Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2015-06-01-D-167 Secukinumab

Stand: April 2015

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

Secukinumab **Cosentyx ist angezeigt für die Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die für eine systemische Therapie in Frage kommen.**	
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: UV-B, Balneo-Phototherapie, 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*
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** Text aus Fachinformation
Zu bewertendes Arzneimittel: 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. "
Systemische Therapie	
Adalimumab L04AB04 Humira®	Humira ist indiziert zur Behandlung der mittelschweren bis schweren chronischen Plaque-Psoriasis bei erwachsenen Patienten, die auf eine andere systemische Therapie, wie Ciclosporin, Methotrexat oder PUVA, nicht angesprochen haben oder bei denen eine Kontraindikation oder Unverträglichkeit gegenüber einer solchen Therapie vorliegt. (Stand 09/2014)
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 (siehe Abschnitt 5.1). (Stand 09/2014)
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 (siehe Abschnitt 5.1). (Stand 07/2014)
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 (siehe Abschnitt 5.1). (Stand 03/2014)
Apremilast L04AA32 Otezla®	Otezla ist indiziert zur Behandlung der mittelschweren bis schweren chronischen Plaque-Psoriasis bei erwachsenen Patienten, die auf eine andere systemische Therapie, wie Ciclosporin oder Methotrexat oder Psoralen in Kombination mit UVA-Licht (PUVA), nicht angesprochen haben oder bei denen eine solche Therapie kontraindiziert ist oder die diese nicht vertragen haben.
Ciclosporin L04AD01 Sandimmun® Optoral Weichkapseln	[…] 4. Schwerste therapieresistente Formen der Psoriasis, insbesondere vom Plaque-Typ, die mit einer konventionellen systemischen Therapie nicht ausreichend behandelbar sind. […] (Stand: 09/2011)

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** Text aus Fachinformation
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: 09/2013)
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 Acicutan 10 mg/ 25mg Hartkapseln	- Großflächige und schwere refraktäre Formen der Psoriasis - Psoriasis pustulosa an Händen und Füßen (Stand: 12/2012)
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)

Quelle: Fachinformationen, arznei-telegramm Arzneimitteldatenbank, AMIS-Datenbank

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

Inhalt

Indikation für die Recherche bei Secukinumab:

Cosentyx ist angezeigt für die Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die für eine systemische Therapie in Frage kommen.

Berücksichtigte Wirkstoffe/Therapien:

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

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation *„Plaque Psoriasis“* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre *(*eingeschränkt und die Recherche am *24.03.2015* abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), arztbibliothek.de (ÄZQ), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 561 Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden 113 Quellen eingeschlossen. Insgesamt ergab dies 30 Quellen, die in die synoptische Evidenzübersicht aufgenommen wurden.

Abkürzungen

ALA-PDT	aminolevulinic acid – photodynamic therapy
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
BB	broadband (Breitband)
BSA	Body surface area
CoI	Conflict of interest
CSA	ciclosporin A
CyA	cyclosporin
DAHTA	Deutsche Agentur für Health Technology Assessment
DLQI	Dermatology Life Quality Index
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
k.A.	keine Angabe
MED	minimal erythema dose
MTC	mixed treatment comparisons
NB	Narrowband (Schmalband)
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NIHR HSC	National Institute for Health Research Horizon Scanning Centre
PASI	Psoriasis Area and Severity Index
PGA	physician’s global assessment
PUVA	Psoralen plus UV-A (auch Photochemotherapie)
REM	Random-Effects-Model
TRIP	Turn Research into Practice Database
UV	ultraviolet
vs	versus

IQWiG Berichte/ G-BA Beschlüsse

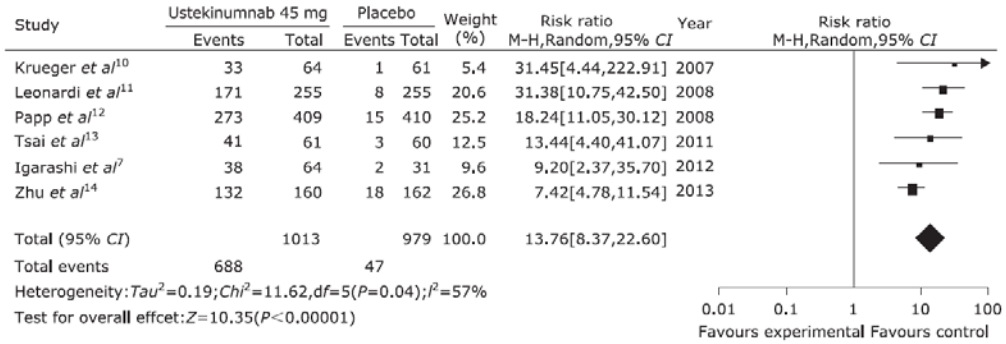
G-BA, 2008 [8] Zusammenfassende Dokumentation zum Beratungsverfahren des Unterausschusses „Ärztliche Behandlung des Gemeinsamen Bundesausschusses." *Siehe auch IQWIG, 2006: Abschlussbericht: Balneophototherapie (IQWiG-Berichte. Jahr: 2006 Nr. 14) [11]*	Unter Balneophototherapie versteht man in Deutschland 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 (Ultraviolettstrahlung-B)-Licht. Bei der asynchronen Bal-neophototherapie wird bei Verwendung 25 %iger Solelösung aus technischen Grün-den erst Leitungswasser in die Wanne eingelassen, eine Folie auf das Wasser gelegt und danach die 25 %ige Sole aufgegossen, in der der Patient dann badet. Die synchrone Balneophototherapie spielt in der Praxis nur in Form der „TOMESA-Therapie" eine Rolle in der Versorgung. Bei der TOMESA-Therapie werden die Patienten während des Bades in Totes-Meer-Salzwasser mit UV-Licht bestrahlt. Totes-Meer-Salzwasser enthält im Gegensatz zu einer üblichen Salzlösung einen hohen Anteil an Magnesium- und Kalziumionen. **Fazit: Psoriasis vulgaris** *<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 Hin-blick auf die Besserung des Hautbeschwerdebildes und eine Reduktion der unerwünschten Wirkungen / Folgeschäden. Diese Aussage gilt nur für eine Mischung der zur Anwendung kommenden UVB-Spektren bei den Vergleichsinterventionen. (...). Für die Bade-PUVA gibt es Hinweise auf einen Zusatznutzen gegenüber der asynchronen Photosoletherapie (Sole + UVB) im Hinblick auf die Besserung des Hautbeschwerdebildes und eine Reduktion der un-erwünschten Wirkungen/Folgeschäden. Diese Aussage gilt nur für eine Mischung der zur Anwendung kommenden UVB-Spektren bei der Vergleichsintervention (...). Für die Bade-PUVA besteht gegenüber der oralen PUVA ein geringeres Schadenspotenzial bezogen auf akute Nebenwirkungen (Übelkeit und Erbrechen). Es finden sich schwache Hinweise auf ein vermindertes Schadenspotenzial bezogen auf langfristige Folgeschäden (Plattenepithelkar-zinome der Haut). Der Behandlungsaufwand ist prozedural bedingt geringer. Ein gleichwerti-ger Nutzen der asynchronen Bade-PUVA

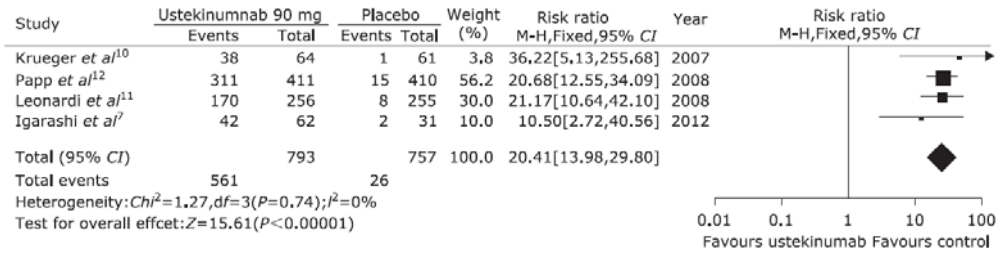
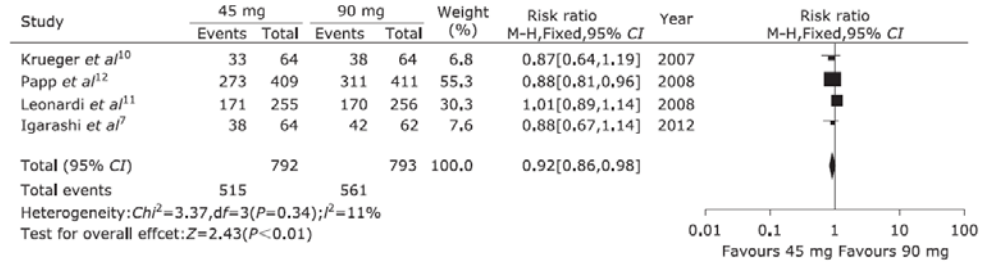
	im Hinblick auf die Besserung des Hautbeschwer-debildes ist allerdings weder belegt noch ausgeschlossen.“ ➔ Die Themengruppe Balneophototherapie des G-BA schloss sich dem Fazit des IQWiG zur Bade-PUVA-Therapie bei Psoriasis vulgaris an. Der Nutzen wurde auf der Basis des IQWiG-Berichtes als belegt angesehen.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

Cochrane Reviews

Es konnten keine Cochrane Reviews zur Fragestellung identifiziert werden.

Systematische Reviews

Liu, 2014 [14] 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 moderate to severe psoriasis Intervention: ustekinumab Komparator: placebo Endpunkte: primary: PASI 75 response rate at the week 12; secondary: adverse events Suchzeitraum (Aktualität der Recherche): bis 11/2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 6 studies (ustekinumab: n= 1012 patients; placebo: n=985 patients) Qualitätsbewertung der Studien: The methodological quality of the trails was assessed by the Jadad scale and high quality studies (Jadad score 5) were included in this study.
	3. Ergebnisdarstellung *Ustekinumab 45 mg vs. placebo (6 studies):* - ustekinumab 45 mg group could get better therapeutic effect compared with the placebo group (*P*<0.00001) - The *RR* was 13.76 and 95% *CI* [8.37, 22.60] *Forest plot of therapeutic effect comparing ustekinumab 45 mg group with the placebo group at 12th week*  *Ustekinumab 90 mg vs. placebo (4 studies):* - ustekinumab 90 mg group could get obviously better therapeutic effect compared with the placebo group (*P*<0.00001)

	- The *RR* was 20.41 and 95% *CI* [13.98, 29.80] *Forest plot of therapeutic effect comparing ustekinumab 90 mg group with the placebo group at 12th week*  *Ustekinumab 45 mg vs. ustekinumab 90 mg (4 studies):* - ustekinumab 90 mg group could get better therapeutic effect compared with ustekinumab 45 mg group (*P*=0.01) - The *RR* was 0.92 and 95% *CI* [0.86, 0.98] *Forest plot of therapeutic effect comparing ustekinumab 45 mg group with 90 mg group at 12th week*  *Adverse events:* - There were no statistically significant differences of these adverse effects among three groups (all *P*>0.05) - except that infection rate in ustekinumab 45 mg group was higher than the placebo group (*P*=0.02).
	4. Anmerkungen/Fazit der Autoren Ustekinumab is an effective and safe therapeutic method for plaque psoriasis. However, further longer time analysis of safety is needed.
Schmitt, 2014 [28] Efficacy and safety of systemic treatments for moderate-to severe psoriasis: meta-analysis	1. Fragestellung The objective of this systematic review was to update and extend our previous review on the comparative efficacy and tolerability of conventional and biological systemic treatments for moderate-to-severe plaque psoriasis by means of direct and indirect meta-analysis.
	2. Methodik Population: patients with moderate to severe psoriasis Intervention: systemic biological treatments and conventional systemic treatments (such as MTX, CSA or fumaric acid esters)

of randomized controlled trials	Komparator: k.A. Endpunkte: primary: PASI 75; secondary: PASI 50, 90 Suchzeitraum (Aktualität der Recherche): 06/2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 48 (n= 16 696 patients (11 178 randomized to biologics, 1 888 to conventional treatments) Qualitätsbewertung der Studien: Risk of bias tool of the Cochrane Collaboration
	3. Ergebnisdarstellung Etanercept (14 studies): • Both high-dose etanercept (50 mg twice weekly) and low-dose etanercept (50 mg once weekly/25 mg twice weekly) were consistently superior to placebo in eight trials • PASI 75 response rates ranged from 40% to 59% in trials investigating high-dose etanercept and from 30% to 45% for low-dose etanercept • In head-to-head trials etanercept 50 mg twice weekly was less efficacious than ustekinumab 90 mg (RD 17%, 95% CI 10–24%) and ustekinumab 45 mg (RD 11%, 95% CI 3–19%), and more efficacious than acitretin. Safety • The rates of withdrawals and adverse events did not differ significantly between etanercept and ustekinumab Infliximab (6 studies): • Infliximab was superior to placebo, with PASI 75 response rates between 68% and 88% • One trial indicated the superiority of infliximab vs. MTX 15 mg (RD 36%, 95% CI 29–43%) Safety: • the rate of adverse events did not differ significantly between infliximab and placebo or between infliximab and MTX in the trials identified Adalimumab (4 studies): • adalimumab for psoriasis, indicating superiority vs. placebo and vs. MTX (initial dose 7.5 mg per week), with PASI 75 response rates between 53% and 80% Safety: • the rate of adverse events did not differ significantly between adalimumab and placebo or between adalimumab and MTX in the trials identified Ustekinumab (5 studies): • Ustekinumab was superior to placebo with PASI 75 response rates in patients receiving ustekinumab 90 mg of between 66% and 76%, and for 45 mg between 59% and 67%. Safety: the risk of adverse events did not differ significantly between ustekinumab and placebo or between ustekinumab and etanercept.
	4. Anmerkungen/Fazit der Autoren

