Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2015-02-15-D-151_Apremilast (Plaque-Psoriasis)

Stand: Februar 2014

I. Zweckmäßige Vergleichstherapie: Kriterien der VerfO

Apremilast
Behandlung von Patienten mit moderater (mittelschwerer) bis schwerer Plaque-Psoriasis

Kriterien gemäß 5. Kapitel § 6 Absatz 3 Satz 2 VerfO	
1. Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	– Adalimumab – Infliximab – Etanercept – Ustekinumab
2. Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	– Phototherapie/Balneo-Phototherapie (Relevanz unter Berücksichtigung der Formulierung des Anwendungsgebiets ist zu beraten; nur relevant für Vergleichsgruppe 1)
3. Als Vergleichstherapie sollen bevorzugt Arzneimittel-anwendungen oder nicht-medikamentöse Behandlungen herangezogen werden, deren patientenrelevanter Nutzen durch den Gemeinsamen Bundesausschuss bereits festgestellt ist.	- Balneo-Phototherapie (Nr. 15 in der Anlage 1 "Anerkannte Untersuchungs- und Behandlungsmethoden" der Richtlinien Methoden der vertragsärztlichen Versorgung) und entsprechend der Qualitätssicherungsvereinbarung zur Balneofototherapie gemäß § 135 Abs. 2 SGB V
4. Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	⇨ *Aufbereitung der Evidenz im Anhang*

I. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation/SmPC)
Apremilast Otezla®	zur Behandlung der mittelschweren bis schweren chronischen Plaque-Psoriasis bei erwachsenen Patienten, die auf eine andere systemische Therapie, wie Ciclosporin oder Methotrexat oder Psoralen in Kombination mit UVA Licht (PUVA), nicht angesprochen haben oder bei denen eine solche Therapie kontraindiziert ist oder die diese nicht vertragen haben.
Systemische Therapie	
Adalimumab Humira® (L04AB04)	Humira ist indiziert zur Behandlung der mittelschweren bis schweren chronischen Plaque-Psoriasis bei erwachsenen Patienten, die auf eine andere systemische Therapie, wie Cyclosporin, Methotrexat oder PUVA, nicht angesprochen haben oder bei denen eine Kontraindikation oder Unverträglichkeit einer solchen Therapie vorliegt.
Etanercept Enbrel® (L04AB01)	Behandlung Erwachsener mit mittelschwerer bis schwerer Plaque-Psoriasis, die auf eine andere systemische Therapie wie Ciclosporin, Methotrexat oder Psoralen und UVA-Licht (PUVA) nicht angesprochen haben oder bei denen eine Kontraindikation oder Unverträglichkeit einer solchen Therapie vorliegt (siehe Abschnitt 5.1). Auszug aus Abschnitt 5.1: Enbrel wird zur Anwendung bei den in Abschnitt 4.1 beschriebenen Patientengruppen empfohlen. Psoriasis-Erkrankte in der Bevölkerung, die „nicht angesprochen haben “, sind definiert durch ein unzureichendes Ansprechen (PASI<50 oder PGA, Patient Global Assessment, weniger als gut) oder eine Verschlechterung der Erkrankung während der Behandlung. Dabei mussten die Patienten für eine ausreichend lange Dauer adäquat dosiert sein, um ein Ansprechen auf mindestens jede der drei maßgeblichen verfügbaren systemischen Therapien beurteilen zu können.
Infliximab Remicade (L04AB02)	Remicade ist indiziert zur Behandlung der mittelschweren bis schweren Psoriasis vom Plaque-Typ bei erwachsenen Patienten, die auf eine andere systemische Therapie, einschließlich Ciclosporin, Methotrexat oder PUVA, nicht angesprochen haben, bei denen eine solche Therapie kontraindiziert ist oder nicht vertragen wird (siehe Abschnitt 5.1).
Ustekinumab Stelara® (L04AC05)	STELARA ist für die Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis indiziert, bei denen andere systemische Therapien einschließlich Ciclosporin, Methotrexat und PUVA nicht angesprochen haben, kontraindiziert sind oder nicht vertragen wurden (siehe Abschnitt 5.1).

Quellen: AMIS-Datenbank, Fachinformationen

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

Inhalt

Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassenen Arzneimittel,

„Übersicht zVT, Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation „Plaque Psoriasis“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 11.09.2013 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, NGC, TRIP, DAHTA, NIHR HSC. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 395 Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen

vorgenommen. Davon wurden 110 Quellen eingeschlossen. Nach der Volltextsichtung wurden 29 Quellen in die synoptische Evidenzübersicht aufgenommen.

Abkürzungen

ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
NHS CRD	National Health Services Center for Reviews and Dissemination
DAHTA	Deutsche Agentur für Health Technology Assessment
DGHO-Onkopedia	*Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie*
ESMO	*European Society for Medical Oncology*
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NCCN	*National Comprehensive Cancer Network*
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NIHR HSC	National Institute for Health Research Horizon Scanning Centre
TRIP	Turn Research into Practice Database
CBC	Complete blood cell
FDA	Food and Drug Administration
GI	gastrointestinal
LFT	liver function test
PASI	Psoriasis Area and Severity Index
REM	Random-Effects-Model
CoI	Conflict of interest
k.A.	keine Angabe
vs	versus
CyA	cyclosporin
MTC	mixed treatment comparisons
PGA	physician’s global assessment
PUVA	Psoralen plus UV-A (auch Photochemotherapie)

G-BA, 2008 (per Handsuche): Zusammenfassende Dokumentation zum Beratungsverfahren des Unterausschusses „Ärztliche Behandlung des Gemeinsamen Bundesausschusses.[1] *Siehe auch IQWIG, 2006: Abschlussbericht: Balneophototherapie (IQWiG-Berichte. Jahr: 2006 Nr. 14)* **[2]**	Unter Balneophototherapie versteht man in Deutschland die Kombination aus einem Bad in verschiedenen Medien und einer UV-Lichttherapie. Es gibt grundsätzlich zwei Typen von Balneophototherapie: • asynchrone Balneophototherapie: zuerst Bad, anschließend Bestrahlung und • synchrone Balneophototherapie: Bestrahlung während des Bades. Die asynchrone Balneophototherapie wiederum kommt in zwei Formen vor: • Bade-PUVA: Das Bad enthält einen Psoralenzusatz (8-Methoxypsoralen, kurz: 8-MOP oder Trioxsalen [Trimethylpsoralen, kurz: TMP] in alkoholischer Lösung), die anschließende Bestrahlung erfolgt mit UVA-Licht. • asynchrone Photosoletherapie: Das Bad ist mit Sole (10 %ig bei atopischer Dermati-tis bis zu 25 %ig bei Psoriasis vulgaris) angereichert, die anschließende Bestrahlung erfolgt in der Regel mit UVB (Ultraviolettstrahlung-B)-Licht. Bei der asynchronen Bal-neophototherapie wird bei Verwendung 25 %iger Solelösung aus technischen Grün-den erst Leitungswasser in die Wanne eingelassen, eine Folie auf das Wasser gelegt und danach die 25 %ige Sole aufgegossen, in der der Patient dann badet. Die synchrone Balneophototherapie spielt in der Praxis nur in Form der „TOMESA-Therapie“ eine Rolle in der Versorgung. Bei der TOMESA-Therapie werden die Patienten während des Bades in Totes-Meer-Salzwasser mit UV-Licht bestrahlt. Totes-Meer-Salzwasser enthält im Gegensatz zu einer üblichen Salzlösung einen hohen Anteil an Magnesium- und Kalziumionen. **Fazit: Psoriasis vulgaris** *Bade-PUVA* Das IQWiG kam zu folgendem Fazit: „Die asynchrone Bade-PUVA hat einen Zusatznutzen gegenüber der trockenen UVB-Therapie beziehungsweise Leitungswasser plus UVB im Hin-blick auf die Besserung des Hautbeschwerdebildes und eine Reduktion der unerwünschten Wirkungen / Folgeschäden. Diese Aussage gilt nur für eine Mischung der zur Anwendung kommenden UVB-Spektren bei den Vergleichsinterventionen. (...). Für die Bade-PUVA gibt es Hinweise auf einen Zusatznutzen gegenüber der asynchronen Photosoletherapie (Sole + UVB) im Hinblick auf die Besserung des Hautbeschwerdebildes und eine Reduktion der un-erwünschten Wirkungen/Folgeschäden. Diese Aussage gilt nur für eine Mischung der zur Anwendung kommenden UVB-Spektren bei der Vergleichsintervention (...). Für die Bade-PUVA besteht gegenüber der oralen PUVA ein geringeres Schadenspotenzial bezogen auf akute Nebenwirkungen (Übelkeit und Erbrechen). Es finden sich schwache Hinweise auf ein vermindertes Schadenspotenzial bezogen auf langfristige Folgeschäden (Plattenepithelkar-zinome der Haut). Der Behandlungsaufwand ist prozedural bedingt geringer. Ein gleichwerti-ger Nutzen der asynchronen Bade-PUVA im Hinblick auf die Besserung des Hautbeschwer-debildes ist allerdings weder belegt noch ausgeschlossen.“ ➔ Die Themengruppe Balneophototherapie des G-BA schloss sich dem Fazit des IQWiG zur Bade-PUVA-Therapie bei Psoriasis vulgaris an. Der Nutzen wurde auf der Basis des IQWiG-Berichtes als belegt angesehen.

	Asynchrone Photo-Sole-Therapie: Das IQWiG kam zu folgendem Fazit: „Die asynchrone Photosoletherapie (Sole plus UVB) hat einen Zusatznutzen gegenüber der trockenen UVB-Therapie (und auch Leitungswasser plus UVB) bezogen auf die Besserung des Hautbeschwerdebildes." ➔ Die Themengruppe schloss sich dem Fazit des IQWiG zur asynchronen Photo-Sole-Therapie bei Psoriasis vulgaris an. Der Nutzen wurde auf der Basis des IQWiG-Berichts als belegt angesehen. *Synchrone Balneophototherapie (TOMESA-Verfahren):* Das IQWiG kam zu folgendem Fazit: „Für die synchrone Balneophototherapie (TOMESA-Verfahren) zeigt sich bei der Indikation Psoriasis vulgaris ein Zusatznutzen gegenüber der trockenen UVB-Therapie im Hinblick auf die Reduktion des Hautbeschwerdebildes und ein-geschränkt auch für das Therapieziel krankheitsbezogene Lebensqualität." ➔ Die Themengruppe schloss sich dem Fazit des IQWiG zur synchronen Balneophototherapie bei Psoriasis vulgaris an. Der Nutzen wurde auf der Basis des IQWiG-Berichtes als belegt angesehen.

Cochrane Reviews

Zur Fragestellung wurden keine Cochrane Reviews identifiziert.

Systematische Reviews

Für diesen Auftrag war keine Aktualisierung der Recherche zum Auftrag 2013-B-078 (Barcitinib) notwendig. In dieser Synopse werden daher nur jene Arbeiten zur vergleichenden Effektivität aus den Jahren 2013 und 2012 extrahiert, welche nach der Publikation der Canadian Agency for Drugs and Technologies in Health (CADTH) 2012 [3] veröffentlicht wurden. Arbeiten zu Fragen der der Sicherheit wurden für die Jahre 2009 bis 2014 extrahiert. Die Ergebnisse der einzigen deutschsprachigen Übersichtsarbeit wurden ebenfalls in der Synopse belassen.

<table>
<tr><td rowspan="4">Gisondi P, et al. 20013 [4]

Impact of TNF-alpha antagonists on the quality of life in selected skin diseases</td><td>1. Fragestellung
Aim of the study was to investigate the impact of TNF-alpha antagonists on health-related quality of life (HRQoL) in selected skin diseases, i.e. chronic plaque psoriasis, Behcet's disease (BD), hidradenitis suppurativa (HS) and pyoderma gangrenosum (PG).</td></tr>
<tr><td>2. Methodik: systematic literature search

Population: adults with psoriasis, BD, HS or PG
Intervention: TNF-alpha antagonists (adalimumab, etanercept and infliximab)
Komperator: placebo
Endpunkt: HRQoL

Datenbank und Suchzeitraum: Medline (2000 to April 2013)
Studiendesign: RCT
Anzahl der eingeschlossenen Studien/Patienten (gesamt): 13</td></tr>
<tr><td>3. Ergebnisdarstellung
• skin diseases can affect physical, psychological, social and occupational aspects of everyday life
• TNF-alpha antagonists induced consistent benefits across health outcomes in psoriasis
• Dermatology Life Quality Index most common used tool for investigating HRQoL
• most important negative impacts on QoL appearance related
• burden on QoL correlated to the severity of skin disease
• improvement in QoL achieved by TNF-alpha blockers was proportional to the degree of disease remission</td></tr>
<tr><td>4. Anmerkungen/Fazit der Autoren
HRQoL issues are becoming even more important in evaluating medical care, including treatment of skin diseases. In general, achieving the highest clearing of skin disease with anti-TNF-alpha agents is required for optimal improvement in QoL</td></tr>
</table>

	Hinweise durch FB Med: • no information about funding and CoI • quality of included studies not adressed • ~~clinical heterogeneity addressed, REM used~~ • publication bias not mentioned
Galván-Banqueri M, et al. 2013 **Biological treatments for moderate-to-severe psoriasis: indirect comparison [5]**	1. Fragestellung The objective of this study is to compare the relative efficacy of the biological agents through a systematic review of the indirect clinical trial evidence**.**
	2. Methodik: Systematischer Review mit indirekten Vergleichen **Population**: Adults with moderate-to-severe plaque-type psoriasis **Intervention:** biological agents (ustekinumab, etanercept, adalimumab, infliximab) **Komparator**: Placebo **Endpunkte**: PASI 75 achievement Suchzeitraum: bis August 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 14/n = k.A.
	3. Ergebnisdarstellung • Ustekinumab (4 Studien); Adalimumab (3 Studien); Infliximab (3 Studien); Etanercept (4 Studien) • The indirect comparison results reveal that ustekinumab, adalimumab and infliximab were statistically superior to etanercept with an absolute risk difference for PASI 75 of 12% (95% CI = 5·9-18%), 11% (95% CI = 5·3-16·7%) and 24% (29·7-18·3%) respectively. • However, in all situations, the 95% confidence interval does not achieve clinical relevance as no delta exceeds the previously set value (25%).
	4. Anmerkungen/Fazit der Autoren ,,*Ustekinumab, Adalimumab, Infliximab und Etanercept werden als klinische Mittel für die Behandlung von Psoriasis angesehen. „Choice between these agents therefore depends on their relative safety profiles, individual contra-indications and cost effectiveness."* Hinweise durch FB Med: • no information about funding and CoI • quality of included studies not adressed • statistical heterogeneity addressed, REM used • publication bias not mentioned
Canadian Agency for Drugs and Technologies in Health (CADTH), 2012 [3]	1. Fragestellung 1. What is the comparative clinical efficacy of infliximab versus methotrexate, etanercept, adalimumab or ustekinumab for the treatment of adults with plaque psoriasis? 2. What is the comparative safety of infliximab versus methotrexate, etanercept, adalimumab or ustekinumab for the treatment of adults with plaque psoriasis? …
	2. Methodik: systematic literature search, review **Population** Adults with plaque psoriasis

Infliximab versus methotrexate, etanercept, adalimumab, and ustekinumab for plaque psoriasis: a review of the comparative clinical efficacy, safety and cost effectiveness. Rapid Resonse Report.	**Intervention** Infliximab **Comparator** Methotrexate, etanercept, adalimumab, ustekinumab **Outcomes** Clinical effectiveness, length of effect, number of treatments for control of symptoms, adverse events, cost effectiveness **Study Designs** Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), economic evaluations Suchzeitraum: 2007 – 2012 (27. Juni) Anzahl der eingeschlossenen Studien/Patienten (gesamt): 12/n = k.A.
	3. Ergebnisdarstellung • 6 systematic reviews,1 open-label RCT included • All systematic reviews based on comprehensive literature searches • meta-analyses performed using RCTs • methodology used to pool data well detailed and appropriate • 3 meta-analyses employed mixed-treatment comparison evidence synthesis • other studies compared each treatment to placebo individually • scientific quality of included studies was assessed in 3 of the 6 reviews • publication bias was not assessed in any of the systematic reviews • weakness of all of the systematic reviews: the lack of head-to-head trials included as majority of existing trials are placebo-controlled • RCT described adequate method of randomization and losses to follow-up • active comparator used rather than placebo and all patients received assigned treatments • weakness: lack of blinding in patients and outcome assessors, which may bias efficacy and safety results • patients were able to switch between treatments if necessary, which may affect reported adverse events due to an imbalance in study medication exposure • no statistical analysis performed for the safety data, making it difficult to compare numbers between the two treatment groups
	4. Anmerkungen/Fazit der Autoren *According to meta-analyses of placebo-controlled RCT trials, infliximab at a dose of 5 mg/kg appears to be more effective than methotrexate, etanercept, adalimumab, and ustekinumab for achieving PASI 75 in patients with moderate-to-severe plaque psoriasis. One open-label RCT found infliximab to be more effective than methotrexate.* *Limited evidence was identified regarding the comparative safety of infliximab versus methotrexate, etanercept, adalimumab, and ustekinumab. Infliximab was found to be associated with an increase in the incidence of adverse events when compared with placebo, and with a slight increase when compared to 50 mg etanercept or methotrexate.* Hinweise durch FB Med: • Governmental funding • CoI not declared

