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: August 2017

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

Anwendungsgebiet:
Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis.

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* *Beschluss zu Secukinumab vom 17.08.2017* *Beschluss zu Ixekizumab vom 17.08.2017*
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)
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.
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.
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.
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®	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)
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. (Stand 10/2016)
Ciclosporin L04AD01 Ciclosporin Pro	Behandlung von schwerer Psoriasis bei Patienten, bei denen eine herkömmliche Therapie nicht geeignet oder nicht wirksam ist. (Stand 01/2014)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: Plaque-Psoriasis

Auftrag von:	Abt. AM
bearbeitet von:	Abt. FB Med
Datum:	30.08.2017

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

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Plaque Psoriasis* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 11.04.2017 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 859 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 22 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

zur Behandlung von Erwachsenen mit mittelschwerer bis schwerer Plaque Psoriasis.

Abkürzungen

ADA	Antidrug antibodies
AE	Adverse event
AGREE	Appraisal of Guidelines Research and Evaluation
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BB	broadband (Breitband)
b.i.w.	Twice weekly
CI	Konfidenzintervall
CoI	Conflict of interest
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
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
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
TNF	Tumornekrosefaktor
TRIP	Turn Research into Practice Database
UV	ultraviolet
vs.	versus
WHO	World Health Organization

G-BA, 2008 [7]. Zusammenfassende Dokumentation zum Beratungsverfahren des Unterausschusses „Ärztliche Behandlung des Gemeinsamen Bundesausschusses." **G-BA, 2010 [8].** Asynchrone Photosoletherapie im Vollbad. *Siehe auch **IQWIG, 2006 [11].*** *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 alkoholischer 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 [9]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewer-tung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Apremilast	**Zugelassenes Anwendungsgebiet:** 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** <u>Zweckmäßige Vergleichstherapie:</u> „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 [10]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln	**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. **Zweckmäßige Vergleichstherapie:** eine patientenindividuell optimierte Standardtherapie unter Berücksichtigung von:

mit neuen Wirkstoffen nach § 35a SGB V – Secukinumab	- Fumarsäureestern oder Ciclosporin oder Methotrexat oder Phototherapie (Balneophototherapie, orale PUVA, NB1-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. **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

Zur Fragestellung wurden keine relevanten Cochrane Reviews identifiziert.

Systematische Reviews

De Carvalho AV et al., 2017 [5]. Efficacy of Immunobiologic and Small Molecule Inhibitor Drugs for Psoriasis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials	1. Fragestellung What is the efficacy, measured by the improvement of 75% over baseline Psoriasis Area and Severity Index (PASI), of biologic and small molecule inhibitor drugs for moderate to severe psoriasis patients when compared to placebo?
	2. Methodik Population: moderate to severe psoriasis patients Intervention: biologic and small molecule inhibitor drugs Komparator: nicht präspezifiziert Endpunkt: PASI 75% Suchzeitraum (Aktualität der Recherche): bis 21.07.2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): 40/22 884 (providing 56 comparisons of 11 different interventions) Head-to-head studies without a placebo arm were excluded from the analysis, and studies that evaluated the improvement of psoriatic arthritis as a primary outcome were also excluded. Qualitätsbewertung der Studien: This systematic review and meta-analysis was conducted using the recommendations of the Cochrane Initiative, and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Heterogenitätsanalysen: assessed using the Q-test and I2, a random-effects model used Publication bias: funnel plot and Egger's test used
	3. Ergebnisdarstellung • medications studied: adalimumab, apremilast, brodalumab, etanercept, infliximab, ixekizumab, secukinumab, tofacitinib and ustekinumab • 6 studies used a 10-week endpoint, 6 used a 16-week endpoint, and 28 used a 12-week endpoint

	• primary endpoints for outcomes assessment were correlated with the induction period of the drugs and can be considered short-term therapy • all studies shared similar inclusion criteria and baseline characteristics • risk of bias assessment showed that high risk of bias was low among the studies • The overall pooled effect favored biologics and small molecule inhibitors over placebo (risk difference [RD] 0.59, 95% confidence interval [CI] 0.58–0.60). o Ixekizumab at a dose of 160 mg on week 0 and then every 2 weeks (RD 0.84, 95% CI 0.81–0.88), o brodalumab 210 mg (RD 0.79, 95% CI 0.76–0.82), o infliximab 5 mg/kg (RD 0.76, 95% CI 0.73–0.79), and o secukinumab 300 mg (RD 0.76, 95% CI 0.71–0.81) showed a greater chance of response (PASI 75) when compared with placebo. Details siehe Abbildung 1 im Anhang
	4. Anmerkungen/Fazit der Autoren Anti-tumor necrosis factor and anti-interleukin (IL)-12/23 have been shown to be effective in treating patients with moderate to severe psoriasis. Anti-IL-17 drugs showed an equal or greater chance of leading patients to a 75% improvement when compared with other biologics/small molecule inhibitors. Ixekizumab showed higher efficacy among FDAapproved drugs when a 90 or 100% improvement over the baseline Psoriasis Area and Severity Index was analyzed. *5. Kommentar zu Review* • *einige der untersuchten Wirkstoffe nicht (mehr) zugelassen* • *Funding None.* • *Conflict of interest Andre´ Vicente Esteves de Carvalho has received research support and is a speaker/advisory board program participant receiving honoraria for Abvie, Jansen, Novartis and Leo Pharma. Rodrigo Pereira Duquia, Bernardo Lessa Horta and Renan Rangel Bonamigo have no conflicts of interest.*
Nast A et al., 2015 [14]. Efficacy and Safety of Systemic Long-	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)

Term Treatments for Moderate-to-Severe Psoriasis: A Systematic Review and Meta-Analysis	2. Methodik Population: adults suffering from moderate-to-severe plaque-type psoriasis Intervention: acitretin, adalimumab, apremilast, CSA, etanercept, fumaric acid ester, infliximab, MTX, secukinumab, or ustekinumab Komparator: placebo, another included active treatment, or combination of two included treatments Primärer Endpunkt: PASI 75 (primary), PASI 90, PGA 'clear/almost clear', reduction in mean DLQI, patients with at least one AE, patients with at least one SAE, and withdrawal due to AE Suchzeitraum: from inception to 5 January 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 25/11 279 Qualitätsbewertung der Studien: quality of evidence was assessed using GRADE (Grading of Recommendations Assessment, Development and Evaluation) Heterogenitätsanalysen: Inconsistencies quantified using the I2 test; if heterogeneity among studies was substantial (Higgins and Green, 2011), results were not pooled but presented individually Publication Bias: funnel plots or statistical tests
	3. Ergebnisdarstellung • likelihood of publication bias was graded as 'undetected' for each outcome, although no analysis for asymmetry could be carried out due to the small number of included studies for each comparison • risk of bias among the included studies partly heterogeneous, overall quality of evidence for efficacy endpoints low to high, for safety outcome moderate to low • ten placebo-controlled trials, 11 trials with placebo and active treatment as control, and four trials with at least one active treatment as control • study sample size varied from 48 to 1 306 • 31 % of all study subjects were female • all included trials performed intention-to-treat analysis • no studies available investigating fumaric acid esters and cyclosporine A (CsA) in long-term treatment • long-term data of direct comparisons of systemic therapies of up to 24 weeks were available for etanercept, infliximab, secukinumab, methotrexate (MTX), and acitretin • one included head-to-head trial reporting efficacy data beyond 28 weeks of treatment for the comparison with etanercept and secukinumab