	The evidence base indicating efficacy of the biologics infliximab, adalimumab, ustekinumab and etanercept is much stronger than the evidence for efficacy of conventional treatment options for moderate-to-severe psoriasis.
Meng, 2014 [15] 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 moderate to severe psoriasis Intervention: ustekinumab Komparator: placebo Endpunkte: PASI 50, 75, 90, Dermatology Life Quality Index, adverse events Suchzeitraum (Aktualität der Recherche): 1990-08/2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 9 RCTs (n=11381) Qualitätsbewertung der Studien: To assess the methodological quality of the included studies, we applied the risk of bias tool recommended by the Cochrane Collaboration. We also evaluated the following criteria proposed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group (http://www.gradeworking group.org/): quality of design, risk of bias, inconsistency, indirectness, imprecision and other considerations of the main outcomes.
	3. Ergebnisdarstellung PASI 50 (3 studies): • PASI50 was higher for both ustekinumab doses (45 and 90 mg) than for the placebo (RR = 7.59, 95% CI 5.66–10.17, P <<0.001; RR = 8.22, 95% CI 5.93–11.39, P << 0.001, respectively) • no significant difference in PASI50 between the two doses of ustekinumab (RR = 0.96, 95% CI 0.90–1.03, P = 0.28). PASI 75 (5 studies): • number of patients achieving PASI75 was higher for both ustekinumab 45 and 90 mg than for the 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 the number of patients achieving PASI75 between the two doses of ustekinumab PASI 90 (3 studies): • number of patients achieving PASI90 was higher for both ustekinumab 45 and 90 mg than for the placebo (RR = 21.51, 95% CI 10.22–45.28, P << 0.001; RR = 18.77, 95% CI 8.38–42.04, P << 0.001, respectively) • no significant difference in the number of patients achieving PASI90 between the two doses of ustekinumab DLQI (4 studies): • number of patients achieving DLQI of 0 or 1 was higher for both ustekinumab 45 and 90 mg than for the placebo (RR = 12.66, 95% CI 8.86–18.10, P << 0.001; RR = 12.87, 95% CI 9.01–18.40, P << 0.001,

	respectively • no significant difference in the number of patients achieving DLQI of 0 or 1 between the two doses of ustekinumab AEs (6 studies): • AEs were higher for ustekinumab 45 mg than for placebo, and included headache and back pain. There was no significant difference in the incidence of upper respiratory tract infection (URTI), nasopharyngitis or arthralgia between the two groups
	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.
Choi, 2014 [6] Photodynamic therapy for psoriasis	1. Fragestellung In this review, we will examine the use of photodynamic therapy in psoriasis, highlighting its efficacy, side effects, and current role in the treatment of this chronic disease.
	2. Methodik Population: patiens with psoriasis Intervention: photodynamic therapy (Details in „3. Ergebnissdarstellung“) Komparator: k.A. Endpunkt: k.A. Suchzeitraum (Aktualität der Recherche): Dezember 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 14 (davon 4 RCTs, davon 2 Phase I/II) Qualitätsbewertung der Studien: k.A.
	3. Ergebnisdarstellung (nur RCTs ab Phase III, n = 2) <u>Efficacy of ALA-PDT for psoriasis</u> Studie 1: Randomized, observer-blinded study of topical ALA-PDT on keratolytic pretreated psoriatic plaques randomly allocated to different light doses • 29 patients with chronic plaque psoriasis • before initiation all plaques pretreated with keratolytic preparation containing 10% salicylic acid • treatment sessions: twice weekly until complete clearance or up to 12 irradiations using topical 1% ALA, 600–740 nm light, power density of 60 m/W/cm^2, and the randomly allocated dose of 5, 10, or 20 J/cm^2 • 8 patients withdrew from the study (four due to time constraints, two due to poor compliance, one due to slow response, and one due to pain) – remaining 63 treatment plaques

	• Results: 8 (13%) completely cleared, 4 (6%) substantially improved, 21 (33%) moderately improved, 28 (45%) showed slight or minimal response, 2 (3%) increased in severity • 59% final reduction in the mean psoriasis severity index (PSI) for the 20 J/cm^2 treated plaques, a statistically significant difference compared to those treated with 10 J/cm^2 (46% reduction, p = 0,003) and 5 J/cm^2 (49% reduction, p = 0,02) • all patients experienced stinging or burning, 1 patient discontinued study due to severe pain Radakovic-Fijan S, et al. Topical aminolaevulinic acid-based photodynamic therapy as a treatment option for psoriasis? Results of a randomized, observer-blinded study. Br J Dermatol. 2005;152:279–83. Studie 2: Randomized, placebo-controlled study of topical ALA-PDT on keratolytic pretreated chronic psoriatic plaques • 8 patients with were enrolled • prior to therapy, lesions were pretreated with 10% salicylic acid for 1 week • treatment: topical 10% ALA or the placebo vehicle, sessions weekly for 4 weeks using 600–750 nm light and power density of 40 m/W/cm^2, plaques first treated with a dose of 2 J/cm^2 followed by another dose of 8 J/cm^2 • results: statistically significant decrease in the mean plaque severity score of the ALA-treated plaques versus placebo (p = 0,009), but minimal or completely clear results not achieved, 2 ALA treated plaques increased in total psoriatic surface area • generally well-tolerated with some patients experiencing mild burning and stinging Smits T, et al. A placebo controlled randomized study on the clinical effectiveness, immune histochemical changes and protoporphyrin IX accumulation in fractionated 5-aminolaevulinic acid-photodynamic therapy in patients with psoriasis. Br J Dermatol. 2006;155:429–36. <u>Side effects</u> • some patients experienced worsening of plaque psoriasis in PDT-treated areas, possibly due to Koebnerization
	4. Anmerkungen/Fazit der Autoren With the current landscape of phototherapy dominated by psoralen combined with ultraviolet A (PUVA) and narrow-band ultraviolet B (NB-UVB), an alternative light therapy utilizing the visible spectrum is certainly promising and a worthwhile endeavor to pursue. 5. *Im Einzelfall*: Hinweise durch FB Med) • *Declaration of interest: J. J. W. received research funding from AbbVie, Amgen, Coherus Biosciences, Eli Lilly, Merck, Pfizer, and Sandoz; he is a consultant for Eli Lilly. Y. M. C. and L. A. do not have any potential conflicts of interest.* • *Keine Angaben zur Finanzierung der Arbeit* • *Keine Angaben zur Schwere der Psoriasis*
Busard, 2014	1. Fragestellung

[3] Combined Use of Systemic Agents for Psoriasis A Systematic Review	To summarize and critically appraise the evidence on efficacy and safety of combination therapy with systemic agents in plaque-type psoriasis.
	2. Methodik Population: patients with psoriasis Intervention*:* combination therapy with systemic agents Komparator: systemic monotherapy or another systemic combination therapy Endpunkte: PASI 75, PASI 90, Physician Global Assessment (PGA), AEs, SAEs, DLQI Suchzeitraum (Aktualität der Recherche): bis 03/2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 17 (n=1071) Qualitätsbewertung der Studien: The risk of bias in the individual studies was assessed in duplicate using the Cochrane Risk of Bias tool. The quality of evidence for each outcome (body of evidence) was assessed according to the GRADE approach Assessment of the risk of bias of the individual studies resulted in low risk for 3 trials, intermediate risk for 5 trials high risk for 9 trials.
	3. Ergebnisdarstellung • Etanercept plus methotrexate was the only combination therapy investigated with an adequate sample size (n = 478). • In the short term, this combination had superior efficacy with a moderate quality of evidence compared with etanercept monotherapy (Psoriasis Area and Severity Index, 75; relative risk, 1.28; 95%CI, 1.14-1.45). Although this finding coincided with an increase in adverse events (relative risk, 1.25; 95%CI, 1.10-1.42), the overall safety profile remained acceptable.
	4. Anmerkungen/Fazit der Autoren This systematic review provides a comprehensive overview on the validity of different systemic combination therapies. For most combinations, insufficient evidence is available. Initial results indicate that combined therapy with etanercept plus methotrexate may be beneficial in patients that are therapy resistant under intensive follow-up. Dose reductions should be taken into account to minimize adverse effects.
Almutawa, 2013 [1] Systematic Review of UV-Based Therapy for Psoriasis	1. Fragestellung The aim of the study was to evaluate the efficacy, short-term safety, and tolerability of UV-based therapy in the treatment of adults with moderate to severe plaque psoriasis.
	2. Methodik We performed a systematic review and metaanalysis of randomized controlled trials (RCTs)**.** **Population:** Adults with moderate to severe plaque-type psoriasis **Intervention/Komparator:** NB-UVB, BB-UVB, and PUVA **Endpunkt:** Psoriasis Area and Severity Index (PASI)-75, clearance, short-term safety, tolerability from the percentage of adverse effects and withdrawal due to

	adverse effects **Suchzeitraum:** 1980 to 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 41 RCTs (N=2.416 patients)
	3. Ergebnisdarstellung: <u>Efficacy:</u> PASI-75: In monotherapy trials, PUVA was the most effective modality (mean: 73 %, 95 % CI 56–88). Trials with BB-UVB also showed a high PASI-75 (73 %) but with a wide CI (18–98) due to heterogeneity of the total available three studies. This was followed by NB-UVB (mean: 62 %, 95 % CI 45–79) then bath PUVA (mean: 47 %, 95 % CI 30–65). Clearance: In the monotherapy trials, PUVA (mean: 79 %, 95 % CI 69–88) was superior to NB-UVB (mean: 68 %, 95 % CI 57–78), BB-UVB (mean: 59 %, 95 % CI 44–72), and bath PUVA (mean: 58 %, 95 % CI 44–72). <u>Safety:</u> The percentages of asymptomatic erythema development in monotherapy trials were 64 % for BB-UVB, 57 % for NB-UVB, 45 % for PUVA, and 34 % for bath PUVA. Symptomatic erythema or blistering percentages for the monotherapy trials were as follows: 7.8 % for NB-UVB, 2 % for BB-UVB, 17 % for PUVA, and 21 % for bath PUVA. <u>Withdrawal due to adverse effects:</u> The percentages of withdrawal due to adverse effects were 2 % for NB-UVB, 4.6 % for BB-UVB, 5 % for PUVA, and 0.7 % for bath PUVA monotherapy trials.
	4. Fazit der Autoren As a monotherapy, PUVA was more effective than NB-UVB, and NB-UVB was more effective than BB-UVB and bath PUVA in the treatment of adults with moderate to severe plaque-type psoriasis, based on clearance as an end point. Based on PASI-75, the results were similar except for BB-UVB, which showed a high mean PASI-75 (73 %) that was similar to PUVA, but with a wide CI (18–98). The short-term adverse effects were mild as shown by the low rate of withdrawal due to adverse effects.
Gisondi, 2013 [10] Impact of TNF-alpha antagonists on the quality of life in selected skin diseases	**1. Fragestellung** Aim of the study was to investigate the impact of TNF-alpha antagonists on health-related quality of life (HRQoL) in selected skin diseases, i.e. chronic plaque psoriasis, Behcet's disease (BD), hidradenitis suppurativa (HS) and pyoderma gangrenosum (PG).
	2. **Methodik:** systematic literature search Population: adults with psoriasis, BD, HS or PG Intervention: TNF-alpha antagonists (adalimumab, etanercept and infliximab) Komperator: placebo Endpunkt: HRQoL

