Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-216z (Deucravacitinib)

Stand: April 2023

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

Deucravacitinib
[mittelschwere bis schwere Plaque-Psoriasis]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Phototherapie: NB-UV-B-Bestrahlungen, Photosoletherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Richtlinie Methoden vertragsärztliche Versorgung: Balneophototherapie vom 13. März 2008; Richtlinie Methoden vertragsärztliche Versorgung, Stand: 3. Oktober 2014 des Gemeinsamen Bundesausschusses zu Untersuchungs- und Behandlungsmethoden der vertragsärztlichen Versorgung (Richtlinie Methoden vertragsärztliche Versorgung) in der Fassung vom 17. Januar 2006 veröffentlicht im Bundesanzeiger 2006 Nr. 48 (S. 1 523) in Kraft getreten am 1. April 2006; zuletzt geändert am 17. Juli 2014 veröffentlicht im Bundesanzeiger (BAnz AT 02.10.2014 B2); in Kraft getreten am 3. Oktober 2014. 15. Balneophototherapie Beschluss zu Apremilast vom 06.08.2015 Beschluss zu Secukinumab vom 27.11.2015 Beschluss zu Secukinumab vom 17.08.2017 Beschluss zu Ixekizumab vom 17.08.2017 Beschluss zu Brodalumab vom 01.03.2018 Beschluss zu Dimethylfumarat vom 16.03.2018 Beschluss zu Guselkumab vom 17.05.2018 Beschluss zu Tildrakizumab vom 02.05.2019 Beschluss zu Risankizumab vom 22.11.2019

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Deucravacitinib [mittelschwere bis schwere Plaque-Psoriasis] Kriterien gemäß 5. Kapitel § 6 VerfO	
	Beschluss zu Ixekizumab vom 21.01.2021 Beschluss zu Secukinumab vom 18.02.2021 Beschluss zu Bimekizumab vom 03.03.2022
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:	
Deucravacitinib L04AA56 Sotyktu®	Sotyktu® wird angewendet zur Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die für eine systemische Therapie infrage kommen.
Acitretin D05BB02 Neotigason®	Zur symptomatischen Behandlung von schwersten, einer konventionellen Therapie nicht zugänglichen Verhornungsstörungen des Hautorgans wie: - Psoriasis vulgaris, vor allem erythrodermatische und pustulöse Formen
Adalimumab L04AB04 Humira®	Humira® wird angewendet zur Behandlung der mittelschweren bis schweren chronischen Plaque-Psoriasis bei erwachsenen Patienten, die Kandidaten für eine systemische Therapie sind.
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.
Bimekizumab L04AC21 Bimzelx®	Bimzelx wird angewendet zur Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die für eine systemische Therapie infrage kommen.
Brodalumab L04AC12 Kyntheum®	Kyntheum® ist angezeigt für die Behandlung von mittelschwerer bis schwerer Plaque-Psoriasis bei erwachsenen Patienten, für die eine systemische Therapie in Frage kommt.
Certolizumab Pegol L04AB05 Cimzia®	Cimzia ist zur Behandlung mittelschwerer bis schwerer Plaque-Psoriasis bei Erwachsenen indiziert, die Kandidaten für eine systemische Therapie sind.
Ciclosporin L04AD01	Behandlung von schwerer Psoriasis bei Patienten, bei denen eine herkömmliche Therapie nicht geeignet oder nicht wirksam ist.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
z.B. Sandimmun Neoral Lösung	
Dimethylfumarat, Ethylhydrogen-fumarat 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.
Dimethylfumarat L04AX07 Skilarence®	Skilarence® wird angewendet zur Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Psoriasis vulgaris, die eine systemische Arzneimitteltherapie benötigen.
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.
Guselkumab L04AC16 Tremfya®	Tremfya ist für die Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis indiziert, die für eine systemische Therapie in Frage kommen.
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.
Ixekizumab L04AC13 Taltz®	Taltz® ist angezeigt für die Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die für eine systemische Therapie in Frage kommen.
Kortikosteroide, z.B. Prednisolon H02AB06 Prednisolon acis	[…] 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: 10/2021)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Methotrexat M01CX01 Lantarel®	Schwere Formen der Psoriasis vulgaris, insbesondere vom Plaque-Typ, und der Psoriasis arthropathica, die mit einer konventionellen Therapie nicht ausreichend behandelbar sind.
Risankizumab L04AC18 Skyrizi®	Skyrizi wird angewendet zur Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die für eine systemische Therapie infrage kommen.
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.
Tildrakizumab L04AC17 Ilumetri®	Ilumetri® ist angezeigt für die Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die für eine systemische Therapie in Frage kommen.
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.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2021-B-216z (Deucravacitinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	28. März 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

AAD	American Academy of Dermatology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DLQI	Dermatology life quality index
DMF	Dimethyl fumarate
FAE	Fumaric acid ester
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HR	Hazard Ratio
IL	Interleukin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
MTX	Methotrexate
(NB) UVB	(Narrowband) ultraviolet B light
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NNT	Number needed to treat
OR	Odds Ratio
PASI	Psoriasis Area and Severity Index
PsA	Psoriatic arthritis
PUVA	Psoralen und Ultraviolett A-Licht
RCT	Randomized controlled trial
RR	Relatives Risiko
(S)AE	(Serious) adverse effects
sPGA	Static physician's global assessment
TNF	Tumour necrosis factor
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die für eine systemische Therapie infrage kommen.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Plaque-Psoriasis* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 14.03.2023 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 1412 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 19 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Sbidian E et al., 2022 [15].

(update of a Cochrane Review first published in 2017 and 2020)

Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis

+ Ravasia R. et al., 2021 [13]

+ Armstrong A., et al., 2022 [1]

+ Fahrbach K., et al., 2021 [7]

+ Sawyer L.M. et al., 2019 [14]

+ Bai F. et al., 2019 [2]

Fragestellung

To compare the efficacy and safety of non-biological systemic agents, small molecules, anti-TNF alpha, anti-IL12/23, anti-IL17, and anti- IL23 for people with moderate-to-severe psoriasis using a network meta-analysis, and to provide a ranking of these treatments according to their efficacy and safety.

Methodik

Population:

- adults (over 18 years of age) with moderate-to-severe plaque psoriasis or psoriatic arthritis whose skin had been clinically diagnosed with moderate-to-severe psoriasis and who were at any stage of treatment

Intervention:

- Non-biological treatments: FAEs, Acitretin, Ciclosporin, Methotrexate
- Small molecules: Apremilast, Deucravacitinib
- Biologic treatments
  - Anti-TNF alpha, Infliximab, Etanercept, Adalimumab, Certolizumab
  - Anti-IL12/23: Ustekinumab
  - Anti-IL17: Secukinumab, Brodalumab, Ixekizumab, Bimekizumab, Sonelokimab, Netakimab
  - Anti-IL23: Tildrakizumab, Guselkumab, Risankizumab

Komparator:

- Placebo
- Another active agent
  - any of the aforementioned systemic treatments; or
  - additional treatment not of primary interest but used for the network synthesis, such as topical treatment or phototherapy

Endpunkte:

- Primary outcomes of this review

  - proportion of participants who achieved clear or almost clear skin (at least Psoriasis Area and Severity Index (PASI) 90 at induction phase
  - proportion of participants with serious adverse effects (SAEs) at induction phase.
- Secondary outcomes
  - Proportion of participants who achieve PASI 75 at induction phase.
  - Proportion of participants who achieve a Physician Global Assessment (PGA) value of 0 or 1 at induction phase.
  - Quality of life measured by a specific scale. Available validated scales are the Dermatology Life Quality Index (DLQI), Skindex, Psoriasis Disability Index (PDI), or Psoriasis Symptom Inventory (PSI) at induction phase.
  - The proportions of participants with adverse events (AEs) at induction phase ('AE outcome' did not include SAE).
  - Proportion of participants who achieve PASI 75 at 52 weeks.
  - Proportion of participants who achieve PASI 90 at 52 weeks.

Recherche/Suchzeitraum:

- We updated our research using the following databases to October 2021: the Cochrane Skin Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, LILACS and the conference proceedings of a number of dermatology meetings. We also searched five trials registers and the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) reports (until June 2019). We checked the reference lists of included and excluded studies for further references to relevant RCTs.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool
- GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 167 studies (19 new trials for the updated review) enrolled 58912 people with moderate-to-severe psoriasis

Charakteristika der Population/Studien:

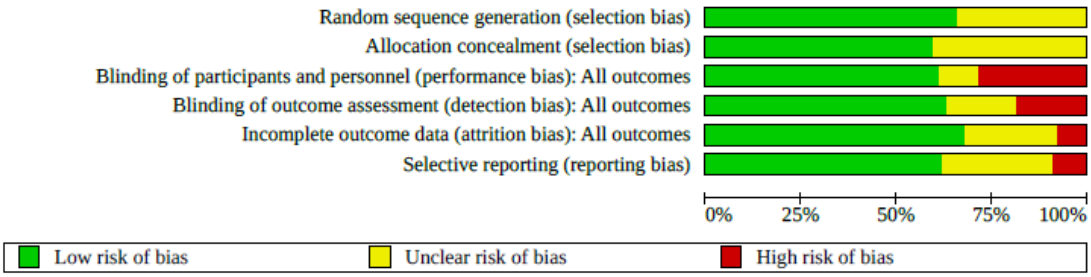
- 34,624 men and 16,529 women (unknown for the remaining 596 participants);
- The participants were reported to be between 27 and 56.5 years old, with an overall mean age of 44.5
- There were more men (39,591) than women (18,814).
- The overall mean Psoriasis Area and Severity Index (PASI) score at baseline was 20.4 (range: 9.5 to 39). The duration of psoriasis was 16.5 years (range 4.5 to 21.5).
- In total, the dataset consisted of 167 studies, which provided information on 297 direct comparisons between 36 different drug dosages, 20 different drugs, six different drug classes, and placebo

Qualität der Studien:

- For overall risk of bias across studies, 87 (52%) trials were at low risk of bias. We categorised a third of the studies (57/167, 34%) as being at high risk of bias. We categorised the remaining 23 studies as being at unclear risk of bias.

- There was variation in how well the studies took measures to blind investigators and participants: a third of trials in this review were rated at high or unclear risk of performance bias (64 out of 167). This is an important point to highlight, as the outcomes used for assessing efficacy were subjective. However, the proportion of trials at high risk of blinding used in the network meta-analyses decreased to 25.5% (34 out of 133).
- The reporting of missing outcome data was largely inadequate in a few studies. Since we chose a likely scenario that any participant with missing outcome data did not experience clearance for the overall analyses, we minimised the risk of overestimating efficacy due to how we reported missing data.
- Finally, we rated a few trials at high risk of selective outcome reporting. However, we chose a stringent definition of studies at high risk of selective outcome reporting: A large proportion of included trials did not report the patient-reported outcomes in the main report but only in secondary publications.

Figure 3. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies



Studienergebnisse:

<u>The proportion of participants who achieved clear or almost clear skin, e.g. PASI 90</u>

- Direct Evidence
  - Infliximab, adalimumab, and ixekizumab were more effective than methotrexate (respectively: RR 2.86, 95% CI 2.15 to 3.80; RR 3.73, 95% CI 2.25 to 6.19; and RR 2.05, 95% CI 1.43 to 2.94).
  - Secukinumab, ixekizumab, guselkumab, risankizumab, and brodalumab were more effective than FAEs (respectively: RR 8.31, 95% CI 4.23 to 16.35; RR 8.60, 95% CI 3.69 to 20.04; RR 6.02, 95% CI 3.13 to 11.60; RR 8.33, 95% CI 3.87 to 17.95; and RR 3.00, 95% CI 2.04 to 4.42).
  - Ustekinumab, secukinumab, infliximab, ixekizumab, and tildrakizumab were more effective than etanercept. Secukinumab, ixekizumab, brodalumab,risankizumab and bimekizumab were more effective than ustekinumab.
  - Guselkumab, risankizumab and bimekizumab were more eNective than adalimumab. Secukinumab and ixekizumab were more effective than guselkumab and bimekizumab was more effective than secukinumab.
  - No significant difference was observed between risankizumab and secukinumab, between sonelokimab and secukinumab, between certolizumab and etanercept, or between etanercept and apremilast for this outcome (reaching PASI 90).
- NMA
  - The PASI 90 outcome was available in 115 trials, involving 48,722 participants (92.7% of the participants in the meta-analysis). Sixty-eight trials, involving 23,539 participants, were placebo-controlled trials; 31 studies, involving 11,426 participants,

were head-to-head comparisons; and 16 studies, involving 13,757 participants, had both a placebo and at least two active treatments arms.

- Anti-IL17 treatment was associated with a higher chance of reaching PASI 90 compared to all of the interventions
  - except anti-IL23 (RR 1.25, 95% CI 0.99 to 1.99):
  - versus anti-IL12/23 (RR 1.52, 95% CI 1.26 to 1.83)
  - versus anti-TNF alpha (RR 2.20, 95% CI 1.80 to 2.69)
  - versus small molecules (RR 3.26, 95% CI 2.27 to 4.67)
  - versus conventional systemic agents (RR 6.31, 95% CI 4.64 to 8.59).
- In terms of reaching PASI 90, all of the biologic interventions (anti-IL17, anti-IL12/23, anti-IL23, anti-TNF alpha) appeared significantly superior to the small molecule class of treatments and the conventional systemic class of treatments.
- Small molecules were associated with a higher chance of reaching PASI 90 compared to conventional systemic agents (RR 1.94, 95% CI 1.28 to 2.94).
- All of the anti-IL17 drugs (ixekizumab, secukinumab and brodalumab) and all of the anti-IL23 drugs (risankizumab and guselkumab) except tildrakizumab were significantly more effective than ustekinumab and three anti-TNF alpha agents:
  - Adalimumab and ustekinumab were superior to certolizumab (RR 1.47, 95% CI 1.05 to 2.06 and RR 1.42, 95% CI 1.05 to 1.92, respectively) etanercept (RR 1.83, 95% CI 1.51 to 2.23 and RR 1.77, 95% CI 1.56 to 2.00, respectively).

- Ranking class-level analysis:
  - Anti-IL17 class had a better chance of reaching PASI 90 using SUCRA (versus placebo: RR 26.78, 95% CI 22.07 to 32.49; SUCRA = 98.7)
  - followed by anti-IL23 (versus placebo: RR 23.53, 95% CI 19.00 to 29.15; SUCRA = 84.5)
  - anti-IL12/23 (versus placebo: RR 18.47, 95% CI 14.82 to 23.02; SUCRA = 66.6)
  - then anti-TNF alpha (versus placebo: RR 13.70, 95% CI 11.22 to 16.73; SUCRA = 48.5).
  - The heterogeneity for this network overall was 0.06, which we considered to be low.
- Ranking drug-level analysis: At drug-level, using SUCRA,
  - infliximab had a better chance of reaching PASI 90 at drug level (versus placebo: RR 50.19, 95% CI 20.92 to 120.45; SUCRA = 95.6; high-certainty evidence)
  - followed by bimekizumab (versus placebo: RR 30.27, 95% CI 25.45 to 36.01; SUCRA = 90; high-certainty evidence)
  - ixekizumab (versus placebo: RR 30.19, 95% CI 25.38 to 35.93; SUCRA = 89.6; high-certainty evidence)
  - risankizumab (versus placebo: RR 28.75, 95% CI 24.03 to 34.39; SUCRA = 83.9; high-certainty evidence)
  - secukinumab (versus placebo: RR 26.26, 95% CI 22.26 to 30.99; SUCRA = 75; high-certainty evidence)
  - sonelokimab (versus placebo: RR 25.60, 95% CI 19.35 to 33.87; SUCRA = 72.5; high-certainty evidence)
  - then brodalumab (versus placebo: RR 24.10, 95% CI 20.06 to 28.97; SUCRA = 65.6; moderate-certainty evidence).
  - The heterogeneity for this network overall was 0, which we considered to be low.

<u>Proportion of participants who achieved PASI 90 at 52 weeks</u>

- Direct evidence

- Nine head-to-head comparisons compared two different biologics; seven compared two different dosages of secukinumab, guselkumab, ixekizumab, risankizumab and apremilast, respectively; and one compared a biologic with placebo.
- Risankizumab was more effective than ustekinumab (RR 1.73, 95% CI 1.46 to 2.05)
- Secukinumab was more effective than ustekinumab to reach PASI 90 at 52 weeks (RR 1.23, 95% CI 1.15 to 1.31)
- Ixekizumab was more effective than ustekinumab to reach PASI 90 at 52 weeks (RR 1.30, 95% CI 1.11 to 1.52)
- Bimekizumab was more effective than ustekinumab to reach PASI 90 at 52 weeks (RR 1.47, 95% CI 1.27 to 1.70)
- Risankizumab was more effective than secukinumab to reach PASI 90 at 52 weeks (RR 1.52, 95% CI 1.31 to 1.76
- Bimekizumab was more effective than secukinumab to reach PASI 90 at 52 weeks (RR 1.19, 95% CI 1.09 to 1.28)
- Guselkumab was more effective than adalimumab to reach PASI 90 at 52 weeks (RR 1.59, 95% CI 1.40 to 1.81)

PASI 75, PGA

- For other efficacy outcomes (PASI 75 and Physician Global Assessment (PGA) 0/1), the results were similar to the results for PASI 90.

Quality of life

- Information on quality of life was often poorly reported and was absent for several of the interventions. The quality-of-life outcome was available in 67 trials, involving 28,702 participants (54.6% of the participants in this review).
- Anti-IL23, anti-IL12/23, anti-IL17 and anti- TNF agents were associated with a higher chance of improving quality of life compared to small molecules. These differences were statistically significant for all of the classes.
- No significant difference was shown between anti-IL23, anti-IL12/23 and anti-IL17. Anti-IL23 and anti-IL17 was more favorable than anti-TNF alpha. There were no significant differences between the small molecules and the non-biological agents.
- Ranking class-level analysis
  - Ranking analysis performed with SUCRA strongly suggested that anti-IL23 had a better chance of improving quality of life at class level (versus placebo: standardized mean difference (SMD) −1.41, 95% confidence interval (CI) −1.63 to −1.18; SUCRA = 84.2), followed by anti-IL17 (versus placebo: SMD −1.37, 95% CI −1.60 to −1.14; SUCRA = 79.2), and anti-IL12/23 (versus placebo: SMD −1.33, 95% CI −1.59 to −1.07; SUCRA = 73.7).
  - The heterogeneity for this network overall was 0.12, which we considered to be low.

Serious adverse events (primary objective)

- The SAE outcome was available in 120 trials, involving 49,045 participants (93.4% of the participants in the meta-analysis).
- We found no significant difference between any of the interventions and the placebo for the risk of SAE. There was no significant difference between all interventions in the number of participants with SAEs, except for methotrexate.
- The risk of SAEs was significantly lower for participants on methotrexate compared with all interventions, except bimekizumab, certolizumab, netakimab, deucravacitinib, apremilast, and FAEs.