	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} q.w. versus combination of etanercept 50 mg b.i.w./q.w. and MTX 7.5–15 mg q.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. Kommentar zu Review • *Dr Nast has received honoraria for CME certified educational talks that received direct or indirect sponsoring from Abbott (now AbbVie) and Pfizer. The Division of Evidence-Based Medicine has received research grants from Pfizer. No other disclosures were reported.* • *This review was accomplished during the update of the European psoriasis guidelines, which was supported financially by the European Dermatology Forum (EDF). There was no funding for the work on this manuscript itself. The EDF had no role in design and conduct of the study.* • *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.*
Liu Y et al., 2014 [12]. 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: assessed by the Jadad scale, only high quality studies (Jadad score 5) included Heterogenitätsanalysen: assessed using Chi-square ($\chi 2$) test with significance level set at $P<0.1$, meta-analysis done using fixed or random effect model Publication Bias: Funnel graph
	3. Ergebnisdarstellung ➔ no significant differences of the baseline comparison before treatment including number of cases, age, sex distribution, duration

	of psoriasis, average PASI score, proportion of psoriatic arthritis (P=0.528, 0.670, 0.283, 0.574, 0.117, 0.872 respectively, all P>0.05). Ustekinumab 45 mg vs. placebo (6 studies): ➔ using a random-effect model (I2 = 57%, p = 0.04) ➔ RR = 13.76 and 95% CI [8.37, 22.60] ➔ ustekinumab 45 mg group could get better therapeutic effect compared with the placebo group (P<0.00001) Quellen: 7. Igarashi A, et al. Efficacy and safety of ustekinumab in Japanese patients with moderate to severe plaque-type psoriasis: Long-term results from a phase 2/3 clinical trial. J Dermatol 2012; 39: 242-52. 10. Krueger GG, et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med 2007; 356: 580-92. 11. Leonardi CL, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008; 371: 1665-74. 12. Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008; 371: 1675-84. 13. Tsai TF, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo- controlled trial in Taiwanese and Korean patients (PEARL). J Dermatol Sci 2011; 63: 154-63. 14. Zhu X, et al. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: Results from a phase 3 clinical trial (LOTUS). J Drugs Dermatol 2013; 12: 166-74. Adverse events: ➔ headache, upper respiratory tract infection, and nasopharyngtis mentioned as adverse events ➔ no significant differences in the adverse effects of headache (P=0.17), upper respiratory tract infection (P=0.51), nasopharyngitis (P=0.19) between ustekinumab 45 mg group and the placebo group (fixed-effect models, I2 = 0%) ➔ infection in ustekinumab 45 mg group significantly higher than the placebo group (p = 0.02; RR = 1,02 and 95% CI [1,03 – 1,40]) ➔ serious infection, cardiovascular events, and malignant tumors mentioned as serious adverse effects with no significant differences between the groups - From the funnel plot, we found that there was no publication bias in the 6 randomized control trials
	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. *5. Kommentar zu Review* • *Informationen zur Finanzierung und zu Interessenkonflikten fehlen*

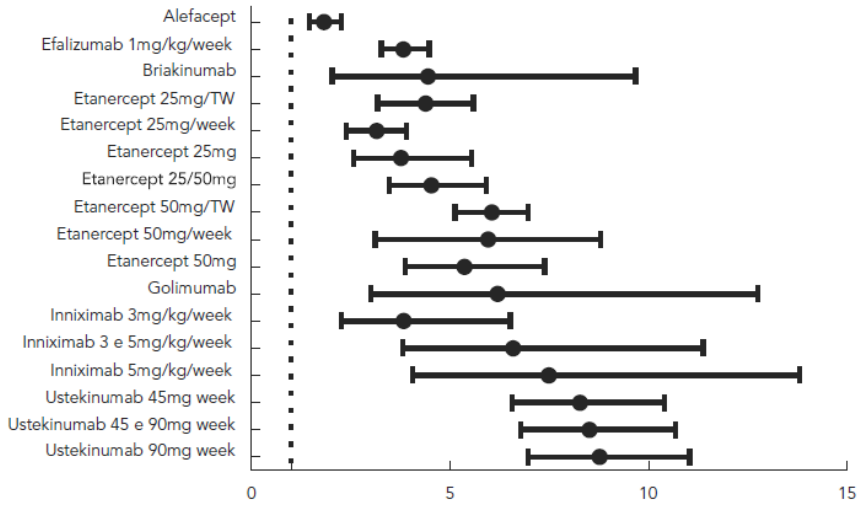
	• *Informationen zu 90mg nicht dargestellt wegen fehlender Zulassung*
Meng Y et al., 2014 [13]. Systematic review and meta-analysis of ustekinumab for moderate to severe psoriasis	1. Fragestellung To systematically evaluate the efficacy and safety of ustekinumab versus placebo for psoriasis.
	2. Methodik Population: patients with psoriasis Intervention: ustekinumab (45 and 90 mg) Komparator: Exclusion criteria for controls included systemic use of corticosteroids, immune-suppressants or agents specifically targeting IL-12 or IL-23 with a withdrawal time of < 2 weeks. Endpunkte: primary: Psoriasis Area and Severity Index (improvement of 50%, 75% and 90% - PASI50, PASI75 and PASI90), Physician's Global Assessment (PGA, judged as clear "no effect on the patient's life" according to the scoring system for psoriasis) and Dermatology Life Quality Index (DLQI, 0 or 1 meant no effect on the patient's life) secondary: adverse events (AEs), serious AEs (SAEs) Suchzeitraum: from 1990 to August 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 9/11 381 Qualitätsbewertung der Studien: GRADE used to evaluate quality of evidence Heterogenitätsanalysen: evaluated with I2 statistic; values of 25%, 50% and 75% defined as low, moderate and high estimates; when significant I2 (> 50%) indicated heterogeneity between studies, the random effects model used for meta-analysis; otherwise, the fixed effects model used Publication Bias: Begg funnel plot and the Egger test
	3. Ergebnisdarstellung • no evidence of publication bias for the analyses of effects according to PASI, PGA and DLQI of 0 or 1 **Quality assessment of the included studies** • all studies were of high methodological quality • three of the trials reported an intention-to-treat analysis • follow-up varied from 12 weeks to 5 years • all studies supported by the same company (Centocor Ortho Biotech Inc.), potential risk of selective reporting bias • no obvious imbalances in baseline data

