Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: Plaque Psoriasis

Stand: November 2016

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

Plaque Psoriasis **[Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die für eine systemische Therapie geeignet sind.]**	
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.	*Phototherapie: NB-UV-B, Balneo-Photo, PUVA*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	*Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Richtlinie Methoden vertragsärztliche Versorgung: Balneophototherapie vom 13. März 2008;* *Richtlinie Methoden vertragsärztliche Versorgung, Stand: 3. Oktober 2014* *des Gemeinsamen Bundesausschusses zu Untersuchungs- und Behandlungsmethoden der vertragsärztlichen Versorgung (Richtlinie Methoden vertragsärztliche Versorgung) in der Fassung vom 17. Januar 2006 veröffentlicht im Bundesanzeiger 2006 Nr. 48 (S. 1 523) in Kraft getreten am 1. April 2006; zuletzt geändert am 17. Juli 2014 veröffentlicht im Bundesanzeiger (BAnz AT 02.10.2014 B2); in Kraft getreten am 3. Oktober 2014.* *15. Balneophototherapie* *Beschluss zu Apremilast vom 06.08.2015* *Beschluss zu Secukinumab vom 27.11.2015*
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel	
Ixekizumab L04AC13 Taltz®	Taltz® ist angezeigt für die Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die für eine systemische Therapie in Frage kommen.
Systemische Therapie	
Adalimumab L04AB04 Humira®	Humira ist indiziert zur Behandlung der mittelschweren bis schweren chronischen Plaque-Psoriasis bei erwachsenen Patienten, die Kandidaten für eine systemische Therapie sind.
Etanercept L04AB01 Enbrel®	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. (Stand 04/2016)
Infliximab L04AB02 Remicade®	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. (Stand 09/2015)
Ustekinumab L04AC05 Stelara®	Stelara ist für die Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis indiziert, bei denen andere systemische Therapien einschließlich Ciclosporin, Methotrexat (MTX) oder PUVA (Psoralen und Ultraviolett A) nicht angesprochen haben, kontraindiziert sind oder nicht vertragen wurden. (Stand 03/2014)
Apremilast L04AA32 Otezla®	Otezla ist indiziert 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. (Stand 01/2016)
Secukinumab L04AC10 Cosentyx® (GB)	Cosentyx ist angezeigt für die Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die für eine systemische Therapie in Frage kommen. (Stand 04/2016)
Ciclosporin L04AD01	Behandlung von schwerer Psoriasis bei Patienten, bei denen eine herkömmliche Therapie nicht geeignet oder nicht wirksam ist. (Stand 01/2014)

Ciclosporin Pro 100 mg/ml Lösung	
Dimethylfumarat, Ethylhydrogenfumarat D05BX51 FUMADERM® initial FUMADERM®	FUMADERM initial: Zur verträglichkeitsverbessernden Einleitung der FUMADERM-Therapie. FUMADERM: Zur Behandlung von mittelschweren bis schweren Formen der Psoriasis vulgaris, sofern eine alleinige äußerliche Therapie nicht ausreichend ist. Eine vorhergehende Verträglichkeitsanpassung mit FUMADERM initial ist erforderlich. (Stand 01/2016)
Methotrexat M01CX01 Lantarel® Tabletten	Schwere Formen der Psoriasis vulgaris, insbesondere vom Plaque-Typ, und der Psoriasis arthropathica, die mit einer konventionellen Therapie nicht ausreichend behandelbar sind. (Stand 01/2014)
Acitretin D05BB02 Neotigason®	Zur symptomatischen Behandlung von schwersten, einer konventionellen Therapie nicht zugänglichen Verhornungsstörungen des Hautorgans wie: - Psoriasis vulgaris, vor allem erythrodermatische und pustulöse Formen
Kortikosteroide, z.B. Prednisolon H02AB06 Prednisolon-ratiopharm® Tabletten	[…] Dermatologie: Erkrankungen der Haut und Schleimhäute, die aufgrund ihres Schweregrades und/oder Ausdehnung bzw. Systembeteiligung nicht oder nicht ausreichend mit topischen Glucocorticoiden behandelt werden können. Dazu gehören: […] - Erythemato-squamöse Dermatosen: z. B. Psoriasis pustulosa, Pityriasis rubra pilaris, Parapsoriasis-Gruppe (DS: c –a) […] (Stand: 08/2010)

Quellen: AMIS-Datenbank, Fachinformationen, Lauer-Taxe® (Stand: 10. Oktober 2016)

Abteilung Fachberatung Medizin

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

Inhalt

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 11.07.2016 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), PubMed (inkl. MEDLINE), AWMF, Clinical Evidence, CADTH, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, SIGN, TRIP und WHO. 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 858 Quellen, die anschließend in einem zweistufigen Screeningverfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 29 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Zur Behandlung von Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die für eine systemische Therapie geeignet sind.

Abkürzungen

AAD	American Academy of Dermatology
ADA	Antidrug antibodies
AE	Adverse event
AGREE	Appraisal of Guidelines Research and Evaluation
AHRQ	Agency for Healthcare Research and Quality
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BAD	British Association of Dermatologists
BADBIR	British Association of Dermatologists Biologic Interventions Register
BB	broadband (Breitband)
b.i.d.	Twice daily
b.i.w.	Twice weekly
BSA	Body surface area
CADTH	Canadian Agency for Drugs and Technologies in Health
CDA	Canadian Dermatology Association
CI	Konfidenzintervall
CoI	Conflict of interest
CrI	Credible interval
CSA	Ciclosporin
DAHTA	Deutsche Agentur für Health Technology Assessment
DLQI	Dermatology Life Quality Index
EADV	European Association for Dermatology and Venereology
EDF	European Dermatology Forum
EOW	Every other week
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendation
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HRQol	Health-related quality of life
IPC	International Psoriasis Council
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
k. A.	keine Angabe
LoE	Level of Evidence
MTC	mixed treatment comparisons
MTX	Methotrexate
NB	Narrowband (Schmalband)
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
PASI	Psoriasis Area and Severity Index
PGA	physician’s global assessment
PUVA	Psoralen plus UV-A (auch Photochemotherapie)
q.d.	Once daily
q.w.	Once weekly
SAE	Severe adverse event
SF-36	Short-Form General Health Survey
SGB	Sozialgesetzbuch
SIGN	Scottish Intercollegiate Guidelines Network
SOE	Strength of evidence
TNF	Tumornekrosefaktor
TRIP	Turn Research into Practice Database
URTI	upper respiratory tract infection

UV	ultraviolet
vs.	versus
WHO	World Health Organization

IQWiG Berichte/ G-BA Beschlüsse

G-BA, 2008 [9,13, #30]. Zusammenfassende Dokumentation zum Beratungsverfahren des Unterausschusses „Ärztliche Behandlung des Gemeinsamen Bundesausschusses." **G-BA, 2010 [12].** Asynchrone Photosolethrapie im Vollbad. *Siehe auch* ***IQWIG, 2006 [14].*** *Abschlussbericht: Balneophototherapie (IQWiG-Berichte. Jahr: 2006 Nr. 14)*	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: • <u>Bade-PUVA:</u> Das Bad enthält einen Psoralenzusatz (8-Methoxypsoralen, kurz: 8-MOP oder Trioxsalen [Trimethylpsoralen, kurz: TMP] in alkoho-lischer Lösung), die anschließende Bestrahlung erfolgt mit UVA-Licht. • <u>asynchrone Photosoletherapie:</u> Das Bad ist mit Sole (10 %ig bei atopischer Dermatitis bis zu 25 %ig bei Psoriasis vulgaris) angereichert, die anschließende Bestrahlung erfolgt in der Regel mit UVB (Ultraviolett-strahlung-B)-Licht. Bei der asynchronen Balneophototherapie wird bei Verwendung 25 %iger Solelösung aus technischen Gründen 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** *<u>Bade-PUVA</u>* Das IQWiG kam zu folgendem Fazit: „Die asynchrone Bade-PUVA hat einen Zusatznutzen gegenüber der trockenen UVB-Therapie beziehungsweise Leitungswasser plus UVB im Hinblick 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 unerwünschten 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 (Plattenepithelkarzinome der Haut). Der

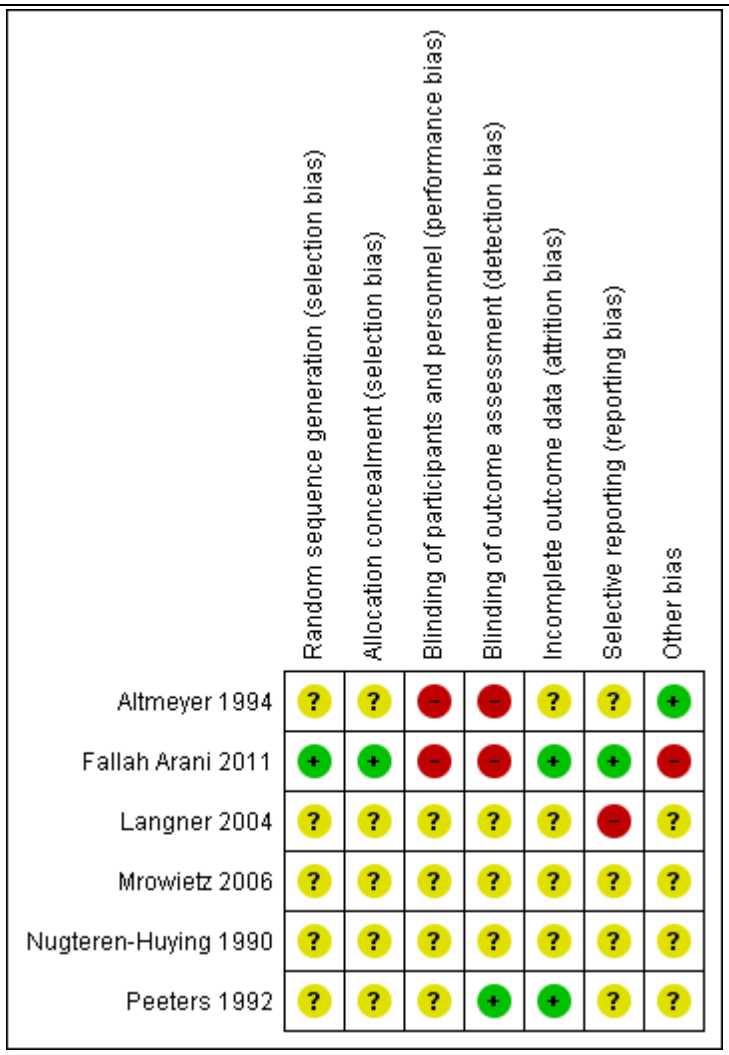
	Behandlungsaufwand ist prozedural bedingt geringer. Ein gleichwertiger Nutzen der asynchronen Bade-PUVA im Hinblick auf die Besserung des Hautbeschwerdebildes ist allerdings weder belegt noch ausgeschlossen.“ ➔ Die Themengruppe Balneophototherapie des G-BA schloss sich dem Fazit des IQWiG zur Bade-PUVA-Therapie 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 Photosole-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 eingeschränkt 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.
	In dem Abschlussbericht des G-BA (2010) [9] erfolgte eine Anpassung des Beschlusses: „Für die Indikationen der mittelschweren und schweren Psoriasis vulgaris kann die Balneophototherapie auf Basis der vorliegenden Richtlinie zukünftig als asynchrone Photosoletherapie sowohl in Form eines Folienbades als auch eines Vollbades im Rahmen der vertragsärztlichen Versorgung erbracht werden. Die bereits in der Richtlinie beschriebenen anderen Behandlungsformen bleiben von diesem Beschluss unberührt.“
	Der Zusammenfassende Bericht des Arbeitsausschusses "Ärztliche Behandlung" des Bundesausschusses der Ärzte und Krankenkassen über die Beratungen des Jahres 1999 zur Bewertung der Balneophototherapie gemäß §135 Abs.1 SGB V wurde aufgrund des Umfangs der vorliegenden Evidenzsynopse hier nicht explizit dargestellt. Der Abschlussbericht befasste sich mit der ambulanten Balneophototherapie in Form der Nicht-synchronen Photosoletherapie bzw. der Bade-PUVA bei schwerer Psoriasis [2].

G-BA, 2015 [10]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Apremilast <u>*Hinweis*</u>: Basierend auf der Nutzenbewertung des IQWiG, 2015 [12]	**Fazit: Psoriasis** „Otezla ist indiziert 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." **Plaque-Psoriasis** **Zweckmäßige Vergleichstherapie:** „Die zweckmäßige Vergleichstherapie für die Behandlung von erwachsenen Patienten mit mittelschwerer bis schwerer chronischen Plaque-Psoriasis, 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, ist: - Adalimumab oder Infliximab oder Ustekinumab" ➔ **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt.
G-BA, 2015 [11]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Secukinumab <u>*Hinweis*</u>:	**Zugelassenes Anwendungsgebiet:** Secukinumab (Cosentyx®) ist angezeigt für die Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die für eine systemische Therapie in Frage kommen. *a) Patientenpopulation A:* Behandlung von erwachsenen Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die für eine systemische und/oder Phototherapie geeignet sind. <u>Zweckmäßige Vergleichstherapie</u>: eine patientenindividuell optimierte Standardtherapie unter Berücksichtigung von: - Fumarsäureestern oder Ciclosporin oder Methotrexat oder Phototherapie (Balneophototherapie, orale PUVA, NB_1-UV-B) Der jeweilige Zulassungsstatus der Arzneimittel ist zu berücksichtigen. ➔ **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Methotrexat:** Ein Zusatznutzen ist nicht belegt. *b) Patientenpopulation B:* Behandlung von erwachsenen Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die auf andere systemische Therapien einschließlich Ciclosporin, Methotrexat oder PUVA (Psoralen und Ultraviolett A-Licht) nur unzureichend angesprochen haben, oder bei denen eine Kontraindikation oder Unverträglichkeit gegenüber solchen Therapien vorliegt.

Basierend auf der Nutzenbewertung des IQWiG, 2015 [15].	Zweckmäßige Vergleichstherapie: Adalimumab oder Infliximab oder Ustekinumab → **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Ustekinumab:** • Patienten mit einer Biologika-Vorbehandlung: Hinweis auf einen beträchtlichen Zusatznutzen. • Patienten ohne eine Biologika-Vorbehandlung: Hinweis auf einen geringen Zusatznutzen.

Cochrane Reviews

Atwan A et al., 2015 [4]. Oral fumaric acid esters for psoriasis.	1. Fragestellung To assess the effects and safety of oral fumaric acid esters for psoriasis.
	2. Methodik Population: We included individuals of either sex and any age and ethnicity, with a clinical diagnosis of psoriasis made by a medical practitioner. We included all subtypes of psoriasis. Intervention/Komparator: - oral fumaric acid esters versus oral placebo; - oral fumaric acid esters versus active treatment; - oral fumaric acid esters in combination with another active treatment versus placebo; or - oral fumaric acid esters in combination with another active treatment versus active treatment. Endpunkt: • Primary outcomes: PASI score; proportion of participants who discontinued treatment due to adverse effects that are common but sufficiently serious that the drug has had to be stopped, such as severe diarrhoea, infections, or cutaneous malignancy. • Secondary outcomes: Quality of life; proportion of participants attaining PASI 50, 75, and 90; proportion of participants experiencing any adverse effects of treatment, i.e., all nuisance side-effects that are common, but do not mean that the drug is stopped; proportion of participants experiencing serious adverse effects of treatment, defined as resulting in death, hospital admission, or increased duration of hospital stay Suchzeitraum (Aktualität der Recherche): up to 7 May 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 6 studies (2 full reports, 2 abstracts, 1 brief communication, and 1 letter), with a total of 544 participants Qualitätsbewertung der Studien: The Cochrane Collaboration's 'Risk of bias' tool. I^2 for heterogeneity
	3. Ergebnisdarstellung Qualität der Studien:



→ *Hinweis*: Two studies included only participants with chronic plaque psoriasis (Fallah Arani 2011; Mrowietz 2006); two included chronic plaque, guttate, pustular, and erythrodermic types (Altmeyer 1994; Langner 2004)

Five studies compared FAE with placebo, and one study (Fallah Arani 2011) compared FAE with methotrexate. All studies reported data at 12 to 16 weeks, and we identified no longer-term studies.

FAE vs. MTX:

- PASI score at follow-up showed superiority of MTX (mean Difference (MD): 3.80, 95% CI 0.68 to 6.92; 51 participants; very low-quality evidence), but the difference was not significant after adjustment for baseline disease severity.
- The difference between groups for the proportion of participants who discontinued treatment due to adverse effects was uncertain because of imprecision (RR: 0.19, 95% CI 0.02 to 1.53; 1 study, 51 participants; very low-quality evidence).
- Overall, the number of participants experiencing common nuisance adverse effects was not significantly different between the 2 groups,

	with 89% of the FAE group affected compared with 100% of the MTX group (RR 0.89, 95% CI 0.77 to 1.03; 54 participants; very low-quality evidence). • Flushing was more frequent in those on FAE, with 13 out of 27 participants affected compared with 2 out of 27 given MTX. • There was no significant difference in the number of participants who attained PASI 50, 75, and 90 in the 2 groups (very low-quality evidence) whereas this study did not measure the effect of treatments on QoL.
	4. Fazit der Autoren: *Evidence suggests that FAE are […] similar in efficacy to MTX for psoriasis; however, the evidence provided in this review was limited, and it must be noted that four out of six included studies were abstracts or brief reports, restricting study reporting. FAE are associated with nuisance adverse effects, including flushing and gastrointestinal disturbance, but short-term studies reported no serious adverse effects.* 5. Hinweise durch FB Med: • Lediglich 2 Studien mit Plaque P. Patienten, nur eine Studie die gegen einen aktiven Komparator (hier MTX) verglichen hat.

