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 (keine Stellungnahmen eingegangen)

Vorgang: 2023-B-139 Lebrikizumab

Stand: Juni 2023

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

Lebrikizumab
Behandlung der mittelschweren bis schweren atopischen Dermatitis

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.	– NB-UVB – UVA (die UVA1 ist hiervon ausgenommen, da ausgeschlossen)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	– Therapiehinweise zu Tacrolimus (Beschluss vom 4. September 2003) und Pimecrolimus (Beschluss vom 4. September 2003) – Beschlüsse über die Nutzenbewertung nach § 35a SGB V für den Wirkstoff Dupilumab vom 17. Mai 2018, 20. Februar 2020 und 1. Juli 2021 – Beschluss über Änderung der Richtlinie Methoden vertragsärztliche Versorgung (MVV-RL): „Balneophototherapie bei atopischem Ekzem“ vom 20. März 2020 – Beschluss über die Nutzenbewertung nach § 35a SGB V für den Wirkstoff Baricitinib vom 6. Mai 2021 – Beschlüsse über die Nutzenbewertung nach § 35a SGB V für den Wirkstoff Tralokinumab vom 6. Januar 2022 und 12.05.2023 – Beschluss über die Nutzenbewertung nach § 35a SGB V für den Wirkstoff Upadacitinib vom 17. Februar 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:	
Lebrikizumab N/N Ebglyss®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Ebglyss wird angewendet zur Behandlung von mittelschwerer bis schwerer atopischer Dermatitis (AD) bei Erwachsenen und Jugendlichen ab 12 Jahren, die für eine systemische Therapie in Betracht kommen.
Hinweis	***Aufgrund der großen Menge an Wirkstoffen im Anwendungsgebiet werden hier einzelne Arzneimittel exemplarisch aufgeführt***
TOPISCHE THERAPIEN	
Glukokortikoide Klasse 1:	
Prednisolon D07AA03 z.B. Prednisolon Creme LAW	Zur Behandlung subakuter und akuter gering ausgeprägter entzündlicher Hauterkrankungen, die auf eine äußerliche Behandlung mit schwach wirksamen Corticosteroiden ansprechen.
Hydrocortison D07AA02 z.B. Hydrocortison Heumann 1 % Creme	Zur Behandlung von entzündlichen Hauterkrankungen, bei denen schwach wirksame, topisch anzuwendende Glucocorticosteroide angezeigt sind.
Glukokortikoide Klasse 2:	
Hydrocortison-17-butyrat D07AB02 z.B. Laticort® Creme 0,1 %	Zur Behandlung entzündlicher Hautkrankheiten, bei denen mittelstark wirksame, topisch anzuwendende Glucocorticoide angezeigt sind. Creme: insbesondere bei akuten und subakuten Formen, in intertriginösen Arealen und beim fettigen Hauttyp. Salbe: insbesondere bei subakuten bis chronischen Formen.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Clobetasonbutyrat 0,5 mg D07AB01 z.B. Emovate® Creme	Leichte Formen von Ekzemen, seborrhoischer Dermatitis und andere leichte Hauterkrankungen, die auf eine lokale Corticoidbehandlung ansprechen. Weiterbehandlung von hartnackigen Hauterkrankungen, die mit einem starker wirkenden Corticoid anbehandelt worden sind. Bei Säuglingen und Kleinkindern zur lokalen Corticoidbehandlung, z. B. Windelekzem oder endogenem Ekzem.
Triamcinolon-acetonid D07AB09 z.B. AbZ Salbe 0,1 %	Zur Behandlung entzündlicher Hautkrankheiten, bei denen mittelstark wirksame topisch anzuwendende Glukokortikoide angezeigt sind. Triamcinolon AbZ 0,1 % Creme eignet sich insbesondere für akute bis subchronische sowie nässende Dermatosen ohne keratotische Veränderungen.
Glukokortikoide Klasse 3:	
Prednicarbat D07AC18 z.B. Prednicarbat acis® Creme	Entzündliche Hauterkrankungen, bei denen eine äußerliche Behandlung mit mittelstark wirksamen Glucocorticoiden angezeigt ist, wie z. B. mäßig stark ausgeprägtes Ekzem.
Methylprednisolon-aceponat D07AC 14 Advantan® 0,1 % Creme	Zur Behandlung des endogenen Ekzems (atopische Dermatitis, Neurodermitis), Kontaktekzems, degenerativen Ekzems und des nummulären Ekzems.
Amcinonid D07AC11 z.B. Amciderm® Fettsalbe	Hauterkrankungen, die auf stark wirksame Kortikoide ansprechen wie z.B. toxische Ekzeme, allergische Kontaktekzeme, atopisches Ekzem (Neurodermitis), Psoriasis vulgaris, Lichen ruber.
Mometasonfuroat D07AC13 z.B. ECURAL® Fettcreme, 1 mg/g Creme	Fettcreme und Salbe sind angezeigt zur Behandlung aller entzündlichen und juckenden Hauterkrankungen, die auf eine äußere Behandlung mit Glukokortikoiden ansprechen wie Psoriasis, atopische Dermatitis und Reiz- und/oder allergische Kontaktdermatitis.

Glukokortikoide Klasse 4:	
Clobetasol-propionat D07AD01 z.B. Clobetasol acis® Creme, 0,5 mg/g	Zur Behandlung lokalisierter therapieresistenter Plaques von entzündlichen Hauterkrankungen bei denen die symptomatische Anwendung topischer Glukokortikoide mit sehr starker Wirkung angezeigt ist.
Calcineurinhemmer	
Tacrolimus D11AH01 Protopic® 0.03% Salbe	Behandlung des mittelschweren bis schweren atopischen Ekzems bei Kindern ab 2 Jahren, die nicht ausreichend auf eine herkömmliche Therapie wie z. B. topische Kortikosteroide angesprochen haben. Als Erhaltungstherapie.
Pimecrolimus D11AH02 Elidel® 10 mg/g Creme	Behandlung von Patienten ab einem Alter von 3 Monaten mit leichtem oder mittelschwerem atopischem Ekzem, wenn eine Behandlung mit topischen Kortikosteroiden entweder nicht angebracht oder nicht möglich ist, wie z. B. bei: Unverträglichkeit gegenüber topischen Kortikosteroiden; mangelnder Wirksamkeit von topischen Kortikosteroiden; Anwendung im Gesicht und Halsbereich, wo eine intermittierende Langzeitbehandlung mit topischen Kortikosteroiden nicht empfehlenswert ist.
SYSTEMISCHE THERAPIEN	
Dupilumab D11AH05 Dupixent®	*Erwachsene und Jugendliche* Dupixent wird angewendet zur Behandlung von mittelschwerer bis schwerer atopischer Dermatitis (AD) bei Erwachsenen und Jugendlichen ab 12 Jahren, die für eine systemische Therapie in Betracht kommen. *Kinder von 6 Monaten bis 11 Jahre* Dupixent wird angewendet zur Behandlung von schwerer atopischer Dermatitis bei Kindern von 6 Monaten bis 11 Jahre, die für eine systemische Therapie in Betracht kommen.
Upadacitinib L04AA44 Rinvoq®	Rinvoq wird angewendet zur Behandlung der mittelschweren bis schweren atopischen Dermatitis bei Erwachsenen und Jugendlichen ab 12 Jahren, die für eine systemische Therapie infrage kommen.
Abrocitinib D11AH08 Cibinqo®	Cibinqo wird angewendet zur Behandlung von mittelschwerer bis schwerer atopischer Dermatitis bei Erwachsenen, die für eine systemische Therapie infrage kommen.
Baricitinib L04AA37 Olumiant®	Baricitinib wird angewendet zur Behandlung von mittelschwerer bis schwerer atopischer Dermatitis bei erwachsenen Patienten, die für eine systemische Therapie infrage kommen.

Tralokinumab D11AH07 Adtralza®	Adtralza wird angewendet zur Behandlung mittelschwerer bis schwerer atopischer Dermatitis bei Erwachsenen und Jugendlichen ab 12 Jahren, die für eine systemische Therapie in Frage kommen.
Ciclosporin L04AD01 z.B. Ciclosporin dura®	Ciclosporin dura ist indiziert bei Patienten mit schwerer atopischer Dermatitis, falls eine systemische Therapie erforderlich ist.
Systemische Glucokortikoide	
Methylprednisolon H02AB04 Methylprednisolon JENAPHARM®	Erkrankungen, die einer systemischen Therapie mit Glucocorticoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad zum Beispiel: Erkrankungen der Haut und Schleimhäute, die aufgrund ihres Schweregrades und/oder Ausdehnung bzw. Systembeteiligung nicht oder nicht ausreichend mit topischen Glucocorticoiden behandelt werden können.
Triamcinolon H02AB08 Volon® 4, 8, 12 mg Tabletten	Orale Anfangsbehandlung ausgedehnter, schwerer akuter, auf Glukokortikoide ansprechender Hautkrankheiten wie: Allergische Dermatosen (z. B. akute Urtikaria, Kontaktdermatitis, Arzneimittelexanthem), atopisches Ekzem (akute Exazerbationen bzw. großflächige nässende Ekzeme), Pemphigus vulgaris.
Antihistaminika	
z.B.Cetirizin-dihydrochlorid R06A E07 Cetirizin beta® Filmtablette	Zur Behandlung von Krankheitssymptomen bei allergischen Erkrankungen wie – Juckreiz bei chronischer Nesselsucht (Urtikaria) und bei atopischer Dermatitis (Neurodermitis) mit Beschwerden wie Rötung der Haut

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2023-B-139 (Lebrikizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	26. Juni 2023

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Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ECRI	ECRI Guidelines Trust
EASI75	Eczema Area and Severity Index
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
H1 AH	Orales H1 Antihistamin
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
POEM	Patient-Oriented Eczema Measure
RR	Relatives Risiko
SAE	Serious Adverse event
SCORAD	SCORing Atopic Dermatitis Index
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Mittelschwere bis schwere atopische Dermatitis (ohne Alterseinschränkung)

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *atopische Dermatitis* 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.

Die Erstrecherche wurde am 26.01.2022 durchgeführt, die folgenden am 23.09.2022 und 19.05.2023. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 1156 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 29 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Matterne U et al., 2019 [12].

Oral H1 antihistamines as ‘add-on’ therapy to topical treatment for eczema.

Fragestellung

To assess the effects of oral H1 antihistamines as 'add-on' therapy to topical treatment in adults and children with eczema.

Methodik

Population:

- adults and children with a clinical diagnosis of eczema, identified as 'atopic eczema' or 'eczema'

Intervention:

- Oral antihistamines (H1 antagonists) of all classes (sedating, non-sedating) given as add-on therapy to topical treatments for eczema (e.g. topical corticosteroids, topical immunomodulators, other topical eczema therapies, either alone or combined).