	Datenbank und Suchzeitraum: Medline (2000 to April 2013) Studiendesign: RCT Anzahl der eingeschlossenen Studien/Patienten (gesamt): 13
	3. Ergebnisdarstellung • skin diseases can affect physical, psychological, social and occupational aspects of everyday life • TNF-alpha antagonists induced consistent benefits across health outcomes in psoriasis • Dermatology Life Quality Index most common used tool for investigating HRQoL • most important negative impacts on QoL appearance related • burden on QoL correlated to the severity of skin disease • improvement in QoL achieved by TNF-alpha blockers was proportional to the degree of disease remission
	4. Anmerkungen/Fazit der Autoren HRQoL issues are becoming even more important in evaluating medical care, including treatment of skin diseases. In general, achieving the highest clearing of skin disease with anti-TNF-alpha agents is required for optimal improvement in QoL *Hinweise durch FB Med:* • *no information about funding and CoI* • *quality of included studies not addressed* • *publication bias not mentioned*
Canadian Agency for Drugs and Technologies in Health (CADTH), 2012 [4] Infliximab versus methotrexate, etanercept, adalimumab, and ustekinumab for plaque psoriasis: a review of the comparative	1. Fragestellung 1. What is the comparative clinical efficacy of infliximab versus methotrexate, etanercept, adalimumab or ustekinumab for the treatment of adults with plaque psoriasis? 2. What is the comparative safety of infliximab versus methotrexate, etanercept, adalimumab or ustekinumab for the treatment of adults with plaque psoriasis? …
	2. Methodik: systematic literature search, review **Population** Adults with plaque psoriasis **Intervention** Infliximab **Comparator** Methotrexate, etanercept, adalimumab, ustekinumab **Outcomes** Clinical effectiveness, length of effect, number of treatments for control of symptoms, adverse events, cost effectiveness **Study Designs** Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), economic evaluations **Suchzeitraum**: 2007 – 2012 (27. Juni) **Anzahl der eingeschlossenen Studien/Patienten** (gesamt): 12/n = k.A.

clinical efficacy, safety and cost effectiveness. Rapid Resonse Report	3. Ergebnisdarstellung • 6 systematic reviews,1 open-label RCT included • All systematic reviews based on comprehensive literature searches • meta-analyses performed using RCTs • methodology used to pool data well detailed and appropriate • 3 meta-analyses employed mixed-treatment comparison evidence synthesis • other studies compared each treatment to placebo individually • scientific quality of included studies was assessed in 3 of the 6 reviews • publication bias was not assessed in any of the systematic reviews • weakness of all of the systematic reviews: the lack of head-to-head trials included as majority of existing trials are placebo-controlled • RCT described adequate method of randomization and losses to follow-up • active comparator used rather than placebo and all patients received assigned treatments • weakness: lack of blinding in patients and outcome assessors, which may bias efficacy and safety results • patients were able to switch between treatments if necessary, which may affect reported adverse events due to an imbalance in study medication exposure • no statistical analysis performed for the safety data, making it difficult to compare numbers between the two treatment groups
	4. Anmerkungen/Fazit der Autoren According to meta-analyses of placebo-controlled RCT trials, infliximab at a dose of 5 mg/kg appears to be more effective than methotrexate, etanercept, adalimumab, and ustekinumab for achieving PASI 75 in patients with moderate-to-severe plaque psoriasis. One open-label RCT found infliximab to be more effective than methotrexate. Limited evidence was identified regarding the comparative safety of infliximab versus methotrexate, etanercept, adalimumab, and ustekinumab. Infliximab was found to be associated with an increase in the incidence of adverse events when compared with placebo, and with a slight increase when compared to 50 mg etanercept or methotrexate. *Hinweise durch FB Med:* • *Governmental funding* • *CoI not declared* • *quality of included studies assessed by standardized tools* • *publication bias discussed*
Lee, 2012 [12] Biologic and nonbiologic systemic	1. Fragestellung To examine the comparative effectiveness of biologic systemic agents versus nonbiologic systemic agents or phototherapy, on an individual drug level, for treatment of chronic plaque psoriasis (CPP) and to determine patient and disease characteristics that modify outcomes of interest.

agents and phototherapy for treatment of chronic plaque psoriasis

2. Methodik

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

3. Ergebnisdarstellung

Effektivität:

Systemic biologic agents versus systemic nonbiologic agents:

Comparison	Outcome*	Type and Number of Studies	Conclusion	SOE
Adalimumab versus methotrexate	HRQoL	1 RCT[30] 1 OBS[23]	Adalimumab improves a patient's HRQoL compared with methotrexate.	L
	PASI	1 RCT[13] 1 OBS[23]	Adalimumab improves a patient's PASI compared with methotrexate.	L
	PGA	1 RCT[113] 1 OBS[23]	Adalimumab increases the number of patients achieving a PGA of "clear" or "minimal" compared with methotrexate.	L
	Patient's assessment of disease severity	1 RCT[30]	Adalimumab improves a patient's assessment of disease severity compared with methotrexate.	L
	Pain	1 RCT[30]	Adalimumab reduces a patient's pain compared with methotrexate.	L
	Pruritus	1 RCT[30]	Adalimumab reduces a patient's pruritus compared with methotrexate.	L
	Infection	1 RCT[13]	Infection rates do not differ between adalimumab and methotrexate.	L
Etanercept versus acitretin	PASI	3 RCT[17-19]	Etanercept improves a patient's PASI compared with acitretin.	M
Infliximab versus methotrexate	HRQoL	1 RCT[15]	Infliximab improves a patient's HRQoL compared with methotrexate.	L
	PASI	1 RCT[15] 1 OBS[21]	Infliximab improves a patient's PASI compared with methotrexate.	L
	PGA	1 RCT[15]	Infliximab increases the number of patients achieving a PGA of "clear" or "minimal" compared with methotrexate.	L
Ustekinumab versus methotrexate	PGA	1 OBS[23]	Ustekinumab increases the number of patients achieving a PGA of "clear" or "minimal" compared with methotrexate.	L

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

Systemic (non)biologic agents and phototherapy: No RCTs evaluated the comparative effectiveness of systemic biologic agents and phototherapy on any

	outcomes. Sicherheit: Systemic biologic agents and systemic nonbiologic agents or phototherapy: Overall five RCTs (two good, two fair, and one poor quality) and two observational studies (both fair quality) directly compared biologics with nonbiolgics and reported at least one adverse outcome of interest. No trials or observational studies directly compared biologics with phototherapy in the evaluation of harms. Infection rate did not differ between adalimumab and methotrexate (low strength of evidence). These data were from a single RCT conducted outside the United States in patients with moderate to severe chronic plaque psoriasis naïve to TNF-alpha antagonists or methotrexate. There was insufficient evidence for other reported outcomes.
	4. Fazit der Autoren In patients with CPP, there were limited data directly comparing systemic biologic agents with either systemic nonbiolgic agents or with phototherapy on an individual drug level. Overall there is insufficient evidence to determine the comparative effectiveness of individual therapies, as compared with each other between the specified classes, with few exceptions. For the comparisons of adalimumab versus methotrexate, infliximab versus methotrexate, ustekinumab versus methotrexate, and etanercept versus acitretin, there is predominantly low strength of evidence favoring the individual biologic agent versus the nonbiologic agent. Additional trials directly comparing biologic systemic agents, systemic nonbiologic agents, and phototherapy are needed. *Hinweise durch FB Med:* • *Governmental funding* • *CoI not declared* • *quality of included studies assessed by standardized tools* • *keine Angaben zur Schwere der Psoriasis*
Reich, 2012 [26] Efficacy of biologics in the treatment of moderate to severe psoriasis: a network meta-analysis of randomized controlled trials	Auf eine Extraktion der Ergebnisse wurde verzichtet, da die Arbeit im “Canadian Agency for Drugs and Technologies in Health (CADTH), 2012: Infliximab versus methotrexate, etanercept, adalimumab, and ustekinumab for plaque psoriasis: a review of the comparative clinical efficacy, safety and cost effectiveness. Rapid Resonse Report.” eingeschlossen ist.
Baker, 2012 [2]	1. Fragestellung Evaluating the impact of biologics on non-Psoriasis Area and Severity Index

Effect of Biologic Agents on Non-PASI Outcomes in Moderate-to-Severe Plaque Psoriasis: Systematic Review and Meta-Analyses	(PASI) health outcomes in patients with moderate-to-severe plaque psoriasis.
	2. Methodik: Systematische Übersichtsarbeit mit Mixed-Treatment Comparison **Population**: Patients with moderate-to-severe plaque psoriasis **Intervention**: alefacept, efalizumab, infliximab, adalimumab, etanercept, ustekinumab, briakinumab **Komparator**: Placebo **Endpunkte**: PGA Static Response Rate; PGA Dynamic Response Rate **Suchzeitraum**: 1966 bis Mai 2009 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 31 Studien/n = k.A.
	3. Ergebnisdarstellung alefacept versus placebo (n = 5); efalizumab versus placebo (n = 7); infliximab versus placebo (n = 6); adalimumab versus placebo (n = 5); etanercept versus placebo (n = 4); ustekinumab versus placebo (n = 3); briakinumab versus placebo (n = 1) **PGA Static Response Rate:** • All biologics showed significant improvement in achieving a good response on the static physician's global assessment (PGA) versus placebo while, in the MTC, differences were noted between individual drugs. **PGA Dynamic Response Rate:** • In achieving a good response on the dynamic PGA, all biologics showed significant improvements over placebo, while the MTC showed significant improvements with the antiinterleukins versus anti-T cells. **Change in DLQI from Baseline and Change in SF-36 from Baseline:** • Relative to placebo, antitumor necrosis factor (TNF) agents and anti-interleukins showed significant improvements in the Dermatology Life Quality Index (DLQI). • Compared with placebo, the anti-TNF agents showed significant improvements in both 36-item Medical Outcomes Study Short-Form General Health Survey (SF-36) mental and physical component scores, while anti-T cell agents showed no improvements. The MTC showed no differences between any biologics for either the DLQI or SF-36.
	4. Anmerkungen/Fazit der Autoren Individual biologics and classes showed consistent benefits across non-PASI health outcomes in patients with moderate-to severe plaque psoriasis while MTC metaanalyses suggested that some differences exist. Anti-TNF agents, as well as anti-IL 12/23 agents, significantly improve clinical efficacy (via the PGA) and HRQoL (via the DLQI) as compared with the anti-T cell agents in patients with moderate-to-severe plaque psoriasis. *Hinweise durch FB Med:* • *einige der untersuchten Wirkstoffe nicht (mehr) zugelassen* • *study supported in part by a contract from Pfizer Inc.* • *Conflict of interest. C.M.M. and J.C.C. employed by Pfizer Inc. No other*

	authors report significant conflicts of interest germane to this project. • *validated Jadad scale used to assess methodological quality of included trials* • *statistical and clinical heterogeneity and publication bias assessed and discussed: "Due to the low number of studies included in many of the analyses, statistical heterogeneity and publication bias could not be determined."*
Lin, 2012 [13] Comparison of Ustekinumab With Other Biological Agents for the Treatment of Moderate to Severe Plaque Psoriasis	1. Fragestellung To compare the efficacy of ustekinumab with that of other biological agents using the Psoriasis Area and Severity Index (PASI) among adult patients with moderate to severe plaque psoriasis.
	2. Methodik **Population**: Adult patients with moderate to severe plaque psoriasis **Intervention**: Biological agents (Adalimumab, Elefacept, Etanercept, Infliximab, Ustekinumab) **Komparator**: Biological agents or placebo **Endpunkte**: 75% reduction in the PASI Suchzeitraum: 1992 - 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 17/n = k.A.
	3. Ergebnisdarstellung • Ustekinumab use was associated with statistically significantly higher odds for achieving PASI 75 compared with adalimumab use (OR, 1.84; 95% credible interval [CI], 1.01-3.54), alefacept use (10.38; 3.44-27.62), and etanercept use (2.07; 1.42-3.06). • Ustekinumab use was associated with lower odds for achieving PASI 75 compared with infliximab use (OR, 0.36; 95% CI, 0.14-0.82). • Infliximab had the highest odds for PASI 75 response compared with adalimumab (5.04; 2.40-14.09), alefacept (28.33; 8.24-94.05), etanercept (5.67; 2.70-14.98), and ustekinumab (2.77; 1.28-7.14). • In the therapeutic class comparison, the interleukin-12/23 inhibitor had the highest odds for achieving a 75% reduction in the PASI compared with placebo (OR, 69.48; 95% CI, 36.89-136.46), followed by tumor necrosis factor inhibitors (OR, 42.22; 95% CI, 27.94-69.34) and the T-cell inhibitor (OR, 5.63; 95% CI, 1.35-24.24).
	4. Anmerkungen/Fazit der Autoren In conclusion, the use of a Bayesian network metaanalysis enabled us to compare the efficacy of ustekinumab with that of other biological agents using PASI responses as the outcome among adult patients with moderate to severe plaque psoriasis during the induction phase of the first 10 to 16 weeks. Ustekinumab, the newest agent that targets IL-12/23, seems to be more efficacious than adalimumab, etanercept, and alefacept but not infliximab. Für die Behandlung von mittelschwerer bis schwerer Plaque-Psoriasis, kann