Systematische Reviews

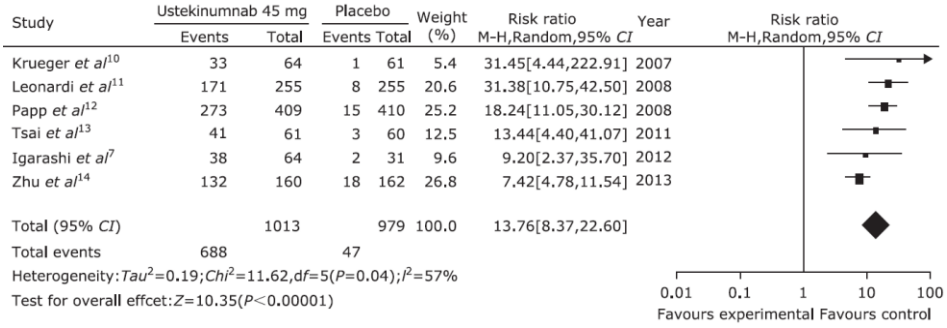
Nast A et al., 2015 [20]. Efficacy and Safety of Systemic Long-Term Treatments for Moderate-to-Severe Psoriasis: A Systematic Review and Meta-Analysis.	1. Fragestellung The aim of this systematic review is to provide a comprehensive overview about evidence on the efficacy and/or safety of systemic treatments for moderate-to-severe psoriasis in long-term therapy in adult patients based on randomized controlled trials (RCTs)
	2. Methodik Population: adults suffering from moderate-to-severe plaque-type Psoriasis Intervention: following treatments in commonly used dosages: acitretin, adalimumab, apremilast, CSA, etanercept, fumaric acid ester, infliximab, MTX, secukinumab, or ustekinumab Komparator: placebo, versus another included active treatment, or versus a combination of two included treatments Endpunkt: PASI 75, 90, at 24-28 weeks of treatment, Physician Global Assessment (PGA), Dermatology Life Quality Index (DLQI), safety (treatment duration of at least 24 weeks) Suchzeitraum (Aktualität der Recherche): from inception to 5 January 2015 (Medline, Medline in Process, and Embase using OvidSP platform, the Cochrane Library was searched via its online search platform) Anzahl eingeschlossene Studien/Patienten (Gesamt): 25 RCTs in

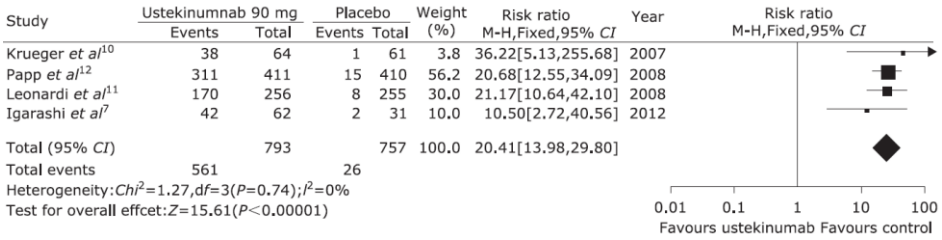
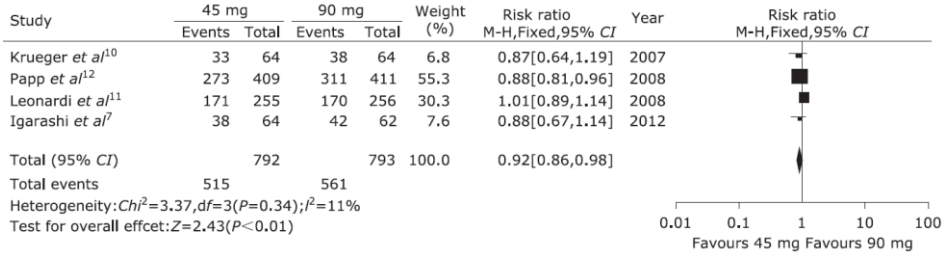
	Meta-Analyse (n=11,279) GRADE-Methodik verwendet Diese Datenbasis wurde zur Erstellung der LL (European Dermatology Forum (EDF), 2015 [7]) herangezogen. Zusätzlich wurde noch Secukinumab in dieser Quelle berücksichtigt
	3. Ergebnisdarstellung **PASI 75**. **(siehe Anhang, Fig 2)** All biologics and apremilast showed superior efficacy compared with placebo with respect to their PASI 75 response pooled risk ratio (RR) vs. placebo for • infliximab: 13.07 (95% CI): 8.60, 19.87, I^2=0%) • secukinumab: 11.97 (95% CI: 8.83, 16.23, I^2=0% • ustekinumab: 11.39 (95% CI: 8.94, 14.51, I^2=0%), • adalimumab: 8.92 (95% CI: 6.33, 12.57, I^2=8%), • etanercept: 8.39 (95% CI: 6.74, 10.45, I^2=0% • apremilast: 5.83 (95% CI: 2.58, 13.17) with low quality of evidence. **PASI 90:** comparison with placebo at weeks 24–28: • secukinumab (RR 40.15 (95% CI: 20.97, 76.89), I^2=0%) • ustekinumab (RR 31.63 (95% CI: 19.43, 51.51), I^2=0%) • infliximab (RR 31.00 (95% CI: 13.45, 71.46), I^2=0%) • adalimumab (RR 23.17 (95% CI: 12.51, 42.91), I^2 = 0%) • etanercept (RR 19.14 (95%CI: 11.59, 31.60), I^2=0%) • apremilast (RR 13.00 (95% CI: 1.74, 97.25)) with low quality of evidence. **PGA:** PGA (Physician Global Assessment) 'clear/almost clear', the biologics and apremilast are superior to placebo. • Infliximab: 13.13 (95% CI: 8.45, 20.38, I^2= 0), • Ustekinumab: 9.91 (95% CI: 7.76, 12.66, I^2=0), • Secukinumab: 9.84 (95% CI: 7.25, 13.36, I^2= 0%), • Adalimumab: 8.06 (95% CI: 5.89, 11.04, I^2=0), • Etanercept: 7.16 (95% CI: 5.35, 9.57, I^2=0), • Apremilast: 5.00 (95% CI: 2.19, 11.41) All results have been assigned a low quality of evidence. **DLQI:** *Absolute reduction in mean DLQI with a mean difference (MD) in absolute reduction in mean DLQI:* • infliximab is statistically significantly superior to placebo in long-term treatment (high quality): 9.80 (95% CI: 8.19, 11.41),

	• adalimumab 80 mg every other week (MD 5.70 (95% CI: 3.13, 8.27), moderate quality) • adalimumab with a loading dose of 80 mg and following 40 mg every other week (MD 4.20 (95% CI: 1.54, 6.86), low quality) • adalimumab 40 mg every other week (MD 3.30 (95% CI: 0.56, 6.04), low quality) *Percentage reduction in mean DLQI*. • Etanercept 50 mg twice weekly (b.i.w.) superior vs placebo in longterm treatment with an MD 57.00 (95% CI: 38.52, 75.48, high quality) **Safety:** *Patients with at least one AE.* No differences were found between adalimumab and placebo and between infliximab and placebo *Patients with at least one SAE*. Compared with placebo, no differences in the risks of SAE were shown for adalimumab, etanercept 50 mg once weekly (q.w.) and infliximab *Withdrawal due to AE.* In comparison with placebo, no statistically significant differences in withdrawal due to AE for adalimumab, and infliximab **Head to Head comparisons:** *Acitretin 0.4 mg kg−1 once daily (q.d.) versus etanercept 25 mg b.i.w.:* no statistically significant differences were found between acitretin and etanercept with respect to PASI 75 and the number of patients with at least one AE *Acitretin 0.4 mg kg− 1 q.d. versus combination of acitretin 0.4 mg kg^{-1} q.d. and etanercept 25 mg q.w.:* No differences were found between acitretin monotherapy and acitretin in combination with etanercept with respect to PASI 75 and in the number of patients with at least one AE *Etanercept 25 mg b.i.w. versus combination of acitretin 0.4 mg kg^{-1} q.d. and etanercept 25 mg q.w.:* There are no differences in PASI 75 response between etanercept combined with acitretin and etanercept monotherapy after long-term treatment period. With respect to the number of patients with at least one AE, it is uncertain whether there is any difference (RR 0.28 (95% CI: 0.01, 6.38). The quality of evidence is very low for both outcomes *Etanercept 50 mg b.i.w. for 12 weeks followed by 50 mg kg^{-1} g.w. versus combination of etanercept 50 mg b.i.w./g.w. and MTX 7.5–15 mg g.w.:* statistically significant differences with a small effect were observed in favor of the combination etanercept/MTX based on PASI 75 (RR 0.78 (95% CI: 0.69, 0.88), low quality), PASI 90 (RR 0.64 (95% CI: 0.51, 0.78), moderate quality), and PGA ‘clear/almost clear’ (RR 0.76 (95% CI: 0.66, 0.88), low quality). In contrast, a slightly increased risk for the occurrence

	of at least one AE was seen with the combination (RR 0.80 (95% CI: 0.70, 0.91), moderate quality), no statistically significant difference was found for the number of patients with at least one SAE *Etanercept 50 mg b.i.w. versus infliximab 5mg kg^{-1}*: After long-term treatment, etanercept was inferior to infliximab based on PASI 75 (RR 0.48 (95% CI: 0.26, 0.89), moderate quality) *Etanercept 50 mg b.i.w./q.w. versus secukinumab 150–300 mg monthly:.* - small statistically significant differences in favor of secukinumab 150 mg based on PASI 75 (RR 0.80 (95% CI: 0.72, 0.89), moderate quality), PASI 90 (RR 0.67 (95% CI: 0.57, 0.79), high quality), and PGA 'clear/almost clear' (RR 0.74 (95% CI: 0.64, 0.86), moderate quality) - Secukinumab 300 mg is superior to etanercept based on PASI 75 (RR 0.72 (95% CI: 0.65, 0.79), moderate quality), PASI 90 (RR 0.54 (95% CI: 0.46, 0.63), high quality), and PGA 'clear/almost clear' (RR 0.61 (95% CI: 0.53, 0.69), high quality) (Langley et al., 2014). *MTX 15–20 mg q.w. versus infliximab 5mg kg−1:* - MTX is inferior to infliximab in long-term treatment based on PASI 75 (RR 0.40 (95% CI: 0.33, 0.49)), PASI 90 (RR 0.29 (95% CI: 0.21, 0.41)), and PGA 'clear/almost clear' (RR 0.38 (95% CI: 0.31, 0.48), moderate quality for all outcomes) - With respect to quality of life, MTX and infliximab showed a percentage reduction in DLQI of 62% and 84%, respectively.
	4. Anmerkungen/Fazit der Autoren From the available evidence, infliximab, secukinumab, and ustekinumab are the most efficacious long-term treatments. Data on conventionals are insufficient. Based on low quality of evidence, all biologics and apremilast have been shown to be clinically effective in long-term therapy compared with placebo. Patient relevant outcomes support this finding with high to low quality of evidence. With respect to the addressed safety outcomes, none of the results showed a statistically significant difference for adalimumab, etanercept, or infliximab compared with placebo. However, a trend of a less favorable safety profile of infliximab over placebo can be assumed from these data. For secukinumab, ustekinumab, and apremilast, no data for the selected safety outcomes were available. Head-to-head trials allow a much better direct comparison of efficacy and safety. However, the number of direct longterm comparisons is limited. With respect to efficacy, based on PASI 75, superiority of secukinumab over etanercept, of infliximab over MTX (dosages of 15–20 mg), and of infliximab over etanercept was shown in head-to-head trials of at least 24

	weeks (moderate quality of evidence). In head-to-head comparisons, the combination of etanercept plus methotrexate has been found to be superior to etanercept monotherapy with a low to moderate quality of evidence. This effect was accompanied by a slight increase in AEs. Acitretin as a combination partner to etanercept low dose was shown to have some dose sparing potential compared with monotherapy with high-dose etanercept. 5. Anmerkung FB Med: Großteil der Studien stoppten Placeboarm nach Induktionsphase (16 Wochen). 3 Studien lieferten Daten zu Patienten unter Placebo bis zu Woche 24, die dann als Vergleich für alle aktiven Substanzen herangezogen wurden (Imputation der Placebodaten in Großteil der Studien durch Ersetzen der „fehlenden“ Werte durch das mittlere Ansprechen in den Placeboarmen der 3 relevanten Studien). Das Verzerrungspotential ist dadurch groß, da keine echte Randomisierung gegeben ist.
Busard C et al., 2014 [6]. Combined Use of Systemic Agents for Psoriasis A Systematic Review	1. Fragestellung To summarize and critically appraise the evidence on efficacy and safety of combination therapy with systemic agents in plaque-type psoriasis.
	2. Methodik Population: patients with psoriasis Intervention: combination therapy with systemic agents Komparator: systemic monotherapy or another systemic combination therapy Endpunkte: PASI 75, PASI 90, PGA, AEs, SAEs, DLQI Suchzeitraum: bis 03/2013 in MEDLINE, PubMed, EMBASE, Cochrane Library und Trial Register Anzahl eingeschlossene Studien/Patienten (Gesamt): 17 (n=1071) Qualitätsbewertung der Studien: • The risk of bias in the individual studies was assessed in duplicate using the Cochrane Risk of Bias tool. • The quality of evidence for each outcome (body of evidence) was assessed according to the GRADE approach. • Assessment of the risk of bias of the individual studies resulted in low risk for 3 trials, intermediate risk for 5 trials high risk for 9 trials.
	3. Ergebnisdarstellung Etanercept plus methotrexate was the only combination therapy investigated with an adequate sample size (n = 478). In the short term, this combination had superior efficacy with a moderate quality of evidence compared with etanercept monotherapy (Psoriasis Area and Severity Index, 75; relative risk, 1.28; 95%CI, 1.14-1.45). Although this finding coincided with an increase in adverse events (relative risk, 1.25; 95%CI, 1.10-1.42), the overall safety profile remained acceptable.

	4. Anmerkungen/Fazit der Autoren This systematic review provides a comprehensive overview on the validity of different systemic combination therapies. For most combinations, insufficient evidence is available. Initial results indicate that combined therapy with etanercept plus methotrexate may be beneficial in patients that are therapy resistant under intensive follow-up. Dose reductions should be taken into account to minimize adverse effects.
Liu Y et al., 2014 [18]. Therapeutic Effect and Safety of Ustekinumab for Plaque Psoriasis: A Meta-analysis	1. Fragestellung To evaluate the efficacy and safety of ustekinumab in the therapy of plaque psoriasis.
	2. Methodik Population: patients with plaque psoriasis Intervention: ustekinumab Komparator: placebo Primärer Endpunkt: PASI 75 response rate at the week 12; sekundärer Endpunkt: adverse events Suchzeitraum: bis 11/2013 in Cochrane Central Register of controlled trials, MEDLINE, PubMed Anzahl eingeschlossene Studien/Patienten (Gesamt): 6 studies (ustekinumab: n= 1012 patients; placebo: n=985 patients) Qualitätsbewertung der Studien: The methodological quality of the trails was assessed by the Jadad scale and high quality studies (Jadad score 5) were included in this study. Publication Bias: From the funnel plot, we found that there was no publication bias in the 6 randomized control trials
	3. Ergebnisdarstellung *Ustekinumab 45 mg vs. placebo (6 studies):* • ustekinumab 45 mg group could get better therapeutic effect compared with the placebo group (P<0.00001) • The RR was 13.76 and 95% CI [8.37, 22.60] *Forest plot of therapeutic effect comparing ustekinumab 45 mg group with the placebo group at 12th week*  *Ustekinumab 90 mg vs. placebo (4 studies):* • ustekinumab 90 mg group could get obviously better therapeutic effect compared with the placebo group (P<0.00001)

	• The RR was 20.41 and 95% CI [13.98, 29.80] *Forest plot of therapeutic effect comparing ustekinumab 90 mg group with the placebo group at 12th week*  *Ustekinumab 45 mg vs. ustekinumab 90 mg (4 studies):* • ustekinumab 90 mg group could get better therapeutic effect compared with ustekinumab 45 mg group (P=0.01) • The RR was 0.92 and 95% CI [0.86, 0.98] *Forest plot of therapeutic effect comparing ustekinumab 45 mg group with 90 mg group at 12th week*  <u>Adverse events:</u> - The serious adverse effects included serious infection, cardiovascular events, and malignant tumors. - There were no statistically significant differences of these adverse effects among three groups (all *P*>0.05) - except that infection rate in ustekinumab 45 mg group was higher than the placebo group (*P*=0.02).
	4. Anmerkungen/Fazit der Autoren Ustekinumab is an effective and safe therapeutic method for plaque psoriasis. However, further longer time analysis of safety is needed.
Meng Y et al., 2014 [19]. Systematic review and meta-analysis of ustekinumab	1. Fragestellung To systematically evaluate the efficacy and safety of ustekinumab versus placebo for psoriasis.
	2. Methodik Population: patients with moderate to severe psoriasis Intervention: ustekinumab Komparator: placebo