Komparator:

- Placebo as add-on therapy to topical treatment, or no additional treatment as add-on therapy to topical treatment

Endpunkte:

- Primary outcomes
  1. Mean change in patient-assessed symptoms of eczema, as measured by a standardised or validated eczema symptoms score
  2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period
- Secondary outcomes
  1. Mean change in physician-assessed clinical signs, as measured by a standardised or validated eczema signs score
  2. Mean change in quality of life, as measured by a standardised or validated quality of life measure
  3. Number of eczema flares, measured by, for example, ‘escalation of treatment’ or ‘use of topical anti-inflammatory medications’

Recherche/Suchzeitraum:

- Up to 9 May 2018 Cochrane Skin Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 4), the Cochrane Library, MEDLINE via Ovid (from 1946), Embase via Ovid (from 1974), The Global Resource of EczemA Trials - Centre of Evidence Based Dermatology
- Several trial registries up to 10 May 2018

Qualitätsbewertung der Studien:

- Risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions

Ergebnisse

Anzahl eingeschlossener Studien:

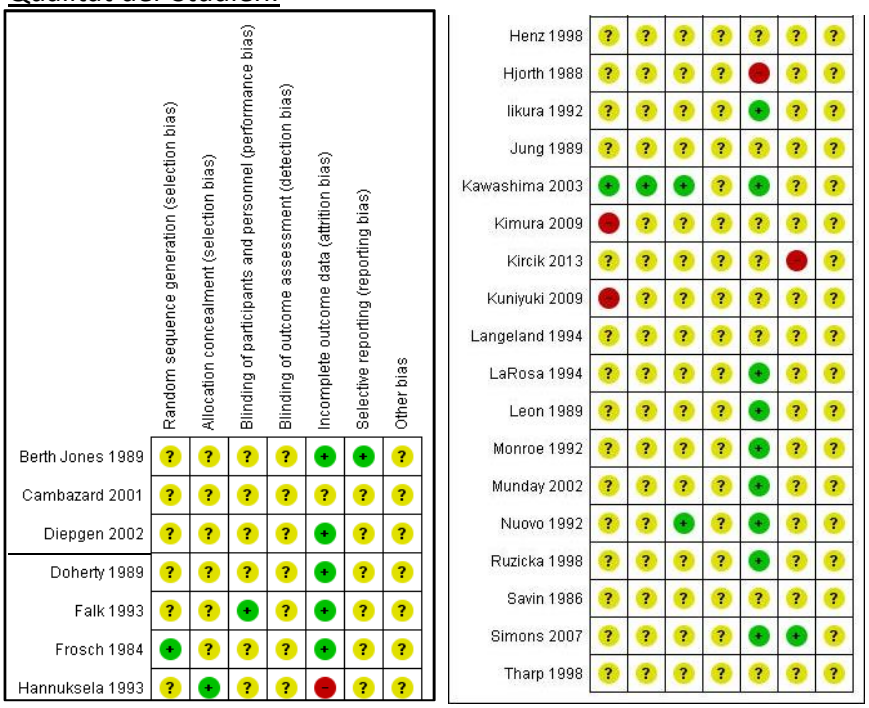
- n=25 RCTs (N=3285)

Charakteristika der Population:

- **Children and adolencents: n=8 Studies (0-12 years, 12-18 years; N=1941)** [Cambazard 2001; Diepgen 2002; Iikura 1992; Jung 1989; LaRosa 1994; Leon 1989; Munday 2002; Simons 2007].
- **Adults: n=17 Studies (aged from 16 to 70 years; N=1344)** [Berth Jones 1989; Doherty 1989; Falk 1993; Frosch 1984; Hannuksela 1993; Henz 1998; Hjorth 1988; Kawashima 2003; Kimura 2009; Kircik 2013; Kuniyuki 2009; Langeland 1994; Monroe 1992; Nuovo 1992; Ruzicka 1998; Savin 1986; Tharp 1998Capella 2001].
- Sample Size ranged from 1 to 795 participants
- Trial duration was between 3 days and 18 month
- Most studies failed to report on the severity of eczema [Berth Jones 1989; Cambazard 2001; Doherty 1989; Falk 1993; Frosch 1984; Henz 1998; Hjorth 1988; Jung 1989; Kawashima 2003; Kimura 2009; Kircik 2013; Kuniyuki 2009; LaRosa 1994; Leon 1989; Munday 2002; Nuovo 1992; Ruzicka 1998; Simons 2007; Tharp 1998].
- Two studies included individuals with at least moderate eczema [Monroe 1992; Savin 1986], two with moderate to severe eczema [Hannuksela 1993; Langeland 1994], one with moderate eczema [Iikura 1992], and one with mild to moderate eczema [Diepgen 2002].
- First-generation H1 AH.
  - * Chlorpheniramine (Frosch 1984; Nuovo 1992).
  - * Chlorpheniramine maleate (Munday 2002).
  - * Hydroxyzine (Monroe 1992).
  - * Ketotifen (Falk 1993; Iikura 1992; Leon 1989).
- Second-generation or newer H1 AH, or both.
  - * Acrivastine (Doherty 1989).
  - * Azelastine (no longer in use) (Henz 1998).
  - * Cetirizine (Cambazard 2001; Diepgen 2002; Hannuksela 1993; Henz 1998; Jung 1989; LaRosa 1994; Tharp 1998).
  - * Levocetirizine (Kircik 2013; Simons 2007).
  - * Fexofenadine (Kawashima 2003).
  - * Loratadine (Kimura 2009; Langeland 1994; Monroe 1992; Ruzicka 1998).
  - * Olapatadine (Kuniyuki 2009).
  - * Tazifylline LN2974 (Savin 1986).
  - * Terfenadine (no longer in use) (Berth Jones 1989; Doherty 1989; Hjorth 1988; Nuovo 1992).
- Duration of the oral application of H1 AH was
  - short term (up to one week) in five studies (Berth Jones 1989; Jung 1989; Kawashima 2003; Monroe 1992; Savin 1986),
  - medium term (from one to six weeks) in 11 studies (Doherty 1989; Frosch 1984; Hannuksela 1993; Henz 1998; Hjorth 1988; Kimura 2009; Kircik 2013; Langeland 1994; Munday 2002; Nuovo 1992; Ruzicka 1998), and

- long term (over more than six weeks) in nine studies (Cambazard 2001; Diepgen 2002; Falk 1993; Iikura 1992; Kuniyuki 2009; LaRosa 1994; Leon 1989; Simons 2007; Tharp 1998).

Qualität der Studien:



Studienergebnisse:

- Due to clinical diversity among studies in terms of duration of the intervention, the H1 AH used, and doses provided, as well as variation in the concomitant topical treatment allowed and in outcome assessment (see Table 3), **we were unable to pool any of the studies that we identified for inclusion in this review. Consequently, we have reported the effects of interventions for each trial individually.**

Cetirizine versus placebo **[Erwachsene und Kinder]**

- One study (*Diepgen 2002*) compared cetirizine 0.5 mg/kg/d against placebo over 18 months in 795 children. Study authors did not report patient-assessed symptoms of eczema separately for pruritus. Cetirizine is probably associated with fewer adverse events (mainly mild) (risk ratio (RR) 0.68, 95% confidence interval (CI) 0.46 to 1.01) and the need for slightly less additional H1 AH use as an indication of eczema flare rate (P=0.035; no further numerical data given). Physician-assessed clinical signs (SCORing Atopic Dermatitis index (SCORAD)) were reduced in both groups, but the difference between groups was reported as non-significant (no P value given). Evidence for this comparison was of moderate quality.
- One study [Hannuksela 1993] assessed cetirizine 10 mg/d against placebo over four weeks in 84 adults. Results show no evidence of differences between groups in patient-assessed symptoms of eczema (pruritus measured as part of SCORAD; no numerical data given), numbers of adverse events (RR 1.11, 95% CI 0.50 to 2.45; mainly sedation, other skin-related problems, respiratory symptoms, or headache), or physician assessed changes in clinical signs, amount of local rescue therapy required, or number of applications as an indicator of eczema flares (no numerical data reported). Evidence for this comparison was of low quality. We judged this study as having high risk regarding attrition bias.

- *Cambazard 2001* reported the results of a long-term intervention (eight weeks; n = 223) of 0.5 mg/d per kg bodyweight versus placebo conducted in children between 11 and 71 months of age. data from the study were available for analysis.

Anmerkung/Fazit der Autorinnen und Autoren

Based on the main comparisons, we did not find consistent evidence that H1 AH treatments are effective as 'add-on' therapy for eczema when compared to placebo; evidence for this comparison was of low and moderate quality. However, fexofenadine probably leads to a small improvement in patient-assessed pruritus, with probably no significant difference in the amount of treatment used to prevent eczema flares. Cetirizine was no better than placebo in terms of physician-assessed clinical signs nor patient-assessed symptoms, and we found no evidence that loratadine was more beneficial than placebo, although all interventions seem safe.

The quality of evidence was limited because of poor study design and imprecise results. Future researchers should clearly define the condition (course and severity) and clearly report their methods, especially participant selection and randomisation; baseline characteristics; and outcomes (based on the Harmonising Outcome Measures in Eczema initiative).

Kommentare zum Review

- Ergebnisse nur für zugelassenen Wirkstoff Cetirizin dargestellt. Ergebnisse nicht-relevanter Wirkstoffe nicht dargestellt
- Ergebnisse lediglich auf Ebene einzelner, kleiner Primärstudien mit Placebovergleichen, vorhanden
- Keine Angabe zum Schweregrad in den relevanten Studien.
- Es ist unklar, ob eine Hintergrundtherapie in den Placeboarmen verabreicht wurde (und wenn ja, welche).

Sawangjit R et al., 2020 [17].

Systemic treatments for eczema: a network meta-analysis

Fragestellung

To assess the comparative efficacy and safety of different types of systemic immunosuppressive treatments for moderate to severe eczema using network meta-analysis and to generate rankings of available systemic immunosuppressive treatments for eczema according to their efficacy and safety.