	• quality of included studies assessed by standardized tools • publication bias discussed
Lucka TC, et al. 2012 **Efficacy of systemic therapies for moderate-to-severe psoriasis: a systematic review and meta-analysis of long-term treatment [6]**	Auf eine Extraktion der Ergebnisse wurde verzichtet, da die Arbeit im "Canadian Agency for Drugs and Technologies in Health (CADTH), 2012: Infliximab versus methotrexate, etanercept, adalimumab, and ustekinumab for plaque psoriasis: a review of the comparative clinical efficacy, safety and cost effectiveness. Rapid Resonse Report." eingeschlossen ist.
Reich K, 2012 **Efficacy of biologics in the treatment of moderate to severe psoriasis: a network meta-analysis of randomized controlled trials [7]**	Auf eine Extraktion der Ergebnisse wurde verzichtet, da die Arbeit im "Canadian Agency for Drugs and Technologies in Health (CADTH), 2012: Infliximab versus methotrexate, etanercept, adalimumab, and ustekinumab for plaque psoriasis: a review of the comparative clinical efficacy, safety and cost effectiveness. Rapid Resonse Report." eingeschlossen ist.
Baker EL, et al. 2012 **Effect of Biologic Agents on Non-PASI Outcomes in Moderate-to-Severe Plaque Psoriasis: Systematic Review and Meta-Analyses [8]**	1. Fragestellung Evaluating the impact of biologics on non-Psoriasis Area and Severity Index (PASI) health outcomes in patients with moderate-to-severe plaque psoriasis.
	2. Methodik: Systematische Übersichtsarbeit mit Mixed-Treatment Comparison **Population**: Patients with moderate-to-severe plaque psoriasis **Intervention**: alefacept, efalizumab, infliximab, adalimumab, etanercept, ustekinumab, briakinumab **Komparator**: Placebo **Endpunkte**: PGA Static Response Rate; PGA Dynamic Response Rate Suchzeitraum: 1966 bis Mai 2009 Anzahl eingeschlossene Studien/Patienten (Gesamt): 31 Studien/n = k.A.
	3. Ergebnisdarstellung

	alefacept versus placebo (n = 5); efalizumab versus placebo (n = 7); infliximab versus placebo (n = 6); adalimumab versus placebo (n = 5); etanercept versus placebo (n = 4); ustekinumab versus placebo (n = 3); briakinumab versus placebo (n = 1) **PGA Static Response Rate:** • All biologics showed significant improvement in achieving a good response on the static physician's global assessment (PGA) versus placebo while, in the MTC, differences were noted between individual drugs. **PGA Dynamic Response Rate:** • In achieving a good response on the dynamic PGA, all biologics showed significant improvements over placebo, while the MTC showed significant improvements with the antiinterleukins versus anti-T cells. **Change in DLQI from Baseline and Change in SF-36 from Baseline:** • Relative to placebo, antitumor necrosis factor (TNF) agents and anti-interleukins showed significant improvements in the Dermatology Life Quality Index (DLQI). • Compared with placebo, the anti-TNF agents showed significant improvements in both 36-item Medical Outcomes Study Short-Form General Health Survey (SF-36) mental and physical component scores, while anti-T cell agents showed no improvements. The MTC showed no differences between any biologics for either the DLQI or SF-36.
	4. Anmerkungen/Fazit der Autoren *Individual biologics and classes showed consistent benefits across non-PASI health outcomes in patients with moderate-to severe plaque psoriasis while MTC metaanalyses suggested that some differences exist. Anti-TNF agents, as well as anti-IL 12/23 agents, significantly improve clinical efficacy (via the PGA) and HRQoL (via the DLQI) as compared with the anti-T cell agents in patients with moderate-to-severe plaque psoriasis.* Hinweise durch FB Med: • einige der untersuchten Wirkstoffe nicht (mehr) zugelassen • study supported in part by a contract from Pfizer Inc. • Conflict of interest. C.M.M. and J.C.C. employed by Pfizer Inc. No other authors report significant conflicts of interest germane to this project. • validated Jadad scale used to assess methodological quality of included trials • statistical and clinical heterogeneity and publication bias assessed and discussed: "Due to the low number of studies included in many of the analyses, statistical heterogeneity and publication bias could not be determined."
Lin VW, et al. 2012 **Comparison of Ustekinumab With Other Biological**	1. Fragestellung To compare the efficacy of ustekinumab with that of other biological agents using the Psoriasis Area and Severity Index (PASI) among adult patients with moderate to severe plaque psoriasis.
	2. Methodik **Population**: Adult patients with moderate to severe plaque psoriasis **Intervention**: Biological agents (Adalimumab, Elefacept, Etanercept,

Agents for the Treatment of Moderate to Severe Plaque Psoriasis. [9]	Infliximab, Ustekinumab) **Komparator**: Biological agents or placebo **Endpunkte**: 75% reduction in the PASI Suchzeitraum: 1992 - 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 17/n = k.A.
	3. Ergebnisdarstellung • Ustekinumab use was associated with statistically significantly higher odds for achieving PASI 75 compared with adalimumab use (OR, 1.84; 95% credible interval [CI], 1.01-3.54), alefacept use (10.38; 3.44-27.62), and etanercept use (2.07; 1.42-3.06). • Ustekinumab use was associated with lower odds for achieving PASI 75 compared with infliximab use (OR, 0.36; 95% CI, 0.14-0.82). • Infliximab had the highest odds for PASI 75 response compared with adalimumab (5.04; 2.40-14.09), alefacept (28.33; 8.24-94.05), etanercept (5.67; 2.70-14.98), and ustekinumab (2.77; 1.28-7.14). • In the therapeutic class comparison, the interleukin-12/23 inhibitor had the highest odds for achieving a 75% reduction in the PASI compared with placebo (OR, 69.48; 95% CI, 36.89-136.46), followed by tumor necrosis factor inhibitors (OR, 42.22; 95% CI, 27.94-69.34) and the T-cell inhibitor (OR, 5.63; 95% CI, 1.35-24.24).
	4. Anmerkungen/Fazit der Autoren *In conclusion, the use of a Bayesian network metaanalysis enabled us to compare the efficacy of ustekinumab with that of other biological agents using PASI responses as the outcome among adult patients with moderate to severe plaque psoriasis during the induction phase of the first 10 to 16 weeks. Ustekinumab, the newest agent that targets IL-12/23, seems to be more efficacious than adalimumab, etanercept, and alefacept but not infliximab.* *Für die Behandlung von mittelschwerer bis schwerer Plaque-Psoriasis, kann Ustekinumab wirksamer sein als Adalimumab, Etanercept und alefacept aber nicht als Infliximab.* Hinweise durch FB Med: • no funding information • Conflict of Interest Disclosures: Dr Lin was supported by an unrestricted postdoctoral fellowship from the University of Washington. Dr Ringold was supported by grant K12HS019482 from the Agency for Healthcare Research and Quality. • validated Jadad scale used to assess methodological quality of included trials • existence of heterogeneity taken into account for model-selection • No publication bias assessed because it is challenging to do so in a Bayesian network meta-analysis and requires further research.
Girolomoni G, et al 2012 [10] **Safety of anti-TNFalpha**	1. Fragestellung This review presents and discusses current evidence on the safety of anti-TNFα agents in patients with psoriasis and PsA, with a focus on European registry studies and case reports of particular importance.
	2. Methodik: systematische Übersichtsarbeit

agents in the treatment of psoriasis and psoriatic arthritis	Population: Patients with psoriasis or psoriatic arthritis Intervention/Komperator: anti TNF-alpha agents (adalimumab, certolizumab, etanercept, golimumab, infliximab) Endpunkte: safety issues (infections, cancer, other) Studiendesign: RCT, phase III, post-marketing study or registry Suchzeitraum und Datenbank: MEDLINE (last updated 10 Nov 2011)
	3. Ergebnisdarstellung • mature data available for adalimumab, etanercept, and infliximab, though in most cases these data are derived from anecdotal reports or registry studies from Europe and other non-European countries • data appear reassuring, some concerns still exist • data suggest a higher incidence of infection and lymphoma amongst patients treated with infliximab and adalimumab compared with etanercept
	4. Anmerkungen/Fazit der Autoren *The overall safety profile of monoclonal antibodies in patients with psoriasis, PsA and RA seems less favorable than that of etanercept, particularly in terms of risk of infection and hepatotoxicity.*
Tzellos T, 2012 [11] **Re-evaluation of the risk for major adverse cardiovascular events in patients treated with anti-IL-12/23 biological agents for chronic plaque psoriasis: a meta-analysis of randomized controlled trials**	1. Fragestellung To detect a detrimental or beneficial effect of anti-IL-12/23 biological agents (ustekinumab and briakinumab) for the treatment of chronic plaque psoriasis on major adverse cardiovascular events (MACEs).
	2. Methodik: Systematic review and meta-analysis Population: adults (psoriatic arthritis excluded) Intervention: monotherapy studies of IL-12/23 antibodies Endpunkt: number of MACEs during the placebo-controlled phase of treatment Datenbank und Suchzeitraum: MEDLINE, EMBASE, the Cochrane Skin Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, SciVerse Scopus and ongoing trial registries, searched from inception until December 2011 Studiendesign: RCTs, double-blind Anzahl eingeschlossener Studien: 9 (5 on Utsekinumab)
	3. Ergebnisdarstellung • MACEs include myocardial infarction, cerebrovascular accident or cardiovascular death • no statistical heterogeneity across the studies using the I(2) statistic (I(2) = 0) found • possible higher risk of MACEs in those patients treated with IL-12/23 antibodies compared with those at placebo (OR = 4.23, 95% CI: 1.07-16.75, P = 0.04) • study unaffected by non-reporting of outcomes with no events
	4. Anmerkungen/Fazit der Autoren *Compared with placebo, there was a significant difference in the rate of MACEs observed in patients receiving anti-IL-12/23 biological agents*

Dommasch ED, et al. 2011 **The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials (Provisional abstract) [12]**	1. Fragestellung Examine the risks of infection and malignancy with the use of TNF antagonists in adult patients with psoriatic disease.
	2. Methodik **Population**: Adults with plaque psoriasis **Intervention**: TNF antagonists (etanercept, infliximab, adalimumab, golimumab, and certolizumab) **Komparator**: Placebo **Endpunkte**: malignancy and infection Suchzeitraum: Beginn bis 30 Juli 2009 Anzahl eingeschlossene Studien/Patienten (Gesamt): 20 RCTs/n = 6 810
	3. Ergebnisdarstellung • ORs for overall infection and serious infection over a mean of 17.8 weeks were 1.18 (95% CI: 1.05, 1.33) and 0.70 (95% CI: 0.40, 1.21), respectively. • When adjusting for patient years, the incidence rate ratio for overall infection was 1.01 (95% CI: 0.92, 1.11). • The OR for malignancy was 1.48 (95% CI: 0.71, 3.09), and 1.26 (95% CI: 0.39, 4.15) when non-melanoma skin cancer was excluded.
	4. Anmerkungen/Fazit der Autoren *Es besteht ein gering erhöhtes Risiko für die Gesamtinfektion mit dem kurzfristigen Einsatz von TNF-Antagonisten zur Psoriasis Behandlung, was auf die Unterschiede in Follow-up-Zeit zwischen Behandlungs- und Placebogruppen zuzuschreiben ist. Es gab keine Hinweise auf ein erhöhtes Risiko für schwerwiegende Infektionen und ein statistisch signifikant erhöhtes Risiko für Krebs wurde mit den kurzfristigen Einsatz von TNF Inhibitoren nicht beobachtet.* Hinweise durch FB Med: • Auch für die einzelnen Arzneistoffe zeigte sich kein signifikanter Unterschied • Funding Sources: Supported in part by grant K23AR051125 from the National Institute of Arthritis, Musculoskeletal, and Skin Diseases (JMG) and a National Research Service Award from the National Institute of Health (EDD). • Financial Disclosures: Dr. Gelfand receives grant support and is an investigator for Amgen and Pfizer. He is a consultant for Pfizer, Genentech, Celgene, Amgen, Centocor, and Luitpold. Dr. Dommasch, Dr. Abuabara, Mr. Shin, Dr. Nguyen, and Dr. Troxel have no relevant financial relationships to declare. • validated Jadad scale used to assess methodological quality of included trials • statistical heterogeneity addressed
Sbidian E, et al. 2011	1. Fragestellung 1 To determine the optimal dosing strategy of systemic retinoid therapy in patients with psoriasis of either plaque type (PV), nail, localized and pustular forms.

Efficacy and safety of oral retinoids in different psoriasis subtypes: a systematic literature review [13]	2 To evaluate the safety profile of systemic retinoid treatment regarding skeletal toxicity.
	2. Methodik **Population**: adults with psoriasis **Intervention**: retinoids (various dosages) **Komparator**: k.A. **Endpunkte**: efficacy, skeletal toxicity • systematic literature search carried out in MEDLINE, EMBASE, and Cochrane Library • search period: from 1975 to 2010 • inclusion criteria: RCTs, observational studies, human subjects, English/French languages Anzahl eingeschlossene Studien/Patienten (Gesamt): 44 trials for efficacy, 15 for potential skeletal toxicity
	3. Ergebnsidarstellung • starting daily dosages between 10 and 25 mg and stepwise escalation associated with higher clinical efficacy and lower incidence of adverse events in comparison with higher doses and regimens rapidly reaching optimal dose • single agent therapy appeared to show limited efficacy in PV • combining with phototherapy appeared to be highly effective in PV • no strong evidence of an increased risk of skeletal abnormalities in psoriasis patients treated with retinoids.
	4. Anmerkungen/Fazit der Autoren *Acitretin is also a treatment option for moderate-to-severe plaque psoriasis primarily through combination regimens with UV light. Low to intermediate doses of acitretin e.g. equal or less than 25 mg/day only result in few side-effects and are safe in both the short-term and long-term treatments of psoriasis.*
Maza A, et al. 2011 [14] **Oral cyclosporin in psoriasis: a systematic review on treatment modalities, risk of kidney toxicity and evidence for use in non-plaque psoriasis**	1. Fragestellung Question A: What are the optimal prescription modalities of CyA in plaque-type psoriasis in adults? Question B: What is the risk of renal toxicity in patients treated with CyA and what type of monitoring should be recommended?
	2. Methodik • systematic search performed on PubMed, Cochrane and Embase databases • search period: from 1980 to June 2010 • inclusion criteria: human subjects, written in English or French, reporting original data, only RCTs for question A, RCT and prospective studies for question B Anzahl eingeschlossene Studien/Patienten (Gesamt): 16 RCTs for treatment strategy, 25 articles (histological studies and RCT) for risk of kidney toxicity
	3. Ergebnisdarstellung

	• higher doses of CyA of 5 mg/ kg produced PASI-75-response in between 50 and 97% of patients • lower doses of 2.5 mg/ kg yielded PASI 75 in between 28 and 85% • maintain remission at doses of at least 3 mg / kg / day • More than 50% of the patients treated with CyA may have an increase in serum creatinin value over 30% of baseline if treatment is prolonged for 2 years.
	4. Anmerkungen/Fazit der Autoren *Oral CyA is indicated for patients with plaque psoriasis, pustular psoriasis or erythrodermic psoriasis. The starting dose of 5 mg /kg is associated with a higher degree of clearance. The benefit-risk appears to be better for patients without risk factors for nephrotoxicity: non-obese patients without hypertension and aged below 60. Although CyA is ideally suited for crisis intervention, continuous maintenance treatment with CyA may be envisaged in some patients provided serum creatinin is regularly monitored and the cumulative treatment duration is preferably limited to 2 years or less.*
Montaudie H, et al. 2011 [15] **Methotrexate in psoriasis: a systematic review of treatment modalities, incidence, risk factors and monitoring of liver toxicity**	1. Fragestellung Q1 What are the optimal prescription and administration methods for using MTX in adult plaque-type psoriasis? …
	2. Methodik **Population**: adults with psoriasis and psoriatic arthritis **Intervention**: methods of administering MTX **Komparator**: k.A. **Endpunkte**: efficacy, risk factors and assessment of liver toxicity • systematic literature search carried out in Medline, Embase and Cochrane Library • search period: from 1980 to 2010 • inclusion criteria: RCTs and observational studies, human subjects over 19 years of age, articles in English or French, original data Anzahl eingeschlossene Studien/Patienten (Gesamt): 23 published studies
	3. Ergebnisdarstellung • no studies focusing directly on the question of MTX treatment modalities (starting dose or dose increments) • no study compared subcutaneous vs. oral administration in the management of psoriasis • data from six RCT designed to measure the efficacy of MTX in plaque-type psoriasis analyzed • treatment outcome appears to be dose dependent.
	4. Anmerkungen/Fazit der Autoren *Based on expert experience, the starting dose of MTX is between 5 and 10 mg/week for the first week. Fast dose escalation is recommended in order to obtain a therapeutic target dose of 15–25 mg/week. The maximum recommended dose is 25 mg/week. A folic acid supplement is necessary.*

	The initiation of treatment by oral administration is preferred. In cases where inadequate response is obtained or in the event of poor gastrointestinal tolerance, subcutaneous dosing can be proposed at the same dose.
Bansback N, et al. 2009 **Efficacy of systemic treatments for moderate to severe plaque: systematic review and meta-analysis [16]**	Auf eine Extraktion der Ergebnisse wurde verzichtet, da die Arbeit im "Canadian Agency for Drugs and Technologies in Health (CADTH), 2012: Infliximab versus methotrexate, etanercept, adalimumab, and ustekinumab for plaque psoriasis: a review of the comparative clinical efficacy, safety and cost effectiveness. Rapid Resonse Report." eingeschlossen ist.
Ryan C, et al. 2011 **Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials [17]**	1. Fragestellung To evaluate a possible association between biologic therapies for CPP and MACEs via meta-analysis.
	2. Methodik Population: Adult patients with moderate to severe psoriasis Intervention: Ustekinumab, Briakinumab, Etanercept, Infliximab und Adalimumab Komparator: Placebo Endpunkte: Major adverse cardiovascular events (MACEs) Suchzeitraum: Beginn bis Juni 2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 22 RCTs/n = 10 183
	3. Ergebnisdarstellung Compared with placebo: • no significant difference in the rate of MACEs observed in patients receiving anti–IL-12/IL-23 antibodies or anti–TNF-Alpha treatments.
	4. Anmerkungen/Fazit der Autoren *Im Vergleich zu Placebo gab es keinen signifikanten Unterschied in der MACE-Rate bei Patienten die mit anti-IL-12/IL-23 Antikörper oder anti-TNF-Alpha behandelt wurden.* Hinweise durch FB Med • No external funding received for this study • CoI widely declared (several relationships to pharmaceutical industry) • quantitative quality assessment performed using a predefined scoring system devised by the Cochrane Collaboration • no evidence of statistical heterogeneity across the studies using the I2 test (I2=0),33 allowing for combination of trial results using the Mantel-Haenszel fixed-effects method • no evidence of publication bias