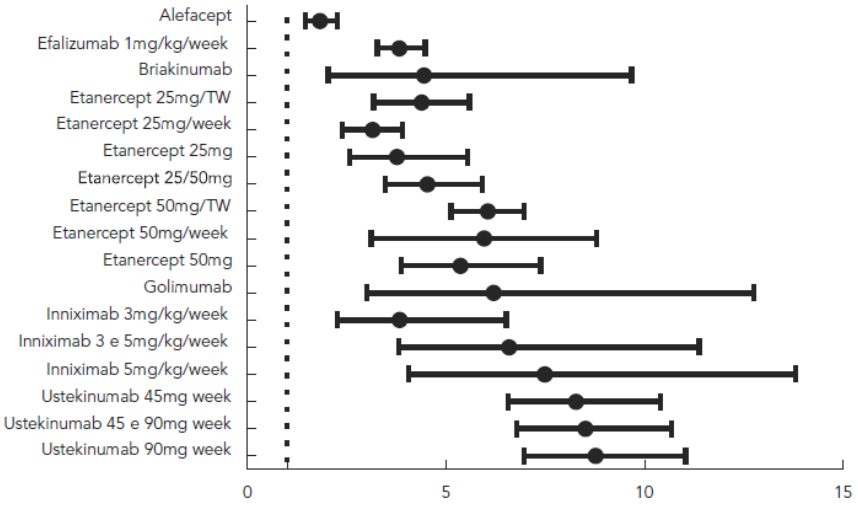
for moderate to severe psoriasis	Endpunkte: PASI 50, PASI 75, PASI 90, DLQI, adverse events Suchzeitraum: 1990-08/2013 in Cochrane Library, PubMed, EMBASE, Chinese Bio-Medical Literature Database, China National Knowledge Infrastructure, WANFANF, Chinese Social Sciences Citation Index Anzahl eingeschlossene Studien/Patienten (Gesamt): 9 RCTs (n=11381) Qualitätsbewertung der Studien: • risk of bias tool recommended by the Cochrane Collaboration • GRADE
	3. Ergebnisdarstellung **PASI 50 (3 Studien):** • PASI 50 was higher for both ustekinumab doses (45 and 90 mg) than for the placebo (RR = 7.59, 95% CI 5.66–10.17, P <<0.001; RR = 8.22, 95% CI 5.93–11.39, P << 0.001, respectively) • no significant difference in PASI 50 between the two doses of ustekinumab (RR = 0.96, 95% CI 0.90–1.03, P = 0.28). **PASI 75:** • siehe Liu Y et al., (2014) [16] **PASI 90** (3 Studien): • number of patients achieving PASI 90 was higher for both ustekinumab 45 and 90 mg than for the placebo (RR = 21.51, 95% CI 10.22–45.28, P << 0.001; RR = 18.77, 95% CI 8.38–42.04, P << 0.001, respectively) • no significant difference in the number of patients achieving PASI 90 between the two doses of ustekinumab **PGA** (4 Studien): The PGA score was higher for both ustekinumab 45 and 90 mg than for the placebo (RR = 64.90, 95% CI 18.69–225.33, P < 0.001; RR = 85.78, 95% CI 21.35–344.63, P << 0.001) respectively. There was no significant difference in PGA between the two doses of ustekinumab (RR = 0.84, 95% CI 0.69–0.02, P = 0.07) **DLQI** (4 Studien): • number of patients achieving DLQI of 0 or 1 was higher for both ustekinumab 45 and 90 mg than for the placebo (RR = 12.66, 95% CI 8.86–18.10, P << 0.001; RR = 12.87, 95% CI 9.01–18.40, P << 0.001, respectively • no significant difference in the number of patients achieving DLQI of 0 or 1 between the two doses of ustekinumab **Adverse Events** **Short-term therapy** (6 Studien):

	• Incidence of AEs at the end of 12 weeks of treatment Aes were higher for ustekinumab 45 mg than for placebo, and included headache and back pain. • There was no significant difference in the incidence of upper respiratory tract infection (URTI), nasopharyngitis or arthralgia between the two groups **Long-term therapy:** • Incidence of AEs at 3 years (1 Studie) There was no significant difference between the two doses of ustekinumab for the incidence of AEs, including headache, URTI, nasopharyngitis, back pain and arthralgia. • Incidence of AEs at 5 years (1 Studie) There was no significant difference between ustekinumab at either dose and the placebo group in the incidence of AEs, including headache, URTI, nasopharyngitis, back pain and arthralgia. There was also no significant difference between the two doses of ustekinumab for the incidence of AEs.
	4. Anmerkungen/Fazit der Autoren Our results indicate that ustekinumab is safe for patients with moderate to severe plaque psoriasis over a period of 5 years, and it is effective after 12 weeks. There was no significant superiority in efficacy between the 45 mg and 90 mg doses for short-term therapy. Results of the long-term safety evaluation are consistent with short-term reports of ustekinumab safety. More long-term studies and RCTs are needed to validate these results. 5. Anmerkung FBMed: Studienpool von Meng Y et al., 2014 zur Bestimmung PASI 75 ist bei Liu Y et al., 2014 vollständig enthalten. Ergebnisse für PASI 75 siehe Liu Y et al., 2014
Schmitt J et al., 2014 [27]. Efficacy and safety of systemic treatments for moderate-to severe psoriasis: meta-analysis of randomized controlled	1. Fragestellung The objective of this systematic review was to update and extend our previous review on the comparative efficacy and tolerability of conventional and biological systemic treatments for moderate-to-severe plaque psoriasis by means of direct and indirect meta-analysis.
	2. Methodik Population: patients with moderate to severe plaque psoriasis Intervention: systemic biological treatments (infliximab, adalimumab,…and/or ustekinumab) and conventional systemic treatments (such as MTX, CSA, retinoids, fumaric acid esters) Komparator: k.A. Endpunkte: primär: ≥ 75% Reduktion in PASI; sekundär: PASI 50, PASI 90 Suchzeitraum:

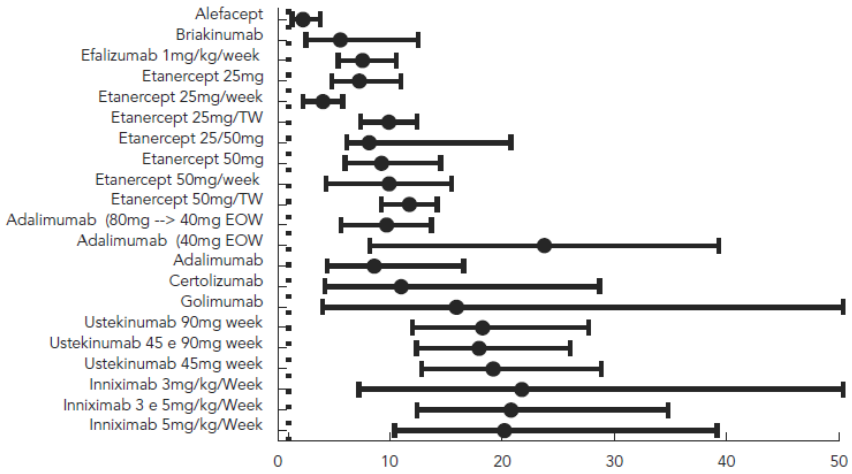
trials	○ Relevant articles published until 4 November 2009 (except on alefacept) were retrieved from the German S3-psoriasis guidelines. ○ Von Januar 2009 bis 18. Oktober 2012 systematische Suche in Medline, Medline in Process, Embase und Cochrane Library ○ Aktualität: We conducted a systematic review on the efficacy and safety of systemic treatments approved for moderate-to-severe or severe psoriasis (as of 1 June 2013). Anzahl eingeschlossene Studien/Patienten (Gesamt): 48 (n= 16 696 patients (11 178 randomized to biologics, 1 888 to conventional treatments) Qualitätsbewertung der Studien: Risk of bias tool of the Cochrane Collaboration
	3. Ergebnisdarstellung **Fumaric acid esters** (2 studies) Efficacy: Two small trials investigated fumaric acid esters for psoriasis, indicating superiority vs. placebo and similar efficacy to MTX. The PASI 75 response rate was 19% after 12 weeks of treatment with fumaric acid esters. Safety: Rates of adverse events and withdrawals did not differ between fumaric acid esters and MTX. **Etanercept** (14 studies): Efficacy: • Both high-dose etanercept (50 mg twice weekly) and low-dose etanercept (50 mg once weekly/25 mg twice weekly) were consistently superior to placebo in eight trials. • PASI 75 response rates ranged from 40% to 59% in trials investigating high-dose etanercept and from 30% to 45% for low-dose etanercept • In head-to-head trials etanercept 50 mg twice weekly was less efficacious than ustekinumab 90 mg (RD 17%, 95% CI 10–24%) and ustekinumab 45 mg (RD 11%, 95% CI 3–19%), and more efficacious than acitretin. Safety: The rates of withdrawals and adverse events did not differ significantly between etanercept and ustekinumab **Infliximab** (6 studies): Efficacy: • Infliximab was superior to placebo, with PASI 75 response rates between 68% and 88% • One trial indicated the superiority of infliximab vs. MTX 15 mg (RD 36%, 95% CI 29–43%) Safety:

	the rate of adverse events did not differ significantly between infliximab and placebo or between infliximab and MTX in the trials identified **Adalimumab** (4 studies): Efficacy: adalimumab for psoriasis, indicating superiority vs. placebo and vs. MTX (initial dose 7.5 mg per week), with PASI 75 response rates between 53% and 80% Safety: the rate of adverse events did not differ significantly between adalimumab and placebo or between adalimumab and MTX in the trials identified **Ustekinumab** (5 studies): Efficacy: Ustekinumab was superior to placebo with PASI 75 response rates in patients receiving ustekinumab 90 mg of between 66% and 76%, and for 45 mg between 59% and 67%. Safety: the risk of adverse events did not differ significantly between ustekinumab and placebo or between ustekinumab and etanercept.
	4. Anmerkungen/Fazit der Autoren The evidence base indicating efficacy of the biologics infliximab, adalimumab, ustekinumab and etanercept is much stronger than the evidence for efficacy of conventional treatment options for moderate-to-severe psoriasis.
Almutawa F et al., 2013 [1]. Systematic Review of UV-Based Therapy for Psoriasis	1. Fragestellung The aim of the study was to evaluate the efficacy, short-term safety, and tolerability of UV-based therapy in the treatment of adults with moderate to severe plaque psoriasis.
	2. Methodik We performed a systematic review and metaanalysis of randomized controlled trials (RCTs)**.** Population: Adults with moderate to severe plaque-type psoriasis Intervention/Komparator: NB-UVB, BB-UVB, and PUVA Endpunkt: PASI 75, clearance, short-term safety, tolerability from the percentage of adverse effects and withdrawal due to adverse effects Suchzeitraum: 1980 to 2011 in MEDLINE, EMBASE, and Cochrane databases Anzahl eingeschlossene Studien/Patienten (Gesamt): 41 RCTs (N=2.416 patients)
	3. Ergebnisdarstellung: Efficacy: • PASI-75: In monotherapy trials, PUVA was the most effective modality (mean: 73 %, 95 % CI 56–88). Trials with BB-UVB also showed a high PASI-75 (73 %) but with a wide CI (18–98) due to heterogeneity of the total available three studies. This was followed

	by NB-UVB (mean: 62 %, 95 % CI 45–79) then bath PUVA (mean: 47 %, 95 % CI 30–65). • Clearance: In the monotherapy trials, PUVA (mean: 79 %, 95 % CI 69–88) was superior to NB-UVB (mean: 68 %, 95 % CI 57–78), BB-UVB (mean: 59 %, 95 % CI 44–72), and bath PUVA (mean: 58 %, 95 % CI 44–72). <u>Safety:</u> The percentages of asymptomatic erythema development in monotherapy trials were 64 % for BB-UVB, 57 % for NB-UVB, 45 % for PUVA, and 34 % for bath PUVA. Symptomatic erythema or blistering percentages for the monotherapy trials were as follows: 7.8 % for NB-UVB, 2 % for BB-UVB, 17 % for PUVA, and 21 % for bath PUVA. <u>Withdrawal due to adverse effects:</u> The percentages of withdrawal due to adverse effects were 2 % for NB-UVB, 4.6 % for BB-UVB, 5 % for PUVA, and 0.7 % for bath PUVA monotherapy trials.
	4. Fazit der Autoren As a monotherapy, PUVA was more effective than NB-UVB, and NB-UVB was more effective than BB-UVB and bath PUVA in the treatment of adults with moderate to severe plaque-type psoriasis, based on clearance as an end point. Based on PASI-75, the results were similar except for BB-UVB, which showed a high mean PASI-75 (73 %) that was similar to PUVA, but with a wide CI (18–98). The short-term adverse effects were mild as shown by the low rate of withdrawal due to adverse effects.
Correr CJ et al., 2013 [7]. Efficacy and safety of biologics in the treatment of moderate to severe psoriasis: a comprehensive meta-analysis of randomized controlled trials	1. Fragestellung As the use of biologic medications for psoriasis is a recent development, the objective of this article is to provide comprehensive and up-to-date evidence regarding the efficacy and safety of the use of all biologic therapies available for moderate to severe psoriasis.
	2. Methodik Population: patients with moderate to severe psoriasis Intervention: adalimumab, alefacept, anakinra, briakinumab, certolizumab, efalizumab, etanercept, infliximab, golimumab, rituximab, siplizumab, onercept or ustekinumab Komparator: Placebo Endpunkt: improvement of 50%, 75%, and 90% in the Psoriasis Area and Severity Index (PASI 50, 75, and 90, respectively) at 10-14 weeks of treatment, serious adverse events, adverse events leading to discontinuation of treatment (withdrawals), and infection occurrence Suchzeitraum (Aktualität der Recherche): Cochrane, EMBASE, IPA (International Pharmaceutical Abstracts), LILACS, PubMed, SciELO, Science Direct, Scopus, and Web of Science. Manual search in relevant periodic, symposium and congress annals and reference lists of articles found in the search were performed, published up until May 2011 and written in English, Portuguese or Spanish

	Anzahl eingeschlossene Studien/Patienten (Gesamt): 41 RCTs in Meta-Analyse Qualitätsbewertung der Studien: Jadad score, Cochrane risk of bias tool: selection, performance, detectrion, attrition, reporting and other biases Untersuchung der Heterogenität mittels: I^2
	3. Ergebnisdarstellung Studiencharakteristika: siehe Anhang Tabelle 1 <u>*Clinical efficacy:*</u> ***PASI 50:*** • highest RR ustekinumab 90mg (RR: 8.77; 95%CI: 6.98-11.03), followed by ustekinumab 45mg (RR: 8.27; I95%CI: 6.57-10.40) vs. placebo • statistically significant difference, when compared with placebo, favoring ustekinumab 90mg and 45mg in relation to infliximab 3mg/kg/week (RR: 3.84; 95%CI: 2.26-6.53]), efalizumab (RR: 3.83; 95%CI: 3.27-4.49), and alefacept (RR: 1.83; 95%CI: 1.46-2.28), see Figure 2a. 2a) PASI 50  **PASI 75:** greatest measure of effect observed were infliximab in both doses (3mg/kg/week – RR: 21.77; 95%CI: 7.24-65.45 and 5mg/kg/week – RR: 20.21; 95%CI: 10.42-39.19) and ustekinumab, also at both doses (45mg – RR: 19.22; 95%CI: 12.82-28.82 and 90mg – RR: 18.26; 95%CI: 12.04-34.82) see Figure 2b.

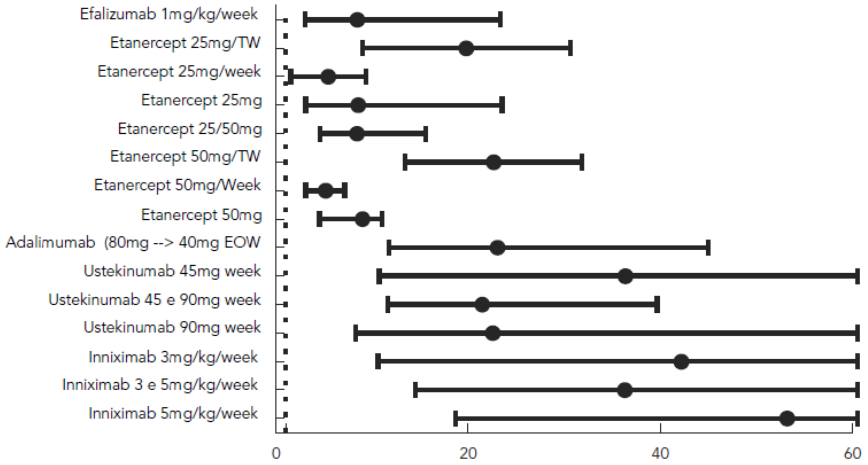
2b) PASI 75



PASI 90:

- infliximab, ustekinumab and adalimumab present the highest results of RR
- no statistically significant difference between placebo and etanercept 25mg OW

2c) PASI 90

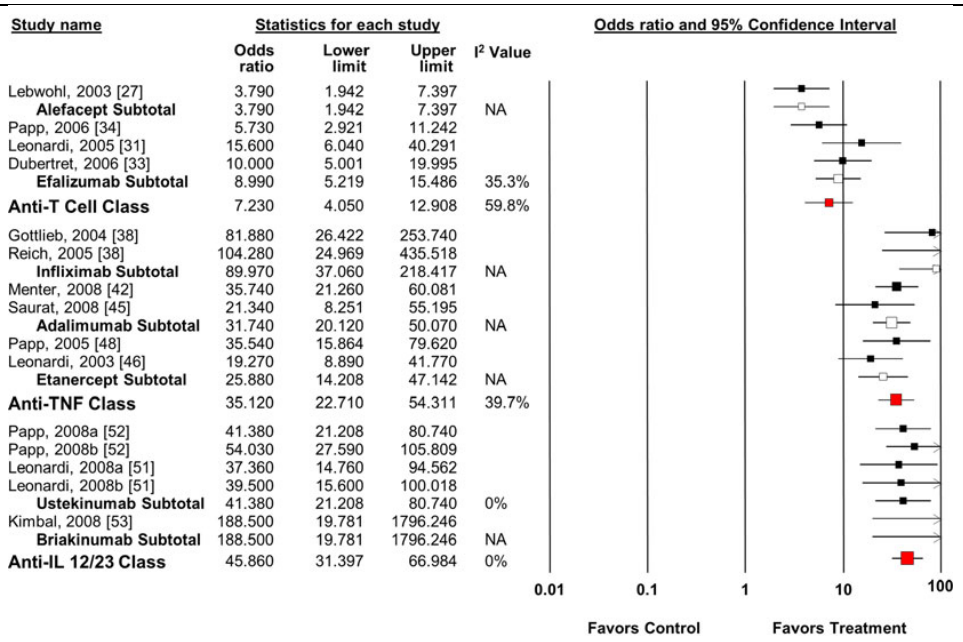


Heterogenität (I^2>50%) in Wirksamkeit bei:
PASI 50 outcome, etanercept 25mg TW (I^2 = 75%), etanercept 50mg W (I^2 = 70%) and infliximab 5mg/kg/ week (I^2 = 64%); PASI 75, adalimumab (80mg > 40mg EOW) (I^2 = 76%), infliximab 3mg/kg/week (I^2 = 55%) and alefacept (I^2 = 70%) and for PASI 90 ustekinumab 45mg (I^2 = 58%)

➔ Keine Veränderung der Heterogenität bei Nichteinbeziehung bestimmter Studien in die MA → Grund für Heterogenität unbekannt.