Methodik

Population:

- participants of all ages with a clinical diagnosis of moderate to severe atopic eczema

Intervention:

- at least one systemic immunosuppressive or immunomodulatory therapy for eczema, or a combination of treatments from the following: systemic corticosteroids, cyclosporin A (ciclosporin), methotrexate, azathioprine, mycophenolate mofetil, interferon gamma, intravenous immunoglobulin (IVIG), psoralen-ultraviolet A (PUVA), apremilast,

dupilumab, mepolizumab, omalizumab, and others, including new immunosuppressive or immunomodulatory agents

Komparator:

- Placebo

Endpunkte:

- Proportions of participants who achieved EASI75 (achieved 75% improvement in EASI score) at short-term (N 16 weeks) and long-term (> 16 weeks) durations, Proportions of participants who achieved POEM50 (achieved 50% improvement in POEM score) at short-term and longterm durations, Proportions of participants who achieved an Investigators' Global Assessment or Physicians' Global Assessment value of 0 or 1 (clear or almost clear) (IGA 0/1) at short-term and long-term durations

Recherche/Suchzeitraum:

- The Cochrane Skin Information Specialist searched the following databases up to 25 August 2019, using the following strategies based on the draP strategy for MEDLINE in our published protocol (Sawangjit 2018): Cochrane Skin Group Specialised Register; Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 8); MEDLINE via Ovid (from 1946); Embase via Ovid (from 1974); GREAT database.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool / GRADE

Ergebnisse

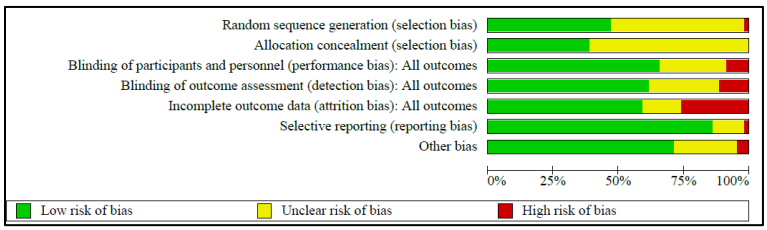
Anzahl eingeschlossener Studien:

- n=74 RCTs (N=8177)

Charakteristika der Population:

- Most of the included trials were placebo controlled (65%), 34% were head-to-head studies (15% assessed the eJects of diJerent doses of the same drug), and 1% were multi-armed studies with both an active comparator and a placebo.
- All trials included participants with moderate to severe eczema, but 62% of studies did not separate data by severity; 38% of studies assessed only severe eczema. The total duration of included trials ranged from 2 weeks to 60 months
- Seventy studies were available for quantitative synthesis; this review assessed 29 immunosuppressive agents from three classes of interventions. These included (1) conventional treatments, with ciclosporin assessed most commonly; (2) small molecule treatments, including phosphodiesterase (PDE)-4 inhibitors, tyrosine kinase inhibitors, and Janus kinase (JAK) inhibitors; and (3) biological treatments, including anti-CD31 receptors, anti-interleukin (IL)-22, anti-IL-31, anti-IL-13, anti-IL-12/23p40, anti-OX40, anti-TSLP, anti-CRTH2, and antiimmunoglobulin E (IgE) monoclonal antibodies, but most commonly dupilumab.

Qualität der Studien:



Studienergebnisse:

Direct evidence

Proportion of participants who achieved **EASI75** with any systemic intervention compared with placebo in the long term (< 16 weeks)

Total studies: 14 RCTs Total participants: 3851	**Relative effect (95% CI)**	**Anticipated absolute effect** (95% CI)			**Certainty of evidence** (CiNEMA)	**SUCRA**
		***Without* intervention**	***With* intervention**	**Difference**		
Dupilumab (8 RCTs; 1978 participants)	**RR 3.04** (2.51 to 3.69) Network estimate	184 per 1000	560 per 1000	376 fewer per 1000 (278 fewer to 496 fewer)	**High**	92.7
Tralokinumab (1 RCT; 153 participants)	**RR 2.54** (1.21 to 5.34) Network estimate	184 per 1000	468 per 1000	284 fewer per 1000 (39 fewer to 800 fewer)	**Low** confidence in estimate due to major concern of within-study bias	78.2
Tezepilumab (1 RCT; 153 participants)	**RR 1.70** (0.85 to 3.40) Network estimate	184 per 1000	313 per 1000	129 fewer per 1000 (442 fewer to 28 more)	**Low** confidence in estimate due to major concern of imprecision	57.3
GBR830 (1 RCT; 55 participants)	**RR 1.91** (0.46 to 8.02) Network estimate	184 per 1000	352 per 1000	168 fewer per 1000 (1293 fewer to 99 more)	**Low** confidence in estimate due to major concern of imprecision	48.6
Lebrikizumab (1 RCT; 46 participants)	**RR 1.40** (0.83 to 2.36) Network estimate	184 per 1000	258 per 1000	74 fewer per 1000 (251 fewer to 31 more)	**Very low** confidence in estimate due to some concern of within-study bias and major concern of imprecision	45
ASN002 (1 RCT; 27 participants)	**RR 1.50** (0.38 to 5.92) Network estimate	184 per 1000	276 per 1000	92 fewer per 1000 (907 fewer to 114 more)	**Low** confidence in estimate due to major concern of imprecision	37.5
Ustekinumab (1 RCT; 52 participants)	**RR 0.91** (0.28 to 2.97) Network estimate	184 per 1000	168 per 1000	17 more per 1000 (363 fewer to 133 more)	**Very low** confidence in estimate due to some concern of within-study bias and major concern of imprecision	19.6
Placebo	Reference comparator	Reference comparator	Not estimable	Not estimable	Reference comparator	21

Proportion of participants who achieved **EASI75** with any systemic intervention compared with placebo in the long term (> 16 weeks)

Total studies: 3 RCTs Total participants: 1241	**Relative effect (95% CI)**	**Anticipated absolute effect** (95% CI)			**Certainty of evidence** (CiNEMA)	**SUCRA**
		***Without* intervention**	***With* intervention**	**Difference**		
Dupilumab (2 RCTs; 764 participants)	**RR** 2.59 (1.87 to 3.60) Pair-wise estimate	200 per 1000	518 per 1000	318 fewer per 1000 (174 fewer to 520 fewer)	**Very low** confidence in estimate due to some concern of within-study bias and major concern of heterogeneity	N/A
Ustekinumab (1 RCT; 52 participants)	**RR** 1.17 (0.4 to 3.45) Pair-wise estimate	200 per 1000	234 per 1000	34 fewer per 1000 (490 fewer to 120 more)	**Very low** confidence in estimate due to some concern of within-study bias and major concern of imprecision	N/A
Placebo	Reference comparator	Reference comparator	Not estimable	Not estimable	Reference comparator	N/A

Patient-Oriented Eczema Measure (POEM) scores with any systemic intervention compared with placebo in the short term (< 16 weeks)

Total studies: 6 RCTs Total participants: 2680	**Relative effect** (95% CI)	**Anticipated absolute effect** (95% CI)			**Certainty of evidence** (CiNEMA)	**SUCRA**
		***Without* intervention**	***With* intervention**	**Difference**		
Dupilumab (5 RCTs; 1997 participants)	-	Mean of improving score was 5.18	Mean of improving score was 12.48 (11.79 to 13.18)	Mean difference in improving POEM score was 7.3 higher (6.61 higher to 8.00 higher)	**High**	N/A
Placebo	Reference comparator	Not estimable	Not estimable	Not estimable	Reference comparator	N/A

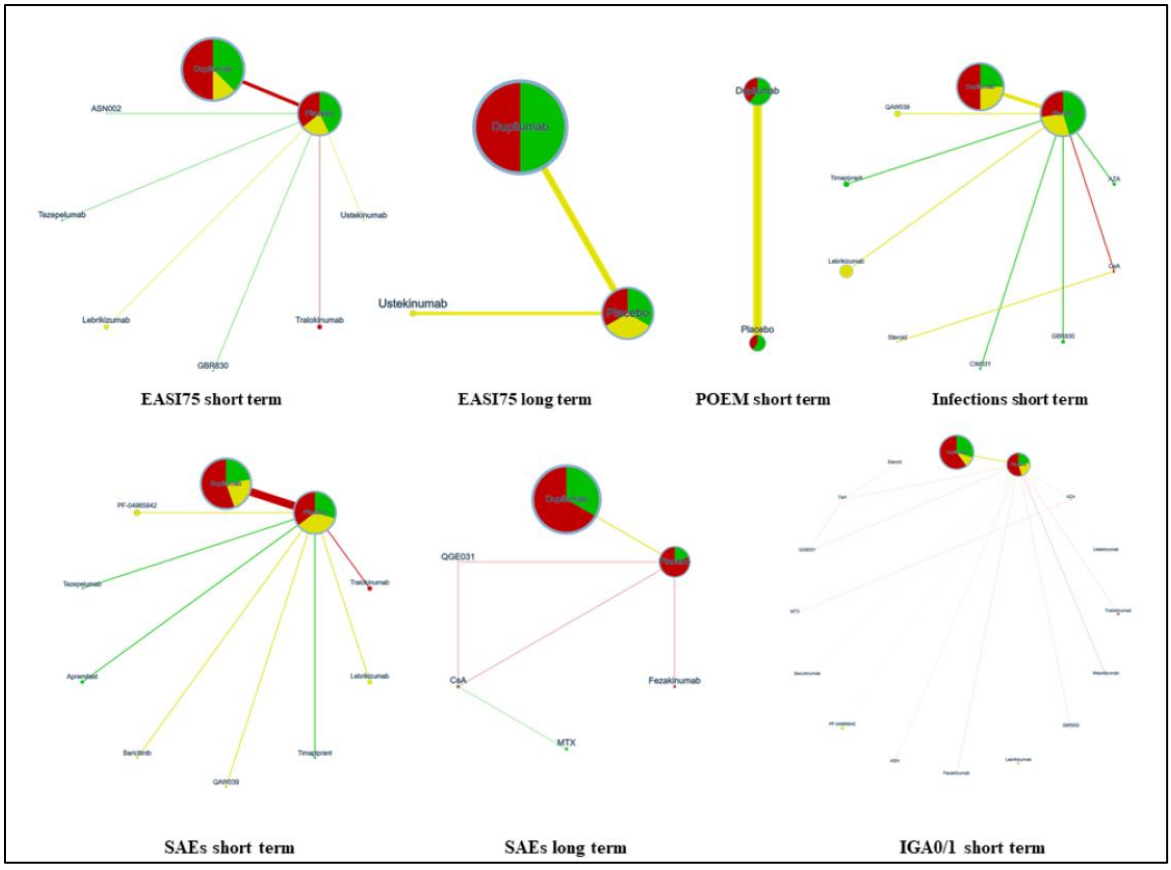
Serious adverse events (SAEs) with any systemic intervention compared with placebo in the short term (< 16 weeks)

Total studies: 17 RCTs Total participants: 3972	**Relative effect (95% CI)**	**Anticipated absolute effect** (95% CI)			**Certainty of evidence** (CiNEMA)	**SUCRA**
		***Without* intervention**	***With* intervention**	**Difference**		
QAW039 (1 RCT; 76 participants)	**RR 0.09** (0.01 to 0.76) Network estimate	54 per 1000	5 per 1000	49 more per 1000 (13 more to 53 more)	**Moderate** confidence in estimate due to some concern of within-study bias	94.2
Dupilumab (9 RCTs; 1663 participants)	**RR 0.37** (0.23 to 0.59) Network estimate	54 per 1000	20 per 1000	34 more per 1000 (22 more to 44 more)	**Low** confidence in estimate due to major concern of within-study bias	75.5
Timapiprant (1 RCT; 70 participants)	**RR 0.34** (0.07 to 1.62) Network estimate	54 per 1000	18 per 1000	36 more per 1000 (33 fewer to 50 more)	**Low** confidence in estimate due to major concern of imprecision	74
Tezepelumab (1 RCT; 56 participants)	**RR 0.65** (0.11 to 3.77) Network estimate	54 per 1000	35 per 1000	19 more per 1000 (149 fewer to 48 more)	**Low** confidence in estimate due to major concern of imprecision	54.9
Lebrikizumab (1 RCT; 156 participants)	**RR 0.85** (0.17 to 4.25) Network estimate	54 per 1000	46 per 1000	8 more per 1000 (175 fewer to 45 more)	**Very low** confidence in estimate due to some concern of within-study bias and major concern of imprecision	47.7
PF-04965842 (1 RCT; 211 participants)	**RR 0.93** (0.20 to 4.35) Network estimate	54 per 1000	50 per 1000	4 more per 1000 (181 fewer to 43 more)	**Very low** confidence in estimate due to some concern of within-study bias and major concern of imprecision	45.5
Tralokinumab (1 RCT; 153 participants)	**RR 1.67** (0.20 to 13.93) Network estimate	54 per 1000	90 per 1000	36 fewer per 1000 (697 fewer to 43 more)	**Very low** confidence in estimate due to major concern of within-study bias and imprecision	31.1
Apremilast (1 RCT; 121 participants)	**RR 3.73** (0.20 to 71.1) Network estimate	54 per 1000	201 per 1000	147 fewer per 1000 (3,780 fewer to 43 more)	**Low** confidence in estimate due to major concern of imprecision	20
Baricitinib (1 RCT; 75 participants)	**RR 4.61** (0.24 to 87.25) Network estimate	54 per 1000	249 per 1000	195 fewer per 1000 (4650 fewer to 41 more)	**Very low** confidence in estimate due to some concern of within-study bias and major concern of imprecision	16.5
Placebo	Reference comparator	Reference comparator	Not estimable	Not estimable	Reference comparator	40.5