	PASI50 (three studies) at the end of 12 weeks of treatment • no statistical heterogeneity between the studies • PASI50 higher for both ustekinumab doses (45 and 90 mg) than for 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 PASI50 between the two doses **PASI75 (five studies) at the end of 12 weeks of treatment** • no statistical heterogeneity between the studies • PASI75 higher for both ustekinumab doses (45 and 90 mg) than for placebo (RR = 18.28, 95% CI 12.76–26.17, P << 0.001; RR = 20.21, 95% CI 13.85–29.49, P << 0.001 respectively) • no significant difference in PASI75 between the two doses **PASI90 (three studies) at the end of 12 weeks of treatment** • PASI90 higher for both ustekinumab doses (45 and 90 mg) than for 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 PASI90 between the two doses **PGA (four studies) at the end of 12 weeks of treatment** • no statistical heterogeneity between the studies • PGA score 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 • no significant difference in PGA between the two doses **DLQI of 0 or 1 (four studies) at the end of 12 weeks of treatment** • no statistical heterogeneity between the studies • number of patients achieving DLQI of 0 or 1 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 between the two doses **AEs (six studies) at the end of 12 weeks of treatment** • no statistical heterogeneity between the studies • AEs higher for ustekinumab 45 mg than for placebo • included headache and back pain • no obvious difference between the ustekinumab and placebo groups in the incidence of AEs over 5 years (one study) **SAEs (six studies) at the end of 12 weeks of treatment** • no significant difference between the ustekinumab 45 mg group and the placebo group no obvious difference between the ustekinumab and placebo groups in the incidence of SAEs over 5 years (one study)

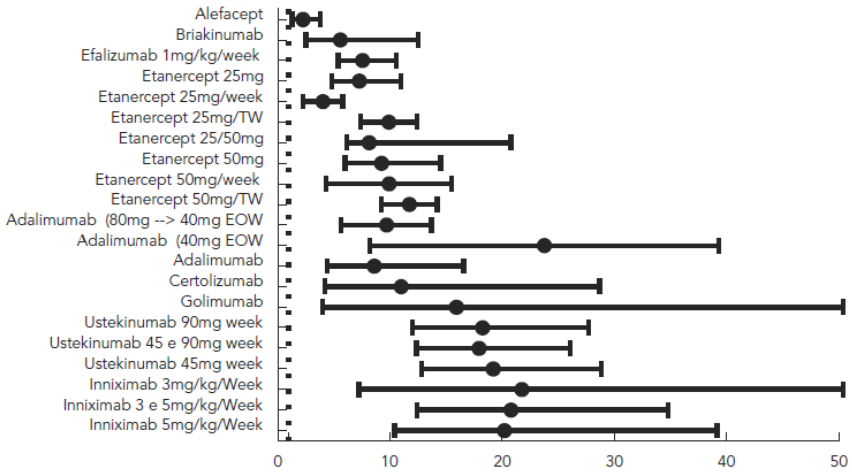
	4. Anmerkungen/Fazit der Autoren Our results indicate that ustekinumab is safe for patients with moderate to severe plaque psoriasis over a period of 5 years, and it is effective after 12 weeks. There was no significant superiority in efficacy between the 45 mg and 90 mg doses for short-term therapy. 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. Kommentar zu Review* • *Zulassung empfiehlt die Dosierung von 45mg, 90mg bei Menschen ab 100kg KG möglich* • *the authors declare that they have no conflicts of interest* • *supported by the Funds for Guangxi Zhuang Autonomous Region Science And Technology Hall (grant no. 1140003B-86)*
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 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/2 416 Qualitätsbewertung der Studien: according to the Jadad scoring system Heterogenitätsanalysen: nicht geplant, random-effects-model verwendet Publication Bias: nicht geplant
	3. Ergebnisdarstellung: • Biasrisiko der Studien heterogen: zwischen 1 und 5 Punkten nach Jadad **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).

	• No studies investigated the effect of combination of NB-UVB, BB-UVB with topical treatments on PASI-75. • combining NB-UVB with methotrexate was very efficacious with an average of 94 % (95 % CI 81–100) of 31 patients from two trials achieving PASI-75 or above • when adalimumab was added to NB-UVB, all four patients achieved PASI-75; when alefacept was added, an average of 97 % (95 % CI 85–100) of 35 patients from two trials achieved PASI-75 • In a study evaluating the combination of oral PUVA and acitretin, only 63 % of the 30 investigated patients achieved PASI-75. • Combining PUVA with calcipotriol showed good efficacy in one trial, with 88 % of the 60 patients meeting PASI-75. • A study investigated the combination of bath PUVA with acitretin or etretinate; it reported 100 % of the 34 patients achieved ≥PASI-75, addition of oral retinoids to bath PUVA appeared to greatly increase the efficacy of bath PUVA. **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). • The combination of 8-methoxypsoralen (8-MOP) with NB-UVB was evaluated in 72 patients from two trials with an average clearance rate of 84 % (95 % CI 74–92). • One trial combined bath PUVA with NB-UVB; this resulted in clearance in 92 % (95 % CI 77–100) of the 12 patients. • the addition of fluocinonide cream, tar oil, and calcipotriol cream or ointment offer no advantage in regard to clearance rate as compared with BB-UVB monotherapy • A study evaluated the combination of oral PUVA and acitretin in 20 patients; it showed a clearance rate of 94 %, which was much higher than a similar study which showed PASI-75 of 63 %. • Combining bath PUVA with acitretin or etretinate in 34 patients resulted in a 100 % clearance rate in both groups **Safety:** 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. **Withdrawal due to adverse effects:** 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 endpoint. 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. *5. Kommentar zu Review* • *no sources of funding were used to prepare this manuscript* • *authors have no conflicts of interest that are directly relevant to the content of this article* • *Vergleichbarkeit der Studien nicht diskutiert* • *Heterogenitätsanalysen nicht nachvollziehbar*
Correr CJ et al., 2013 [4]. 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/k.A. 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 *Clinical efficacy:* ***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.

