Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-187-z Tofacitinib

Stand: September 2018

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

zur Behandlung der aktiven 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) Therapiehinweise: -Adalimumab (Beschluss vom 21. November 2006) -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:	
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.
Krankheitsmodifizierende Antirheumatika (DMARD)	
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).
Biologika	
TNF-alpha-Inhibitoren	
Etanercept L04AB01 Enbrel®	Psoriasis-Arthritis (Arthritis psoriatica) Behandlung der aktiven und progressiven Psoriasis-Arthritis bei Erwachsenen, wenn das Ansprechen auf eine vorhergehende Basistherapie unzureichend ist. Enbrel verbessert die körperliche Funktionsfähigkeit bei Patienten mit Psoriasis-Arthritis und reduziert das Fortschreiten der radiologisch nachweisbaren strukturellen Schädigungen der peripheren Gelenke bei Patienten mit polyartikulären symmetrischen Subtypen der Erkrankung.
Infliximab L04AB02 Remicade®/ Inflectra®	Psoriasis-Arthritis Remicade® ist indiziert zur Behandlung der aktiven und fortschreitenden Psoriasis-Arthritis bei erwachsenen Patienten, wenn deren Ansprechen auf eine vorhergehende krankheitsmodifizierende, antirheumatische Arzneimitteltherapie (DMARD-Therapie) unzureichend gewesen ist. Inflectra™ sollte verabreicht werden • in Kombination mit Methotrexat

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	• oder als Monotherapie bei Patienten, die eine Unverträglichkeit gegenüber Methotrexat zeigen oder bei denen Methotrexat kontraindiziert ist. Infliximab verbessert die körperliche Funktionsfähigkeit bei Patienten mit Psoriasis-Arthritis und reduziert die Progressionsrate peripherer Gelenkschaden, wie radiologisch bei Patienten mit polyartikularem symmetrischem Subtyp der Krankheit belegt wurde.
Adalimumab L04AB04 Humira®	Psoriasis-Arthritis Humira ist indiziert zur Behandlung der aktiven und progressiven Psoriasis-Arthritis (Arthritis psoriatica) bei Erwachsenen, die nur unzureichend auf eine vorherige Basistherapie angesprochen haben. Humira reduziert das Fortschreiten der radiologisch nachweisbaren strukturellen Schädigungen der peripheren Gelenke bei Patienten mit polyartikularen symmetrischen Subtypen der Erkrankung und verbessert die körperliche Funktionsfähigkeit.
Golimumab L04AB06 Simponi®	Psoriasis-Arthritis (PsA) Simponi ist zur Anwendung als Monotherapie oder in Kombination mit MTX zur Behandlung der aktiven und fortschreitenden Psoriasis-Arthritis bei Erwachsenen indiziert, wenn das Ansprechen auf eine vorhergehende Therapie mit krankheitsmodifizierenden Antirheumatika (DMARD) unzureichend gewesen ist. Simponi verringert nachweislich die Progressionsrate der peripheren Gelenkschäden, bestimmt anhand von Röntgenaufnahmen bei Patienten mit polyartikulären symmetrischen Subtypen der Erkrankung und verbessert die körperliche Funktionsfähigkeit.
Certolizumab Pegol L04AB05. Cimzia®	*Psoriasis-Arthritis* Cimzia ist in Kombination mit Methotrexat (MTX) für die Behandlung der aktiven Psoriasis-Arthritis bei Erwachsenen angezeigt, wenn das vorherige Ansprechen auf eine Therapie mit DMARDS ungenügend war. In Fällen von Unverträglichkeit gegenüber Methotrexat oder wenn die Fortsetzung der Behandlung mit Methotrexat ungeeignet ist, kann Cimzia als Monotherapie verabreicht werden.
PDE4-Hemmer	
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.
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.
Secukinumab L04AC10	Secukinumab, 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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Cosentyx®	gewesen ist.
Ixekizumab L04AC13 Taltz®	Ixekizumab, allein oder in Kombination mit Methotrexat, ist angezeigt für die Behandlung erwachsener Patienten mit aktiver Psoriasis-Arthritis, die unzureichend auf eine oder mehrere krankheitsmodifizierende Antirheumatika (DMARD) angesprochen oder diese nicht vertragen haben .
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.
Steroidale Antirheumatika (Glucokortikoide)	
Prednisolon H02AB06 generisch	• andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können: – Spondarthritiden (Spondylitis ankylosans mit Beteiligung peripherer Gelenke (DS b, c), Arthritis psoriatica (DS c, d), enteropathische Arthropathie mit hoher Entzündungsaktivität (DS a)
Prednison H02AB07 generisch	Andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können: – Spondarthritiden (Spondylitis ankylosans mit Beteiligung peripherer Gelenke (DS b, c), Arthritis psoriatica (DS c, d), enteropathische Arthropathie mit hoher Entzündungsaktivität (DS a)
Triamcinolon H02AB08 Volon®	Andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können: Spondarthritiden (Spondylitis ankylosans mit Beteiligung peripherer Gelenke, Arthritis psoriatica, enteropathische Arthropathie mit hoher Entzündungsaktivität);
Nichtsteroidale Antirheumatika (NSAR oder NSAID)	
z. B. Acemetacin M01AB11 generisch	Acemetacin 60 Heumann zusätzlich bei: – akuten Arthritiden (einschließlich Gichtanfall) – chronischen Arthritiden, insbesondere bei rheumatoider Arthritis (chronische Polyarthritis), (Acemetacin Heumann FI, Stand April 2015)

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

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: Psoriasis-Arthritis

Auftrag von:	Abt. AM
bearbeitet von:	Abt. FB Med
Datum:	05.03.2018

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation Psoriasis-Arthritis durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 15.02.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 392 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 27 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Behandlung von erwachsenen Patienten mit aktiver Psoriasis-Arthritis.

Berücksichtigte Wirkstoffe/Therapien:

Übersicht zVT, Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Abkürzungen:

AE	Adverse event
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DAHTA	Deutsche Agentur für Health Technology Assessment
DMARD	Disease-modifying antirheumatic drug
EULAR	European League Against Rheumatism
G-BA	Gemeinsamer Bundesausschuss
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MTX	Methotrexat
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drugs
PsA	Psoriasis Arthritis
PsARC	Psoriatic Arthritis Response Criteria
SAE	Serious adverse event
SIGN	Scottish Intercollegiate Guidelines Network
TNF	Tumor necrosis factor
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

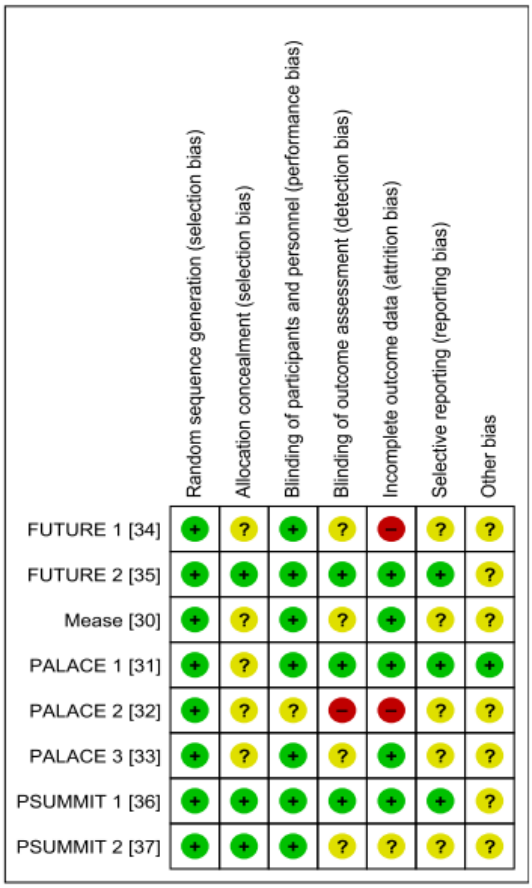
G-BA, 2016 [10]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Secukinumab vom 2. Juni 2016 *Siehe auch:* **IQWIG, 2016 [15].**	**Secukinumab** 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. *Zweckmäßige Vergleichstherapie:* ein TNF-alpha-Hemmer (Etanercept oder Adalimumab oder Infliximab oder Golimumab) ggf. in Kombination mit Methotrexat *Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:* Ein Zusatznutzen ist nicht belegt.
G-BA, 2015 [9]. 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 – Apremilast vom 6. August 2015 *Siehe auch:* **IQWiG, 2015 [14].**	**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. *Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie* Ein Zusatznutzen ist nicht belegt.
G-BA, 2006 [12]. Bekanntmachung des Beschlusses über eine Änderung der Arzneimittel-Richtlinie/AMR in	**Adalimumab (Humira®)** Bei Rheumatoider Arthritis und Psoriasis-Arthritis (Arthritis psoriatica), Empfehlungen zur wirtschaftlichen Verordnungsweise Beschluss vom: 21.11.2006; In Kraft getreten am: 12.07.2007 **Indikation** Adalimumab ist ein rekombinanter humaner monoklonaler