Serious adverse events (SAEs) with any systemic intervention compared with placebo in the long term (> 16 weeks)

Total studies: 6 RCTs Total participants: 1720	**Relative effect (95% CI)**	**Anticipated absolute effect** (95% CI)			**Certainty of evidence** (CiNEMA)	**SUCRA**
		***Without* intervention**	***With* intervention**	**Difference**		
Dupilumab (3 RCTs; 1082 participants)	**RR 0.68** (0.38 to 1.21) Network estimate	10 per 1000	7 per 1000	3 more per 1000 (2 fewer to 6 more)	**Low** confidence in estimate due to major concern of imprecision	78.7
Methotrexate (1 RCT; 50 participants)	**RR 1.15** (0.01 to 151.54) Network estimate	10 per 1000	12 per 1000	2 fewer per 1000 (1,539 fewer to 10 more)	**Very low** confidence in estimate due to some concern of within-study bias and major concern of imprecision	58.5
Fezakinumab (1 RCT; 40 participants)	**RR 2.56** (0.13 to 50.95) Network estimate	10 per 1000	26 per 1000	16 fewer per 1000 (511 fewer to 9 more)	**Very low** confidence in estimate due to major concern of within-study bias and imprecision	38.8
QGE031 (1 RCT; 10 participants)	**RR 3.00** (0.14 to 65.90) Network estimate	10 per 1000	31 per 1000	20 fewer per 1000 (664 fewer to 9 more)	**Very low** confidence in estimate due to major concern of within-study bias and imprecision	35.3
Cyclosporin A (2 RCTs; 49 participants)	**RR 3.67** (0.09 to 149.20) Network estimate	10 per 1000	38 per 1000	27 fewer per 1000 (1515 fewer to 9 more)	**Very low** confidence in estimate due to major concern of within-study bias and imprecision	31.3
Placebo	Reference comparator	Reference comparator	Not estimable	Not estimable	Reference comparator	57.5

Network meta-analysis



- In terms of **achieving EASI75**, dupilumab and tralokinumab were superior to placebo (RR 3.04, 95% CI, 2.51 to 3.69; RR 2.54, 95% CI 1.21 to 5.34, respectively). These results supported the finding from direct evidence. Dupilumab was probably associated with a higher likelihood of achieving EASI75 compared to lebrikizumab (RR 2.18, 95% CI 1.25 to 3.81) and ustekinumab (RR 3.35, 95% CI 1.01 to 11.10). When only trials with low risk of bias were included, only dupilumab was still more effective than placebo (RR 2.53, 95% CI, 2.04 to 3.15) for this outcome.

Short term EASI75

a. Main analysis: inconsistency test, p-value=0.8739

ASN002							
0.49 (0.12,1.97)	Dupilumab						
0.78 (0.11,5.71)	1.59 (0.37,6.75)	GBR830					
1.07 (0.25,4.67)	**2.18 (1.25,3.81)**	1.37 (0.30,6.30)	Lebrikizumab				
0.88 (0.19,4.12)	1.79 (0.87,3.68)	1.13 (0.23,5.54)	0.82 (0.34,1.96)	Tezepelumab			
0.59 (0.12,2.81)	1.20 (0.56,2.58)	0.75 (0.15,3.78)	0.55 (0.22,1.36)	0.67 (0.24,1.84)	Tralokinumab		
1.65 (0.27,10.12)	**3.35 (1.01,11.10)**	2.11 (0.33,13.51)	1.54 (0.42,5.61)	1.87 (0.47,7.36)	2.80 (0.69,11.31)	Ustekinumab	
1.50 (0.38,5.92)	**3.04 (2.51,3.69)**	1.91 (0.46,8.02)	1.40 (0.83,2.36)	1.70 (0.85,3.40)	**2.54 (1.21,5.34)**	0.91 (0.28,2.97)	Placebo

- Ranking analysis for **short-term EASI75** outcomes performed with SUCRA strongly suggest that dupilumab was the most effective treatment among all systemic treatments in the network (versus placebo: 3.04, 95% CI 2.51 to 3.69; SUCRA = 92.7; high-certainty evidence), followed by tralokinumab (versus placebo: RR 2.54, 95% CI 1.21 to 5.34; SUCRA = 72; low-certainty evidence) and tezepelumab (versus placebo: RR 2.54, 95% CI 1.21 to 5.34; SUCRA = 49.6; low-certainty evidence). We are uncertain of the effect of dupilumab on achieving EASI75 in the long term when compared against placebo, as the certainty of this evidence is very low.
- Dupilumab was the only agent evaluated for improvement in POEM during short-term follow-up.
- QAW039 and dupilumab appeared safer than placebo in terms of having a lower proportion of participants with **SAEs** at short-term follow-up. Among the active treatments, apremilast and baricitinib appeared to be associated with a higher rate of SAEs compared to QAW039 (RR 41.99, 95% CI 1.09 to 1610.39; RR 51.85, 95% CI 1.36 to 1978.53). There was no difference between other active treatments for this outcome.
- Evidence for effects of immunosuppressive agents on risk of any infection during short-term follow-up and SAEs during long-term follow-up compared with placebo was of low or very low certainty but did not indicate a difference.
- We did not identify differences in other adverse events (AEs), but dupilumab is associated with specific AEs, including eye inflammation and eosinophilia.

Anmerkung/Fazit der Autoren

With a high degree of certainty, network meta-analysis (NMA) indicates that when compared to placebo, dupilumab is likely to be the more effective treatment for eczema and is ranked highest among the biological treatments in terms of achieving EASI75 and improving POEM scores during short-term follow-up (Summary of findings 1; Summary of findings 3). Dupilumab was the only immunosuppressive agent for which improvement in POEM in the short term was evaluated.

We are uncertain of the effect of dupilumab on achieving EASI75 in the long term when compared against placebo, as the certainty of this evidence is very low (Summary of findings 2). We are uncertain how conventional immunosuppressive treatments rank for our primary efficacy or safety outcomes compared with newer treatments such as the biological agent dupilumab due to lack of comparative data.

NMA suggests that tralokinumab may be more effective than placebo in achieving EASI75 in the short term (low-certainty evidence; Summary of findings 1). None of the included studies assessing tralokinumab measured POEM in the short term or EASI75 in the long term.

Based on our NMA, we are uncertain of the effect of ustekinumab on achieving EASI75 in the short or long term when compared with placebo (very low-certainty evidence; Summary of findings 1). None of the included studies assessing ustekinumab measured POEM.

Low- and very low-certainty evidence means we are uncertain how the other immunosuppressive agents in Summary of findings 1 and Summary of findings 2 influence the achievement of short-term EASI75 when compared with placebo. Dupilumab and ustekinumab were the only immunosuppressive agents for which achievement of long-term EASI75 was evaluated.

Compared to placebo, QAW039 and dupilumab may be safer based on association of these treatments with fewer SAEs during short term follow-up, with evidence judged to have a low to moderate degree of certainty. For the other immunosuppressive agents when compared to placebo, we found no difference in SAEs during short term follow-up, but this finding is based on low- to very low certainty evidence (Summary of findings 4).

Evidence of a very low to low degree of certainty indicates there was no difference in the rate of any infection with systemic immunosuppressive treatments compared to placebo during short-term follow-up (Summary of findings 6).

When safety outcomes during long-term follow-up were assessed, evidence (which was of very low to low certainty) indicates there was no statistical difference in the proportions of participants with SAE when any immunosuppressive agent was compared to placebo (Summary of findings 5).

We did not identify differences in other adverse events (AEs), but dupilumab is associated with specific AEs, including eye inflammation and eosinophilia.

3.2 Systematische Reviews

Drucker AM et al. 2022 [6,7].

Systemic Immunomodulatory Treatments for Patients With Atopic Dermatitis: A Systematic Review and Network Meta-analysis

Siehe auch folgende systematische Reviews zur Behandlung der atopischen Dermatitis:

- Wan H et al. 2022 [22]. Comparative efficacy and safety of abrocitinib, baricitinib, and upadacitinib for moderate-to-severe atopic dermatitis: A network meta-analysis
  - ⇨ In our network meta-analysis, however, we find that upadacitinib 30 mg was associated with increased IGA and EASI response compared with all other regimens, and upadacitinib 15 mg was also superior to other regimens except for abrocitinib 200 mg in terms of IGA and EASI response.
- Silverberg JI et al. 2021 [21]. Comparative efficacy and safety of systemic therapies used in moderate-to-severe atopic dermatitis: a systematic literature review and network meta-analysis
  - ⇨ In conclusion, results of this NMA highlight that efficacy outcomes of JAK1 inhibitors (abrocitinib and upadacitinib) were consistently higher than those of dupilumab and baricitinib in moderate-to-severe AD.
- Silverberg JI et al. 2022 [20]. Comparative Efficacy of Targeted Systemic Therapies for Moderate to Severe Atopic Dermatitis without Topical Corticosteroids: Systematic Review and Network Meta-analysis
  - ⇨ The study found that upadacitinib 30 mg daily, upadacitinib 15 mg daily, and abrocitinib 200 mg daily may be the most efficacious targeted systemic therapies across 12–16 weeks of therapy.
- Pereyra-Rodriguez JJ et al. 2021 [16]. Short-Term Effectiveness and Safety of Biologics and Small Molecule Drugs for Moderate to Severe Atopic Dermatitis: A Systematic Review and Network Meta-Analysis
  - ⇨ In summary, with the existing evidence, the new JAK inhibitors (Upadacitinib and Abrocitinib), at higher doses, are the most effective drugs for the short-term treatment of moderate-to-severe atopic dermatitis. However, these doses showed the highest risk for any adverse event. Furthermore, the concomitant use of TCS modifies the ranking and ORs.
- Lee KP et al. 2023 [11]. Oral Janus kinase inhibitors in the treatment of atopic dermatitis: A systematic review and meta-analysis
  - ⇨ JAK inhibitors were found to be an effective treatment for AD. Upadacitinib, at 30 mg, was found to be the most efficacious oral JAK inhibitor for AD.

Fragestellung

To compare the effectiveness and safety of systemic immunomodulatory treatments for patients with atopic dermatitis in a systematic review and network meta-analysis.