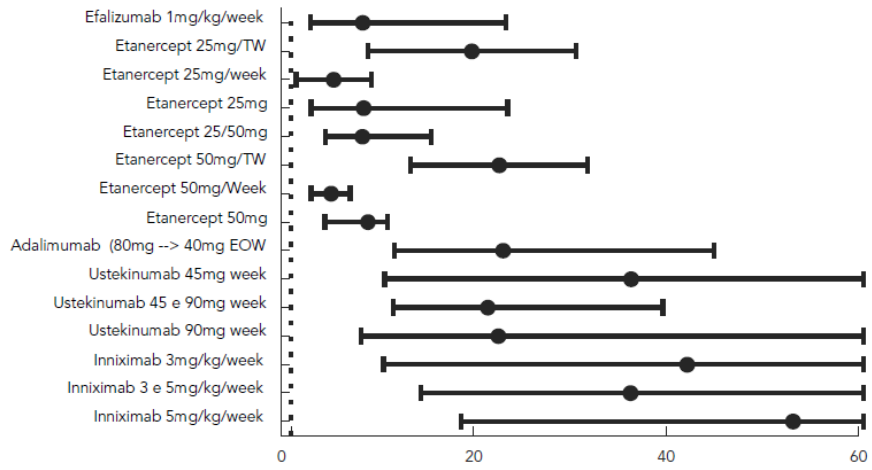
2b) PASI 75



PASI 90:

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

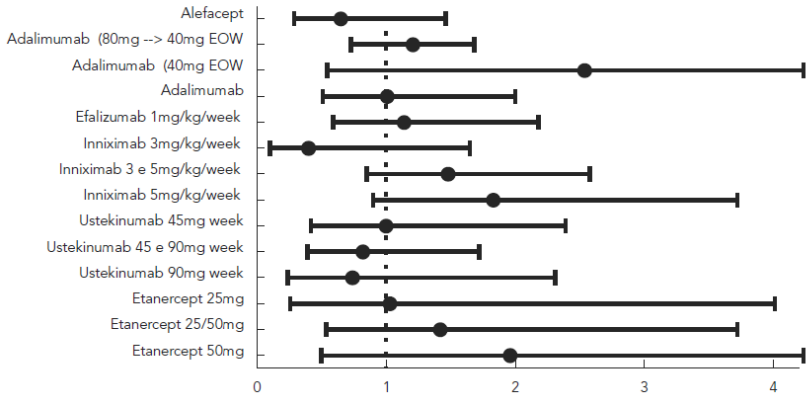
2c) PASI 90

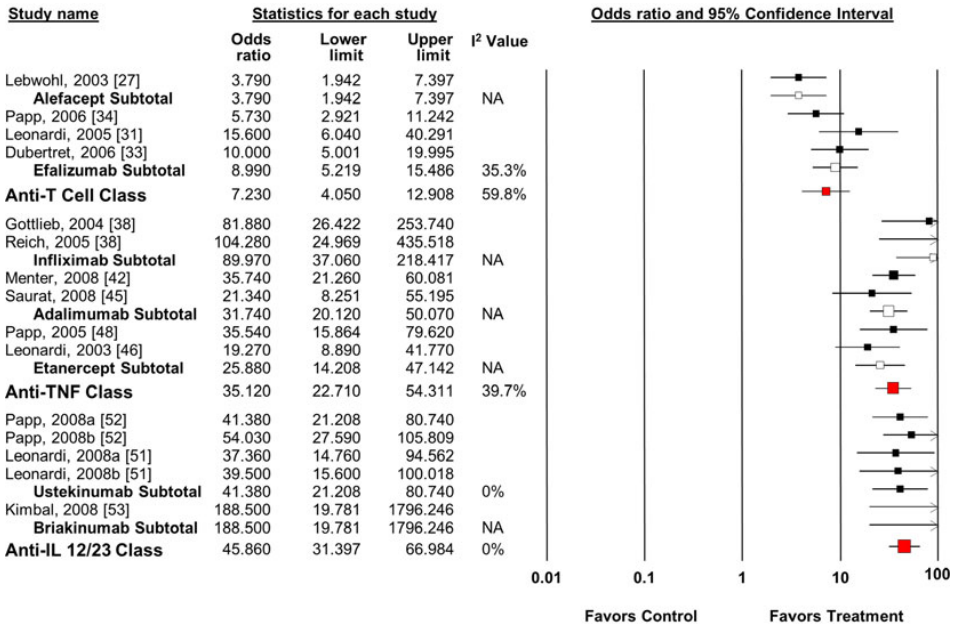


Heterogenität (I^2>50%) in Wirksamkeit bei:
PASI 50 outcome, etanercept 25mg TW (I^2 = 75%), etanercept 50mg W (I^2 = 70%) and infliximab 5mg/kg/ week (I^2 = 64%); PASI 75, adalimumab (80mg > 40mg EOW) (I^2 = 76%), infliximab 3mg/kg/week (I^2 = 55%) and alefacept (I^2 = 70%) and for PASI 90 ustekinumab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

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

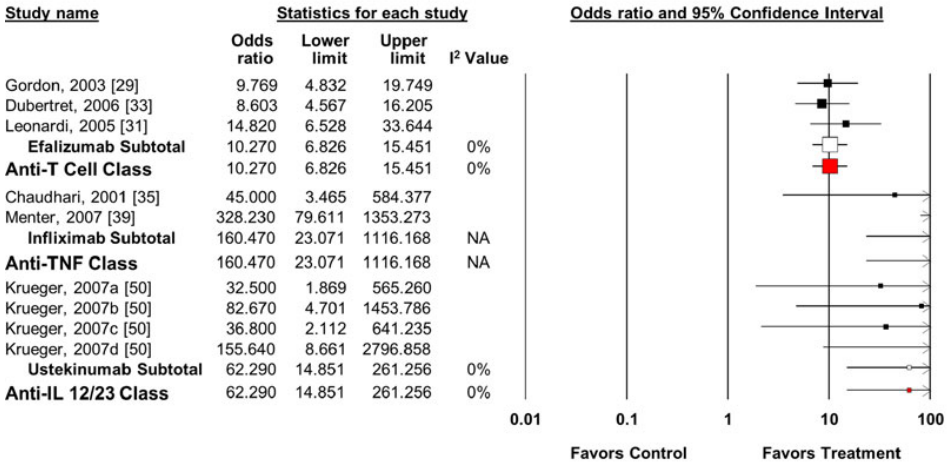
<u>Safety outcomes:</u>
safety outcomes including infections and serious adverse events did not present statistically significant differences between biologic and placebo considering withdrawal due to adverse events, the rate for ustekinumab 45mg was lower than that for the placebo group and the difference was