	Ustekinumab wirksamer sein als Adalimumab, Etanercept und Alefacept aber nicht als Infliximab. *Hinweise durch FB Med:* • *no funding information* • *Conflict of Interest Disclosures: Dr Lin was supported by an unrestricted postdoctoral fellowship from the University of Washington. Dr Ringold was supported by grant K12HS019482 from the Agency for Healthcare Research and Quality.* • *validated Jadad scale used to assess methodological quality of included trials* • *existence of heterogeneity taken into account for model-selection* • *No publication bias assessed because it is challenging to do so in a Bayesian network meta-analysis and requires further research.*
Girolomoni, 2012 [9] Safety of anti-TNFalpha agents in the treatment of psoriasis and psoriatic arthritis	1. Fragestellung This review presents and discusses current evidence on the safety of anti-TNFα agents in patients with psoriasis and PsA, with a focus on European registry studies and case reports of particular importance.
	2. Methodik: systematische Übersichtsarbeit **Population**: Patients with psoriasis or psoriatic arthritis **Intervention/Komperator**: anti TNF-alpha agents (adalimumab, certolizumab, etanercept, golimumab, infliximab) **Endpunkte**: safety issues (infections, cancer, other) **Studiendesign**: RCT, phase III, post-marketing study or registry Suchzeitraum und Datenbank: MEDLINE (last updated 10 Nov 2011)
	3. Ergebnisdarstellung • mature data available for adalimumab, etanercept, and infliximab, though in most cases these data are derived from anecdotal reports or registry studies from Europe and other non-European countries • data appear reassuring, some concerns still exist • data suggest a higher incidence of infection and lymphoma amongst patients treated with infliximab and adalimumab compared with etanercept
	4. Anmerkungen/Fazit der Autoren *The overall safety profile of monoclonal antibodies in patients with psoriasis, PsA and RA seems less favorable than that of etanercept, particularly in terms of risk of infection and hepatotoxicity.*
Dommasch, 2011 [7] The risk of infection and	1. Fragestellung Examine the risks of infection and malignancy with the use of TNF antagonists in adult patients with psoriatic disease.
	2. Methodik

malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials	**Population**: Adults with plaque psoriasis **Intervention**: TNF antagonists (etanercept, infliximab, adalimumab, golimumab, and certolizumab) **Komparator**: Placebo **Endpunkte**: malignancy and infection Suchzeitraum: Beginn bis 30 Juli 2009 Anzahl eingeschlossene Studien/Patienten (Gesamt): 20 RCTs/n = 6 810
	3. Ergebnisdarstellung • ORs for overall infection and serious infection over a mean of 17.8 weeks were 1.18 (95% CI: 1.05, 1.33) and 0.70 (95% CI: 0.40, 1.21), respectively. • When adjusting for patient years, the incidence rate ratio for overall infection was 1.01 (95% CI: 0.92, 1.11). • The OR for malignancy was 1.48 (95% CI: 0.71, 3.09), and 1.26 (95% CI: 0.39, 4.15) when non-melanoma skin cancer was excluded.
	4. Anmerkungen/Fazit der Autoren Es besteht ein gering erhöhtes Risiko für die Gesamtinfektion mit dem kurzfristigen Einsatz von TNF-Antagonisten zur Psoriasis Behandlung, was auf die Unterschiede in Follow-up-Zeit zwischen Behandlungs- und Placebogruppen zuzuschreiben ist. Es gab keine Hinweise auf ein erhöhtes Risiko für schwerwiegende Infektionen und ein statistisch signifikant erhöhtes Risiko für Krebs wurde mit den kurzfristigen Einsatz von TNF Inhibitoren nicht beobachtet. *Hinweise durch FB Med:* • *Auch für die einzelnen Arzneistoffe zeigte sich kein signifikanter Unterschied* • *Funding Sources: Supported in part by grant K23AR051125 from the National Institute of Arthritis, Musculoskeletal, and Skin Diseases (JMG) and a National Research Service Award from the National Institute of Health (EDD).* • *Financial Disclosures: Dr. Gelfand receives grant support and is an investigator for Amgen and Pfizer. He is a consultant for Pfizer, Genentech, Celgene, Amgen, Centocor, and Luitpold. Dr. Dommasch, Dr. Abuabara, Mr. Shin, Dr. Nguyen, and Dr. Troxel have no relevant financial relationships to declare.* • *validated Jadad scale used to assess methodological quality of included trials* • *statistical heterogeneity addressed*
Montaudie, 2011 [18] Methotrexate in psoriasis: a	1. Fragestellung Q1 What are the optimal prescription and administration methods for using MTX in adult plaque-type psoriasis? …

systematic review of treatment modalities, incidence, risk factors and monitoring of liver toxicity	2. Methodik **Population**: adults with psoriasis and psoriatic arthritis **Intervention**: methods of administering MTX **Komparator**: k.A. **Endpunkte**: efficacy, risk factors and assessment of liver toxicity **Suchzeitraum und Datenbanken**: • systematic literature search carried out in Medline, Embase and Cochrane Library • search period: from 1980 to 2010 **Studienkriterien** • RCTs and observational studies, human subjects over 19 years of age, articles in English or French, original data **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 23 published studies
	3. Ergebnisdarstellung • no studies focusing directly on the question of MTX treatment modalities (starting dose or dose increments) • no study compared subcutaneous vs. oral administration in the management of psoriasis • data from six RCT designed to measure the efficacy of MTX in plaque-type psoriasis analyzed • treatment outcome appears to be dose dependent.
	4. Anmerkungen/Fazit der Autoren Based on expert experience, the starting dose of MTX is between 5 and 10 mg ⁄ week for the first week. Fast dose escalation is recommended in order to obtain a therapeutic target dose of 15–25 mg⁄ week. The maximum recommended dose is 25 mg⁄ week. A folic acid supplement is necessary. The initiation of treatment by oral administration is preferred. In cases where inadequate response is obtained or in the event of poor gastrointestinal tolerance, subcutaneous dosing can be proposed at the same dose.
Sbidian, 2011 [27] Efficacy and safety of oral retinoids in different psoriasis subtypes: a systematic literature review	1. Fragestellung 1 To determine the optimal dosing strategy of systemic retinoid therapy in patients with psoriasis of either plaque type (PV), nail, localized and pustular forms. 2 To evaluate the safety profile of systemic retinoid treatment regarding skeletal toxicity.
	2. Methodik **Population**: adults with psoriasis **Intervention**: retinoids (various dosages) **Komparator**: k.A. **Endpunkte**: efficacy, skeletal toxicity • systematic literature search carried out in MEDLINE, EMBASE, and

	Cochrane Library • search period: from 1975 to 2010 • inclusion criteria: RCTs, observational studies, human subjects, English/French languages Anzahl eingeschlossene Studien/Patienten (Gesamt): 44 trials for efficacy, 15 for potential skeletal toxicity
	3. Ergebnsidarstellung • starting daily dosages between 10 and 25 mg and stepwise escalation associated with higher clinical efficacy and lower incidence of adverse events in comparison with higher doses and regimens rapidly reaching optimal dose • single agent therapy appeared to show limited efficacy in PV • combining with phototherapy appeared to be highly effective in PV • no strong evidence of an increased risk of skeletal abnormalities in psoriasis patients treated with retinoids.
	4. Anmerkungen/Fazit der Autoren Acitretin is also a treatment option for moderate-to-severe plaque psoriasis primarily through combination regimens with UV light. Low to intermediate doses of acitretin e.g. equal or less than 25 mg/day only result in few side-effects and are safe in both the short-term and long-term treatments of psoriasis.

	1. Ergebnisdarstellung Overall, there were six different general treatment comparisons. Two RCTs compared ultraviolet wavelength sources, five RCT compared different forms of phototherapy, four RCTs compared phototherapy monotherapy with phototherapy and balneotherapy (i.e. prior spa saline bathing), nine RCTs combined phototherapy with topical agents, and two RCTs combined phototherapy with systemic immunosuppressive agents (methotrexate or alefacept), one RCT compared phototherapy with an excimer laser as additional light source, and one RCT compared phototherapy monotherapy with a combination of phototherapy and audiotape intervention involving mindfulness and stress reduction. Two RCT trials examined the effect of treatment setting on the effectiveness of phototherapy, one involved inpatient versus outpatient treatment; the other compared outpatient clinic treatment to home-based phototherapy. RCT Evidence for Ultraviolet Phototherapy Treatment of Moderate-To-Severe Plaque Psoriasis: • Phototherapy is an effective treatment for moderate-to-severe plaque psoriasis (Moderate quality and adequate study evidence). • Narrow band PT is more effective than broadband PT for moderate-to-severe plaque psoriasis (High quality but limited study evidence) • Oral-PUVA has a greater clinical response, requires fewer treatments and has a greater cumulative UV irradiation dose than UVB to achieve treatment effects for moderate-to-severe plaque psoriasis (High quality and adequate study evidence) • Spa salt water baths prior to phototherapy increases the short-term clinical response of moderate-to-severe plaque psoriasis but does not decrease cumulative UV irradiation dose (High quality and adequate study evidence) • Addition of topical agents (vitamin D3 calcipotriol) to NB-UVB did not increase mean clinical response or decrease treatments or cumulative UV irradiation dose (High quality and adequate study evidence) • Methotrexate prior to NB-UVB in high need psoriasis patients significantly increases clinical response, decreases number of treatment sessions, and decreases cumulative UV irradiation dose (High quality but limited study evidence) • Phototherapy following alefacept increases the early clinical response in moderate-to-severe plaque psoriasis (Inadequate study evidence) • Effectiveness and safety of home NB-UVB phototherapy is not inferior to NB-UVB phototherapy provided in a clinic to patients with psoriasis. Treatment burden is lower and patient satisfaction higher with home therapy and patients in both groups prefer future phototherapy treatments at home (High quality study but limited study evidence)

	4. Fazit der Autoren In summary, phototherapy provides good control of clinical symptoms in the short term for patients with moderate-to-severe plaque-type psoriasis that have failed or are unresponsive to management with topical agents. However, many of the evidence gaps identified in the NIHR 2000 evidence review on psoriasis management persisted. In particular, the lack of evidence on the comparative effectiveness and/or cost-effectiveness between the major treatment options for moderate-to-severe psoriasis remained. The evidence on effectiveness and safety of longer term strategies for disease management has also not been addressed. Evidence for the safety, effectiveness, or cost-effectiveness of phototherapy delivered in various settings is emerging but is limited. In addition, because all available treatments for psoriasis – a disease with a high prevalence, chronicity, and cost – are palliative rather than curative, strategies for disease control and improvements in self-efficacy employed in other chronic disease management strategies should be investigated.

Leitlinien

National Institute for Health and Clinical Excellence (NICE), 2012 [21] Assessment and management of psoriasis	Fragestellung In people with psoriasis (all types), what are the clinical effectiveness, safety, tolerability and cost effectiveness of BBUVB, NBUVB and PUVA compared with each other or placebo/no treatment? In people with psoriasis (all types), what are the clinical effectiveness, safety, tolerability and cost effectiveness of acitretin plus UVB (NBUVB and BBUVB) and acitretin plus PUVA compared with their monotherapies and compared with each other? In people with psoriasis (all types), what are the clinical effectiveness, safety, tolerability and cost effectiveness of UVB (NBUVB or BBUVB) combined with dithranol, coal tar or vitamin D and vitamin D analogues compared with UVB alone or topical therapy alone? In people with psoriasis (all types), what are the clinical effectiveness, safety, tolerability and cost effectiveness of systemic methotrexate, ciclosporin and acitretin compared with each other or with placebo? … In people with chronic plaque psoriasis eligible to receive biologics, if the first biological fails, which is the next effective, safe and cost effective strategy? …
	Methodik Grundlage der Leitlinie: NICE Guidelines Manual 2009 (Formulierung klinischer Fragestellungen und Endpunkte apriori, systemtaische Recherchen, Bewertung der Literatur anhand GRADE,

	Konsensusprozess ohne Beschreibung formaler Verfahren) Suchzeitraum: bis März 2012 *Weitere Kriterien für die Qualität einer LL:* • *alle eingeschlossenen Studien in Evidenztabellen dargestellt* LoE: nach GRADE, GoR: Formulierung Sonstige methodische Hinweise • *governmental funding* • *CoI declared*
	Freitext/Empfehlungen/Hinweise **General recommendations** 25. Offer people with psoriasis topical therapy as first-line treatment. Offer second- or third-line treatment options (phototherapy or systemic therapy) at the same time when topical therapy alone is unlikely to adequately control psoriasis, such as: - extensive disease (for example more than 10% of body surface area affected) or - at least 'moderate' on the static Physician's Global Assessment or - where topical therapy is ineffective, such as nail disease. **Phototherapy (broad- or narrow-band (UVB) light and PUVA)** 60. Offer narrowband ultraviolet B (UVB) phototherapy to people with plaque or guttate-pattern psoriasis that cannot be controlled with topical treatments alone. Treatment with narrowband UVB phototherapy can be given 3 or 2 times a week depending on patient preference. Tell people receiving narrowband UVB that a response may be achieved more quickly with treatment 3 times a week. 61. Offer alternative second- or third-line treatment when: - narrowband UVB phototherapy results in an unsatisfactory response or is poorly tolerated or - there is a rapid relapse following completion of treatment (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months) or - accessing treatment is difficult for logistical reasons (for example, travel, distance, time off work or immobility) or - the person is at especially high risk of skin cancer. **Systemic nonbiological therapy** 81. Offer systemic non-biological therapy to people with any type of psoriasis if: - it cannot be controlled with topical therapy and - it has a significant impact on physical, psychological or social

	wellbeing and • one or more of the following apply: - psoriasis is extensive (for example, more than 10% of body surface area affected or a Psoriasis Area and Severity Index (PASI) score of more than 10) or - psoriasis is localised and associated with significant functional impairment and/or high levels of distress (for example severe nail disease or involvement at high-impact sites) or - phototherapy has been ineffective, cannot be used or has resulted in rapid relapse (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months). **Choice of drugs** 82. Offer methotrexate[ttt] as the first choice of systemic agent for people with psoriasis who fulfil the criteria for systemic therapy (see recommendation 81) except in the circumstances described in recommendations 84 and 92. … 84. Offer ciclosporin[uuu] as the first choice of systemic agent for people who fulfil the criteria for systemic therapy (see recommendation 81) and who: - need rapid or short-term disease control (for example a psoriasis flare) or - have palmoplantar pustulosis or - are considering conception (both men and women) and systemic therapy cannot be avoided. 85. Consider changing from methotrexate to ciclosporin (or vice-versa) when response to the first-choice systemic treatment is inadequate. 86. Consider acitretin for adults, and in exceptional cases only for children and young people, in the following circumstances: - if methotrexate and ciclosporin are not appropriate or have failed or - for people with pustular forms of psoriasis. [ttt] At the time of publication (October 2012), methotrexate did not have UK marketing authorisation for this indication in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information. [uuu] At the time of publication (October 2012), ciclosporin did not have