Methodik

Population:

- children and adults with moderate-to severe AD

Intervention:

- systemic (ie, oral, intravenous, or subcutaneous) immunomodulatory therapies

Komparator:

- any comparator, including placebo

Endpunkte:

- primary outcomes are (1) change in score on a scale measuring investigator-reported clinical signs, such as the Eczema Area and Severity Index (EASI)9; (2) change in score on a scale measuring patient-reported overall symptoms, such as the Patient-Oriented Eczema Measure (POEM)10; (3) withdrawal from systemic treatment owing to adverse events; and (4) occurrence of serious adverse events.
- secondary outcomes are (1) change in score on a scale measuring skin-specific health-related quality of life, such as the Dermatology Life Quality Index (DLQI),11 and (2)

change in score on a scale measuring itch severity.

Recherche/Suchzeitraum:

- We searched the Cochrane Central Register of Controlled Trials, MEDLINE via Ovid (from1946), Embase via Ovid (from1974), the Latin American and Caribbean Health Science Information database (from 1982), and the Global Resource of Eczema Trials database. We searched all databases from inception until October 28, 2019.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- n=39 RCTs (N=6360)

Charakteristika der Population:

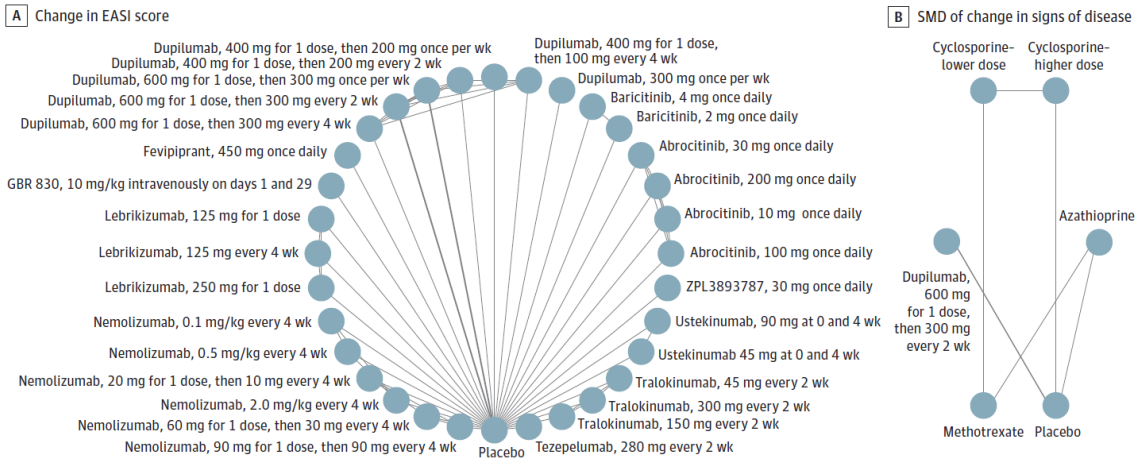
- included studies evaluated 20 different systemic immunomodulatory therapies and most comparisons were with placebo
- Mean sample size per group was 60 (range, 4-319), the mean proportion of females per trial group was 45%, and the mean or median age in trial groups ranged between 6 and 44 years. Most trials (n = 29) were sponsored by industry.
- Very few studies (n = 6) included outcomes beyond 16 weeks, and network meta-analyses were therefore limited to short-term outcomes

Qualität der Studien:

- Sixteen studies had at least 1 element at high risk of bias

Studienergebnisse:

Figure 2. Network Graphs of Studies Included in the Analysis of Atopic Dermatitis Treatment Between 8 and 16 Weeks



mean change in EASI score

- Dupilumab 300 mg every 2 weeks (the approved dosage for adults) was superior to placebo (mean difference, 11.3-point reduction; 95%CrI, 9.7-13.1[GRADE assessment: high certainty]). Several investigational medications demonstrated reduction in EASI score compared with placebo, including baricitinib, 2 mg daily (mean difference, 5.6- point reduction; 95%CrI, 0.4-10.9 [GRADE assessment: moderate certainty]) and 4 mg daily (mean difference, 5.2-point reduction; 95% CrI, 0.1-10.4 [GRADE assessment: moderate certainty]), and tralokinumab, 150 mg every 2 weeks (mean difference, 4.3-point reduction; 95% CrI, –0.2 to 8.9 [GRADE assessment: moderate certainty]) and 300mg every 2 weeks (mean difference, 4.9-point reduction; 95% CrI, 0.4-9.3 [GRADE assessment: moderate certainty]).
- Azathioprine, lower dose cyclosporine, higher-dose cyclosporine, methotrexate, and dupilumab had moderate or large benefits relative to placebo. Higher-dose cyclosporine (SMD,−1.1;95%CrI,−1.7 to−0.5 [low certainty]) and dupilumab (SMD, −0.9; 95% CrI, −1.0 to −0.8 [high certainty]) were similarly effective vs placebo in clearing clinical signs of AD and may be superior to methotrexate (SMD, −0.6; 95% CrI, −1.1 to 0.0 [low certainty]) and azathioprine (SMD, −0.4; 95% CrI, −0.8 to −0.1 [low certainty]). Higher-dose cyclosporine may be associated with improvement in clinical signs compared with azathioprine (SMD, −0.6; 95% CrI, −1.2 to 0.0 [low certainty]) and methotrexate (SMD, −0.5; 95%CrI, −1.1 to 0.0 [low certainty]), with similar improvement to dupilumab (SMD, −0.2; 95%CrI, −0.8 to 0.4 [low certainty]).

improvements in the POEM score

- Dupilumab,300mg every 2weeks (mean difference, –7.5; 95% CrI, –8.5 to –6.4 [high certainty]), and investigational drugs abrocitinib, 100mg daily (mean difference, –7.6; 95%CrI, –11.6 to –3.6 [low certainty]) and 200 mg daily (mean difference, –11.3; 95%CrI, –15.0 to –7.5 [low certainty]), and upadacitinib, 15mg daily (mean difference, –7.0; 95%CrI, –11.4 to –2.6 [low certainty]) and 30mg daily (mean difference, –10.7; 95% CrI, –15.1 to –6.3 [low certainty])were associated with clinically relevant improvements in the POEM score compared with placebo

DLQI score

- Dupilumab,300 mg every 2weeks (mean difference, –4.8; 95%CrI, –5.8 to –3.7 [high certainty]), and abrocitinib, 100mg daily (mean difference, –5.2; 95% CrI, –9.3 to –1.1 [low certainty]) and 200 mg daily (mean difference, –4.9; 95% CrI, –8.8 to –1.0 [low certainty]), were associated with clinically important differences in the DLQI score compared with placebo
- Azathioprine dosed according to thiopurine methyltransferase levels was associated with clinically meaningful improvement in the DLQI score compared with placebo, but this improvement was based on low certainty evidence owing to imprecision (mean difference, −3.4; 95% CrI, −7.1 to 0.2). Comparisons between cyclosporine, dupilumab, methotrexate, and azathioprine in improvement in quality of life on the SMD scale were imprecise

itch scales

- In the analysis of SMDs in change in itch scales, cyclosporine, 5 mg/kg daily (SMD, −0.8; 95% CrI, −1.7 to 0.1 [very low certainty]), and dupilumab,300mg every 2weeks (SMD, −0.8; 95% CrI, −1.0 to −0.7 [high certainty]), were associated with improvements in itch relative to placebo. Comparisons between cyclosporine, dupilumab, methotrexate, and azathioprine on the SMD scale for itch were imprecise

Safety

- Given low adverse event rates, robust, interpretable relative safety estimates, particularly among medications currently in use, are not possible. Many of the studies reported 0 events for 1 or more treatments, which generates results that cannot be estimated or results with high uncertainty, even in our analyses with more informative priors.

Anmerkung/Fazit der Autoren

This network meta-analysis is based on 39 RCTs including 6360 patients taking 20 systemic AD medications. In analyses of outcomes in adult patients receiving between 8 and 16 weeks of treatment, dupilumab was efficacious based on high certainty evidence with regards to improving clinical signs, including clinically important differences in EASI scores. Dupilumab and the investigational Janus kinase inhibitors upadacitinib and abrocitinib provided clinically meaningful improvement in POEM scores and dupilumab and abrocitinib were associated with clinically meaningful improvements in the DLQI score compared with placebo.
Our analyses using the SMD scale permitted comparisons of dupilumab with older systemic AD medications, for which no head-to-head trials exist, to our knowledge. Dupilumab and higher-dose cyclosporine appear to have better effectiveness during the first 4 months of therapy in improving clinical signs, itch, and quality of life relative to methotrexate and azathioprine. These analyses are limited by pooling outcome measures such as peak itch and mean itch, which measure the same domain but in different ways, and their inclusion of trials only up to 16 weeks, which may favor medications with more rapid onset of action. Despite these concerns and low certainty according to GRADE, our stratification of the currently available treatments should be useful to stakeholders including patients, clinicians, guideline developers, and health technology assessors.

Conclusions

Cyclosporine and Dupilumab may have better short-term effectiveness than methotrexate and azathioprine for treatment of AD in adults. In the absence of well-powered head-to-head trials comparing all possible combinations of active treatments, our study provides the best available comparative effectiveness estimates to inform treatment decisions, guidelines, and health technology assessments. Ongoing and planned RCTs will give more precision to our effect estimates and provide estimates for children and longer-term outcomes.

Kommentare zum Review

Nicht alle untersuchten Arzneimittel sind in Deutschland zur Behandlung der atopischen Dermatitis zugelassen.

Siegels D et al., 2020 [19].

Systemic treatments in the management of atopic dermatitis: A systematic review and meta-analysis

Fragestellung

This systematic review analysed and critically appraised the current research evidence on systemic treatments in children, adolescents and adults with moderate-to-severe AD.