- Ranking class-level analysis
  - Anti-IL23 had the highest SUCRA at class level in terms of serious adverse events (versus placebo: RR 0.80, 95% CI 0.57 to 1.16; SUCRA = 75.4), followed by non-biological systemic treatments (versus placebo: RR 0.74, 95% CI 0.35 to 1.57; SUCRA = 69.3), small molecules (versus placebo: RR 0.85, 95% CI 0.50 to 1.45; SUCRA = 58), and then anti-TNF alpha agents (versus placebo: RR 0.92, 95% CI 0.71 to 1.19; SUCRA = 47.7). The heterogeneity for this network overall was 0, which we considered to be low.
- Ranking drug-level analysis
  - Methotrexate had the highest SUCRA at drug level in terms of serious adverse events (versus placebo: RR 0.08, 95% CI 0.01 to 0.68; SUCRA = 97.2; high-certainty evidence), followed by bimekizumab (versus placebo: RR 0.52, 95% CI 0.25 to 1.09) SUCRA = 80.4; moderate-certainty evidence), risankizumab (versus placebo: RR 0.73, 95% CI 0.47 to 1.13; SUCRA = 66.9; moderate certainty evidence), certolizumab (versus placebo: RR 0.70, 95% CI 0.31 to 1.58; SUCRA = 64.4; moderate-certainty evidence), then deucravacitinib (versus placebo: RR 0.61, 95% CI 0.06 t 5.71; SUCRA = 60.7; moderate-certainty evidence).
  - However, no significant difference was observed between drugs and placebo. The heterogeneity for this network overall was 0, which we considered to be low.

<u>Adverse events (secondary objective)</u>

- The adverse events (AEs) outcome was available in 110 trials, involving 46,502 participants (88.5% of the participants in this review).
- Ranking class-level analysis
  - Placebo had the highest SUCRA (SUCRA 94.9)at class-level for all adverse events, followed by anti-IL23 (versus placebo: RR 1.02, 95% CI 0.96 to 1.08; SUCRA = 85.1), anti-TNF agents (versus placebo: RR 1.07, 95% CI 1.03 to 1.12; SUCRA = 56.3), then anti-IL12/23 (versus placebo: RR 1.08, 95% CI 1.02 to 1.14; SUCRA = 54.7). The heterogeneity for this network overall was 0.01, which we considered to be low.
- Ranking drug-level analysis
  - Tildrakizumab had the highest SUCRA at drug-level for all adverse events (versus placebo: RR 0.93, 95% CI 0.82 to 1.04; SUCRA = 93.5), followed by certolizumab (versus placebo: RR 1.01, 95% CI 0.89 to 1.15; SUCRA = 86.6), placebo (SUCRA = 85.4), then netakimab (versus placebo: RR 0.99, 95% CI 0.81 to 1.22; SUCRA = 81.1). The heterogeneity for this network overall was 0, which we considered to be low.

Fazit der Autoren

- In terms of achieving PASI 90 with induction therapy (evaluation from 8 to 24 weeks after the randomisation), we found the following results, based on network meta-analysis. For the other efficacy outcomes (PASI 75 and PGA0/1), the results were similar to the results for PASI 90.
  - At class level, the biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha showed significant superiority compared with non-biological systemic agents; anti-IL17 treatment was associated with a better chance of reaching PASI 90 compared to all of the interventions, except anti-IL23.
  - For reaching PASI 90, the most effective drugs when compared to placebo were (in SUCRA (surface under the cumulative ranking curve) rank order): infliximab (high certainty evidence), bimekizumab (high-certainty evidence), ixekizumab (high-certainty evidence), and risankizumab (high certainty evidence). The clinical effectiveness of these drugs was similar when compared against each other.

  - Bimekizumab, ixekizumab and risankizumab were significantly more effective in reaching PASI 90 than other anti-IL17 drugs (secukinumab and brodalumab) and guselkumab. Infliximab, bimekizumab, ixekizumab, secukinumab, brodalumab, risankizumab and guselkumab were significantly more effective in reaching PASI 90 than ustekinumab, tildrakizumab and the three anti-TNF alpha agents (adalimumab, certolizumab and etanercept).
  - Anti-IL17 drugs (bimekizumab, ixekizumab, secukinumab and brodalumab) and anti-IL23 drugs (risankizumab and guselkumab) except tildrakizumab were significantly more effective in reaching PASI 90 than ustekinumab and three anti- TNF alpha agents (adalimumab, certolizumab and etanercept). Ustekinumab was superior to certolizumab; adalimumab and ustekinumab were superior to etanercept.
  - No significant difference was shown between apremilast and two non-biological drugs: ciclosporin and methotrexate.
- For serious adverse events, there was no significant difference between any of the assessed interventions and placebo. Nonetheless, analyses of SAE events were based on a very low number of events with low-to-moderate certainty for the majority of the comparisons. The findings therefore have to be viewed with caution.
- Considering both efficacy (PASI 90 outcome) and acceptability (SAE outcome), highly-effective treatments had more SAEs than the other treatments: risankizumab and bimekizumab appeared to be the better compromise between efficacy and acceptability
- Conservative interpretation is warranted for the results for netakimab, sonelokimab, deucravacitinib, acitretin, ciclosporin, fumaric acid esters, and methotrexate, as these drugs in the NMA have only been evaluated in few trials.

Kommentare zum Review

- Sbidian E et al., 2022 [15]: The evidence is limited to a selected trial population (participants were young (mean age of 44.5 years), had a high level of disease severity (with an overall mean score of PASI 20.4 at baseline, and were long-time sufferers), and had few major comorbidities), and the NMA evidence was limited to the induction treatment phase (all results were measured from 8 to 24 weeks after randomisation), which is not relevant enough for a chronic disease, which would require long-term treatment.
- Ravasio, R. et al., 2022 [13]: The clinical efficacy was evaluated in terms of NNT, based on the results of a recent network meta-analysis (NMA) by the Cochrane Database of Systematic Reviews (Sbidian et al., 2020). One-hundred and forty trials (51,749 patients) were included in the NMA. Considering the proportion of patients who achieve PASI90, ixekizumab showed the lowest NNT among all comparators (ixekizumab 2.01 [2.46-3.00]; risankizumab 2.05 [2.50-3-05]; guselkumab 2.16 [2.68-3.36]; secukinumab 2.40 [2.90-3.51]; brodalumab 2.61 [3.18-3.88]; ustekinumab 3.44 [4.12-4.95]; tildrakizumab 3.10 [4.15-5.59]. The findings show that ixekizumab is the most effective option (NNT) for the treatment of moderate to-severe plaque psoriasis.

3.2 Systematische Reviews

Feng Y et al., 2022 [8].

Risk of Candida Infection and Serious Infections in Patients with Moderate-to-Severe Psoriasis Receiving Biologics: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Fragestellung

This systematic review and metaanalysis intended to review RCTs that enrolled adults with moderate-to-severe plaque psoriasis to determine the risk of Candida infection and serious infections among these biological therapies against placebos or conventional systemic therapeutics.

Methodik

Population:

- Patients were ≥18 years old and had moderate to-severe plaque psoriasis;

Intervention:

- anti-IL-17 agents and other biologic agents

Komparator:

- another biological agent or conventional systematic therapy or placebo

Endpunkte:

- Candida infection

Recherche/Suchzeitraum:

- PubMed, EMBASE, and Cochrane Library databases were searched for all studies from their inception to December 2021

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool; GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 52 RCTs involving 27297 patients

Charakteristika der Population/Studien:

- There were 51 RCTs [22–63, 65–69] that reported the number of serious infections, with 10 RCTs (19.6%) [31, 32, 36, 39, 40, 43, 46, 56, 57, 66] that had no serious infection in either study arm.
- Eighteen RCTs (34.6%) [44, 47–55, 64, 65, 67–69] provided the number of patients who developed Candida infection.
- The randomized controlled phase lasted 12–52 weeks in all RCTs.

Qualität der Studien:

- The bias risk of the included RCTs was critically assessed using the Cochrane collaboration tool. We found that 45 RCTs (86.53%) described the methods of patient randomization, 44 RCTs (84.61%) reported concealment of allocation, 40 RCTs (76.92%)

described blinding of participants and personnel, and 31 RCTs (59.61%) mentioned about an assessor of outcomes. Incomplete outcome data were well balanced in 49 RCTs (94.23%). Selective outcome reporting and other sources of bias were not identified in 38 RCTs (73.08%) and 31 RCTs (59.61%), respectively

Studienergebnisse:

Candida infection

Comparison between Biological Agents

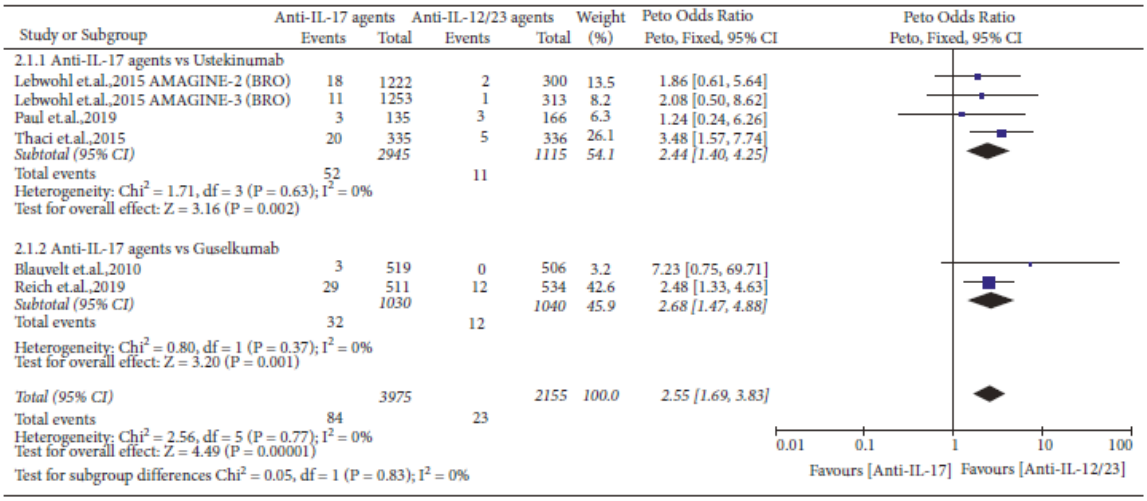


FIGURE 3: Forest plot of pooled data regarding *Candida* infections between anti-interleukin (IL)-17 agents and anti-IL-12/23 agents. CI, confidence interval.

Comparison of Biological Agents with Methotrexate (MTX)

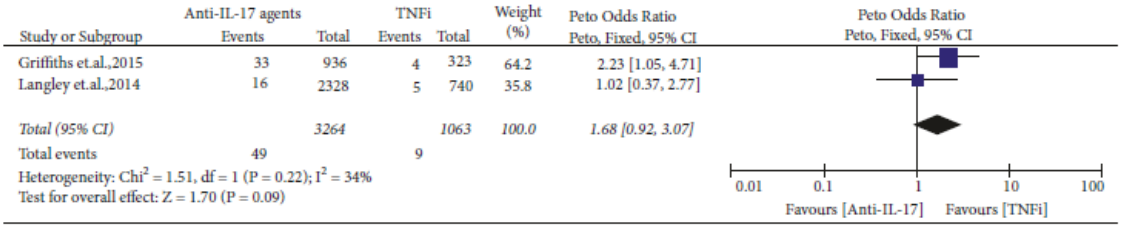


FIGURE 4: Forest plot of pooled data regarding *Candida* infections between anti-interleukin (IL)-17 agents and tumor necrosis factor inhibitors (TNFi). CI, confidence interval.

Serious infection

Comparison between Biological Agents

- A total of 11 RCTs assessed the risk of serious infection between biological agents, of which two RCTs compared anti-IL-17 agents and TNFi (Peto OR= 0.99, 95% CI = 0.42–2.34, P = 0.98) [44, 47], five RCTs compared anti-IL-17 agents and anti-IL-12/23 agents (Peto OR= 0.95, 95% CI = 0.44–2.05, P = 0.90) [48, 50, 65, 68], and four RCTs compared anti-IL-12/23 agents and TNFi (Peto OR= 1.67, 95% CI = 0.63–4.42, P =0.31) [34, 46, 56, 58].
- No significant difference in the risk of serious infection and no evidence of significant heterogeneity (I2 =0% for both comparisons)

Comparison of Biological Agents with Methotrexate (MTX)

- Two RCTs [31, 66] assessed the difference in the risk of serious infections between biological agents and methotrexate. However, no serious infection events occurred in any of the treatment arms.

Anmerkung/Fazit der Autoren

Taken together, the present study suggested that the anti-IL17 agents, especially secukinumab, significantly increased the risk of Candida infection in adults with moderate-tosevere plaque psoriasis. Moreover, an increase in such risk was also found in the anti-IL-17 agents compared with the anti-IL-12/23 agents. No difference in this risk was identified between the anti-IL-17 agents and TNFi. Furthermore, there was no evidence that the biological agents increased the risk of serious infections in adult psoriasis or that the biologics differed in the risk of serious infections.

Singh S et al., 2021 [16].

Efficacy and safety of Risankizumab in moderate to severe psoriasis: A systematic review and meta-analysis

+ siehe Yu Q. et al., 2022 [19]

Fragestellung

In this meta-analysis, we aim to collate information from several clinical trials that were conducted to study the safety and therapeutic efficacy of risankizumab, as a key player in the treatment arsenal against psoriasis.

Methodik

Population:

- Participants with moderate to severe psoriasis

Intervention:

- Risankizumab

Komparator:

- Ustekinumab, Adalimumab, placebo

Endpunkte:

- Primary outcome: Psoriasis Area Severity Index (PASI 90)
- Secondary outcomes: Dermatology Life Quality Index (DLQI) 0 or 1, static Physician's Global Assessment (sPGA) 0 or 1 and sPGA 0

Recherche/Suchzeitraum:

- PubMed, EMBASE, Central Register of Controlled Trials (CENTRAL) and international clinical trial register (clinicaltrials.gov)
- Until June 2020

Qualitätsbewertung der Studien:

- Cochrane Collaboration risk of bias assessment tool, version 2

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 studies
  - Risankizumab vs Ustekinumab: 3 studies
  - Risankizumab vs Adalimumab: 1 study

- Risankizumab vs Placebo: 4 studies

Charakteristika der Population:

- Homogenität der Charakteristik eingeschlossenen Studienpopulation

Qualität der Studien:

- All RCT included in systematic review had low ROB with regard to randomization, deviation from intended intervention, missing data, measurement and reporting of results, except some concerns with randomization concealment in study done by Ohtsuki et al. Hence, the overall risk of bias was recorded as low for all included studies except Ohtsuki et al, which enlisted overall some concerns. However, as all outcomes were assessed by person blinded to treatment, concerns with randomization concealment did not affect the assessment of outcomes

Studienergebnisse: *(Anmerkung FBMed: Fokus auf Ergebnisse aktiv-kontrollierter Studien)*

- Psoriasis area severity index (PASI 90)
  - A total of seven studies were included in analysis with 1533 and 710 patients in Risankizumab and Control group, respectively.
  - Statistically significant more number of patients achieved 90**%** percent improvement in PASI in risankizumab group as compared with control (OR = 11.01 (95% CI = 8.67-13.99); I2 = 94%, P-value <.00001). Similarly, significantly high number of individuals achieved PASI 90 in risankizumab as compared with placebo (OR = 94.33 [95% CI = 50.04-177.82]; I2 = 0%, P-value =.52) as well as **active control group (OR = 3.16 [95% CI = 2.31-4.31]; I2 = 33%, P-value =.22)**
- Dermatology life quality index (DLQI)
  - Statistically significant more number of patients achieved DLQI 0 or 1 scores in risankizumab group as compared to control (OR = 6.95 (95% CI = 5.53-8.75); I2 = 95%, P-value <.00001). Similarly, significantly high number of individuals achieved DLQ1 0 or 1 scores in risankizumab as compared to placebo (OR = 35.54 [95% CI = 21.72-58.15]; I2 = 0%, P-value =.45) as well as **active control group (OR = 2.11 [95% CI = 1.55-2.88]; I2 = 0%, P-value =.49)**.
  - A total of six studies with 1486 and 686 patients in risankizumab and control group, respectively were included in analysis.
- Static physician's global assessment (sPGA) 0 or 1 or sPGA 0
  - Similarly, significantly high number of individuals achieved sPGA 01 or sPGA0 scores in risankizumab as compared to placebo (sPGA01-OR = 76.92 (95% CI = 49.41-119.76); sPGA0-OR = 40.70 (95% CI = 17.85-92.80) as well as **active control group (sPGA01-OR = 3.57 (95% CI = 2.50-5.09); sPGA0-OR = 2.30 (95% CI = 1.62-3.27)**.
  - A total of seven studies with 1533 and 710 patients in risankizumab and control group, respectively were included in analysis.
- Safety outcomes
  - No difference in total serious adverse events (SAE) in risankizumab as compared with control group (OR = 0.86 [95% CI = 0.52-1.41]; I2 = 33%, P-value =.18). However, 44% significant increase in odds of infections with risankizumab (OR = 1.44 [95% CI = 1.13-1.83]; I2 = 30%, P-value =.20) as compared to control group.

Anmerkung/Fazit der Autoren

In conclusion, the benefit with risankizumab is significantly more as compared to other biologics like adalimumab and ustekinumab.

The chronic and relapsing nature of psoriasis and monoclonal bodies have been explored and recommended for treatment of psoriasis on the basis of accumulated evidence and well-conducted RCT. However, quality of evidence of risankizumab as compared with placebo and other monoclonal antibodies is not well documented.

Xie Y et al., 2021 [18].

Are biologics combined with methotrexate better than biologics monotherapy in psoriasis and psoriatic arthritis: A meta-analysis of randomized controlled trials

Fragestellung

In this meta-analysis, we compared the clinical efficiency and safety profile of biologics plus MTX with biologic monotherapy systemically, trying to elucidate whether biologics plus MTX performs better than biologic monotherapy.

Methodik

Population:

- Adult patients (≥18 years old) with psoriasis or PsA

Intervention:

- Biologics therapy combined with MTX

Komparator:

- biologics monotherapy

Endpunkte:

- Efficiency
  - Psoriasis Area and Severity Index (PASI) responses (including PASI 50, 75, and 90)
  - proportion of patients with Physician's Global Assessment Scale (sPGA) scored 0 or 1
  - American College of Rheumatology (ACR) 20/50/70 responder indices were used to assess the efficiency for PsA
- Safety: Adverse effects number of patients with positive antidrug antibodies (ADAs)
- number of patients with positive antidrug antibodies (ADAs) to biologics

Recherche/Suchzeitraum:

- Pubmed, EMBASE, and the Cochrane Library databases was performed from conception through 5 November 2020.