	UK marketing authorisation for this indication in children and young people under 16 years of age. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information. **Systemic biological therapy** … **Adalimumab** The recommendations in this section are from Adalimumab for the treatment of adults with psoriasis (NICE technology appraisal guidance 146). 100. Adalimumab is recommended as a treatment option for adults with plaque psoriasis for whom anti-tumour necrosis factor (TNF) treatment is being considered and when the following criteria are both met. • The disease is severe as defined by a total PASI of 10 or more and a DLQI of more than 10. • The psoriasis has not responded to standard systemic therapies including ciclosporin, methotrexate and PUVA; or the person is intolerant of, or has a contraindication to, these treatments. 101. Adalimumab should be discontinued in people whose psoriasis has not responded adequately at 16 weeks. An adequate response is defined as either: • 75% reduction in the PASI score (PASI 75) from when treatment started or • 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from start of treatment. **Etanercept** The recommendations in this section are from Etanercept and efalizumab for the treatment of adults with psoriasis (NICE technology appraisal guidance 103). 102. Etanercept, within its licensed indications, administered at a dose not exceeding 25 mg twice weekly is recommended for the treatment of adults with plaque psoriasis only when the following criteria are met. • The disease is severe as defined by a total PASI of 10 or more and a DLQI of more than 10. • The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA; or the person is intolerant to, or has a contraindication to, these treatments.

	103. Etanercept treatment should be discontinued in patients whose psoriasis has not responded adequately at 12 weeks. Further treatment cycles are not recommended in these patients. An adequate response is defined as either: • a 75% reduction in the PASI score from when treatment started (PASI 75) or • a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from when treatment started. **Infliximab** The recommendations in this section are from Infliximab for the treatment of adults with psoriasis (NICE technology appraisal guidance 134). 104. Infliximab, within its licensed indications, is recommended as a treatment option for adults with plaque psoriasis only when the following criteria are met. • The disease is very severe as defined by a total PASI of 20 or more and a DLQI of more than 18. • The psoriasis has failed to respond to standard systemic therapies such as ciclosporin, methotrexate or PUVA, or the person is intolerant to or has a contraindication to these treatments. 105. Infliximab treatment should be continued beyond 10 weeks only in people whose psoriasis has shown an adequate response to treatment within 10 weeks. An adequate response is defined as either: • a 75% reduction in the PASI score from when treatment started (PASI 75) or • a 50% reduction in the PASI score (PASI 50) and a five-point reduction in the DLQI from when treatment started. **Ustekinumab** The recommendations in this section are from Ustekinumab for the treatment of adults with moderate to severe psoriasis (NICE technology appraisal guidance 180). 106. Ustekinumab is recommended as a treatment option for adults with plaque psoriasis when the following criteria are met. • The disease is severe, as defined by a total PASI score of 10 or more and a DLQI score of more than 10. • The psoriasis has not responded to standard systemic therapies, including ciclosporin, methotrexate and PUVA, or the person is intolerant of or has a contraindication to these treatments. • The manufacturer provides the 90 mg dose (two 45 mg vials) for people who weigh more than 100 kg at the same total cost as for a single 45 mg vial.

	107. Ustekinumab treatment should be stopped in people whose psoriasis has not responded adequately by 16 weeks after starting treatment. An adequate response is defined as either: • a 75% reduction in the PASI score (PASI 75) from when treatment started or • a 50% reduction in the PASI score (PASI 50) and a five-point reduction in the DLQI score from when treatment started. ***Changing to an alternative biological drug*** 108. Consider changing to an alternative biological drug in adults if: · the psoriasis does not respond adequately to a first biological drug as defined in NICE technology appraisalsjj (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.
Nast, 2011 [19] **Deutsche Dermatologische Gesellschaft (DDG)** S3-Leitlinie zur Therapie der Psoriasis vulgaris Update. AWMF Leitlinien-Register Nr 013/001	Fragestellung/Ziele: Verbesserung der Versorgung der Patienten durch Umsetzung der Empfehlungen der Leitlinie und Optimierung der Kenntnisse der Ärzte bzgl. der in den Studien nachgewiesenen Wirksamkeit. Hilfe zur optimalen Durchführung der Therapien
	Methodik (S3-Leitlinie) Grundlage der Leitlinie: Aktualisierung der ersten Version der S3-Leitlinie zur Therapie der Psoriasis vulgaris aus 2006 sowie des Kurzupdates von 2009, basiert auf EU-LL (siehe Pathirana D, et al. 2009 [23], ergänzende Recherchen durchgeführt Methodenreport zur Leitlinie (www.psoriasis-leitlinie.de) Suchzeitraum: k.A. LoE: A1 Meta-Analyse, die wenigstens eine randomisierte Studie vom A2-Level beinhaltet, wobei die Ergebnisse unterschiedlicher Studien konsistent sind A2 Randomisierte, doppelblind klinisch vergleichende Studie von guter Qualität (z. B. Fallzahlberechnung, Flussdiagramm, ITT-Analyse, ausreichender Umfang) B Randomisierte, klinische Studie von weniger guter Qualität oder andere vergleichende Studie (nicht-randomisiert: Kohorten-, oder Fall-Kontroll-Studie) C Nicht-vergleichende Studie

	GoR: ↑↑ wird empfohlen (starke Empfehlung für eine Maßnahme) ↑ kann empfohlen werden (Empfehlung für eine Maßnahme) → kann erwogen werden (offene Empfehlung) ↓ kann nicht empfohlen werden (Empfehlung gegen eine Maßnahme) ↓↓ wird nicht empfohlen (starke Empfehlung gegen eine Maßnahme) Sonstige methodische Hinweise • Finanzierung durch die Fachgesellschaft • Interessenkonflikterklärungen durch die AWMF geprüft
	Freitext/Empfehlungen/Hinweise Therapieempfehlungen (Algorithmus siehe Anhang dieser Synopse) **6. Phototherapie** UV-B und PUVA werden zur Induktionstherapie bei mittelschwerer und schwerer Psoriasis vulgaris vor allem bei großflächiger Erkrankung empfohlen. (↑↑) Trotz der besseren Wirksamkeit von PUVA im Vergleich zur reinen UV-B-Therapie kann auf Grund der besseren Praktikabilität und auf Grund des geringeren Malignitätsrisikos eine Schmalspektrum UVB-Therapie als Phototherapie der ersten Wahl empfohlen werden. (↑) Der Einsatz des Excimer Lasers kann für die gezielte Behandlung einzelner psoriatischer Plaques empfohlen werden. (↑) Eine Kombination mit topischem Vitamin D_3-Derivaten kann zur Verbesserung der Ansprechrate empfohlen werden. (↑) Die übliche Kombination mit Dithranol und Kortikoiden kann nur auf Grund klinischer Erfahrung empfohlen werden, nicht aber aufgrund der Datenlage. (↑) Wegen der geringen Praktikabilität und der Assoziation langfristiger unerwünschter Wirkungen mit der kumulativen UV-Dosis kann die Phototherapie nicht für Langzeitbehandlungen empfohlen werden. (↓) **7. Systemische Therapie** Adalimumab wird zur Induktionstherapie für Patienten mit mittelschwerer bis schwerer Psoriasis vulgaris empfohlen (↑↑), vor allem wenn andere Therapieformen keinen ausreichenden Therapieerfolg gezeigt haben, unverträglich oder kontraindiziert sind. Ciclosporin kann vor allem zur Induktionstherapie bei mittelschwerer bis schwerer Psoriasis vulgaris empfohlen werden (↑). Eine Kombination von Ciclosporin mit topischen Präparaten zur Behandlung der Psoriasis vulgaris kann empfohlen werden (↑). Etanercept wird in der Dosierung von 2x50 mg zur Induktionstherapie für Patienten mit mittelschwerer bis schwerer Psoriasis vulgaris empfohlen (↑↑), vor allem wenn andere Therapieformen keinen ausreichenden Therapieerfolg gezeigt haben, unverträglich oder kontraindiziert sind.

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

	Suchzeitraum: bis 2009 LoE: defined by the Oxford Centre for Evidence-Based Medicine GoR: according to the Oxford Levels of Evidence, level of agreement was measured on a 10-point visual analogue scale (1, no agreement; 10, full agreement) Sonstige methodische Hinweise Conflicts of interest: All the authors have been paid consu!tants of Abbott. ln addition, C. Paul has been investigator and consuftant for Novartis and Wyeth. H. Bachelez has been paid for consulting activities for Centocor, Janssen-Cllag, Leo Pharma, Novartis, Pfizer and Schering-Plough. L. Misery has been a paid consultant of Novartis, Janssen-Cilag, Leo Pharma, Pfizer and Pierre Fabre. MA Richard has consulting activities for Janssen·Cilag, Novartis, Pfizer and talking for Janssen-Cilag, Leo Pharma and Pfizer. Funding sources: Abbott France provided financial support for publication but took no further part in the project. The authors have no financial interest in the subject matter or materials discussed in the manuscript.
	Freitext/Empfehlungen/Hinweise **Recommendations** MTX should be started at 5-10 mg/week the first week. Depending on the presence of risk factors, a rapid dose-escalation over 4 weeks is recommended to reach a target therapeutic dose between 15 and 25 mg/week. The maximum dose of methotrexate in psoriasis is 25 mg/week. Grade B lt is recommended to start cyclosporin at a dose between 2.5 and 5 mg/kg/day, preferabty 5 mg/kg/day for rapid action in the absence of comorbidities (obesity', older age). Grade A The recommended initial dose of acitretin is between 10 and 25 mg/day. Grade B

Paul, 2012 [24] Evidence-based recommendations on topical treatment and phototherapy of psoriasis: systematic review and expert opinion of a panel of dermatologists	**Fragestellungen** Q1 - What is the respective efficacy of NB-UVB and PUVA (Psoralen + UVA Light)] in the treatmen tof adult psoriasis? … Q4 - What are the optimal treatment modalities with topical corticosteroids in psoriasis? … Q8 - What is the level of compliance with topical treatments in psoriasis?
	The Population was defined as adult with psoriasis, and Interventions, Comparisons and Outcomes were specifically defined for each question **Methodik** Grundlage der Leitlinie: systematische Evidenzrecherche und –bewertung, formale Konsensusprozesse (Delphi Methode) beschrieben Suchzeitraum: November 2010 LoE: defined by the Oxford Centre for Evidence-Based Medicine GoR: according to the Oxford Levels of Evidence, level of agreement was measured on a 10-point visual analogue scale (1, no agreement; 10, full agreement) Sonstige methodische Hinweise Conflicts of interest: All the authors have been paid consultants of Abbott. In addition C. Paul has been investigator and consultant for Janssen-Cilag, Leo, Novartis and Wyeth. H. Bachelez has been paid for consulting activities for Centocor, Janssen- Cilag, Leo Pharma, Novartis, Pfizer, and Schering-Plough. B. Cribier has been paid for consulting activities for Pfizer, for redaction activities by Leo Pharma and Janssen Cilag. and speaker for Pfizer, Leo Pharma and Schering Plough. D. Jullien has been consultant for Merck, Janssen-Cilag, Novartis, Pfizer, and Schering-Plough/MSD. J.P. Ortonne has been investigator, speaker and advisor for Schering-Plough/MSD, Abbott, Merck Serono, Centocor, Pfizer, Janssen Cilag, Pierre Fabre, Galderma, Leo Pharma, Meda. L. Misery has been a paid consultant of Novartis, Janssen-Cilag, Leo Pharma, Pfizer and Pierre Fabre. M.A. Richard has been investigator and consultant for Janssen-Cilag, Novartis, Pfizer. Funding sources: Abbott France provided financial support for publication but took no further part in the project. The authors have no financial interest in the subject matter or materials discussed in the

<table>
<tr><td></td><td>manuscript.</td></tr>
<tr><td></td><td>Freitext/Empfehlungen/Hinweise

Recommendations

1. PUVA is more effective than NB-UVB. It has a response rate of approximately 80% compared with 70% for NB-UVB (grade A). However, NB-UVB is preferred because of higher convenience except for very thick plaques (grade D).
2. The optimal treatment regimen for phototherapy is 2–3 sessions per week (grade A).
3. Between 20 and 30 treatment sessions are generally required for clearance (grade A). An absence of improvement after 30 sessions is considered a treatment failure (grade D).
4. The starting UV dose and increases in dosage are defined according to phototype and tolerability (grade A).
5. Topical treatments should not be applied less than 30 min before a phototherapy session (grade D).
6. The risk of skin cancer is significantly increased with PUVA and there is a theoretical risk with NB-UVB (grade B).
7. The number of cumulative (PUVA／NBUVB) sessions during a lifetime must not exceed 250–300 (grade D).</td></tr>
<tr><td>SIGN, 2010 [29]</td><td>Scottish Intercollegiate Guidelines Network</td></tr>
<tr><td>Diagnosis and management of psoriasis and psoriatic arthritis in adults: A national clinical guideline</td><td>Methodik

Grundlage der Leitlinie: The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Information Officer.
Suchzeitraum: This guideline was issued in 2010 and will be considered for review in three years.