Methodik

Population:

- children ≤ 12 years, adolescents 13-17 years and/or adults ≥ 18 years with moderate-to-severe AD

Intervention:

- Trials that examined one of the following treatments for AD, or a combination thereof, were included: Adalimumab, Apremilast, Azathioprine (AZA), Baricitinib, Brodalumab, Ciclosporin A (CSA), Corticosteroids, , Dupilumab, Etanercept, Infliximab, Interferon-gamma (IFN-γ), intravenous immunoglobulins (IVIG), Ixekizumab, Mepolizumab, Methotrexate (MTX), Mycophenolate mofetil/sodium, Omalizumab, Rituximab, Secukinumab, Tofacitinib, Upadacitinib, Ustekinumab

Komparator:

- any

Endpunkte:

TABLE 2 Outcomes

Primary outcomes		Secondary outcomes	
Efficacy	**Safety**	**Efficacy**	**Safety**
▪ Physician-assessed clinical signs score (eg mean change in Eczema Area and Severity Index (EASI), EASI75, mean change in SCOring Atopic Dermatitis (SCORAD), Six Area Six Sign Atopic Dermatitis (SASSAD)) ▪ Patient-reported symptoms score (eg mean change in Patient Oriented Eczema Measure (POEM)) ▪ Skin or AD-specific health-related quality of life (eg mean change in Dermatology Life Quality Index (DLQI))	▪ Incidence rate of all adverse events (AE) ▪ Incidence rate of serious adverse events (SAE)	▪ Investigator Global Assessment (IGA) ▪ Patient Global Assessment (PGA)	▪ Total withdrawal rates ▪ Withdrawal due to AE ▪ Withdrawal due to treatment failure

Recherche/Suchzeitraum:

- MEDLINE (via OVID), EMBASE (via OVID), Cochrane Controlled Register of Trials (CENTRAL) and Global Resource of Eczema Trials (GREAT) up to February 2020

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias 2.0 Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- N=50 RCTs (N=6681)

Charakteristika der Population:

- We identified trial evidence for 13 systemic treatments available and licensed in Europe: one trial (including 185 patients) evaluated apremilast,83 three trials (totalling 140 patients) evaluated AZA, three trials (including 1 363 patients) evaluated baricitinib, 19 trials (totalling 820 patients) evaluated CSA, three trials (totalling 85 patients) evaluated corticosteroids, 11 trials (totalling 3529 patients) evaluated dupilumab, two trials (totalling 134 patients) evaluated IFN-γ, three trials (totalling 64 patients) evaluated IVIG, one trial (including 43 patients) evaluated mepolizumab, three trials (totalling 179 patients) evaluated MTX, three trials (totalling 91 patients) evaluated omalizumab, one trial (totalling 167 patients) evaluated upadacitinib and two trials (totalling 112 patients) evaluated ustekinumab.

- Of the 50 RCTs included, 20 (40%) were placebo-controlled trials, 9 (18%) were trials with active comparator, 13 (26%) were placebo-controlled trials including different treatment doses, two (4%) compared different dosing regimens, one (2%) compared different treatment formulations, two (4%) compared different treatment durations and three (6%) compared different concomitant treatments.
- According to our age definitions, the included patients were clearly consistent with our definition of children (<12 years) in one (2%) RCT, 30 (60%) trials were conducted in adults (≥ 18 years), one (2%) trial was conducted in adolescents (≥12 and < 18 years), and 18 (36%) trials were not clearly consistent with our age definition of children, adolescents and/or adults. In one RCT, "children" with no age definition were reported.

TABLE 3 Qualitative efficacy overview of included RCTs

Treatment	Total n	Number of RCTs	Effectiveness reported scores	Reference, year	Treatment duration[a]	Age[b]
Apremilast	185	1	Apremilast superior to placebo for: EASI, DLQI[83]	Simpson et al, 2018[83]	Short-term (12 weeks)	Adults
Azathioprine (AZA)	140	2	AZA superior to placebo for: SASSAD: Meta-Analysis favours AZA[20,28]	Berth-Jones et al, 2002[20]	Short-term (12 weeks)	Mixed (≥16 years)
		1	VAS pruritus and VAS sleep disturbance[20,28] DLQI[28]	Meggit et al, 2006[28]	Short-term (12 weeks)	Mixed (≥16 years)
			AZA equally effective as MTX for: EASI, SCORAD, Skindex-17 and POEM[33,74]	Schram et al, 2011[33]	Short-term (12 weeks)	Adults
				Gerbens et al, 2018[74]	Long-term (5 years)	Adults
Baricitinib	1363	3	Baricitinib superior to placebo for: EASI75/EASI90: Meta-Analyses favour baricitinib[76,84]	Guttmann-Yassky et al, 2018[76]	Short-term (16 weeks)	Adults
			EASI, SCORAD, DLQI, POEM and NRS pruritus[76,84]	Simpson et al, 2020[84]	Short-term (16 weeks)	Adults
Ciclosporin A (CSA)	820	19	CSA superior to placebo for: nonvalidated scores: Meta-Analysis favours CSA[34,36,53]	Wahlgren et al, 1990[57]	Short-term (10 days)	Adults
			nonvalidated severity scores and VAS pruritus[34,36,53,57]	Sowden et al, 1991[34]	Short-term (8 weeks)	Mixed (≥17 years)
			VAS sleeplessness[34,53]	Salek et al, 1993[31]	Short-term (8 weeks)	Mixed (≥17 years)
			EDI and UKSIP[31]	Munro et al, 1994[53]	Short-term (8 weeks)	Adults
				van Joost et al, 1994[36]	Short-term (6 weeks)	Mixed (≥17 years)
			CSA equally effective as MTX for: SCORAD[22,75]	El-Khalawany et al, 2013[22]	Short-term (12 weeks)	Mixed (8-14 years)
			EASI and DLQI[75]	Goujon et al, 2017[75]	Short- and long-term (12 and 24 weeks)	Adults
			CSA superior to UVAB phototherapy after 8 weeks (for SCORAD) and equally effective after 52 weeks (for SCORAD and EDI)[23]	Granlund et al, 2001[23]	Short- and long-term (8 and 52 weeks)	Adults
			CSA equally effective as tacrolimus ointment for: SCORAD, nonvalidated pruritus score and nonvalidated sleep score[54]	Pacor et al, 2004[54]	Short-term (6 weeks)	Mixed (≥13 years)
			CSA superior to IVIG for: SCORAD[46]	Bemanian et al, 2005[46]	Short-term (12 weeks)	Not reported (only "children" reported)
			CSA superior to prednisolone for: SCORAD[32]	Schmitt et al, 2010[32]	Short-term (12 weeks)	Adults
			CSA superior to ECP for: SCORAD and VAS pruritus[61]	Koppelhus et al, 2014[61]	Short-term (16 weeks)	Adults
			CSA not superior to EC-MPS (for SCORAD; all patients had 6 pretreatment with CSA)[24]	Haeck et al, 2011[24]	Short- and long-term (12 and 30 weeks)	Adults

			CSA compared different treatment dose regimen: nonvalidated disease severity scores equally effective[21,58] DLQI, VAS pruritus and VAS sleeplessness equally effective[21]	Zonneveld et al, 1999[58]	Long-term (52 weeks)	Adults
				Czech et al, 2000[21]	Short-term (8 weeks)	Adults
			CSA compared different treatment formulations: nonvalidated disease severity scores, pruritus and sleeplessness equally effective[37]	Zurbriggen et al, 1999[37]	Short-term (8 weeks)	Adults
			CSA compared different treatment durations: SASSAD,VAS pruritus and Quality of life equally effective[25]	Harper et al, 2000[25]	Short- and long-term (12 and 52 weeks)	Mixed (3-16 years)
			CSA compared with different concomitant treatments: SCORAD equally effective with concomitant glucosamine[82] SCORAD superior with concomitant glucosamine[79] EASI equally effective with "topical agents"[80]	Kwon et al, 2013[82]	Short-term (2 weeks)	Mixed (≥12 years)
				Jin et al, 2015[79]	Short-term (8 weeks)	Mixed (≥7 years)
				Kim et al, 2016[80]	Long-term (24 weeks)	Mixed (any age allowed)
Corticosteroids	85	3	Corticosteroids superior to placebo for: nonvalidated disease severity and symptom scores[27,45]	Heddle et al, 1984[26]	Short-term (12 weeks)	Mixed (3-14 years)
				La Rosa et al, 1995[45]	Short-term (2 weeks)	Children
			Corticosteroids not superior to prednisolone for: SCORAD[32]	Schmitt et al, 2010[32]	Short-term (6 weeks)	Adults
Dupilumab	3529	11	Dupilumab superior to placebo for: EASI75/EASI/SCORAD/NRS pruritus/GISS/POEM/ DLQI: Meta-Analyses favour dupilumab[19,35,47,56,73,86] EASI[19,35,47,56,71,73,78,85,86,88] SCORAD[35,47,56,73,78,85] POEM[35,47,56,71,73,78,85] NRS pruritus[19,35,47,56,71,73,78,85] DLQI[35,47,56,73] cDLQI[85] QoLIAD[87] IGA[19] GISS[47,56,73,78]	Beck et al, 2014[19]	Short-term (4 and 12 weeks)	Adults
				Thaci et al, 2016[35] Simpson et al, 2016[56]	Short-term (16 weeks)	Adults
				Simpson et al, 2016[86]	Short-term (16 weeks)	Adults
				Blauvelt et al, 2017[47]	Short- and long-term (16 and 52 weeks)	Adults
				Bruin-Weller et al, 2017[73]	Short-term (16 weeks)	Adults
				Blauvelt et al, 2018[71]	Short-term (16 weeks)	Adults
				Tsianikas et al, 2018[87]	Short-term (12 weeks)	Adults
				Guttmann-Yassky et al, 2019[78]	Short-term (16 weeks)	Adults
				Simpson et al, 2020[85]	Short-term (16 weeks)	Adolescents
				Worm et al, 2019[88]	Long-term (36 weeks)	Adults
Interferon-gamma (IFN-γ)	134	2	IFN-γ superior to placebo for: nonvalidated clinical severity scores[50,90]	Hanifin et al, 1993[48]	Short-term (12 weeks)	Mixed (≥2 years)
				Jang et al, 2000[50]	Short-term (12 weeks)	Mixed (≥15 years)
Intravenous immunoglobulins (IVIG)	64	3	IVIG superior to placebo for: SCORAD[51]	Jee et al, 2011[51]	Short-term (12 weeks)	Mixed (children ≥ 2 years reported)
			IVIG not superior to CSA for: SCORAD[46]	Bemanian et al, 2005[46]	Short-term (12 weeks)	Not reported (only "children" reported)
			IVIG compared different treatment durations: no effectiveness for both treatment durations for SCORAD[30]	Paul et al, 2002[30]	Short-term (60 days)	Adults
Mepolizumab	43	1	Mepolizumab not superior to placebo for: SCORAD and VAS pruritus[29]	Oldoff et al, 2005[29]	Short-term (2 weeks)	Adults
Methotrexate (MTX)	179	3	MTX equally effective as AZA for: EASI, SCORAD, Skindex-17, POEM, IGA and PGA[33,74]	Schram et al, 2011[33]	Short-term (12 weeks)	Adults
				Gerbens et al, 2018[74]	Long-term (5 years)	Adults
			MTX equally effective as CSA for: SCORAD[22,75] EASI and DLQI[75]	El-Khalawany et al, 2013[22]	Short-term (12 weeks)	Mixed (8-14 years)
				Goujon et al, 2017[75]	Short- and long-term (12 and 24 weeks)	Adults
Omalizumab	91	3	Omalizumab superior to placebo for: SCORAD, EASI and (c)DLQI[72]	Chan et al, 2020[72]	Long-term (24 weeks)	Mixed (4-19 years)
			Omalizumab not superior to placebo for: SCORAD[49] EASI and IGA[27]	Iyengar et al, 2013[49]	Long-term (24 weeks)	Mixed (4-22 years)
				Heil et al, 2010[27]	Short-term (16 weeks)	Mixed (≥12 years)
Upadacitinib	167	1	Upadacitinib superior to placebo for: EASI, SCORAD and NRS pruritus[77]	Guttmann-Yassky et al, 2019[77]	Short-term (16 weeks)	Adults
Ustekinumab	112	2	Ustekinumab not superior to placebo for: SCORAD[52] EASI[55] DLQI[52,55] ADIS[55]	Khattri et al, 2017[52]	Short-term (16 weeks)	Adults
				Saeki et al, 2017[55]	Short- and long-term (12 and 24 weeks)	Adults

Abbreviations: (c)DLQI, (Children's) Dermatology Life Quality Index; ADIS, Atopic Dermatitis Itch Scale; AZA, azathioprine; CSA, ciclosporin A; EASI, Eczema Area and Severity Index; EC-MPS, entericcoated mycophenolate sodium; ECP, extracorporeal photopheresis; EDI, Eczema Disability Index; GISS, Global Individual Sign Score; IFN-γ, interferon-gamma; IGA, Investigator Global Assessment; IVIG, intravenous immunoglobulins; MTX, methotrexate; PGA, Patient Global Assessment; POEM, Patient Oriented Eczema Measure; QoLIAD, Quality of Life Index for Atopic Dermatitis; RCT, randomized controlled trial; SASSAD, Six Area Six Sign Atopic Dermatitis; SCORAD, SCOring Atopic Dermatitis; UKSIP, United Kingdom Sickness Impact Profile; UVAB, ultraviolet A/B rays; VAS, visual analogue scale.