Qualitätsbewertung der Studien:

- Cochrane risk of bias methods

Ergebnisse

Anzahl eingeschlossener Studien:

- Of those, 15 studies with a total of 4221 patients met the inclusion criteria and were involved in our study.
- Of the 15 included studies, 10 studies used TNF inhibitors (4 for etanercept, 3 for adalimumab, and each of the rest 3 for infliximab, golimumab, and Yisaipu, respectively), while four studies used IL-17A inhibitors (3 for ixekizumab and one for secukinumab). Only two studies examined IL-12/23 inhibitors (ustekinumab)

Charakteristika der Population:

TABLE 1 Characteristics of included studies

References	Country	Age (mean ± SD, years)	Gender (male/female)	Name of biologics	No. of participants	
					Biologics + MTX	Biologics
Combe et al[13]	France	/	/	Ixekizumab	183	193
Edwards et al[14]	Switzerland	48.3 ± 12.3	150/133	Adalimumab	169	114
		47.5 ± 12.0	162/121	Ixekizumab	167	116
Gladman et al[15]	Canada	48.6 ± 12.5	85/66	Adalimumab	75	76
Gottlieb et al, 2012[16]	United States	44.1 ± 13.0	320/158	Etanercept	239	239
Kavanaugh et al[17]	United States	47.1 ± 12.8	71/29	Infliximab	47	53
Kavanaugh et al[18]	United States	45.7 ± 11.3	128/113	Golimumab	163	78
Kraaig et al[19]	Netherlands	/	/	Adalimumab	31	30
Liu et al, 2019[20]	China	43.1 ± 12.4	355/100	rhTNFR-Fc	226	229
McInnes et al[21]	United Kingdom	47.5	222/187	Ustekinumab	200	209
McInnes et al[22]	United Kingdom	47.3 ± 11.9	153/146	Secukinumab	135	164
Mease et al, 2019[23]	United States	48.3 ± 13.1	295/272	Etanercept	283	284
Nash et al, 2018[24]	United States	52.3 ± 12.5	104/117	Ixekizumab	109	112
Ritchlin et al, 2014[25]	United States	48.5	97/111	Ustekinumab	106	102
Yu et al, 2019[26]	China	51.9 ± 14.7	20/10	Etanercept	15	15
Zachariae et al, 2008[27]	Denmark	48.1	43/16	Etanercept	31	28

Abbreviations: MTX, methotrexate; rhTNFR-Fc, recombinant human TNF-α receptor II: IgG Fc fusion protein.

Qualität der Studien:

- 3 of the 15 RCT studies were categorized as low risk of bias, nine studies as unclear, and three as high.
- The high risk of bias was mainly caused by incomplete blinding. Ten of the 15 studies reported adequate random sequence generation, while the rest reported no related information. And allocation concealment was adequate in 6 studies, but could not be assessed in 8 studies. For the blinding of patients and personnel, the number of studies reported complete blinding, incomplete blinding, and no information of blinding was 4, 3, and 8, respectively.

Studienergebnisse: *(Anmerkung FBMed: Fokus auf Ergebnissen zu Psoriasis Patienten)*

- Improvement in skin lesions of psoriasis was reported in 9 studies and measured by PASI 50, 75, 90, and sPGA.
- All of the 9 RCTs were about TNF inhibitors.
- […] no matter at week 12 (PASI 50, RR = 1.14, 95%CI 1.07-1.20; PASI 75, RR = 1.37, 95%CI 1.23-1.53; PASI 90, RR = 1.58, 95%CI 1.28-1.95; sPGA, RR = 1.56, 95%CI 1.34-1.82) or at week 24 (PASI 50, RR = 1.09, 95%CI 1.04-1.14; PASI 75, RR = 1.25, 95%CI 1.15-1.35; PASI 90, RR = 1.57, 95%CI 1.37-1.80; sPGA, RR = 1.31, 95%CI 1.20-1.43), all of these measurements revealed **significantly greater improvement in combination group** than monotherapy group. And the same favor of combination therapy as at week 12 and week 24 was also observed at week 48, even only the combined estimate of PASI 75 (RR = 1.41, 95%CI 1.09-1.82) was obtained.
- Besides, no substantial heterogeneity was detected among all of these estimates, except for sPGA.

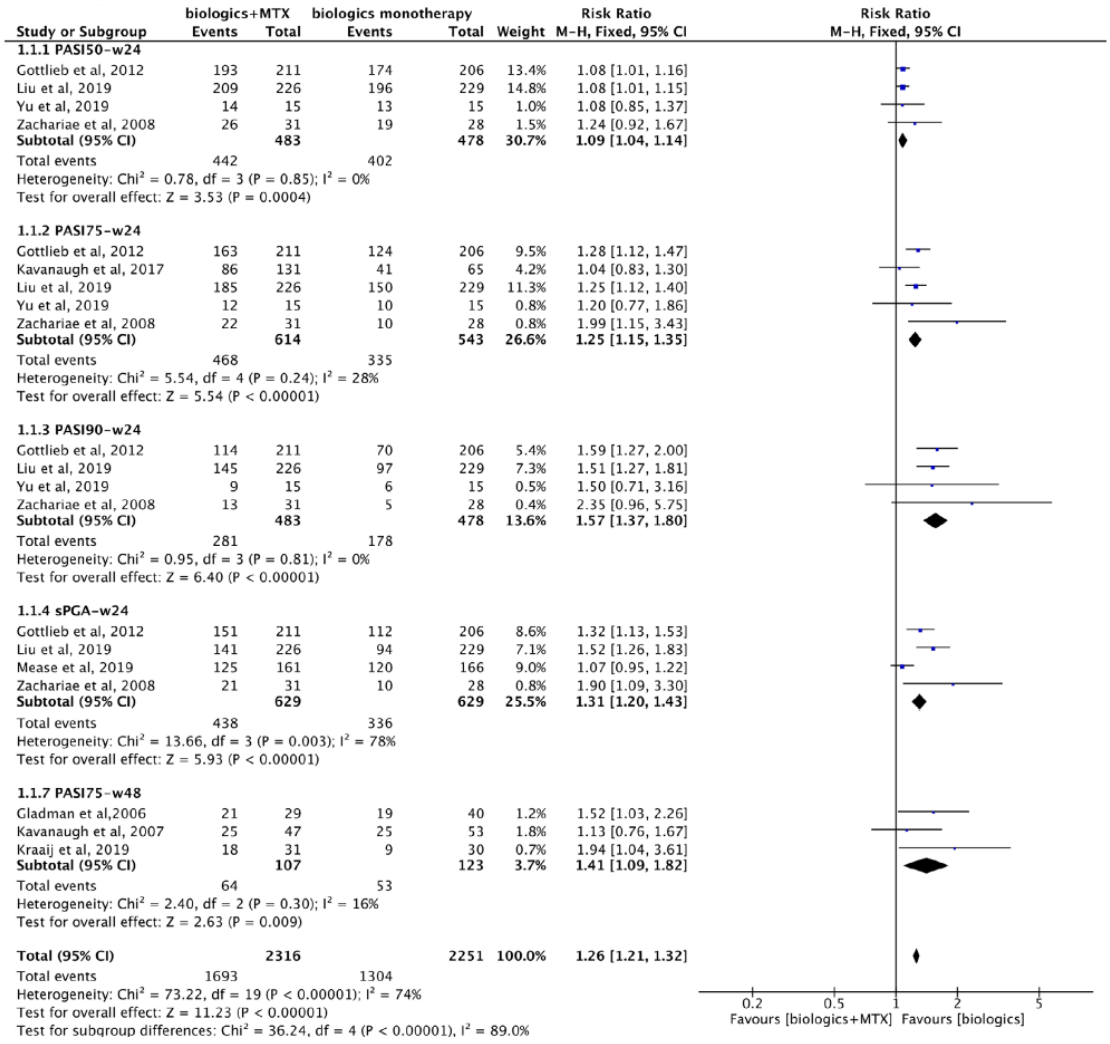


FIGURE 2 The forest plot for clinical efficiency of psoriasis, estimated by PASI and sPGA response, at week 24 and week 48. PASI, Psoriasis Area and Severity Index; sPGA, Physician's Global Assessment Scale

Anmerkung/Fazit der Autoren

In conclusion, this study suggested that biologics plus MTX performed better on improving the clinical efficiency of treating psoriasis when compared with biologic monotherapy, without a difference in tolerability. However, this combination failed to improve the clinical efficiency when treating PsA. More studies are needed to elucidate relevant problems.

Erichsen CY et al., 2020 [6].

Biologic therapies targeting the interleukin (IL)-23/IL-17 immune axis for the treatment of moderate-to-severe plaque psoriasis: a systematic review and meta-analysis

Fragestellung

This systematic review and meta-analysis evaluated the efficacy and safety of induction therapy (12–16 weeks) with biologic therapies targeting the IL-23/IL-17 immune axis for the treatment of moderate-to-severe plaque psoriasis.

Methodik

Population:

- Participants had to be adults (18 years of age or above) with clinically diagnosed moderate-to-severe plaque psoriasis at any stage of treatment. Moderate-to-severe plaque psoriasis was defined as disease involvement of 10% or more of the total body surface area and a Psoriasis Area and Severity Index (PASI) score of 10 or more

Intervention:

- biological therapy targeting the IL-23/IL-17: ustekinumab, ixekizumab, secukinumab, brodalumab, guselkumab, tildrakizumab and risankizumab

Komparator:

- placebo or a systemic therapy approved for treatment of moderate-to-severe plaque psoriasis

Endpunkte:

- Outcomes were reported in week 12 or 16:
  - Proportion of study population who achieved a 90% reduction in Psoriasis Area and Severity Index (PASI90).
  - Proportion of study population that experienced adverse events (AEs) and serious adverse events (SAEs)

Recherche/Suchzeitraum:

- EMBASE and PubMed databases up to 2 January 2019

Qualitätsbewertung der Studien:

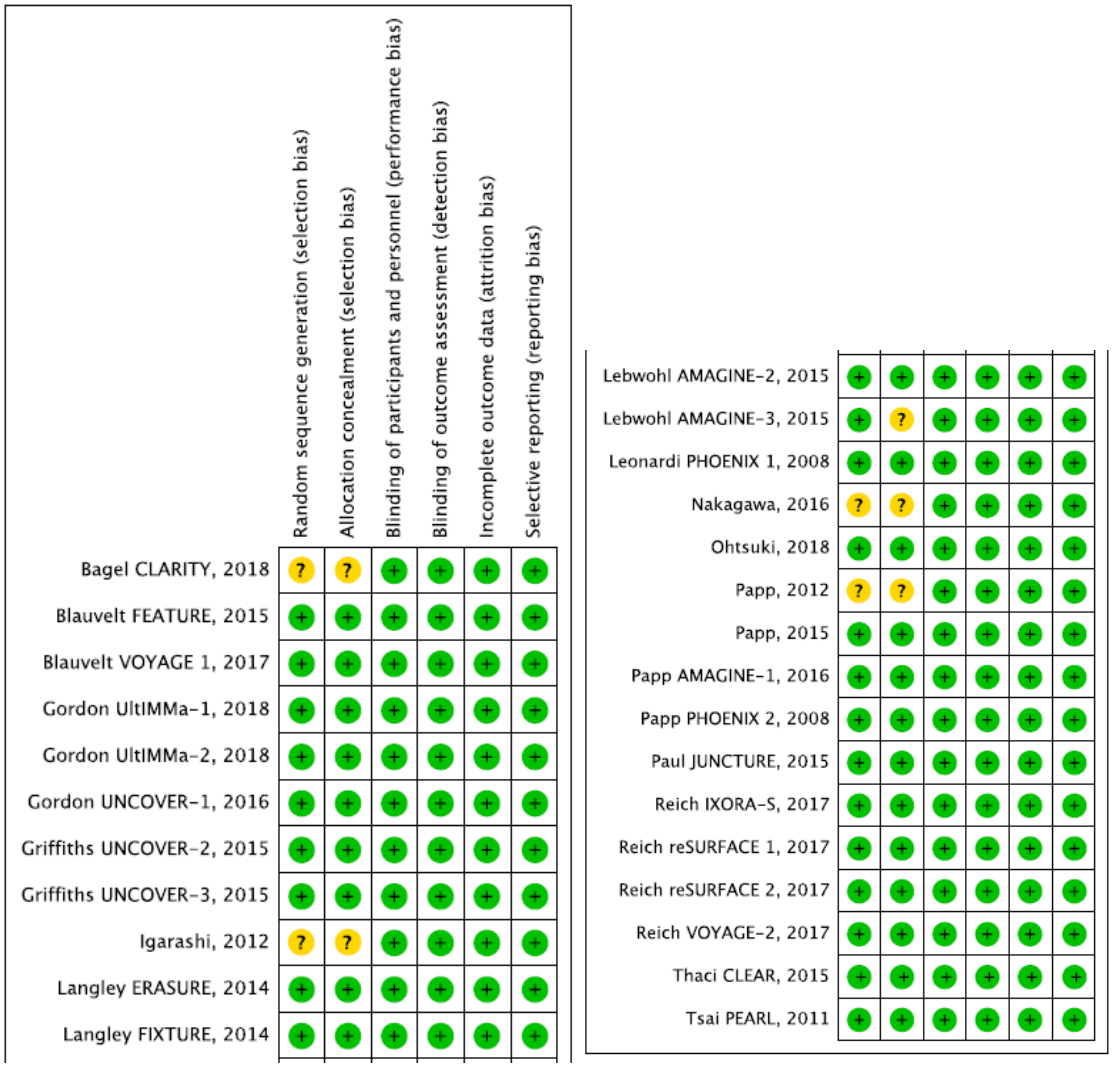
- risk of bias (RoB) was assessed using Cochrane's 'RoB' tool

Ergebnisse

Anzahl eingeschlossener Studien:

- The 27 eligible RCTs included four trials of ustekinumab,(13–16) four of ixekizumab,(17–19) six of secukinumab,(20–24) five of brodalumab, (25–28) three of guselkumab,(29–31) three of tildrakizumab (32,33) and two of risankizumab (34).

Qualität der Studien:



Studienergebnisse: *(Anmerkung FBMed: Fokus auf Ergebnisse aktiv-kontrollierter Studien)*

- Etanercept-controlled trials
  - Three biologics were compared to etanercept, and they were all superior to etanercept in terms of achieving PASI 90 at week 12
  - There was no increased risk of AEs or SAEs with any of the biologics compared to etanercept, and there was a lower risk of AEs with tildrakizumab 100 mg
- Adalimumab-controlled trials
  - Guselkumab was the only biologic to be compared to adalimumab. At week 16, guselkumab 100 mg was superior to adalimumab in terms of achieving PASI 90,
  - was no increased risk of AEs or SAEs
- Ustekinumab-controlled trials
  - Four biologics were compared to ustekinumab and were all, except brodalumab 140 mg, superior to ustekinumab in terms of achieving PASI 90 at weeks 12–16. Compared to ustekinumab, ixekizumab q2w had thegreatest RR of achieving PASI 90 followed by risankizumab 150 mg, brodalumab 210 mg and secukinumab 300 mg (Table 2).
  - There was no increased risk of AEs or SAEs with any of the biologics compared to ustekinumab, and there was a lower risk of SAEs with risankizumab 150 mg

Compared against etanercept		
Ixekizumab q2w	3.14 [2.22, 4.45]	2
Ixekizumab q4w	2.83 [2.29, 3.49]	2
Secukinumab 150 mg	2.02 [1.58, 2.59]	1
Secukinumab 300 mg	2.61 [2.06, 3.31]	1
Tildrakizumab 100 mg	1.81 [1.40, 2.34]	1
Tildrakizumab 200 mg	1.71 [1.32, 2.21]	1
Compared against adalimumab		
Guselkumab 100 mg	1.48 [1.35, 1.63]	2
Compared against ustekinumab		
Ixekizumab q2w	1.73 [1.41, 2.12]	1
Secukinumab 300 mg	1.40 [1.30, 1.50]	2
Brodalumab 140 mg	1.06 [0.96, 1.18]	2
Brodalumab 210 mg	1.46 [1.34, 1.60]	2
Risankizumab 150 mg	1.67 [1.42, 1.96]	2

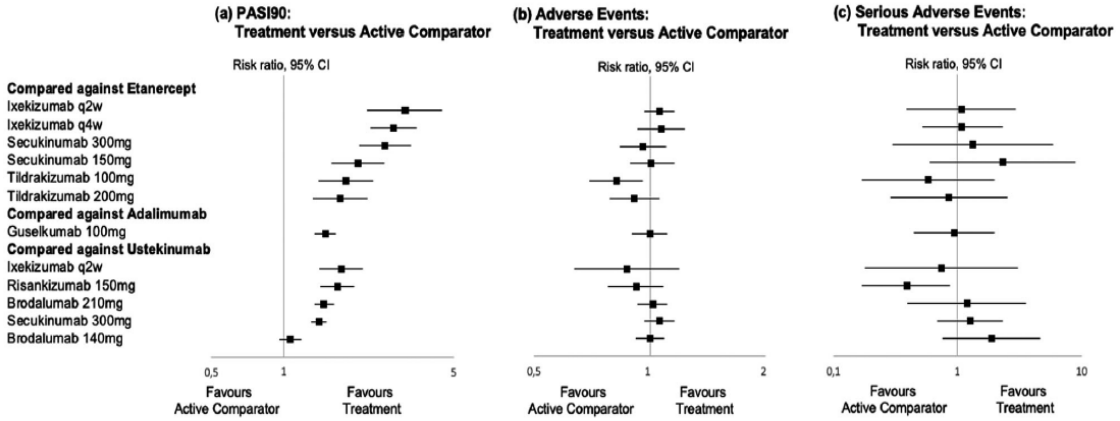


Figure 4 Relative risk with 95% confidence interval for (a) achieving 90% reduction in Psoriasis Area and Severity Index, (b) adverse events and (c) serious adverse events for biologic therapy compared against an active comparator.

Fazit der Autoren

The IL-17 inhibitors were overall shown to have a higher efficacy than the IL-23 inhibitors during induction therapy. However, the IL-17 inhibitors had an increased risk of adverse events when compared to placebo, while there was no increased risk with any of the IL-23 inhibitors. In conclusion, induction therapy with IL-17 inhibitors is highly efficacious but carries a higher risk of adverse events than induction therapy with IL-23 inhibitors.

3.3 Leitlinien

DDG 2021 [3].

Deutsche Dermatologische Gesellschaft (DDG)

Deutsche S3-Leitlinie zur Therapie der Psoriasis vulgaris

\+ Nast A et al. [12]

Zielsetzung/Fragestellung

Allgemeines Ziel der Leitlinie ist es, Ärztinnen und Ärzte in der Praxis und Klinik eine anerkannte, evidenzbasierte Entscheidungshilfe für die Auswahl sowie Durchführung einer geeigneten und adäquaten Therapie für Patientinnen und Patienten mit mittelschwerer bis schwerer Psoriasis vulgaris an die Hand zu geben. Damit sollen die durch die Psoriasis verursachte Morbidität vermindert und Beeinträchtigungen der gesundheitsbezogenen Lebensqualität besser vermieden werden.

Methodik

Grundlage der Leitlinie

Diese Leitlinie ist ein Update der Fassung von 2017 “S3 Leitlinie zur Behandlung der Psoriasis vulgaris”

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: Gültigkeit der Leitlinie nach inhaltlicher Überprüfung durch das Leitliniensekretariat verlängert bis 30.6.2023.

Recherche/Suchzeitraum:

- Since Cochrane reviews represent the gold standard with regard to methodological rigor, a member of the EuroGuiDerm Team (CD) joined the Cochrane Team to support efficient work and save resources and to foster the production of one rigorously conducted, high quality systematic review and network-meta analysis.
- Furthermore, a number of special topics were supported by systematic searched or systematic literature reviews:

TABLE 5: OVERVIEW OF SPECIFIC TOPICS & TYPE OF EVIDENCE REVIEW THE RECOMMENDATIONS ARE BASED ON

Topic	Type of evidence review
Evidence review methods for part 1: general recommendation for adult patients with plaque type psoriasis:	
Psoriasis vulgaris	Sbidian E, Chaimani A, Afach S, Doney L, Dressler C, Hua C, Mazaud C, Phan C, Hughes C, Riddle D, Naldi L, Garcia-Doval I, Le Cleach L. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD011535. DOI: 10.1002/14651858.CD011535.pub3. The methods are reported in the full review document : https://doi.org/10.1002/14651858.CD011535.pub3 (also available upon request euroguiderm@debm.de) A protocol 'Systemic pharmacological treatments for chronic plaque psoriasis' (Sbidian 2015) was published for the first review. This review is an update of 'Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis' (Sbidian 2017).

