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: 2020-B-241 Spesolimab

Stand: September 2020

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

Spesolimab **Generalisierte pustulöse 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.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor.
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**
Zu bewertendes Arzneimittel:	
Spesolimab	„Spesolimab ist indiziert bei erwachsenen Patienten mit generalisierter pustulöser Psoriasis (GPP) mit einem akuten Schub.“
Prednisolon H02AB06 Prednisolon JENAPHARM®	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 bis a)
Prednison H02AB07 Decortin®	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 bis a)
Triamcinolonacetonid/ Zinkoxid D07XB02 Volon® A-Schüttelmix	Insbesondere zur Akutbehandlung von: – Ekzemen – Kontaktdermatitiden allergischer oder toxischer Genese – Atopischem Ekzem (syn. Neurodermitis atopica, endogenes Ekzem) – Nicht-mykotischer Intertrigo Andere Dermatosen: – Lichen ruber cutis und Sonderformen **– Psoriasis pustulosa**
Dapson D10AX05 DAPSON-Fatol®	Blasenbildende Dermatosen wie Pemphigus vulgaris, Pemphigus herpetiformis, chronisch familiärer Pemphigus, Schleimhautpemphigoid, Dermatitis herpetiformis. Ein Therapieversuch mit Dapson (DDS) ist bei folgenden Hauterkrankungen bei fehlender risikoärmerer Behandlungsmöglichkeit angezeigt: -beim bullösen Pemphigoid (allein oder in Kombination mit Kortikoiden und Immunsuppressiva); -bei seltenen Erkrankungen, wie subcorneale pustulöse Dermatosen, Erythema elevatum diutinum, Granuloma annulare, Granuloma faciale, Prurigo pigmentosa, rezidivierende Polychondritis. Außerdem bei **Psoriasis pustulosa**, bullösen, urticariellen oder ulcerösen Exazerbationen des Erythematodes.

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2020-B-241 (Spesolimab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	3. September 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DLQI	Dermatology Life Quality Index
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GPP	generalisierte pustulöse Psoriasis
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PASI	Psoriasis Area and Severity Index
PUVA	Psoralen plus UV-A
QOL	quality of life
RCT	randomized controlled trial
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization
wk	week

1 Indikation

Zur Behandlung bei erwachsenen Patienten mit generalisierter pustulöser Psoriasis (GPP) mit einem akuten Schub.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Psoriasis* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 04.06.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1058 Quellen. 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 Quellen 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 3 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es wurden keine relevanten G-BA Beschlüsse/IQWiG Berichte identifiziert.

3.2 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Es wurden keine relevanten systematischen Reviews identifiziert.

3.4 Leitlinien

NICE, 2012 [3].

National Institute for Health and Care Excellence (NICE)

Psoriasis: assessment and management; Update 09/2017

Zielsetzung/Fragestellung

This guideline covers people of all ages and aims to provide clear recommendations on the management of all types of psoriasis.

Methodik

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.

Recherche/Suchzeitraum:

- bis 8/03/2012, **Update 09/2017**

LoE

- nach GRADE

GoR

- sprachliche Formulierung

Sonstige methodische Hinweise

- In September 2017, we revised the guideline throughout to link to other NICE guidance (including technology appraisals) and some relevant non-NICE guidelines, as well as including new MHRA safety advice and updated licensing information.
- nur wenige Empfehlungen für die GPP formuliert.

Recommendations for pustular forms

- 1.2.1.11 People with generalised pustular psoriasis or erythroderma should be referred immediately for same-day specialist assessment and treatment.

  (…)
- 1.5.2.1 Offer systemic non-biological therapy to people with any type of psoriasis if:
  - it cannot be controlled with topical therapy and
  - it has a significant impact on physical, psychological or social wellbeing and
  - one or more of the following apply:
    - psoriasis is extensive (for example, more than 10% of body surface area affected or a PASI score of more than 10) or
    - psoriasis is localised and associated with significant functional impairment and/ or high levels of distress (for example severe nail disease or involvement at high impact sites) or
    - phototherapy has been ineffective, cannot be used or has resulted in rapid relapse (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months).