Zhang Z, et al. 2009: **[Treatment of plaque psoriasis with biologics. A meta-analysis of randomized controlled trials] Behandlung der Plaque-Psoriasis mit Biologics. Eine Metaanalyse randomisierter kontrollierter Studien. Med Klin (Munich) 2009; [18].**	1. Fragestellung Wirksamkeit von Biologica zur Behandlung der mittelschweren bis schweren Psoriasis vulgaris.
	2. Methodik Population: Erwachsene Patienten mit mittelschwerer bis schwerer Psoriasis vulgaris Intervention: Biologika Komparator: Placebo Endpunkte: Anteil der Patienten mit mindestens 75%iger Reduktion im PASI Suchzeitraum: Beginn der DB bis Januar 2008 Anzahl eingeschlossene Studien/Patienten (Gesamt): 15/n = 8 057
	3. Ergebnisdarstellung *Ergebnisse der Meta-Analyse zur Risikodifferenz (95% KI) für PASI 75 Response vs. Placebo nach 10-16 Wochen* • Infliximab 0,76 (0,72-0,80), p<0,00001, I=15,7% • Etanercept (25 mg BIW) 0,30 (0,25-0,35), p<0,00001, I=0% • Etanercept (50 mg BIW) 0,44 (0,40-0,48), p<0,00001, I=0% Adalimumab 0,59 (0,45-0,73), p<0,00001, I=70,6%
	4. Anmerkungen/Fazit der Autoren *Die Zusammenschau der Daten legt nahe, dass sich die einzelnen Biologics in ihrer Wirksamkeit quantitativ unterscheiden. Infliximab ist angesichts der Daten als das wirksamste Biologic anzusehen. Adalimumab ist wirksamer als Etanercept.* • ***Infliximab ist häufiger mit Infusionsreaktionen assoziiert, Etanercept mit Reaktionen an der Injektionsstelle, Adalimumab mit Atemwegsinfektionen****.* • *Studienabbrüche wegen UEs: Infliximab (1,2%), Adalimumab (0,5%) und Etanercept (0,5%)* • ***Die Effektivität von Placebo in diesen Studien war homogen(gepoolte RD [95% KI]: 4% [3-4]) und weist daher auf eine gute Vergleichbarkeit hin.*** • *Die untersuchten Patienten sind hinsichtlich relevanter demographischer und krankheitsspezifischer Charakteristika vergleichsarm so dass ein Selektionsbias unwahrscheinlich ist.* • *Große kontrollierte Studien deuten auf eine hohe Sicherheit der Präparate in der Kurzzeitanwendung hin.* *Der Mangel an head-to-head-Studien wird kritisiert* Hinweise durch FB Med • Keine Angaben zur Finanzierung der Arbeit sowie zu CoI • Qualität der Studien mit dem Jadad-Score bewertet • Heterogenität untersucht • Publikationsbias nicht erwähnt

National Institute for Health and Clinical Excellence (NICE), 2012 Assessment and management of psoriasis [19]	Fragestellung In people with psoriasis (all types), what are the clinical effectiveness, safety, tolerability and cost effectiveness of systemic methotrexate, ciclosporin and acitretin compared with each other or with placebo? … In people with chronic plaque psoriasis eligible to receive biologics, if the first biological fails, which is the next effective, safe and cost effective strategy? …
	Methodik Grundlage der Leitlinie: NICE Guidelines Manual 2009 (Formulierung klinischer Fragestellungen und Endpunkte apriori, systemtaische Recherchen, Bewertung der Literatur anhand GRADE, Konsensusprozess ohne Beschreibung formaler Verfahren) Suchzeitraum: bis März 2012 *Weitere Kriterien für die Qualität einer LL:* • *alle eingeschlossenen Studien in Evidenztabellen dargestellt* LoE: nach GRADE, GoR: Formulierung Sonstige methodische Hinweise • *governmental funding* • *CoI declared*
	Freitext/Empfehlungen/Hinweise **Systemic nonbiological therapy** 81. Offer systemic non-biological therapy to people with any type of psoriasis if: • it cannot be controlled with topical therapy and • it has a significant impact on physical, psychological or social wellbeing and • one or more of the following apply: - psoriasis is extensive (for example, more than 10% of body surface area affected or a Psoriasis Area and Severity Index (PASI) score of more than 10) or - psoriasis is localised and associated with significant functional impairment and/or high levels of distress (for example severe nail disease or involvement at high-impact sites) or - phototherapy has been ineffective, cannot be used or has resulted

	in rapid relapse (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months). **Choice of drugs** 82. Offer methotrexate[ttt] as the first choice of systemic agent for people with psoriasis who fulfil the criteria for systemic therapy (see recommendation 81) except in the circumstances described in recommendations 84 and 92. … 84. Offer ciclosporin[uuu] as the first choice of systemic agent for people who fulfil the criteria for systemic therapy (see recommendation 81) and who: • need rapid or short-term disease control (for example a psoriasis flare) or • have palmoplantar pustulosis or • are considering conception (both men and women) and systemic therapy cannot be avoided. 85. Consider changing from methotrexate to ciclosporin (or vice-versa) when response to the first-choice systemic treatment is inadequate. 86. Consider acitretin for adults, and in exceptional cases only for children and young people, in the following circumstances: • if methotrexate and ciclosporin are not appropriate or have failed or • for people with pustular forms of psoriasis. [ttt] At the time of publication (October 2012), methotrexate did not have UK marketing authorisation for this indication in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information. [uuu] At the time of publication (October 2012), ciclosporin did not have UK marketing authorisation for this indication in children and young people under 16 years of age. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information. **Systemic biological therapy**

	… **Adalimumab** The recommendations in this section are from Adalimumab for the treatment of adults with psoriasis (NICE technology appraisal guidance 146). • Adalimumab is recommended as a treatment option for adults with plaque psoriasis for whom anti-tumour necrosis factor (TNF) treatment is being considered and when the following criteria are both met. • The disease is severe as defined by a total PASI of 10 or more and a DLQI of more than 10. • The psoriasis has not responded to standard systemic therapies including ciclosporin, methotrexate and PUVA; or the person is intolerant of, or has a contraindication to, these treatments. • Adalimumab should be discontinued in people whose psoriasis has not responded adequately at 16 weeks. An adequate response is defined as either: • 75% reduction in the PASI score (PASI 75) from when treatment started or • 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from start of treatment. **Etanercept** The recommendations in this section are from Etanercept and efalizumab for the treatment of adults with psoriasis (NICE technology appraisal guidance 103). • Etanercept, within its licensed indications, administered at a dose not exceeding 25 mg twice weekly is recommended for the treatment of adults with plaque psoriasis only when the following criteria are met. • The disease is severe as defined by a total PASI of 10 or more and a DLQI of more than 10. • The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA; or the person is intolerant to, or has a contraindication to, these treatments. • Etanercept treatment should be discontinued in patients whose psoriasis has not responded adequately at 12 weeks. Further treatment cycles are not recommended in these patients. An adequate response is defined as either: • a 75% reduction in the PASI score from when treatment started (PASI 75) or • a 50% reduction in the PASI score (PASI 50) and a five-point

	reduction in DLQI from when treatment started. **Infliximab** The recommendations in this section are from Infliximab for the treatment of adults with psoriasis (NICE technology appraisal guidance 134). • Infliximab, within its licensed indications, is recommended as a treatment option for adults with plaque psoriasis only when the following criteria are met. • The disease is very severe as defined by a total PASI of 20 or more and a DLQI of more than 18. • The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate or PUVA, or the person is intolerant to or has a contraindication to these treatments. • Infliximab treatment should be continued beyond 10 weeks only in people whose psoriasis has shown an adequate response to treatment within 10 weeks. An adequate response is defined as either: • a 75% reduction in the PASI score from when treatment started (PASI 75) or • a 50% reduction in the PASI score (PASI 50) and a five-point reduction in the DLQI from when treatment started. **Ustekinumab** The recommendations in this section are from Ustekinumab for the treatment of adults with moderate to severe psoriasis (NICE technology appraisal guidance 180). • Ustekinumab is recommended as a treatment option for adults with plaque psoriasis when the following criteria are met. • The disease is severe, as defined by a total PASI score of 10 or more and a DLQI score of more than 10. • The psoriasis has not responded to standard systemic therapies, including ciclosporin, methotrexate and PUVA, or the person is intolerant of or has a contraindication to these treatments. • The manufacturer provides the 90 mg dose (two 45 mg vials) for people who weigh more than 100 kg at the same total cost as for a single 45 mg vial. • Ustekinumab treatment should be stopped in people whose psoriasis has not responded adequately by 16 weeks after starting treatment. An adequate response is defined as either: • a 75% reduction in the PASI score (PASI 75) from when treatment started or • a 50% reduction in the PASI score (PASI 50) and a five-

	point reduction in the DLQI score from when treatment started.
Nast A, et al. 2011 S3-Leitlinie zur Therapie der Psoriasis vulgaris Update. AWMF Leitlinien-Register Nr 013/001 [20]	Fragestellung/Ziele: Verbesserung der Versorgung der Patienten durch Umsetzung der Empfehlungen der Leitlinie und Optimierung der Kenntnisse der Ärzte bzgl. der in den Studien nachgewiesenen Wirksamkeit. Hilfe zur optimalen Durchführung der Therapien
	Methodik (S3-Leitlinie) Grundlage der Leitlinie: Aktualisierung der ersten Version der S3-Leitlinie zur Therapie der Psoriasis vulgaris aus 2006 sowie des Kurzupdates von 2009, basiert auf EU-LL (siehe Pathirana D, et al. 2009 [21], ergänzende Recherchen durchgeführt Methodenreport zur Leitlinie (www.psoriasis-leitlinie.de) Suchzeitraum: k.A. LoE: A1 Meta-Analyse, die wenigstens eine randomisierte Studie vom A2-Level beinhaltet, wobei die Ergebnisse unterschiedlicher Studien konsistent sind A2 Randomisierte, doppelblind klinisch vergleichende Studie von guter Qualität (z. B. Fallzahlberechnung, Flussdiagramm, ITT-Analyse, ausreichender Umfang) B Randomisierte, klinische Studie von weniger guter Qualität oder andere vergleichende Studie (nicht-randomisiert: Kohorten-, oder Fall-Kontroll-Studie) C Nicht-vergleichende Studie GoR: ↑↑ wird empfohlen (starke Empfehlung für eine Maßnahme) ↑ kann empfohlen werden (Empfehlung für eine Maßnahme) → kann erwogen werden (offene Empfehlung) ↓ kann nicht empfohlen werden (Empfehlung gegen eine Maßnahme) ↓↓ wird nicht empfohlen (starke Empfehlung gegen eine Maßnahme) Sonstige methodische Hinweise • Finanzierung durch die Fachgesellschaft • Interessenkonflikterklärungen durch die AWMF geprüft
	Freitext/Empfehlungen/Hinweise Therapieempfehlungen <u>Adalimumab</u> wird zur Induktionstherapie für Patienten mit mittelschwerer bis schwerer Psoriasis vulgaris empfohlen (↑↑), vor allem wenn andere Therapieformen keinen ausreichenden Therapieerfolg gezeigt haben, unverträglich oder kontraindiziert sind. <u>Ciclosporin</u> kann vor allem zur Induktionstherapie bei mittelschwerer bis schwerer Psoriasis vulgaris empfohlen werden (↑).

	Eine Kombination von Ciclosporin mit topischen Präparaten zur Behandlung der Psoriasis vulgaris kann empfohlen werden (↑). Etanercept wird in der Dosierung von 2x50 mg zur Induktionstherapie für Patienten mit mittelschwerer bis schwerer Psoriasis vulgaris empfohlen (↑↑), vor allem wenn andere Therapieformen keinen ausreichenden Therapieerfolg gezeigt haben, unverträglich oder kontraindiziert sind. In der Dosierung von 1 x 50 mg oder 2 x 25 mg kann eine Anwendung zur Induktionstherapie empfohlen (↑) werden. Kommentar: Im Rahmen der Konsensuskonferenz konnte kein starker Konsens (>75 %) bezüglich der Therapieempfehlung für Etanercept erzielt werden. Die Empfehlung erfolgte daher mit einem Mehrheitsvotum von 62 % der Experten. Alternativ wurde für die Formulierung „kann empfohlen werden“ (2 x 50 mg) sowie „kann erwogen werden“ (1 x 50 oder 2 x 25) gestimmt. Grund der Diskussion war die initial im Vergleich zu den anderen Biologics niedrigere Wirksamkeit von Etanercept mit einem Erreichen der maximalen Wirksamkeit erst nach der Induktionsphase. Die Behandlung mit Fumarsäureestern kann als Induktionstherapie der mittelschweren bis schweren Psoriasis vulgaris bei Erwachsenen empfohlen werden (↑). Infliximab wird zur Induktionstherapie für Patienten mit mittelschwerer bis schwerer Psoriasis vulgaris empfohlen (↑↑), vor allem wenn andere Therapieformen keinen ausreichenden Therapieerfolg gezeigt haben, unverträglich oder kontraindiziert sind. MTX kann zur Induktionstherapie der mittelschweren bis schweren Psoriasis vulgaris empfohlen werden (↑). Acitretin kann in niedriger Dosis für eine Monotherapie auf Grund mangelnder Wirksamkeit nicht empfohlen werden (↓). Ustekinumab wird zur Induktionstherapie bei erwachsenen Patienten mit mittelschwerer bis schwerer Psoriasis vulgaris empfohlen (↑↑), vor allem wenn andere Therapieformen keinen ausreichenden Therapieerfolg gezeigt haben, unverträglich oder kontraindiziert sind.
Paul C, et al. 2011 [22] Evidence-based recommendations on conventional systemic treatments in psoriasis: systematic review and expert	Fragestellungen Q1 - What are the optimal prescription and administration modalities for using MTX in adult plaque~type psoriasis? … Q4 - What are the optimal prescription modalitles of cyctosporin in plaque-type psoriasis in adults? … Q7- What are the practical and optimal treatment modalities of acitretin in adult plaque psoriasis?

opinion of a panel of dermatologists	…
	Methodik Grundlage der Leitlinie: systematische Evidenzrecherche und –bewertung, formale Konsensusprozesse (Delphi Methode) beschrieben Suchzeitraum: bis 2009 LoE: defined by the Oxford Centre for Evidence-Based Medicine [http:/ 1\V'.VW.cebm .net/index.aspx? o::::; 1 025]. GoR: according to the Oxford Levels of Evidence, level of agreement was measured on a 10-point visual analogue scale (1, no agreement; 10, full agreement) Sonstige methodische Hinweise Conflicts of interest: All the authors have been paid consu!tants of Abbott. ln addition, C. Paul has been investigator and consuftant for Novartis and Wyeth. H. Bachelez has been paid for consulting activities for Centocor, Janssen-Cllag, Leo Pharma, Novartis, Pfizer and Schering-Plough. L. Misery has been a paid consultant of Novartis, Janssen-Cilag, Leo Pharma, Pfizer and Pierre Fabre. MA Richard has consulting activities for Janssen·Cilag, Novartis, Pfizer and talking for Janssen-Cilag, Leo Pharma and Pfizer. Funding sources: Abbott France provided financial support for publication but took no further part in the project. The authors have no financial interest in the subject matter or materials discussed in the manuscript.
	Freitext/Empfehlungen/Hinweise **Recommendations** MTX should be started at 5-10 mg/week the first week. Depending on the presence of risk factors, a rapid dose-escalation over 4 weeks is recommended to reach a target therapeutic dose between 15 and 25 mg/week. The maximum dose of methotrexate in psoriasis is 25 mg/week. Grade B lt is recommended to start cyc!osporin at a dose between 2.5 and 5 mg/kg/day, preferabty 5 mg/kg/day for rapid actlon in the absence of comorbidities (obesity', older age). Grade A The recommended initial dose of acitretin is between 10 and 25 mg/day. Grade B
Ormerod AD, et al. 2010 [23] **British Association**	Fragestellung In which conditions should acitretin be used?
	Methodik

of Dermatologists Guidelines on the efficacy and use of acitretin in dermatology.	• Searches of Electronic Databases • Systematic Review with Evidence Tables • Expert Consensus • Internal Peer Review LoE/GoR nach SIGN (siehe Anlage dieser Synopse)
	Freitext/Empfehlungen/Hinweise Acitretin monotherapy is recommended in the treatment of: Severe psoriasis, or psoriasis with severe effects on quality of life, meriting systemic therapy, which is resistant to topical therapy, phototherapy or is unsuitable for these treatments (Strength of recommendation A, Quality of evidence 1+).
Canadian Psoriasis Guidelines Committee, 2009 [24] Canadian Guidelines for the Management of Plaque Psoriasis siehe auch: **Papp** et al [25]. Canadian guidelines for the management of plaque psoriasis: overview. J Cutan Med Surg 2011; 15 (4): 210-9.	Fragestellung *???*
	Methodik Grundlage der Leitlinie: systematische Evidenzrecherche und –bewertung, keine Konsensusprozesse beschrieben Suchzeitraum: 1980 – 02/2008 LoE/GoR (siehe Anhang zu dieser Synopse) Sonstige methodische Hinweise • CoI of all Committee members declared • Financial assistance for the development of these Guidelines was generously provided by the following sponsors (in alphabetical order): Abbott Laboratories, Limited; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; EMD Serono Canada Inc.; Galderma Canada Inc.; Isotechnika Inc.; Janssen-Ortho Inc.; LEO Pharma Inc.; Schering-Plough Canada Inc.; and Wyeth.
	Freitext/Empfehlungen/Hinweise Therapeutic options for ameliorating moderate to severe plaque psoriasis (alphabetical list, grouped by class) **Oral systemic agents** Acitretin: Retinoid drug; highly teratogenic and strictly contraindicated in pregnancy. Not to be used in women of childbearing age unless they are able and willing to use contraception for 3 years after discontinuing acitretin - Rarely used as monotherapy, but often combined with topical agents such as potent corticosteroids, or with other therapeutics to allow for more rapid/complete control, with reduced exposure to the other therapeutic (LoE 1-) Cyclosporine: Immunosuppressive drug; leads to cumulative renal