- Several chapters /author groups were supported by a methodologist who conducted systematic search. The non-systematic selection of published materials was not restricted by publication type. Guideline were included, also from other specialisties. We used the AGREE II instrument domain 8 to evaluate the 13 identified evidence-based guidelines

LoE/GoR

Strength	Wording	Symbols	Implications
Starke Empfehlung für eine Vorge-hensweise	„wird empfohlen“ / „wir empfehlen“	↑↑	Wir sind der Auffassung, dass alle oder fast alle informierten Menschen eine Entscheidung zugunsten dieser Intervention treffen würden. Kliniker*innen müssen sich weniger Zeit für den Prozess der Entscheidungsfindung mit den Patient*innen nehmen und können diese Zeit stattdessen für die Überwindung von Barrieren bei der Implementierung und der Therapieadhärenz einsetzen. In den meisten

			klinischen Situationen kann die Empfehlung als allgemeine Vorgehensweise übernommen werden.
Schwache Empfehlung für eine Vorgehensweise	„kann empfohlen werden“	↑	Wir sind der Auffassung, dass die meisten informierten Menschen, ein substanzieller Anteil jedoch nicht, eine Entscheidung zugunsten dieser Intervention treffen würden. Kliniker*innen und andere Anbieter*innen von Gesundheitsleistungen müssen sich mehr Zeit für den Prozess der Entscheidungsfindung mit dem Patienten nehmen. Entscheidungsprozesse im Gesundheitssystem erfordern eine tiefgehende Diskussion und die Einbeziehung vieler Interessengruppen.
Empfehlung **offen /** keine Empfehlung	„es kann keine Empfehlung für oder gegen … ausgesprochen werden“	0	Zur Zeit kann eine Empfehlung für oder gegen diese Interventionaufgrund bestimmter Gege-benheiten nicht getroffen werden (z.B. unklares oder ausgeglichenes Nutzen-/Risiko-Verhältnis, keine verfügbare Evidenz, etc.)
Schwache Empfehlung **gegen** eine Vorgehensweise	„kann nicht empfohlen werden“	↓	Wir sind der Auffassung, dass die meisten informierten Menschen, ein substanzieller Anteil jedoch nicht, eine Entscheidung gegen diese Intervention treffen würden.
Starke Empfehlung **gegen** eine Vorgehensweise	„wird nicht empfohlen“	↓↓	Wir sind der Auffassung, dass alle oder fast alle informierten Menschen eine Entscheidung gegen diese Intevention treffen würden. In den meisten klinischen Situationen kann die Empfehlung als allgemeine Vorgehensweise übernommen werden.

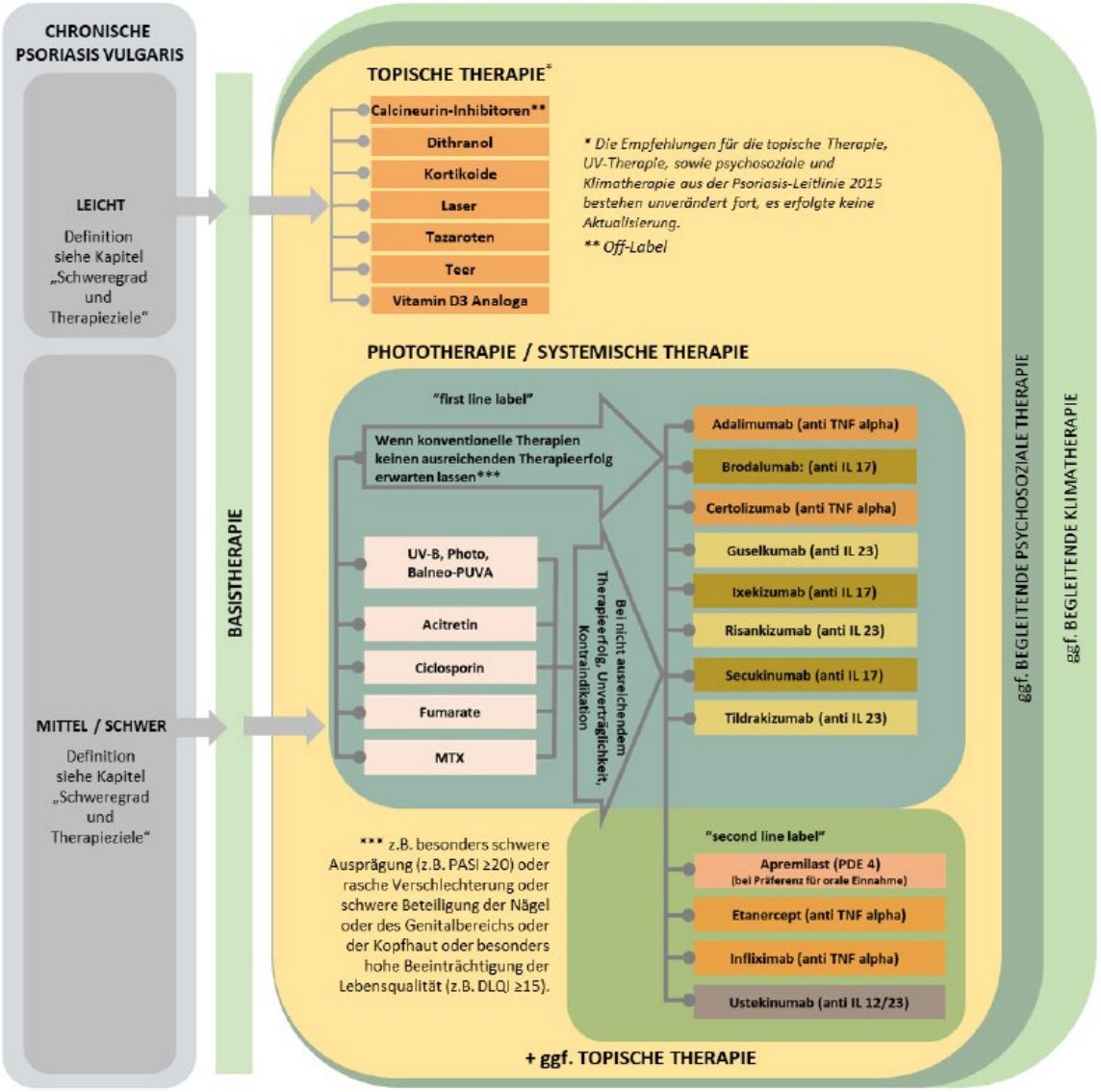
Sonstige methodische Hinweise

- Bei dieser Leitlinie handelte es sich um eine Adaption der EuroGuiDerm Guideline On The Systemic Treatment Of Psoriasis von Nast A et al. [12]

Allgemeine Empfehlungen

Es wird empfohlen, Wirksamkeit, Sicherheit *(siehe jeweilige Abb./Cochrane Review und Medikamentenkapitel)*, die Zeit bis zum Wirkungseintritt, Komorbiditäten *(siehe "decision grid" und jeweilige Kapitel)*, und individuelle Patientenfaktoren bei der Auswahl einer systemischen Therapie bei mittelschwerer bis schwerer Psoriasis vulgaris zu berücksichtigen.	↑↑	KONSENS EVIDENZ- UND KONSENSZBASIERT, SIEHE APPENDIX 1
Bei Patienten mit mittelschwerer bis schwerer *(Definition siehe Kapitel „Schweregrad und Therapieziele")* Psoriasis vulgaris **wird** die Einleitung einer systemischen Therapie **empfohlen.**	↑↑	STARKER KONSENS KONSENSBASIERT
Für Patienten, die eine systemische Therapie benötigen, **wird** in der Regel die Einleitung einer "konventionellen" Systemtherapie **empfohlen** (entsprechend des Wirtschaftlichkeitsgebotes).	↑↑	STARKER KONSENS EVIDENZ- UND KONSENSZBASIERT, SIEHE APPENDIX 1
Die Einleitung einer Therapie mittels Biologikum **wird empfohlen**, wenn die konventionelle Therapie keinen ausreichenden Therapieerfolg gezeigt hat oder unverträglich ist oder kontraindiziert ist.	↑↑	STARKER KONSENS EVIDENZ- UND KONSENSZBASIERT, SIEHE APPENDIX 1
Bei Vorliegen einer Psoriasis, bei der konventionelle Therapie keinen ausreichenden Therapieerfolg erwarten lässt*, **kann** die Einleitung einer Therapie mit einem Biologikum mit einem "first line label"** **empfohlen werden**. **z.B. besonders schwere Ausprägung (z.B. PASI >=20) oder rasche Verschlechterung oder schwere Beteiligung der Nägel oder des Genitalbereichs oder der Kopfhaut oder besonders hohe Beeinträchtigung der Lebensqualität (z.B. DLQI >=15)* *** "First line label" bezieht sich auf die therapeutischen Indikation entsprechend der Zulassung der EMA (European Medical Agency).*	↑	STARKER KONSENS KONSENSBASIERT
Wenn eine orale Therapieoption gewünscht ist und eine „konventionelle" Systemtherapie keinen ausreichenden Therapieerfolg erbracht hat, unverträglich oder kontraindiziert, **kann** eine Therapie mit Apremilast **empfohlen werden**.	↑	STARKER KONSENS EVIDENZ- UND KONSENSZBASIERT, SIEHE APPENDIX 1

Übersicht der Therapieoptionen



Zusammenfassung der Netzwerk-Metaanalyse (aus Sbidian et al. 2020)

"[...] Auf der Ebene der Wirkstoffgruppen zeigte sich in der Netzwerk-Metaanalyse, dass alle Interventionen (d.h. konventionelle Systemtherapeutika, niedermolekulare Wirkstoffe und Biologika) in Bezug auf das Erreichen einer PASI 90-Antwort signifikant wirksamer waren als Placebo.

Ebenfalls auf der Wirkstoffgruppenebene waren die biologischen Systemtherapien mit anti-IL17-, anti-IL12/23-, anti-IL23- oder anti-TNF-alpha-Substanzen signifikant wirksamer in Bezug auf das Erreichen einer PASI 90-Antwort als die niedermolekularen Wirkstoffe und die konventionellen Systemtherapeutika.

Auf der Ebene der einzelnen Wirkstoffe zeigten sich Infliximab, alle der anti-IL17-Substanzen (Ixekizumab, Secukinumab, Bimekizumab und Brodalumab) sowie die anti-IL23-Substanzen (Risankizumab und Guselkumab, aber nicht Tildrakizumab) signifikant wirksamer als Ustekinumab und drei anti-TNF-alpha-Substanzen (Adalimumab, Certolizumab und Etanercept), was das Erreichen einer PASI-90-Antwort betrifft. Adalimumab und Ustekinumab waren im Erreichen einer PASI-90-Antwort signifikant wirksamer als Certolizumab und Etanercept. Es zeigte sich kein signifikanter Unterschied zwischen Tofacitinib oder Apremilast und zwischen zwei konventionellen Wirkstoffen: Ciclosporin und Methotrexat.

Die Netzwerk-Metaanalyse zeigte außerdem, dass im Vergleich mit Placebo Infliximab, Ixekizumab, Risankizumab, Bimekizumab, Guselkumab, Secukinumab und Brodalumab wirksamer waren als andere Substanzen, was das Erreichen einer PASI-90-Antwort betrifft. Die klinische Wirksamkeit aller sieben Wirkstoffe erwies sich, wie im Folgenden dargestellt, als ähnlich: Infliximab (versus Placebo): relatives Risiko (RR) 29,52; 95%-Konfidenzintervall (KI) 19,94 bis 43,70; Fläche unter der kumulativen Rangkurve

(Surface Under the Cumulative Ranking, SUCRA) = 88,5; moderate Vertrauenswürdigkeit der Evidenz; Ixekizumab (versus Placebo): RR 28,12; 95%-KI 23,17 bis 34,12; SUCRA = 88,3; moderate Vertrauenswürdigkeit der Evidenz; Risankizumab (versus Placebo): RR 27,67; 95%-KI 22,86 bis 33,49; SUCRA = 87,5; hohe Vertrauenswürdigkeit der Evidenz; Bimekizumab (versus Placebo): RR 58,64; 95%-KI 3,72 bis 923,86; SUCRA = 83,5; niedrige Vertrauenswürdigkeit der Evidenz; Guselkumab (versus Placebo): RR 25,84; 95%-KI 20,90 bis 31,95; SUCRA = 81; moderate Vertrauenswürdigkeit der Evidenz; Secukinumab (versus Placebo): RR 23,97; 95%-KI 20,03 bis 28,70; SUCRA = 75,4; hohe Vertrauenswürdigkeit der Evidenz; Brodalumab (versus Placebo): RR 21,96; 95%-KI 18,17 bis 26,53; SUCRA = 68,7; moderate Vertrauenswürdigkeit der Evidenz.
Die Ergebnisse für Bimekizumab (sowie auch für den Tyrosinkinase-2-Inhibitor, Acitretin, Ciclosporin, Fumarsäureester und Methotrexat) bedürfen einer konservativen Auslegung, da diese im Rahmen der Netzwerk-Metaanalyse in nur wenigen Studien evaluiert wurden.
Bei keinen der Interventionen fanden wir im Placebovergleich einen signifikanten Unterschied in Bezug auf das Risiko, ein schwerwiegendes unerwünschtes Ereignis zu erleiden. Dabei muss aber berücksichtigt werden, dass die Analysen hierzu auf einer sehr niedrigen Anzahl von Ereignissen basieren und unser Vertrauen in insgesamt knapp die Hälfte der betreffenden Effektschätzer gering bis sehr gering war, und in die restlichen war unser Vertrauen moderat. Aus diesen Gründen müssen die Ergebnisse mit Vorsicht interpretiert werden und war die Erstellung einer Rangliste nicht möglich.
Für andere Effektivitätsendpunkte (PASI 75 und Physician Global Assessment (PGA) 0/1) waren die Ergebnisse denen für PASI 90 ähnlich. [...]" (Seite 2, Sbidian et al 2020 20)

Fortbestand der Empfehlungen vom Update 2015

Topische Therapie

a) Wirksamkeit

Die Bewertung in der Spalte Wirksamkeit spiegelt die Prozentzahl der Patienten wieder, die eine PASI-Reduktion um >75 % erreichen.

Skala	topische Therapie
++++	ca. 60 %
+++	ca. 45 %
++	ca. 30 %
+	ca. 15 %
+/-	ca. 5 %
-	n.d. (nicht definiert)

Topische Monotherapie

Therapie	Wirksamkeit	Evidenzniveau Induktionstherapie	Sicherheit / Verträglichkeit bei Erhaltungstherapie	Sicherheit / Verträglichkeit bei	Praktikabilität (Patient)	Praktikabilität (Arzt)	Kosten/ Nutzen
Calcineurin-Inhibitoren	++	2/3	++	nicht indiziert	++	- [1]	++
Dithranol	+++	2	++	nicht indiziert	+ [2] / - [3]	+ [2] / - [3]	+++
Kortikoide	++++ [4]	1	+++	+	++	+++	+++
Steinkohlen-teer	+/-	4	+	nicht indiziert	-	+/-	-
Tazaroten	++	2	++	++	+/- [5]	+/- [5]	++
Vitamin D_3 - Derivate	+++	1	+++	+++	++	+++	++

Globale Einschätzung: schlecht ← → gut

- +/-
- +
- ++
- +++
- ++++

[1] Im Rahmen des Delphi Verfahrens konnte kein starker Konsens (>75%) erzielt werden. Die Empfehlung erfolgte daher mit einem Mehrheitsvotum von 54 % der Experten. Alternativ wurde für "++" gestimmt. Grund der Diskussion war die Verordnung als "off label". Der Aufwand wurde sehr unterschiedlich bewertet.

[2] stationär

[3] ambulant

[4] mindestens Klasse III-Steroid, gilt auch für Fix-Kombinationen

[5] Im Rahmen des Delphi Verfahrens konnte kein starker Konsens (>75%) erzielt werden. Die Empfehlung erfolgte daher mit einem Mehrheitsvotumvon 69 % der Experten. Alternativ wurde für „ - " gestimmt. Grund der Diskussion war die schlechte Verfügbarkeit nur über die Auslandsapotheke. Der Aufwand wurde sehr unterschiedlich bewertet.

Therapieempfehlung

Tacrolimus und Pimecrolimus topisch angewendet 1 - 2 x/d können zur Behandlung der Psoriasis vulgaris bei besonderen Lokalisationen der Psoriasisläsionen, wie Gesicht, Intertrigines und Genito-Anal-Bereich, erwogen werden. →

Eine Anwendung am übrigen Körper kann aufgrund der nicht ausreichenden Datenlage bei vorhandenen Therapiealternativen sowie aufgrund der fehlenden Zulassung nicht empfohlen werden. ↓

Therapieempfehlung

Eine Monotherapie kann bei Patienten mit leichter und mittelschwerer Psoriasis vulgaris zur Induktionstherapie im stationären Bereich empfohlen werden. ↑

Eine Monotherapie kann bei Patienten mit leichter und mittelschwerer Psoriasis vulgaris zur Induktionstherapie im ambulanten Bereich erwogen werden. →

Therapieempfehlung	
Eine Induktionstherapie mit topischen Kortikoiden der Wirkstoffklasse III wird bei leichter bis mittelschwerer Psoriasis vulgaris empfohlen.	↑↑
Eine Induktionstherapie mit topischen Kortikoiden der Wirkstoffklasse IV kann unter Abwägung von erhöhter Wirksamkeit und theoretisch erhöhtem Risiko unerwünschter Arzneimittelwirkungen bei leichter bis mittelschwerer Psoriasis vulgaris empfohlen werden.	↑

Therapieempfehlung	
Die Anwendung von Steinkohlenteer bei Psoriasis vulgaris wird als Monotherapie nicht empfohlen.	↓↓
Die Anwendung von Steinkohlenteer bei Psoriasis in Kombination mit einer UV-Therapie kann in Einzelfällen ausnahmsweise erwogen werden.	→

Therapieempfehlung	
Die topische Anwendung von Tazaroten kann bei der Behandlung von leichter bis mittelschwerer Psoriasis vulgaris erwogen werden.	→

Therapieempfehlung	
Vitamin D_3-Derivate werden zur Induktionstherapie der leichten bis mittelschweren Psoriasis empfohlen.	↑↑
Die fixe Kombination von Vitamin D_3-Derivaten mit Kortikoiden wird in den ersten vier Wochen zur Induktionstherapie der leichten bis mittelschweren Psoriasis empfohlen.	↑↑

Phototherapie

Zusammenfassende Beurteilung
Bezüglich einer Monotherapie erfüllen 35 Studien zur UV-Phototherapie, 40 Studien zur PUVA Therapie sowie neun Studien zu Therapieverfahren mittels Laser die Einschlusskriterien der Leitlinie. Etwa 50 - 75 % aller mit UV-B-Phototherapien behandelten Patienten erreichen eine mindestens 75 %ige Verbesserung des PASI nach vier bis sechs Wochen, häufig wird eine vollständige Erscheinungsfreiheit erzielt (EN 2). Etwa 75 - 100 % aller mit PUVA-Therapie behandelten Patienten erreichen eine mindestens 75 %ige Verbesserung des PASI nach vier bis sechs Wochen, häufig wird eine vollständige Erscheinungsfreiheit erzielt (EN 2). Unter den unerwünschten Wirkungen steht die Dermatitis solaris durch Überdosierung weit im Vordergrund und wird häufig beobachtet. Bei wiederholter oder längerfristiger Anwendung müssen die Folgen hoher kumulativer UV-Dosen bedacht werden wie beispielsweise vorzeitige Hautalterung. Daneben besteht ein kanzerogenes Risiko, das bei oraler PUVA gesichert, für lokale PUVA und UV-B wahrscheinlich ist. Die Praktikabilität der Therapie wird durch die Bindung räumlicher, finanzieller und personeller / zeitlicher Ressourcen auf ärztlicher Seite sowie durch den hohen zeitlichen Aufwand für den Patienten deutlich eingeschränkt. Für die Phototherapie resultiert ein gutes Kosten-Nutzen-Verhältnis aus der Perspektive der Kostenträger. Zu beachten ist jedoch der möglicherweise erhebliche Kosten- und Zeitaufwand für den Patienten.