Anlage 4: Therapiehinweis zu Adalimumab	Antikörper. Adalimumab ist zugelassen zur Behandlung − der mäßigen bis schweren aktiven Rheumatoiden Arthritis bei Erwachsenen, die nur unzureichend auf krankheits-modifizierende Antirheumatika, einschließlich MTX, angesprochen haben, − der schweren, aktiven und progressiven Rheumatoiden Arthritis bei Erwachsenen, die zuvor nicht mit MTX behandelt wurden, − der aktiven und progressiven Psoriasis-Arthritis (Arthritis psoriatica) bei Erwachsenen, die nur unzureichend auf die vorherige Therapie mit krankheitsmodifizierenden Antirheumatika angesprochen haben, − der schweren aktiven ankylosierenden Spondylitis bei Erwachsenen, die nur unzureichend auf eine konventionelle Therapie angesprochen haben. … Die Behandlung mit TNF-alpha-Hemmern stellt dabei eine Alternative zur Reduktion der Symptomatik und Verbesserung der körperlichen Funktionsfähigkeit bei Patienten mit aktiver Rheumatoider Arthritis oder Arthritis psoriatica dar, wenn eine Therapie mit allen individuell indizierten DMARDs und deren Kombinationen, mindestens jedoch 2 einschließlich Methotrexat (MTX) - soweit keine Kontraindikationen dafür vorliegen - bis zur individuell angezeigten Höchstdosis (in der Regel 20 bis 25 mg pro Woche, ggf. als Injektion und ggf. Folsäure- bzw. Folinsäurepräparate), erfolglos geblieben ist. Diese müssen lange genug (in der Regel je nach DMARD mindestens jeweils 3 bis 6 Monate) in adäquater Dosis und unter fachlich kompetenter Überwachung eingesetzt worden sein. Für einen breiten Einsatz von Adalimumab als erstes DMARD bei neu diagnostizierter Rheumatoider Arthritis fehlen derzeit u. a. evaluierte prädiktive Faktoren für den Krankheits-verlauf, die eine ausreichend sichere Auswahl der Patienten mit schwerer progressiver Arthritis in frühen Krankheitsstadien ermöglichen würde. In der Regel ist die Primäranwendung daher bei der derzeitigen Studienlage nicht angezeigt. Bei seltenen individuellen Besonderheiten (Kontraindikationen gegen alle DMARDs oder hohe Krankheitsprogression) kann ein frühzeitiger Einsatz von TNF-alpha-Hemmern angemessen sein. Bei der Wahl eines TNF-alpha-Hemmers können aus medizinisch-therapeutischer Sicht aufgrund der derzeitigen Studienlage oder evidenzbasierter Leitlinien bei der Indikation Rheumatoide Arthritis keine allgemeinen Prioritäten gesetzt werden. Bei der Indikation Psoriasis-Arthritis ist der unterschiedliche Zulassungsstatus bzgl. der Hautmanifestation der Psoriasis zu beachten, insbesondere da die Zulassung von Etanercept und Infliximab die Anwendung bei Arthritis psoriatica und bei therapieresistenter mittelschwerer bis schwerer Plaque psoriasis abdeckt. Die voraussichtlichen Therapiekosten für das ausgewählte Präparat stellen damit bei Beginn einer TNF-alpha-Therapie den wesentlichen Gesichtspunkt bei der Produktwahl dar. Davon kann abgewichen werden, wenn individuelle klinische Faktoren (z.B. Neben- und Wechselwirkungen) bzw. die spezifischen Eigenschaften oder die Anwendungsmodalitäten des

	Arzneimittels eine nachvollziehbare Kontraindikation darstellen oder die bevorzugte Anwendung im Einzelfall begründen. Auch die Praxisausstattung (z.B. Lagerungsmöglichkeit für Infusionen und Nachüberwachung beim Einsatz von Infliximab) begründet keine unwirtschaftliche Produktwahl. Ein Ansprechen auf die Therapie ist bereits nach 1 bis 2 Wochen zu erwarten. Soweit auch nach 3 Monaten kein deutliches klinisches Ansprechen (klinische Symptomatik, DAS-Score, Labor) zu verzeichnen ist, ist die Therapie mit Adalimumab abzusetzen.
G-BA, 2007 [11]. Tragende Gründe zum Beschluss über eine Änderung der Arzneimittel-Richtlinie in Anlage 4: Therapiehinweis zu Leflunomid	**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.

Systematische Reviews

Kawalec P et al., 2018 [16]. Comparative effectiveness of abatacept, apremilast, secukinumab and ustekinumab treatment of psoriatic arthritis: a systematic review and network meta-analysis	1. 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.
	2. 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 **Endpunkt:** ACR20, ACR50, PASI75 (efficacy outcomes) and any AEs, SAEs, and withdrawals due to AEs **Recherche:** from inception to 07/2017 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 8 RCTs/k.A. **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.
	3. Ergebnisdarstellung 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

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);
  - (2) apremilast reduced the rate of withdrawal due to AEs in comparison with ustekinumab (*P* = 0.002);
  - (3) 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
	4. Anmerkungen/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., 2017 [23]. Relative efficacy and safety of apremilast, secukinumab, and ustekinumab for the treatment of psoriatic arthritis	1. Fragestellung To assess the relative efficacy and safety of apremilast, secukinumab, and ustekinumabat different doses in patients with active psoriatic arthritis (PsA).
	2. Methodik **Population:** patients with active PsA **Intervention:** apremilast, secukinumab, and ustekinumab **Komparator:** placebo **Endpunkt:** clinical efficacy with ACR20 and safety **Recherche:** 01/2017 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 8 RCTs/3289 patients **Qualitätsbewertung der Studien:** Jadad score
	3. Ergebnisdarstellung Qualität der Studien: Jadad scores of the studies were 3–4, which indicated a high quality study. Networkmeta-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 • there was no significant difference in the efficacy among the eight interventions. Networkmeta-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
	4. Anmerkungen/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 [8]. Treatment modifying factors of biologics for psoriatic arthritis: a systematic review and Bayesian meta-regression	1. Fragestellung The aim of this study was to explore factors that modify treatment effects of non-conventional biologics versus placebo in patients with psori- atic arthritis.
	2. 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 **Endpunkt:** 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:** from inception to 10/2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 12

	Qualitätsbewertung der Studien: Cochrane risk-of-bias tool
	3. Ergebnisdarstellung Qualität der Studien: The risk-of-bias assessment indicated that most included studies had a low risk of bias. 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
	4. Anmerkungen/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., 2017 [27]. Efficacy and safety of biologics targeting interleukin-6, -12/23 and -17 pathways for peripheral psoriatic arthritis: a network meta-analysis	1. Fragestellung To investigate the comparative efficacy, safety and tolerability of IL-6, IL-12/23 and IL-17 inhibitors for patients with active PsA.
	2. Methodik **Population:** patients with PsA **Intervention:** IL-6, IL-12/23 and IL-17 inhibitors **Komparator:** placebo **Endpunkt:** 20% or 50% improvement in ACR criteria reported as the primary or major secondary outcome at week 24. **Recherche:** 12/2016 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 6 RCTs /n=2411 participants **Qualitätsbewertung der Studien:** Cochrane Collaboration's tool
	3. Ergebnisdarstellung Qualität der Studien: The risk-of-bias assessment indicated that all included studies were of high quality. • 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)]
	4. Anmerkungen/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 [21]. Pharmacological treatment of psoriatic arthritis: a systematic literature review	1. Fragestellung *Update von Ash et al. 2012* 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.
	2. Methodik **Population:** adults with PsA

for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis	**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) **Suchzeitraum** (Aktualität der Recherche): 2010 – 12/2014 **Anzahl eingeschlossene Studien** (Gesamt): 17 **Qualitätsbewertung der Studien:** Risk of Bias Cochrane tool
	3. Ergebnisse Detaillierte Studiencharakteristika siehe Anhang: • 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 *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:

	<table><tr><th>Treatment arm vs PBO</th><th>ACR20 RR (95% CI)</th><th>ACR50 RR (95% CI)</th><th>ACR70 RR (95% CI)</th><th>PAIS75 RR (95% CI)</th><th>PASI90 RR (95% CI)</th></tr><tr><td>UST 90mg</td><td>2.17 (1.71; 2.76)</td><td>3.25 (2.14; 4.95)</td><td>4.63 (2.18; 9.82)</td><td>6.94 (3.79; 12.72)</td><td>11.85 (3.80; 36.93)</td></tr><tr><td>UST 45mg</td><td>1.95 (1.52; 2.50)</td><td>2.78 (1.81; 4.27)</td><td>3.90 (1.81; 8.39)</td><td>6.39 (3.46; 11.78)</td><td>8.00 (2.51; 25.51)</td></tr><tr><td>SEC 300mg</td><td>3.31 (2.04; 5.36)</td><td>4.90 (2.29; 10.50)</td><td>19.60 (2.68; 143.23)</td><td>3.90 (1.90; 7.98)</td><td>5.24 (1.96; 14.04)</td></tr><tr><td>SEC 150mg</td><td>5.82 (1.56; 21.71)</td><td>4.74 (3.08; 7.29)</td><td>11.14 (4.52; 27.44)</td><td>4.76 (1.92; 11.78)</td><td>6.62 (1.88; 23.30)</td></tr><tr><td>SEC 75mg</td><td>4.47 (0.66; 30.26)</td><td>3.59 (2.30; 5.61)</td><td>7.94 (3.18; 19.83)</td><td>3.75 (0.82; 17.06)</td><td>4.26 (0.40; 45.59)</td></tr><tr><td>APR 30mg</td><td>1.98 (1.64; 2.38)</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr><tr><td>APR 20mg</td><td>1.70 (1.40; 2.06)</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr></table>* 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 (eg, 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 diarrhoea, 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.
	4. 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. *5. 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-	1. Fragestellung This meta-analysisis aimed at 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.
	2. Methodik **Population**: patients with active PsA despite of DMARDs/NSAIDs or could not tolerate DMARDs/NSAIDs **Intervention:** targeted therapies **Komparator:** placebo **Endpunkt:** ACR20 **Suchzeitraum (Aktualität der Recherche):** up to 11/2014

modifying anti-rheumatic drugs or to non-steroidal anti-inflammatory drugs: A meta-analysis	**Anzahl eingeschlossene Studien** (Gesamt):12 **Qualitätsbewertung der Studien:** modified Jadad scale *Sonstige methodische Hinweise* • Bewertung der Homogenität der Studienergebnissse anhand der I^2-Statistik, Meta-analyse mittels Random effects model, • Indirekter Vergleich nach Bucher und Song
	3. Ergebnisdarstellung *Study characterstics* 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 All studies with Jadad score ≥3 • Substantial heterogeneity between all bDMARDs with respect to ACR20 (I^2= 72%) *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 (ACR Response rates for verum and placebo: → Anhang) *Indirect comparison (siehe Tabelle)* • 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

4. Anmerkungen/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.

5. Kommentare zum Review

- *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*
Wang J et al., 2016 [25]. A systematic review on the effcacy and safety of Infliximab in patients with psoriasis	1. 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.
	2. 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%. The adverse events were also observed during treatment **Suchzeitraum** (Aktualität der Recherche): bis 2014 **Anzahl eingeschlossene Studien** (Gesamt): 13 (davon 5 articles regarding the treatment of psoriasis arthritis (PsA) by infliximab) **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.
	3. Ergebnisdarstellung 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).