Levels of evidence

<table>
<tr><td>1++</td><td>High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td></tr>
<tr><td>1+</td><td>Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias</td></tr>
<tr><td>1-</td><td>Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias</td></tr>
<tr><td>2++</td><td>High-quality systematic reviews of case–control or cohort studies
High-quality case–control or cohort studies with a very low risk of</td></tr>
</table>
</td></tr>
</table>

	confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Nonanalytical studies (e.g. case reports, case series)
4	Expert opinion

Strength of recommendation:

A	At least one meta-analysis, systematic review, or RCT rated as 1_{++}, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1_{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2_{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1_{++} or 1_{+}
C	A body of evidence including studies rated as 2_{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2_{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2_{+}
GOOD PRACTICE POINTS	
✓ Recommended best practice based on the clinical experience of the guideline development group	

Empfehlungen

7.2 Phototherapy and photochemotherapy

BBUVB phototherapy is not recommended. (GoR A, LoE 1++ bis 2++)

All practices that use BBUVB should aim to change to NBUVB as soon as possible.

Patients with psoriasis who do not respond to topical therapy should be offered NBUVB phototherapy. (GoR B, LoE 2+)

B PUVA photochemotherapy should be considered for those patients who do not respond to NBUVB. (GoR B, LoE 2+)

7.3.1 Systemic therapy

Patients with severe or refractory psoriasis should be considered for systemic therapy with ciclosporin, methotrexate or acitretin, following discussion of benefits and risks. (GoR B, LoE 1++ bis 1+)

Methotrexate is recommended for longer term use and where there is concomitant psoriatic arthritis. (GoR B, LoE 1++ bis 1+)

Ciclosporin is recommended for short term intermittent use. (GoR A, LoE 1++ bis 1+)

Acitretin can be considered as an alternative. (GoR B, LoE 1++ bis 1+)

Fumaric acid esters can be considered as an alternative maintenance therapy for patients who are not suitable for other systemic therapies

	or have failed other therapies. (GoR B, LoE 1++ bis 1+) Hydroxycarbamide can be considered as an alternative maintenance therapy for patients who are not suitable for other systemic therapies or have failed other therapies. (GoR C, LoE 1++ bis 1+) Patienten mit schwerer Psoriasis, die nicht auf eine Phototherapie und systemische Therapien inklusive Ciclosporin und Methotrexat ansprechen, die hierfür nicht in Frage kommen oder diese Therapien nicht vertragen, sollte eine Biologika-Therapie angeboten werden (wenn diese nicht kontraindiziert ist oder die Patienten nicht ein erhöhtes Schadenrisiko durch diese Therapien haben). (GoR: A) • Adalimumab loading regimen followed by 40 mg every other week is recommended in the treatment of severe psoriasis. (GoR: A) • Etanercept 25 mg twice weekly or 50 mg weekly is recommended in the treatment of severe psoriasis. (GoR: A) • Infliximab 5 mg/kg at weeks 0, 2, 6 and repeated as maintenance treatment every two months is recommended in the treatment of severe psoriasis, especially when rapid disease control is required. (GoR: A) • Ustekinumab 45 mg for patients weighing under 100 kg and 90 mg for patients weighing over 100 kg given at weeks 0 and 4 then every 12 weeks as maintenance is recommended in the treatment of severe psoriasis. (GoR: A) Ergänzende Anmerkung: Women who are or may be pregnant should not be treated with systemic agents; The use of biologic treatments should conform to BAD guidelines; Patients on biologic therapies should be offered the opportunity to join the long term safety register BADBIR.
Canadian Psoriasis Guidelines Committee, 2009 [5] Canadian Guidelines for the Management of Plaque Psoriasis *siehe auch:* ***Papp** et al, 2011 [22]. Canadian guidelines for the management of plaque psoriasis: overview. J Cutan Med Surg 2011; 15 (4): 210-9.*	Fragestellung *k.A.* Methodik Grundlage der Leitlinie: systematische Evidenzrecherche und –bewertung, keine Konsensusprozesse beschrieben Suchzeitraum: 1980 – 02/2008 LoE/GoR (siehe Anhang zu dieser Synopse) Sonstige methodische Hinweise • CoI of all Committee members declared • Financial assistance for the development of these Guidelines was generously provided by the following sponsors (in alphabetical order): Abbott Laboratories, Limited; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; EMD Serono Canada Inc.; Galderma Canada Inc.; Isotechnika Inc.;

	Janssen-Ortho Inc.; LEO Pharma Inc.; Schering-Plough Canada Inc.; and Wyeth.
	Freitext/Empfehlungen/Hinweise Therapeutic options for ameliorating moderate to severe plaque psoriasis (alphabetical list, grouped by class) **Oral systemic agents** Acitretin: Retinoid drug; highly teratogenic and strictly contraindicated in pregnancy. Not to be used in women of childbearing age unless they are able and willing to use contraception for 3 years after discontinuing acitretin - Rarely used as monotherapy, but often combined with topical agents such as potent corticosteroids, or with other therapeutics to allow for more rapid/complete control, with reduced exposure to the other therapeutic (LoE 1-) Cyclosporine: Immunosuppressive drug; leads to cumulative renal toxicity; can exacerbate hypertension and hypertriglyceridemia - Can be highly effective in severe disease, but best employed intermittently, rather than for continuous long-term use (LoE 1++) Methotrexate: Immunomodulatory and anti-proliferative drug, often chosen for long-term management - Use is limited by risk of liver toxicity and the requirement for ongoing monitoring of liver function. Sometimes administered with folate supplement to reduce systemic toxicity (LoE 1+) **Biologic agents** Adalimumab: Targets TNF-a. Safety profile, primarily based on record of use in rheumatoid and psoriatic arthritis, suggests some overlap in adverse events with other TNF-a antagonists - Approved for use in psoriatic arthritis as well as psoriasis. Appears to be appropriate for long-term continuous use (LoE 1++) Etanercept: Targets TNF-a; may be associated with risk of infections, demyelinating disorders, and reactivation of latent TB or melanoma - Approved for use in psoriatic arthritis as well as psoriasis. Appropriate for long-term continuous use (LoE 1++) Infliximab: Targets TNF-a. Highly effective on initial exposure, even in severe, acute flares. Variable efficacy following reinitiation or beyond the first year of continuous treatment. - Associated with infusion reactions and risk of infections, demyelinating disorders, and reactivation of latent TB or tumour. - Approved for use in psoriatic arthritis as well as psoriasis (LoE 1++) **Photo(chemo)therapeutic methods** UVA with psoralen (PUVA): Psoralen may be administered orally or by immersion of affected areas in a psoralen solution, prior to irradiation

	with UVA (oral versus bath PUVA). Associated with cumulative risk of non-melanoma skin cancer, primarily squamous cell carcinoma. May be combined with other agents in suitable patients to reduce UV exposure (LoE 2++) UVB: Broadband UVB has been used for decades; now often applied using narrowband irradiation at 311 nm, a more effective option. Less durable remission than with PUVA but believed to have a more benign safety profile. May be combined with topical, systemic, or biologic agents for more rapid and more complete control, potentially reducing exposure to both UV light and other therapeutic agents (LoE 2++)
Menter, 2009 [17] **American Academy of Dermatology (AAD)** Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents	Fragestellung This fourth section will cover the management and treatment of psoriasis with traditional systemic therapies. Methodik Grundlage der Leitlinie: systematische Recherche, k.A. zu Konsensusprozessen Suchzeitraum: 1960 - 2008 *Weitere Kriterien für die Qualität einer LL:* • *Bewertung der Evidenz nach Ebell MH, et al. Simplifying the language of evidence to improve patient care: Strength of recommendation taxonomy (SORT): a patient centered approach to grading evidence in medical literature. J Fam Pract 2004;53:111-20* • *Empfehlungen sind mit Literaturstellen verknüpft* LoE/GoR: Evidence was graded using a 3-point scale based on the quality of methodology as follows: I. Good-quality patient-oriented evidence. II. Limited-quality patient-oriented evidence. III. Other evidence including consensus guidelines, opinion, or case studies. Clinical recommendations were developed on the best available evidence tabled in the guideline. These are ranked as follows: A. Recommendation based on consistent and good quality patient-oriented evidence. B. Recommendation based on inconsistent or limited-quality patient-oriented evidence. C. Recommendation based on consensus, opinion, or case studies. Sonstige methodische Hinweise • Funding sources: None.

	• CoI declared
	Freitext/Empfehlungen/Hinweise <u>Table VII. Recommendations for methotrexate</u> Therapeutic results • In the only placebo-controlled trial of methotrexate for psoriasis, 36% of patients treated with 7.5 mg/wk orally, increased as needed up to 25 mg/wk, reached PASI 75 after 16 wk <u>Table X. Recommendations for cyclosporine</u> Short-term results • At 3 and 5 mg/kg/d, 36% and 65%, respectively, achieved a clear or almost clear result after 8 wk • After 8-16 wk, 50%-70% of patients achieve PASI 75 Long-term results • Not recommended because of toxicities • Rapid relapse after abrupt discontinuation of cyclosporine <u>Table XI. Recommendations for acitretin</u> Short-term results • Efficacy rates not well defined but are high, based on studies of high dosages that are poorly tolerated • Efficacy rates when used in combination with phototherapy are higher Long-term results • Not reported <u>Table XIII. Recommendations for fumaric acid esters</u> <u>Indications</u> Short-term results • Multicenter, randomized, double-blind placebo-controlled trial of 100 patients showed that after 16 wk, patients treated with fumarate reached a mean PASI 50 compared with patients given placebo whose PASI was essentially changed • Randomized, double-blind controlled trial of 143 patients given either fumarate plus calcipotriol or fumarate alone found that patients given combination therapy reached PASI 50 in 3 wk vs those treated with fumarate alone reaching PASI 50 in 9 wk Long-term results • Case series of patients treated up to 14 y suggest no increased risk for infections or malignancies; large, long-term follow-up studies are necessary to confirm these observations <u>Table VIII. The strength of recommendations for the treatment of psoriasis using traditional systemic therapies</u> Methotrexate*: Strength of Recommendation B, Level of Evidence II Cyclosporine*: Strength of Recommendation B, Level of Evidence II Acitretin*: Strength of Recommendation B, Level of Evidence II Fumaric acid esters**: Strength of Recommendation B, Level of Evidence I The reader is advised not to use this table alone for decision making regarding the choice of traditional systemic therapies.