Therapieempfehlung	
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 geringern Malignitätsrisikos eine Schmalspektrum UV-B-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.	↓

Referenzen aus Leitlinien

Sbidian E, Chaimani A, Afach S, Doney L, Dressler C, Hua C, Mazaud C, Phan C, Hughes C, Riddle D, Naldi L, Garcia-Doval I, Le Cleach L. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD011535. DOI: 10.1002/14651858.CD011535.pub3.

Goulden V et al.,2022 [9].

British Photodermatology Group and the British Association of Dermatologists (BAD)

British Association of Dermatologists and British Photodermatology Group guidelines for narrowband ultraviolet B phototherapy 2022

Zielsetzung/Fragestellung

The document aims to

• offer an appraisal of all relevant literature up to 18 February 2021, focusing on any key developments;

• address important, practical clinical questions relating to the primary guideline objective;

• provide guideline recommendations and, if appropriate, research recommendations.

Methodik

Grundlage der Leitlinie

Produced in 1997 by the British Photodermatology Group and the British Association of Dermatologists (BAD). Reviewed and updated 2004, 2022.

- Repräsentatives Gremium; …
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; …
- Systematische Suche, Auswahl und Bewertung der Evidenz; …
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt; …
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; ….

- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- PubMed, MEDLINE, EMBASE and Cochrane databases: 1st August 2018, updated 18th February 2021
- Additional targeted literature search (for RCTs and SRs) was conducted on the 29th March 2022

LoE

***Table T.2**: Principle domains of bias in randomized controlled trials*

Limitation	**Explanation**
Selection bias – sequence generation and allocation concealment	If those enrolling patients are aware of the group to which the next enrolled patient will be allocated, either because of a non-random sequence that is predictable, or because a truly random sequence was not concealed from the researcher, this may translate into systematic selection bias. This may occur if the researcher chooses not to recruit a participant into that specific group because of 1) knowledge of that participant's likely prognostic characteristics and 2) a desire for one group to do better than the other.
Performance and detection bias – lack of patient and healthcare professional blinding	Patients, care-givers, those adjudicating and/or recording outcomes, and data analysts should not be aware of the arm to which patients are allocated. Knowledge of group can influence 1) the experience of the placebo effect, 2) performance in outcome measures, 3) the level of care and attention received, and 4) the methods of measurement or analysis, all of which can contribute to systematic bias.
Attrition bias	Attrition bias results from loss of data beyond a certain level (a differential of 10% between groups) which is not accounted for. Loss of data can occur when participants are compulsorily withdrawn from a group by the researchers (for example, when a per-protocol approach is used) or when participants do not attend assessment sessions. If the missing data are likely to be different from the data of those remaining in the groups, and there is a differential rate of such missing data from groups, systematic attrition bias may result.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results can also lead to bias, as this may distort the overall impression of efficacy.
Other limitations	For example: Stopping early for benefit observed in randomized trials, particularly in the absence of adequate stopping rules Use of unvalidated patient-reported outcomes Lack of washout periods to avoid carry-over effects in crossover trials Recruitment bias in cluster randomized trials

Table T.3: Overall quality of outcome evidence in GRADE

Level	**Description**
High	Further research is very unlikely to change our confidence in the estimate of effect

Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

GoR

Table 1 Strength of recommendation ratings

Strength	Wording	Symbol	Definition
Strong recommendation for the use of an intervention	'Offer' (or similar, e.g. 'use', 'provide', 'take', 'investigate' etc.)	↑↑	Benefits of the intervention outweigh the risks; most patients would choose the intervention while only a small proportion would not; for clinicians, most of their patients would receive the intervention; for policymakers, it would be a useful performance indicator
Weak recommendation for the use of an intervention	'Consider'	↑	Risks and benefits of the intervention are finely balanced; most patients would choose the intervention, but many would not; clinicians would need to consider the pros and cons for the patient in the context of the evidence; for policymakers it would be a poor performance indicator where variability in practice is expected
No recommendation		Θ	Insufficient evidence to support any recommendation
Strong recommendation against the use of an intervention	'Do not offer'	↓↓	Risks of the intervention outweigh the benefits; most patients would not choose the intervention while only a small proportion would; for clinicians, most of their patients would not receive the intervention

Sonstige methodische Hinweise

- Eine Überprüfung der Leitlinie ist für das Jahr 2027 geplant.

Empfehlungen

General (applies to all treated conditions)

R7 (↓↓) Do not offer NB-UVB phototherapy to people who are taking ciclosporin, mycophenolate, azathioprine or oral tacrolimus (see contraindications) for their skin disease or other conditions, either as combination therapy or as rescue therapy to control flares.

Psoriasis

R10 (↑↑) Offer NB-UVB to people with psoriasis who have an inadequate response to topical therapy, or when topical therapy is not suitable, prior to offering systemic immunosuppression or immunomodulation therapies, including psoralen plus ultraviolet A (PUVA).

R11 (↑) Consider adding NB-UVB to a selected systemic psoriasis treatment (i.e. acitretin, methotrexate, fumaric acid esters, apremilast or biologics) as a short-term rescue therapy to control flares, if psoriasis is normally well controlled on these treatments.

R12 (↑) Consider combination therapy of NB-UVB and acitretin in adults and young people with severe chronic psoriasis, but this must be avoided in anyone of childbearing potential.

NB-UVB in combination with systemic treatments

Methotrexate in combination with NB-UVB has been shown to result in rapid improvement with less cumulative doses of methotrexate or NB-UVB as monotherapy in two RCTs. In the first study 113 of 120 patients completed the trial, with outcome measured at 6 months or when PASI 90 was reached. The combination methotrexate and NB-UVB group cleared significantly quicker than the methotrexate monotherapy group with significantly lower number of phototherapy sessions.16

The second study assessed outcome when PASI 90 was achieved or at 6 months and showed that 35 patients receiving combination methotrexate and NB-UVB achieved a higher clearance rate compared to those receiving methotrexate monotherapy (100% versus 83%). The combination group noted significantly quicker onset of improvement and shorter duration until clearance with a significantly lower cumulative dose than the monotherapy group ($p < 0.05$).18 A higher number of patients on combination therapy were also found to achieve PASI 75 in a recent cohort study.52
There is one study comparing combination acitretin/NB-UVB to NB-UVB monotherapy which showed a greater number of patients achieving both PASI 90 and PASI 60 on the combination arm.53 A RCT of 60 patients comparing combination acitretin/PUVA to combination acitretin/NB-UVB showed no significant difference at the end of treatment between the two groups.54
In a randomized study of 39 psoriasis patients receiving combination NB-UVB/isotretinoin (0.5 mg/kg/day) or combination NB-UVB/placebo for 12 weeks there was no significant difference in clearance between the two groups. However, there was a significant reduction in the number of sessions in favour of the combined group. Although this combination is rarely used, the group argued that isotretinoin is a more suitable option in women of child-bearing potential in comparison to acitretin.
In a RCT of 30 patients, fumaric acid esters in combination with NB-UVB resulted in greater number of patients achieving PASI 75 at week 6 compared with fumaric acid esters monotherapy. However, at 6 months follow-up the outcomes were similar between the two groups.20

<u>NB-UVB in combination with biological therapy</u>
In a RCT, patients with chronic plaque psoriasis and a BMI of ≥35 were randomized to receive a combination of etanercept and NB-UVB or etanercept monotherapy. Addition of NB-UVB did not make a difference to outcomes in 25 patients based on PASI 75.15 Similarly, in a study by Lynde et al., patients treated with combination NB-UVB and etanercept achieved similar PASI 75 to the etanercept monotherapy group at week 24.14
However, some small studies do show this combination to be effective. A prospective within-patient study of 13 subjects showed a significant reduction in the relative modified PASI of selectively UVB treated plaques in patients on etanercept compared to non-irradiated plaques in the same patient.33 In another study, where 20 patients were treated with etanercept, the combination etanercept and NB-UVB was given in eight patients with poor response to both phototherapy and etanercept monotherapy. All patients achieved PASI 75 and three of them had a complete remission after 14.6 ± 3.3 NB-UVB exposures. However, all of these patients relapsed, with PASI > 10 within 2.8 ± 1.7 months.55
A small within-patient RCT compared phototherapy in combination with ustekinumab to ustekinumab monotherapy in ten patients.34 The NB-UVB treated side responded quicker and had a significantly greater PASI reduction than the non-irradiated side.
None of the above studies highlighted increased adverse risks associated with combining a course of NB-UVB and biologics. The studies assessed adding NB-UVB to a biologic and demonstrated that adding NB-UVB to a biologic can in some cases be beneficial compared to biologic monotherapy. However, it is not known whether or not adding a biologic to NB-UVB will be beneficial in comparison to NB-UVB monotherapy.

Smith CH et al., 2020 [17].

British Association of Dermatologists (BAD)

British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020 - a rapid update

Zielsetzung

The overall aim of the guideline is to provide up-to-date, evidence-based recommendations on the use of biologic therapies targeting TNF (adalimumab, etanercept, certolizumab pegol, infliximab), IL12/23p40 (ustekinumab), IL17A (ixekizumab, secukinumab), IL17RA (brodalumab) and IL23p19 (guselkumab, risankizumab, tildrakizumab) in adults, children and young people for the treatment of psoriasis; consideration is given to the specific needs of people with psoriasis and psoriatic arthritis.

Methodik

These guidelines were first produced in 2005 by the British Association of Dermatologists; they have been reviewed and updated in 2009, 2017 and 2020.

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: This rapid update is part of an annual evidence review to factor in the latest evidence for biologic drugs evaluated in the 2017 publication of the guideline.

Recherche/Suchzeitraum:

- All searches were completed on 7th September 2018
- PubMed, MEDLINE, EMBASE and Cochrane databases

LoE

- quality of the evidence will be assessed by GRADE for each outcome

Table I.3 Overall quality of outcome evidence in GRADE

Level	**Description**
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

GoR

Table 1 Strength of recommendation ratings

Strength	Wording	Symbols	Definition
Strong recommendation for the use of an intervention	'Offer' (or similar, e.g. 'provide', 'advise', 'screen')	↑↑	Benefits of the intervention outweigh the risks; most patients would choose the intervention while only a small proportion would not; for clinicians, most of their patients would receive the intervention; for policymakers, it would be a useful performance indicator
Weak recommendation for the use of an intervention	'Consider'	↑	Risks and benefits of the intervention are finely balanced; many patients would choose the intervention but many would not; clinicians would need to consider the pros and cons for the patient in the context of the evidence; for policymakers, it would be a poor performance indicator where variability in practice is expected
No recommendation		Θ	Insufficient evidence to support any recommendation
Strong recommendation against the use of an intervention	'Do not offer'	↓↓	Risks of the intervention outweigh the benefits; most patients would not choose the intervention while only a small proportion would; for clinicians, most of their patients would not receive the intervention

Empfehlungen

Using biologic therapy

R1 (↑↑) Initiation and supervision of biologic therapy for people with psoriasis should be undertaken by specialist physicians experienced in the diagnosis and treatment of

psoriasis. Routine monitoring may be delegated to other healthcare professionals, for example clinical nurse specialists. Manage psoriatic arthritis and/or multimorbidity in consultation with the relevant healthcare professionals.

R3 (↑↑) Offer people with psoriasis who are starting biologic therapy the opportunity to participate in long-term safety registries (the British Association of Dermatologists Biologics and Immunomodulators Registry, BADBIR, in the UK and Republic of Ireland; www.badbir.org).

Criteria for biologic therapy

R4 (↑↑) Offer biologic therapy to people with psoriasis requiring systemic therapy if methotrexate and ciclosporin have failed, are not tolerated or are contraindicated [see National Institute for Health and Care Excellence (NICE) guidelines CG153]7 and the psoriasis has a large impact on physical, psychological or social functioning [for example, Dermatology Life Quality Index (DLQI) or Children's DLQI > 10 or clinically relevant depressive or anxiety symptoms] and one or more of the following disease severity criteria apply:

- the psoriasis is extensive [defined as body surface area (BSA) > 10% or Psoriasis Area and Severity Index (PASI) ≥ 10]
- the psoriasis is severe at localized sites and associated with significant functional impairment and/or high levels of distress (for example nail disease or involvement of high impact and difficult-to-treat sites such as the face, scalp, palms, soles, flexures and genitals).

R5 (↑) Consider biologic therapy earlier in the treatment pathway (e.g. if methotrexate has failed, is not tolerated or is contraindicated) in people with psoriasis who fulfil the disease severity criteria and who also have active psoriatic arthritis […] or who have psoriasis that is persistent, i.e. that relapses rapidly (defined as > 50% baseline disease severity within 3 months of completion of any treatment) off a therapy that cannot be continued in the long term (e.g. narrowband ultraviolet B and ciclosporin).

Reviewing biologic therapy

R11 (↑↑) Assess whether the minimal response criteria have been met, as defined by:

- a 50% or greater reduction in baseline disease severity (e.g. PASI 50 response, or percentage BSA where PASI is not applicable) and
- clinically relevant improvement in physical, psychological or social functioning (e.g. ≥ 4-point improvement in DLQI or resolution of low mood).

R12 (↑) Consider changing to an alternative therapy, including another biologic therapy, if any of the following applies:

- the psoriasis does not achieve the minimum response criteria (primary failure – see R11)
- the psoriasis initially responds but subsequently loses this response (secondary failure)
- the current biologic therapy cannot be tolerated or becomes contraindicated.

Choice of biologic therapy: general considerations

R13 (↑↑) Before initiating or making changes to biologic therapy, take into account both psoriasis and psoriatic arthritis and manage treatment in consultation with a rheumatologist or paediatric rheumatologist.

R14 (↑↑) Tailor the choice of agent to the needs of the person. Take into account the following factors:

Psoriasis factors:

- the goal of therapy [for example, Physician's Global Assessment of clear or nearly clear]

- disease phenotype and pattern of activity
- disease severity and impact
- the presence of psoriatic arthritis (in consultation with an adult or paediatric rheumatologist)
- the outcomes of previous treatments for psoriasis.

Other individual factors:

- person's age
- past or current comorbid conditions (e.g. inflammatory bowel disease, heart failure)
- conception plans
- body weight
- the person's views and any stated preference on administration route or frequency
- likelihood of adherence to treatment.

Drug costs:

- including administration costs, dosage, price per dose and commercial arrangements.

Choice of biologic therapy in adults

R15 (↑↑) Offer any of the currently licensed biologic therapies as first-line therapy (and with reference to R18 and R19) to adults with psoriasis who fulfil the criteria for biologic therapy (see R4 and R5), using the Decision Aid (see File S1: Table S2 in the Supporting Information) to inform treatment choice.

R16 (↑↑) Offer any of the currently licensed biologic therapies (and with reference to R18 and R19) when psoriasis has not responded to a first biologic therapy..

R17 (↑↑) Offer a TNF antagonist (and with reference to R18 and R19) or an IL-17 antagonist* as a first-line therapy to adults with psoriasis and who also have psoriatic arthritis

R18 (↑) Consider etanercept for use in people where a TNF antagonist is indicated and other available biological agents have failed or cannot be used, or where a short half-life is important.

R19 (↑↑) Reserve infliximab for use in people with very severe disease, or where other available biological agents have failed or cannot be used, or where weight-based dosing is a priority.

What to do when a second or subsequent biologic therapy fails in adults

R21 (↑↑) When a person's psoriasis responds inadequately to a second or subsequent biological agent, review treatment goals, seek advice from a dermatologist with expertise in biologic therapy and consider any of the following strategies:

- reiterate advice about modifiable factors contributing to poor response such as obesity and poor adherence (intentional or nonintentional)
- consider whether drug exposure is adequate (see R20)
- optimize adjunctive therapy (e.g. switch from oral to subcutaneous methotrexate)
- switch to an alternative biological agent
- alternative or supplementary nonbiologic therapy approaches (e.g. inpatient topical therapy, phototherapy or systemic therapies).

Psoriasis

A total of 21 new studies, representing 19 new RCTs and 5 previously identified RCTs with additional data, were included in the updated meta-analysis. There was no new evidence for infliximab or secukinumab

that met the inclusion criteria. The NMA was updated to include new data from relevant studies, with analyses performed for all doses, and also licensed doses only, separating certolizumab pegol 200 mg and 400 mg into two networks. The GDG were made aware of minor data entry errors in the 2017 NMA2 and had taken this into account when reviewing the final version with all data checked and corrected.

- For the critical efficacy outcome of clear/nearly clear (PASI90), ixekizumab ranked joint best alongside risankizumab (for analyses involving all doses); risankizumab ranked first and ixekizumab second for analyses involving licensed doses only with certolizumab pegol 200 mg, with their positions swapped when only data for certolizumab pegol 400 mg were used.
- Considering the p19 drug class, guselkumab and risankizumab were consistently ranked higher than tildrakizumab for clear/nearly clear (PASI90) (for analyses involving all doses, and licensed doses only with certolizumab pegol 200 mg and 400 mg).
- For IL17 agents, for clear/nearly clear (PASI90), ixekizumab ranked higher than secukinumab and brodalumab (for analyses involving all doses, and licensed doses only with certolizumab pegol 200 mg and 400 mg).
- With respect to TNF antagonists, both adalimumab and certolizumab pegol were ranked higher than etanercept, and equivalent to ustekinumab for clear/nearly clear (PASI90) outcome (for analyses involving all doses, and licensed doses only with certolizumab pegol 200 mg and 400 mg).
- The GDG also noted head-to-head trials data (GRADE evidence tables, Appendix E) indicating both ixekizumab and brodalumab to be more effective than ustekinumab, and guselkumab to be more effective than adalimumab.

Changes in DLQI broadly paralleled efficacy findings, although have not been published for risankizumab (as of the cut-off date for the literature searches for updating this guideline). […]

In the hierarchical cluster analyses, the GDG noted that (as previously reported)2,3 when considering efficacy (clear/nearly clear) or QoL (DLQI) and tolerability (withdrawal due to adverse events), ixekizumab and infliximab clustered together when all doses are factored in (Appendix B1, pages 17-18), and almost clustered together when only licensed doses are included (pages 22-25, with certolizumab pegol 200 mg and 400 mg). With respect to the other biologics, in general, p19 and IL17 agents clustered or almost together, as did ustekinumab, adalimumab and certolizumab pegol, although these groupings were not consistent and varied depending on the outcome (clear/nearly clear vs. DLQI) and the dose (all doses vs. licensed doses only with certolizumab pegol 200 mg and 400 mg). […]

With respect to data beyond 16 weeks, there were only three additional head-to-head RCTs; guselkumab vs. adalimumab, ixekizumab vs. ustekinumab, and risankizumab vs. ustekinumab reporting at 1 year; all reported on efficacy, with guselkumab, and both ixekizumab and risankizumab showing benefit over adalimumab and ustekinumab, respectively. When reviewing the two new observational cohort studies (registry data)7,8 the GDG noted effectiveness findings broadly consistent with findings in clinical trials, with adalimumab, secukinumab and ustekinumab being more effective than etanercept (biologic-naïve or biologic-experienced).