	statistically significant. For other biologics, at all dosages, there was no statistically significant difference between the drug´s result and placebo 3b) Serious adverse events 
	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. *5. Kommentar zu Review* • *einige der untersuchten Wirkstoffe nicht (mehr) zugelassen* • *The authors wish to thank the Brazilian Ministry of Education's Program to Support Restructuring an Expansion Plans in the Federal Universities.* • *Conflict of interest: None declared.*
Baker EL et al., 2012 [3]. 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: 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/k. A. Qualitätsbewertung der Studien: Jadad Score Heterogenitätsanalysen: I2 statistic, ranges from 0% to 100% with the higher percentage representing a higher likelihood of the existence of heterogeneity Publication bias: Visual inspection of funnel plots and Egger's weighted regression statistics
	3. Ergebnisdarstellung • infliximab versus placebo (n = 6); adalimumab versus placebo (n = 5); etanercept versus placebo (n = 4); ustekinumab versus placebo (n = 3); • weitere untersuchte Vergleiche sind nicht zulassungskonform • alle Studien mit mindestens 4 Punkten Jadad Score **PGA Static Response Rate:** • Each individual agent, as well as each class, showed an increase in the odds of achieving a positive response (Fig. 2) • When all anti-T cell agent RCTs (OR 5.89, 95% CI 4.34–7.99) and anti-TNF agent RCTs (OR 24.27, 95% CI 15.66–37.61) were pooled, regardless of dose, slightly smaller overall effects were seen. Fig. 2: Impact of biologic agents on static PGA response rate:  **PGA Dynamic Response Rate:**

- Each individual agent, as well as each class, showed an increase in the odds of achieving a positive response (Fig. 3).
- When all anti-T cell agent RCTs (OR 9.73, 95% CI 6.54–14.49) and anti-TNF agent RCTs (OR 140.58, 95% CI 39.14–504.97) were pooled, regardless of dose, similar overall effects were seen.

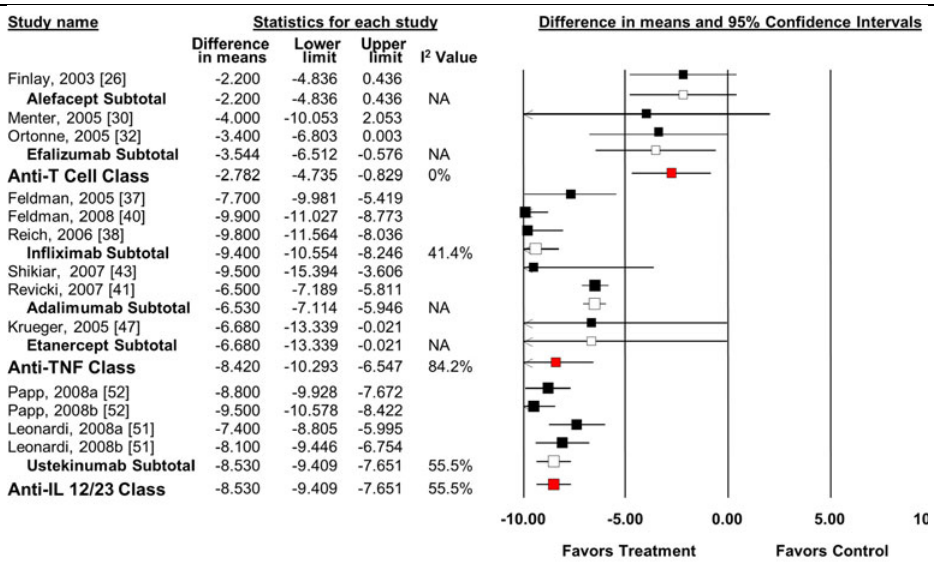
Fig. 3: Impact of biologic agents on dynamic PGA response rate:



Change in DLQI from Baseline:

- The anti-T cell agents as a class, as well as efalizumab alone significantly reduced the DLQI score from baseline (Fig. 4).
- Each individual anti-TNF agent, as well as the pooled class, significantly reduced the DLQI score from baseline.
- Similar effects were seen with ustekinumab.
- When all anti-T cell agent RCTs (WMD -2.377, 95% CI -3.286 to -1.469), anti-TNF agent RCTs (WMD -8.03, 95% CI -9.24 to -6.81), and anti-IL-12/23 RCTs (WMD -7.94, 95% CI -8.83 to -7.05) were pooled, regardless of dose, similar overall effects were seen.

Fig. 4: Impact of biologic agents on change in DLQI from baseline:



Change in SF-36 from Baseline:

- Each anti-TNF agent as well as the class significantly improved both SF-36 endpoints from baseline.
- When all anti-T cell agent RCTs (MCS =WMD 2.18, 95% CI -1.61 to 5.97; PCS =WMD 1.95, 95% CI -1.44 to 5.34), and anti-TNF agent RCTs (MCS =WMD 4.56, 95% CI 3.59–5.54; PCS =WMD 3.93, 95% CI 3.09–4.78) were pooled, regardless of dose, similar overall effects were seen.

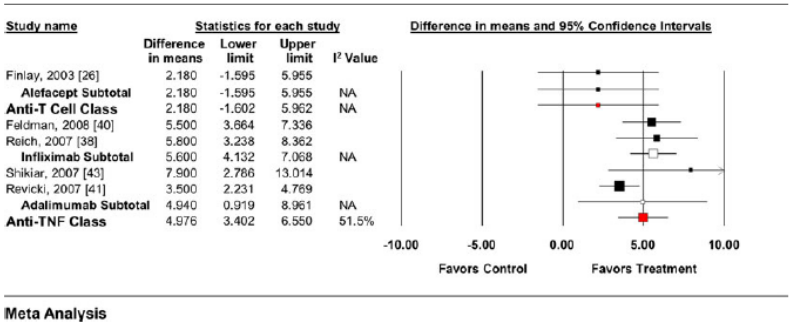


Fig. 5 Impact of biologic agents on change in SF-36 MCS from baseline. *MCS* mental component summary, *SF-36* 36-item Medical Outcomes Study Short-Form General Health Survey, *TNF* tumor necrosis factor