	toxicity; can exacerbate hypertension and hypertriglyceridemia - Can be highly effective in severe disease, but best employed intermittently, rather than for continuous long-term use (LoE 1++) Methotrexate: Immunomodulatory and anti-proliferative drug, often chosen for long-term management - Use is limited by risk of liver toxicity and the requirement for ongoing monitoring of liver function. Sometimes administered with folate supplement to reduce systemic toxicity (LoE 1+) **Biologic agents** Adalimumab: Targets TNF-a. Safety profile, primarily based on record of use in rheumatoid and psoriatic arthritis, suggests some overlap in adverse events with other TNF-a antagonists - Approved for use in psoriatic arthritis as well as psoriasis. Appears to be appropriate for long-term continuous use (LoE 1++) Etanercept: Targets TNF-a; may be associated with risk of infections, demyelinating disorders, and reactivation of latent TB or melanoma - Approved for use in psoriatic arthritis as well as psoriasis. Appropriate for long-term continuous use (LoE 1++) Infliximab: Targets TNF-a. Highly effective on initial exposure, even in severe, acute flares. Variable efficacy following reinitiation or beyond the first year of continuous treatment. - Associated with infusion reactions and risk of infections, demyelinating disorders, and reactivation of latent TB or tumour. - Approved for use in psoriatic arthritis as well as psoriasis (LoE 1++)
Menter A, et al. 2009 [26] Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents	Fragestellung This fourth section will cover the management and treatment of psoriasis with traditional systemic therapies. Methodik Grundlage der Leitlinie: systematische Recherche, k.A. zu Konsensusprozessen) Suchzeitraum: 1960 - 2008 *Weitere Kriterien für die Qualität einer LL:* • *Bewertung der Evidenz nach Ebell MH, et al. Simplifying the language of evidence to improve patient care: Strength of recommendation taxonomy (SORT): a patient centered approach to grading evidence in medical literature. J Fam Pract 2004;53:111-20* • *Empfehlungen sind mit Literaturstellen verknüpft* LoE/GoR: Evidence was graded using a 3-point scale based on the quality of methodology as follows: I. Good-quality patient-oriented evidence. II. Limited-quality patient-oriented evidence.

	III. Other evidence including consensus guidelines, opinion, or case studies. Clinical recommendations were developed on the best available evidence tabled in the guideline. These are ranked as follows: A. Recommendation based on consistent and good quality patient-oriented evidence. B. Recommendation based on inconsistent or limited-quality patient-oriented evidence. C. Recommendation based on consensus, opinion, or case studies. Sonstige methodische Hinweise • Funding sources: None. • CoI declared
	Freitext/Empfehlungen/Hinweise <u>Table VII. Recommendations for methotrexate</u> Therapeutic results • In the only placebo-controlled trial of methotrexate for psoriasis, 36% of patients treated with 7.5 mg/wk orally, increased as needed up to 25 mg/wk, reached PASI 75 after 16 wk <u>Table X. Recommendations for cyclosporine</u> Short-term results • At 3 and 5 mg/kg/d, 36% and 65%, respectively, achieved a clear or almost clear result after 8 wk • After 8-16 wk, 50%-70% of patients achieve PASI 75 Long-term results • Not recommended because of toxicities • Rapid relapse after abrupt discontinuation of cyclosporine <u>Table XI. Recommendations for acitretin</u> Short-term results • Efficacy rates not well defined but are high, based on studies of high dosages that are poorly tolerated • Efficacy rates when used in combination with phototherapy are higher Long-term results • Not reported <u>Table XIII. Recommendations for fumaric acid esters</u> <u>Indications</u> Short-term results • Multicenter, randomized, double-blind placebo-controlled trial of 100 patients showed that after 16 wk, patients treated with fumarate reached a mean PASI 50 compared with patients given placebo whose PASI was essentially changed • Randomized, double-blind controlled trial of 143 patients given either fumarate plus calcipotriol or fumarate alone found that patients given combination therapy reached PASI 50 in 3 wk vs those treated with fumarate alone reaching PASI 50 in 9 wk Long-term results • Case series of patients treated up to 14 y suggest no increased risk for infections or malignancies; large, long-term follow-up studies are necessary to confirm these observations <u>Table VIII. The strength of recommendations for the treatment of</u>

	psoriasis using traditional systemic therapies Methotrexate*: Strength of Recommendation B, Level of Evidence II Cyclosporine*: Strength of Recommendation B, Level of Evidence II Acitretin*: Strength of Recommendation B, Level of Evidence II Fumaric acid esters**: Strength of Recommendation B, Level of Evidence I The reader is advised not to use this table alone for decision making regarding the choice of traditional systemic therapies. *Although methotrexate, cyclosporine, and acitretin are all Food and Drug Administration approved for the treatment of psoriasis and have been used for many years by dermatologists with good to excellent results, the quality of the evidence supporting their use is as listed. ** The fumaric acid esters studies are well-designed placebo-controlled trials but because this treatment is not approved in the United States, it has been given strength of recommendation of B with a level I of evidence.
Pathirana D, et al. 2009 European S3-guidelines on the systemic treatment of psoriasis vulgaris [21]	Fragestellung *k.A.*
	Methodik (S3-Leitlinie) Grundlage der Leitlinie: 3 Quellleitlinien und ergänzende Recherchen, nominaler Gruppenprozess zur Verabschiedung der Empfehlungen, externes Reviewverfahren Suchzeitraum: 2005 - 2007 *Weitere Kriterien für die Qualität einer LL:* • *Standardisiertes Verfahren zur Literaturbewertung* • *transparente Ergebnisdarstellung* LoE/GoR Grades of evidence A1 Meta-analysis that includes at least one randomized clinical trial with a grade of evidence of A2; the results of the different studies included in the meta-analysis must be consistent. A2 Randomized, double-blind clinical study of high quality (e.g. sample-size calculation, flow chart of patient inclusion, ITT analysis, sufficient size) B Randomized clinical study of lesser quality, or other comparative study (e.g. non-randomized cohort or case-control study). C Non-comparative study D Expert opinion In addition, the following levels of evidence were used to provide an overall rating of the available efficacy data for the different treatment

	options: Levels of evidence 1 Studies assigned a grade of evidence of A1, or studies that have predominantly consistent results and were assigned a grade of evidence of A2. 2 Studies assigned a grade of evidence of A2, or studies that have predominantly consistent results and were assigned a grade of evidence of B. 3 Studies assigned a grade of evidence of B, or studies that have predominantly consistent results and were assigned a grade of evidence of C. 4 Little or no systematic empirical evidence; extracts and information from the consensus conference or from other published guidelines. Sonstige methodische Hinweise • no information about funding • CoI declared
	Freitext/Empfehlungen/Hinweise Therapeutic recommendations · Part of the guidelines group believes that methotrexate (15‑22.5 mg/week) should be recommended based on many years of clinical experience with this agent and on the included studies; other members believe that methotrexate should only be suggested for the treatment of psoriasis vulgaris because of the limited evidence available (only one A2 trial) in the studies. · Methotrexate is, as a result of its slow onset of action, less desirable for short-term induction therapy than for long-term therapy. · Ciclosporin is suggested primarily for induction therapy in adults with moderate to severe psoriasis vulgaris who cannot be sufficiently treated with topical therapy and/or phototherapy. · Ciclosporin can be considered for long-term therapy (up to 2 years) in individual cases, but patients should be monitored closely for signs of increasing toxicity, especially for decreases in renal function or the efficacy of treatment. · Acitretin is not suggested as a first choice for monotherapy among the conventional systemic treatments. · Treatment with fumaric acid esters is suggested as an effective induction therapy for moderate to severe psoriasis vulgaris in adult patients. · Treatment is limited by gastrointestinal adverse effects and flush symptoms. · A combination of fumaric acid esters and topical treatments is recommended. · Because of the favourable risk-benefit profile with good safety during long-term treatment, fumarates are suggested.* * For this point, a consensus (defined as agreement by at least 75% of the voting experts) could not be reached. The percentage of

	positive votes in this case was 64%. (level of evidence 2) · Adalimumab is recommended for induction therapy for moderate to severe psoriasis if photo(chemo)therapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated. · If, after 10 to 16 weeks, induction therapy is considered successful, maintenance therapy can be considered with the lowest effective dose. (level of evidence 1) · Etanercept is suggested for induction therapy (25 mg or 50 mg biweekly) for moderate to severe psoriasis if photo(chemo)- therapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated. · If, after 10 to 16 weeks, induction therapy is considered successful, maintenance therapy can be considered with the lowest effective dose. (level of evidence 1) · Infliximab is recommended for induction therapy for moderate to severe psoriasis if photo(chemo)therapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated. · The advantage of this drug is its rapid and marked clinical efficacy. · If, after 10 to 16 weeks, induction therapy is considered successful, maintenance therapy can be considered. (level of evidence 1) 3.8 Ustekinumab Ustekinumab has been registered for systemic treatment of moderate to severe psoriasis in 2009.~~186~~ A formal evaluation is not included in these guidelines because of the deadline of literature research being prior to the registration of ustekinumab but will be given in the next guideline update.
Smith CH, et al. 2009 [27] **British Association of Dermatologists'** guidelines for biologic interventions for psoriasis	Fragestellung • to provide up-to-date, evidence-based recommendations on use of biologic therapies Methodik Grundlage der Leitlinie: evidenzbasierte LL (systematische Suche und Bewertung der Literatur) Suchzeitraum: 1990 - 2009 *Weitere Kriterien für die Qualität einer LL:* • *transparente Ergebnisdarstellung* • *Empfehlungen sind mit Literaturstellen verknüpft* LoE/GoR: siehe Anhang dieser Synopse

	Sonstige methodische Hinweise • *CoI declared* • *Guidelines produced in 2005 by the British Association of Dermatologists; reviewed and updated June 2009.*
	Freitext/Empfehlungen/Hinweise <u>Recommendations: Etanercept</u> · Etanercept is recommended for the treatment of patients with severe psoriasis who fulfil the stated disease severity criteria – refer to section 8.0 (Strength of recommendation A; level of evidence 1++) · Etanercept therapy may be initiated at either 50 or 25 mg twice weekly and disease response assessed at 3–4 months (Strength of recommendation A; level of evidence 1++) · The choice of which dose to use will depend on clinical need, disease severity, body weight and, in the U.K., the dose that will be funded (Strength of recommendation B; level of evidence 1++) · Patients established on etanercept 25 mg twice weekly may wish to consider switching to etanercept 50 mg once weekly as these two dosing regimens are equivalent in terms of efficacy (Strength of recommendation A; level of evidence 1+) · In patients who respond, treatment may be continued according to clinical need, although long-term data on efficacy are limited to 2 years (Strength of recommendation C; level of evidence 2+) · Treatment may be discontinued without risk of disease rebound, although there may be a lower response rate on restarting therapy (Strength of recommendation B; level of evidence 1+) <u>Recommendations: Infliximab</u> · Infliximab is recommended for the treatment of patients with severe psoriasis who fulfil the stated disease severity criteria – refer to section 8Æ0 (Strength of recommendation A; level of evidence 1++) · Infliximab therapy should be initiated at a dose of 5 mg kg)1 at weeks 0, 2 and 6 and disease response assessed at 3 months (Strength of recommendation A; level of evidence 1++) · In patients who respond, subsequent infusions (5 mg kg)1) should be given at 8-week intervals to maintain disease control although long-term data are available only up to 1 year (Strength of recommendation A; level of evidence 1++) · Interrupted therapy should be avoided given the associated increased risk of infusion reactions and poorer disease control (Strength of recommendation A; level of evidence 1+) · Methotrexate may be recommended comedication in certain clinical circumstances, e.g. where it is required for associated arthropathy, to improve efficacy or to reduce the development of

	antibodies to infliximab (Strength of recommendation D; level of evidence 3) Recommendations: Adalimumab · Adalimumab is recommended for the treatment of patients with severe psoriasis who fulfil the stated disease severity criteria – refer to section 8.0 (Strength of recommendation A; level of evidence 1++) · Adalimumab therapy should be initiated according to the licensed dosing regimen (i.e. 80 mg subcutaneously at week 0, 40 mg at week 1, and then every other week thereafter) and disease response assessed at 3–4 months (Strength of recommendation A; level of evidence 1++) · Consideration may be given to increasing the dose of adalimumab to 40 mg weekly in certain clinical circumstances (e.g. in those with PASI > 10 despite achieving a response* to adalimumab 40 mg every other week), although this is unlicensed and not approved by NICE (and in the U.K. may not be funded) (Strength of recommendation A; level of evidence 1+) · In patients who respond, treatment may be continued according to clinical need although long-term efficacy data are available only up to 1 year (Strength of recommendation A; level of evidence 1++) · If necessary, treatment may be discontinued without risk of disease rebound, although there may be a lower response rate on restarting therapy (Strength of recommendation A; level of evidence 1+) · Methotrexate may be recommended comedication in certain clinical circumstances, e.g. where it is required for associated arthropathy, or to increase efficacy (Strength of recommendation B; level of evidence 3) * as defined in section 9.0 (PASI 50, DLQI –5) Recommendations: Ustekinumab · In light of limited patient exposure, ustekinumab should be reserved for use in patients with severe psoriasis who fulfil the stated disease severity criteria AND where TNF antagonist therapy has failed or is contraindicated – refer to section 8.0 (Strength of recommendation A; level of evidence 1+) · For logistical and safety reasons, drug injections should be supervised by a health care professional (Strength of recommendation D (GPP); level of evidence 4)

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NIHR Horizon Scanning Centre (NIHR HSC), 2013 [28] Apremilast for psoriasis	Existing comparators and treatments Current treatment options for plaque psoriasis include: <u>Topical (alone or in combination)</u> ・ Corticosteroids: betamethasone dipropionate. ・ Vitamin D analogues: calcipotriol, calcitriol, tacalcitol and tazarotene (with or without phototherapy). ・ Tars (with or without phototherapy). ・ Dithranol (with or without phototherapy). ・ Salicyclic acid. ・ Tacrolimus ointment (not licensed for this indication). <u>Phototherapy</u> ・ Narrow band UVB or psoralen and UVA combination (PUVA). <u>Systemic therapies (for the treatment of patients with severe or refractory psoriasis)</u> ・ Oral retinoids: acitretin (with or without phototherapy). ・ Hydroxycarbamide (not licensed for this indication). ・ Fumaric acid esters: monoethylfumarate and dimethylfumarate (licensed in the EU but not in the UK). ・ Drugs affecting the immune response: ciclosporin, methotrexate, azathioprine and mycophenolate mofetil. <u>Biologics (for the treatment of patients intolerant, contraindicated or refractory to other treatments)</u> Drugs affecting the immune response: ・ *Anti-tumour necrosis factor: etanercept, infliximab and adlaimumab* ・ *Anti-interleukin 12/23: ustekinumab.*
NIHR Horizon Scanning Centre (NIHR HSC), 2013 [29] Dimethyl fumarate for plaque psoriasis	Siehe oben
NIHR Horizon Scanning Centre (NIHR HSC) [30] Secukinumab for plaque psoriasis	Siehe oben
National Institute for Health and Clinical Excellence (NICE), 2009 [31] Ustekinumab for the treatment of adults with moderate to severe psoriasis	1.1 Ustekinumab is recommended as a treatment option for adults with plaque psoriasis when the following criteria are met. • The disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) score of 10 or more **and** a Dermatology Life Quality Index (DLQI) score of more than 10. • The psoriasis has not responded to standard systemic therapies, including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or the person is intolerant of or has a contraindication to these treatments. • The manufacturer provides the 90 mg dose (two 45 mg vials) for

	people who weigh more than 100 kg at the same total cost as for a single 45 mg vial. 1.2 Ustekinumab treatment should be stopped in people whose psoriasis has not responded adequately by 16 weeks after starting treatment. An adequate response is defined as either: • a 75% reduction in the PASI score (PASI 75) from when treatment started **or** • a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in the DLQI score from when treatment started. 1.3 When using the DLQI, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the DLQI and make any adjustments they consider appropriate.