(i) Persistence on therapy

There were a number of new studies on persistence of biologics in psoriasis patients. However, many studies were excluded as they did not include a comparator arm and therefore clinical relevance was difficult to interpret. There were no data for secukinumab, ixekizumab or the five new drugs in either of the two additional (registry) studies that were included.7,9.The majority of studies had 1 year's follow-up, but one study had 3 and 5 years' follow-up. Ustekinumab was noted to show consistently high rates of persistence across multiple real-world cohort studies

(ii) Risk of serious infection

Data from BADBIR showed that there were no significant differences in the associated serious infection risk between etanercept, adalimumab, ustekinumab and traditional systemic therapies in biologic-naïve patients. In an incident cohort of patients, inclusive of both biologic-naïve and biologic-experienced patients, infliximab was shown to be associated with a higher risk of serious infection compared with traditional systemic therapies. The GDG noted that this result may be affected by residual confounding due to the fact that only a select group of patients with severe psoriasis were allowed to be treated with infliximab.

Treatment failure

The only new evidence identified comprised one RCT investigating switching to guselkumab vs. continuing on ustekinumab after an inadequate response to the latter at week 16,15 and reported switching to guselkumab at 26 weeks to be more efficacious (PASI 90) compared to ustekinumab. A meta-analysis was not possible due to insufficient data which is the reason for no GRADE tables or clinical evidence summaries produced.

Hinweis zur Leitlinie:

- Leitlinie für Patienten/Patientinnen mit Psoriasis und Psoriasis Arthritis

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Elmets CA et al., 2021 [4].

American Academy of Dermatology (AAD)

Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures

Zielsetzung

This guideline will cover the use of topical agents and alternative medicine (AM) in the treatment of psoriasis in adults as well as the assessment of disease severity

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Konsensusprozesse; externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert, Gültigkeit 5 Jahre.

Recherche/Suchzeitraum:

- Evidence was obtained by using a search of the PubMed and MEDLINE databases from January 1, 2008, to December 31, 2017

LoE / GoR

I. Good-quality patient-oriented evidence (ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life).
II. Limited-quality patient-oriented evidence.
III. Other evidence, including consensus guidelines, opinion, case studies, or disease-oriented evidence (ie, evidence measuring intermediate,

physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes).

Clinical recommendations were developed on the basis of the best available evidence. 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, case studies, or disease-oriented evidence.

Empfehlungen

Table III. Recommendations and strength of recommendation for topical corticosteroids

Reference number	Recommendations	Strength of recommendation
1.1	The use of class 1, class 2, and class 3-5 topical corticosteroids for up to 4 weeks is recommended for the treatment of plaque psoriasis not involving intertriginous areas	A
1.2	The use of class 1-7 topical corticosteroids for a minimum of up to 4 weeks is recommended as initial and maintenance treatment of scalp psoriasis	A
1.3	The use of topical corticosteroids for >12 weeks can be considered if done under the careful supervision of a physician	C

Table IV. Level of evidence for topical corticosteroids

Recommendation	Reference number	Level of evidence	Studies
Topical corticosteroid for plaque psoriasis not involving intertriginous areas	1.1	I	9-11,13,15,45-47
Topical corticosteroid for scalp psoriasis	1.2	I	16,17,20
Long-term use of topical corticosteroid	1.3	III	Expert opinion

Table XIX. Recommendations and strength of recommendation for the combination of topical agents with biologics

Recommendation number	Recommendation	Strength of recommendation
9.1	The addition of an ultrahigh potency (class 1) topical corticosteroid to standard dose etanercept for 12 weeks is recommended for the treatment of moderate to severe psoriasis	A
9.2	The addition of calcipotriene/betamethasone to standard dose adalimumab for 16 weeks is recommended for the treatment of moderate to severe psoriasis to accelerate clearance of psoriatic plaques.	B
9.3	All topical corticosteroids can be used in combination with any biologics for the treatment of moderate to severe psoriasis	C

Table XX. Level of evidence for the combination of topical agents with biologics

Recommendation	Recommendation number	Level of evidence	Studies
Addition of class 1 topical corticosteroid to standard dose etanercept for psoriasis	9.1	I	[146]
Addition of calcipotriene/betamethasone to standard dose adalimumab for psoriasis	9.2	III	Expert opinion
Topical corticosteroid with biologic for treatment of psoriasis	9.3	III	Expert opinion

Table XXI. Recommendation and strength of recommendation for the combination of topical calcipotriene and methotrexate

Recommendation number	Recommendation	Strength of recommendation
10.1	The addition of topical calcipotriene to standard dose methotrexate therapy is recommended for the treatment of moderate to severe psoriasis. It may lead to lower cumulative doses of methotrexate and increased time to relapse after methotrexate discontinuation	A

Table XXII. Level of evidence for the combination of topical calcipotriene and methotrexate

Recommendation	Recommendation number	Level of evidence	Studies
Calcipotriene and methotrexate for psoriasis	10.1	I	[148]

Table XXIII. Recommendation and strength of recommendation for combination of topical agents and cyclosporine

Recommendation number	Recommendation	Strength of recommendation
11.1	The addition of calcipotriene/ betamethasone dipropionate ointment to low dose (2 mg/kg/d) cyclosporine can be used for the treatment of moderate to severe psoriasis	B

Table XXIV. Level of evidence for the combination of topical agents and cyclosporine

Recommendation	Recommendation number	Level of evidence	Studies
Cyclosporine and calcipotriene/ betamethasone dipropionate for psoriasis	11.1	I	[149]

Table XXV. Recommendation and strength of recommendation for the combination of calcipotriene and acitretin

Recommendation number	Recommendation	Strength of recommendation
12.1	The addition of calcipotriene to standard dose acitretin is recommended for the treatment of moderate to severe psoriasis.	A

Table XXVI. Level of evidence for the combination of calcipotriene and acitretin

Recommendation	Recommendation number	Level of evidence	Studies
Calcipotriene and acitretin for psoriasis	12.1	I	[4]

Elmets CA et al., 2019 [5].

American Academy of Dermatology (AAD)

Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with phototherapy

Zielsetzung

This section covers the use of phototherapy in the treatment of psoriasis in adults.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Konsensusprozesse; externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert, Gültigkeit 5 Jahre.

Recherche/Suchzeitraum:

- Evidence was obtained by using a search of the PubMed and MEDLINE databases from January 1, 2008, to December 31, 2017

LoE / GoR

I. Good-quality patient-oriented evidence (ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life).
II. Limited-quality patient-oriented evidence.
III. Other evidence, including consensus guidelines, opinion, case studies, or disease-oriented evidence (ie, evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes).

Clinical recommendations were developed on the basis of the best available evidence. 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, case studies, or disease-oriented evidence.

Empfehlungen

Table III. Strength of recommendations for NB-UVB

Recommendation No.	Recommendation	Strength of recommendation
1.1	NB-UVB phototherapy is recommended for adults with plaque psoriasis as monotherapy	A
1.2	The recommended starting dose for NB-UVB phototherapy for adults with generalized plaque psoriasis should be based on the MED or determined by using a fixed dose or skin phototype protocol	A
1.3	During the treatment phase, 3-times/wk dosing of NB-UVB phototherapy for adults with generalized plaque psoriasis is recommended	B
1.4	Short-term PUVA monotherapy is more efficacious than NB-UVB for treatment of psoriasis in adults	B
1.5	Though less effective, NB-UVB is preferred to PUVA monotherapy for the treatment of psoriasis in adults because of enhanced safety, convenience, and cost savings	A
1.6	NB-UVB is recommended over BB-UVB monotherapy for adults with generalized plaque psoriasis	A
1.7	NB-UVB monotherapy is recommended for patients with guttate psoriasis, regardless of age	A
1.8	Home NB-UVB phototherapy is recommended for appropriate patients with generalized plaque psoriasis as an alternative to in-office NB-UVB phototherapy	B
1.9	NB-UVB phototherapy is recommended for pregnant women with generalized plaque psoriasis and guttate psoriasis	C
1.10	Concomitant topical therapy with vitamin D analogues, retinoids, and corticosteroids during NB-UVB phototherapy can be used safely with a	B
1.11	Combination therapy with oral retinoids and NB-UVB phototherapy is recommended for appropriate patients with generalized plaque psoriasis who do not respond adequately to monotherapy	B
1.12	Long-term combination therapy with cyclosporine and NB-UVB phototherapy is not recommended for adults with generalized plaque psoriasis because of increased incidence of skin cancer	C
1.13	Combination therapy with apremilast and NB-UVB phototherapy can be considered for adult patients with generalized plaque psoriasis who do not respond adequately to monotherapy	C
1.14	Genital shielding is recommended in all patients during NB-UVB phototherapy to reduce the risk of genital skin cancer	C
1.15	Eye protection with goggles is recommended during NB-UVB phototherapy to reduce the risk of UVB-related ocular toxicity	C
1.16	NB-UVB should be used with caution in patients with a history of melanoma or multiple nonmelanoma skin cancers, history of arsenic intake, and/or prior exposure to ionizing radiation due to the potential risk of photocarcinogenesis	C
1.17	Women of childbearing age receiving NB-UVB phototherapy should take folate supplementation	B
1.18	Maintenance phototherapy can be considered to maintain clinical response	B

BB, Broadband; *MED*, minimal erythema dose; *NB*, narrowband; *PUVA*, psoralen plus ultraviolet A; *UVB*, ultraviolet B.

Table IV. Level of evidence for NB-UVB recommendations

Recommendation	Recommendation No.	Level of evidence	Studies
NB-UVB for adults	1.1	I-II	1-4
Dosing			
• NB-UVB dose based on skin type	1.2	I-II	10,26
• NB-UVB therapy 2-3 times/wk	1.3	I-II	1,12,13
Treatment comparison			
• NB-UVB vs short-term PUVA	1.4	I-II	1-4,18-26
• NB-UVB vs PUVA monotherapy	1.5	I-II	1-4,18-26
• NB-UVB vs BB-UVB	1.6	I-II	1,4,27-30
• NB-UVB home vs in-office	1.8	I	32
Special psoriasis cases			
• NB-UVB and guttate psoriasis	1.7	I-II	11,31,32,72
• NB-UVB and pregnancy	1.9	III	66,67,70,73
Combination therapy			
• NB-UVB + topical therapies	1.10	I-II	33,34,36,74-78
• NB-UVB + oral retinoid	1.11	I-III	43-45
• NB-UVB + cyclosporine	1.12	II	46
• NB-UVB + apremilast	1.13	II	57,58
Precautions			
• Shield genital area	1.14	II	79
• Wear eye protection	1.15	III	Expert opinion
• Screen for a history of skin cancer and previous phototherapy or photochemotherapy	1.16	I-II	26,65,80
• Women who are of childbearing age and taking a folic supplement	1.17	III	66,70
• NB-UVB maintenance dose for remission	1.18	I	8

BB, Broadband; *NB*, narrowband; *PUVA*, psoralen plus ultraviolet A; *UVB*, ultraviolet B.

Table V. Strength of recommendations for BB-UVB

Recommendation No.	Recommendation	Strength of recommendation
2.1	In cases where NB-UVB is unavailable, BB-UVB phototherapy is recommended for use as monotherapy in adults with generalized plaque psoriasis	A
2.2	BB-UVB monotherapy should be considered inferior in efficacy to NB-UVB and oral PUVA monotherapy for use in adults with generalized plaque psoriasis	A
2.3	BB-UVB monotherapy may be offered for use in adults but is considered inferior in efficacy to topical PUVA monotherapy	B
2.4	BB-UVB monotherapy may be considered for use in adults with guttate psoriasis	C
2.5	Genital shielding is recommended in all patients during BB-UVB phototherapy to reduce the risk of genital skin cancer	B
2.6	Eye protection with goggles is recommended during BB-UVB phototherapy to reduce the risk of UVB-related ocular toxicity	C
2.7	Due to the potential risk of photocarcinogenesis, BB-UVB should be used with caution in patients with a history of melanoma or multiple nonmelanoma skin cancers, history of arsenic intake, or prior exposure to ionizing radiation	B
2.8	Acitretin can be considered in combination with BB-UVB for adults with generalized plaque psoriasis	B

BB, Broadband; *NB*, narrowband; *PUVA*, psoralen plus ultraviolet A; *UVB*, ultraviolet B.

Table VI. Level of evidence for BB-UVB recommendations

Recommendation	Recommendation No.	Level of evidence	Studies
BB-UVB for adults	2.1	I-III	1,4,15,81
Comparison			
• BB-UVB vs PUVA	2.2	I-II	1,2,4,19,27
Special psoriasis cases			
• Palmoplantar psoriasis	2.3	I-II	2,19,82
• Guttate psoriasis	2.4	II-III	79,86
Combination therapy			
• BB-UVB + acitretin	2.8	I-II	83,84
Precautions			
• Shield genital area	2.5	II	62,79
• Wear eye protection	2.6	III	Expert opinion
• Screen for a history of skin cancer and previous phototherapy	2.7	II	62,65,87-89

BB, Broadband; *NB*, narrowband; *PUVA*, psoralen plus ultraviolet A; *UVB*, ultraviolet B.

Table VIII. Strength of recommendations for targeted UVB

Recommendation No.	Recommendation	Strength of recommendation
3.1	Targeted UVB phototherapy, including excimer laser (308 nm), excimer light (308 nm), and targeted NB-UVB light (311-313 nm), is recommended for use in adults with localized plaque psoriasis (<10% BSA), for individual lesions, or in patients with more extensive disease	A
3.2	To achieve maximal efficacy, treatment with targeted UVB phototherapy for adults with localized plaque psoriasis should be carried out 2-3 times/wk rather than once every 1-2 wk	A
3.3	The starting dose for targeted UVB phototherapy for adults with localized plaque psoriasis can be determined on the basis of the MED or by a fixed dose or skin phototype protocol	A
3.4	An excimer laser (308 nm) is more efficacious than an excimer light (308 nm), which is more efficacious than localized NB-UVB light (311-312 nm) for the treatment of localized plaque psoriasis in adults	B
3.5	Targeted UVB phototherapy, including excimer laser (308 nm) and excimer light (308 nm), is recommended for use in adults with plaque psoriasis, including palmoplantar psoriasis	A
3.6	Excimer laser (308 nm) may be combined with topical corticosteroids in the treatment of plaque psoriasis in adults	B
3.7	Excimer laser (308 nm) is recommended in the treatment of scalp psoriasis in adults	B

BSA, Body surface area; *MED*, minimal erythema dose; *NB*, narrowband; *UVB*, ultraviolet B.

Table IX. Level of evidence for targeted UVB phototherapy recommendations

Recommendation	Recommendation No.	Level of evidence	Studies
Targeted UVB for adult psoriasis	3.1	I-II	80,90,92-95,110
Dose			
• 2-3 times/wk vs 1-2 times/wk	3.2	I	80
• Initial dose based on minimal erythema dose	3.3	I	80
Comparison			
• Excimer laser vs excimer light vs NB-UVB	3.4	I	80
Special psoriasis type			
• Excimer laser and light for palmoplantar psoriasis	3.5	I-II	80,96-100
• Excimer laser and scalp psoriasis	3.7	II-III	91,93
Combination			
• Excimer laser + topical therapy	3.6	II	108

NB, Narrowband; *UVB*, ultraviolet B.

Table XII. PUVA therapy strength of recommendation

Recommendation No.	Recommendation	Strength of recommendation
4.1	Topical PUVA phototherapy is superior to localized NB-UVB light (311 to 313 nm) in the treatment of localized plaque psoriasis, particularly for palmoplantar psoriasis and palmoplantar pustular psoriasis, in adults	B
4.2	Oral PUVA is recommended for the treatment of psoriasis in adults	A
4.3	Bath PUVA is recommended for the treatment of moderate to severe plaque psoriasis in adults	B

NB, Narrowband; *PUVA*, psoralen plus ultraviolet A; *UVB*, ultraviolet B.

Table XIII. Level of evidence of PUVA recommendations

Recommendation	Recommendation No.	Level of evidence	Studies
Type of PUVA therapy administration for adult psoriasis			
• Topical	4.1	I-III	80,103,105
• Oral	4.2	I-II	26,117,119,121-123,130
• Bath	4.3	I-III	1,113-116

PUVA, Psoralen plus ultraviolet A.

Table XIV. Strength of recommendations for PDT

Recommendation No.	Recommendation	Strength of recommendation
5.1	For localized psoriasis, including palmoplantar psoriasis and nail psoriasis, in adults, topical ALA-PDT and MAL-PDT are not recommended	A

ALA, 5-Aminolevulinic acid; *MAL*, methyl aminolevulinic acid; *PDT*, photodynamic therapy.

Table XV. Level of evidence for PDT

Recommendation	Recommendation No.	Level of evidence	Studies
• Topical ALA-PDT and MAL-PDT are not recommended for localized psoriasis, nail psoriasis and palmoplantar psoriasis	5.1	I-II	80,133,134

ALA, 5-Aminolevulinic acid; *MAL*, methyl aminolevulinic acid; *PDT*, photodynamic therapy.

Table XVI. Strength of recommendations for grenz ray, climatotherapy, visible light, Goeckerman, PDL, and IPL therapies

Recommendation No.	Recommendation	Strength of recommendation
6.1	There is insufficient evidence to recommend grenz ray for the treatment of psoriasis	C
7.1	There is sufficient evidence to recommend the use of climatotherapy for the treatment of psoriasis	B
8.1	There is insufficient evidence to recommend the use of visible light to be more effective for the treatment of psoriasis, except in the case of nail psoriasis	C
9.1	There is sufficient evidence to recommend the use of Goeckerman for the treatment of psoriasis	B
10.1	PDL may be considered for nail psoriasis	B

IPL, Intense pulsed light; *PDL*, pulsed dye laser.

Table XVII. Level of evidence for grenz ray, climatotherapy, visual light, Goeckerman, PDL, and IPL therapy recommendations

Recommendation	Recommendation No.	Level of evidence	Studies
Grenz ray	6.1	III	136
Climatotherapy	7.1	II-III	137-139
Visible light therapy	8.1	II-III	141-144
Goeckerman therapy	9.1	II-III	147,148
PDL for nail psoriasis	10.1	II	152

IPL, Intense pulsed light; *PDL*, pulsed dye laser.

Menter A et al., 2020 [10].

American Academy of Dermatology (AAD)

Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies

Zielsetzung

This guideline will cover the use of oral-systemic, nonbiologic medication in the treatment of psoriasis.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Konsensusprozesse; externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert; Gültigkeit der LL 5 Jahre.