A Karanaugh[18]	Random Double-blinded	A	45 patients in placebo 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, 32 patients in placebo	16 weeks infliximab 5 mg/kg and placebo	ACR 20 efficiency	4

- The 5 research studies had clinical homogeneity and statistical homogeneity (x2=8.28, p=0.08).
- The results of metaanalysis 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)][18-22] (see Fig. 4).

4. 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 [7]. Risk of liver injury among methotrexate users: A meta-analysis of randomized controlled trials	1. Fragestellung To evaluate the relative risk and severity of liver disease among patients treated with methotrexate.
	2. Methodik **Population:** Adults with rheumatoid arthritis, psoriasis, psoriatic arthritis or inflammatory bowel disease **Intervention:** MTX **Komparator:** No MTX **Endpunkte** Liver adverse events **Suchzeitraum** (Aktualität der Recherche): April 2014 **Anzahl eingeschlossene Studien** (Gesamt): 32 including 1 RCT on PsA **Qualitätsbewertung der Studien:** Cochrane Risk of Bias tool
	3. Ergebnisdarstellung Qualitätsbewertung: low risk of bias in the included studies • 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)
	4. 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 [6]. 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	1. Fragestellung To evaluate the relative risk of pulmonary disease among patients with psoriasis, psoriatic arthritis, and inflammatory bowel disease treated with methotrexate.
	2. Methodik **Population:** Adults with rheumatoid arthritis, psoriasis, psoriatic arthritis or inflammatory bowel disease **Intervention:** MTX **Komparator:** No MTX **Endpunkte:** respiratory adverse events **Suchzeitraum** (Aktualität der Recherche): Jan 2014 **Anzahl eingeschlossene Studien** (Gesamt): 7 RCTs including 1 RCT on PsA **Qualitätsbewertung der Studien:** Cochrane Risk of Bias tool
	3. Ergebnisdarstellung Qualitätsbewertung: low risk of bias in the included studies • 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])

<table>
<tr><td></td><td>4. 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.</td></tr>
<tr><td rowspan="3">Lemos LL et al., 2014 [17].

Treatment of psoriatic arthritis with anti-TNF agents: a systematic review and meta-analysis of efficacy, effectiveness and safety</td><td>1. Fragestellung

To provide a comprehensive and up to date review on the efficacy and safety of the anti-TNF drugs adalimumab, etanercept, golimumab and infliximab used in active PsA. Additionally, to present results of observational studies aiming to reveal the results of these anti-TNFs in real life settings.</td></tr>
<tr><td>2. Methodik

Population: Patients with PsA older than 18 y
Intervention: anti-TNFs
Kontrolle: other anti-TNFs or controls
Endpunkte
• Improvements of 20, 50 and 70 % in the American College of Rheumatology (ACR) criteria;
• PsARC, the EULAR response, PASI70/75, DAS28, HAQ, SF-36, FACIT-F
• adverse events
Suchzeitraum (Aktualität der Recherche): from inception to 11/08/2013
Anzahl eingeschlossene Studien (Gesamt): 15 , davon 9 RCT, 6 Observationsstudien (davon waren 5 Registerstudien)
Qualitätsbewertung der Studien: methodological quality by modified Jadad Score (RCT) /Newcastle Ottawa scale (observational studies); risk of bias by Cochrane Risk of Bias Tool</td></tr>
<tr><td>3. Ergebnisdarstellung

Quality of studies based on Jadad sore: 7 RCT high quality, 2 RCT fair quality

Anti-TNF vs Placebo

ACR20 response
<table>
<tr><th>Comparison</th><th>Number of studies</th><th>Risk Ratio (95% CI)</th><th>I^2</th></tr>
<tr><td>Adalimumab vs Placebo</td><td>2 (n=413)</td><td>3.42 (2.08; 5.63)</td><td>38%</td></tr>
<tr><td>Etanercept vs Placebo</td><td>2 (n=265)</td><td>4.15 (2.71; 6.36)</td><td>0%</td></tr>
<tr><td>Golimumab vs Placebo</td><td>1 (n=259)</td><td>4.20 (2.51; 7.03)</td><td>n.a</td></tr>
<tr><td>Infliximab vs Placebo</td><td>3 (n=403)</td><td>3.50 (0.76;16.13)</td><td>96%</td></tr>
</table>
ACR50 response
<table>
<tr><th>Comparison</th><th>Number of studies</th><th>Risk Ratio (95% CI)</th><th>I^2</th></tr>
<tr><td>Adalimumab vs Placebo</td><td>2 (n=413)</td><td>10.02 (4.71; 21.28)</td><td>0%</td></tr>
<tr><td>Etanercept vs Placebo</td><td>2 (n=265)</td><td>9.12 (4.06; 20.49)</td><td>0%</td></tr>
<tr><td>Golimumab vs</td><td>1 (n=259)</td><td>6.81 (2.79; 16.62)</td><td>n.a.</td></tr>
</table></td></tr>
</table>

Placebo			
Infliximab vs Placebo	3 (n=414)	8.24 (0.85; 79.73	91%

ACR70 response

Comparison	Number of studies	Risk Ratio (95% CI)	I^2
Adalimumab vs Placebo	2 (n=413)	4.81(0.69; 33.42)	10%
Etanercept vs Placebo	2 (n=265)	14.75 (1.97;110.51)	0%
Golimumab vs Placebo	1 (n=259)	3.48 (0.77; 15.80)	n.a.
Infliximab vs Placebo	3 (n=414)	7.93 (1.24; 50.57)	71%

Direct comparison (1 RCT, n=100): ACR20

- Adalimumab vs infliximab: RR 0.92 (95%CI 0.69;1.23)
- Etanercept vs infliximab: RR 0.94 (95%CI 0.71;1.25)
- Adalimumab vs etanercept: RR 0.98 (95%CI 0.73; 1.32)

→ no stat. sign. difference

Safety

- no difference between anti-TNF and control in the occurrence of AEs and SAEs; analysis of AEs had substantial heterogeneity.
- Treatment discontinuation due to AEs was not different between anti-TNF and control groups, except for the subgroup of patients who used infliximab.

Subgroup analysis: Use of methotrexate

In most of the included studies, the concomitant use of MTX by patients in the anti-TNF group provided no additional benefit.

4. Anmerkungen/Fazit der Autoren

It was not possible to draw conclusions of efficacy differences between anti-TNF agents since the few studies comparing biologicals with each other were included, and in addition, these studies were not designed for such a purpose. All the same, the results suggest that there are no differences among the anti-TNF drugs and other factors should be taken into account in the choice of medication, such as costs and patient convenience, since these drugs have different dosing and schemes regimens and different routes of administration.

Coates LC et al., 2014 [4].

Systematic Review of Treatments for Psoriatic Arthritis: 2014 Update for the GRAPPA

Summary based

1. Fragestellung

To performed a systematic review of current literature on the efficacy of different therapies, management, and therapeutic strategies for PsA, in order to provide information for the development of the new GRAPPA treatment recommendations.

2. Methodik

Population: patients with PsA
Intervention: all therapies used in PsA: NSAID, DMARDs; biologics
Komparator: Included interventions
Endpunkte: Efficacy (e.g. ACR response, measures of enthesitis, dactylitis) safety

on: **Acosta Felquer ML et al., 2014 [1].** **Orbai AM et al., 2014 [20].** **Rose S et al., 2014 [22].**	**Suchzeitraum** (Aktualität der Recherche): up to February 2013/ March 2014 **Qualitätsbewertung der Studien:** k.A. Grading of the body evidence using GRADE
	3. Ergebnisdarstellung: **Summary** ***Peripheral arthritis (Acosta Felquer et al 2014)*.** Although nonsteroidal anti-inflammatory drugs (NSAID) have been commonly prescribed for peripheral arthritis, little new evidence supporting efficacy could be documented. However, new data were reported on traditional use of disease-modifying antirheumatic drugs (DMARD), specifically methotrexate (MTX), where results from 2 RCT suggested its potential efficacy. Limited data from observational and open-label studies provide additional lower-level evidence for the efficacy of MTX, leflunomide, and cyclosporine in PsA. Higher levels of evidence support the use of anti-tumor necrosis factor (TNF) agents in PsA. Statistically significant improvements in measures of joint disease were demonstrated with etanercept, adalimumab, infliximab, golimumab, and certolizumab pegol compared with placebo, although effect sizes were not always available. Other biological DMARD, specifically ustekinumab, abatacept, brodalumab, and secukinumab, also demonstrated statistically significant improvements compared to placebo. Apremilast, a small molecule that specifically inhibits phosphodiesterase 4, was superior to placebo in a series of 4 Phase III studies. Results with combination therapies were also reported, particularly MTX in combination with anti-TNF therapies and other biologics in trials without placebo controls. (siehe Tab.)