[a] According to the methods section, short-term is defined as ≤ 16 weeks and long-term as > 16 weeks.

[b] Age categorized as children (age < 12 years), adolescents (age 13-17 years), adults (≥18 years), mixed ages and not reported.

TABLE 4 Qualitative safety overview of included RCTs

Treatment	Total n	Number of RCTs	Reported safety	Reference, year	Safety assessment timepoint[a]	Age[b]
Apremilast	185	1	Cumulative incidence rate of AEs: 70% for apremilast 40mg twice daily, 62% for apremilast 20mg twice daily, 47% for placebo[83] Cumulative incidence rate of SAEs: 5% for apremilast 40mg twice daily, 2% for apremilast 20mg twice daily, 0% for placebo[83] Most common AEs for apremilast: diarrhoea, nausea, headache, nasopharyngitis, upper respiratory tract infection, abdominal discomfort, dyspepsia[83] Most common SAEs for apremilast: cellulitis led to discontinuation of 40mg group (41)[83]	Simpson et al, 2018[83]	Long-term (24 weeks)	Adults
Azathioprine (AZA)	140	3	Cumulative incidence rate of AEs: 50%-100% for AZA, 11%-100% for comparator[20,28,33] Cumulative incidence rate of SAEs: 0%-10% for AZA, 0% for comparator[28,33] Most common AEs for AZA: myelosuppression, hepatotoxicity, diarrhoea, infections/infestations, gastrointestinal adverse events/nausea/abdominal pain/diarrhoea, headache[20,28,33,74] Most common SAEs for AZA: AZA hypersensitivity, abnormal transaminases, severe nausea[20,28,33,74]	Berth-Jones et al, 2002[20]	Long-term (24 weeks)	Mixed (≥16 years)
				Meggit et al, 2006[28]	Short-term (12 weeks)	Mixed (≥16 years)
				Schram et al, 2011[33]	Long-term (24 weeks)	Adults
				Gerbens et al, 2018[74]	Long-term (5 years)	Adults
Baricitinib	1363	3	Cumulative incidence rate of AEs: 54%-71% for baricitinib 4 mg/day, 46%-58% for baricitinib 2 mg/day, 49%-56% for placebo[76,84] Cumulative incidence rate of SAEs: 1%-3% for baricitinib 4 mg/day, 0%-2% for baricitinib 2 mg/day, 0%-4% for placebo[76,84] Most common AEs for baricitinib: acne, nasopharyngitis, upper respiratory tract inflammation, elevated blood creatine phosphokinase levels and headache[76,84] Most common SAEs for baricitinib: benign polyp[76,84]	Guttmann-Yassky et al, 2018[76]	Short-term (16 weeks)	Adults
				Simpson et al, 2020[84]	Short-term (16 weeks)	Adults
Ciclosporin A (CSA)	820	19	Cumulative incidence rate of AEs: range between 0%-100% for CSA and comparison groups[21,23,25,31,34,36,46,54,57,58,75,79-82] Cumulative incidence rate of SAEs: range between 0%-13% for CSA and comparison groups[21,23,24,31,32,34,36,46,54,57,58,75,79-82] Most common AEs for CSA: hypertension, nephrotoxicity, gastrointestinal symptoms, headache, hypertrichosis, upper respiratory tract infection, infections, fatigue, paraesthesia[21,23-25,31,32,34,36,46,54,57,58,75,79-82] Most common SAEs for CSA: severe headache, paraesthesia, abdominal pain, hypertension, nausea, upper respiratory tract infection[21,23-25,31,32,34,36,46,54,57,58,75,79-82]	Wahlgren et al, 1990[57]	Short-term (6 weeks)	Adults
				Sowden et al, 1991[34]	Short-term (16 weeks)	Mixed (≥17 years)
				Salek et al, 1993[31]	Short-term (16 weeks)	Mixed (≥17 years)
				Munro et al, 1994[53]	Short-term (16 weeks)	Adults
				van Joost et al, 1994[36]	Short-term (6 weeks)	Mixed (≥17 years)
				El-Khalawany et al, 2013[22]	Short-term (12 weeks)	Mixed (8-14 years)
				Goujon et al, 2017[75]	Long-term (24 weeks)	Adults
				Granlund et al, 2001[23]	Long-term (52 weeks)	Adults
				Pacor et al, 2004[54]	Short-term (6 weeks)	Mixed (≥13 years)
				Bemanian et al, 2005[46]	Short-term (12 weeks)	Not reported (only "children" reported)
				Schmitt et al, 2010[32]	Long-term (18 weeks)	Adults
				Koppelhus et al, 2014[81]	Short-term (16 weeks)	Adults
				Haeck et al, 2011[24]	Long-term (30 weeks)	Adults
				Zonneveld et al, 1999[58]	Long-term (52 weeks)	Adults
				Czech et al, 2000[21]	Short-term (12 weeks)	Adults
				Zurbriggen et al, 1999[37]	Short-term (16 weeks)	Adults
				Harper et al, 2000[25]	Long-term (52 weeks)	Mixed (3-16 years)
				Kwon et al, 2013[82]	Long-term (26 weeks)	Mixed (≥12 years)
				Jin et al, 2015[79]	Short-term (8 weeks)	Mixed (≥7 years)
				Kim et al, 2016[80]	Long-term (36 weeks)	Mixed (any age allowed)
Corticosteroids	85	3	Cumulative incidence rate of AEs: no AEs reported for corticosteroids and comparison groups[26,32,45] Cumulative incidence rate of SAEs: SAEs occurred in one trial (10% for prednisolone, 0% for comparator CSA)[32] Most common AEs for corticosteroids: not AEs reported[26,32,45] Most common SAEs for corticosteroids: SAEs occurred in one trial (exacerbation of AD with hospitalization)[32]	Heddle et al, 1984[26]	Short-term (12 weeks)	Mixed (3-14 years)
				La Rosa et al, 1995[45]	Short-term (5 weeks)	Children
				Schmitt et al, 2010[32]	Long-term (18 weeks)	Adults

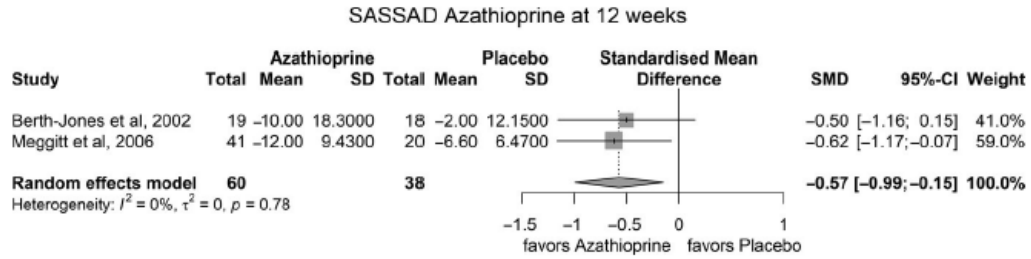
Dupilumab	3529	11	Cumulative incidence rate of AEs: 56%-92% for dupilumab, 62%-88% for placebo[19,35,47,56,71,73,78,85] Cumulative incidence rate of SAEs: 0%-8% for dupilumab, 0%-13% for placebo[19,35,47,56,71,73,78,85] Most common AEs for dupilumab: conjunctivitis, (peri-)ocular clinical signs, nasopharyngitis, herpes virus infection, upper respiratory tract infection[19,35,47,56,71,73,78,85] Most common SAEs for dupilumab: respiratory disorder, Severe conjunctivitis[19,35,47,56,71,73,78,85]	Beck et al, 2014[19]	Short-term (4 and 12 weeks)	Adults
				Thaci et al, 2016[35] Simpson et al, 2016[56]	Long-term (32 weeks)	Adults
				Simpson et al, 2016[86]	Short-term (16 weeks)	Adults
				Blauvelt et al, 2017[47]	Long-term (52 weeks)	Adults
				Bruin-Weller et al, 2017[73]	Short-term (16 weeks)	Adults
				Blauvelt et al, 2018[71]	Long-term (32 weeks)	Adults
				Tsianikas et al, 2018[87]	-	Adults
				Guttmann-Yassky et al, 2019[78]	Long-term (32 weeks)	Adults
				Simpson et al, 2020[85]	Short-term (16 weeks)	Adolescents
				Worm et al, 2019[88]	Long-term (36 weeks)	Adults
Interferon-gamma (IFN-γ)	134	2	Cumulative incidence rate of AEs: not reported[48,50] Cumulative incidence rate of SAEs: not reported[48,50] Most common AEs for IFN-γ: headache, myalgia, chill, constitutional symptoms, disease flare, granulocytopenia, fever, LDH elevation[48,50] Most common SAEs for IFN-γ: disease flare, hepatic transaminase elevation[48,50]	Hanifin et al, 1993[48]	Short-term (12 weeks)	Mixed (≥2 years)
				Jang et al, 2000[50]	Short-term (12 weeks)	Mixed (≥15 years)
Intravenous immunoglobulins (IVIG)	64	3	Cumulative incidence rate of AEs: 17 and 33% for IVIG, 0 and 25% for comparators[46,51] Cumulative incidence rate of SAEs: 0% for IVIG, 0% for comparator[30,46] Most common AEs for IVIG: fever, chill, headache, nausea, vomiting[30,46,51] Most common SAEs for IVIG: severe headache, nausea, vomiting[30,46,51]	Jee et al, 2011[51]	Long-term (36 weeks)	Mixed (children ≥ 2 years reported)
				Bemanian et al, 2005[46]	Short-term (12 weeks)	Not reported (only "children" reported)
				Paul et al, 2002[30]	Short-term (90 days)	Adults
Mepolizumab	43	1	Cumulative incidence rate of AEs: not reported[29] Cumulative incidence rate of SAEs: not reported[29] Most common AEs for Mepolizumab: ´mild side effects`[29] Most common SAEs for Mepolizumab: no SAEs reported[29]	Oldoff et al, 2005[29]	Short-term (4 weeks)	Adults
Methotrexate (MTX)	179	3	Cumulative incidence rate of AEs: 82 and 100% for MTX, 79 and 100% for comparators[33,75] Cumulative incidence rate of SAEs: 0% for MTX, 0%-2% for comparators[33,75] Most common AEs for MTX: elevation of liver enzymes, gastrointestinal issues, infections, neuromuscular disorders, lymphocytopenia[33,75] Most common SAEs for MTX: no SAEs reported[22,33,74,75]	Schram et al, 2011[33]	Long-term (24 weeks)	Adults
				Gerbens et al, 2018[74]	Long-term (5 years)	Adults
				El-Khalawany et al, 2013[22]	Short-term (12 weeks)	Mixed (8-14 years)
				Goujon et al, 2017[75]	Long-term (24 weeks)	Adults
Omalizumab	91	3	Cumulative incidence rate of AEs: 77%-94% for omalizumab, 57%-100% for placebo[27,72] Cumulative incidence rate of SAEs: 0%-19% for omalizumab, 0%-19% for placebo[27,49,72] Most common AEs for omalizumab: vertigo, headache, nausea, abdominal pain, allergic reactions, aggravated eczema[27,49,72] Most common SAEs for omalizumab: anaphylaxis (one patient with history of idiopathic anaphylaxis)[72]	Chan et al, 2020[72]	Long-term (24 weeks)	Mixed (4-19 years)
				Iyengar et al, 2013[49]	Long-term (24 weeks)	Mixed (4-22 years)
				Heil et al, 2010[27]	Short-term (16 weeks)	Mixed (≥12 years)
Upadacitinib	167	1	Cumulative incidence rate of AEs: 74%-79% for upadacitinib, 61% for placebo[77] Cumulative incidence rate of SAEs: 0%-5% for upadacitinib, 2% for placebo[77] Most common AEs for upadacitinib: upper respiratory tract infection, acne, AD worsening[77] Most common SAEs for upadacitinib: atrial fibrillation (multimorbid patient), pericoronitis (patient with history of tooth infections), exacerbation of AD in context with contact dermatitis (one patient), appendicitis (one patient)[77]	Guttmann-Yassky et al, 2019[77]	Short-term (16 weeks)	Adults
Ustekinumab	112	2	Cumulative incidence rate of AEs: 12%-75% for ustekinumab, 30%-74% for placebo[52,55] Cumulative incidence rate of SAEs: 0% for ustekinumab, 0% for placebo[52,55] Most common AEs for ustekinumab: nasopharyngitis, contact dermatitis, worsening of skin infection (eczema herpeticatum)[52,55] Most common SAEs for ustekinumab: no SAEs occurred[52,55]	Khattri et al, 2017[52]	Long-term (24 weeks)	Adults
				Saeki et al, 2017[55]	Long-term (24 weeks)	Adults