	*Although methotrexate, cyclosporine, and acitretin are all Food and Drug Administration approved for the treatment of psoriasis and have been used for many years by dermatologists with good to excellent results, the quality of the evidence supporting their use is as listed. ** The fumaric acid esters studies are well-designed placebo-controlled trials but because this treatment is not approved in the United States, it has been given strength of recommendation of B with a level I of evidence.
Menter, 2010 [16] **American Academy of Dermatology (AAD)** Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy	Fragestellung This fifth section will cover the management and treatment of psoriasis with phototherapy. Methodik: siehe Menter A, et al. 2009, Suchzeitraum 1960 bis 2009 Freitext/Empfehlungen/Hinweise <u>Table III. Recommendation for ultraviolet B (broadband and narrowband)</u> Indication: Generalized psoriasis (including guttate) unresponsive to topicals Short-term results (clearance): • BB: Average of 20-25 treatments to induce clearance • NB: More effective than BB-UVB, clearance within 2 wk may be seen, Average of 15-20 treatments to achieve clearance Long-term results (remission): • BB: Remission rate of 5% after 1 y • NB: Remission rate of 38% after 1 y <u>Table VI. Recommendations for use of topical targeted phototherapy</u> Indications: Adult and pediatric patients with mild, moderate, or severe psoriasis with\10% BSA involvement Short-term results: Initial response within 8-10 treatments; depends on multiple factors such as device used, protocol used, lesion characteristics, and site Long-term results: Mean remission times of 3.5-6 mo <u>Table IX. Recommendations for use of systemic psoralen plus ultraviolet A</u> Indications: Adults with generalized psoriasis who are resistant to topical therapy Short-term results: 89% Clearing with average of 25 treatments in US and 20 treatments in Europe 11.6 wk to Clear in US studies compared with 5.3 wk to clear in European studies Long-term results: Once clearance has been achieved, maintenance treatment may or may not be used, Remission times: 3-12 mo <u>Table X. Recommendations for use of topical psoralen plus ultraviolet A</u> Indications: Topical PUVA for adults with psoriasis of palms and soles, Bath PUVA for adults and children with generalized psoriasis Short-term results: Clinically is beneficial

	Long-term results: Once clearance has been achieved, maintenance treatment may be used, Remission: 3-12 mo **Table IV.** Strength of recommendations for use of phototherapy and photochemotherapy Agent | Strength of recommendation | Level of evidence | References BB-UVB | C | III | 8, 24–27, 31 NB-UVB | B | II | 28–30, 52, 63 Combination of UVB and topical agents | B | II | 55, 57, 58, 60, 61, 63–65 Combination of UVB and systemic agents | B | II | 74–76, 78 Combination of UVB and biologics agents | B | II | 84, 86 Combination of UVB and PUVA | C | III | 82, 156, 157 Excimer laser | B | II | 94, 95, 100, 101 Topical PUVA | B | II | 107, 108 Oral PUVA | A | I | 103, 104 Combination PUVA and topical agents | A | I | 139, 141 Combination of PUVA and systemic agents | B | II | 145, 146 *BB*, Broadband; *NB*, narrowband; *PUVA*, psoralen plus ultraviolet A; *UV*, ultraviolet.
Pathirana, 2009 [23] **European Dermatology Forum (EDF)** European S3-guidelines on the systemic treatment of psoriasis vulgaris	Fragestellung *k.A.*
	Methodik (S3-Leitlinie) Grundlage der Leitlinie: 3 Quellleitlinien und ergänzende Recherchen, nominaler Gruppenprozess zur Verabschiedung der Empfehlungen, externes Reviewverfahren Suchzeitraum: 2005 - 2007 *Weitere Kriterien für die Qualität einer LL:* • *Standardisiertes Verfahren zur Literaturbewertung* • *transparente Ergebnisdarstellung* LoE/GoR Grades of evidence A1 Meta-analysis that includes at least one randomized clinical trial with a grade of evidence of A2; the results of the different studies included in the meta-analysis must be consistent. A2 Randomized, double-blind clinical study of high quality (e.g. sample-size calculation, flow chart of patient inclusion, ITT analysis, sufficient size) B Randomized clinical study of lesser quality, or other comparative

	study (e.g. non-randomized cohort or case-control study). C Non-comparative study D Expert opinion In addition, the following levels of evidence were used to provide an overall rating of the available efficacy data for the different treatment options: Levels of evidence 1 Studies assigned a grade of evidence of A1, or studies that have predominantly consistent results and were assigned a grade of evidence of A2. 2 Studies assigned a grade of evidence of A2, or studies that have predominantly consistent results and were assigned a grade of evidence of B. 3 Studies assigned a grade of evidence of B, or studies that have predominantly consistent results and were assigned a grade of evidence of C. 4 Little or no systematic empirical evidence; extracts and information from the consensus conference or from other published guidelines. Sonstige methodische Hinweise • no information about funding • CoI declared
	Freitext/Empfehlungen/Hinweise Therapeutic recommendations · Part of the guidelines group believes that methotrexate (15‑22.5 mg/week) should be recommended based on many years of clinical experience with this agent and on the included studies; other members believe that methotrexate should only be suggested for the treatment of psoriasis vulgaris because of the limited evidence available (only one A2 trial) in the studies. · Methotrexate is, as a result of its slow onset of action, less desirable for short-term induction therapy than for long-term therapy. · Ciclosporin is suggested primarily for induction therapy in adults with moderate to severe psoriasis vulgaris who cannot be sufficiently treated with topical therapy and/or phototherapy. · Ciclosporin can be considered for long-term therapy (up to 2 years) in individual cases, but patients should be monitored closely for signs of increasing toxicity, especially for decreases in renal function or the efficacy of treatment. · Acitretin is not suggested as a first choice for monotherapy among the conventional systemic treatments. · Treatment with fumaric acid esters is suggested as an effective induction therapy for moderate to severe psoriasis vulgaris in adult patients. · Treatment is limited by gastrointestinal adverse effects and flush

	symptoms. · A combination of fumaric acid esters and topical treatments is recommended. · Because of the favourable risk-benefit profile with good safety during long-term treatment, fumarates are suggested.* * For this point, a consensus (defined as agreement by at least 75% of the voting experts) could not be reached. The percentage of positive votes in this case was 64%. (level of evidence 2) · Adalimumab is recommended for induction therapy for moderate to severe psoriasis if photo(chemo)therapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated. · If, after 10 to 16 weeks, induction therapy is considered successful, maintenance therapy can be considered with the lowest effective dose. (level of evidence 1) · Etanercept is suggested for induction therapy (25 mg or 50 mg biweekly) for moderate to severe psoriasis if photo(chemo)- therapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated. · If, after 10 to 16 weeks, induction therapy is considered successful, maintenance therapy can be considered with the lowest effective dose. (level of evidence 1) · Infliximab is recommended for induction therapy for moderate to severe psoriasis if photo(chemo)therapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated. · The advantage of this drug is its rapid and marked clinical efficacy. · If, after 10 to 16 weeks, induction therapy is considered successful, maintenance therapy can be considered. (level of evidence 1) 3.8 Ustekinumab Ustekinumab has been registered for systemic treatment of moderate to severe psoriasis in 2009. A formal evaluation is not included in these guidelines because of the deadline of literature research being prior to the registration of ustekinumab but will be given in the next guideline update.
Smith, 2009 [30] **British Association of Dermatologists** Guidelines for biologic interventions for psoriasis	Fragestellung • to provide up-to-date, evidence-based recommendations on use of biologic therapies
	Methodik Grundlage der Leitlinie: evidenzbasierte LL (systematische Suche und

	Bewertung der Literatur) Suchzeitraum: 1990 - 2009 *Weitere Kriterien für die Qualität einer LL:* • *transparente Ergebnisdarstellung* • *Empfehlungen sind mit Literaturstellen verknüpft* LoE/GoR: siehe Anhang dieser Synopse Sonstige methodische Hinweise • *CoI declared* • *Guidelines produced in 2005 by the British Association of Dermatologists; reviewed and updated June 2009.*
	Freitext/Empfehlungen/Hinweise <u>Recommendations: Etanercept</u> · Etanercept is recommended for the treatment of patients with severe psoriasis who fulfil the stated disease severity criteria – refer to section 8.0 (Strength of recommendation A; level of evidence 1++) · Etanercept therapy may be initiated at either 50 or 25 mg twice weekly and disease response assessed at 3–4 months (Strength of recommendation A; level of evidence 1++) · The choice of which dose to use will depend on clinical need, disease severity, body weight and, in the U.K., the dose that will be funded (Strength of recommendation B; level of evidence 1++) · Patients established on etanercept 25 mg twice weekly may wish to consider switching to etanercept 50 mg once weekly as these two dosing regimens are equivalent in terms of efficacy (Strength of recommendation A; level of evidence 1+) · In patients who respond, treatment may be continued according to clinical need, although long-term data on efficacy are limited to 2 years (Strength of recommendation C; level of evidence 2+) · Treatment may be discontinued without risk of disease rebound, although there may be a lower response rate on restarting therapy (Strength of recommendation B; level of evidence 1+) <u>Recommendations: Infliximab</u> · Infliximab is recommended for the treatment of patients with severe psoriasis who fulfil the stated disease severity criteria – refer to section 8Æ0 (Strength of recommendation A; level of evidence 1++) · Infliximab therapy should be initiated at a dose of 5 mg kg)1 at

	weeks 0, 2 and 6 and disease response assessed at 3 months (Strength of recommendation A; level of evidence 1++) · In patients who respond, subsequent infusions (5 mg kg)1) should be given at 8-week intervals to maintain disease control although long-term data are available only up to 1 year (Strength of recommendation A; level of evidence 1++) · Interrupted therapy should be avoided given the associated increased risk of infusion reactions and poorer disease control (Strength of recommendation A; level of evidence 1+) · Methotrexate may be recommended comedication in certain clinical circumstances, e.g. where it is required for associated arthropathy, to improve efficacy or to reduce the development of antibodies to infliximab (Strength of recommendation D; level of evidence 3) <u>Recommendations: Adalimumab</u> · Adalimumab is recommended for the treatment of patients with severe psoriasis who fulfil the stated disease severity criteria – refer to section 8.0 (Strength of recommendation A; level of evidence 1++) · Adalimumab therapy should be initiated according to the licensed dosing regimen (i.e. 80 mg subcutaneously at week 0, 40 mg at week 1, and then every other week thereafter) and disease response assessed at 3–4 months (Strength of recommendation A; level of evidence 1++) · Consideration may be given to increasing the dose of adalimumab to 40 mg weekly in certain clinical circumstances (e.g. in those with PASI > 10 despite achieving a response* to adalimumab 40 mg every other week), although this is unlicensed and not approved by NICE (and in the U.K. may not be funded) (Strength of recommendation A; level of evidence 1+) · In patients who respond, treatment may be continued according to clinical need although long-term efficacy data are available only up to 1 year (Strength of recommendation A; level of evidence 1++) · If necessary, treatment may be discontinued without risk of disease rebound, although there may be a lower response rate on restarting therapy (Strength of recommendation A; level of evidence 1+) · Methotrexate may be recommended comedication in certain clinical circumstances, e.g. where it is required for associated arthropathy, or to increase efficacy (Strength of recommendation B; level of evidence 3) * as defined in section 9.0 (PASI 50, DLQI –5) <u>Recommendations: Ustekinumab</u> · In light of limited patient exposure, ustekinumab should be reserved

	for use in patients with severe psoriasis who fulfil the stated disease severity criteria AND where TNF antagonist therapy has failed or is contraindicated – refer to section 8.0 (Strength of recommendation A; level of evidence 1+) · For logistical and safety reasons, drug injections should be supervised by a health care professional (Strength of recommendation D (GPP); level of evidence 4)

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

National Institute for Health and Clinical Excellence (NICE), 2009 [20] Ustekinumab for the treatment of adults with moderate to severe psoriasis	1.1 Ustekinumab is recommended as a treatment option for adults with plaque psoriasis when the following criteria are met. • The disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) score of 10 or more **and** a Dermatology Life Quality Index (DLQI) score of more than 10. • The psoriasis has not responded to standard systemic therapies, including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or the person is intolerant of or has a contraindication to these treatments. • The manufacturer provides the 90 mg dose (two 45 mg vials) for people who weigh more than 100 kg at the same total cost as for a single 45 mg vial. 1.2 Ustekinumab treatment should be stopped in people whose psoriasis has not responded adequately by 16 weeks after starting treatment. An adequate response is defined as either: • a 75% reduction in the PASI score (PASI 75) from when treatment started **or** • a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in the DLQI score from when treatment started. 1.3 When using the DLQI, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the DLQI and make any adjustments they consider appropriate.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 18.03.2015**

#	Suchfrage	Treffer
1	MeSH descriptor: [Psoriasis] explode all trees	1892
2	(Psoriasis):ti,ab,kw	3482
3	#1 or #2	3601
4	#3 from 2010 to 2015	857

SR, HTAs in Medline (PubMed) am 18.03.2015

#	Suchfrage	Treffer
1	Psoriasis[MeSH Terms]	30328
2	Psoriasis[Title/Abstract]	28072
3	(#1) OR #2	37413
4	(#3) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])	767
5	(#4) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))	462
6	(#4) OR #5	767
7	(#6) AND ("2010/03/01"[PDAT] : "2015/03/18"[PDAT])	450

Leitlinien in Medline (PubMed) am 18.03.2015

#	Suchfrage	Treffer
1	Psoriasis[MeSH Terms]	30328
2	Psoriasis[Title/Abstract]	28072
3	(#1) OR #2	37413
4	(#3) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title])	156
5	(#4) AND ("2010/03/01"[PDAT] : "2015/03/18"[PDAT])	71

Literatur

1. **Almutawa F, Thalib L, Hekman D, Sun Q, Hamzavi I, Lim HW**. Efficacy of localized phototherapy and photodynamic therapy for psoriasis: a systematic review and meta-analysis. Photodermatol Photoimmunol Photomed 2015; 31 (1): 5-14.

2. **Baker EL, Coleman CI, Reinhart KM, Phung OJ, Kugelman L, Chen W, White CM, Mamolo CM, Cappelleri JC, Baker WL**. Effect of Biologic Agents on Non-PASI Outcomes in Moderate-to-Severe Plaque Psoriasis: Systematic Review and Meta-Analyses. Dermatol Ther (Heidelb) 2012; 2 (1): 9.

3. **Busard C, Zweegers J, Limpens J, Langendam M, Spuls PI**. Combined Use of Systemic Agents for Psoriasis: A Systematic Review. JAMA Dermatol 2014; [Epub ahead of print].