Table 1. Effect size and number needed to treat (NNT) in controlled trials in patients with psoriatic arthritis.

	MTX[9]	CSA[19]	LFN[17]	ADA[28]	ADA[23] ADEPT	ADA[29]	ETA[20]	INF[31] IMPACT	INF[20] IMPACT 2	GOL[24]	CZP[27]	UST[39]	ABAT[39]	Apremilast[52]
Patients (n) on treatment/ control	16/19	38/34	95/91	51/49	151/ 162	58/55	101/ 104	52/52	100/ 100	146/ 113	138/ 136	76/70	40/42	67/68
Mean dose	10 mg / wIM	2.5–4 mg/k/d	20 mg /d	40 mg eow	40 mg eow	40 mg eow	25 mg biw	5 mg/kg	5 mg /kg	50 mg/mo	200 q2w	90 mg qw	10 mg/kg	20 mg bid, 40 mg qd
Comparator	NSAID	PBO	PBO	PBO	PBO	CSA 2.5–3.75 mg/kg/d +ADA	PBO	PBO	PBO	PBO	PBO	PBO	PBO	PBO
Followup, weeks	24	48	24	12	24	48	24	16	24	24	24	12	24	12
Tender joint score, ES			0.22											
Swollen joint score, ES			0.17											
Pain, VAS; ES	–0.15	0.26		0.64	0.94			1.74	1.96					
HAQ, ES		–0.18	0.29	0.49	0.67			0.87	1.17	0.65		0.65		
Tender joint count, 0–78; ES				0.25				1.14	1.14					
Swollen joint count, 0–76; ES	0.33	0.13		0.3				1.17	0.81					
ACR20, NNT				5	3		3	2	3	3	3	4	4	4 bid 5 qd
PsARC, NNT			4			10								
Primary endpoint	Tender Joint Index (Ritchie)		PsARC	ACR20 wk 12	ACR20 wk 12 and x-ray	PsARC 12 mo	ACR20 wk 12	ACR20 wk 16	ACR20 wk 14 and vdH-S wk 24	ACR20 wk 14	ACR20 wk 12 and x-ray	ACR20 wk 12	ACR20 day 169	ACR20 wk 12

MTX: methotrexate; CSA: cyclosporine; LFN: leflunomide; ADA: adalimumab; ETA: etanercept, INF: infliximab; GOL: golimumab; CZP: certolizumab pegol; UST: ustekinumab; ABAT: abatacept; ES: effect size; NNT: number needed to treat; ACR20: American College of Rheumatology 20% response; PsARC: Psoriatic Arthritis Response Criteria; VAS: visual analog scale; vdH-S Sharp/van der Heijde score; eow: every other week; biw: twice weekly; q2w: every 2 weeks; q4w: every 4 weeks; bid: twice/daily; qd : once daily.

Axial disease (Nash et al. 2014)

Scant data are available on traditional therapies for axial disease in PsA (e.g., NSAID, MTX, etc.), but limited new data are available for targeted biologics and novel agents. Although improvement in axial disease is not often specified as an endpoint, significant benefits have been noted in RCT of anti-TNF therapies in AS, psoriasis, and PsA, particularly regarding disease activity, range of motion, physical function, and quality of life, both as monotherapy and in combination with other DMARD. Other biologics (e.g., ustekinumab, brodalumab) have reported some success in axial PsA in small open-label studies.

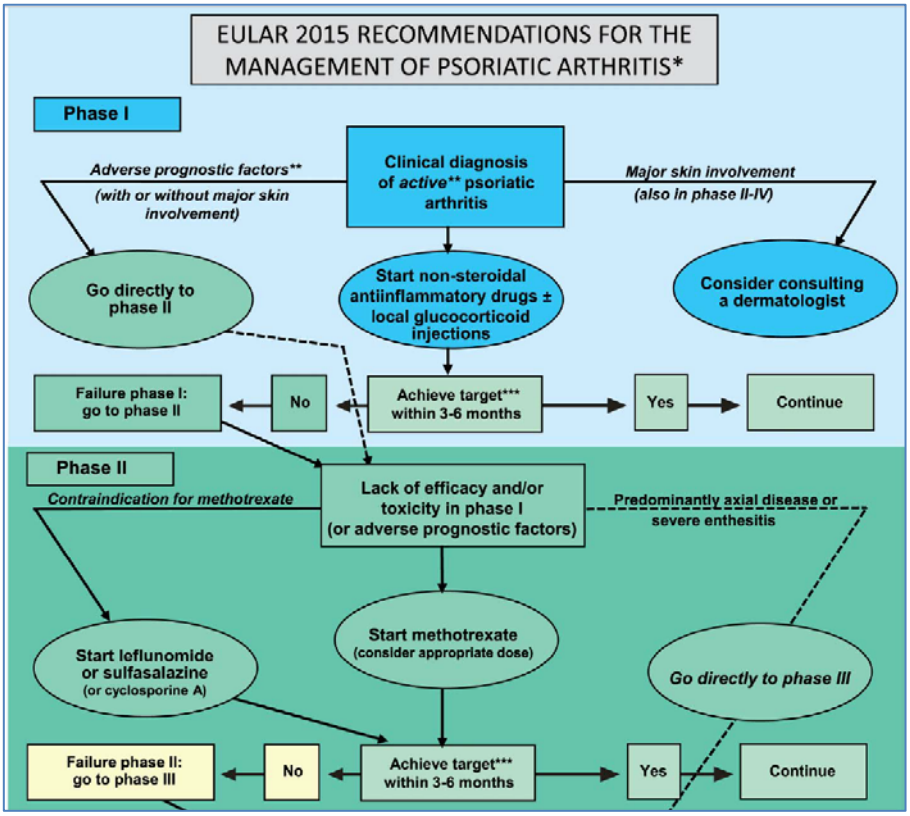
Enthesitis (Orbai et al 2014): 12 studies

Effectiveness of Various Agents for Enthesitis in PsA (level of evidence).

	• Effective (1b): Infliximab; golimumab; certolizumab; ustekinumab; apremilast (30 mg twice daily). • Not effective (1b): Sulfasalazine (2 g daily). • Not adequately studied: Adalimumab; other disease-modifying antirheumatic drugs (including methotrexate); nonsteroidal antiinflammatory drugs; physiotherapy. ***Dactylitis (Rose, et al 2014): 29 studies*** Traditionally, NSAID, local corticosteroid injections, and DMARD have been used to treat dactylitis. In this review, the authors found large variabilities in study designs, outcome measures, and availability of primary data. However, significant improvements in dactylitis were observed with the use of ustekinumab, certolizumab, and infliximab. One etanercept study demonstrated improvementin dactylitis scores, but a placebo-controlled trial is required that targets dactylitis as an endpoint. The role of anakinra remains uncertain.
	4. Fazit/Anmerkungen der Autoren Treatment recommendations from GRAPPA will follow, based on this systematic assessment of the literature. *5. Kommentare zum Review* • *Bewertung der internen Validität (Risk of Bias) der Primärstudien unklar Aktualisierte GRAPPA-Leitlinie: Siehe Coates et al. 2016 [3]*

Leitlinien

Gossec L et al., 2016 [13]. **EULAR** European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update.	Fragestellung/Zielsetzung: 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: Update der LL-Version 2012 – Evidence- und consens-based process – Task Force: 34 persons from 14 European countries: 27 rheumatologists, 3 people affected with PsA, 2 health professionals, 1 dermatologist and 1 rheumatologist) – 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]) – 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 – The Task Force members were provided with the category of evidence and grade of recommendation for each item. – 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 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 *Abbreviation: bDMARD biological DMARD; cs DMARD conventional synthetic DMARD, such as MTX, sulfasaline or leflunomide* 1. 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) 2. In patients with PsA, NSAIDs may be used to relieve musculoskeletal signs and symptoms (1b; A) 3. 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 manifestations[a], csDMARDs should be considered[b] at an early stage[a,] with methotrexate preferred in those with relevant skin involvement[b] (a: 3; B/ b:1b; B) 4. 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) 5. 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) 6. 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) 7. 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) 8. 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) 9. 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) 10. In patients who fail to respond adequately to a bDMARD, switching to another bDMARD should be considered, including switching between TNF inhibitors. (1b; B) 

