occupational therapy, smoking cessation, weight loss, massage therapy, exercise
Symptomatic treatments	• nonsteroidal anti-inflammatory drugs, glucocorticoids, local glucocorticoid injections
OSM	• methotrexate, sulfasalazine, cyclosporine, leflunomide, apremilast
TNFi	• etanercept, infliximab, adalimumab, golimumab, certolizumab pegol
IL12/23i	• ustekinumab
IL17i	• secukinumab, ixekizumab, brodalumab
CTLA4-Ig	• abatacept
JAK inhibitor	• tofacitinib

Tab.1. Übersicht der bei der PsA eingesetzten Arzneimittel (nach (4)).

Mehrere Kategorien von Arzneimitteln sind heute für die PsA zugelassen: cDMARDs, TNF-Inhibitoren, Interleukin-12/23-Inhibitoren, Interleukin-17-Inhibitoren, „cytotoxic T-lymphocyte-associated protein 4-immunoglobuline“ (CTLA4-Ig), und der Janus-Kinase-Inhibitor Tofacitinib. Allein innerhalb der beiden letzten Jahre wurden Abatacept, Ixekizumab, Brodalumab und Tofacitinib aufgrund günstiger Wirksamkeit- und Sicherheits-Parameter in klinischen Phase-III-Studien für die Behandlung der PsA zugelassen. (OSM = oral small molecules, entspricht unseren cDMARDs plus Apremilast, schließt aber nicht die small targeted molecules (tsDMARDs) der Jak/Stat-Inhibitoren ein).

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von “aktiver Psoriasis-Arthritis (PsA) bei erwachsenen Patienten, die unzureichend auf ein oder mehrere krankheitsmodifizierende Antirheumatika (DMARDs) angesprochen oder diese nicht vertragen haben“, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

1. Eine aktive PsA, die nicht auf cDMARDs anspricht soll rasch mit TNFα-Inhibitoren behandelt werden, vorausgesetzt es gibt keine Kontraindikation (Herzinsuffizienz, schwere Infekte, chronische Lungenkrankheit, chronische Hepatitis, v. a. demyelinisierende Erkrankung).
2. Bei aktiver PsA, die nicht auf einen TNF-Inhibitor anspricht kann ein zweiter TNF-Inhibitor versucht werden ggfs. kombiniert mit einem noch nicht erprobten cDMARD.
3. Eine aktive PsA sollte nach zwei erfolglosen TNF-Inhibitor-Therapieversuchen mit einem IL-17-Inhibitor behandelt werden, alternativ mit einem IL-12/IL-23-Inhibitor, insbesondere wenn eine Kontraindikation für IL-17-Inhibitoren besteht (z. B. v. a. IBD, Neigung zu Pilzinfekten).
4. Eine aktive PsA nach TNF-Versagen kann mit einem IL-17-Inhibitor behandelt werden, bei Kontra-indikationen für IL-17-Inhibitoren (hohe Infektanfälligkeit, IBD, Neigung zu Pilzinfekten) und bei Wunsch nach oraler Therapie kann der Jak-1-Inhibitor Tofacitinib versucht werden.
5. Eine aktive PsA mit starker Hautbeteiligung (> 10 % Body Surface Area, BSA) kann initial mit einem IL-17-Inhibitor behandelt werden, bei Therapieversagen kann ein anderer IL-17-Inhibitor versucht werden.

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Indikation gemäß Beratungsantrag

6. Bei aktiver PsA nach Versagen oder Kontraindikation von TNF-Inhibitor, cDMARD (inklusive Apremilast) und IL-17-Inhibitoren sind Versuche mit Abatacept, Tofacitinib oder neuen Substanzen indiziert, z. B. Guselkumab (Anti-p19 sub-unit von IL-23), Upadacitinib, Filgotinib (in Deutschland noch nicht auf dem Markt) (Jak-Inhibitoren).

Aus diesen Darlegungen wird deutlich welch breite medikamentöse Palette (mindestens 17 Substanzen) es bei der PsA/Ps zu berücksichtigen gilt und wie sehr ein individuelles therapeutisches Vorgehen erforderlich ist. Dieses orientiert sich einerseits an den Organ-Manifestationen der PsA/Ps, prognostischen Markern, Komorbiditäten, Wirkungen und Nebenwirkungen der Arzneimittel, sowie an bekannten Kontraindikationen einzelner Substanzen.

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Deutsche Dermatologische Gesellschaft

Indikation gemäß Beratungsantrag: Psoriasisarthritis

Was ist der Behandlungsstandard in der Behandlung der „aktiven Psoriasis-Arthritis (PsA) bei erwachsenen Patienten, die unzureichend auf ein oder mehrere krankheitsmodifizierende Antirheumatika (DMARDs) angesprochen oder diese nicht vertragen haben“?

TNF – alpha Antagonisten (Adalimumab, Certolizumab, Etanercept), anti-IL 17A Antikörper (Ixekizumab, Secukinumab) (Dressler et al.)

Untergeordnet sind im Bereich der Dermatologie noch Ustekinumab (siehe unten), Apremilast und Tofacitinib zu nennen.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von “aktiver Psoriasis-Arthritis (PsA) bei erwachsenen Patienten, die unzureichend auf ein oder mehrere krankheitsmodifizierende Antirheumatika (DMARDs) angesprochen oder diese nicht vertragen haben“, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

1) Ausmaß der Beteiligung der Haut (bevorzugte Auswahl eines Präparates mit guter Wirksamkeit an der Haut): TNF – alpha Antagonisten (Adalimumab, Certolizumab), anti-IL 17A Antikörper (Ixekizumab, Secukinumab 300 mg) (Sibidian et al.)

2) Unterscheidung nach Manifestationsorten der Psoriasis-Arthritis

a) peripher, b) axial, c) Dactylitis

TNF – alpha Antagonisten (Adalimumab, Certolizumab, Etanercept), anti-IL 17A Antikörper (Ixekizumab, Secukinumab)

Aktuell unzureichende Datenlage zur weiteren Bevorzugung eines Medikamentes, Behandlungsstandard für a), b), c) ident. (Dressler et al.)

d) Enthesitis: Aufgrund guter Datenlage: Ustekinumab (Araujo et al.)

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