Choice of drugs

- 1.5.2.2 Offer methotrexate [33] as the first choice of systemic agent for people with psoriasis who fulfil the criteria for systemic therapy (see previous recommendation 1.5.2.1) except in the circumstances described in recommendations 1.5.2.4 and 1.5.2.12.
- 1.5.2.3 In people with both active psoriatic arthritis and any type of psoriasis that fulfils the criteria for systemic therapy (see recommendation 1.5.2.1) consider the choice of systemic agent in consultation with a rheumatologist.
- 1.5.2.4 Offer ciclosporin [34] as the first choice of systemic agent for people who fulfil the criteria for systemic therapy (see recommendation 1.5.2.1) and who:
  - need rapid or short-term disease control (for example a psoriasis flare) or
  - have palmoplantar pustulosis or
  - are considering conception (both men and women) and systemic therapy cannot be avoided.
- 1.5.2.5 Consider changing from methotrexate to ciclosporin (or vice-versa) when response to the first-choice systemic treatment is inadequate.
- 1.5.2.6 Consider acitretin for adults, and in exceptional cases only for children and young people, in the following circumstances:
  - if methotrexate and ciclosporin are not appropriate or have failed or

- for people with pustular forms of psoriasis.

(…)

- 1.5.2.11 Use incremental dosing of acitretin to minimise mucocutaneous side effects and achieve a target dose of 25 mg daily in adults. Consider dose escalation to a maximum of 50 mg daily when no other treatment options are available. Assess the treatment response after 4 months at the optimum dose of acitretin and stop treatment if the response is inadequate, for example:
  - in plaque-type psoriasis, less than a 75% decrease in PASI score or less than a 50% decrease in PASI score and less than 5 points in DLQI score
  - in pustular forms of psoriasis, not achieving clear or nearly clear on the static Physician's Global Assessment.

Methotrexate and risk of hepatotoxicity

- 1.5.2.12 When considering the risks and benefits of treating any type of psoriasis with methotrexate, be aware that methotrexate can cause a clinically significant rise in transaminases and that long-term therapy may be associated with liver fibrosis (…)

Referenzen

[31] At the time of publication (October 2012), psoralen did not have UK marketing authorisation for this or any indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the GMC's Good practice in prescribing medicines – guidance for doctors for further information.

[33] At the time of publication (October 2012), methotrexate did not have UK marketing authorisation for this indication in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[34] At the time of publication (October 2012), ciclosporin did not have UK marketing authorisation for this indication in children and young people under 16 years of age. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or their parent or carer) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Menter, A. et al., 2019 [2].

American Academy of Dermatology (AAD)

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

Zielsetzung/Fragestellung

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

LoE/GoR

- Evidence was graded by using a 3-point scale based on the quality of methodology as follows:

  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 endpoints that may or may not reflect improvements in patient outcomes).

- Clinical recommendations 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.

In those situations in which documented evidence based data are not available, we have utilized expert opinion to generate our clinical recommendations or opted not to issue a recommendation.

Recommendations

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

TNF-α, Tumor necrosis factor-α.

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 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

Menter, A. et al., 2020 [1].

American Academy of Dermatology (AAD)

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

Zielsetzung/Fragestellung

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

Methodik

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.

Recherche/Suchzeitraum:

- PubMed and MEDLINE databases from January 1, 2011, through December 31, 2017, for clinical questions addressed in the previous version of this guideline published in 2008-2011

LoE/GoR

- Evidence was graded by using a 3-point scale based on the quality of methodology (eg, randomized controlled trial [RCT], case-control study, prospective or retrospective cohort study, case series) and the overall focus of the study (ie, diagnosis; treatment, prevention, and/or screening; or prognosis) as follows:

  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 endpoints 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.

In those situations in which documented evidence based data are not available, we have utilized expert opinion to generate our clinical recommendations or opted not to issue a recommendation.

Recommendations

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	3.2	I	112
• Erythrodermic			
• General pustular			
• Palmoplantar			
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	4.2	II	154-157,159,161,162
• Erythrodermic			
• Pustular			
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.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 6 of 12, June 2020) am 04.06.2020

#	Suchfrage
1	[mh Psoriasis]
2	psoriasis:ti,ab,kw
3	#1 OR #2
4	#3 with Cochrane Library publication date from Jun 2015 to present

Systematic Reviews in Medline (PubMed) am 04.06.2020

#	Suchfrage
1	psoriasis[mh]
2	psoriasis[tiab]
3	(#1 OR #2) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
4	((#3) AND ("2015/06/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
5	(#4) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 04.06.2020

#	Suchfrage
1	psoriasis [mh]
2	psoriasis[tiab]
3	(#1 OR #2) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
4	(((#3) AND ("2015/06/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
5	(#4) NOT (retracted publication [pt] OR retraction of publication[pt])

Referenzen

1. **Menter A, Gelfand JM, Connor C, Armstrong AW, Cordoro KM, Davis DMR, et al.** Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. 2020;82(6):1445-1486.