Recherche/Suchzeitraum:

- PubMed and MEDLINE databases from January 1, 2011, through December 31, 2017

LoE / GoR

I. Good-quality patient-oriented evidence (ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life)
II. Limited-quality patient-oriented evidence
III. Other evidence, including consensus guidelines, opinion, case studies, or disease-oriented evidence (ie, evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes)

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, case studies, or disease-oriented evidence

Empfehlungen

Table III. Strength of recommendation for methotrexate in psoriasis therapy

Recommendation No.	Recommendation	Strength of recommendation
1.1	Methotrexate is recommended for the treatment of moderate to severe psoriasis in adults.	A
1.2	Methotrexate is less effective than adalimumab and infliximab for cutaneous psoriasis.	A
1.3	Methotrexate is efficacious for treatment of psoriatic arthritis (peripheral arthritis, but not for axial involvement); in psoriatic arthritis, the efficacy of methotrexate is lower than TNF-inhibitors.	B
1.4	Recommended methotrexate dosage typically ranges from 7.5 to 25 mg weekly. The dose can be given as a single dose or in 3 doses over 24 hours.	B
1.5	Methotrexate can be administered orally or subcutaneously.	A
1.6	A test dose should be considered, especially in patients with impaired kidney function.	B
1.7	Administration of folic acid or folinic acid is recommended to reduce the incidence of GI and hepatic adverse effects. Large folic acid and folinic acid doses may reduce the efficacy of methotrexate.	A
1.8	Combination therapy with methotrexate and NB-UVB phototherapy can be considered for adult patients with generalized plaque psoriasis to enhance efficacy and lower cumulative doses of both treatments.	B

GI, Gastrointestinal; *TNF*, tumor necrosis factor; *NB-UVB*, narrowband ultraviolet B.

Table IV. Level of evidence of methotrexate therapy in psoriasis

Recommendation	Recommendation No.	Level of evidence	Studies
• Methotrexate use in psoriasis patients	1.1	I-III	19,27,28,33,35,37-39,65-69
• Methotrexate less effective than ADA or IFX	1.2	I-II	27,28,33,68,69
• Methotrexate treatment for psoriatic arthritis	1.3	I	31,32
• Methotrexate weekly dosage • Methotrexate taken orally or subcutaneously • Methotrexate test dose • Folic acid and folinic acid use with methotrexate treatment	1.4-1.7	I, III	15,16,18,20,22,23 and expert consensus (1.7)
Combination therapy • Methotrexate and NB-UVB	1.8	I	37-39

ADA, Adalimumab; *IFX*, infliximab; *NB-UVB*, narrowband ultraviolet B.

Table VII. Strength of recommendation for the apremilast in psoriasis therapy

Recommendation No.	Recommendation	Strength of recommendation
2.1	Apremilast is recommended for the treatment of moderate to severe psoriasis in adults.	A

Table VIII. Level of evidence for apremilast in psoriasis therapy

Recommendation	Recommendation No.	Level of evidence	Studies
Apremilast and psoriasis	2.1	I	86,93-97

Table X. Strength of recommendation for cyclosporine therapy in psoriasis

Recommendation No.	Recommendation	Strength of recommendation
3.1	Cyclosporine is recommended for patients with severe, recalcitrant psoriasis.	A
3.2	Cyclosporine can be recommended for the treatment of erythrodermic, generalized pustular, and/or palmoplantar psoriasis.	B
3.3	Cyclosporine can be recommended as short-term interventional therapy in patients who flare up while on a pre-existing systemic therapy.	C

Table XI. Level of evidence for cyclosporine in psoriasis therapy

Recommendation	Recommendation No.	Level of evidence	Studies
Cyclosporine for psoriasis treatment	3.1	I-III	33,105,112,146 149
Cyclosporine treatment in different types of psoriasis • Erythrodermic • General pustular • Palmoplantar	3.2	I	112
Cyclosporine for psoriasis flare	3.3	III	Expert consensus

Table XII. Strength of recommendations for acitretin in psoriasis therapy

Recommendation No.	Recommendation	Strength of recommendation
4.1	Acitretin can be recommended as monotherapy for plaque psoriasis.	B
4.2	Acitretin can be recommended for treatment of erythrodermic, pustular, and palmar-plantar psoriasis.	B
4.3	Acitretin can be recommended as combination therapy with PUVA for psoriasis.	B
4.4	Acitretin can be combined with BB-UVB for plaque psoriasis.*	B

BB-UVB, Broadband ultraviolet B; *PUVA*, psoralen plus ultraviolet A.
*From the 2019 American Academy of Dermatology/National Psoriasis Foundation phototherapy psoriasis guideline.[192]

Table XIII. Level of evidence for acitretin therapy in psoriasis

Recommendation	Recommendation No.	Level of evidence	Studies
Acitretin monotherapy for psoriasis	4.1	II	33,150,152,154 157,159,161,162,193
Acitretin in other psoriasis types • Erythrodermic • Pustular	4.2	II	154 157,159,161,162
Combination therapy			
• Acitretin + PUVA	4.3	I-II	154,155,174 177
• Acitretin + BB-UVB	4.4	I-II	170,171

BB-UVB, Broadband ultraviolet B; *PUVA*, psoralen plus ultraviolet A.

Menter A et al., 2019 [11].

American Academy of Dermatology (AAD)

Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics

Zielsetzung

This guideline will cover the use of biologic agents in the treatment of psoriasis in adults

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Konsensusprozesse; externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert; Gültigkeit 5 Jahre.

Recherche/Suchzeitraum:

- PubMed and MEDLINE databases from January 1, 2008, to December 31, 2017

LoE / GoR

I. Good-quality patient-oriented evidence (ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life [QOL]).
II. Limited-quality patient-oriented evidence.
III. Other evidence including consensus guidelines, opinion, case studies, or disease-oriented evidence (ie, evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes).

Clinical recommendations were developed on the basis of best available evidence, as summarized in the tables 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, case studies, or disease-oriented evidence.

Empfehlungen

Table II. Strength of recommendations on the TNF-α inhibitor etanercept

Recommendation No.	Recommendation	Strength of recommendation
1.1	Etanercept is recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis	A
1.2	The recommended starting dose of etanercept is 50 mg taken as a self-administered subcutaneous injection twice weekly for 12 consecutive wk	A
1.3	The recommended maintenance dose of etanercept after the initial 12 wk is 50 mg once weekly. Etanercept administered at a dose of 50 mg twice weekly is more efficacious than a dose of 50 mg once weekly and may be required for better disease control in some patients	A
1.4	Etanercept is recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the scalp	A
1.5	Etanercept is recommended as a monotherapy treatment option for use in adult patients with moderate-to-severe plaque psoriasis affecting the nails	A
1.6	Etanercept can be recommended as a monotherapy treatment option for use in adult patients with other subtypes (pustular or erythrodermic) of moderate-to-severe plaque psoriasis	B
1.7	Etanercept is recommended as a monotherapy treatment option in adult patients with plaque psoriasis of any severity when associated with significant psoriatic arthritis	A
1.8	Combination of etanercept and topicals, such as high-potency corticosteroids with or without a vitamin D analogue, is recommended as a treatment option to augment efficacy for the treatment of moderate-to-severe plaque psoriasis	A
1.9	Etanercept may be combined with acitretin to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B
1.10	Combination of etanercept and methotrexate is recommended as a treatment option to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B
1.11	Etanercept may be combined with apremilast to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	C
1.12	Etanercept may be combined with cyclosporine to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults when clinically indicated	C
1.13	Etanercept may be combined with narrowband ultraviolet phototherapy to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B

TNF-α, Tumor necrosis factor-α.

Table III. Level of evidence on the TNF-α inhibitor etanercept

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults	1.1-1.3	I-III	10,11,14 20,22 34,51,56,61,72 75
Dosing range			
• Start with 50 mg twice per wk for 12 wk			
• Maintenance dose: 50 mg/wk; 50 mg twice per wk may be required in some patients			
Type of psoriasis			
• Scalp	1.4	I	39
• Nail	1.5	I-III	35 38,40
• Pustular, erythrodermic, inverse	1.6	II-III	41 43,45,47,48,76
Monotherapy for psoriasis with psoriatic arthritis	1.7	I	77,78
Combination therapy			
• Topical	1.8	I-II	50 54,79
• Acitretin	1.9	I-II	55,56,59
• Methotrexate	1.10	I-II	60 62
• Apremilast	1.11	II	63
• Cyclosporine	1.12	II	64
• Narrowband ultraviolet B phototherapy	1.13	II	67,68,80

TNF-α, Tumor necrosis factor-α.

Table IV. Strength of recommendations on the TNF-α inhibitor infliximab

Recommendation No.	Recommendation	Strength of recommendation
2.1	Infliximab is recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis	A
2.2	The recommended starting dose of infliximab is an infusion of 5 mg/kg administered at wk 0, wk 2, and wk 6, and thereafter it is administered every 8 wks	A
2.3	Infliximab is recommended to be administered at a more frequent interval (less than every 8 weeks and as frequently as every 4 weeks during the maintenance phase) and/or at a higher dose up to 10 mg/kg for better disease control in some adult patients	B
2.4	Infliximab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the palms and soles (plaque-type palmoplantar psoriasis)	B
2.5	Infliximab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the nails	B
2.6	Infliximab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the scalp	B
2.7	Infliximab may be recommended as a monotherapy treatment option in adult patients with other subtypes (pustular or erythrodermic) of moderate-to-severe plaque psoriasis	C
2.8	Infliximab is recommended as a monotherapy treatment option in adult patients with plaque psoriasis of any severity when associated with significant psoriatic arthritis. Infliximab also inhibits radiographically detected damage of joints in patients with psoriatic arthritis	A
2.9	Combination of infliximab and topicals such as high-potency corticosteroids with or without a vitamin D analogue can be recommended as a treatment option to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B
2.10	Infliximab may be combined with acitretin to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	C
2.11	Infliximab may be combined with methotrexate to possibly augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B
2.12	Infliximab may be combined with apremilast to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults when clinically indicated	C

Table V. Level of evidence on the TNF-α inhibitor infliximab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults	2.1-2.3	I-III	51,81,83 88,112
Dosing range			
• 5 mg/kg at wk 0, wk 2, and wk 6, then every 8 wk			
• Frequent dosing (at least every 8 wk during maintenance phase) up to 10 mg/kg			
Type of psoriasis			
• Palmoplantar	2.4	I-II	89,92
• Nail	2.5	I-II	35,38,90,91,93
• Scalp	2.6	II	94
• Pustular, erythrodermic, or Inverse	2.7	II	42,43,96
Monotherapy for psoriasis with psoriatic arthritis	2.8	I-II	113 119
Combination therapy			
• Topical	2.9	II	50,51
• Acitretin	2.10	II-III	101,102
• Methotrexate	2.11	I-II	60,103
• Apremilast	2.12	II	63

TNF-α, Tumor necrosis factor-α.

Table VI. Strength of recommendations on the TNF-α inhibitor adalimumab

Recommendation No.	Recommendation	Strength of recommendation
3.1	Adalimumab is recommended as a monotherapy treatment option for adult patients with moderate-to-severe plaque psoriasis	A
3.2	The recommended starting dose of adalimumab is 80 mg taken as 2 self-administered subcutaneous 40-mg injections of the initial dose, followed by a 40-mg self-administered subcutaneous injection 1 wk later, followed by 40 mg self-administered every 2 wk thereafter	A
3.3	A maintenance dose of adalimumab 40 mg/wk is recommended for better disease control in some patients	A
3.4	Adalimumab is recommended as a monotherapy treatment option for adult patients with moderate-to-severe plaque psoriasis affecting the palms and soles (palmoplantar psoriasis)	A
3.5	Adalimumab is recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the nails	A
3.6	Adalimumab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the scalp	B
3.7	Adalimumab can be recommended as a monotherapy treatment option in adult patients with other subtypes (pustular or erythrodermic) of moderate-to-severe psoriasis	B
3.8	Adalimumab is recommended as a monotherapy treatment option in adult patients with plaque psoriasis of any severity when associated with psoriatic arthritis	A
3.9	Combination of adalimumab and topicals such as high-potency corticosteroids with or without a vitamin D analogue can be recommended as a treatment option to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B
3.10	Adalimumab may be combined with acitretin to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	C
3.11	Adalimumab may be combined with methotrexate to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B
3.12	Adalimumab may be combined with apremilast to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	C
3.13	Adalimumab may be combined with cyclosporine to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	C
3.14	Adalimumab may be combined with narrowband ultraviolet phototherapy to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B

TNF-α, Tumor necrosis factor-α.

Table VII. Level of evidence on the TNF-α inhibitor adalimumab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults	3.1-3.3	I-II	51,120 128,151 154
Dosing range			
• 80 mg during wk 1, followed by 40 mg at wk 2, then 40 mg every 2 wk thereafter			
• Maintenance dose: 40 mg/wk			
Type of psoriasis			
• Palmoplantar	3.4	I	129,130
• Nail	3.5	I-II	35,38,90,130 132
• Scalp	3.6	II	132
• Erythrodermic or Pustular	3.7	II	42,43
Monotherapy for psoriasis with psoriatic arthritis	3.8	I-II	155 159
Combination therapy			
• Topical	3.9	I-III	50,51,133,134
• Acitretin	3.10	II-III	101,102
• Methotrexate	3.11	I	60
• Apremilast	3.12	II	63
• Cyclosporine	3.13	II-III	138 141
• Narrowband ultraviolet phototherapy	3.14	II	142,143

TNF-α, Tumor necrosis factor-α.

Table IX. Strength of recommendations on the IL-12/IL-23 antagonist ustekinumab

Recommendation No.	Recommendation	Strength of recommendation
4.1	Ustekinumab is recommended as a monotherapy treatment option for use in adult patients with moderate-to-severe plaque psoriasis	A
4.2	The recommended starting doses of ustekinumab are as follows: (a) For patients weighing ≤100 kg, 45 mg administered subcutaneously initially and 4 wk later, followed by 45 mg administered subcutaneously every 12 wk (b) For patients weighing >100 kg, 90 mg administered subcutaneously initially and 4 wk later, followed by 90 mg administered subcutaneously every 12 wk	A
4.3	The recommended alternate dosage for ustekinumab is administered at higher doses (90 mg instead of 45 mg in patients weighing ≥100 kg) or at a greater frequency of injection (eg, every 8 wk in its maintenance phase) for those with an inadequate response to standard dosing	A
4.4	Ustekinumab can be used as monotherapy for adult patients with moderate-to-severe plaque psoriasis affecting the palms and soles (plaque type palmoplantar psoriasis)	B
4.5	Ustekinumab can be recommended as a monotherapy treatment option for use in adult patients with moderate-to-severe plaque psoriasis affecting the nails	B
4.6	Ustekinumab can be used as monotherapy for use in adult patients with moderate-to-severe plaque psoriasis affecting the scalp	C
4.7	Ustekinumab can be used as monotherapy for use in adult patients with other subtypes (palmoplantar, pustular, or erythrodermic) of moderate-to-severe plaque psoriasis. There is limited evidence for its use in inverse and guttate psoriasis	C
4.8	Ustekinumab is recommended as a monotherapy treatment option for use in adult patients with plaque psoriasis of any severity when associated with psoriatic arthritis	A
4.9	Combination of ustekinumab and topicals such as high-potency corticosteroids with or without a vitamin D analogue can be recommended as a treatment option to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	C
4.10	Ustekinumab may be combined with acitretin to augment efficacy for the treatment of moderate-to-severe plaque psoriasis	B
4.11	Ustekinumab may be combined with methotrexate to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B
4.12	Ustekinumab may be combined with apremilast to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	C
4.13	Ustekinumab may be combined with cyclosporine to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	C
4.14	Ustekinumab may be combined with narrowband ultraviolet phototherapy to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults	B

IL-12/IL-23, Interleukin 12/interleukin 23.

Table X. Level of evidence on the IL-22/IL-23 inhibitor ustekinumab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults	4.1-4.3	I, III	204 216,241,243
Dosage range • 45 mg if patient weighs ≤100 kg, 90 mg if patient is >100 kg. At wk 1 and wk 4, then every 12 wk • 90 mg for patients ≤100 kg, or maintenance therapy every 8 wk for patients with inadequate response			
Types of psoriasis			
• Palmoplantar	4.4	II-III	218,220,222,229
• Nail	4.5	I-II	90,224 226,230,244
• Scalp	4.6	III	227
• Palmoplantar, pustular, or erythrodermic	4.7	II-III	42,43,223,245
Monotherapy for psoriasis with psoriatic arthritis	4.8	I	246 250
Combination therapy			
• Topical	4.9	II	51
• Acitretin	4.10	II-III	101,102,238
• Methotrexate	4.11	I-II	238,239
• Apremilast	4.12	II	63
• Cyclosporine	4.13	III	238
• Narrowband ultraviolet B phototherapy	4.14	I	240

IL-12/23, Interleukin 12/interleukin 23.

Table XII. Strength of recommendations on the IL-17 antibody secukinumab

Recommendation No.	Recommendation	Strength of recommendation
5.1	Secukinumab is recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis	A
5.2	The recommended starting dose of secukinumab is 300 mg by self-administered subcutaneous injection at wk 0, wk 1, wk 2, wk 3, and wk 4, followed by 300 mg every 4 wk	A
5.3	The recommended maintenance dose of secukinumab after the initial 12 wk is 300 mg every 4 wk	A
5.4	Secukinumab is recommended at a dose of 300 mg, which is more effective than 150 mg	A
5.5	Secukinumab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the head and neck, including the scalp	B
5.6	Secukinumab is recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the nails	A
5.7	Secukinumab is recommended as a monotherapy treatment option in adult patients with moderate-to-severe palmoplantar plaque psoriasis	A
5.8	Secukinumab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe palmoplantar pustulosis	B
5.9	Secukinumab can be used as monotherapy in adult patients with erythrodermic psoriasis	C
5.10	Secukinumab may be used as monotherapy for adult patients with plaque psoriasis when associated with psoriatic arthritis	A

IL-17, Interleukin 17.

Table XIII. Level of evidence on the IL-17 antibody secukinumab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults	5.1-5.4	I-II	29,32,213 215,257 261,267
Dose range • 300 mg at wk 0, wk 1, wk 2, wk 3, and wk 4, then every 4 wk • Maintenance dose: 300 mg every 4 wk after initial 12 wk • Recommended effective dose: 300 mg vs 150 mg			
Type of psoriasis			
• Scalp	5.5	II	262
• Nails	5.6	I	213
• Palmoplantar psoriasis	5.7	I	266
• Palmoplantar pustulosis	5.8	N/A	Expert opinion
• Erythrodermic	5.9	III	264,265
Monotherapy for patients with psoriatic arthritis	5.10	I	261

IL-17, Interleukin 17.

Table XIV. Strength of recommendations on the IL-17 antagonist ixekizumab

Recommendation No.	Recommendation	Strength of recommendation
6.1	Ixekizumab is recommended as a monotherapy treatment option for use in adult patients with moderate-to-severe plaque psoriasis	A
6.2	The recommended starting dose of ixekizumab is 160 mg by self-administered subcutaneous injection followed by 80 mg at wk 2, wk 4, wk 6, wk 8, wk 1, and wk 12	A
6.3	The recommended maintenance dose of ixekizumab after the initial 12 wk is 80 mg every 4 wk	A
6.4	Ixekizumab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the scalp	B
6.5	Ixekizumab can be recommended as a monotherapy treatment option in adult patients with erythrodermic psoriasis	B
6.6	Ixekizumab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the nails	B
6.7	Ixekizumab can be recommended as a monotherapy treatment option in adult patients with generalized pustular psoriasis	B
6.8	Ixekizumab is recommended as a monotherapy treatment option in adult patients with plaque psoriasis when associated with psoriatic arthritis	A

IL-17, Interleukin 17.