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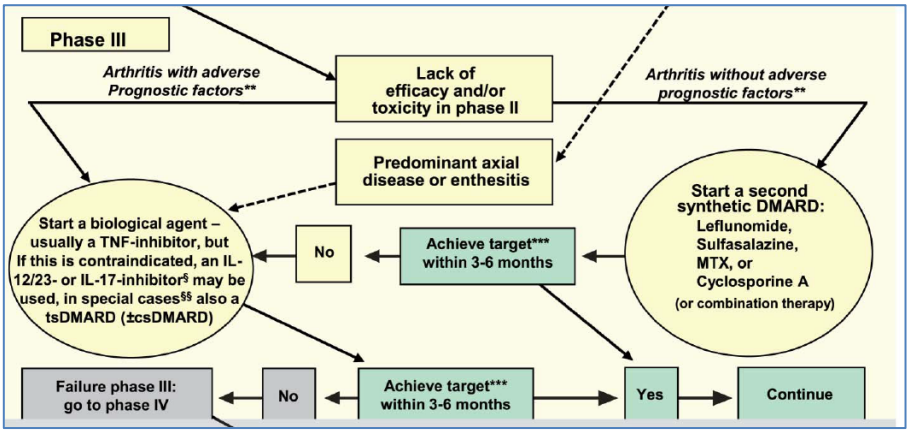
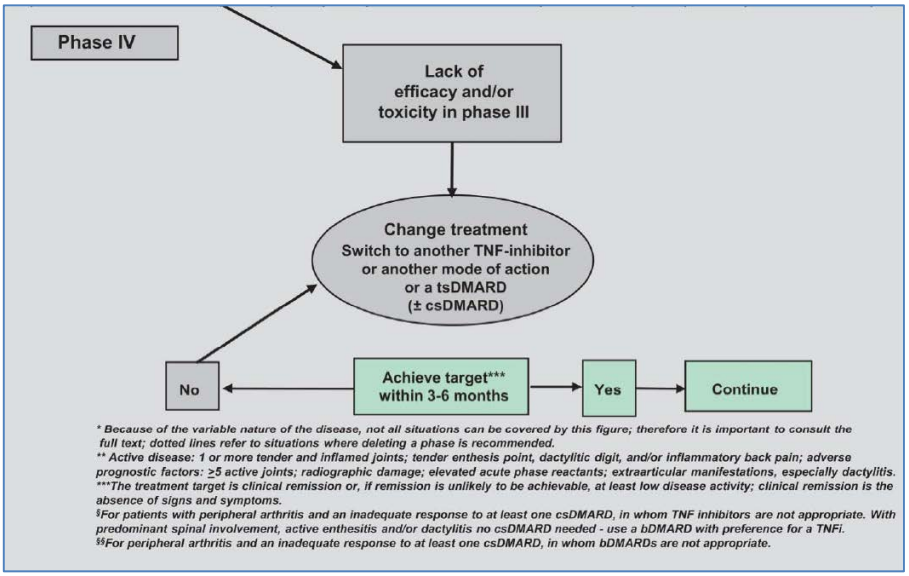
<tr><td></td><td> 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<tr><td>Coates LC et al., 2016 [3].

GRAPPA

Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis</td><td>Fragestellung/Zielsetzung

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).</td></tr>
<tr><td></td><td>Methodik

Grundlage der Leitlinie:

• 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).
• the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was applied
• GRAPPA rheumatologists, dermatologists, and PsA patients drafted recommendations
• recommendations were critically reviewed and edited via in-person discussion and online survey.

Sonstige methodische Hinweise:

• Bewertung der internen Validität der Einzelstudien unklar
• Konsensprozess unklar
• Z.T. keine eindeutige Zuordnung der zugrundeliegenden Evidenz zu den Empfehlungen</td></tr>
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Table 2. Summary of GRADE recommendations for PsA therapies, by disease domain*

Indication	Recommended (strong)	Recommended (conditional)	Not recommended (strong)	No recommendations due to lack of evidence
Peripheral arthritis, DMARD-naive	DMARDs (MTX, SSZ, LEF), TNFi	NSAIDs, oral CS, IA CS, *PDE-4i*		IL-12/23i, IL-17i
Peripheral arthritis, inadequate response to DMARDs	TNFi, IL-12/23i, PDE-4i	NSAIDs, oral CS, IA CS, *IL-17i*		
Peripheral arthritis, inadequate response to biologic treatment	TNFi	NSAIDs, oral CS, IA CS, IL-12/23i, *IL-17i*, PDE-4i		
Axial PsA, biologic-naive†	NSAIDs, physiotherapy, simple analgesia, TNFi	*IL-17i*, SI joint CS injections, bisphosphonates, [*IL-12/23i*]	DMARDs, IL-6i, CD20i	
Axial PsA, inadequate response to biologic treatment†	Physiotherapy, simple analgesia	NSAIDs, TNFi, *IL-12/23i, IL-17i*		
Enthesitis	TNFi, IL-12/23i	NSAIDs, physiotherapy, CS injections (with extreme caution since injecting CS in weight-bearing entheseal sites can lead to rupture of entheses), *PDE-4i*, *IL-17i*		DMARDs
Dactylitis	TNFi (infliximab, adalimumab, golimumab, CZP)	CS injections, DMARDs (MTX, SSZ, LEF), TNFi (etan.), IL-12/23i, *IL-17i*, *PDE-4i*		
Psoriasis (plaque)	Topical therapies, phototherapy, DMARDs (MTX, LEF, CSA), TNFi, IL-12/23i, IL-17i, PDE-4i			
Nail psoriasis	TNFi, IL-12/23i	Topical therapies, procedural therapies, DMARDs (CSA, LEF, acitretin, MTX), IL-17i, *PDE-4i*		

* Italicized text signifies conditional recommendations for drugs without current regulatory approvals or for which recommendations are based on data published in abstract form only; italicized text in brackets signifies conditional recommendations based only on data from a small open-label proof-of-concept trial, published in abstract form only. GRADE = Grading of Recommendations, Assessment, Development and Evaluation; PsA = psoriatic arthritis; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; SSZ = sulfasalazine; LEF = leflunomide; TNFi = tumor necrosis factor inhibitor; NSAIDs = nonsteroidal antiinflammatory drugs; CS = corticosteroids; IA = intraarticular; PDE-4i = phosphodiesterase 4 inhibitor (apremilast); IL-12/23i = interleukin-12/23 inhibitor; SI = sacroiliac; CZP = certolizumab pegol; etan. = etanercept; CSA = cyclosporin A.
† Based on ankylosing spondylitis literature.

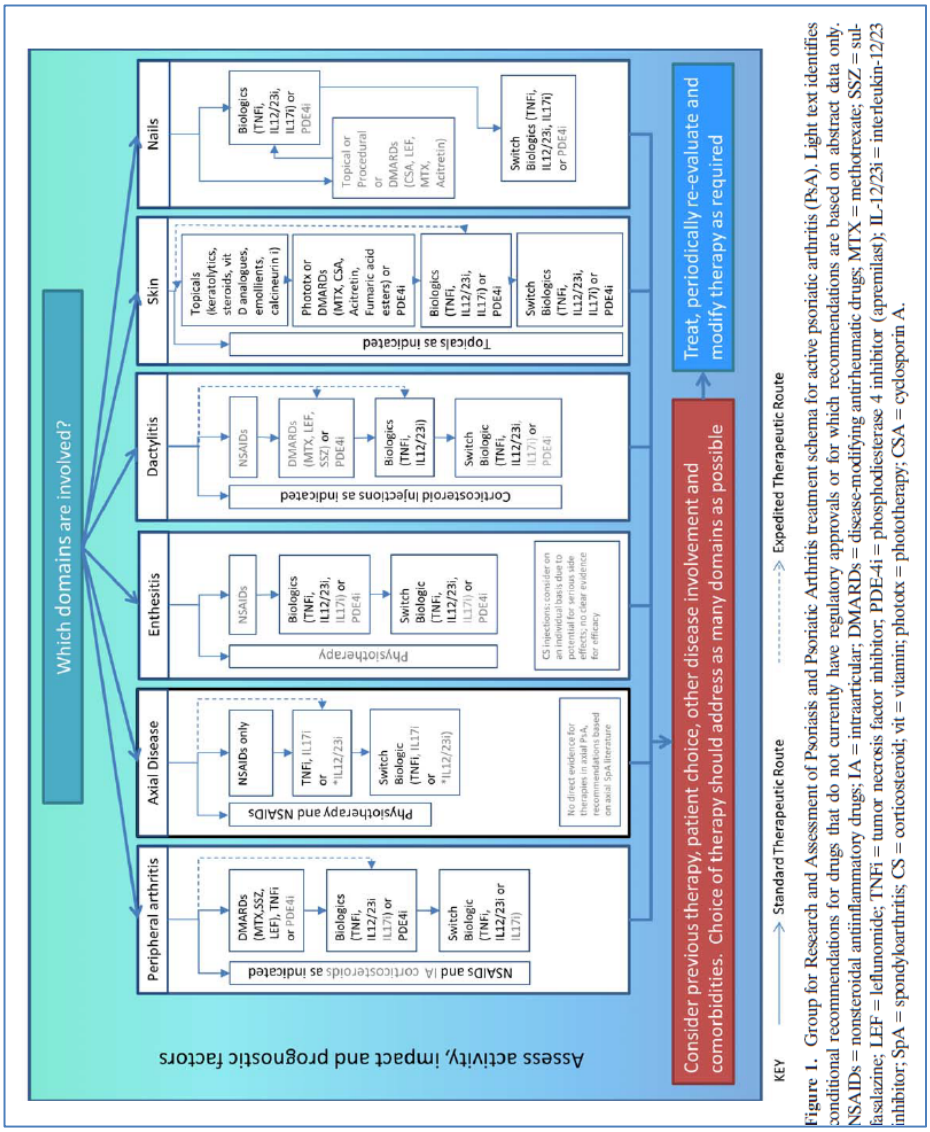


Figure 1. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis treatment schema for active psoriatic arthritis (PsA). Light text identifies conditional recommendations for drugs that do not currently have regulatory approvals or for which recommendations are based on abstract data only. NSAIDs = nonsteroidal antiinflammatory drugs; IA = intraarticular; DMARDs = disease-modifying antirheumatic drugs; MTX = methotrexate; SSZ = sulfasalazine; LEF = leflunomide; TNFi = tumor necrosis factor inhibitor; PDE4i = phosphodiesterase 4 inhibitor (apremilast); IL-12/23i = interleukin-12/23 inhibitor; SpA = spondyloarthritis; CS = corticosteroid; vit = vitamin; phototx = phototherapy; CSA = cyclosporin A.

<u>Peripheral Arthritis</u>

- 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.