2. **Menter A, Strober BE, Kaplan DH, Kivelevitch D, Prater EF, Stoff B, et al.** Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. 2019;80(4):1029-1072.

3. **National Institute for Health and Care Excellence (NICE).** Psoriasis: assessment and management [online]. 09.2017. London (GBR): NICE; 2012. [Zugriff: 04.06.2020]. (NICE Clinical Guideline; Band 153). URL: https://www.nice.org.uk/guidance/cg153/resources/psoriasis-assessment-and-management-35109629621701.

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

2020-B-241

Kontaktdaten

Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 18.09.2020

Indikation gemäß Beratungsantrag

Behandlung erwachsener Patienten mit generalisierter pustulöser Psoriasis (GPP) mit einem akuten Schub.

Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz bei/in erwachsenen Patienten mit GPP mit einem akuten Schub? Wie sieht die Versorgungspraxis in Deutschland aus?

Aktuell werden die meisten Patienten mit Psoriasis pustulosa generalisata (Typ von Zumbusch) in der Akutphase mit systemischen Kortikosteroiden behandelt. Es handelt sich um ein seltenes, aber schweres Krankheitsbild, das mit einer ausgeprägten Entzündungsreaktion und oftmals Fieber und allgemeinem Krankheitsgefühl einhergeht. Daher werden diese Patienten i. d. R. stationär – i. d. R. in einer Hautklinik oder dermatologischen Abteilung behandelt. In den geltenden Leitlinien zur Psoriasistherapie finden sich nur eingeschränkt Aussagen zur Behandlung der generalisierten pustulösen Psoriasis, zumal weder randomisierte Therapiestudien noch größer angelegte Beobachtungsstudien zur Therapie vorliegen, sondern lediglich Fallberichte und kleine Fallserien. Zudem gibt es keine spezifische Leitlinie zur Behandlung der Psoriasis pustulosa, doch wird sie in der geltenden Leitlinie zur Behandlung der Psoriasis erwähnt (1). In der S2k-Leitlinie zur Therapie der Psoriasis bei Kindern und Jugendlichen ist der Psoriasis pustulosa ein Kapitel gewidmet (2).

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von erwachsenen Patienten mit GPP die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Ist der akute Schub durch systemische Kortikosteroide abgefangen, kommen ggf. zusätzlich oder stattdessen andere immunmodulierende Therapieansätze zum Tragen. Die Entscheidung hierfür richtet sich v. a. nach dem Verlauf bzw. dem Eruptionsdruck. Kommt es bereits bei der Reduktion der Kortikosteroide zum Wiederaufflammen der pustulösen Entzündungsreaktion, so wird man weitere Therapieoptionen evaluieren müssen. Hierzu gehören Retinoide (Etretinat) und Dapson (aufgrund ihrer Wirkung gegen die neutrophile Entzündung), aber auch Azathioprin, Cyclosporin oder Biologika. Betreffend die letztgenannten Wirkstoffe liegen Berichte über die Therapie mit verschiedenen TNF-alpha-Rezeptorenblockern wie Infliximab, Etanercept sowie Adalimumab, aber auch mit Secukinumab (IL-17-Antikörper) vor (vgl. beide o. g. Leitlinien). Allerdings scheint weniger Interleukin (IL)-17 eine entscheidende Rolle bei der Entzündungsmediation der pustulösen Psoriasis zu spielen als vielmehr IL-36 (3).

Da die betroffenen Patienten nicht selten an verschiedenen Grunderkrankungen leiden, müssen vor dem therapeutischen Einsatz von immunmodulierenden Wirkstoffen die jeweiligen Risikofaktoren und/oder Kontraindikationen geprüft werden.

Kontaktdaten

Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 18.09.2020

Indikation gemäß Beratungsantrag

Behandlung erwachsener Patienten mit generalisierter pustulöser Psoriasis (GPP) mit einem akuten Schub.

Literatur

1. Nast A, Amelunxen L, Augustin M et al.: S3 - Leitlinie zur Therapie der Psoriasis vulgaris – Update 2017: https://www.awmf.org/uploads/tx_szleitlinien/013-001l_S3_Therapie_Psoriasis-vulgaris_2017-12.pdf (letzter Zugriff: 17. September 2020). AWMF-Register Nr. 013-001. Stand: Oktober 2017.

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