<u>Safety outcomes:</u>
safety outcomes including infections and serious adverse events did not present statistically significant differences between biologic and placebo considering withdrawal due to adverse events, the rate for ustekinumab 45mg was lower than that for the placebo group and the difference was statistically significant. For other biologics, at all dosages, there was no

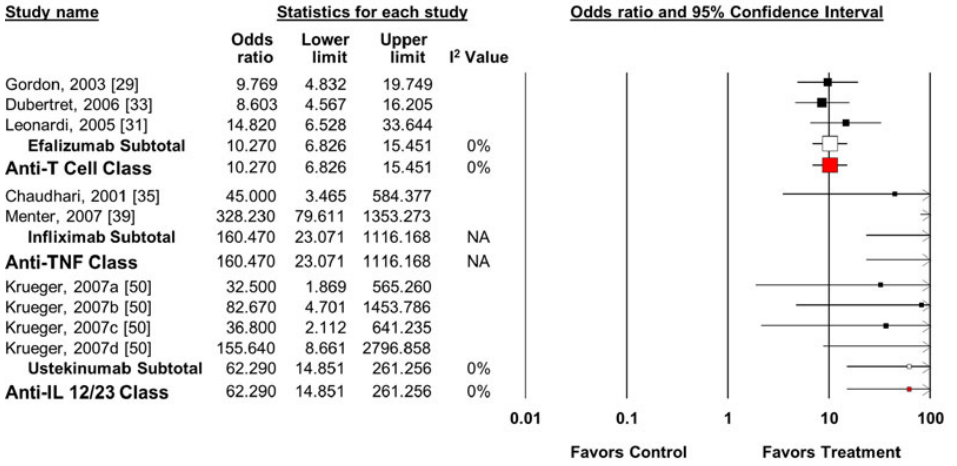
	statistically significant difference between the drug´s result and placebo
	4. Anmerkungen/Fazit der Autoren Although we cannot conclude which bioagent is the best to treat moderate to severe psoriasis, we can point to a trend from ustekinumab 45mg and 90mg and infliximab 3mg/kg and 5mg/kg to be the best ones on achieving PASI response of 50%, 75% and 90% after 10 to 14 weeks of treatment Moreover, considering the current evidence about safety in RCTs, our findings show a similar safety profile among biologics in the short-term treatment and a result signalizing ustekinumab 45mg as the most well tolerated biological agent in the first three months of treatment.
Baker EL et al., 2012 [5]. Effect of Biologic Agents on Non-PASI Outcomes in Moderate-to-Severe Plaque Psoriasis: Systematic Review and Meta-Analyses	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 (MTC) Population: Patients with moderate-to-severe plaque psoriasis Intervention: infliximab, adalimumab, etanercept, ustekinumab (nicht relevant: briakinumab alefacept, efalizumab) Komparator: Placebo Endpunkte: PGA Static Response Rate und PGA Dynamic Response Rate Suchzeitraum: 1966 bis Mai 2009 in MEDLINE und Cochrane Central Register of Controlled Trials Anzahl eingeschlossene Studien/Patienten (Gesamt): 31 Studien/ n = k. A.
	3. Ergebnisdarstellung infliximab versus placebo (n = 6); adalimumab versus placebo (n = 5); etanercept versus placebo (n = 4); ustekinumab versus placebo (n = 3) **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. Impact of biologic agents on static PGA response rate:



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.

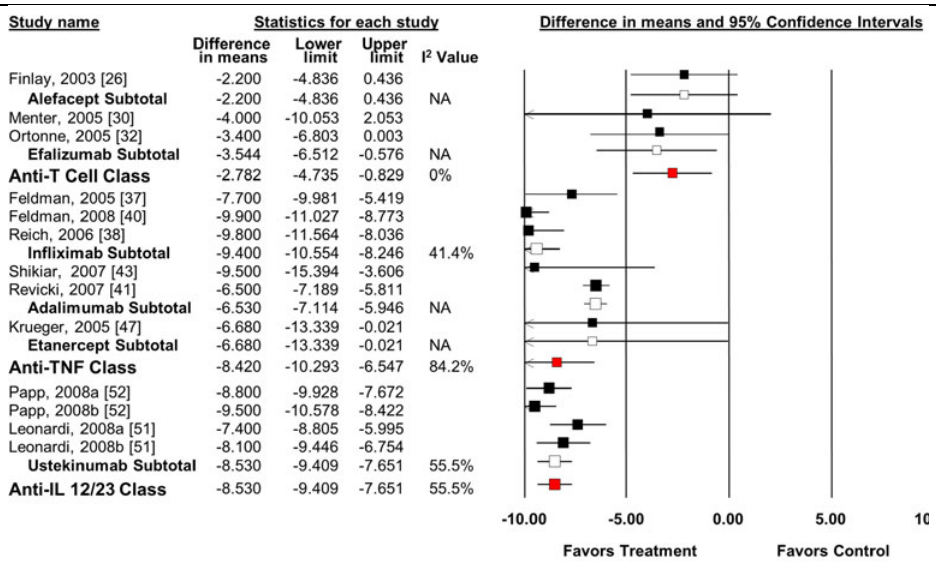
Impact of biologic agents on dynamic PGA response rate:



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.

Impact of biologic agents on change in DLQI from baseline:

	
	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. 5. 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 [17]. 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, Etanercept, Infliximab, Ustekinumab (Elefacept nicht relevant)

Agents for the Treatment of Moderate to Severe Plaque Psoriasis	Komparator: Biological agents or placebo Endpunkte: 75% reduction in the PASI Suchzeitraum: 1992 – 2012 in MEDLINE (PubMed), EMBASE, the Cochrane Library, and clinicaltrials.gov Data analysis: A Bayesian network meta-analysis was performed by fitting 3 regression models: a fixed-effects model, a random-effects model, and a random-effects model with meta-regression coefficients. 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), …, 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), …, 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).

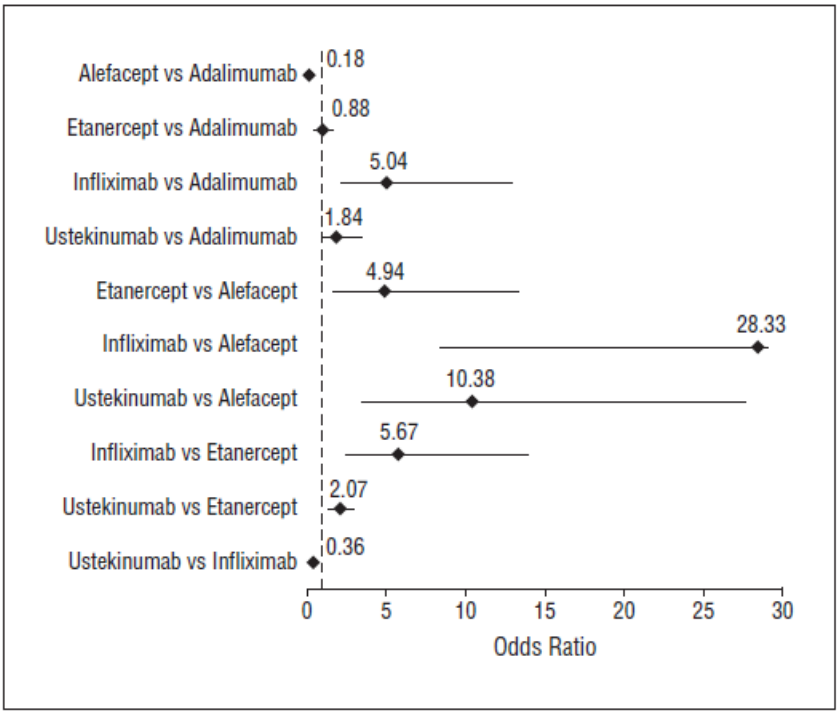


Figure 3. Random-effects model showing pairwise comparisons of 75% reductions in the Psoriasis Area and Severity Index among Food and Drug Administration–approved dosing of biological agents for the treatment of plaque psoriasis. Diamonds represent odds ratios; lines, 95% credible intervals.

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.

5. 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.
Reich K et al., 2012 [25]. Efficacy of biologics in the treatment of moderate to severe psoriasis: a network meta-analysis of randomized controlled trials	1. Fragestellung To estimate the comparative effectiveness of all biologic agents indicated in the treatment of moderate to severe psoriasis currently available in Europe based on the primary trial endpoints.
	2. Methodik A network meta-analysis conducted on the ordered probit scale and implemented as a Bayesian hierarchical model provided estimates for the probability of response and relative risk vs. placebo, based on all observed comparisons. Population: plaque-type psoriasis in adult patients Intervention: Biological agents Komparator: placebo or biological agents (adalimumab, etanercept, infliximab, ustekinumab) as monotherapy (efalizumab nicht relevant) Endpunkte: PASI 50, PASI 75, PASI 90 response rates Suchzeitraum: Januar 1995 – Oktober 2008 in MEDLINE, EMBASE, Cochrane Library, Studienregister und graue Literatur Anzahl eingeschlossene Studien/Patienten (Gesamt): 20/n = k.A. Risk of publication bias not assessed Summary of study characteristics provided Quality of studies assessed: Jadad score
	3. Ergebnisdarstellung • RRs for achieving PASI 50 vs. placebo, PASI 75 vs. placebo and PASI 90 vs. placebo: Results of evidence synthesis (all patients)

	PASI 50, mean (95% CrI)	PASI 75, mean (95% CrI)	PASI 90, mean (95% CrI)
Estimated probabilities of response			
Placebo	13% (12–14)	4% (3–4)	1% (0–1)
Efalizumab	51% (45–58)	26% (21–32)	8% (6–11)
Etanercept 25 mg	65% (56–73)	39% (30–48)	15% (10–21)
Etanercept 50 mg	76% (71–81)	52% (45–59)	24% (19–30)
Adalimumab	81% (74–87)	58% (49–68)	30% (23–39)
Ustekinumab 45 mg	88% (84–91)	69% (62–75)	40% (33–48)
Ustekinumab 90 mg	90% (87–93)	74% (68–80)	46% (39–54)
Infliximab	93% (89–96)	80% (70–87)	54% (42–64)
Relative risks			
Placebo	1 (–)	1 (–)	1 (–)
Efalizumab	4·0 (3·5–4·5)	7·4 (6·1–8·9)	15·5 (11·7–20·3)
Etanercept 25 mg	5·1 (4·4–5·8)	10·9 (8·6–13·7)	28·1 (19·3–39·8)
Etanercept 50 mg	6·0 (5·4–6·6)	14·7 (12·5–17·1)	45·2 (35·2–56·8)
Adalimumab	6·4 (5·7–7·1)	16·5 (13·7–19·8)	55·5 (40·9–73·7)
Ustekinumab 45 mg	6·9 (6·3–7·6)	19·5 (16·8–22·6)	74·2 (59·5–93·0)
Ustekinumab 90 mg	7·1 (6·5–7·8)	20·9 (18·1–24·0)	84·8 (68·6–104·6)
Infliximab	7·3 (6·6–8·1)	22·6 (19·3–26·5)	100·2 (76·0–126·9)

CrI, credible interval; PASI, Psoriasis Area and Severity Index.

(95% CrI are the Bayesian equivalent to confidence intervals)

	• Based on the indirect comparison and given a placebo PASI 50 response of 13%, infliximab had the highest predicted mean probability of response at PASI levels 50 (93%), 75 (80%) and 90 (54%), followed by ustekinumab 90 mg at 90%, 74% and 46%, respectively, and then ustekinumab 45 mg, adalimumab, etanercept and efalizumab. • There is an estimated 93% probability that infliximab is the most effective treatment followed by an 81% probability that ustekinumab 90 mg is the second most effective treatment and a 79% probability that ustekinumab 45 mg is the third most-effective treatment.
	4. Anmerkungen/Fazit der Autoren The analysis suggests a ranking of treatments in terms of effectiveness from infliximab, through ustekinumab, adalimumab, etanercept to efalizumab. 5. Hinweise durch FB Med • Heterogene Studienpopulation: unterschiedliche Patientencharakteristika, Vortherapie, Erkrankungsdauer, Behandlungsdauer bis zum primären Endpunkt • Funding: This study has been funded by Janssen-Cilag Ltd. but no restrictions have been placed on the design or results of the analysis. • CoI: KR has served as consultant and/or paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis including Abbott, Biogen Idec, Celgene, Centocor, Janssen-Cilag, Leo, Medac, Merck, MSD (formerly Essex, Schering- Plough), Novartis, Pfizer (formerly Wyeth). ADB has acted as lecturer, consultant and researcher for Abbott, Janssen, Leo, MSD, Novartis and Pfizer. JNE and NSH work for an international consultancy and as such have received funding from numerous device and and pharmaceutical companies to conduct studies similar to that presented in this paper.
Yamauchi PS et al., 2016 [28]. Systematic review of efficacy of antietumor necrosis factor (TNF) therapy in patients with psoriasis previously	1. Fragestellung We sought to systematically investigate the efficacy and safety of a second TNF antagonist after failure of a first TNF antagonist
	2. Methodik Population: patients with psoriasis Intervention/Komparator: TNF antagonists for the treatment of moderate to severe psoriasis in adults who previously experienced treatment failure with another TNF antagonist. Endpunkte: Physician Global Assessment (PGA), PASI 50, or 75, adeverse events, Lebensqualität (Dermatology Life Quality Index) Suchzeitraum: February 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 15 studies Quality of studies assessed: k.A.
	3. Ergebnisdarstellung

treated with a different antieTNF agent	*Hinweis*: All patients from the included studies had moderate to severe plaque psoriasis. • Although response rates to a second TNF antagonist were lower than for a first, a substantial proportion of patients in every study achieved treatment success. • Week-24 response rates for a second antagonist were 30% to 74% for a 75% improvement in PASI score and 20% to 70% for achieving a PGA score of 0/1 → *siehe Anhang: Figure 1 aus Yamauchi et al. 2016* • Mean improvements in Dermatology Life Quality Index ranged from -3.5 to -13. • In general, patients who experienced secondary failure achieved better responses than patients with primary failure. • Adverse event incidences ranged from 20% to 71%, without unexpected adverse events; 0% to 11% of patients experienced serious adverse events.
	4. Fazit der Autoren: *This systematic literature review suggests that a lack of response to an initial TNF antagonist does not preclude patients from responding favorably to a subsequent TNF antagonist. Switching patients who are not responding to treatment with an antieTNF agent to another TNF antagonist can be considered as a therapeutic option that may produce clinically meaningful responses in a substantial proportion of patients, with improved quality of life.* 5. Hinweise durch FB Med • Differences in study designs precluded conducting a meta-analysis or making direct comparisons between studies.
Zweegers J et al. 2016 [29]. Effectiveness of Biologic and Conventional Systemic Therapies in Adults with Chronic Plaque Psoriasis in Daily Practice: A	1. Fragestellung This systematic review searched PubMed and EMBASE and summarized the real-world evidence on effectiveness of biologics (adalimumab, etanercept, infliximab and ustekinumab) and conventional systemic therapies (acitretin, cyclosporine, fumarates and methotrexate) for the treatment of plaque psoriasis in adults.
	2. Methodik Population: Adults with Chronic Plaque Psoriasis Intervention/Komparator: Biologics and Conventionaly systemic therapies (siehe Ergebnisteil) Endpunkte: • Primary outcome: PASI75 score at week 12–16. • Secondary outcomes: PASI75 with intermediate-term (17–28 weeks) and long-term (≥ 1 year data) treatment, PASI50, PASI90, PASI100 and decrease in mean PASI, PhGA and BSA with short-, intermediate- and long-term treatment. All measures were

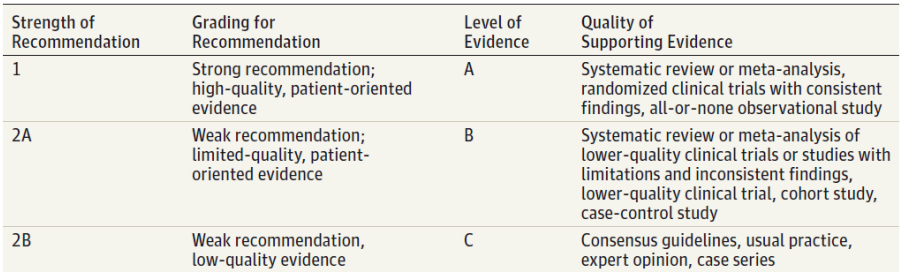
Systematic Review	compared with baseline except if stated otherwise. Suchzeitraum: from 1990 until May 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): A total of 32 articles were included (Fig. 1): 28 on biologics, 3 on conventional systemic therapies, and 1 describing both biologic and conventional systemic treatment. Seven articles reported results of adalimumab therapy, 20 of etanercept, 4 of infliximab, 4 of ustekinumab, 1 of acitretin, 2 of fumarates, 1 of cyclosporine and 3 of methotrexate. There were 12 prospective and 20 retrospective studies. Quality of studies assessed: k.A.
	3. Ergebnisdarstellung **<u>Biologic therapies</u>** **Adalimumab (basierend auf 7 studien):** <u>PASI75 outcome for Adalimumab</u>: Overall, PASI75 was attained by 27–68% with short-term, 31–82% with intermediate-term and 44–89% with long-term (1 and 2 year) adalimumab treatment. <u>Adalimumab monotherapy:</u> In the one retrospective study, adalimumab reached PASI75 percentages of 38% at week 16, 62% at week 24 and 69% at one year. <u>Cohorts using adalimumab with conventional systemic treatments</u>: PASI75 results from prospective studies were 27–54% at week 12, 31% (17) at week 24, and 44% at 2 years of adalimumab treatment. In retrospective studies, 56–68% of patients reached PASI75 at week 16 (of which only one study used licensed dosing), 50–82% at week 24, 48–89% at 1 year and 83% at 2 years. **Etanercept (basierend auf 20 Studien):** <u>PASI75 outcome for etanercept.</u> Overall, PASI75 was attained by 12–66% with short-term, 19–85% with intermediate-term, and 49–92.3% with long-term (1-and 2-year) etanercept treatment. <u>Etanercept monotherapy:</u> Retrospective studies reported a PASI75 of 36.1–54.1 at week 12, 66% at week 16 and 60.5–85% (21, 25, 29, 31) at week 24. At 1 year PASI75 was 71.4–92.3% and at 2 years 86.9%. <u>Cohorts using etanercept with conventional systemic treatments:</u> In prospective studies, etanercept achieved a PASI75 in 12–63% at week 12 and 19–73.2% at week 24 in prospective studies and 25–69.2% at 1 year. In retrospective studies 21.4–26% of patients achieved PASI75 at week 12, 37–53% at week 24, and 49–54% at one year. **Infliximab (basierend auf 4 Studien)** <u>PASI75 outcome for infliximab:</u> Overall, PASI75 was attained by 38–53% at short-term and 69% at intermediate-term treatment with infliximab. <u>Infliximab monotherapy</u>: There were no PASI75 results from studies at week 12, 24 or on long-term treatment with infliximab monotherapy. At week 28, PASI75 was 69% in one prospective study. <u>Cohorts using infliximab with conventional systemic treatments:</u> In the prospective study with combination therapy and dose adjustment, 38% of the patients who previously used biologics and 53% of biologic naïve patients reached PASI75 at week 12.