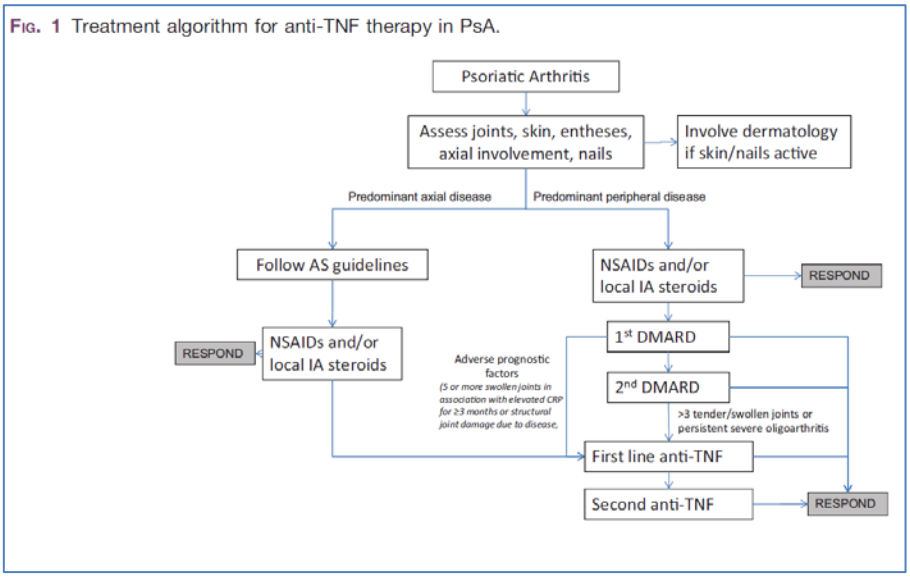
32. Sakkas LI, Alexiou I, Simopoulou T, Vlychou M. Enthesitis in psoriatic arthritis. Semin Arthritis

	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 <u>Dactylitis.</u> • 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 <u>Skin disease</u> • 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. <u>Nail disease.</u> • 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.
Coates LC et al., 2013 [5]. The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics	Guideline of British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) Fragestellung: The guidelines cover adult patients with PsA affecting all domains of psoriatic disease. They provide a stepwise management plan giving clear advice on treatment, including inclusion/exclusion criteria for treatment, monitoring requirements and how to quantify response to biologics. They provide evidence-based advice for the use of anti-TNF therapies in difficult situations, including pregnancy and significant comorbidities. A review on the use of conventional DMARDs prior to the use of anti-TNF therapies was not undertaken.
	Methodik Grundlage der Leitlinie – developed by a multidisciplinary working party set up by the British Society for Rheumatology (BSR), including rheumatologists, a dermatologist, specialist nurses and a patient representative. – CoI fully declared – systematic literature search, including electronic bibliographic databases (Medline and Embase) and systematic review databases (Cochrane) up to 1 July 2011. – Consensus agreement: Following evaluation of the literature, draft guidelines were developed by the working party for presentation at the BSR Annual Meeting in 2011 and 2012. Comments from the wider rheumatology community were invited via the BSR website and were incorporated into later drafts. Final draft guidelines were circulated to all members of the working party for a vote on levels of agreement with each recommendation. Voting was performed anonymously, with possible levels of agreement ranging from 0 (total disagreement) to 10 (total agreement). Results of this vote are included with each specific recommendation. **LoE:** The literature was reviewed and the quality of evidence was graded by the working party according to the Royal College of Physicians' Concise Guidance to Good Practice. **GoR**: (i) Grade A: meta-analysis of RCTs or an RCT. (ii) Grade B: controlled trial or quasi-experimental study or descriptive study. (iii) Grade C: expert committee recommendation. *Sonstige methodische Hinweise* Keine eindeutige Zuordnung der zugrundeliegenden Evidenz zu den

	Empfehlungen
	Empfehlungen <u>Peripheral arthritis</u> • Anti-TNF therapy should be considered for those patients with active arthritis (defined as at least three tender and three swollen joints) who have failed treatment with at least two conventional DMARDs*. Anti-TNF therapy may be considered for patients who have failed only one DMARD especially where there is evidence of adverse prognostic factors**. (*LoE: Grade A*) • All of the licensed anti-TNF therapies are recommended for use in patients eligible for treatment and choice of therapy should be left to the treating physician after considering concomitant medical problems, patients preference and cost effectiveness. For patients requiring rapid control of skin psoriasis an anti-TNF monoclonal antibody is preferred in accordance with the British Association of Dermatology (BAD) guidelines. (*LoE: Grade A*). • Anti-TNF therapies should be continued in patients who have responded after 3 months of treatment. In the case of non-responders, consideration should be given to a further 12 weeks of therapy if there has been a partial response and then continuing therapy if there has been a full response compared with baseline (LOE: Grade B). • Anti-TNF therapies should be considered in patients with severe persistent oligoarthritis (fewer than three tender/swollen joints), which has a major demonstrable influence on well-being and who have failed treatment with at least two conventional DMARDs and appropriate intra-articular therapy (LOE: Grade C). ** An adequate therapeutic trial is defined either as failure to tolerate a DMARD or active disease despite treatment of at least 12 weeks at target therapeutic dose of a conventional DMARD e.g. leflunomide, methotrexate, sulfasalazine, ciclosporin* *** adverse prognostic factors defined as 5 or more swollen joints with elevated C-reactive protein (CRP) persisting for more than three months, and/or structural joint damage due to disease, and/or previous use of systemic corticosteroids.* <u>Axial disease</u> • Anti-TNF therapy should be considered for those patients with active axial PsA according to the 2010 update of the Assessment of SpondyloArthritis international Society (ASAS)/ European League Against Rheumatism (EULAR) recommendations for the management of AS (LOE: Grade A) <u>Safety—infections</u> • Anti-TNF therapy should not be initiated or continued in the presence of serious active infection, but can be recommenced once the infection

	has resolved clinically (LOE: Grade B). • Anti-TNF therapy should be used with caution in patients at high infection risk after discussing the relative risks and benefits (LOE: Grade C). • Patients on anti-TNF therapy should be informed of appropriate food hygiene. Patients should also be advised to avoid eating foods that contain unpasteurized milk, uncooked eggs or raw meat (LOE: Grade C). • There should be a high index of suspicion for the possibility of atypical or opportunistic infections and treatment should be stopped and advice sought in suspected cases (LOE: Grade B). <u>Safety—tuberculosis</u> • Prior to starting treatment with anti-TNF therapy, all patients should be screened for mycobacterial infection in accordance with the latest national guidelines. Active mycobacterial infection should be adequately treated before anti-TNF therapy is started. Prior to starting anti-TNF therapy, prophylactic anti-tuberculosis • (TB) therapy (as directed by the latest national guidelines) should be given to patients with evidence of potential latent disease (LOE: Grade B). • Physicians should be vigilant for the development of mycobacterial infections throughout treatment with anti-TNF and for at least 6 months after discontinuation (LOE: Grade C). • If patients develop evidence of mycobacterial infection while on anti-TNF therapy, they should receive a full course of anti-mycobacterial chemotherapy— the anti-TNF therapy may be continued during this time if clinically indicated (LOE: Grade C). <u>Safety—HIV and hepatitis</u> • Patients at risk should be screened for HIV, HBV and HCV prior to anti-TNF therapy (LOE: Grade C). • HIV or HCV infection should not preclude treatment with anti-TNF therapy, although treatment should only be commenced in those with well-controlled disease and with appropriate monitoring under the care of a hepatologist or HIV specialist (LOE: Grade B). • Anti-TNF therapy in those with chronic HBV should be approached with caution given the potential risk of reactivation and fulminant hepatitis. Anti-TNF therapy should only be commenced in those with well-controlled disease, with appropriate antiviral treatment and regular monitoring in collaboration with a hepatologist. Consideration should be given to vaccinating those at risk of HBV prior to treatment (LOE: Grade C).

	
Wendling D et al., 2014 [26]. Recommendations of the French Society for Rheumatology (SFR) on the everyday management of patients with spondyloarthritis	Guidelines of the French Society for Rheumatology (SFR): Development of practice guidelines for spondyloarthritis spondyloarthritis (including psoriatic arthritis)
	Methodik Grundlage der LL – Update and French adaptation of existing recommendations issued by the ASAS/EULAR and ASAS (Assessment in Spondyloarthritis International Society) – Funding: SFR participated in organizing the task force meeting and contributed to the publication and translation costs – Systematic literature review: o Search in Medline, Cochrane, Embase: Jan 2010 – Jun 2013; manual search in conference proceedings o level of evidence of each publication was assessed – Presentation of the literature review data, discussion among experts, and development of the practice guidelines during conference of interdisciplinary expert group **LoE/ GoR** The strength of the practice guidelines (based on the level of evidence) and the level of agreement among experts (rated from 0 [strongly disagrees] to 10 [strongly agrees]) are given for each practice guideline. Strength was graded according to standard practice: • A: guideline based on level 1 evidence (meta-analysis of RCTs or at least 1 RCT); • B: guideline based on level 2 evidence (at least 1 non-RCT or quasi-experimental study) or extrapolated from level 1 evidence; • C: guideline based on level 3 evidence (descriptive study) or extrapolated from level 1 or 2 evidence; D: guideline based on level 4 evidence (expert opinion) or extrapolated from