Table XV. Level of evidence on the IL-17 antagonist ixekizumab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adult	6.1-6.3	I-II	30,72,216,269 274
Dosing range			
• 160 mg at wk 0, then 80 mg every 2 wk until wk 12			
• Maintenance dose 80 mg every 4 wk after wk 12			
Type of psoriasis			
• Scalp	6.4	I-II	271,272,275,276
• Erythrodermic	6.5	I-II	272,273
• Nail	6.6	I-II	27,271,272,275
• Pustular	6.7	I-II	272,273
Monotherapy for psoriasis with psoriatic arthritis	6.8	I	278,279

IL-17, Interleukin 17.

Table XVI. Strength of recommendations on the IL-17 antibody brodalumab

Recommendation No.	Recommendation	Strength of recommendation
7.1	Brodalumab is recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis	A
7.2	Brodalumab can be used as monotherapy in adult patients with generalized pustular psoriasis	B
7.3	The recommended dose of brodalumab is 210 mg by self-administered subcutaneous injection at wk 0, wk 1, and wk 2 followed by 210 mg every 2 wk	A

Table XVII. Level of evidence on the IL-17 antibody brodalumab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults for plaque psoriasis, pustular psoriasis, and dosing range (210 mg at 0, 1, and 2 wk, and 210 mg every 2 wk thereafter)	7.1-7.3	I-II	72,213,281 285

Table XIX. Strength of recommendations on the IL-23 inhibitor guselkumab

Recommendation No.	Recommendation	Strength of recommendation
8.1	Guselkumab is recommended as a monotherapy treatment option for use in adult patients with moderate-to-severe plaque psoriasis	A
8.2	The recommended dose of guselkumab is 100 mg by self-administered subcutaneous injection at wk 0, wk 4, and every 8 wk thereafter	A
8.3	Guselkumab is recommended as a monotherapy treatment option in adult patients with scalp, nail, and plaque-type palmoplantar psoriasis	A

Table XX. Level of evidence on the IL-23 inhibitor guselkumab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults	8.1	I	125,127,128,291 293
Dosing range • 100 mg in wk 0 and wk 4, then every 8 wk	8.2	I	125,127,128,291 293
Types of psoriasis • Scalp, nail, palmoplantar	8.3	I	127,128

Table XXI. Strength of recommendations on the IL-23 inhibitor tildrakizumab

Recommendation No.	Recommendation	Strength of recommendation
9.1	Tildrakizumab is recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis	A
9.2	The recommended dose is 100 mg given by in office physician-administered subcutaneous injection at wk 0 and wk 4 and every 12 wks thereafter	A

Table XXII. Level of evidence on the IL-23 inhibitor tildrakizumab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults	9.1-9.2	I	34,294,295
Dosage range • 100 mg at wk 0 and wk 4, then every 12 wk			

Table XXIII. Strength of recommendations on the IL-23 inhibitor risankizumab

Recommendation No.	Recommendation	Strength of recommendation
10.1	Risankizumab is not FDA-approved but can be used as monotherapy in adult patients with moderate-to-severe plaque psoriasis	B
10.2	The approved dose will likely be 150 mg given by self-administered subcutaneous injection at wk 0, wk 4, and then every 12 wk	A

Table XXIV. Level of evidence on the IL-23 inhibitor risankizumab

Recommendation	Recommendation No.	Level of evidence	Studies
Monotherapy for adults	10.1-10.2	I	297,299
Dose range • 150 mg at wk 0 and wk 4, then every 12 wk			

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 3 of 12, March 2023) am 14.03.2023

#	Suchfrage
1	[mh Psoriasis]
2	psoriasis:ti,ab,kw
3	#1 OR #2
4	#3 with Cochrane Library publication date Between Mar 2018 and Mar 2023, in Cochrane Reviews

Systematic Reviews in PubMed am 14.03.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	psoriasis[mh] OR psoriasis[tiab]
2	(#1) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
3	(#2) AND ("2018/03/01"[PDAT] : "3000"[PDAT])

#	Suchfrage
4	(#3) NOT "The Cochrane database of systematic reviews"[Journal]
5	(#4) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 14.03.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	Psoriasis[mh] OR Psoriasis [tiab]
2	(#1) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
3	(#2) AND ("2018/03/01"[PDAT] : "3000"[PDAT])
4	(#3) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 14.03.2023

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2021-B-216z

Verfasser	
Name der Institution	Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) Bundesärztekammer, Dezernat 1 – Ärztliche Versorgung und Arzneimittel, Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de)
Datum der Erstellung	23. März 2023

Indikation
Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die für eine systemische Therapie infrage kommen.
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Vorbemerkung
Eine systemische Therapie der Psoriasis vulgaris kommt infrage, wenn eine topische Therapie nicht oder nur unzureichend erfolgreich war. Zur Beurteilung des Therapieerfolgs können Therapieziele herangezogen werden (vgl. (1)). Außerdem muss beurteilt werden, ob eine „mittelschwere bis schwere" Psoriasis vorliegt. Bei mittelschwerer bis schwerer Psoriasis liegt der BSA > 10 oder PASI > 10 und DLQI > 10 (PASI: Psoriasis Area and Severity Index, BSA: Body Surface Area, DLQI: Dermatology Life Quality Index. Einzelheiten dazu bei (1), S. 935).

Therapeutische Optionen
Es lassen sich unterscheiden: konventionelle Systemtherapeutika, niedermolekulare Wirkstoffe und Biologika. Bezüglich der Wirksamkeit wurde festgestellt, dass diese drei Gruppen in Bezug auf das Erreichen einer PASI-90-Antwort signifikant wirksamer waren als Placebo (1). Außerdem waren die biologischen Systemtherapien mit Anti-IL17-, Anti-IL12/23-, Anti-IL23- oder Anti-TNFα-Substanzen signifikant wirksamer in Bezug auf das Erreichen einer PASI-90-Antwort als die niedermolekularen Wirkstoffe und die konventionellen Systemtherapeutika (1).
Für die systemische Therapie kommen zunächst konventionelle Systemtherapeutika für die Therapie in Betracht, entsprechend den aktuellen Leitlinien: „Für Patienten, die eine systemische Therapie benötigen, wird in der Regel die Einleitung einer „konventionellen" Systemtherapie empfohlen (entsprechend des Wirtschaftlichkeitsgebotes)". Hierzu ergänzende Ausnahme: „Bei Vorliegen einer Psoriasis, bei der konventionelle Therapie keinen ausreichenden Therapieerfolg erwarten lässt, kann die Einleitung einer Therapie mit einem Biologikum mit einem „first line label" empfohlen werden" (1).
Die Therapie mit PUVA (Psoralen, eine lichtsensibilisierende Substanz plus Bestrahlung mit UVA) setzt eine entsprechende und nicht regelhaft vorliegende Ausstattung der Praxis voraus, und wird hier nicht berücksichtigt.
Bei den konventionellen Systemtherapeutika handelt sich um:

- Acitretin (ein Retinoid),

- Fumarsäureester (z. B. Fumaderm®),
- Ciclosporin (ein immunsuppressiver Calcineurinantagonist),
- Methotrexat (ein immunsupressiver Antimetabolit).

Zu den Biologika und niedermolekularen Wirkstoffen, die bei mittelschwerer bis schwerer Psoriasis vulgaris angewendet werden, gehören:

- First-Line-Therapie: Adalimumab, Brodalumab, Certolizumab, Guselkumab, Ixekizumab, Risankizumab, Secukinumab, Tildrakizumab,
- Second-Line-Therapie: Apremilast, Etanercept, Infliximab, Ustekinumab.

Weitere Arzneimittel, darunter Bimekizumab (Bimzelx®) und Deucravacitinib (Sotyktu®), sind bisher nicht in den Therapiealgorithmus der aktuellen Leitlinie aufgenommen.

Allgemeine Empfehlung: Es wird in den aktuellen Leitlinien (1) empfohlen, Wirksamkeit und Sicherheit, die Zeit bis zum Wirkungseintritt, Komorbiditäten und individuelle Patientenfaktoren bei der Auswahl einer systemischen Therapie bei mittelschwerer bis schwerer Psoriasis vulgaris zu berücksichtigen.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o. g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Kriterien für unterschiedliche Behandlungsentscheidungen sollten u. a. sein: a) Häufigkeit und Schwere der UAW und b) Komorbiditäten (Details siehe (2)).
Bezüglich UAW: Bei keiner der Interventionen fanden die Autoren der Leitlinien (1) im Placebovergleich einen signifikanten Unterschied in Bezug auf das Risiko, ein schwerwiegendes unerwünschtes Ereignis (SAE) zu erleiden. „Dabei muss aber berücksichtigt werden, dass die Analysen hierzu auf einer sehr niedrigen Anzahl von Ereignissen basieren und unser Vertrauen in insgesamt knapp die Hälfte der betreffenden Effektschätzer gering bis sehr gering war, und in die restlichen war unser Vertrauen moderat. Aus diesen Gründen müssen die Ergebnisse mit Vorsicht interpretiert werden und die Erstellung einer Rangliste war nicht möglich“.

Ich erlaube mir aber**, rein subjektiv (anekdotisch**), ohne publizierte Evidenz, eine Gewichtung der UAW, gegründet auf die Schwere (und nicht nur Häufigkeit), vorzunehmen, geordnet nach ansteigender Schwere:

- Acitretin: Die Teratogenität erfordert ein strikt einzuhaltendes Regime, ansonsten sind die UAW überschaubar.
- Bei den übrigen Substanzen kann es zu teils schweren UAW kommen:
    - Fumarsäureester: Lymphopenie und fatale (ZNS-) Infektionen (die bei strikter Laborkontrolle hätten vermieden werden können),
    - Ciclosporin: u. a. schwere Nieren-UAW,
    - MTX: u. a. UAW in den Organbereichen Blut und Leber,
    - Bei langfristiger Therapie mit Ciclosporin und MTX ist das Risiko für das Auftreten von Neoplasien erhöht.

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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2021-B-216z

Verfasser	
Name der Institution	Deutsche Dermatologische Gesellschaft (DDG)
Datum der Erstellung	10. März 2023

Indikation
Behandlung erwachsener Patienten mit mittelschwerer bis schwerer Plaque-Psoriasis, die für eine systemische Therapie infrage kommen.
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?
A) Leitlinien und Datenquellen 1. Evidenz-basierte Leitlinien: Standards für die Therapie der mittelschweren bis schweren Psoriasis vulgaris in Deutschland sind in der S3-Leitlinie der AWMF formuliert. Diese bezieht sich allerdings nur auf die Induktionstherapie. Die Leitlinie wurde kürzlich aktualisiert. Die ergänzende topische Therapie wurde letztmals in der Leitlinienfassung von 2011 ergänzt. Für die topische Langzeittherapie der Psoriasis wurde in 5/2018 ein Konsensuspapier publiziert. 2. Praxisempfehlungen: Zur Implementierung der Leitlinien-Empfehlungen der AWMF hat eine Gruppe von Dermatologen ferner einen Behandlungspfad konsentiert, der besonders im niedergelassenen Bereich Beachtung findet. Eine weitere Implementierungshilfe im Kontext der regionalen KV-Prüfungen stellt das Konsensuspapier „Empfehlungen zur sachgerechten Therapie mit Systemtherapeutika“ dar, welche über die Leitlinie hinaus Anwendungsempfehlungen gibt. Diese beiden Schriften stellen Kriterien für unterschiedliche Behandlungsentscheidungen auf. 3. Datenquellen: Die nachfolgend ausgeführten Deskriptionen der Versorgungspraxis beruhen auf: a) GKV-Datenauswertungen 2019, b) den Daten des Deutschen Psoriasis-Registers PsoBest, c) querschnittlichen Analysen der Versorgung von Psoriasis durch Dermatologen. B) Behandlungsstandards der mittelschweren bis schweren Psoriasis Die S3-Leitlinie sowie die weiteren vorgenannten Konsensuspapiere empfehlen gleichlautend, die mittelschwere bis schwere Psoriasis grundsätzlich mit einer Systemtherapie zu behandeln, optional ggf. mit einer Phototherapie. Letztere wird jedoch als meist weniger praktikabel bewertet und zeigt zudem keine Wirkungen gegen die systemische Entzündung inklusive der daraus resultierenden

Komorbidität. Sie ist bei Daueranwendung ferner limitiert durch das Langzeitrisiko von Malignomen der Haut.
Unter den Systemtherapeutika wird zwischen Wirkstoffen mit Zulassung im Erstlinienmodus und solchen im „Second-Line"-Modus unterschieden.

Erstlinienmodus: Sofern eine hinreichende Wirkung mit den Wirkstoffen Fumarsäureester und Methotrexat (MTX) zu erwarten ist und keine Kontraindikationen bestehen, werden diese nichtbiologischen Präparate als erste eingesetzt, in selteneren Fällen auch Ciclosporin. Letzteres ist jedoch nicht für die Langzeitbehandlung geeignet und weist ein hohes Aufkommen an Kontraindikationen auf. Nach Versagen oder fehlender Indikation für die nicht-biologische Erstlinientherapie werden die folgenden Biologika mit Zulassung im Erstlinienmodus eingesetzt (Nennung wirkgruppenweise, dann chronologisch nach Zulassungszeitpunkt): Adalimumab, Certolizumab (TNF-Blocker), Secukinumab, Ixekizumab, Brodalumab (IL-17-Blocker), Guselkumab, Tildrakizumab, Risankizumab (IL-23-Blocker). Für deren Differenzierung und Reihenfolge gibt es keine Empfehlungen, die eine eindeutige Wahl des Präparates festlegen. Von Bedeutung ist die zu erwartende Wirkwahrscheinlichkeit sowie die Präferenz des Patienten u.a. für die Applikationshäufigkeit und unterschiedliche Nebenwirkungsprofile.
Bei sehr schwerer Psoriasis und hoher Belastung der Lebensqualität werden die Biologika aufgrund ihrer weitaus größeren Erfolgswahrscheinlichkeit auch als erste Systemtherapeutika eingesetzt (first line – first drug).

Zweitlinienmodus: In zweiter Linie werden bei Nichtansprechen, Unverträglichkeiten oder Kontraindikationen gegen die Erstlinien-Präparate die TNF-Blocker Infliximab und Etanercept sowie der IL12-/23-Blocker Ustekinumab und das nicht-Biologikum Apremilast eingesetzt. Für deren Wahl und Reihung gibt es in den vorgenannten Leitlinien und Konsensuspapieren keine eindeutig fixierten Empfehlungen. Bei Bedarf nach einer oralen Substanz wird Apremilast als zugelassenes Medikament eingesetzt. Demgegenüber kommen Etanercept wegen geringer Wirksamkeit und Infliximab wegen Sicherheitsrisiken und des iv-Applikationsmodus seltener zum Einsatz.

C) Beschreibung der Versorgungspraxis

Die vorgenannten Präparate stellen die gängige Versorgungspraxis in folgender Weise dar: Zu versorgen sind in Deutschland etwa 2 Mio. Personen mit Psoriasis, davon etwa 400.000 mit mittelschweren bis schweren Formen und damit regelhaft mit Systemtherapien. Von diesen erhalten derzeit unter 200.000 Patienten Systemtherapien sowie ein relevanter Teil entgegen der Leitlinie systemische Glukokortikosteroide.
Die mit Abstand am häufigsten eingesetzten zugelassenen Systemtherapeutika sind Fumarsäureester und MTX, welche derzeit bei etwa 110.000 Patienten in Deutschland mit Psoriasis zum Einsatz kommen (GKV-Daten 2019). Auf Biologika sind derzeit insgesamt etwa 82000 Patienten (inklusive Psoriasis-Arthritis) eingestellt, dies am häufigsten auf Secukinumab, gefolgt von Adalimumab, Ustekinumab und Guselkumab. Auch die anderen vorgenannten Biologika (Certolizumab, Ixekizumab, Brodalumab, Risankizumab, Tildrakizumab) sind versorgungsrelevant und werden in jährlichen Zahlen von >3000 Personen mit Psoriasis eingesetzt (GKV-Daten und Daten des deutschen Psoriasis-Registers PsoBest). Eine systemische Ersteinstellung auf ein Biologikum findet sich in PsoBest bei derzeit etwa 30% der Patienten. Diese weisen im Vergleich zu den primär auf nicht-biologische Präparate eingestellten Patienten signifikant höhere Einbußen der Lebensqualität und höhere klinische Schweregrade auf.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
In der Klassifikation der mittelschweren bis schweren Psoriasis wird keine international einheitliche Definition angewendet und zwischen „mittelschwer“ und „schwer“ oft nicht unterschieden. Als Anhaltspunkt wird von „mittelschwer bis schwer“ oft bei einem Schweregrad von mind. 10 im PASI (oder BSA) sowie ebenfalls mind. 10 im DLQI gesprochen. Einige Autoren ordnen die „schwere“ Psoriasis einem PASI von über 20 zu, z.T. auch einem DLQI über 15 oder über 20. In jedem Falle werden für die Einstufung als mittelschwere bis schwere Psoriasis und damit als Indikationsstellung zur Systemtherapie auch weitere Aufgreifkriterien eingesetzt, bei denen von einem höheren Schweregrad ausgegangen werden kann. Dies sind v.a. der Befall der Kopfhaut, der sichtbaren Areale, des genitalen und analen Bereiches sowie der Nägel, die bei über 50% der Patienten in relevanter Weise betroffen sind. Auch markante refraktäre Symptome (z.B. pustulöse Beteiligung) und ein insgesamt therapierefraktärer Verlauf konstituieren einen höheren Schweregrad. Bei der Auswahl der Therapeutika spielt die Datenlage aus klinischen Studie eine Rolle, wobei nicht alle Sonderformen der Psoriasis hinreichend in Studien geprüft wurden und damit die Evidenz begrenzt ist. Die Einstellung auf die Systemtherapeutika weist in der deutschen Versorgung eine große Variation auf (PsoHealth-Daten). Tendenziell werden Patienten mit sehr schwerer Psoriasis (orientierend: PASI>20, DLQI>15) frühzeitiger oder sogar primär auf Biologika eingestellt. Auch therapeutisch schlecht ansprechende Formen wie eine schwere Nagelpsoriasis werden bei hohem Leidensdruck eher mit hochwirksamen Biologika behandelt. In jedem Falle ist als Kriterium der Therapieentscheidung die Komorbidität mit in Betracht zu ziehen. Dies gilt insbesondere für das Vorliegen einer Psoriasis-Arthritis, die bei etwa 20% der Patienten mit Psoriasis in dermatologischer Versorgung vorkommt. Hier werden die Präparate mit einer Zulassung für PsA bevorzugt (TNF-Blocker, Secukinumab, Ixekizumab, Guselkumab, Risankizumab, Ustekinumab, Apremilast). Von Bedeutung können besondere Therapiesituation wie vorausgehende Malignome, schwere Immunkrankheiten oder Schwangerschaft und Stillzeit sein. Bei Letzteren wird derzeit die Behandlung mit Certolizumab favorisiert, bei immunsupprimierten und Personen mit Anfälligkeit für Infektionen kommen vermehrt Apremilast, IL17- und IL23- Blocker sowie Ustekinumab zum Einsatz, wobei spezifische Risiken zu beachten sind, etwa für Candidosen bei Einsatz von IL-17Inhibitoren. Zusammengefasst ist das arzneimitteltherapeutische Spektrum der Psoriasis breit und kommen in der Regel für die jeweiligen Formen und Schweregrade mehrere Präparate ohne spezifische Priorisierungen auf der Basis von Studienevidenz in Betracht.

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