	Ustekinumab (basierend auf 4 Studien) PASI75 outcome for ustekinumab: Overall, PASI75 was attained by 63–80% at short-term, 58–75.9% at intermediate-term, and 65.5% at long-term (1 year data) with ustekinumab treatment. Ustekinumab monotherapy: Prospectively, PASI75 was attained by 80% (37) of patients at week 16 and 58% (36) at week 28 with ustekinumab monotherapy. Cohorts using ustekinumab with conventional systemic therapy: Two retrospective studies, of which one was with dose adjustments, were included and presented a PASI75 of 79.3% at week 12 and 63% at week 16, 66.7–75.9% at week 24, and 65.5% at 1 year. **Conventional systemic therapies** **Acitretin** Monotherapy: In one retrospective study, PASI75 response was attained by 27% of patients with a mean dose of 0.38 mg/kg/day at week 12. No prospective or retrospective data were available on long-term treatment with acitretin. **Fumarates** Monotherapy: One retrospective study showed a PASI75 of 47% (44) at week 12, 63% (44) at week 24, and 76% (44) at 1 year. No long-term results from prospective studies were available. **Cyclosporine** Monotherapy: In one retrospective study, 46% of patients reached a PASI75 at week 12. **Methotrexate** Monotherapy: In the retrospective studies, between 40% and 49% of patients treated with methotrexate 10–20 mg weekly achieved PASI75 at week 12 and 62% at week 24. Eighty-one percent achieved PASI75 at 1 year. No prospective data were available.
	4. Fazit der Autoren: *In conclusion, biologic and conventional systemic agents are effective in daily practice. Combination therapies of biologics with conventional systemic treatments and dose adjustments of biologics were frequently applied strategies, especially for adalimumab and etanercept, and could explain the large ranges in PASI75 results. […] Gaps identified were daily practice data on infliximab, ustekinumab, conventional systemic therapies, long-term treatment, combination therapy and results of direct comparisons on effectiveness between anti-psoriatic agents.* 5. Hinweise durch FB Med There was a high heterogeneity in study design, treatment regimen and patient population between included studies.
Almutawa F et al., 2015 [2]. Efficacy of	1. Fragestellung In this study, we aimed to conduct a systematic eview and meta-analyses to provide a pooled estimate of the efficacy and short-term safety of targeted UVB phototherapy(including excimer (308-nm) laser, excimer (308-nm) light, and localized NB-UVB (311–313-nm) light), topical PUVA,

localized phototherapy and photodynamic therapy for psoriasis: a systematic review and meta-analysis	and PDT in the treatment of localized plaque psoriasis including palmoplantar psoriasis. We also performed a meta-analysis of all published clinical trials that compared the UVB to PUVA.
	2. Methodik Population: Intervention/Komparator: topical PUVA vs. targeted UVB phototherapy Endpunkte: PASI75 (primary endpoint), side effects Suchzeitraum: January 1980 to June 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 23 studies. Of the 23 studies, 13 evaluated targeted UVB, 4 evaluated topical PUVA, 3 compared topical PUVA vs. targeted UVB, and 3 evaluated PDT. Quality of studies assessed: The quality of the randomized clinical trials were assessed by the Jadad scoring system
	3. Ergebnisdarstellung **1. Analyse:** Meta-analysis of topical PUVA vs. targeted UVB phototherapy (basierend auf 3 RCTs) • Fixed effects models showed significantly better patient outcome using PUVA compared with targeted UVB. *Hinweis*: Cochrane Q statistics (6.244, df = 2) showed significant heterogeneity between studies (P = 0.044) and I^2 was almost closer to 70%. Therefore, our conclusion was based on the random effects model, which indicated that PUVA had a statistically nonsignificant advantage over targeted UVB. **2. Analyse:** Quantification of the patient outcome, defined by a 75% reduction in psoriasis score after each of the phototherapy and PDT treatment. We computed the pooled weighted estimates of each treatment separately using all available research publications, including randomized and nonrandomized studies. • Targeted UVB phototherapy (basierend auf 15 Studien): The pooled weighted estimate of the percentage of patients achieving 75% reduction in their severity score from these studies was 61% (95%CI 50–71%). The main side effects, which are painful erythema and blistering, ranged from 0% to 92%. The pooled weighted estimate for painful erythema and blistering was 16% (95% CI 4–31%). • Topical PUVA (basierend auf 6 Studien): The pooled weighted estimate of the efficacy from these studies was 77% (95% CI 62–89%). The percentage of patients who developed painful erythema or blisters ranged from 0% to 27% with an average of 5%. • PDT (basierend auf 3 Studien): The pooled efficacy estimate from these studies was 22% (95% CI 10–37%) (Fig. 10). The main side effect was pain that occurred in 80–100% of the patients, and in 30–38% of them, it was described as intolerable.
	4. Fazit der Autoren: *Despite the limitations of this systematic review, it can be concluded that topical PUVA and targeted UVB phototherapy are very effective in the treatment of localized psoriasis. Both should be*

	considered if topical treatments fail prior to progressing to systemic treatments or biologics. Topical PUVA therapy appears to be more effective than non-laser targeted UVB phototherapy. However, some studies showed that the efficacy of excimer (308-nm) laser approximates that of topical PUVA. PDT with ALA showed low efficacy and high incidence of side effects when used to treat localized psoriasis. 5. Hinweise durch FB Med • limited number of randomized controlled studies that assessed efficacy and safety with small number of patients (→ largest trial including only 163 patients) • High heterogeneity of the treatment protocols in regard to the starting dose, increment, treatment frequency, and the use of different severity scores

Leitlinien

Armstrong AW et al., 2015 [3]. Combining biologic therapies with other systemic treatments in psoriasis: evidence-based, best-practice recommendations from the Medical Board of the National Psoriasis Foundation	Fragestellung/Ziel "To make evidence-based, best-practice recommendations regarding combining biologics with other systemic treatments, including phototherapy, oral medications, or other biologics, for psoriasis treatment." Methodik Suchzeitraum: 1. Januar 1946 bis 18. Juni 2013 in MEDLINE Grading Skala in Anlehnung an Robinson et al.: Systematic reviews: grading recommendations and evidence quality. *Arch Dermatol*. 2008;144(1):97-99. Table 1. Grading for Recommendation and Evidence[a]  **CoI**: Dr Armstrong reported serving as an investigator for or consultant to AbbVie, Lilly, Janssen, Amgen, Merck, and Pfizer. Dr Bagel reported serving as a consultant, speaker, and investigator for Amgen and AbbVie. Dr Van Voorhees reported serving as an advisor for Amgen, AbbVie, Janssen, LEO Pharma, and Warner Chilcott. She reported receiving grants from Amgen and AbbVie. She reported serving as a consultant for Amgen and as a speaker for Amgen, AbbVie, and Janssen. Dr Robertson reported being employed by the National Psoriasis Foundation, which receives unrestricted financial support from companies that make products used to treat psoriasis and psoriatic

Strength of Recommendation	Grading for Recommendation	Level of Evidence	Quality of Supporting Evidence
1	Strong recommendation; high-quality, patient-oriented evidence	A	Systematic review or meta-analysis, randomized clinical trials with consistent findings, all-or-none observational study
2A	Weak recommendation; limited-quality, patient-oriented evidence	B	Systematic review or meta-analysis of lower-quality clinical trials or studies with limitations and inconsistent findings, lower-quality clinical trial, cohort study, case-control study
2B	Weak recommendation, low-quality evidence	C	Consensus guidelines, usual practice, expert opinion, case series

arthritis, including AbbVie, Amgen, Celgene Corporation, Lilly, Galderma Laboratories, Janssen, LEO Pharma, Novartis, Pfizer Inc, and Stiefel, a GSK company. No other disclosures were reported.

Freitext/Empfehlungen/Hinweise

Table 2. Strength of Recommendations for the Use of Biologics in Combination With Phototherapy for Psoriasis Treatment

Agent	Strength of Recommendation	Level of Evidence	Source
Etanercept and phototherapy	2A	B	Kircik et al,[21] 2008; Gambichler et al,[17] 2011; Park et al,[18] 2013; De Simone et al,[22] 2011; Wolf et al,[23] 2009; Lynde et al,[24] 2012
Adalimumab and phototherapy	2A	B	Bagel,[25] 2011; Wolf et al,[19] 2011
Ustekinumab and phototherapy	2B	C	Wolf et al,[20] 2012

Evidenzbasis

[17] Gambichler T et al. Etanercept plus narrowband ultraviolet B phototherapy of psoriasis is more effective than etanercept monotherapy at 6 weeks. *Br J Dermatol*. 2011;164(6):1383-1386.

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Table 3. Strength of Recommendations for the Use of Biologics in Combination With Traditional Oral Systemic Medications for Psoriasis Treatment

Agent	Strength of Recommendation	Level of Evidence	Source
Biologics and Methotrexate in Combination Therapy			
Etanercept and methotrexate	1	A	Zachariae et al,[26] 2008; Gottlieb et al,[27] 2012; Driessen et al,[29] 2008
Infliximab and methotrexate	2A	B	Dalaker and Bonesrønning,[28] 2009; Goedkoop et al,[30] 2004; Kavanaugh et al,[31] 2007
Adalimumab and methotrexate	2B	C	De Groot et al,[32] 2008
Biologics and Acitretin in Combination Therapy			
Etanercept and acitretin	2A, etanercept plus acitretin similar efficacy to etanercept alone	B	Gisondi et al,[34] 2008; Smith et al,[35] 2008
Infliximab and acitretin	2B, favors combination	C	Smith et al,[35] 2008
Adalimumab and acitretin	2B, favors combination	C	Smith et al,[35] 2008
Biologics and Cyclosporine in Combination Therapy			
Etanercept and cyclosporine	2B	C	Yamauchi and Lowe,[36] 2006; Lee et al,[37] 2010
Adalimumab and cyclosporine	2B	C	Gattu et al,[38] 2009

Evidenzbasis

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	[37] Lee EJ et al. A clinical trial of combination therapy with etanercept and low dose cyclosporine for the treatment of refractory psoriasis. *Ann Dermatol*. 2010;22(2): 138-142. [38] Gattu S et al. Can adalimumab make a smooth and easy transition from cyclosporine a reality? a case series of successful transitions. *Psoriasis Forum.* 2009;15(2):33-35. **Table 4. Strength of Recommendations for the Use of a Biologic in Combination With Another Biologic for Psoriasis Treatment** | Agent | Strength of Recommendation | Level of Evidence | Source | | --- | --- | --- | --- | | Etanercept and ustekinumab | 2B | C | Cuchacovich et al,[48] 2012; Heinecke et al,[49] 2013 | | Etanercept and alefacept | 2B | C | Krell,[50] 2006 | | Etanercept and efalizumab | 2B | C | Hamilton,[45] 2008; Adişen et al,[46] 2008; Kitamura et al,[47] 2009 | | Adalimumab and ustekinumab | 2B | C | Heinecke et al,[49] 2013 | | Infliximab and efalizumab | 2B | C | Lowes et al,[44] 2005; Hamilton,[45] 2008 | *Evidenzbasis* [44] LowesMA et al. Psoriasis vulgaris flare during efalizumab therapy does not preclude future use: a case series. BMC Dermatol. 2005;5:9. [45] Hamilton TK. Treatment of psoriatic arthritis and recalcitrant skin disease with combination therapy. J Drugs Dermatol. 2008;7(11):1089-1093. [46] Adişen E et al. When there is no single best biological agent: psoriasis and psoriatic arthritis in the same patient responding to two different biological agents. Clin Exp Dermatol. 2008;33(2):164-166. [47] Kitamura G et al. A case of tuberculosis in a patient on efalizumab and etanercept for treatment of refractory palmopustular psoriasis and psoriatic arthritis. Dermatol Online J. 2009;15(2):11. [48] Cuchacovich R et al. Combination biologic treatment of refractory psoriasis and psoriatic arthritis. J Rheumatol. 2012; 39(1):187-193. [49] Heinecke GM et al. Combination use of ustekinumab with other systemic therapies: a retrospective study in a tertiary referral [center]. J Drugs Dermatol. 2013;12 (10):1098-1102. [50] Krell JM. Use of alefacept and etanercept in 3 patients whose psoriasis failed to respond to etanercept. J AmAcad Dermatol. 2006;54(6): 1099-1101. Clinical Review & Education Review Biologic Therapies and Other Psoriasis Treatments 438
European Dermatolo-gy Forum (EDF), 2015 [8].	Ziel “The primary goal of these guidelines was to assist health care professionals in the choice of the optimal systemic treatment for their psoriasis patients with the specific circumstances of the individual patient.” “…ultimately improving patient care.“
European S3-Guidelines	Methodik These guidelines are an update of the existing European Psoriasis Guidelines published in 2009.

on the systematic treatment of psoriasis vulgaris. Update 2015

EDF in cooperation with EADV and IPC

The guidelines have a validity until 31.12.2019. However, an update with respect to new medications will be added before that date.

Methods Report: siehe Nast A. et al. (2015) [21]

systematische Recherche in Cochrane Library, Medline, Medline In-Process und Embase

Suchzeitraum: bis 12. September 2013, anschließend automatische monatliche Benachrichtigung in allen Datenbanken bis 12. Oktober 2014

evidence and consensus-based guidelines: Erstellung nach AGREE II

"All recommendations were consented using formal consensus methodologies (Delphi process and nominal group technique)."
Bewertung über GRADE / GoR (siehe Anhang Tabelle 2)

Level of consensus: ‚strong consensus' = agreement of > 90 % of the members of the expert group; 'consensus' = 75 to 89 % agreement; 'weak consensus' = 50 to 74 % agreement.

Sonstige methodische Hinweise

- Für die Themenbereiche 'Special considerations and special patient populations' wurden die Empfehlungen auf Basis von Expertenmeinung generiert. Keine systematische Bewertung.
- "The guidelines project has kindly been supported by the EDF. The financial support did not influence the guidelines development."
- CoI aller Mitarbeitenden
- Outcome-Erfassung 16 Wochen nach Therapiebeginn, Ausschluss falls nur Outcome vor der 8. Woche nach Therapiebeginn vorlag. Für long-term therapy: Ergebnisse ab der 24. Woche nach Therapiebeginn.

Freitext/Empfehlungen/Hinweise

Acitretin

Recommendation		Strength of consensus	Comment
Based on the available evidence we cannot make a recommendation for or against the use of acitretin as a mono-therapy.	**o**	Consensus	Evidence and consensus based
Based on clinical experience and depending on the most important outcome for the individual patient, we suggest a low dose (20 to 30 mg daily) with respect to tolerability and a high dose (> 30 mg daily) with respect to efficacy.	↑	Consensus	Expert opinion

Therapeutic combinations		Strength of consensus	Comments
Adalimumab	**o**	Consensus	No evidence available
Ciclosporin	↓	Strong consensus	Expert opinion: competition cytochrome P450 inactivation
Etanercept	↑	Consensus	Expert opinion: good safety profile assumed, possibly increased efficacy

Fumaric acid esters	o	Consensus	No evidence available
Infliximab	o	Consensus	No evidence available
Methotrexate	↓	Strong consensus	Expert opinion: increased risk of hepatotoxicity possible
Ustekinumab	o	Consensus	No evidence available

Evidenzbasis

[34] Caproni M et al. Serum levels of IL-17 and IL-22 are reduced by etanercept, but not by acitretin, in patients with psoriasis: a randomized-controlled trial. J Clin Immunol. 2009;29(2):210-4.

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[36] Gisondi P et al. Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: a 24-week, randomized, controlled, investigator-blinded pilot trial. Br J Dermatol. 2008;158(6):1345-9.