	level 1, 2, or 3 evidence.
	Empfehlungen **…7.4. Treatment with conventional medications** 15) In the absence of contraindications, NSAIDs constitute the first-line pharmacological treatment of symptomatic spondyloarthritis(A) (10). In most patients, NSAID therapy effectively controls the jointsymptoms and signs of spondyloarthritis [39,40]. NSAIDs havenon-significant effects on laboratory markers for inflammation[39]; in contrast, various results suggest a beneficial effect onaxial structural damage [41]. When NSAIDs are contraindicated,analgesics and physical therapy should be given preference to thefirst-line treatment. The response to a given NSAID varies across individuals, and several NSAIDs should therefore be tried beforeconcluding that this drug class is not effective. 16) The NSAID regimen should be tailored to each individualpatient, and the lowest dosage and duration ensuring symptomcontrol should be used. When selecting the NSAID, the risks ofadverse cardiovascular, gastrointestinal, and renal effects shouldbe among the factors taken into consideration (C) (9,7). Before initiating NSAID therapy, the cardiovascular, gastroin-testinal, and renal risk factors should be assessed. The risk profilevaries across NSAIDs and, consequently, the presence of spe-cific patient characteristics should be taken into account whenselecting the NSAID. For instance, a COX2 inhibitor should begiven preference in patients with gastrointestinal risk factors andnaproxen in those with cardiovascular risk factors. All patientsshould be monitored carefully and regularly for adverse effects.Given the risks associated with continuous full-dose NSAID ther-apy, the lowest dose that ensures disease control should be sought[42,43]. 17) Analgesics can be used in patients with residual pain despiteNSAID therapy and in patients with failure of, contraindications to, or intolerance to NSAIDs (D) (9,8). No data on analgesic treatments in spondyloarthritis have beenpublished recently [44]. 18) Local glucocorticoid injections at symptomatic sites (mostnotably sites of arthritis or enthesitis) can be considered (D) (9,8). The evidentiary basis for this guideline is described in theprevious recommendations. The only recent data come from anon-randomized study comparing locally injected betamethasone(n = 7) to locally injected etanercept in patients with refractoryenthesitis. Significant improvements occurred in both groups withno significant between group difference after 12 weeks [45]. 19) In general, systemic glucocorticoid therapy is not warran-ted for treating the axial manifestations of spondyloarthritis(D) (9,7). Given the numerous and potentially severe adverse effects ofsystemic glucocorticoid therapy, together with the paucity ofpublished data, this treatment is not warranted for the axialmanifestations of spondyloarthritis. The only therapeutic trialof systemic glucocorticoid therapy included a limited numberof patients (n = 39) who had an inadequate response to NSAIDtherapy; in addition, the trial evaluated high dosages (50 mg/dversus 20 mg/d versus placebo) [46] given for only 2 weeks. Conse-quently, the improvements recorded with the higher

dose cannotbe construed as supporting the widespread use of this treat-ment. However, systemic glucocorticoid therapy may deserveconsideration when the peripheral joint manifestations are notsatisfactorily controlled, in the absence of effective or feasi-ble treatment options (e.g., in patients with contraindicationsto TNF _ antagonist therapy) or in unusual situations (e.g., flareassociated with inflammatory bowel disease). In these cases,the lowest possible dosage of systemic glucocorticoid must beused.

20) To date, there is no indication for conventional disease-modifying antirheumatic drugs ([DMARDs], methotrexate, leflunomide, and sulfasalazine) to treat isolated axial manifesta-tions or enthesitis (C) (9,3).

Since the publication of the previous recommendations, nostudies have produced evidence that conventional DMARDs areeffective on the axial manifestations. For methotrexate, a Cochranereview published in 2013 [47] found no new studies since 2007.Two randomized trials from Germany compared etanercept andsulfasalazine in patients with axial spondyloarthritis [48–50];etanercept was superior over sulfasalazine for the various out-come measures studied (ASAS20, ASAS 40, and partial remission).The absence of a placebo group precluded an evaluation of theeffects of sulfasalazine.

21) The use of conventional DMARDs (methotrexate, leflunomide,and sulfasalazine) can be considered in patients with peripheralarthritis that fails to respond to symptomatic therapy (D) (9,8).

There is little or no scientific evidence on this point [51,52].Nevertheless, clinical experience supports a beneficial effect of conventional DMARDs (methotrexate, leflunomide, and sul-fasalazine), whose use can be considered in patients with peripheral arthritis that is inadequately controlled by NSAIDs and/or local glucocorticoid injections. The DMARD should be selected on a case-by-case basis, according to the patient's pro-file. For instance, preference should be given to methotrexate in patients with cutaneous psoriasis. In France, leflunomide andmethotrexate are licensed for use in psoriatic arthritis. No stud-ies have assessed the potential structural effects of conventionalDMARDs on peripheral joints. Some conventional DMARDs (sulasalazine, methotrexate) may also improve the extraarticular manifestations (uveitis, bowel disease). Experts agree that con-ventional DMARDs are not indicated in patients with isolate dentheseal involvement, a situation about which no scientific evidence is available [5,7,8].

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… 7.5. Biologic agents

22) TNF alpha antagonist therapy should be offered to patients with persistent disease activity despite conventional treatment, according to the recommendations shown in Fig. 1 (D) (9,8).

All the TNF alpha antagonists available to date for use in spondyloarthritis have been proven effective in various forms of the disease [17,57–59]. TNFalpha antagonist therapy improved the symptoms and signs of spondyloarthritis, quality of life, productivity, and bone mineral density. The safety profile of TNF alpha antagonists in spondyloarthritis is similar to the overall safety profile of these drugs [10,53]. It is worth noting that some patients may experience paradoxical effects [57], defined as the occurrence during TNF alpha antagonist therapy of manifestations that are among the indications for TNF alpha antagonists (e.g., uveitis, psoriasis, or denovo Crohn's disease at a time when the rheumatic manifestations of spondyloarthritis are well controlled by TNF alpha antagonist therapy).

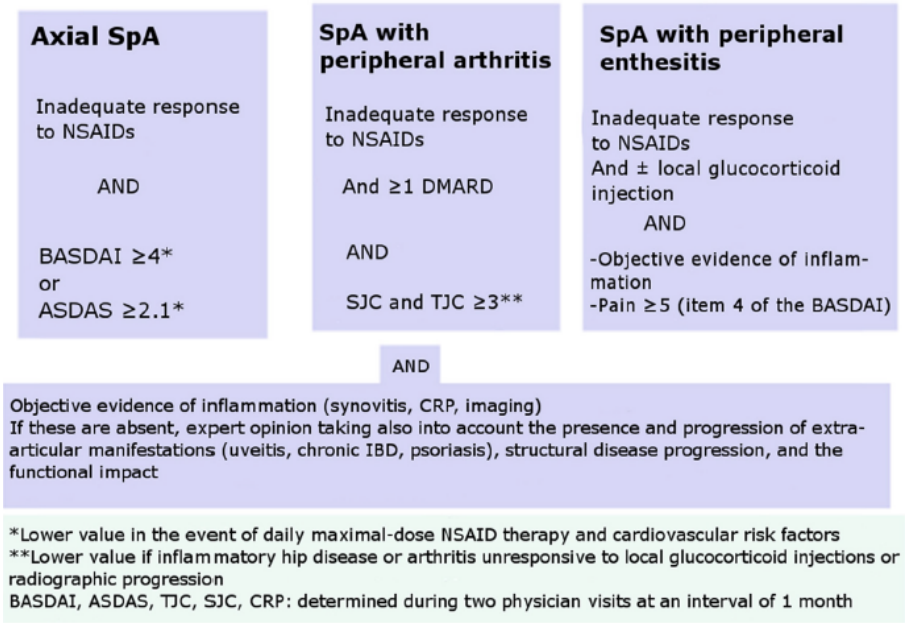

Fig. 1. Indications for TNFα antagonist therapy.

[...]

24) In the event of primary or secondary lack of effectiveness of a TNF alpha antagonist, there is no proof to date that increasing the dosage is beneficial. After reappraising the diagnosis of spondy-loarthritis and ruling out a differential diagnosis or complication of the disease, a switch to another TNF alpha antagonist deserves consideration (D) (9,7).

Switching to a second TNF alpha antagonist may be beneficial, in particular in the event of escape phenomenon, primary ineffectiveness, or intolerance to a first TNF alpha antagonist (C) (9,7).
[...]

26) There is no evidence to support differences across TNF alpha antagonists regarding effectiveness on the axial or peripheral manifestations/enthesitis. In patients with chronic inflammatory bowel disease (IBD), there is a difference in effectiveness on the gastrointestinal manifestations, which should be taken into account. (D) (9.7).

27) There is no evidence to date to support the use of biological agents other than TNF alpha antagonists in patients with axial spondyloarthritis (D) (9,6).

In patients who fail treatment with conventional DMARDs and TNFalpha antagonists, no treatment options exist [74]. Abatacept has not been proven effective [75]; rituximab is not effective inpatients having failed TNF alpha antagonist therapy and remains to be evaluated in biotherapy-naive patients with peripheral joint manifestations [76–78]. Retrospective data on IL-6-antagonists are inconclusive [79] and controlled studies show no effect [80].Options currently under investigation for spondyloarthritis and psoriatic arthritis include the anti-IL-17 secukinumab [81,82], the anti-IL-23 ustekinumab [83], and apremilast [84,85]. Ustekinumab(anti-p40 IL-12/23) is licensed for use in patients with psoriatic arthritis and an inadequate response to the

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Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NICE, 2017 [18]. Apremilast for treating active psoriatic arthritis. NICE Technology Appraisal Guidance 372	1 Recommendations 1.1 Apremilast, alone or in combination with disease-modifying antirheumatic drugs (DMARDs), is recommended as an option for treating active psoriatic arthritis in adults only if: • they have peripheral arthritis with 3 or more tender joints and 3 or more swollen joints and • their disease has not responded to adequate trials of at least 2 standard DMARDs, given either alone or in combination and • the company provides apremilast with the discount agreed in the patient access scheme. Evidence for clinical effectiveness Availability, nature and quality of evidence • The main sources of evidence were the PSA-002, PSA-003 and PSA-004 trials that compared apremilast (20 mg and 30 mg) with placebo. The methods used to identify both published and unpublished studies for the company's network meta-analysis were appropriate and the studies were mostly well reported. Uncertainties generated by the evidence • Placebo responses for some outcomes were high, which made it difficult to compare the relative efficacies of apremilast with the different comparators. • There were uncertainties about the PSA-002, PSA-003 and PSA-004 results because the trials were not blinded after 24 weeks and there were no stopping rules. The committee also considered the lack of radiographic assessment in the trials. • Because it is a new treatment, there is a lack of long-term clinical-effectiveness data for apremilast.
NICE, 2015 [19]. Ustekinumab for treating active psoriatic arthritis. NICE technology appraisal guidance 340	This guidance replaces Ustekinumab for treating active psoriatic arthritis (NICE technology appraisal guidance 313 issued in May 2014). 1.1 Ustekinumab is recommended as an option, alone or in combination with methotrexate, for treating active psoriatic arthritis in adults only when: • treatment with tumour necrosis factor (TNF) alpha inhibitors is contraindicated but would otherwise be considered (as described in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and golimumab for the treatment of psoriatic arthritis) or • the person has had treatment with 1 or more TNF–alpha inhibitors. Ustekinumab is recommended only if the company provides the 90 mg dose of ustekinumab for people who weigh more than 100 kg at the same cost as the 45 mg dose, as agreed in the patient access scheme. 1.2 Ustekinumab treatment should be stopped if the person's psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 24 weeks. An adequate response is defined as an improvement in at least 2 of the 4 criteria (1 of which must be joint tenderness or swelling score), with no worsening in any of the 4 criteria. As recommended in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis, people whose disease has a Psoriasis Area and Severity Index (PASI) 75 response but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response (see NICE technology appraisal guidance on ustekinumab for the treatment of adults with moderate to severe psoriasis).