Primärstudien

Das ausreichend Information aus aggregierter Evidenz vorliegt, ist eine Suche nach Primärstudien nicht notwendig.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library am 11.09.2013

#	Suchfrage	Treffer
1	MeSH descriptor: [Psoriasis] explode all trees	1747
2	(Psoriasis):ti,ab,kw	2970
3	#1 or #2, from 2008 to 2013	542

All Results (524)
Cochrane Reviews (14) Other Reviews (39) Trials (405) Methods Studies (1) Technology Assessments (30) Economic Evaluations (35) Cochrane Groups (0)

MEDLINE (PubMed) am 11.09.2013

#	Suchfrage	Treffer
#1	Psoriasis[MeSH Terms]	28284
#2	Psoriasis[Title/Abstract]	25031
#3	(#1) OR #2	34143
#4	(#3) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])	589
#5	((((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]))))	148631
#6	(#3) AND #5	440
#7	(#4) OR #6	705
#8	(#7) AND ("2008/09/01"[PDAT] : "2013/09/11"[PDAT])	464

MEDLINE (PubMed) nach Leitlinien am 11.09.2013

#	Suchfrage	Treffer
#1	Psoriasis[MeSH Terms]	28284
#2	Psoriasis[Title/Abstract]	25031
#3	(#1) OR #2	34143
#9	(#3) AND (Guideline[ptyp] OR Practice Guideline[ptyp])	55

#10	(#3) AND guideline*[Title]	100
#11	(#9) OR #10	129
#12	(#11) AND ("2008/09/01"[PDAT] : "2013/09/11"[PDAT])	69

Anhang:

Table 1. The modified SIGN scale[4] used by the Evidence and Recommendations Committees

Levels of evidence	
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2–	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g., case reports, case series
4	Expert opinion

Grades of recommendation	
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 1–, 2–, or 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Abbildung 1: aus Canadian Psoriasis Guidelines Committee, 2009 [24]

Level of evidence

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias[a]
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias or chance and a signifi cant risk that the relationship is not causal[a]
3	Nonanalytical studies (e.g. case reports, case series)
4	Expert opinion, formal consensus

RCT, randomized controlled trial. [a]Studies with a level of evidence '−' should not be used as a basis for making a recommendation.

Strength of recommendation

Class	Evidence
A	• At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population, **or** • A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results • Evidence drawn from a NICE technology appraisal
B	• A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results, **or** • Extrapolated evidence from studies rated as 1++ or 1+
C	• A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, **or** • Extrapolated evidence from studies rated as 2++
D	• Evidence level 3 or 4, **or** • Extrapolated evidence from studies rated as 2+, **or** • Formal consensus
D (GPP)	• A good practice point (GPP) is a recommendation for best practice based on the experience of the guideline development group

RCT, randomized controlled trial.

Abbildung 2: aus Smith CH, et al. 2009 [27]

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Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2015-02-15-D-151_Apremilast (Psoriasis Arthritis)

Stand: Februar 2014

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

Apremilast 2014-B-005 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	Therapiehinweise im Anwendungsgebiet liegen für folgende Wirkstoffe vor: **Adalimumab** (Beschluss vom 21. November 2006) und **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** Psoriasis Arthritis
Apremilast	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
Biologika: Tumornekrosefaktor-alpha(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. […] Plaque-Psoriasis Behandlung Erwachsener mit mittelschwerer bis schwerer Plaque-Psoriasis, die auf eine andere systemische Therapie wie Ciclosporin, Methotrexat oder Psoralen und UVA-Licht (PUVA) nicht angesprochen haben oder bei denen eine Kontraindikation oder Unverträglichkeit einer solchen Therapie vorliegt (FI Enbrel® 2013-02)
Infliximab L04AB02 Remicade®	[…] Psoriasis-Arthritis Remicade ist indiziert zur Behandlung der aktiven und fortschreitenden Psoriasis-Arthritis bei erwachsenen Patienten, wenn deren Ansprechen auf eine vorhergehende krankheitsmodifizierende, antirheumatische Arzneimitteltherapie (DMARD-Therapie) unzureichend gewesen ist. Remicade sollte verabreicht werden – in Kombination mit Methotrexat – oder als Monotherapie bei Patienten, die eine Unverträglichkeit gegenüber Methotrexat zeigen oder bei denen Methotrexat kontraindiziert ist. Remicade verbessert die körperliche Funktionsfähigkeit bei Patienten mit Psoriasis-Arthritis und reduziert die Progressionsrate peripherer Gelenkschäden, wie radiologisch bei Patienten mit polyartikulärem symmetrischen Subtyp der Krankheit belegt wurde […]. Psoriasis Remicade ist indiziert zur Behandlung der mittelschweren bis schweren Psoriasis vom Plaque-Typ bei erwachsenen Patienten, die auf eine andere systemische Therapie, einschließlich Ciclosporin, Methotrexat oder PUVA, nicht angesprochen haben, bei denen eine solche Therapie kontraindiziert ist oder nicht vertragen wird […]. FI Remicade® 2013-02)
Adalimumab L04AB04	[…] Psoriasis-Arthritis Humira ist indiziert zur Behandlung der aktiven und progressiven Psoriasis-Arthritis (Arthritis psoriatica) bei Erwachsenen, die nur unzureichend

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Humira®	auf eine vorherige Basistherapie angesprochen haben. Humira reduziert das Fortschreiten der radiologisch nachweisbaren strukturellen Schädigungen der peripheren Gelenke bei Patienten mit polyartikulären symmetrischen Subtypen der Erkrankung […] und verbessert die körperliche Funktionsfähigkeit. Psoriasis Humira ist indiziert zur Behandlung der mittelschweren bis schweren chronischen Plaque-Psoriasis bei erwachsenen Patienten, die auf eine andere systemische Therapie, wie Ciclosporin, Methotrexat oder PUVA, nicht angesprochen haben oder bei denen eine Kontraindikation oder Unverträglichkeit gegenüber einer solchen Therapie vorliegt. […] (FI Humira® 2013-02)
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-Therapie) 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. […] (FI Simponi® 2013-03) (Zulassung der Indikation: 10/2009)
Ustekinumab L04AC05 Stelara®	[…] Psoriasis-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 Therapie mit nicht-biologischen krankheitsmodifizierenden Antirheumatika (DMARDs) unzureichend gewesen ist (Zulassung der Indikation: 01/2014)
Certolizumab Pegol L04AB05. Cimzia ®	[…] Psoriasis-Arthritis (PsA) 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. (FI Cimzia® 2013-11) (Zulassung der Indikation: 10/2013)
Steroidale Antirheumatika (Glucocorticoide)	
Prednisolon H02AB06 generisch	Decortin H 1 mg/5 mg/10 mg/20 mg/50 mg Tabletten sind angezeigt zur Behandlung von Erkrankungen, die einer systemischen Therapie mit Glucocorticoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad […]: […] Andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können: […] Arthritis psoriatica […] (FI Decortin® 2013-05)
Prednison H02AB07 generisch	Prednison acis ist angezeigt zur Behandlung von Erkrankungen, die einer systemischen Therapie mit Glucocorticoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad […]: […] Andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	[…] Arthritis psoriatica […] (FI Prednison acis® 2011-04)
Triamcinolon H02AB08 Volon®	[…] Andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können: […] Arthritis psoriatica […] (FI Volon® 2011-04)
Nichtsteroidale Antirheumatika (NSAR oder NSAID)	
z. B. Indometacin M01AB01 generisch	Symptomatische Behandlung von Schmerz und Entzündung bei akuten Arthritiden chronischen Arthritiden […] (FI Indomet-ratiopharm® 2011-12)

Gemeinsamer Bundesausschuss

Recherche und Synopse der Evidenz zur Bestimmung der zVT:

Inhalt

Berücksichtigte Wirkstoffe/Therapien

Für das Anwendungsgebiet zugelassenen Arzneimittel, s. Unterlage zur Beratung in AG: „Übersicht zVT, Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet“

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 21.01.2014 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AkdÄ, AWMF, GIN, NGC, TRIP, DAHTA, NIHR HSC. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Es wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab insgesamt 337 Treffer, welche anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Die erste Durchsicht ergab 81 eingeschlossene Quellen, die anschließend im Volltext überprüft wurden. Daraus konnten 26 Referenzen, die in die synoptische Evidenz-Übersicht aufgenommen werden.

Abkürzungen

ACR	Arthritis Research Campaign
AAD	Academy of Dermatology
ACR	American College of Rheumatology
AM	Arzneimittel
CCT	controlled clinical trials
DMARD	disease-modifying anti-rheumatic drugs
ES	Erosion Score
GoR	Grade of Recommendations
HAQ	Health Assessment Questionnaire
HRQoL	Health related quality of live
HSC	Horizon Scanning Centre
HTA	health technology assessment
JSNS	Joint Space Narrowing Score
LEF	leflunomide
LoE	Level of Evidence
LFT	liver function test
MTX	Methotrexat
NICE	National Institute for Health and Care Excellence
NSAID	nonsteroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PsA	Psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
RA	Rheumatoid arthritis
RCT	randomised controlled trials
RR	Risk reduction
TNF	tumor necrosis factor
TSS	Total Sharp Score

G-BA-Beschlüsse

Erstautor, Jahr Titel	**Inhalt**
Gemeinsamer Bundesausschuss (G-BA) 2007: Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie in Anlage 4. [8]	Die Anlage 4 nach Nummer 14 der Arzneimittel-Richtlinie wird um den folgenden Therapiehinweis ergänzt: **Leflunomid (Arava®)** Empfehlungen zur wirtschaftlichen Verordnungsweise Beschluss vom: 16.08.2007 / 15.05.2008 In Kraft getreten am: 21.12.2007 / 03.09.2008 BAnz. 2007, Nr. 238 vom 20.12.2007, S. 8 316 / BAnz. 2008, Nr. 132 vom 02.09.2008, S. 3 216 **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.
Gemeinsamer Bundesausschuss (G-BA) 2006: Anlage IV zum Abschnitt H der Arzneimittel-Richtlinie Verordnungseinschränkungen und -ausschlüsse in der Arzneimittelversorgung. [7]	**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 BAnz. 2007 Nr. 126; 11. Juli 2007, S. 6932 **Indikation** Adalimumab ist ein rekombinanter humaner monoklonaler Antikörper. Adalimumab ist zugelassen zur Behandlung − der mäßigen bis schweren aktiven Rheumatoiden Arthritis bei Erwachsenen, die nur unzureichend auf krankheitsmodifizierende 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. Patienten mit Rheumatoider Arthritis (RA) sollen möglichst früh mit Disease Modifying Antirheumatic Drugs (DMARDs = „Basistherapeutika“) behandelt werden. Es gibt Hinweise darauf, dass hierdurch die Prognose der RA günstig beeinflusst wird und dass dieses Vorgehen entscheidend zum Erhalt der Funktion und zur Verminderung späterer Funktions-einschränkungen beiträgt. 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.

Cochrane Reviews

Colebatch et al. 2011: Safety of non-steroidal anti-inflammatory drugs, including aspirin and paracetamol (acetaminophen) in people receiving methotrexate for inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis) [3].	Systematische Literaturrecherche bis 2009 **Population:** Erwachsene Patienten (mind. 18 Jahre) mit einer inflammatorischen Arthritis (rheumatoide Arthritis, ankylosierende Spondylitis, psoriatrische Arthritis und andere Formen einer Spondyloarthritis) **Vergleich:** Methotrexat Monotherapie vs. Methotrexat plus NSAIDs (inkl. Aspirin, oder Paracetamol oder beidem) **Endpunkte:** • Hauptendpunkte: gesteigerte Toxizität unter MTX (durch gastrointestinale, hepatische, pulmunale, hämatologische oder renale Nebenwirkungen), Studienabbrüche aufgrund von Nebenwirkungen • Weitere Endpunkte: Alle Nebenwirkungen (inkl. Mortalität) **Ergebnisse:** Es wurden lediglich Studien zu Patienten mit einer rheumatoiden Arthritis identifiziert. Es liegen keine Studien zu anderen Formen einer inflammatorischen Arthritis vor. **Hinweis der Autoren:** ‘It was not possible to give precise descriptions of the adverse events because the data collected did not lend itself to a meta-analysis due to heterogeneity and, in some cases, due to lack of data.’
Radner et al. 2012: Pain management for inflammatory arthritis (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and other spondyloarthritis) and gastrointestinal or liver comorbidity [19]	Systematische Literaturrecherche bis 2010 **Population:** Erwachsene Patienten (mind. 18 Jahre) mit einer rheumatoiden Arthritis, ankylosierenden Spondylitis, psoriatrischen Arthritis oder anderen Form einer Spondyloarthritis, sowie einer gleichzeitig berichteten gastrointestinalen oder hepatischen Komorbidität. (Hinweis: Für kontrollierte Studien wurden sowohl Patienten mit und ohne gastrointestinalen oder hepatischen Komorbiditäten eingeschlossen). **Vergleich:** Untersuchung der Wirksamkeit und Sicherheit von folgenden Wirkstoffe: Paracetamol, NSAIDs, Opioid-ähnliche AMs (z.B. Tramadol) und Neuromodulatoren (inkl. Antidepressiva, Antikonvulsiva und Muskelrelaxantien)

	Endpunkte: • Hauptendpunkte: Patienten-berichtete Schmerzlinderung von ≥50 % (berichtet auf einer Visual-Analogue-Skala oder Nummerische bzw. verbale Rating-Skalen; Studienabbrüche aufgrund von Nebenwirkungen • Weitere Endpunkte: Verschlechterung der Komorbidität, jegliche Nebenwirkung, Nebenwirkungen aufgrund von inadäquater Analgesie, Patienten-berichtete Schmerzlinderung von ≥30 %, Patienten-berichtete 'global impression of clinical change (PGIC) 'much' or 'very much' improved; Anteil Patienten die einen Schmerzscore unter 30/100 auf einer Visual-Analogue-Skala erreichen, durchschnittl. Schmerzscore auf einer Visual-Analogue-Skala oder Nummerischen Rating-Skala, Funktion, Lebensqualität **Ergebnisse:** • Es konnte nur eine relevante Studie identifiziert werden. Diese Studie bestand aus Patienten mit einer rheumatoiden Arthritis. Es lagen keine Studien vor zu dem hier relevanten Indikationsgebiet der Psoriasis-Arthritis.
Ramiro et al. 2010: Combination therapy for pain management in inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis). [20]	Systematische Literaturrecherche bis 2010 **Population**: Erwachsene Patienten (mind. 18 Jahre) mit einer inflammatorischen Arthritis (rheumatoide Arthritis, ankylosierende Spondylitis, psoriatrische Arthritis und andere Formen einer Spondyloarthritis) **Vergleich:** Kombinationstherapie vs. Monotherapie Folgende AM-Klassen wurden betrachtet: • Analgetika • NSAIDs • Opioide • Tramadol (z.B. opioid-ähnliche AM) • Neuromodulatoren (Antidepressiva, Antikonvulsiva und Muskelrelxantien) **Endpunkte:** • Hauptendpunkte: Patienten-berichtete Schmerzlinderung von ≥50% (berichtet auf einer Visual-Analogue-Skala oder Nummerische bzw. Verbale Rating-Skalen; Studienabbrüche aufgrund von Nebenwirkungen

	• Weitere Endpunkte: Verschlechterung der Komorbidität, jegliche Nebenwirkung, Nebenwirkungen aufgrund von inadäquater Analgesie, Patienten-berichtete Schmerzlinderung von ≥30 %, Patienten-berichtete 'global impression of clinical change (PGIC) 'much' or 'very much' improved; Anteil Patienten die einen Schmerzscore unter 30/100 auf einer Visual-Analogue-Skala erreichen, durchschnittl. Schmerzscore auf einer Visual-Analogue-Skala oder Nummerischen Rating-Skala, Funktion, Lebensqualität **Ergebnisse:** Es wurden insgesamt 23 Studien identifiziert. Darunter schlossen 22 Studien Patienten mit rheumatoider Arthritis ein und eine Studie wies eine gemischte Studienpopulation auf, bestehend aus rheumatoider Arthritis- und Osteoarthritis-Patienten. Es lagen keine Studien vor zu dem hier relevanten Indikationsgebiet der Psoriasis-Arthritis.