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Ciclosporin

Recommendation		Strength of consensus	Comment
If a short course for induction treatment is intended we recommend CSA.	↑↑	Strong consensus	Evidence and consensus based
For long-term treatment we suggest CSA only in selected patients.	↑	Strong consensus	Expert opinion
In case of continuous long-term treatment, we suggest CSA for a maximum of up to two years.	↑	Consensus	Expert opinion
In case a longer treatment is needed, we suggest the consultation with a nephrologist.	↑	Consensus	Expert opinion
Based on weighting of risk and benefit we suggest using CSA with a starting dose of 2.5 mg/kg bodyweight QD for up to four weeks, with a dosage increase up to 5 mg/kg bodyweight once daily thereafter.	↑	Weak con-sensus	Evidence and consensus based

Therapeutic combinations		Strength of consensus	Comments
Acitretin	↓	Strong consensus	Expert opinion: competition cytochrome P450 inactivation
Adalimumab	↓	Consensus	Expert opinion: increased risk of immunosuppression
Etanercept	↓	Consensus	Expert opinion: increased risk of immunosuppression
Fumaric acid esters	o	Consensus	No evidence available
Infliximab	↓	Consensus	Expert opinion: increased risk of immunosuppression
Methotrexate	↓	Weak consensus	Expert opinion: increased risk of immunosuppression
Ustekinumab	↓	Consensus	Expert opinion: increased immunosuppression, anecdotal evidence of increased toxicity 69

Evidenzbasis

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[57] Flytstrom I et al. Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. Br J Dermatol. 2008;158(1):116-21.
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Fumarsäureester

Recommendation		Strength of consensus	Comment
We recommend fumaric acid esters for the induction treatment.	↑↑	Consensus	Evidence and consensus based
We recommend fumaric acid esters for the long-term treatment.	↑↑	Consensus	Expert opinion
We recommend fumaric acid esters with a slow increase dosing regimen.	↑↑	Consensus	Expert opinion

Therapeutic combinations		Strength of consensus	Comments
Acitretin	o	Consensus	No evidence available
Adalimumab	o	Strong consensus	No evidence available
Ciclosporin	o	Consensus	No evidence available
Etanercept	o	Strong consensus	No evidence available
Infliximab	↓	Consensus	Expert opinion: increased risk of
Methotrexate	↓	Consensus	Expert opinion: increased risk of immunosuppression
Ustekinumab	o	Consensus	No evidence available

Evidenzbasis
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Methotrexat

Recommendation		Strength of consensus	Comment
We recommend MTX for the induction and long-term treatment.	↑↑	Strong consensus	Evidence and consensus based
Methotrexate can be given by oral or subcutaneous delivery. In general, a starting dose of 15 mg/week is used but individual dosages can range from 5 to 25 mg/week depending on individual factors.	Statement	Strong consensus	Expert opinion

Therapeutic combinations		Strength of consensus	Comments
Acitretin	↓	Strong consensus	Expert opinion: increased risk of hepatotoxicity possible
Adalimumab	↑	consensus	Expert opinion: combination widely used in rheumatology; combination with low-dose MTX (e. g., 7.5 to 10 mg/week) is likely sufficient to reduce formation of anti-drug antibodies (ADA) and increase trough levels of adalimumab
Ciclosporin	↓	Weak consensus	Expert opinion: increased risk of immunosuppression
Etanercept	↑	consensus	Evidence (additional benefit of adding MTX to etanercept ocompared to etanercept monotherapy) and consensus based
Fumaric acid esters	↓	Consensus	Expert opinion: increased risk of immunosuppression
Infliximab	↑	Consensus	Expert opinion: combination widely used in rheumatology; combination with low-dose MTX (e. g., 7.5 to 10 mg/week) is likely sufficient to reduce formation of anti-drug antibodies (ADA) and increase trough levels of infliximab
Ustekinumab	**o**	Consensus	No evidence available

Evidenzbasis

[57] Flytstrom I et al. Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. Br J Dermatol. 2008;158(1):116-21

[60] Heydendael VM et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med. 2003;349(7):658-65.

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Adalimumab

Recommendation		Strength of consensus	Comment
We recommend adalimumab as second line* medication for the induction and long-term treatment.	↑↑	Strong consensus	Evidence and consensus based
We recommend using adalimumab with an initial loading dose of 80 mg, week 1 40 mg followed by 40 mg every other week.	↑	Strong consensus	Expert opinion

* if phototherapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated

Therapeutic combinations		Strength of consensus	Comments
Acitretin	**o**	Consensus	No evidence available
Ciclosporin	↓	Consensus	Expert opinion: increased risk of immunosuppression
Fumaric acid esters	**o**	Strong consensus	No evidence available
Methotrexate	↑	Consensus	Expert opinion: combination widely used in rheumatology; combination with low-dose MTX (e. g., 7.5 to 10 mg/week is likely sufficient to reduce for-mation of ADA and increase trough levels of adalimumab
Ustekinumab	↓	Consensus	Expert opinion: increased risk of immunosuppression

Evidenzbasis

[90] Revicki D et al. Impact of adalimumab treatment on health-related quality of life and

other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. Br J Dermatol. 2008;158(3):549-57.
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Etanercept

Recommendation		Strength of consensus	Comment
We recommend etanercept as second line* medication for the induction and long-term treatment.	↑↑	Strong consensus	Evidence and consensus based
In general, a starting dose of 50 mg once or twice weekly is used depending on individual factors.	Statement	Strong consensus	Expert opinion
For maintenance therapy 50 mg once weekly is a commonly used dose.	Statement	Strong consensus	Expert opinion

* if phototherapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated.

Therapeutic combinations		Strength of consensus	Comments
Acitretin	↑	Consensus	Expert opinion: good safety profile assumed, possibly increased efficacy
Ciclosporin	↓	Consensus	Expert opinion: increased risk of immunosuppression
Fumaric acid esters	o	Strong consensus	No evidence available
Methotrexate	↑	Consensus	Evidence (additional benefit of adding MTX to etanercept compared to etanercept monotherapy) and consensus based
Ustekinumab	↓	Consensus	Expert opinion: increased risk of immunosuppression

Evidenzbasis

[34] Caproni M et al. Serum levels of IL-17 and IL-22 are reduced by etanercept, but not by acitretin, in patients with psoriasis: a randomized-controlled trial. J Clin Immunol. 2009;29(2):210-4.
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Infliximab

Recommendation		Strength of consensus	Comment
We recommend infliximab as second line* medication for the induction and long-term treatment.	↑↑	Strong consensus	Evidence and consensus based
We recommend using infliximab 5 mg/kg bodyweight continuously every eight weeks during long-term treatment.	↑↑	Strong consensus	Evidence and consensus based

* if phototherapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated.

Therapeutic combinations		Strength of consensus	Comments
Acitretin	o	Consensus	No evidence available
Ciclosporin	↓	Consensus	Expert opinion: increased risk of immunosuppression
Fumaric acid esters	↓	Strong consensus	Expert opinion: increased risk of immunosuppression, lymphocytopenia
Methotrexate	↑	Consensus	Expert opinion: combination widely used in rheumatology; combination with low-dose MTX (e. g., 7.5 to 10 mg/week is likely sufficient to reduce for-mation of ADA and increase trough levels of
Ustekinumab	↓	Consensus	Expert opinion: increased risk of immunosuppression

Evidenzbasis

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Ustekinumab

Recommendation		Strength of consensus	Comment
We recommend ustekinumab as second line* medication for the induction and long-term treatment.	↑↑	Strong consensus	Evidence and consensus based
We suggest using 45 mg for patients with a bodyweight of ≤ 100 kg and 90 mg ustekinumab for patients with a body weight of > 100 kg.	↑	Strong consensus	Evidence and consensus based

* if phototherapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated (the label currently states: if PUVA or other systemic therapies including ciclosporin, methotrexate were inadequate in response or if they are contraindicated or not tolerated). No strong consensus on definition of 'second line' for usteki-numab was achieved, the definition passed with 'weak consensus' (55%).

Therapeutic combinations		Strength of consensus	Comments
Acitretin	o	Consensus	No evidence available
Adalimuab	↓	Consensus	Expert opinion: increased risk of immunosuppression
Ciclosporin	↓	Consensus	Expert opinion: increased immunosuppression, anecdotal evidence of increased toxicity
Etanercept	↓	Consensus	Expert opinion: increased risk of immunosuppression
Fumaric acid esters	o	Consensus	No evidence available
Infliximab	↓	Consensus	Expert opinion: increased risk of immunosuppression
Methotrexate	o	Consensus	No evidence available

Evidenzbasis

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Sánchez-Regaña M et al., 2014 [26]. Evidence-Based Guidelines of the Spanish Psoriasis Group on the Use of Biologic Therapy in Patients With Psoriasis in Difficult-to-Treat Sites (Nails, Scalp, Palms, and Soles)	Consensus Document: Spanish Psoriasis Group of the Spanish Academy of Dermatology and Venerology "The Spanish Psoriasis Group of the Spanish Academy of Dermatology and Venereology (AEDV) has published an update of their evidence-based guidelines on the treatment of psoriasis with biologic agents. To complement those guidelines, this article reviews the scientific evidence available on the treatment of psoriasis in difficult-to-treat sites, such as the nails, scalp, palms and soles."
	Methodik Recherche in PubMed(MEDLINE), Englisch und Spanisch, cut-off date: 07.09.2013 LoE und GoR (siehe Anhang zu dieser Synopse) Sonstige Hinweise: CoI: Manuel Sánchez-Regaña, Isabel Belinchón, José Manuel Carrascosa, Carlos Ferrándiz, David Vidal, Ricardo Ruiz and Eduardo Fonseca have participated in clinical trials, acted as consultants, and/or have received lecture fees or grants to attend training events from one or more of the following pharmaceutical companies: Abbvie (formerly Abbott), Janssen, MSD, and Pfizer. Esteban Daudén has received or is currently receiving grants, funding, or honoraria in respect of diverse activities (advisory board membership, consultancy work, research, participation in clinical trials, and lectures) from the following pharmaceutical companies: Abbvie (Abbott), Amgen, Astellas, Biogen, Centocor Ortho Biotech Inc., Galderma, Glaxo, Janssen-Cilag, Leo Pharma, MSD, Pfizer, Novartis, Stiefel and Celgene.
	Freitext/Empfehlungen/Hinweise **Nail Psorasis** Levels of evidence: Infliximab is a good treatment for nail psoriasis (grade of recommendation, A; level of evidence, I). Levels of evidence: Etanercept is a good treatment for nail psoriasis (grade of recommendation, A; level of evidence, I). Levels of evidence: Adalimumab is a good treatment for nail psoriasis (grade of recommendation, A; level of evidence, I). Levels of evidence: Ustekinumab is a good treatment for nail psoriasis (grade of recommendation, A; level of evidence, I). **Scalp Psoriasis**

	Levels of evidence: Infliximab is a good treatment for scalp psoriasis (grade of recommendation, A; level of evidence, I). Levels of evidence: Etanercept is a good treatment for scalp psoriasis (grade of recommendation, A; level of evidence, I). Levels of evidence: Adalimumab appears to be effective in the treatment of scalp psoriasis (grade of recommendation: B; level of evidence, I). Levels of evidence: Ustekinumab may be useful in the treatment of scalp psoriasis (grade of recommendation, C; level of evidence, III). **Palmoplantar Psoriasis** Levels of evidence: Infliximab is a good treatment for palmoplantar psoriasis (grade of recommendation: A; level of evidence, I). Levels of evidence: Etanercept is a good treatment for palmoplantar pustular psoriasis (grade of recommendation, A; level of evidence, I). Levels of evidence: Ustekinumab has been shown to be moderately effective in the treatment of palmoplantar psoriasis (grade of recommendation, B; level of evidence, II-III). Levels of evidence: Adalimumab is effective in the treatment of palmoplantar psoriasis (grade of recommendation: A; level of evidence, I). Die Evidenzbasis zu den einzelnen Indikationen bzw. Arzneimitteln ist in den jeweiligen Abschnitten von den Autoren aufgeführt.
National Institute for Health and Clinical Excellence (NICE), 2012 [21]. Assessment and management of psoriasis (NICE Clinical Guidelines No. 153)	Fragestellung In people with psoriasis (all types), what are the clinical effectiveness, safety, tolerability and cost effectiveness of BBUVB, NBUVB and PUVA compared with each other or placebo/no treatment? In people with psoriasis (all types), what are the clinical effectiveness, safety, tolerability and cost effectiveness of acitretin plus UVB (NBUVB and BBUVB) and acitretin plus PUVA compared with their monotherapies and compared with each other? In people with psoriasis (all types), what are the clinical effectiveness, safety, tolerability and cost effectiveness of UVB (NBUVB or BBUVB) combined with dithranol, coal tar or vitamin D and vitamin D analogues compared with UVB alone or topical therapy alone? 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 a priori, systematische Recherchen, Bewertung der Literatur anhand GRADE, Konsensusprozess ohne Beschreibung formaler Verfahren)

	Suchzeitraum: bis 8. März 2012 LoE: nach GRADE, GoR: Formulierung Sonstige methodische Hinweise • The National Clinical Guideline Centre was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline. • *CoI declared*
	Freitext/Empfehlungen/Hinweise "None of the interventions, with the exception of topical calcipotriol, potent steroids (for those over 1 year of age) and acitretin, are licensed for use in psoriasis in children and there is little or no evidence in children." **Topical therapy** **General recommendations** 25. Offer people with psoriasis topical therapy as first-line treatment. Offer second- or third-line treatment options (phototherapy or systemic therapy) at the same time when topical therapy alone is unlikely to adequately control psoriasis, such as: - extensive disease (for example more than 10% of body surface area affected) or - at least 'moderate' on the static Physician's Global Assessment or - where topical therapy is ineffective, such as nail disease. **Phototherapy (broad- or narrow-band (UVB) light and PUVA)** 60. Offer narrowband ultraviolet B (UVB) phototherapy to people with plaque or guttate-pattern psoriasis that cannot be controlled with topical treatments alone. Treatment with narrowband UVB phototherapy can be given 3 or 2 times a week depending on patient preference. Tell people receiving narrowband UVB that a response may be achieved more quickly with treatment 3 times a week. 61. Offer alternative second- or third-line treatment when: - narrowband UVB phototherapy results in an unsatisfactory response or is poorly tolerated or - there is a rapid relapse following completion of treatment (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months) or - accessing treatment is difficult for logistical reasons (for example, travel, distance, time off work or immobility) or - the person is at especially high risk of skin cancer. **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[gg] 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[hh] 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.

gg 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.

hh 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). 100. 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. 101. 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). 102. 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. 103. 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).

	104. 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. 105. 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). 106. 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. 107. 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. ***Changing to an alternative biological drug*** 108. Consider changing to an alternative biological drug in adults if: • the psoriasis does not respond adequately to a first biological drug as defined in NICE technology appraisals[jj] (at 10 weeks after starting treatment for infliximab, 12 weeks for etanercept, and 16 weeks for adalimumab and ustekinumab; primary failure) or

	• the psoriasis initially responds adequately but subsequently loses this response, (secondary failure) or • the first biological drug cannot be tolerated or becomes contraindicated. [jj] NICE technology appraisals 103, 134, 146 and 180.
Paul C et al., 2012 [23]. Evidence-based recommendations on topical treatment and phototherapy of psoriasis: systematic review and expert opinion of a panel of dermatologists	"In November 2010, the 11 psoriasis experts from the scientific committee (CP, SA, FA, HB, BC, PJ, DJ, MLM, LM, MAR, JPO) selected nine clinically relevant questions regarding topical treatments and phototherapy of psoriasis (Table 1). These questions were generated using a Delphi voting process." Fragestellungen Q1 - What is the respective efficacy of NB-UVB and PUVA (Psoralen + UVA Light)] in the treatment of adult psoriasis? … Q4 - What are the optimal treatment modalities with topical corticosteroids in psoriasis? … Q8 - What is the level of compliance with topical treatments in psoriasis?
	The Population was defined as adult with psoriasis, and Interventions, Comparisons and Outcomes were specifically defined for each question. Methodik Grundlage der Leitlinie: systematische Evidenzrecherche und Evidenzbewertung, formale Konsensusprozesse (Delphi Methode) beschrieben Suchzeitraum: November 2010 **LoE**: defined by the Oxford Centre for Evidence-Based Medicine **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 consultants of Abbott. In addition C. Paul has been investigator and consultant for Janssen-Cilag, Leo, Novartis and Wyeth. H. Bachelez has been paid for consulting activities for Centocor, Janssen- Cilag, Leo Pharma, Novartis, Pfizer, and Schering-Plough. B. Cribier has been paid for consulting activities for Pfizer, for redaction activities by Leo Pharma and Janssen Cilag and speaker for Pfizer, Leo Pharma and Schering Plough. D. Jullien has been consultant for Merck, Janssen-Cilag, Novartis, Pfizer, and Schering-Plough/MSD. J.P. Ortonne has been investigator, speaker and advisor for Schering-Plough/MSD, Abbott, Merck Serono, Centocor, Pfizer, Janssen Cilag, Pierre Fabre, Galderma, Leo Pharma, Meda. L. Misery has been a paid consultant of Novartis, Janssen-Cilag, Leo Pharma, Pfizer and Pierre Fabre. M.A. Richard has been investigator and consultant for Janssen-Cilag, Novartis, 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 1. PUVA is more effective than NB-UVB. It has a response rate of approximately 80% compared with 70% for NB-UVB (grade A). However, NB-UVB is preferred because of higher convenience except for very thick plaques (grade D). 2. The optimal treatment regimen for phototherapy is 2–3 sessions per week (grade A). 3. Between 20 and 30 treatment sessions are generally required for clearance (grade A). An absence of improvement after 30 sessions is considered a treatment failure (grade D). 4. The starting UV dose and increases in dosage are defined according to phototype and tolerability (grade A). 5. Topical treatments should not be applied less than 30 min before a phototherapy session (grade D). ***Expert's agreement (mean): 8.80/10*** The risk of skin cancer is significantly increased with PUVA and there is a theoretical risk with NB-UVB (grade B). The number of cumulative (PUVA／NB-UVB) sessions during a lifetime must not exceed 250–300 (grade D). ***Expert's agreement (mean): 8.50/10***
	Freitext/Empfehlungen/Hinweise Therapieempfehlungen (Algorithmus siehe Anhang dieser Synopse) Die Evidenzbasis zu den einzelnen Indikationen bzw. Therapien ist in den jeweiligen Abschnitten in der Leitlinie aufgeführt. **6. Phototherapie** <u>UV-B und PUVA</u> werden zur Induktionstherapie bei mittelschwerer und schwerer Psoriasis vulgaris vor allem bei großflächiger Erkrankung empfohlen. (↑↑) Trotz der besseren Wirksamkeit von PUVA im Vergleich zur reinen UV-B-Therapie kann auf Grund der besseren Praktikabilität und auf Grund des geringeren Malignitätsrisikos eine Schmalspektrum UVB-Therapie als Phototherapie der ersten Wahl empfohlen werden. (↑) Der Einsatz des Excimer Lasers kann für die gezielte Behandlung einzelner psoriatischer Plaques empfohlen werden. (↑) Eine Kombination mit topischem Vitamin D3-Derivaten kann zur Verbesserung der Ansprechrate empfohlen werden. (↑) Die übliche Kombination mit Dithranol und Kortikoiden kann nur auf Grund klinischer Erfahrung empfohlen werden, nicht aber aufgrund der Datenlage. (↑)