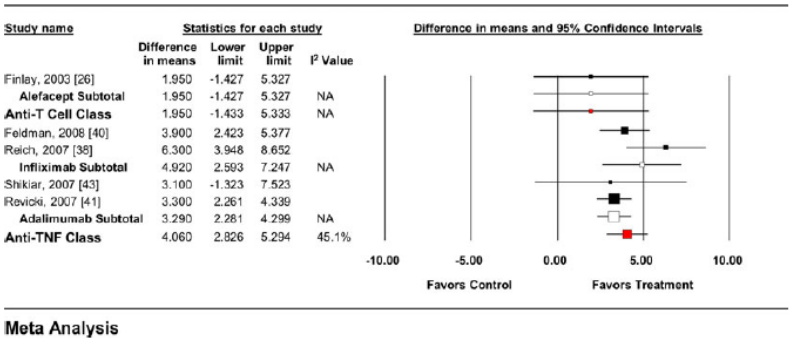


Fig. 6 Impact of biologic agents on change in SF-36 PCS from baseline. *PCS* physical component summary, *SF-36* 36-item Medical Outcomes Study Short-Form General Health Survey, *TNF* tumor necrosis factor

	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. Kommentar zu Review* • *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.* • *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."*

Leitlinien

Armstrong AW et al., 2015 [2].

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]

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

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 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.

[18] Park KK et al. A randomized, "head-to-head" pilot study comparing the effects of etanercept monotherapy vs. etanercept and narrowband ultraviolet B (NB-UVB) phototherapy in obese psoriasis patients. *J Eur Acad Dermatol Venereol*. 2013; 27(7):899-906.

[19] Wolf P et al. 311 nm Ultraviolet B–accelerated response of psoriatic lesions in adalimumab-treated patients. *Photodermatol Photoimmunol Photomed*. 2011;27(4):186-189.

[20] Wolf P et al. Treatment with 311-nm ultraviolet B enhanced response of psoriatic lesions in ustekinumab-treated patients: a randomized intraindividual trial. *Br J Dermatol*. 2012;166(1):147-153.

[21] Kircik L et al. UNITE Study Group. Utilization of Narrow-band Ultraviolet Light B Therapy and Etanercept for the Treatment of Psoriasis (UNITE): efficacy, safety, and patient-reported outcomes. *J Drugs Dermatol*. 2008;7(3):245-253.

[22] De Simone C et al. Combined treatment with etanercept 50mg once weekly and narrow-band ultraviolet B phototherapy in chronic plaque psoriasis. *Eur J Dermatol*. 2011;21(4):568-572.

[23] Wolf P et al. Treatment with 311-nm ultraviolet B accelerates and improves the clearance of psoriatic lesions in patients treated with etanercept. *Br J Dermatol*. 2009;160(1):186-189.

[24] Lynde CW et al. A randomized study comparing the combination of nbUVB and etanercept to etanercept monotherapy in patients with psoriasis who do not exhibit an excellent response after 12 weeks of etanercept. *J Dermatolog Treat*. 2012;23(4):261-267.

[25] Bagel J. Adalimumab plus narrowband ultraviolet B light phototherapy for the treatment of moderate to severe psoriasis. *J Drugs Dermatol*. 2011;10(4):366-371.

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

[26] Zachariae Cet al. The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect ofmethotrexate therapy. *Acta Derm Venereol*. 2008;88(5):495-501.

[27] Gottlieb AB et al. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. *Br J Dermatol*. 2012;167(3):649-657.

[28] Dalaker M, Bonesrønning JH. Long-term maintenance treatment of moderate-to-severe plaque psoriasis with infliximab in combination with methotrexate or azathioprine in a retrospective cohort. *J Eur Acad Dermatol Venereol*. 2009;23(3): 277-282.

[29] Driessen RJ et al. Etanercept combined with methotrexate for high-need psoriasis. *Br J Dermatol*. 2008;159(2): 460-463.

[30] Goedkoop AY et al. Deactivation of endothelium and reduction in angiogenesis in psoriatic skin and synovium by low dose infliximab therapy in combination with stable methotrexate therapy: a prospective single-centre study. *Arthritis Res Ther*. 2004;6(4):R326-R334.

[31] Kavanaugh et al. IMPACT 2 Study Group. Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. *Ann Rheum Dis*. 2007;66(4):498-505.

[32] De Groot M et al. Adalimumab in combination with methotrexate more effectively reduces the numbers of different inflammatory cell types in lesional psoriatic skin than

does single treatment with adalimumab or methotrexate. *Br J Dermatol*. 2008;158(6):1401.
[34] 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):1345-1349.
[35] Smith EC et al. Combining systemic retinoids with biologic agents for moderate to severe psoriasis. *Int J Dermatol*. 2008;47(5):514-518.
[36] Yamauchi PS et al. Cessation of cyclosporine therapy by treatment with etanercept in patients with severe psoriasis. *J AmAcad Dermatol*. 2006;54(3) (suppl 2):S135-S138.
[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 Dermatology Forum (EDF), 2015 [6].

European S3-Guidelines on the systematic treatment of psoriasis vulgaris. Update 2015

EDF in cooperation with EADV and IPC

Fragestellung/Zielsetzung

"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."

Methodik

These guidelines are an update of the existing European Psoriasis Guidelines published in 2009.

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) [14]

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.
35 Dogra S et al. Efficacy and safety of acitretin in three fixed doses of 25, 35 and 50 mg in adult patients with severe plaque type psoriasis: A randomized, double blind, parallel group, dose ranging study. J Eur Acad Dermatol Venereol. 2013;27(3):e305-e11.
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.
37 Rim JH et al. The efficacy of calcipotriol + acitretin combination therapy for psoriasis: comparison with acitretin monotherapy. Am J Clin Dermatol. 2003;4(7): 507-10.
38 van de Kerkhof PC et al. The effect of addition of calcipotriol ointment (50 micrograms/g) to acitretin therapy in psoriasis. Br J Dermatol. 1998;138(1):84-9.

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 [60]

Evidenzbasis

[56] Ellis CN et al. Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. N Engl J Med. 1991;324(5):277-84.

[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.

[58] Gisondi P et al. Weight loss improves the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy: a randomized, controlled, investigator-blinded clinical trial. Am J Clin Nutr. 2008;88(5):1242-7.

[59] Grossman RM et al. A novel therapeutic approach to psoriasis with combination calcipotriol ointment and very low-dose cyclosporine: results of a multicenter placebo-controlled study. J Am Acad Dermatol. 1994;31(1):68-74.