Systematische Reviews

AHRQ, 2012: Drug Therapy for Psoriatic Arthritis in Adults: Update of a 2007 Report. [23]	Systematische Literaturrecherche bis 2011. **Ziel**: 'This report summarizes the evidence on the comparative efficacy, effectiveness, and harms of corticosteroids, oral DMARDs, and biologic DMARDs in the treatment of patients with Psoriatic arthritis (PsA).' **Population:** Erwachsene PsA Patienten **Vergleich:** Vergleich der Wirksamkeit und Sicherheit von Kortikosteroiden, oralen DMARDs, und biologischen DMARDs **Ergebnisse**: Allgemein: Es wurden keine kontrollierten head-to-head Studien identifiziert. Die Ergebnisse basieren auf 2 direkt vergleichenden Kohorten Studien und Placebo-kontrollierten Studien. • For oral DMARDs, including sulfasalazine and methotrexate, the sparse data available involved placebo comparisons. For biologic DMARDs, evidence supported the efficacy of adalimumab, etanercept, golimumab, and infliximab for the treatment of PsA when compared with placebo. • Qualitatively, these biologic DMARDs appeared to achieve similar improvements in disease activity, functional capacity, and health-related quality of life (American College of Rheumatology 20 percent improvement from baseline to endpoint, Health Assessment Questionnaire, and Short Form 36 Physical Component scores) in these trials. • No difference in treatment response was found between the combination of an antitumor necrosis factor (TNF) (adalimumab, etanercept, or infliximab) with methotrexate compared with anti-TNF only. Evidence was insufficient to draw conclusions about the comparative harms for oral DMARDs. • Among biologics, low evidence indicated that etanercept had a lower rate of withdrawals due to adverse events compared with infliximab. • Compared with placebo, adalimumab and etanercept had more injection site reactions and adalimumab had few events of aggravated psoriasis. No comparative evidence was identified for subgroups. **Fazit der Autoren**: 'Overall, the data are quite limited and the evidence is insufficient to draw firm conclusions on comparative efficacy, effectiveness, and harms of either oral or biologic DMARDs for PsA. This report's findings did not

	reveal any differences with current standard of care. Head-to-head (RCTs) are needed to establish the comparative efficacy and safety of different treatments with and without corticosteroids, oral DMARDs, and biologic DMARDs, to determine the best therapy to prevent or minimize debilitating joint damage and optimize quality of life for people with PsA.' **Kommentare der Autoren und FBMed:** Die Patienten in den Studien haben meistens schon vorherige Therapien ausprobiert und nicht angesprochen: *‚Prior medications tried before these studies were variable, but in general patients had failed a DMARD prior to starting any of the biologic agents.'*
Rodgers et al. 2011: Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. [22]	Basierend auf einer system. Literaturrecherche bis 2009 mit Metaanalyse **Ziel/Fragestellung:** 'To determine the clinical effectiveness, safety and cost-effectiveness of etanercept, infliximab and adalimumab' **Population:** Patients with active and progressive PsA who have an inadequate response to standard treatment (including DMARD therapy). **Endpunkte:** Primär: • measures of anti-inflammatory response [Psoriatic Arthritis Response Criteria (PsARC), American College of Rheumatology 20% Improvement Criteria (ACR 20)], skin lesion response [Psoriasis Area and Severity Index (PASI)] and functional status [Health Assessment Questionnaire (HAQ)]. • safety outcome: incidence of serious adverse events. • cost-effectiveness was incremental cost per additional quality-adjusted lifeyear (QALY). **Ergebnisse** (basierend auf 6 RCTs): Note: Ergebnisse basieren auf direkten und indirekten Vergleichen! *Wirksamkeit:* • Pooled estimates of effect demonstrated a significant improvement in patients with PsA for all joint disease and functional status outcomes at 12–14 weeks' follow-up. • The biologic treatment significantly reduced joint symptoms assessed by PsARC for etanercept [relative risk (RR) 2.60, 95% confidence interval (CI) 1.96 to 3.45], infliximab (RR 3.44, 95% CI 2.53 to 4.69) and adalimumab (RR 2.24, 95% CI 1.74 to 2.88). This was consistent with the results from the pooled estimates of ACR 20. • Furthermore, the statistically significant reduction in HAQ score also indicated a beneficial effect of these biologic therapies on patients'

	functional status. • Significant heterogeneity was observed only in the outcome of PsARC in infliximab. • The 24-week data for all three biologics demonstrated that the treatment effects are maintained. Trial data demonstrate a significant effect of all three biologics on skin disease in terms of PASI response, at 12 or 24 weeks. • The results of evidence synthesis found that infliximab appears to be the most effective of the three biologics. Across all outcomes of joint and skin disease at 12 weeks, infliximab is associated with the highest probabilities of response. The response in joint disease (PsARC and ACR) is greater with etanercept than with adalimumab, whereas the response in skin disease (PASI) is greater with adalimumab than with etanercept, although these differences are not statistically significant. • In those patients who achieve a PsARC response to treatment the highest mean reductions in the functional and psychological impact of the disease, measured by HAQ, are seen with infliximab and etanercept (–0.657 for infliximab and –0.630 for etanercept). • For all three biologics the changes in HAQ for those patients who did not respond to treatment were below the minimum clinically significant threshold (–0.3). • Short-term radiographic measures indicate that these agents can slow disease progression in the short term (< 24 weeks). The available follow-up data, although promising, are inadequate to determine if these effects persist in the longer term. *Sicherheit:* • Thirty-two relevant studies were identified for the evaluation of safety of these biologics. • The rates of serious infection were etanercept 0.6%–13.2%, infliximab 0.8%–13.8% and adalimumab 0.4%–5.1%. The rates of malignancy were etanercept 1%–5.7%, infliximab 0.16%–5.1% and adalimumab 0.1%–1.1%. The rates of activation of TB for the treatment were etanercept 0%–1.4%, infliximab 0.06%–4.6% and adalimumab 0%–0.4%. **Kommentare der Autoren:** Limited available efficacy data and difficulty in assessing PsA activity and its response to biologic therapy.

Fenix-Caballero et al. 2013: Direct and indirect comparison of the efficacy and safety of adalimumab, etanercept, infliximab and golimumab in psoriatic arthritis. [5]	**Methodik**: Für die direkte Evidenz wurde eine systematische Literaturrecherche (Suchzeitraum nicht angegeben; lediglich das die Recherche 2011 durchgeführt wurde) durchgeführt; für den indirekten Vergleich wurde die Bucher Methode gewählt und Infliximab als Referenzsubstanz genommen. **Population**: Patienten mit einer Psoriasis-Arthritis **Vergleich**: Wirksamkeit zwischen Adalimumab, Etanercept, Infliximab und Golimumab **Endpunkte**: Primärer Endpunkt: ARC50 Sekundäre Endpunkte: ACR20 und ACR70 **Ergebnisse**: Direkter Vergleich: Insgesamt wurden 4 Studien mit insgesamt 977 Patienten (für jede Substanz eine) identifiziert. Folgende Unterschiede hinsichtlich des primären Endpunktes (ACR50) zwischen Infliximab und den anderen Substanzen wurden gefunden: • Adalimumab (ARR 4%, 95% KI -9,5 to 17,5), • Etanercept (ARR 4%, 95% KI -10,5 to 18,5) und • Golimumab (ARR 9%, 95% CI -5,4 to 23,4). Analog dazu zeigten sich ebenfalls keine stat. signifikanten Unterschiede zwischen den Substanzen hinsichtlich der sekundären Endpunkte mit Ausnahme von Etanercept welches weniger wirksam war hinsichtlich dem ARC70 Ansprechen. In Bezug auf Nebenwirkungen zeigten sich keine stat. signifikanten Unterschiede, mit Ausnahme hinsichtlich Injektionsbezogene Reaktionen welche vermehrt unter Etanercept zu finden waren (Mean Diff.: 26 % relativ zu Infliximab). **Fazit der Autoren**: ‘ No significant differences were found in ACR50 responses to the four drugs after 24 weeks. Injection-site reactions were more common with etanercept, but this was insufficient to invalidate the inference that clinically the four drugs can be regarded as clinically equivalent for the treatment of psoriatic arthritis.’ Etanercept caused more injection-site adverse effects. Despite this, we consider that infliximab, adalimumab, etanercept and golimumab offer

	similar benefit/risk ratios in PsA and could be regarded as ETAs. **Kommentare der FBMed:** Unklar hinsichtlich der Vortherapie (z.B. Wie viele Patienten inadäquat auf DMARDs)
Goulabchand et al. 2013: Effect of tumour necrosis factor blockers on radiographic progression of psoriatic arthritis: a systematic review and meta-analysis of randomised controlled trials. [10]	Systematische Literaturrecherche bis 2012 mit Metaanalyse **Population:** Patienten mit einer Psoriasis-Arthritis **Zielsetzung:** We performed a systematic review and meta-analysis of RCTs of PsA to examine the effect of TNF blockers on radiographic evidence of disease progression. A second objective was to determine whether treatment combining TNF blockers with MTX was superior to TNF-blocker monotherapy. **Endpunkte:** Primärer Endpunkt: Anteil an Patienten die keine Progression aufwiesen (nach 24 Wochen Behandlung) **Ergebnisse:** • The studies involved 1110 patients, 584 receiving TNF blockers with or without MTX, and 526 placebo with or without MTX. • No study compared a TNF blocker with a synthetic DMARD. • In total, 494/584 (84.5%) of patients receiving TNF blockers for PsA were considered non-progressors at week 24 as compared with 362/526 (68.8%) receiving placebo (OR 2.68 (95% CI 1.99 to 3.60), p<0.001), without significant heterogeneity (I2=3%, p=0.39) (figure 2). • At week 24, patients in both groups started receiving TNF blockers: at week 48, one group had received TNF blockers for 24 weeks, and the other for • 48 weeks. Thus, at week 48, results again favoured TNF blockers (OR 2.42 (1.57 to 3.71); I2=0%; p=0.91) (figure 3). • Only a few data were available for TNF blocker therapy combined with MTX. No RCT directly compared the three groups of treatment: TNF blockers combined with synthetic DMARDs and each therapy alone. • No study evaluated the effect of biologics added to MTX on radiographic and clinical outcomes in PsA. ***Hinweis***: *Mease et al. in a subanalysis, found no difference in structural progression between two groups (ETN treatment alone vs ETN with MTX) after 24 weeks, but no statistical analysis was available. Gladman et al., in a subanalysis, found no difference in radiographic disease progression*

	between ADA_alone and ADA with MTX (mean difference in mTSS at 24 weeks −0.2±1.17 vs −0.2±1.59).
Thorlund et al. 2012: Anti-tumor necrosis factor (TNF) drugs for the treatment of psoriatic arthritis: an indirect comparison meta-analysis. [26]	**Zielsetzung/Fragestellung:** Evaluation der Wirksamkeit von TNF-alpha Inhibitoren (adalimumab, etanercept, golimumab, and infliximab). Systematische Literaturrecherche bis 2012 nach RCTs. **Population:** Patienten mit einer Psoriasis-Arthritis mit einem inadäquaten Ansprechen auf DMARDs. **Intervention:** anti-TNFs (adalimumab, etanercept, golimumab, and infliximab) **Kontrolle:** Placebo **Endpunkte:** • PsARC Ansprechen, • HAQ (durchschnittl. Veränderung zu Baseline für responder und non-responder), • PASI (durchschnittl. Veränderung zu Baseline) **Eingeschossene Primärstudien:** • Adalimumab: n= 2 • Etanercept: n= 2 • Infliximab: n= 2 • Golimumab: n= 1 Mittlere bis hohe Studienqualität **Ergebnisse:** We retrieved data from 20 publications representing seven trials, as well as two HTAs.

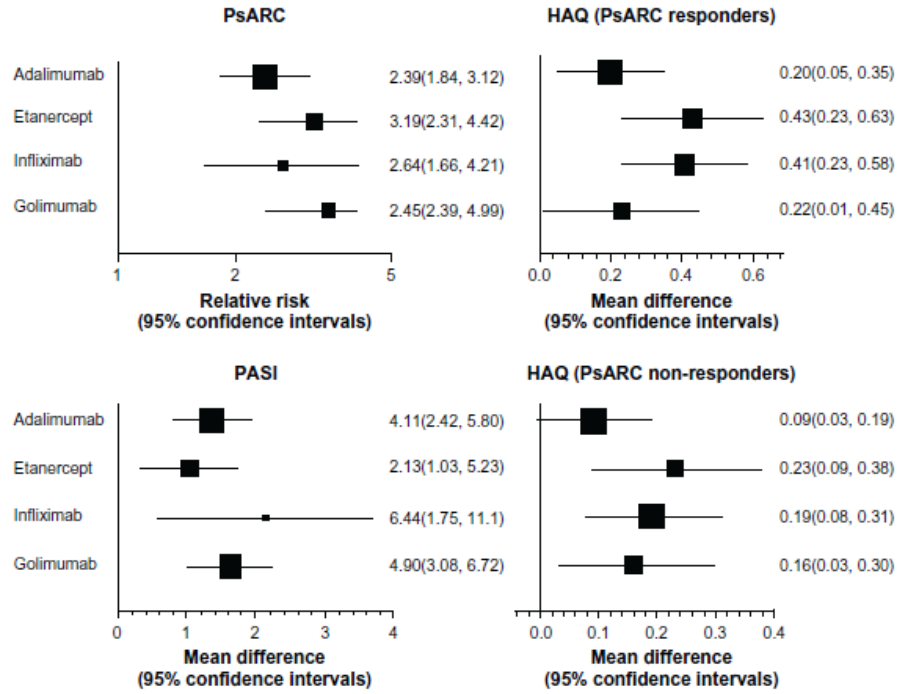


Figure Forest plots of direct estimates for anti-TNFs versus placebo comparisons.

Table 3 Expected response rates and 95% confidence intervals for the three considered outcomes with the four anti-TNF drugs

Outcome	Placebo response	Anti-TNF treatment response			
		ADA	ETN	INF	GOL
PsARC response (proportion)	0.25 (0.21, 0.28)	0.60 (0.50, 0.70)	0.80 (0.70, 0.88)	0.66 (0.48, 0.81)	0.86 (0.76, 0.93)
HAQ responders (mean response)	0.24 (0.18, 0.31)	0.44 (0.29, 0.51)	0.67 (0.47, 0.87)	0.65 (0.47, 0.83)	0.47 (0.24, 0.69)
HAQ nonresponders (mean response)	0.01 (–0.3, 0.04)	0.09 (–0.02, 0.18)	0.24 (0.10, 0.39)	0.19 (0.09, 0.32)	0.17 (0.04, 0.31)
PASI (mean response)	0.68 (0.31, 1.04)	4.79 (3.10, 6.48)	3.81 (1.71, 5.91)	7.12 (2.43, 11.78)	5.58 (3.76, 7.40)

Note: Confidence intervals are derived assuming a fixed placebo response.
Abbreviations: ADA, adalimumab; anti-TNF, anti-tumor necrosis factor; ETN, etanercept; GOL, golimumab; HAQ, Health Assessment Questionnaire; INF, infliximab; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria.

All anti-TNFs were significantly better than control, but the indirect comparison did not reveal any statistically significant difference between the anti-TNFs. For PsARC response, golimumab yielded the highest RR and etanercept the second highest; adalimumab and infliximab both yielded notably smaller RRs. For HAQ improvement, etanercept and infliximab yielded the largest MD among PsARC responders. For PsARC nonresponders, etanercept, infliximab, and golimumab yielded similar MDs, and adalimumab a notably lower MD. For PASI improvement, infliximab yielded the largest MD and golimumab the second largest, while etanercept yielded the smallest MD. In some instances, the estimated magnitudes of effect were notably different from the estimates of previous HTA indirect comparisons.

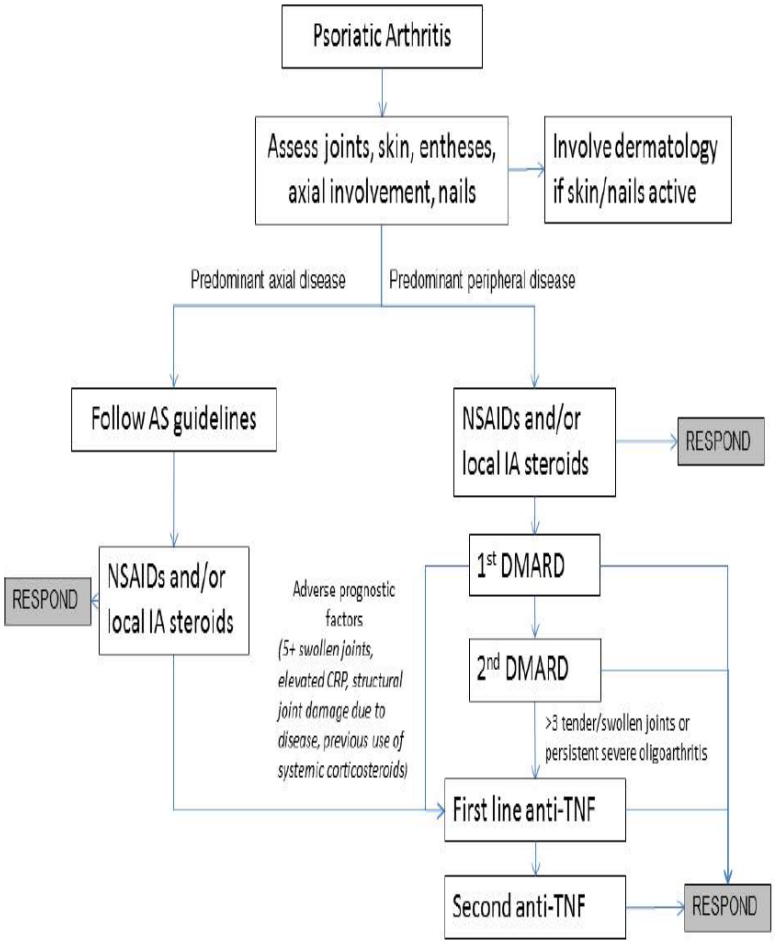
Dommasch et al. 2011: The risk of	**Fragestellung:** Sicherheit von TNF-alpha Inhibitoren (Infliximab, Adalimumab, Golimumab und Certolizumab)

infection and malignancy with rumor necrosis factor antagonists in adult patients with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials. [4]	**Methodik:** Systematische Literaturrecherche bis 2009 nach RCTs. **Population:** Patienten mit einer Psoriasis-Arthritis und Plaque-Arthritis **Vergleiche**: TNF-alpha Inhibitoren gegeneinander (via indirekten Vergleich) und gegenüber Placebo (via direkten Vergleich) **Endpunkte**: Malignome, Infektionen **Ergebnisse**: Allgemein: Ergebnisse basieren allgemein auf 20 klinischen Studien mit insgesamt 6810 Patienten. Darunter befanden sich 7 Studien mit insgesamt 1383 Patienten mit einer aktiven Psoriasis-Arthritis, die unzureichend auf eine vorherige DMARD und/oder NSAID-Therapie angesprochen haben. Alle Studien zu den Patienten mit einer aktiven Psoriasis-Arthritis erlaubten eine begleitende Therapie mit einem DMARD. ***Malignome:*** • Es zeigte sich kein stat. signifikanter Unterschied zwischen TNF-alpha Inhibitoren und Placebo (28 vs. 6 Malignome; gepooltes OR: 1.48; 95%KI: 0.71-3.09; keine Heterogenität). Dabei handelte es sich überwiegend um nicht-malignen Hautkrebs (70.6%). Hierfür wurde ein nicht stat. signifikanter Unterschied mit einem OR von 1.33; 95%KI: 0.58-3.04 identifiziert. • Es zeigte sich weiterhin ein nicht stat. signifikanter Unterschied auch bei den anderen Malignomen (ausgeschlossen nicht-maligner Hautkrebs). • Die Subgruppenanalyse nach Krankheitsbild zeigte ebenfalls keine Unterschiede zwischen der Intervention und Plazebo. ***Infektionen:*** • Es zeigten sich stat. signifikant mehr Infektionen unter einer Therapie mit TNF-alpha Inhibitoren (OR: 1.18; 95%KI: 1.05-1.33); dabei handelte es sich jedoch bei 97.6 % der Fälle um nicht-schwere Infektionen. • Subgruppenanalysen zeigten keinen Unterschied zwischen den Gruppen bei Patienten mit einer aktiven Psoriasis-Arthritis. • hinsichtlich der schweren Infektionen zeigten sich sowohl in der gepoolten, als auch in der Subgruppenanalyse zu Psoriasis-Arthritis Patienten keine stat. signifikanten Unterschiede zwischen TNF-alpha Inhibitoren und Placebo.