	Wegen der geringen Praktikabilität und der Assoziation langfristiger unerwünschter Wirkungen mit der kumulativen UV-Dosis kann die Phototherapie nicht für Langzeitbehandlungen empfohlen werden. (↓) **7. Systemische Therapie** Adalimumab 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 (↑↑). Ciclosporin 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 (↓). Acitretin kann bei gebärfähigen Frauen mit Plaque-Psoriasis 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 (↑↑).
Papp K et al., 2011 [22]. Canadian guidelines for the management of plaque psoriasis: overview	Fragestellung "The Guidelines offer treatment recommendations for mild and moderate to severe body psoriasis, as well as for psoriasis affecting specific areas of the skin, such as the facial, flexural, and genital areas; nails; scalp; and palms and soles."
	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) Evidenzbasis siehe Papp K et al. (2011) Tabelle 5, Seite 214-216) **Oral systemic agent** 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-α. Safety profile, primarily based on record of use in rheumatoid and psoriatic arthritis, suggests some overlap in adverse events with other TNF-α 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-α; 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-α. 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++) **Photo(chemo)therapeutic methods** UVA with psoralen (PUVA): Psoralen may be administered orally or by immersion of affected areas in a psoralen solution, prior to irradiation with UVA (oral versus bath PUVA). Associated with cumulative risk of non-melanoma skin cancer, primarily squamous cell carcinoma. May be combined with other agents in suitable patients to reduce UV exposure (LoE 2++) UVB: Broadband UVB has been used for decades; now often applied using narrowband irradiation at 311 nm, a more effective option. Less durable remission than with PUVA but believed to have a more benign safety profile. May be combined with topical, systemic, or biologic agents for more rapid and more complete control, potentially reducing exposure to both UV light and other therapeutic agents (LoE 2++)
Paul C et al., 2011 [24]. 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 modalities of cyclosporin in plaque-type psoriasis in adults? … Q7 - What are the practical and optimal treatment modalities of acitretin in adult plaque psoriasis?
	Methodik Grundlage der Leitlinie: systematische Evidenzrecherche und -bewertung, formale Konsensusprozesse (Delphi Methode) beschrieben Suchzeitraum: bis 2009

opinion of a panel of dermatologists	**LoE**: defined by the Oxford Centre for Evidence-Based Medicine **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 CoI: All the authors have been paid consultants of Abbott. ln addition, C. Paul has been investigator and consultant 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 Die Evidenzbasis zu den einzelnen Arzneimitteln ist in den jeweiligen Abschnitten in der Leitlinie aufgeführt. 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 ***Expert's agreement (mean): 8.64/10*** lt is recommended to start cyclosporin at a dose between 2.5 and 5 mg/kg/day, preferably 5 mg/kg/day for rapid action in the absence of comorbidities (obesity*, older age). Grade A *threshold value for overweight, according to WHO classification: BMI > 25 ***Expert's agreement (mean): 8.38/10*** The recommended initial dose of acitretin is between 10 and 25 mg/day. Grade B ***Expert's agreement (mean): 7.83/10***
	Die Evidenzbasis zu den einzelnen Arzneimitteln ist in den jeweiligen Abschnitten in der Leitlinie aufgeführt. **Empfehlungen** 7.2 Phototherapy and photochemotherapy BBUVB phototherapy is not recommended. (GoR A, LoE 1++ bis 2++) ☑All practices that use BBUVB should aim to change to NBUVB as soon as possible.

	Patients with psoriasis who do not respond to topical therapy should be offered NBUVB phototherapy. (GoR B, LoE 2+) PUVA photochemotherapy should be considered for those patients who do not respond to NBUVB. (GoR B, LoE 2+) <u>7.3.1 Systemic therapy</u> Patients with severe or refractory psoriasis should be considered for systemic therapy with ciclosporin, methotrexate or acitretin, following discussion of benefits and risks. (GoR B, LoE 1++ bis 1+) Methotrexate is recommended for longer term use and where there is concomitant psoriatic arthritis. (GoR B, LoE 1++ bis 1+) Ciclosporin is recommended for short term intermittent use. (GoR A, LoE 1++ bis 1+) Acitretin can be considered as an alternative. (GoR B, LoE 1++ bis 1+) Fumaric acid esters can be considered as an alternative maintenance therapy for patients who are not suitable for other systemic therapies or have failed other therapies. (GoR B, LoE 1++ bis 1+) Patients with severe psoriasis who fail to respond to, or have a contraindication to, or are intolerant of phototherapy and systemic therapies including ciclosporin and methotrexate, should be offered biologic therapy unless they have contraindications or are at increased risk of hazards from these therapies. (GoR: A) • Adalimumab loading regimen followed by 40 mg every other week is recommended in the treatment of severe psoriasis. (GoR: A) • Etanercept 25 mg twice weekly or 50 mg weekly is recommended in the treatment of severe psoriasis. (GoR: A) • Infliximab 5 mg/kg at weeks 0, 2, 6 and repeated as maintenance treatment every two months is recommended in the treatment of severe psoriasis, especially when rapid disease control is required. (GoR: A) • Ustekinumab 45 mg for patients weighing under 100 kg and 90 mg for patients weighing over 100 kg given at weeks 0 and 4 then every 12 weeks as maintenance is recommended in the treatment of severe psoriasis. (GoR: A) Ergänzende Anmerkung: Women who are or may be pregnant should not be treated with systemic agents; The use of biologic treatments should conform to BAD guidelines; Patients on biologic therapies should be offered the opportunity to join the long term safety register BADBIR.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Lee S et al., 2012 [16]. Biologic and nonbiologic systemic	1. Fragestellung To examine the comparative effectiveness of biologic systemic agents versus nonbiologic systemic agents or phototherapy, on an individual drug level, for treatment of chronic plaque psoriasis (CPP) and to determine patient and disease characteristics that modify outcomes of interest.

agents and phototherapy for treatment of chronic plaque psoriasis

2. Methodik

Randomized controlled trials (RCTs) and observational studies were included. No quantitative analyses were performed and all data were qualitatively synthesized.
Population: Adults with Chronic Plaque Psoriasis
Intervention/Komparator: biologic systemic agents versus either an approved nonbiologic systemic agent or phototherapy
Endpunkt: HRQoL, Psoriasis Area and Severity Index (PASI), Physician's Global Assessment (PGA) score, and patient's assessment of disease severity score (BSA), pain, infection rates
Suchzeitraum: Medline, the Cochrane Central Register of Controlled Trials, and Web of Science from inception to June 2012
Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 RCTs and 4 observational studies directly compared therapies from the specified classes. An additional 5 studies provided data on the transition of patients from one therapy to another.

3. Ergebnisdarstellung

Effektivität:

Systemic biologic agents versus systemic nonbiologic agents:

Comparison	Outcome*	Type and Number of Studies	Conclusion	SOE
Adalimumab versus methotrexate	HRQoL	1 RCT[30] 1 OBS[23]	Adalimumab improves a patient's HRQoL compared with methotrexate.	L
	PASI	1 RCT[13] 1 OBS[23]	Adalimumab improves a patient's PASI compared with methotrexate.	L
	PGA	1 RCT[113] 1 OBS[23]	Adalimumab increases the number of patients achieving a PGA of "clear" or "minimal" compared with methotrexate.	L
	Patient's assessment of disease severity	1 RCT[30]	Adalimumab improves a patient's assessment of disease severity compared with methotrexate.	L
	Pain	1 RCT[30]	Adalimumab reduces a patient's pain compared with methotrexate.	L
	Pruritus	1 RCT[30]	Adalimumab reduces a patient's pruritus compared with methotrexate.	L
	Infection	1 RCT[13]	Infection rates do not differ between adalimumab and methotrexate.	L
Etanercept versus acitretin	PASI	3 RCT[17-19]	Etanercept improves a patient's PASI compared with acitretin.	M
Infliximab versus methotrexate	HRQoL	1 RCT[16]	Infliximab improves a patient's HRQoL compared with methotrexate.	L
	PASI	1 RCT[16] 1 OBS[21]	Infliximab improves a patient's PASI compared with methotrexate.	L
	PGA	1 RCT[16]	Infliximab increases the number of patients achieving a PGA of "clear" or "minimal" compared with methotrexate.	L
Ustekinumab versus methotrexate	PGA	1 OBS[23]	Ustekinumab increases the number of patients achieving a PGA of "clear" or "minimal" compared with methotrexate.	L

HRQoL = health related quality of life; L = low; M = moderate; OBS = observational study; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; RCT = randomized controlled trial; SOE = strength of evidence
*Outcomes with an insufficient strength of evidence are not listed in this table.

Systemic (non)biologic agents and phototherapy:

No RCTs evaluated the comparative effectiveness of systemic biologic agents and phototherapy – neither NB-UVB nor PUVA – on any

	outcomes. **Sicherheit:** <u>Systemic biologic agents and systemic nonbiologic agents or phototherapy:</u> ○ Overall five RCTs (two good, two fair, and one poor quality) and two observational studies (both fair quality) directly compared biologics with nonbiologics and reported at least one adverse outcome of interest. ○ No trials or observational studies directly compared biologics with phototherapy in the evaluation of harms. ○ Infection rate did not differ between adalimumab and methotrexate (low strength of evidence). These data were from a single RCT conducted outside the United States in patients with moderate to severe chronic plaque psoriasis naïve to TNF-alpha antagonists or methotrexate. ○ There was insufficient evidence for other reported outcomes.
	4. Fazit der Autoren In patients with CPP, there were limited data directly comparing systemic biologic agents with either systemic nonbiolgic agents or with phototherapy on an individual drug level. Overall there is insufficient evidence to determine the comparative effectiveness of individual therapies, as compared with each other between the specified classes, with few exceptions. For the comparisons of adalimumab versus methotrexate, infliximab versus methotrexate, ustekinumab versus methotrexate, and etanercept versus acitretin, there is predominantly low strength of evidence favoring the individual biologic agent versus the nonbiologic agent. Additional trials directly comparing biologic systemic agents, systemic nonbiologic agents, and phototherapy are needed. Hinweise durch FB Med: • Prepared for Agency for Healthcare Research and Quality (AHRQ) • Governmental funding • CoI: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report. • quality of included studies assessed by standardized tools: strength of evidence (risk of bias, consistency, directness, precisions) • keine Angaben zur Schwere der Psoriasis

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) **am 11.07.2016**

#	Suchfrage
1	MeSH descriptor: [Psoriasis] explode all trees
2	(Psoriasis):ti,ab,kw
3	#1 or #2
4	#3 Publication Year from 2011 to 2016

SR, HTAs in Medline (PubMed) am 11.07.2016

#	Suchfrage
1	Psoriasis[MeSH]
2	Psoriasis[Title/Abstract]
3	(#1) OR #2
4	(#3) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((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]))))
5	(#4) AND ("2011/07/01"[PDAT] : "2016/07/11"[PDAT])
#	Suchfrage

Leitlinien in Medline (PubMed) am 11.07.2016

#	Suchfrage
1	Psoriasis[MeSH]
2	Psoriasis[Title/Abstract]
3	(#1) OR #2
4	(#3) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title/Abstract])
5	(#4) AND ("2011/07/01"[PDAT] : "2016/07/11"[PDAT])

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Anhang

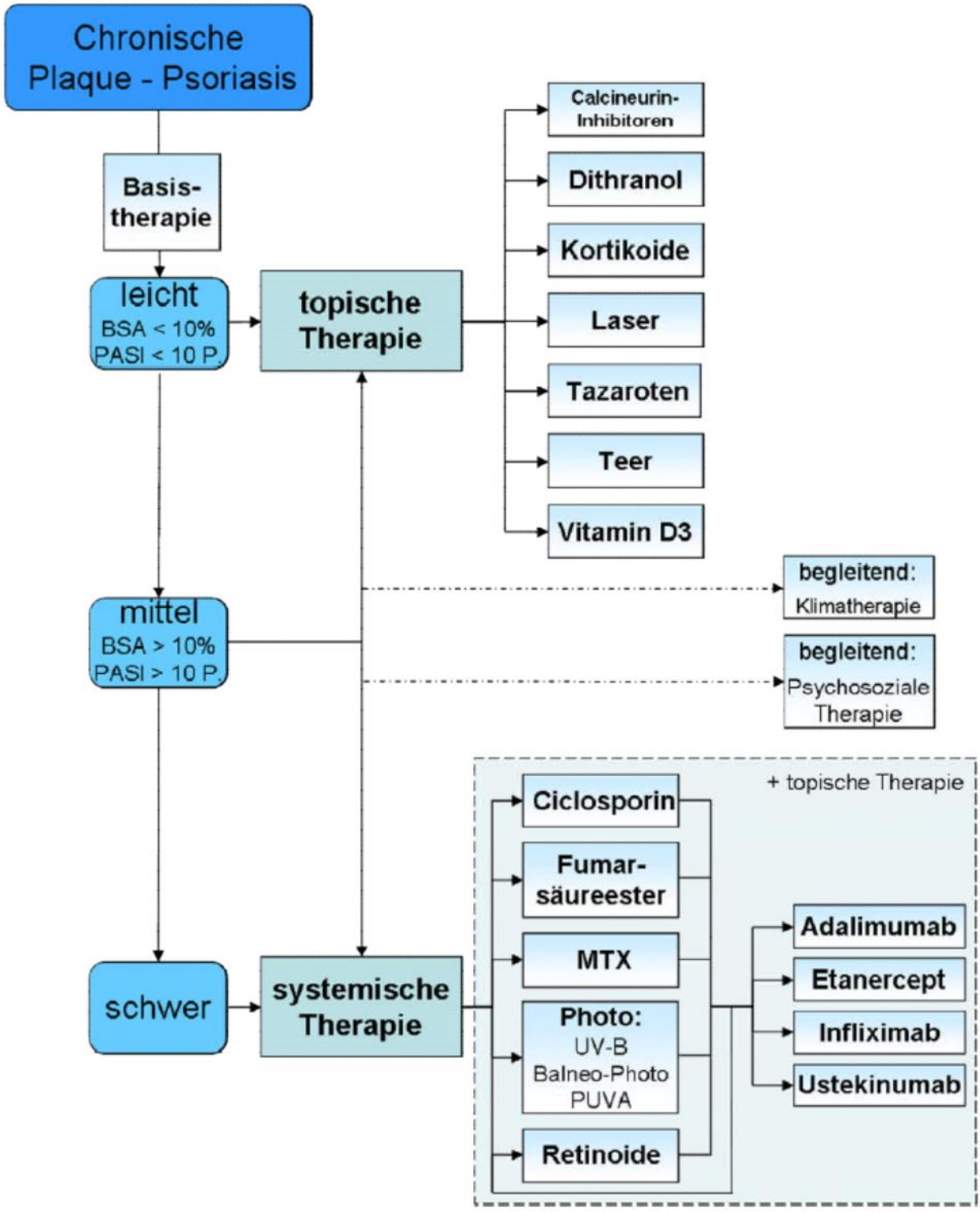

Abbildung 2: Übersicht der beurteilten Therapieoptionen bei der chronischen Plaque-Psoriasis (die Anordnung der Therapieoptionen ist alphabetisch und stellt keine Wertung dar)

Abbildung 1: aus Nast A et al., 2011

Tabelle 1: Studiencharakteristika aus Correr C et al., 2013

Table 1

Details of trials.

Study			Patients		Drug	
Trials	Year	Jadad	n	Inclusion criteria	Intervention	Dosage
Asahina [17]	2010	4	169	Diagnosis ≥ 6 months; stable 2 months; PASI ≥ 12 ou BSA ≥ 10	Adalimumab	80mg e posterior 40mg EOW – 16 week
CHAMPION [24,26,27]		5	271	BSA ≥ 10%; PASI score ≥ 10	Adalimumab	80mg e posterior 40mg EOW – 16 week
Genovese [18]	2007	4	100	≥ 18 years; ≥ 3 swollen joints and ≥ 3 tender or painful joints	Adalimumab	40mg EOW – 16 week
Gordon [19]	2006	4	148	≥ 18 years; diagnosis ≥ 12 months; BSA ≥ 5%;	Adalimumab	40mg EOW – 16 week
REACH [21]		4	72	Chronic plaque psoriasis on the hands and/ or feets with PGA ≥ 3	Adalimumab	80mg e posterior 40mg EOW – 16 week
REVEAL [20,22,23,25]		5	1,212	Psoriasis ≥ 6 months, Plaque psoriasis; BSA ≥ 10%; PASI score ≥ 12	Adalimumab	80mg e posterior 40mg EOW – 16 week
Ellis [28,29]	2001	3	229	Diagnosis ≥ 12 months; BSA ≥ 10; candidates to systemic therapy	Alefacept	0,075mg/kg/week (average weight 96,7kg) – 12 week
Krueger [30,1,32,33]	2002	4	553	Diagnosis ≥ 6 months; BSA ≥ 10; CD4+ normal; ≥ 16 years	Alefacept	7,5mg/week – 12 week
Ortonne [34,36,37]	2003	4	507	PGA score mild to moderate (17%) and moderate to severe (83%); Plaque psoriasis; BSA ≥ 10%; PASI score ≥ 12	Alefacept	10mg/week – 24 week
Mease [35]	2006	4	180	≥ 3 swollen joints and ≥ 3 tender joints	Alefacept + metotrexato	15mg/week
Kimball [38,39]	2008	3	180	Diagnosis ≥ 6 months; 2 months stable; PASI ≥ 12; BSA ≥ 10; PGA moderate	Briakinumab	200mg EOW 12 week
Ortonne [40]	2007	3	176	Plaque psoriasis; BSA ≥ 10%; PASI score ≥ 12	Certolizumab	200mg EOW 12 week
CLEAR [41,47,51]		4	793	Psoriasis ≥ 6 months, Plaque psoriasis; BSA ≥ 10%; PASI score ≥ 12	Efalizumab	1mg/kg/week – 12 week
Gordon [42,45,46]	2003	4	556	18-75 years; diagnosis ≥ 6 months; BSA ≥ 10; PASI ≥ 12; use systemic therapy	Efalizumab	1mg/kg/week – 12 week
Lebwohl [43]	2003	5	597	18-75 years; diagnosis ≥ 6 months; 3 months stable; BSA ≥ 10; PASI ≥ 12	Efalizumab	1mg/kg/week – 12 week
Leonardi [44]	2005	4	498	PASI ≥ 12; BSA ≥ 10%; diagnosis ≥ 6 months; stable for 3 months	Efalizumab	1mg/kg/week – 12 week
Papp [48]	2001	3	145	Psoriasis ≥ 6 months, plaque psoriasis; BSA ≥ 10%; PASI score ≥ 12	Efalizumab	1mg/kg/week – 12 week
Papp [49]	2006	4	686	Psoriasis ≥ 6 months, plaque psoriasis; BSA ≥ 10%; PASI score ≥ 12	Efalizumab	1mg/kg/week – 12 week
Papp [50]	2007	4	107	Moderate to severe PSA – one of five subtypes and classified as ACR functional class 1, 2 or 3	Efalizumab	1mg/kg/week – 12 week
Gottlieb [52]	2003	4	112	≥ 18 years; plaque psoriasis stable; BSA ≥ 10%; use systemic therapy	Etanercept	25mg TW – 24 week
Leonardi [54]	2003	3	672	≥ 18 years; PASI ≥ 10; BSA ≥ 10%; candidates to phototherapy or systemic therapy	Etanercept	25mg W, 25mg TW, 50mg TW – 12 week
Mease [55]	2000	5	60	≥ 3 swollen joints and ≥ 3 tender or painful joints	Etanercept	25mg TW – 12 week
Mease [56,57]	2004	4	205	PSA with at least 3 swollen and 3 tender joints; plaque psoriasis with a qualifying target lesion (at least 2cm in diameter)	Etanercept	25mg TW – 12 week