	1.3 When using the Psoriatic Arthritis Response Criteria (PsARC) healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses to components of the PsARC and make any adjustments they consider appropriate. 1.4 People whose treatment with ustekinumab is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue ustekinumab until they and their NHS clinician consider it appropriate to stop. **Consideration of the evidence - clinical effectiveness** …The Committee reviewed the overall clinical effectiveness of ustekinumab. It noted that the evidence for the clinical effectiveness of ustekinumab had been taken from 2 randomised placebo-controlled trials (PSUMMIT 1 and 2), and acknowledged the need for head-to-head studies between ustekinumab and TNF-alpha inhibitors for psoriatic arthritis. The Committee considered that the evidence suggested that ustekinumab is more effective than placebo after 24 weeks of treatment across a number of joint, skin and soft tissue outcomes. It considered that, although the effect is likely to persist for up to 1 year, there is some uncertainty about this because in the trials people switched from placebo to ustekinumab at week 24. The Committee heard from the clinical experts that ustekinumab appeared to be effective across a wide range of skin and joint outcomes and also soft tissue conditions associated with psoriatic arthritis. The Committee also noted that the results from the PSUMMIT studies suggested there was no statistically significant difference in the clinical effectiveness of ustekinumab compared with placebo between TNF-alpha inhibitor-naive and TNF-alpha inhibitor-exposed populations for the Psoriatic Arthritis Response Criteria (PsARC) response. The Committee concluded that ustekinumab is clinically effective compared with conventional management, in both TNF-alpha inhibitor-naive and TNF-alpha inhibitor-exposed populations, but acknowledged that there remains some uncertainty about the long-term effects of ustekinumab. … The Committee considered the clinical effectiveness of ustekinumab compared with TNF-alpha inhibitors in the TNF-alpha inhibitor-naïve population. The Committee reviewed the findings of the company's mixed treatment comparison and noted that the analysis explored the 3 outcomes used as clinical effectiveness inputs in the economic model (Psoriasis Area and Severity Index [PASI] 75, PASI 90 and PsARC response rates). It discussed this analysis with the clinical experts, and was aware of the limitations of the mixed treatment comparison. The Committee concluded that ustekinumab appeared to be less effective than TNF-alpha inhibitors for PASI 75, PASI 90 and PsARC response, particularly for the joint outcome. The Committee also considered the clinical effectiveness of ustekinumab compared with TNF-alpha inhibitors in the TNF-alpha inhibitor-exposed population. It was aware that there was limited clinical trial evidence in this setting. It understood from comments received during consultation that there is some evidence for the effectiveness of TNF-alpha inhibitors in the TNF-alpha inhibitor-exposed population, but was aware that there was not enough evidence to compare ustekinumab and TNF-alpha inhibitors. The Committee therefore considered the effectiveness of ustekinumab and TNF-alpha inhibitors compared with conventional management. Although in the PSUMMIT trials there was no difference in clinical effectiveness between TNF-alpha inhibitor-naive and TNF-alpha inhibitor-exposed populations in terms of PsARC response, the Committee heard from the clinical experts that evidence presented at a conference suggested that the effectiveness of ustekinumab measured using the American College of Rheumatology (ACR) criteria may decrease with increasing numbers of prior TNF-alpha inhibitors. The clinical experts noted that the diminishing effectiveness of ustekinumab in TNF-alpha inhibitor-exposed populations is broadly consistent with clinical experience with the TNF-alpha inhibitors, which appear to show diminishing effectiveness as the number of prior therapies increases. The Committee heard from the clinical experts that there is some uncertainty about the size of the diminishing effect. The Committee heard estimates for the response rate with second-line TNF-alpha inhibitors ranging from 20% to 70%. Conversely, the Committee noted comments received during consultation from a company that manufactures a comparator drug

	(including evidence from a randomized controlled trial of certolizumab pegol and open-label and observation studies of adalimumab) that suggested that the lower estimates in this range may be too low. The Committee also considered whether there may be any variation in clinical effectiveness depending on the reason for withdrawal of the first TNF-alpha inhibitor (for example, initial lack of efficacy, gradual loss of efficacy over time or adverse reactions), but it acknowledged that there was not enough evidence for this aspect to be considered further. The Committee concluded that there is still uncertainty about the relative effectiveness of ustekinumab and TNF-alpha inhibitors in people who have previously had TNF-alpha inhibitors. ...

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) **am 15.02.2018**

#	**Suchfrage**
#1	MeSH descriptor: [Arthritis, Psoriatic] explode all trees
#2	((Psoriatic* or psoriasis) and arthritis):ti,ab,kw
#3	((Psoriatic* or psoriasis) and arthropath*):ti,ab,kw
#4	#1 or #2 or #3
#5	#4 Publication Year from 2013 to 2018

SR, HTAs in Medline (PubMed) am 15.02.2018

#	**Suchfrage**
1	Arthritis, Psoriatic[MeSH]
2	(Psoriatic*[Title/Abstract] OR psoriasis[Title/Abstract]) AND arthritis[Title/Abstract]
3	(Psoriatic*[Title/Abstract] OR psoriasis[Title/Abstract]) AND arthropath*[Title/Abstract]
4	#1 OR #2 OR #3
5	(#4) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
6	(#4) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
7	(#5 OR #6)
8	(#7) AND ("2013/02/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT "The Cochrane database of systematic reviews"[Journal]

Leitlinien in Medline (PubMed) am 15.02.2018

#	Suchfrage
1	Arthritis, Psoriatic[MeSH]
2	(Psoriatic*[Title/Abstract] OR psoriasis[Title/Abstract]) AND arthritis[Title/Abstract]
3	(Psoriatic*[Title/Abstract] OR psoriasis[Title/Abstract]) AND arthropath*[Title/Abstract]
4	#1 OR #2 OR #3
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title])
6	(#5) AND ("2013/02/01"[PDAT] : "3000"[PDAT])

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Gemeinsamer Bundesausschuss

Anhang:

Ramiro et al. , 2016: Study characteristics

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
UST						
—PSUMMIT 1[1 45]	1 (1)	UST 90 mg, UST 45 mg, PBO	DMARD or NSAIDs failure	24W	ACR20	Low
—PSUMMIT 2[2 34]	2 (0)		DMARD or NSAIDs or TNFi failure	24W	ACR20	Low
SEC						
—FUTURE 1[5]	1 (0)	SEC 150 mg, SEC 75 mg, PBO	DMARD or NSAIDs or TNFi failure	24W	ACR20	Low
—FUTURE 2[4]	1 (0)	SEC 300 mg, SEC 150 mg, SEC 75 mg, PBO	DMARD or NSAIDs or TNFi failure	24W	ACR20	Low
APR						
—PALACE 1[3 35–37]	1 (3)	APR 30 mg, APR 20 mg, PBO	DMARD or TNFi failure (<10%)	16W	ACR20	Unclear
—PALACE 2[38]	0 (1)		DMARD or TNFi failure	16W	ACR20	NA*
—PALACE 3[39]	0 (1)		DMARD or TNFi failure	16W	ACR20	NA*
—PALACE 4[40–43]	0 (4)		DMARD or TNFi failure	16W	ACR20	NA*
Strategy trial (TICOPA)[44]	1 (0)	Tight control, standard care	DMARD naive	48W	ACR20	Low

No trials were available for glucocorticoids or non-steroidal anti-inflammatory drugs (NSAIDs).
†25 publications and 12 abstracts have been included.
ACR20, American College of Rheumatology 20% improvement; ADA, adalimumab; ADEPT, adalimumab effectiveness in psoriatic arthritis trial; APR, apremilast; CYC, ciclosporine; CZP, certolizumab pegol; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; GOL, golimumab; IFX, infliximab; LEF, leflunomide; MIPA, methotrexate in psoriatic arthritis; MTX, methotrexate; NA*, not assessed, risk of bias assessment not possible as only abstract data; NA, not available; NSAID, non-steroidal anti-inflammatory drug; PALACE, psoriatic arthritis long-term assessment of clinical efficacy; PBO, placebo; PRESTA, psoriasis randomized etanercept study in subjects with psoriatic arthritis; PsA, psoriatic arthritis; PsARC, PsA response criteria; RCTs, randomised controlled trials; SEC, secukinumab; TICOPA, tight control of psoriatic arthritis; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

Ungprasert et al. 2016 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