	Kommentare der Autoren und FBMed: • Subgruppenanalysen zu den beiden unterschiedlichen Krankheitsformen wurden durchgeführt. • kurze und kleine Studien • Es handelt sich um allgemein seltene Ereignisse (Konfidenzintervalle teilweise sehr breit) • Studien in der Metaanalyse waren teilweise sehr heterogen hinsichtlich: Studienmedikation, design, Krankheitsbild, vorherige und begleitende Therapie, Krankheitsdauer.
Steiman et al. 2013: Non-biologic disease-modifying antirheumatic drugs (DMARDs) improve pain in inflammatory arthritis (IA): a systematic literature review of randomized controlled trials. [25]	**Fragestellung**: Investigation of the effect of non-biologic DMARDs **Methodik**: Systematische Literaturrecherche bis 2010 **Population**: Patienten (mind. 18 Jahre) mit einer inflammatorischen Arthritis (rheumatoide Arthritis, ankylosierende Spondylitis, Psoriasis-Arthritis) Vergleiche: ‚Conventional non-biologic DMARDs (azathioprine, chloroquine, cyclosporine, gold (auranofin, aurothioglucose, or gold sodium thiomalate (GST), myochrysine), hydroxychloroquine, leflunomide, methotrexate, or sulfasalazine) either as monotherapy or in combination therapy' **Endpunkte**: Schmerzempfinden **Ergebnisse**: • Insgesamt wurden 33 Quellen eingeschlossen: Darunter 8 Quellen zu AS, 6 Quellen zu PsA und 9 Quellen zur frühen RA und 10 Quellen zu einer bestätigten RA. • Es konnte lediglich zu dem Wirkstoff Sulfasalazin eine Metaanalyse durchgeführt werden. • Verglichen mit Placebo, zeigte sich unter Sulfalazin ein stat. signifikanter Vorteil hinsichtlich dem der VAS-Schmerzscore in der Indikation PsA (-7.70; 95%; KI: -12.53; -2.87; I^2= 0%; basierend auf 2 Studien).
Loveman E et al., 2009: Infliximab for the treatment of adults with psoriasis [11]	This paper presents a summary of the evidence review group (ERG) report into the clinical and cost-effectiveness of infliximab for the treatment of moderate to severe plaque psoriasis, in accordance with the licensed indication, based on the evidence submission from Schering-Plough to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The outcomes stated in the manufacturer's definition of the decision problem were severity [Psoriasis Area and Severity Index (PASI) score], remission rates, relapse rates and

	health-related quality of life. **Population**: Infliximab is licensed for the treatment of adults with moderate to severe psoriasis who have not responded to (or who are intolerant of) other systemic therapies. **Evidenzbasis**: The main evidence in the submission comes from four international randomised controlled trials (RCTs) comparing infliximab with placebo. A further eight RCTs were also included: four comparing etanercept with placebo and four comparing efalizumab with placebo. Evidence in trials was presented as changes in baseline PASI scores, i.e. a PASI 75 refers to an individual who had a 75% reduction in their baseline PASI score. **Ergenisse**: • At week 10, patients on infliximab had a significantly higher likelihood of attaining a PASI 75 than placebo patients (range 75‑88% versus 2‑18% respectively) (four trials). It should be noted that there were wide confidence intervals around all four point estimates. There was also a statistically significant difference at 10 weeks in favour of infliximab for the proportion of patients achieving a PASI 50 and 90 (three trials). • For both efalizumab and etanercept a significantly higher proportion of patients achieved a PASI 75 at week 12 compared with patients receiving placebo. • In terms of secondary outcomes there were statistically significant differences between infliximab and placebo in Physician's Global Assessment (PGA) score, DLQI and Nail Psoriasis Severity Index (NAPSI). The incidence of any adverse event was slightly higher in those receiving infliximab compared with those receiving placebo, although this was not tested statistically.

Leitlinien

Coates et al. 2012: The British Society for Rheumatology 2012 guidelines for the treatment of psoriatic arthritis with biologics. [2]	**Behandlungsalgorhythmus:**  **Recommendations**: <u>Peripheral arthritis (polyarticular disease):</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*). <u>Active axial psoriatic arthritis:</u> • Anti-TNF therapy should be considered for those patients with active axial psoriatic arthritis according to the recommendation of the BSR guidelines for ankylosing spondylitis (LoE: Grade A) ** 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.*
SIGN, 2010: Diagnosis and management of psoriasis and psoriatic arthritis in adults. [24]	**Ziel:** This guideline provides recommendations based on current evidence for best practice in the diagnosis and management of psoriasis and PsA in adults. It covers early diagnosis of PsA, screening for comorbidities, assessment of disease severity, non-pharmacological treatment, psychological interventions, occupational health, topical treatment, phototherapy, systemic therapy, biologic treatment, referral pathways and the provision of patient information. […] A minority of patients with PsA develop inflammatory joint disease prior to the development of cutaneous disease. In most cases such patients will be managed as having an undifferentiated inflammatory arthritis and will follow the care pathway appropriate to such conditions. **Methodik:** Methodenreport beschreibt systematische Evidenzaufbereitung mit formalem Konsensusprozess (considered judgement) - eigene Checklisten - Anwendung von GRADE - eigenes Graduierungssystem

	LoE/ GoR **A -** At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results **B -** A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+ **C -** A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++ **D-** Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+ **[✓] -** Recommended best practice based on the clinical experience of the guideline development group **Empfehlungen** ***Treatment of psoriatic arthritis in secondary care:*** <u>pharmacological treatment</u> *NSAIDS:* • NSAIDs are recommended for short term symptom relief in patients with psoriatic arthritis where not contraindicated. (LoE: C) *Kortikosteroide:* • The judicious use of intra-articular corticosteroids to treat persistent synovitis of a given joint is recommended, particularly for mono- or oligoarthritis, or for bridging therapy whilst waiting for systemic therapy to become effective. (LoE: ✓) *DMARDS:* • Leflunomide is recommended for the treatment of active peripheral psoriatic arthritis (LoE: A)

	• Sulfasalazine may be considered as an alternative in the treatment of peripheral psoriatic arthritis. (LoE: C) • Methotrexate may be considered in the treatment of psoriatic arthritis. (LoE: C) • The addition of ciclosporin to methotrexate in the treatment of psoriatic arthritis is not recommended for routine therapy. (LoE: D) • P atients should not be expected to fail ciclosporin before being eligible for biologic therapy for psoriatic arthritis. (LoE: ✓) • The use of intramuscular or oral gold in the treatment of psoriatic arthritis is not recommended where less toxic treatments are an option. (LoE: B) • Choice of DMARD and sequence of DMARD should take into account: o patient preference o severity of joint disease o severity of skin disease o comorbidities o risk of adverse reactions. (LoE: ✓) *Biologic therapy:* • Adalimumab, etanercept or infliximab are recommended for treatment of active psoriatic arthritis in patients who have failed to respond to, are intolerant of, or have had contraindications to, at least two disease-modifying therapies.(LoE: A) • Appropriate patients on biologic therapies should be offered the opportunity to join the BADBIR long term safety register.(LoE: ✓) • The use of biologic treatments in psoriatic arthritis should conform to British Society for Rheumatology guidelines.(LoE: ✓)
Fernández Sueiro et al. 2011: Consensus statement of the Spanish Society	*Therapeutic aim:* The aim of PsA treatment is for the disease to remit or, if it does not, to reduce its inflammatory activity to the minimum (MAE) so as to attain significant improvement in symptoms and signs,

of Rheumatology on the management of biologic therapies in psoriatic arthritis. [6]	preserve functional capacity, maintain a good quality of life and control structural damage (LE 5; GR D; AL 100%). <u>Indications for biological therapy for patients with psoriatic arthritis:</u> *Peripheral forms:* DMARD or a combination of them is used: sulfasalazine (SSZ), leflunomide (LEF), methotrexate (MTX) and cyclosporine A. • Biological therapy is indicated for active patients refractory to conventional treatment (NSAIDs, infiltrations, DMARD), except in specific circumstances when the seriousness of PsA (spread of psoriasis, dactylitis, enthesitis, monoarthritis, uveitis, etc.) clearly limit the individual's quality of life and capabilities for leisure and work, making it possible to indicate BT without the need for exhausting conventional treatment possibilities (LE 5; GR D; AL 93.3%). <u>Hinweis</u>*: There is no data supporting one TNFa antagonist as better than another. That is why the specific choice will depend on the doctor's criteria and the particular circumstances of each patient.* *…It is essential to give patients with peripheral forms of PsA proper treatment with at least one DMARD, which has documented evidence of its efficacy before using BT.17,19,20 For polyarticular forms, NSAIDs and low doses of oral GCs can be useful. In monoarticular or oligoarticular forms, dactylitis or enthesopathy, the use of local GC infiltrations is also recommended. In refractory monoarthritis, intraarticular therapy with radioisotopes can be used.* • In patients with PsA and peripheral manifestations, the DMARDs recommended, due to their benefit-risk ratio, are MTX and LEF (LE 2b; GR B; AL 93.3%). • Biological therapy use should be considered in peripheral predominance PsA when there is no proper response to a DMARD or a combination of them, over a period of at least 3 months, of which at least 2 months must have been at full dose (except if tolerance or toxicity problems limit the dose) (LE 5; GR D; AL 100%). <u>Hinweis zur Empfehlung</u>*: Even the isolated presence of monoarthritis, enthesitis, dactylitis or cutaneous psoriasis, which is sufficiently serious to condition the individual's quality of life (in this case, according to the dermatologist) or working or leisure capability, could be an indication for BT if conventional treatment*

	fails. *Axial forms:* • In predominantly axial PsA, BT should be considered if at least two NSAIDs with demonstrated anti-inflammatory potency have failed during a period of 4 weeks, with each NSAID at the maximum recommended or tolerated dose, except if there is evidence of toxicity or contraindication to NSAIDs (LE 5; GR D; AL 100%). *Mixed forms:* • The indication for BT will be carried out if any of the aforementioned criteria are fulfilled.
Gossec et al. 2012: European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. [9]	European League Against Rheumatism (EULAR) **Ziel**: Psoriatic arthritis (PsA) is a clinically heterogeneous disease. Clear consensual treatment guidance focused on the musculoskeletal manifestations of PsA would be advantageous. The authors present European League Against Rheumatism (EULAR) recommendations for the treatment of PsA with systemic or local (non-topical) symptomatic and disease-modifying antirheumatic drugs (DMARD). DMARDs: methotrexate, sulfasalazine, leflunomide TNF inhibitors: adalimumab, etanercept, golimumab and infl iximab **Methode**: The recommendations are based on evidence from systematic literature reviews performed for non-steroidal anti-infl ammatory drugs (NSAID), glucocorticoids, synthetic DMARD and biological DMARD. This evidence was discussed, summarized and recommendations were formulated by a task force comprising 35 representatives, and providing levels of evidence, strength of recommendations and levels of agreement. **LoE**

Table 2 Categories of evidence

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

GoR

Table 3 Strength of recommendations

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

Empfehlungen:

	Recommendations	Level of evidence	Grade of recommendation
1.	In patients with psoriatic arthritis, non-steroidal anti-inflammatory drugs may be used to relieve musculoskeletal signs and symptoms.	1b	A
2.	In patients with active disease (particularly those with many swollen joints, structural damage in the presence of inflammation, high ESR/CRP and/or clinically relevant extraarticular manifestations), treatment with disease-modifying drugs, such as methotrexate, sulfasalazine, leflunomide, should be considered at an early stage.	*1b, †4	B
3.	In patients with active psoriatic arthritis and clinically relevant psoriasis, a disease-modifying drug that also improves psoriasis, such as methotrexate, should be preferred.	1b	A
4.	Local injections of corticosteroids should be considered as adjunctive therapy in psoriatic arthritis; systemic steroids at the lowest effective dose may be used with caution.	‡3b, §4	C
5.	In patients with active arthritis and an inadequate response to at least one synthetic disease-modifying antirheumatic drug, such as methotrexate, therapy with a tumour necrosis factor inhibitor should be commenced.	1b	B
6.	In patients with active enthesitis and/or dactylitis and insufficient response to non-steroidal anti-inflammatory drugs or local steroid injections, tumour necrosis factor inhibitors may be considered.	1b	B
7.	In patients with predominantly axial disease that is active and has insufficient response to non-steroidal anti-inflammatory drugs, tumour necrosis factor inhibitors should be considered.	2b	C
8.	Tumour necrosis factor inhibitor therapy might exceptionally be considered for a very active patient naive of disease-modifying treatment (particularly those with many swollen joints, structural damage in the presence of inflammation, and/or clinically relevant extra-articular manifestations, especially extensive skin involvement).	4	D
9.	In patients who fail to respond adequately to one tumour necrosis factor inhibitor, switching to another tumour necrosis factor inhibitor agent should be considered.	2b	B
10.	When adjusting therapy, factors apart from disease activity, such as comorbidities and safety issues, should be taken into account.	4	D

	Siehe auch Anlage 1: ,,Therapiealgorhymthmus" **Hinweis der Autoren und der FBMed:** *'No RCTs reported results separately for the different subtypes of PsA.'* Literaturaufbereitung erfolgte in Ash et al. 2012 [1] (Literatur) A systematic literature review (SLR) of available treatments for PsA was performed using the largest electronic databases (MEDLINE, EMBASE and COCHRANE) by two working groups formed within the EULAR taskforce. This comprised a comprehensive sample of rheumatologists, dermatologists, epidemiologists and patients. The available evidence was reviewed for NSAIDs, synthetic disease modifying antirheumatic drugs (DMARDs), local and systemic corticosteroids and biologic drugs. All articles and abstracts published between 1962 and January 2010 were reviewed and considered and a meta-analysis of data on biological therapies was performed.
Ritchlin et al. 2009: Treatment recommendations for psoriatic arthritis. (GRAPPA Guideline). [21]	**Ziel**: To develop comprehensive recommendations for the treatment of the various clinical manifestations of psoriatic arthritis (PsA) based on evidence obtained from a systematic review of the literature and from consensus opinion. **Methode**: Formal literature reviews of treatment for the most significant discrete clinical manifestations of PsA (skin and nails, peripheral arthritis, axial disease, dactylitis and enthesitis) were performed and published by members of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). Treatment recommendations were drafted for each of the clinical manifestations by rheumatologists, dermatologists and PsA patients based on the literature reviews and consensus opinion. The level of agreement for the individual treatment recommendations among GRAPPA members was assessed with an online questionnaire. Empfehlungen basieren auf 6 Publikationen (systematischen Reviews) aus dem Jahr 2006 **GoR/ LoE**

	Table 1 Grading of evidence sources and recommendations **Evidence or recommendation** Evidence source as recommended by the Agency for Health Care Policy Research (AHCPR): Meta-analysis of randomised controlled trials (RCT) One or more RCT One or more controlled trials (without randomisation) Other well designed studies (quasiexperimental) Non-experimental studies (descriptive studies such as comparative or correlation studies, or case-control studies Expert committee opinions, clinical experience Preliminary recommendations for treatment of psoriatic arthritis (using the best available evidence extracted from published literature): Category 1 evidence Category 2 evidence, or extrapolation from category 1 evidence Category 3 evidence, or extrapolation from category 1 or 2 evidence Category 4 evidence or extrapolation from category 2 or 3 evidence **Empfehlungen** *Siehe Anlage - Ergebnistabelle Ritchlin et al 2009*
Work Group [Menter A et al.] 2010 Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: Case-based presentations and evidence-based conclusions. [12]	**Ziel** This sixth and final section of the psoriasis guidelines will cover the approach to the treatment of patients across the entire clinical spectrumof psoriasis including limited skin disease,moderate to severe skin disease, and concurrent psoriatic arthritis (PsA). This guideline has been developed in accordance with the American Academy of Dermatology (AAD) ‘‘Administrative Regulations for Evidence-based Clinical Practice Guidelines,’’ which include the opportunity for review and comment by the entire AAD membership and final review and approval by the Council of Science and Research and the AAD Board of Directors. **Recherchezeitraum**: 1960 bis 2010 **LoE** I. Good-quality patient-oriented evidence. II. Limited-quality patient-oriented evidence. III. Other evidence including consensus guidelines, expert opinion, or case studies. **GoR** A. Recommendation based on consistent and goodquality patient-oriented evidence. B. Recommendation based on inconsistent or limited-quality

patient-oriented evidence.

C. Recommendation based on consensus, opinion, or case studies.

Empfehlungen:

Table III. Comparative efficacy of biologics for psoriasis and psoriatic arthritis—results of pivotal trials

	Adalimumab	Etanercept	Golimumab	Infliximab	Ustekinumab
Primary end point for PsA trials, wk	12	12	14	14	12‡
Percent of patients achieving ACR 20*	58	59	51	58	42‡
Percent of patients in PsA trials on concurrent MTX	50	46	46	49	20‡
Mean MTX dose in PsA trials, mg/wk	17	16	15	15	16
Primary end point for psoriasis trials, wk	16	12	14	10	12
Percent of patients achieving PASI-75*	75	49	40†	80	67

ACR, American College of Rheumatology; *MTX*, methotrexate; *PASI-75*, 75% improvement from baseline in Psoriasis Area and Severity Index score; *PsA*, psoriatic arthritis.
For psoriasis trials, no patients were on concurrent MTX.
*At primary end point.
†Data are for patients receiving 50 mg every 4 wk.
‡Data derived from phase II PsA trial.