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

[61] Laburte C et al. Efficacy and safety of oral cyclosporin A (CyA; Sandimmun) for long-term treatment of chronic severe plaque psoriasis. Br J Dermatol. 1994;130(3):366-75.

[62] Meffert H et al. Low-dose (1.25 mg/kg) cyclosporin A: treatment of psoriasis and investigation of the influence on lipid profile. Acta Derm Venereol. 1997;77(2):137-41.

63 Reitamo S et al. Efficacy of sirolimus (rapamycin) administered concomitantly with a subtherapeutic dose of cyclosporin in the treatment of severe psoriasis: a randomized controlled trial. Br J Dermatol. 2001;145(3):438-45.

64 Shintani Y et al. Safety and efficacy of a fixed-dose cyclosporin microemulsion (100 mg) for the treatment of psoriasis. J Dermatol. 2011;38(10):966-72.

65 Takahashi H et al. Application of 3 mg/kg of cyclosporine a (NEORAL) once daily is effective for severe and moderate psoriasis. [Japanese]. Nishinihon Journal of Dermatology. 2009;71(1):63-9.

66 Thaci D et al. Body-weight-independent dosing of cyclosporine micro-emulsion and three times weekly maintenance regimen in severe psoriasis. A randomised study. Dermatology. 2002;205(4):383-8.

67 Vena GA et al. Combined treatment with low-dose cyclosporine and calcipotriol/betamethasone dipropionate ointment for moderate-to-severe plaque psoriasis: a randomized controlled open-label study. J Dermatolog Treat. 2012;23(4):255-60.

68 Yoon HS et al. A comparison of two cyclosporine dosage regimens for the treatment of severe psoriasis. J Dermatolog Treat. 2007;18(5):286-90.

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 immunosuppression
Methotrexate	↓	Consensus	Expert opinion: increased risk of immunosuppression
Ustekinumab	**o**	Consensus	No evidence available

Evidenzbasis

71 Altmeyer PJ et al. Antipsoriatic effect of fumaric acid derivatives. Results of a multicenter double-blind study in 100 patients. J Am Acad Dermatol. 1994;30(6):977-81.

72 Fallah Arani S et al. Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis: a multicentre prospective randomized controlled clinical trial. Br J Dermatol. 2011;164(4):855-61.

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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

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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 formation 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

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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 formation of ADA and increase trough levels of infliximab
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

133 Griffiths CE et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med. 2010;362(2):118-28.

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178 Janssen-Cilag International NV. Summary of product characteristics STELARA® 90 mg Injektionslösung in einer Fertigspritze. As of March 2014. Janssen-Cilag International NV, Beerse, Belgium. License number: EU/1/08/494/004. 2014.

179 Janssen-Cilag International NV. Summary of product characteristics STELARA® 45 mg Injektionslösung in einer Fertigspritze. As of March 2014. Janssen-Cilag International NV, Beerse, Belgium. License number: EU/1/08/494/003. 2014.

National Institute for Health and Care Excellence (NICE), 2012 [20].

Psoriasis: assessment and management of

Fragestellung/Zielsetzung

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?

psoriasis NICE clinical guidelines No. 153 *Siehe auch Kurzversion* **NICE, 2012 [19].**	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: sprachliche 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* • *nur wenige Empfehlungen speziell für moderate bis schwere Psoriasis formuliert*
	Freitext/Empfehlungen/Hinweise **Topical therapy** <u>General recommendations</u> 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: o 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 o 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. <u>Infliximab</u> 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. <u>Ustekinumab</u> 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. <u>Changing to an alternative biological drug</u> 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.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

National Institute for Health and Care Excellence (NICE), 2016 [16]. Apremilast for treating moderate to severe plaque psoriasis (TA419) This guidance replaces TA368	1 Recommendations 1.1 Apremilast is recommended as an option for treating chronic plaque psoriasis in adults whose disease has not responded to other systemic therapies, including ciclosporin, methotrexate and PUVA (psoralen and ultraviolet-A light), or when these treatments are contraindicated or not tolerated, only if: – the disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10 – treatment is stopped if the psoriasis has not responded adequately at 16 weeks; an adequate response is defined as: o a 75% reduction in the PASI score (PASI 75) from when treatment started or o a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from start of treatment – the company provides apremilast with the discount agreed in the patient access scheme. 1.2 When using the DLQI, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties, that could affect the responses to the DLQI and make any adjustments they consider appropriate. 1.3 This guidance is not intended to affect the position of patients whose treatment with apremilast was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.
National Institute for Health and Care Excellence (NICE), 2015 [21]. Secukinumab for treating moderate to severe plaque psoriasis (TA350)	1 Guidance 1.1 Secukinumab is recommended, within its marketing authorisation, as an option for treating adults with plaque psoriasis only when: – the disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10 – the disease has failed to respond to standard systemic therapies, for example, ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or these treatments are contraindicated or the person cannot tolerate them – the company provides secukinumab with the discount agreed in the patient access scheme. 1.2 Secukinumab treatment should be stopped in people whose psoriasis has not responded adequately at 12 weeks. Further treatment cycles are not recommended in these people. 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 5-point reduction in DLQI from when treatment started. 1.3 People whose treatment with secukinumab is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop. 1.4 When using the DLQI, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties, that could affect the responses to the DLQI and make any adjustments they consider appropriate.
National Institute for Health and Care Excellence (NICE), 2009 [22]. Ustekinumab for the treatment of adults with moderate to severe psoriasis (TA180) Review decision - September 2010: "the guidance should remain on the 'static guidance list'"	<u>1 Guidance</u> 1.1 Ustekinumab is recommended as a treatment option for adults with plaque psoriasis when the following criteria are met. – The disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) score of 10 or more and a Dermatology Life Quality Index (DLQI) score of more than 10. – The psoriasis has not responded to standard systemic therapies, including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or the person is intolerant of or has a contraindication to these treatments. 1.2 Ustekinumab treatment should be stopped in people whose psoriasis has not responded adequately by 16 weeks after starting treatment. An adequate response is defined as either: – a 75% reduction in the PASI score (PASI 75) from when treatment started or – a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in the DLQI score from when treatment started. 1.3 When using the DLQI, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the DLQI and make any adjustments they consider appropriate.
National Institute for Health and Care Excellence (NICE), 2008 [15]. Adalimumab for the treatment of adults with psoriasis (TA146) Review decision - September	<u>1 Guidance</u> 1.1 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 Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10. – The psoriasis has not responded to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant of, or has a contraindication to, these treatments. 1.2 Adalimumab should be discontinued in people whose psoriasis has not responded adequately at 16 weeks. An adequate response is defined as either:

2010: "the guidance should remain on the 'static guidance list'"	– 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 DLQI from start of treatment. 1.3 When using the DLQI, healthcare professionals should ensure that when reaching conclusions on the severity of plaque psoriasis they take into account a person's disabilities (such as physical impairments) and linguistic or other communication difficulties. In such cases, healthcare professionals should ensure that their use of the DLQI continues to be a sufficiently accurate measure. The same approach should apply in the context of a decision about whether to continue the use of adalimumab in accordance with section 1.2.
National Institute for Health and Care Excellence (NICE), 2008 [18]. Infliximab for the treatment of adults with psoriasis (TA134) Review decision - September 2010: "the guidance should remain on the 'static guidance list'"	<u>1 Guidance</u> 1.1 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 Psoriasis Area Severity Index (PASI) of 20 or more and a Dermatology Life Quality Index (DLQI) of more than 18. – The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate or PUVA (psoralen and long-wave ultraviolet radiation), or the person is intolerant to or has a contraindication to these treatments. 1.2 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. 1.3 When using the DLQI healthcare professionals should take care to ensure that they take account of a patient's disabilities (such as physical impairments) or linguistic or other communication difficulties, in reaching conclusions on the severity of plaque psoriasis. In such cases healthcare professionals should ensure that their use of the DLQI continues to be a sufficiently accurate measure. The same approach should apply in the context of a decision about whether to continue the use of the drug in accordance with section 1.2.
National Institute for Health and Care Excellence (NICE), 2006 [17]. Etanercept and efalizumab for the treatment of	<u>1 Guidance</u> 1.1 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 Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10. – The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-

adults with psoriasis (TA103) Review decision - September 2010: “the guidance should remain on the ‘static guidance list’”	wave ultraviolet radiation); or the person is intolerant to, or has a contraindication to, these treatments. 1.2 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. … 1.5 It is recommended that the use of etanercept for psoriasis should be initiated and supervised only by specialist physicians experienced in the diagnosis and treatment of psoriasis. If a person has both psoriasis and psoriatic arthritis their treatment should be managed by collaboration between a rheumatologist and a dermatologist.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 07.04.2017

#	Suchfrage
1	MeSH descriptor: [Psoriasis] explode all trees
2	Psoriasis:ti,ab,kw
3	#1 or #2
4	#3 Publication Year from 2012 to 2017, in Cochrane Reviews (Reviews and Protocols) and Technology Assessments

SR, HTAs in Medline (PubMed) am 07.04.2017

#	**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 ("2012/04/01"[PDAT] : "2017/04/30"[PDAT])

Leitlinien in Medline (PubMed) am 07.04.2017

#	**Suchfrage**
1	Psoriasis[MeSH]
2	psoriasis[Title/Abstract]
3	#1 OR #2
4	#3 AND ((((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]) OR recommendation*[Title])
5	(#4) AND ("2012/04/01"[PDAT] : "2017/04/30"[PDAT])

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Anhang

Table 2 Summary of results for drugs and doses sorted by drug class

Drug class	Drug/dose	PASI 75		PASI 90		PASI 100		Primary endpoint (weeks)
		RD (95% CI)	NNT	RD (95% CI)	NNT	RD (95% CI)	NNT	
Anti-TNF	Adalimumab load (80 mg week 0 + 40 mg week 1) + 40 mg EOW	0.62 (0.58–0.67)	1.61	0.43 (0.39–0.46)	2.32	0.18 (0.12–0.24)	5.55	12–16
	Etanercept 100 mg/wk	0.44 (0.40–0.48)	2.27	0.22 (0.18–0.25)	4.54	0.05 (0.04–0.07)	20	12
	Etanercept 50 mg/wk	0.31 (0.27–0.35)	3.22	0.10 (0.07–0.13)	10	0.06 (0.01–0.10)	16.6	12
	Infliximab 5 mg/kg	0.76 (0.73–0.79)	1.31	0.53 (0.46–0.60)	1.88	ND	ND	10
	Overall pooled effect	0.54 (0.47–0.60)	1.85	0.28 (0.21–0.35)	3.57	0.10 (0.04–0.16)	10	–
Anti-IL-12/23	Ustekinumab 90 mg	0.67 (0.60–0.74)	1.49	0.42 (0.30–0.54)	2.38	0.15 (0.07–0.22)	6.66	12
	Ustekinumab 45 mg	0.64 (0.60–0.69)	1.56	0.45 (0.35–0.55)	2.22	0.16 (0.10–0.21)	6.25	12
	Overall pooled effect	0.65 (0.62–0.69)	1.53	0.44 (0.37–0.51)	2.27	0.15 (0.11–0.19)	6.66	–
Anti-IL-17	Brodalumab 210 mg	0.79 (0.76–0.82)	1.26	0.75 (0.61–0.89)	1.33	0.44 (0.35–0.53)	2.27	12
	Brodalumab 140 mg	0.64 (0.57–0.70)	1.56	0.72 (0.57–0.86)	1.38	0.26 (0.23–0.30)	3.84	12
	Ixekizumab 160 mg week 0 and 80 mg every 2 weeks	0.84 (0.81–0.88)	1.19	0.69 (0.65–0.72)	1.44	0.37 (0.35–0.40)	2.70	12
	Secukinumab 300 mg	0.76 (0.71–0.81)	1.31	0.53 (0.46–0.60)	1.88	0.28 (0.22–0.34)	3.57	12
	Overall pooled effect	0.76 (0.70–0.82)	1.31	0.61 (0.54–0.68)	1.63	0.35 (0.30–0.40)	2.85	–
Small molecule inhibitors (anti-JAK/anti-PD4)	Tofacitinib 10 mg	0.53 (0.47–0.58)	1.88	0.36 (0.33–0.39)	2.77	ND	ND	12
	Tofacitinib 5 mg	0.34 (0.31–0.38)	2.94	0.19 (0.17–0.22)	5.26	ND	ND	12
	Apremilast 30 mg bid	0.30 (0.23–0.36)	3.33	ND	ND	ND	ND	16
	Overall pooled effect	0.43 (0.30–0.55)	2.32	0.27 (0.13–0.42)	3.7	ND	ND	–

PASI Psoriasis Area and Severity Index, *RD* risk difference, *CI* confidence interval, *NNT* number needed to treat, *EOW* every other week, *bid* twice daily, *JAK* Janus kinase, *PD4* phosphodiesterase 4, *ND* not determined, *TNF* tumor necrosis factor, *IL* interleukin

Abbildung 1: aus de Carvalho AV, et al. 2017

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.