4. **Canadian Agency for Drugs and Technologies in Health (CADTH)**. Infliximab versus methotrexate, etanercept, adalimumab, and ustekinumab for plaque psoriasis: a review of the comparative clinical efficacy, safety and cost effectiveness. Rapid Resonse Report. Ottawa (CAN): The Agency 2012; (2): http://www.cadth.ca/media/pdf//htis/aug-2012/RC0369%20Infliximab%20Final.pdf, Zugriff am 18.03.2015.

5. **Canadian Psoriasis Guidelines Committee**. Canadian guidelines for the management of plaque psoriasis. Canadian Psoriasis Guidelines Committee 2009; www.dermatology.ca/guidelines/cdnpsoriasisguidelines.pdf, Zugriff am 18.03.2015.

6. **Choi YM, Adelzadeh L, Wu JJ**. Photodynamic therapy for psoriasis. J Dermatolog Treat 2014; 1-6.

7. **Dommasch ED, Abuabara K, Shin DB, Nguyen J, Troxel AB Gelfand JM**. The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials. J Am Acad Dermatol 2011; 64 (6): 1035-50.

8. **Gemeinsamer Bundesausschuss (G-BA)**. Balneophototherapie: Zusammenfassende Dokumentation zum Beratungsverfahren des Unterausschusses „Ärztliche Behandlung des Gemeinsamen Bundesausschusses". Stand 05/2008. Berlin (GER): G-BA 2008; (BAnz. Nr. 80 (S. 1950) vom 03.06.2008): http://www.g-ba.de/informationen/beschluesse/645/, Zugriff am 18.03.2015.

9. **Girolomoni G, Altomare G, Ayala F, Berardesca E, Calzavara-Pinton P, Chimenti S, Peserico A, Puglisi GA, Vena GA**. Safety of anti-TNFalpha agents in the treatment of psoriasis and psoriatic arthritis. Immunopharmacol Immunotoxicol 2012; 34 (4): 548-60.

10. **Gisondi P, Girolomoni G**. Impact of TNF-alpha antagonists on the quality of life in selected skin diseases. G Ital Dermatol Venereol 2013; 148 (3): 243-8.

11. **Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)**. Balneophototherapie (Abschlußbericht N04-04). Köln (GER): IQWiG 2005; (IQWiG-Berichte - Jahr: 2006 Nr. 14).https://www.iqwig.de/download/N04-04_Abschlussbericht_Balneophototherapie..pdf, Zugriff am 18.03.2015.

12. **Lee S, Coleman CI, Limone B, Kaur R, White CM, Kluger J, Sobieraj DM**. Biologic and nonbiologic systemic agents and phototherapy for treatment of chronic plaque psoriasis. Database of Abstracts of Reviews of Effects 2012; (2): -1.

13. **Lin VW, Ringold S, Devine EB**. Comparison of Ustekinumab With Other Biological Agents for the Treatment of Moderate to Severe Plaque Psoriasis: A Bayesian Network Meta-analysis. Arch Dermatol 2012; 148 (12): 1403-10.

14. **Liu Y, Gong JP, Li WF**. Therapeutic effect and safety of ustekinumab for plaque psoriasis: a meta-analysis. Chin Med Sci J 2014; 29 (3): 131-8.

15. **Meng Y, Dongmei L, Yanbin P, Jinju F, Meile T, Binzhu L, Xiao H, Ping T, Jianmin L**. Systematic review and meta-analysis of ustekinumab for moderate to severe psoriasis. Clin Exp Dermatol 2014; 39 (6): 696-707.

16. **Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, Gottlieb A, Koo JY, Lebwohl M, Lim HW, Van Voorhees AS, Beutner KR, Bhushan R**. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy. J Am Acad Dermatol 2010; 62 (1): 114-35.

17. **Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, Gottlieb AB, Koo JY, Lebwohl M, Lim HW, Van Voorhees AS, Beutner KR, Bhushan R**. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol 2009; 61 (3): 451-85.

18. **Montaudie H, Sbidian E, Paul C, Maza A, Gallini A, Aractingi S, Aubin F, Bachelez H, Cribier B, Joly P, Jullien D, Le MM, Misery L, Richard MA, Ortonne JP**. Methotrexate in psoriasis: a systematic review of treatment modalities, incidence, risk factors and monitoring of liver toxicity. J Eur Acad Dermatol Venereol 2011; 25 Suppl 2 12-8.

19. **Nast A, Boehncke WH, Mrowietz U, Ockenfels HM, Philipp S, Reich K, Rosenbach T, Sammain A, Schlaeger M, Sebastian M, Sterry W, Streit V, Augustin M, Erdmann R, Klaus J, Koza J, Muller S, Orzechowski HD, Rosumeck S, Schmid-Ott G, Weberschock T, Rzany B**. Therapie der Psoriasis vulgaris, S3-Leitlinie (08.07.2014: Gültigkeit der Leitlinie nach Überprüfung durch das Leitliniensekretariat bis zum 31.12.2015 verlängert). Berlin (Ger): Deutsche Dermatologische Gesellschaft (DDG) 2011; (AWMF Leitlinien-Register Nr.013-01).http://www.awmf.org/uploads/tx_szleitlinien/013-001l_S3_Psoriasis_vulgaris_Therapie_01.pdf, Zugriff am 18.03.2015.

20. **National Institute for Health and Care Excellence (NICE)**. Ustekinumab for the treatment of adults with moderate to severe psoriasis (TA180). London (UK):NICE 2009; http://www.nice.org.uk/guidance/ta180/resources/guidance-ustekinumab-for-the-treatment-of-adults-with-moderate-to-severe-psoriasis-pdf, Zugriff am 18.03.2015.

21. **National Institute for Health and Care Excellence (NICE)**. Psoriasis: the assessment and management of psoriasis (CG153). London (UK): NICE 2012; http://www.nice.org.uk/guidance/cg153/resources/guidance-psoriasis-pdf, Zugriff am 18.03.2015.

22. **Papp K, Gulliver W, Lynde C, Poulin Y, Ashkenas J**. Canadian guidelines for the management of plaque psoriasis: overview. J Cutan Med Surg 2011; 15 (4): 210-9.

23. **Pathirana D, Ormerod AD, Saiag P, Smith C, Spuls PI, Nast A, Barker J, Bos JD, Burmester GR, Chimenti S, Dubertret L, Eberlein B, Erdmann R, Ferguson J, Girolomoni G, Gisondi P, Giunta A, Griffiths C, Honigsmann H, Hussain M, Jobling**

R, Karvonen SL, Kemeny L, Kopp I, Leonardi C, Maccarone M, Menter A, Mrowietz U, Naldi L, Nijsten T, Ortonne JP, Orzechowski HD, Rantanen T, Reich K, Reytan N, Richards H, Thio HB, van de Kerkhof P, Rzany B. European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol 2009; 23 Suppl 2 1-70.

24. **Paul C, Gallini A, Archier E, Castela E, Devaux S, Aractingi S, Aubin F, Bachelez H, Cribier B, Joly P, Jullien D, Le MM, Misery L, Richard MA, Ortonne JP**. Evidence-based recommendations on topical treatment and phototherapy of psoriasis: systematic review and expert opinion of a panel of dermatologists. J Eur Acad Dermatol Venereol 2012; 26 Suppl 3 1-10.

25. **Paul C, Gallini A, Maza A, Montaudie H, Sbidian E, Aractingi S, Aubin F, Bachelez H, Cribier B, Joly P, Jullien D, Le MM, Misery L, Richard MA, Ortonne JP**. Evidence-based recommendations on conventional systemic treatments in psoriasis: systematic review and expert opinion of a panel of dermatologists. J Eur Acad Dermatol Venereol 2011; 25 Suppl 2 2-11.

26. **Reich K, Burden AD, Eaton JN, Hawkins NS**. Efficacy of biologics in the treatment of moderate to severe psoriasis: a network meta-analysis of randomized controlled trials. Br J Dermatol 2012; 166 (1): 179-88.

27. **Sbidian E, Maza A, Montaudie H, Gallini A, Aractingi S, Aubin F, Cribier B, Joly P, Jullien D, Le MM, Misery L, Richard MA, Paul C, Ortonne JP, Bachelez H**. Efficacy and safety of oral retinoids in different psoriasis subtypes: a systematic literature review. J Eur Acad Dermatol Venereol 2011; 25 Suppl 2 28-33.

28. **Schmitt J, Rosumeck S, Thomaschewski G, Sporbeck B, Haufe E, Nast A**. Efficacy and safety of systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol 2014; 170 (2): 274-303.

29. **Scottish Intercollegiate Guidelines Network (SIGN)**. Diagnosis and management of psoriasis and psoriatic arthritis in adults: A national clinical guideline 121. Edinburgh (UK): SIGN 2010; http://www.sign.ac.uk/pdf/sign121.pdf, Zugriff am 08.01.2015.

30. **Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler DA, Finlay AY, Griffiths CE, Jackson K, McHugh NJ, McKenna KE, Reynolds NJ, Ormerod AD**. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. Br J Dermatol 2009; 161 (5): 987-1019.

Anhang

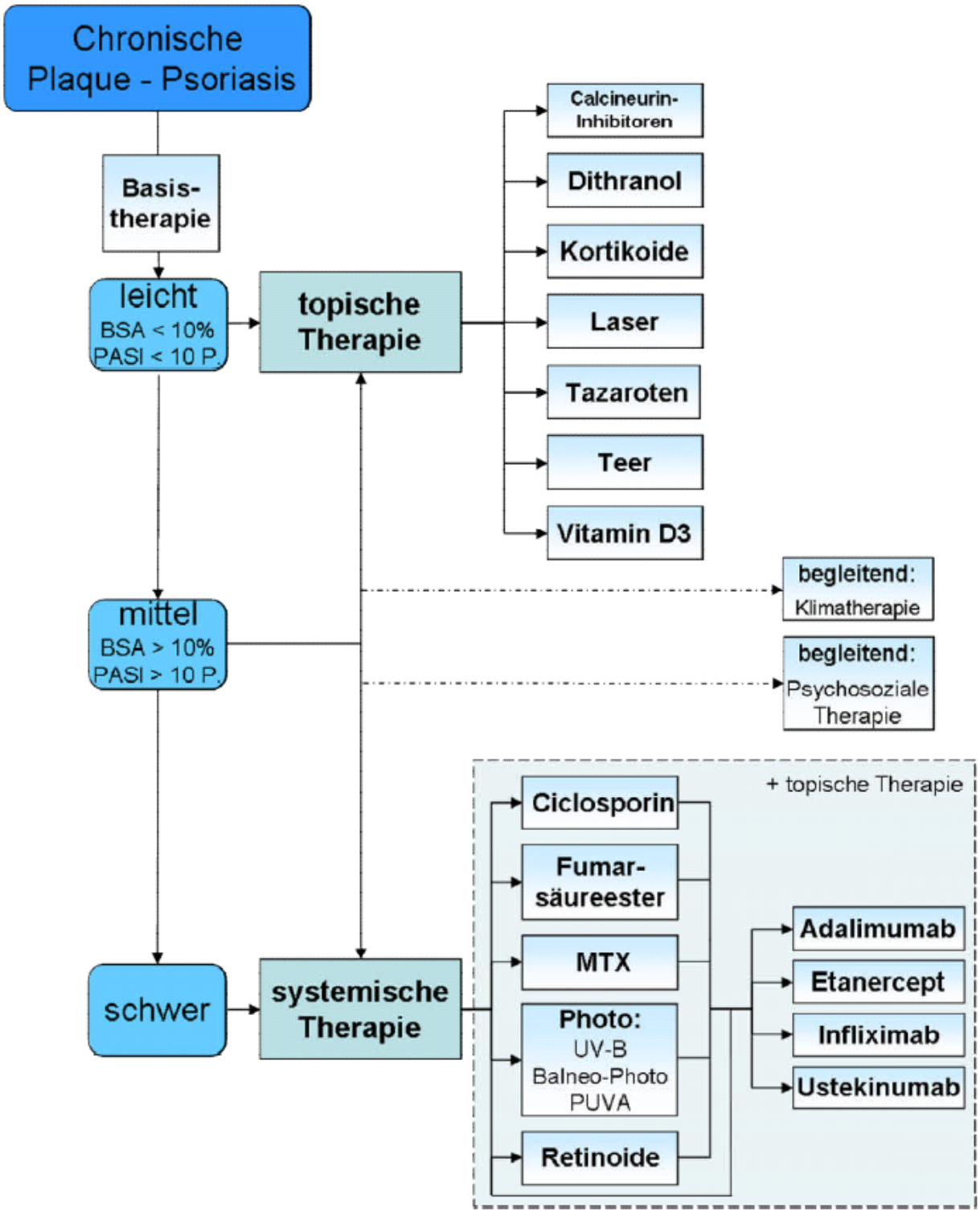


Abbildung 2: Übersicht der beurteilten Therapieoptionen bei der chronischen Plaque-Psoriasis (die Anordnung der Therapieoptionen ist alphabetisch und stellt keine Wertung dar)

Abbildung 1: aus Nast A., et al. 2011

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

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

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

Abbildung 2: aus Canadian Psoriasis Guidelines Committee, 2009 [5]

Level of evidence

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

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

Strength of recommendation

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

RCT, randomized controlled trial.

Abbildung 3: aus Smith CH, et al. 2009