Leitlinie verweist auf Section II, Tab. VII-IX (Work Group Gottlieb A et al., 2008): Guidelines of care for the management of psoriasis and psoriatic arthritis Section 2. Psoriatic arthritis: Overview and guidelines of care for treatment with an emphasis on the biologics. J Am Acad Dermatol 2008. 58:851-64.).

Table VII. The strength of recommendations for treatment of psoriatic arthritis using tumor necrosis factor inhibitors

Recommendation	Strength of recommendation	Level of evidence	References
Adalimumab	A	I	26, 31
Etanercept	A	I	17, 27, 32
Infliximab	A	I	25, 33

Table VIII. Recommendations for adalimumab

- Indications: moderate/severe psoriatic arthritis; moderate/severe psoriasis; adult and juvenile rheumatoid arthritis (as young as 4 y); ankylosing spondylitis; and adult Crohn's disease
- Dosing: 40 mg every other wk subcutaneously
- Response: ACR20 at wk 12 is 58%
- Toxicities: see Table VII in Psoriasis Guidelines in Section 1

ACR, American College of Rheumatology.

Table IX. Recommendations for etanercept

- Indications: moderate/severe psoriatic arthritis; moderate/severe psoriasis; adult and juvenile rheumatoid arthritis (as young as 4 y); and ankylosing spondylitis
- Dosing for psoriatic arthritis: 25 mg twice wk or 50 mg once wk given subcutaneously
- Response: ACR20 at wk 12 is 59%
- Toxicities: see Table VIII in Psoriasis Guidelines in Section 1
- Baseline and ongoing monitoring: see Table VIII in Psoriasis Guidelines in Section 1

ACR, American College of Rheumatology.

Table X. Recommendations for infliximab

- Indications: moderate/severe psoriatic arthritis; severe psoriasis; adult rheumatoid arthritis; ankylosing spondylitis; and Crohn's disease (pediatric and adult)
- Dosing: 5 mg/kg given intravenously at wk 0, 2, and 6, and then every 6-8 wk; dose and interval of infusions may be adjusted as needed
- Response: ACR20 at wk 14 is 58%
- Toxicities: see Table IX in Psoriasis Guidelines in Section 1
- Baseline and ongoing monitoring: see Table IX in Psoriasis Guidelines in Section 1

ACR, American College of Rheumatology.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

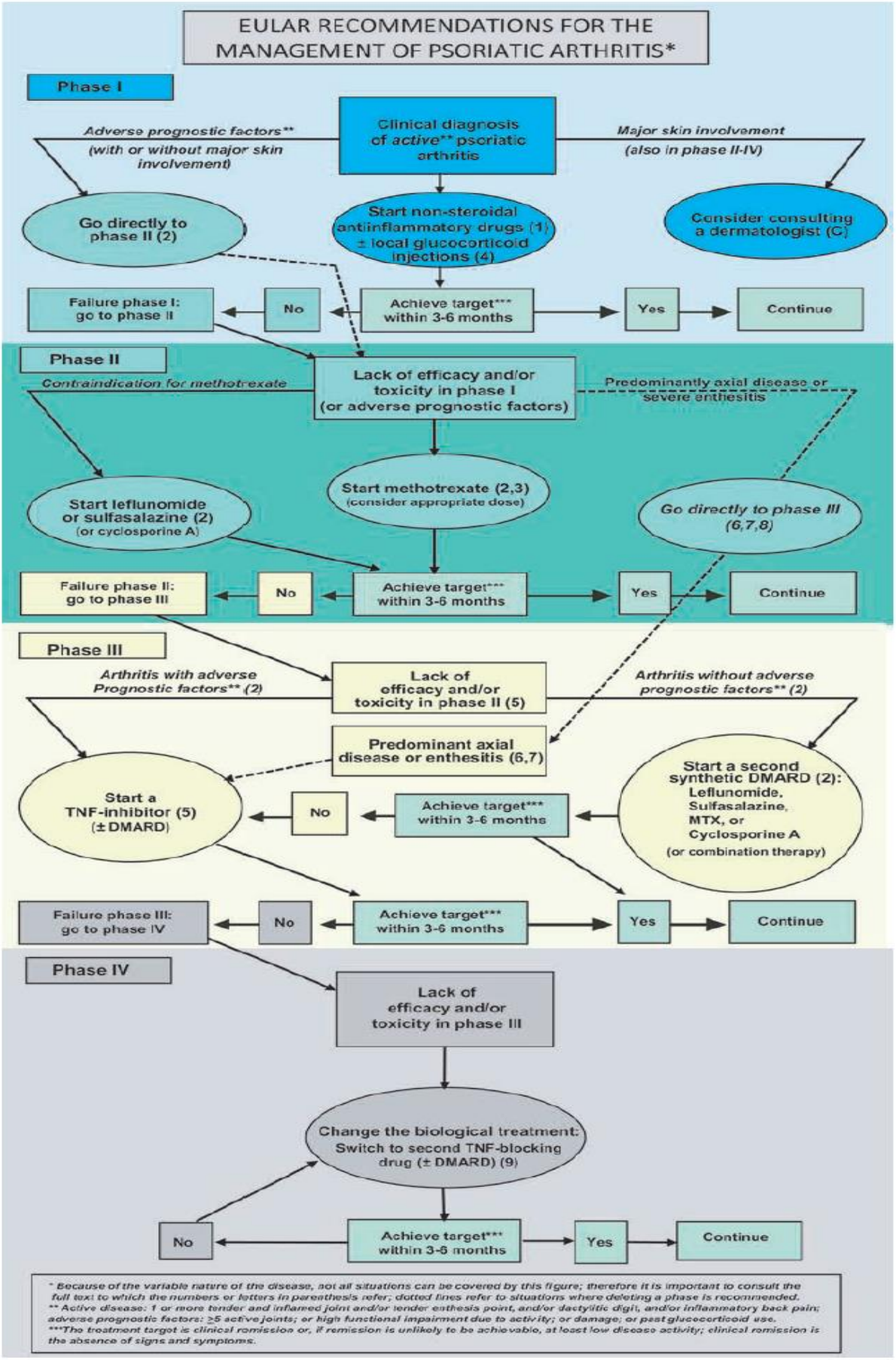
NICE, 2010: Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. NICE technology appraisal guidance 199. [14]	Etanercept, infliximab and adalimumab are recommended for the treatment of adults with active and progressive psoriatic arthritis when the following criteria are met. • The person has peripheral arthritis with three or more tender joints and three or more swollen joints, and • The psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying antirheumatic drugs (DMARDs), administered either individually or in combination. Treatment should normally be started with the least expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules. Etanercept, adalimumab or infliximab treatment should be discontinued in people whose psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks. An adequate response is defined as an improvement in at least two of the four PsARC criteria, (one of which has to be joint tenderness or swelling score) with no worsening in any of the four criteria. People whose disease has a Psoriasis Area and Severity Index (PASI) 75 response at 12 weeks but whose PsARC response does not justify continuation of treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response. **Evidenzbasis**: The Assessment Group identified six double-blind, placebocontrolled, randomised controlled trials (RCTs) in people with psoriatic arthritis for the technologies: two for etanercept, two for infliximab and two for adalimumab. **Hinweis**: HTA-Bericht war für ein Review im Juni 2013 vorgesehen
NICE, 2011: Golimumab for the treatment of psoriatic arthritis.[13]	Golimumab is recommended as an option for the treatment of active and progressive psoriatic arthritis in adults only if: • it is used as described for other tumour necrosis factor (TNF) inhibitor treatments in 'Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis' (NICE technology appraisal guidance 199), and • the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose. When using the Psoriatic Arthritis Response Criteria (PsARC; as set out in NICE technology appraisal guidance 199), 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.

NIHR HSC, 2012: Ustekinumab (Stelara) for psoriatic arthritis – second line after disease modifying anti – rheumatic drugs (DMARDs). [15]	Ustekinumab is licensed in EU for the treatment of moderate to severe plaque psoriasis after failure of systemic therapies. It is also in phase II/IIIs trial for Crohn's disease. **Target group:** Psoriatic arthritis (PsA) – adults; second line after failure of disease modifying anti-rheumatic drugs (DMARDs). **Existing comparators and treatments:** The clinical management of PsA is aimed at suppressing joint, tendon and entheseal inflammation and includes physical therapy, and a range of pharmacological treatments including: Non-biologic therapies • Analgesics. • Corticosteroids. • Non-steroidal anti-inflammatory drugs (NSAIDs). • DMARDs including methotrexate (MTX), sulfasalazine, gold, anti-malarials and leflunomide. Usually administered within three months of diagnosis to stabilise joint function, either as monotherapies or in combination with biologic agents. Biologic therapies • TNF-α inhibitors such as etanercept (Enbrel), infliximab (Remicade) and adalimumab (Humira).
NIHR HSC, 2012: Secukinumab for active and progressive psoriatic arthritis. [16]	Secukinumab is currently in a phase III clinical trial comparing its effect on clinically important improvements in arthritis outcomes against placebo in patients with active and progressive PsA who have responded inadequately to previous therapy with DMARDs. Secukinumab is currently also in a phase II extension trial assessing safety and tolerability. Both trials were expected to complete in July 2012 and November 2012 respectively **Target group:** Psoriatic arthritis (PsA): active and progressive – patients who have responded inadequately to previous therapy with disease modifying anti-rheumatic drugs (DMARDs). **Existing comparators and treatments:** The clinical management of PsA aims to suppress joint, tendon and entheseal inflammation, and reduce functional limitations and joint damage. This includes a range of physical therapy and pharmacological treatments such as: Non-biologic therapies • Analgesics. • Corticosteroids – limited role in PsA. • Non-steroidal anti-inflammatory drugs (NSAIDs). • DMARDs, including methotrexate (MTX), sulfasalazine, leflunomide, gold salts (very rarely used), and anti-malarials (very rarely used). Usually administered within three months of diagnosis to stabilise joint function, either as monotherapy or in combination with biologic agents. Biologic therapies • TNF-α inhibitors such as etanercept, infliximab, adalimumab and golimumab. Should be administered when there has been no response to adequate trials of at least two DMARDs administered either individually or in

	combination.
NIHR HSC, 2012: Inflectra (infliximab biosimilar) for psoriatic arthritis. [18]	Treatment options for PsA include non-biologic therapies, such as analgesics, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and conventional disease-modifying anti-rheumatic drugs (DMARDs) and biologic therapies, such as TNF-α inhibitors. There are currently no clinical trials of Inflectra for this patient population. **Target group:** Psoriatic arthritis (PsA): active and progressive - adults with an inadequate response to disease-modifying anti-rheumatic drugs (DMARDs). **Existing comparators and treatments:** The clinical management of PsA aims to suppress joint, tendon and entheseal inflammation, and reduce functional limitations and joint damage. Treatments include a range of physical therapy and pharmacological treatments. Guidelines recommend treatment with 1 or 2 conventional DMARDs before proceeding to TNF inhibitors. Treatment options include: Non-biologic therapies • Analgesics. • Corticosteroids – limited role in PsA4. • Non-steroidal anti-inflammatory drugs (NSAIDs). • DMARDs, including methotrexate (MTX), sulfasalazine, leflunomide, gold salts (very rarely used), and anti-malarials (very rarely used). Usually administered within three months of diagnosis to stabilise joint function, either as monotherapy or in combination with biologic agents. Biologic therapies • TNF-α inhibitors such as etanercept, infliximab, adalimumab and golimumab.
NIHR HSC, 2013: Apremilast for psoriatic arthritis. [17]	Apremilast is currently in phase III clinical trials comparing its effect on reducing arthritis against treatment with placebo. The first trial is expected to complete in September 2015. **Target group:** Psoriatic arthritis (PsA): active – patients with inadequate response, contraindication, or intolerance to disease-modifying anti-rheumatic drugs (DMARDs) and/or tumour necrosis factor (TNF) inhibitor. The clinical management of PsA aims to suppress joint, tendon and entheseal inflammation, and reduce functional limitations and joint damage. Treatments include a range of physical therapy and pharmacological treatments. Guidelines recommend treatment with 1 or 2 conventional DMARDS before proceeding to TNF inhibitors. Treatment options include: Non-biologic therapies • Analgesics. • Corticosteroids – limited role in PsA. • Non-steroidal anti-inflammatory drugs (NSAIDs). • DMARDs, including methotrexate (MTX), sulfasalazine, leflunomide, gold salts (very rarely used), and anti-malarials

	(very rarely used). Usually administered within three months of diagnosis to stabilise joint function, either as monotherapy or in combination with biologic agents. Biologic therapies • TNF-α inhibitors such as etanercept, infliximab, adalimumab and golimumab.

Anlage 1: ‚Therapiealgorhymthmus EULAR-Leitlinien *Gossec et al. 2012 [9]*



Anlage 2: Ergebnistabelle *Ritchlin et al. 2009 [21]*

Table 2 Treatment recommendations

	Disease status	Treatment recommendation	Level of evidence*	Level of agreement†	Comments
Peripheral arthritis	Mild	NSAIDs	A	90.9%	For control of joint but not skin symptoms
	NA	Intra-articular glucocorticoid injections	D		May be given judiciously to treat persistently inflamed joints, if care is taken to avoid injection through psoriatic plaques. Injections to any one joint should be repeated with caution according to clinical judgment
	Moderate or severe	DMARDs (specific recommendations follow):			For all patients with severe or moderate peripheral arthritis. Consider for mild disease if patients do not respond to NSAIDS or intra-articular steroids. No evidence supporting DMARDs ahead of TNF inhibitors, although the effect size for TNF inhibitors is much larger than that for traditional DMARDs
		Sulfasalazine	A		
		Leflunomide	A		
		Methotrexate	B		
		Ciclosporine	B		
	Moderate or severe	TNF inhibitors	A		For patients who fail to respond to at least one DMARD therapy. The three currently available TNF inhibitors (etanercept, infliximab and adalimumab) are equally effective for the treatment of peripheral arthritis and for the inhibition of radiographic progression. Patients with poor prognosis could be considered for TNF inhibitors even if they have not failed a standard DMARD
Skin disease	Moderate to severe	Phototherapy	A	69.2%	First-line therapies: Phototherapy includes UVB/nbUVB, oral PUVA, bath PUVA, with or without acitretin. An initial trial of phototherapy should be made, unless it is not appropriate or if psoriasis is in areas that preclude phototherapy (ie, scalp, groin, axilla). All forms of phototherapy are considered as a group, although many consider that PUVA therapy carries increased risk of skin cancer compared with other UV modalities. Aggressive immunosuppression should not follow extensive phototherapy (especially PUVA), given the increased risk of melanoma and non-melanoma skin cancer in this scenario
		Methotrexate	A		
		Fumaric acid esters	A		
		TNF inhibitors	A		TNF inhibitors include etanercept, adalimumab and infliximab
		Efalizumab	A		
		Ciclosporine	A		Ciclosporine should be limited to less than 12 consecutive months because cumulative toxicity (ie, multiple courses) is not well studied
		Acitretin	A		Second-line therapies
		Alefacept	A		
		Sulfasalazine	A		Third-line therapies
		Hydroxyurea	C		
		Leflunomide	A		
		Mycophenolate mofetil	C		
		Thioguanine	C		
Nail disease	NA	Retinoids	C	69.2%	
		Oral PUVA	C		
		Ciclosporine	C		
		TNF inhibitors	C		TNF inhibitors include infliximab and alefacept
Spinal disease	Mild to moderate	NSAIDs	A	86.4%	For patients who fail therapies for mild to moderate disease
		Physiotherapy	A		
		Education, analgesia and injection of sacroiliac joint	A		
	Moderate to severe	TNF inhibitors	A		Infliximab, etanercept and adalimumab have all demonstrated efficacy in AS; the consensus was that similar treatment responses reported in AS were also likely to be observed in axial PsA
Enthesitis	Mild	NSAIDS, physical therapy, corticosteroids	D	87.9%	
	Moderate	DMARDs	D		
	Severe	TNF inhibitors	A		Evidence has been demonstrated for infliximab or for etanercept (in spondyloarthropathies)

Continued

Table 2 Continued

	Disease status	Treatment recommendation	Level of evidence*	Level of agreement†	Comments
Dactylitis	NA	NSAIDs	D	90.2%	Usually employed initially
	NA	Corticosteroids	D		Many clinicians rapidly progress to injected steroids
	Resistant	DMARDs	D		Nearly always in the context of co-existing active disease
	NA	Infliximab	A		Some evidence available

*See Methods section of manuscript for description of categories and levels of evidence.
†Percentage of survey responders who agreed or strongly agreed (see supplementary material).
AS, ankylosing spondylitis; DMARD, disease-modifying antirheumatic drug; NA, not applicable or not specifically defined; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; PUVA, psoralen–ultraviolet light; TNF, tumour necrosis factor; UVB, ultraviolet B light.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library am 20.01.2014

#	Suchfrage
1	MeSH descriptor: [Arthritis, Psoriatic] explode all trees
2	(Psoriatic* or psoriasis) and arthritis:ti,ab,kw
3	psa:ti,ab,kw
4	(Psoriatic* or psoriasis) and arthropath*:ti,ab,kw
5	#1 or #2 or #3 or #4
6	#5 from 2009 to 2014

Leitlinien in PubMed am 20.01.2014

#	Suchfrage
#1	Arthritis, Psoriatic[MeSH Terms]
#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])
6	(#5) AND ("2009/01/01"[PDAT] : "2014/01/20"[PDAT])

SR, HTAs PubMed am 20.01.2014

#	Suchfrage
1	Arthritis, Psoriatic[MeSH Terms]
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 ("2009/01/01"[PDAT] : "2014/01/20"[PDAT])

Literatur

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