(continues)

Fortsetzung Tabelle 1: Studiencharakteristika aus Correr C et al., 2013

Table 1 (continued)

Study			Patients		Drug	
Trials	Year	Jadad	n	Inclusion criteria	Intervention	Dosage
Paller [58,59]	2008	4	211	Plaque psoriasis; static PGA at lease 3; BSA ≥ 10%	Etanercept	0,8mg/kg/week – 12 week
Papp [53,60]	2005	5	583	Plaque psoriasis; BSA ≥ 10%; PASI score ≥ 10	Etanercept	25mg TW, 50mg TW – 12 week
Siegfried [62]	2010	3	138	Plaque psoriasis; PGA ≥ 3; BSA ≥ 10%; PASI score ≥ 12	Etanercept	50mg OW – 12 week
Tyring [63]	2006	5	618	PASI score ≥ 10; BSA ≥ 10%; candidates to phototherapy or systemic therapy	Etanercept	50mg TW – 12 week
van der Kerkhof [64]	2008	4	142	Plaque psoriasis; BSA 6-10%; PASI score ≥ 10	Etanercept	50mg OW – 12 week
Bissonnette [70]	2011	5	24	≥ 18 years; palmoplanar psoriasis	Infliximab	5mg/kg/week – 14 week
Chaudari [71,74]	2001	4	33	Plaque psoriasis; diagnosis ≥ 6months; BSA ≥ 5%	Infliximab	5mg/kg/week – 6 week
EXPRESS I [82,83,84,85,86]		5	378	Psoriasis ≥ 6 months, plaque psoriasis; BSA ≥ 10%; PASI score ≥ 12	Infliximab	5mg/kg/week – 10 week
EXPRESS II [72,80,81]		5	835	Plaque psoriasis; BSA ≥ 10%; PASI score ≥ 12	Infliximab	3mg/kg/week, 5mg/kg/week – 10 week
Gottlieb [75]	2004	5	249	≥ 18years; diagnosis ≥ 6 months; PASI ≥ 12; BSA ≥ 10%; candidates to phototherapy or systemic therapy	Infliximab	3mg/kg/week, 5mg/kg/week – 10 week
IMPACT I [68,69,78]		4	104	Diagnosis ≥ 6 months; peripheral polyarthritis active, morning stiffness ≥ 15 min, negative rheumatoid factor, tuberculosis negative	Infliximab	5mg/kg/week – 16 week
IMPACT II [67,73,76,77,79,87,89]		4	200	Diagnosis ≥ 6 months; swelling of the tendon or joints by at least 5; CRP ≥ 15mg/L	Infliximab	3mg/kg/week, 5mg/kg/week – 10 week
Torii [92]	2010	4	54	Plaque psoriasis; BSA ≥ 10%; PASI score ≥ 12	Infliximab	5mg/kg/week – 10 week
Kavanaugh [75,76]	2009	4	405	Active psoriasis; 3 swollen and painful joints, rheumatoid factor negative, at least one type of psoriasis and plaque psoriasis than 2cm in diameter	Golimumab	50mg EOW – 16 week
Gottlieb [90]	2009	5	146	≥ 18 years; psoriatic arthrits; ≥ 3 swollen joints and ≥ 3 tender or painful joints; CRP ≥ 15mg/L; diagnosis ≥ 6 months; plaque psoriasis ≥ 2cm	Ustekinumab	90mg week 0, 4 and every 12 week
PHOENIX I [92,93,94,95,98]		5	766	Psoriasis ≥ 6 months, PASI score ≥ 12, BSA ≥ 10%, candidates to phototherapy or systemic therapy	Ustekinumab	45mg, 90mg week 0, 4 and every 12 week
PHOENIX II [91,96,95]		4	1,230	BSA ≥ 10%; PASI score ≥ 10	Ustekinumab	45mg, 90mg week 0, 4 and every 12 week

ACR: American College of Rheumatology; BSA: body surface area; CRP: C-reactive protein; PASI: *Psoriasis Area and Severity Index*; PGA: *Physician's Global Assessment*; PSA: psoriatic arthritis.

Tabelle 2: aus EDF, 2015: Table 1: Strength of recommendations: wording, symbols and implications

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

Appendix 1. Levels of Evidence (US Preventive Service Task Force)

Level of Evidence	Type of study
I	Evidence obtained from at least one properly randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.
IV	Evidence deemed inadequate because of methodological problems (for example, sample size, length of follow-up, conflicting evidence).

Source: Harris et al.[83]

Grade of Recommendation and Quality of Evidence for Treatment with Biologic Agents for Psoriasis in Difficult-to-Treat Sites

Grade of Recommendation	Definition
A	Strongly recommended (good evidence that the intervention is effective and that the benefits substantially outweigh harms)
B	Recommended (at least fair evidence that the intervention is effective and the benefits outweigh harms)
C	No Recommendation (at least fair evidence that the intervention is effective, but concludes that the balance of benefits and harms is too close to justify a general recommendation)
D	Not recommended (at least fair evidence that the intervention is ineffective or that harms outweigh benefits
E	Insufficient Evidence to Make a Recommendation (evidence that the intervention is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined)

Abbildung 2: aus Sánchez-Regaña M et al., (2014) [27]

Table 1. Modified SIGN System 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	Nonanalytic 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 3: aus Papp K et al., 2011 [23]

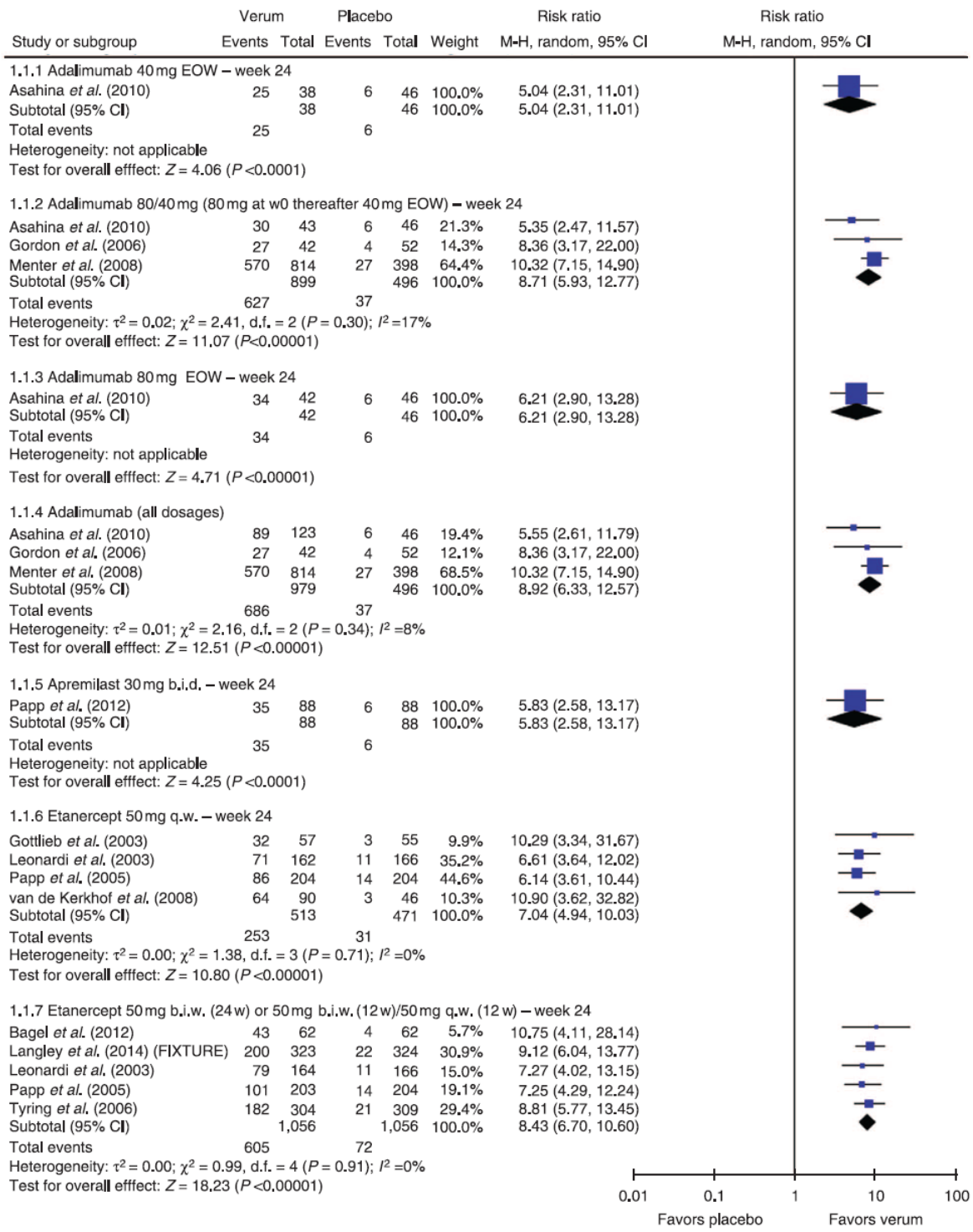

Figure 2 aus Nast A et al., 2015 [20]; Fortsetzung auf nächster Seite

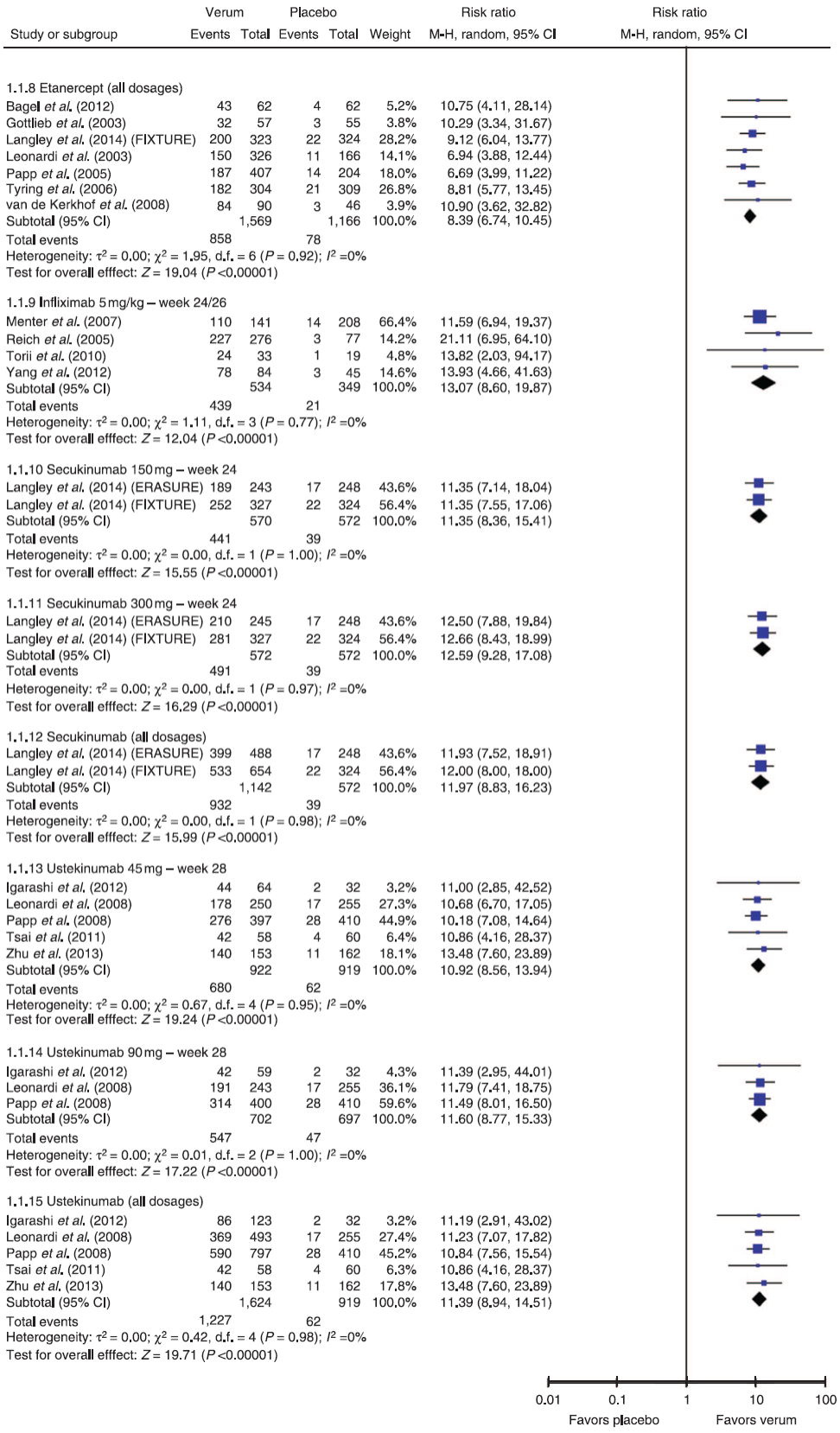

Figure 2. Forest plot: Verum versus placebo—PASI 75 at weeks 24–28. CI, confidence interval; b.i.d., twice daily; b.i.w., twice weekly; EOW, every other week; PASI, psoriasis area and severity index; q.w., once weekly; w, week.

Figure 2 aus Nast A et al., 2015 [20]

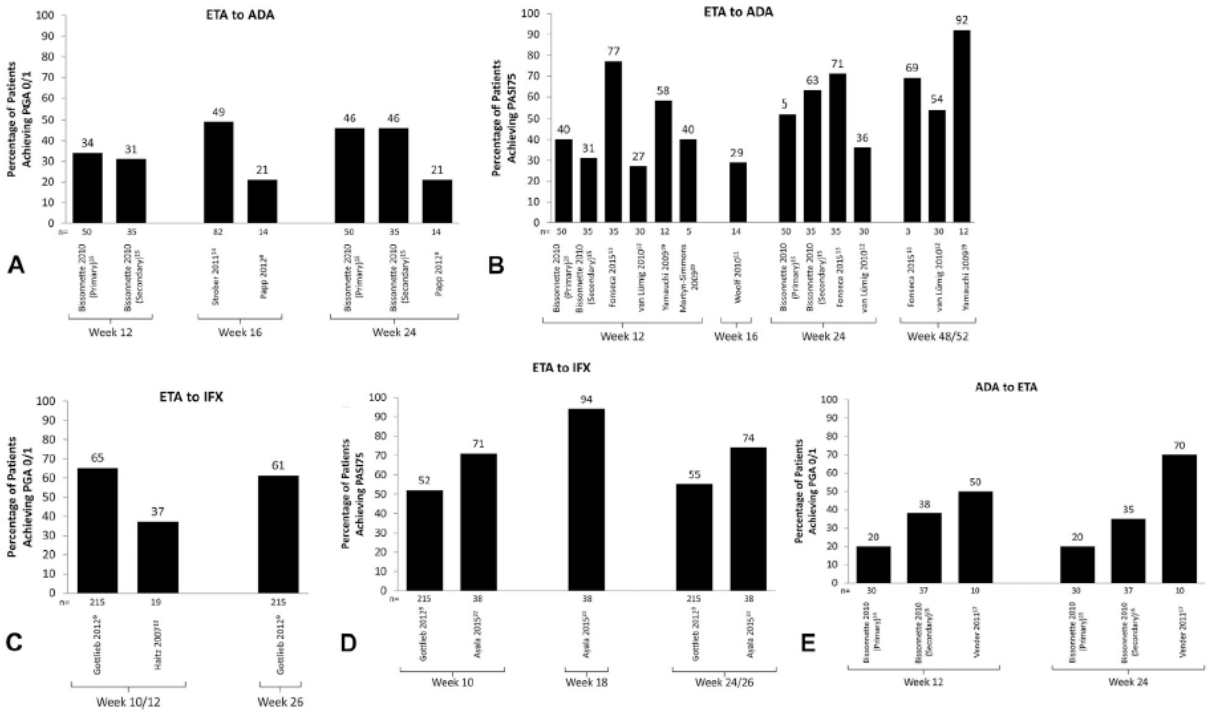

Fig 1. Percentage of patients achieving Physician Global Assessment (*PGA*) score 0/1 or 75% improvement in Psoriasis Area and Severity Index score (*PASI75*) by type of treatment switch with 3 or more included studies. Achievement of: PGA score 0/1 in patients switching from etanercept (*ETA*) to adalimumab (*ADA*) (**A**), PASI75 in patients switching from ETA to ADA (**B**), PGA score 0/1 in patients switching from ETA to infliximab (*IFX*) (**C**), PASI75 in patients switching from ETA to IFX (**D**), and PGA score 0/1 in patients switching from ADA to ETA (**E**).

Figure 1 aus Yamauchi et al. 2016