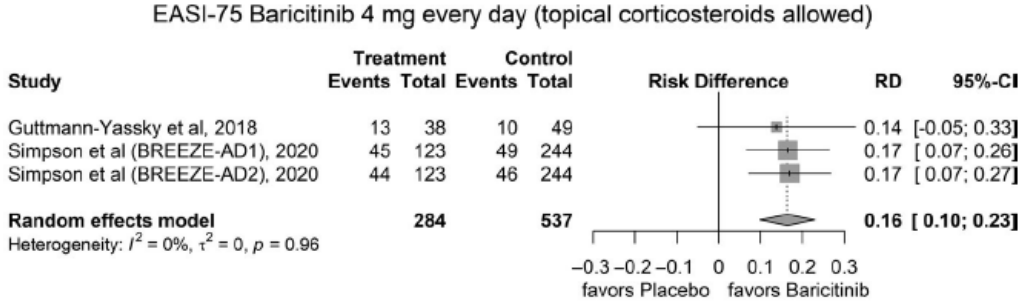
Abbreviations: AE, adverse event(s); AZA, azathioprine; CSA, ciclosporin A; IFN-γ, interferon-gamma; MTX, methotrexate; RCT, randomized controlled trial; SAE, severe adverse event(s).
[a] According to the methods section, short-term is defined as ≤ 16 weeks and long-term as > 16 weeks.
[b] Age categorized as children (age < 12 years), adolescents (age 13-17 years), adults (≥18 years), mixed ages and not reported.

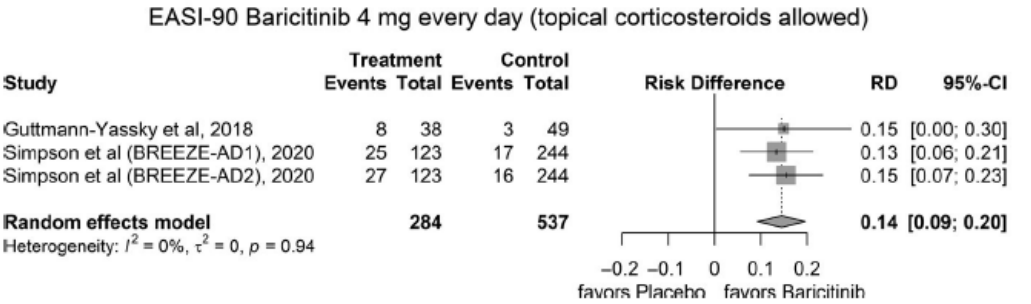
Qualität der Studien:

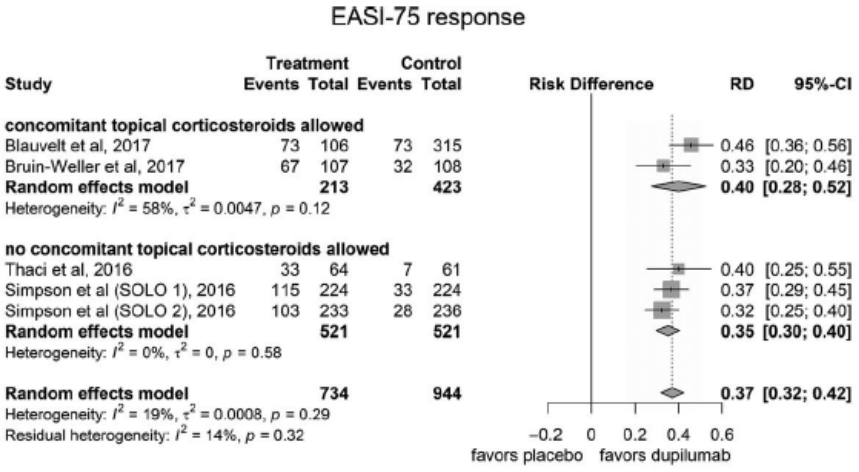
- The overall RoB was rated “high” in 20 (40%) RCTs with “some concerns” in 16 (32%) trials and “low” in 14 (28%)trials. The reporting and/or methodological quality tends to be higher in trials more recently published.

Studienergebnisse:









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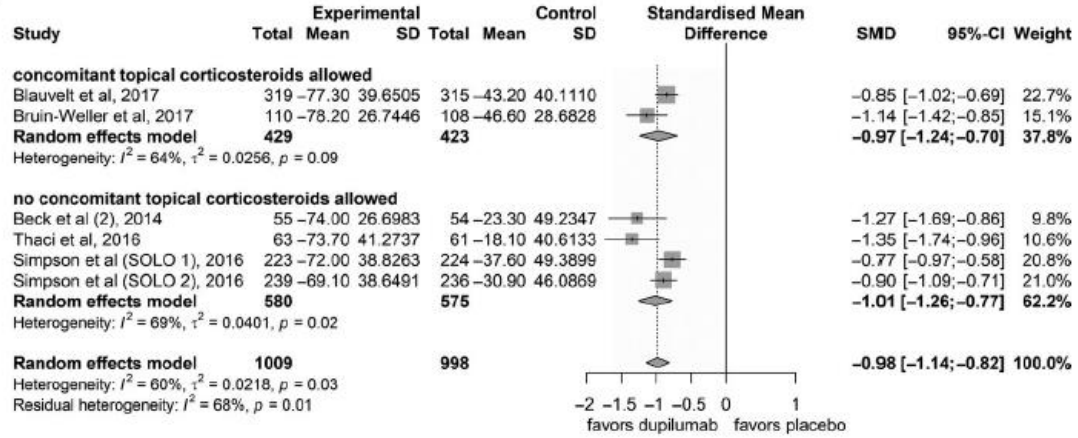
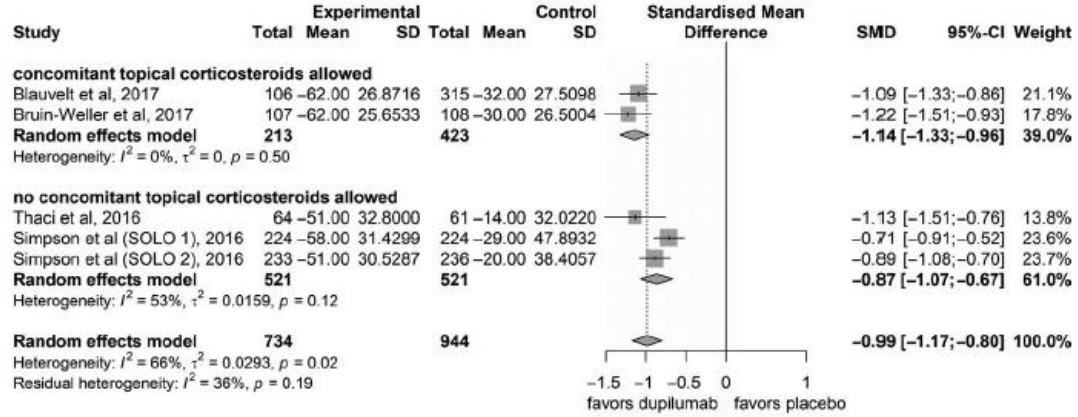
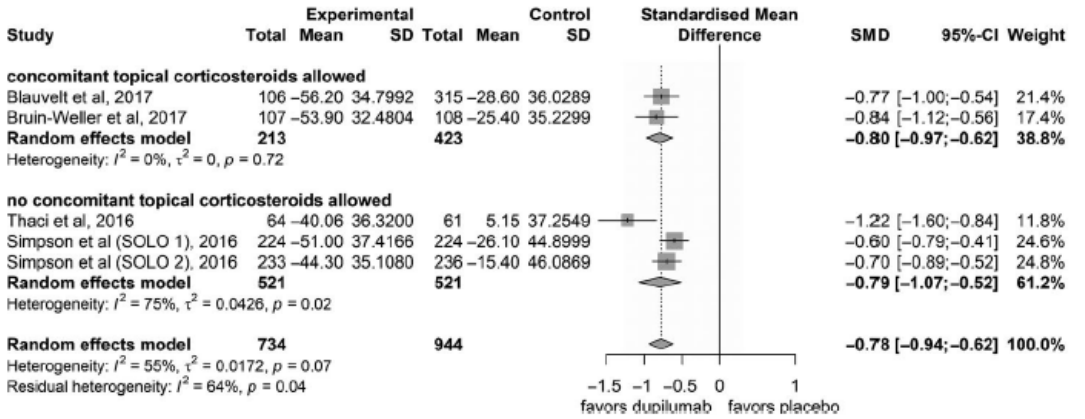
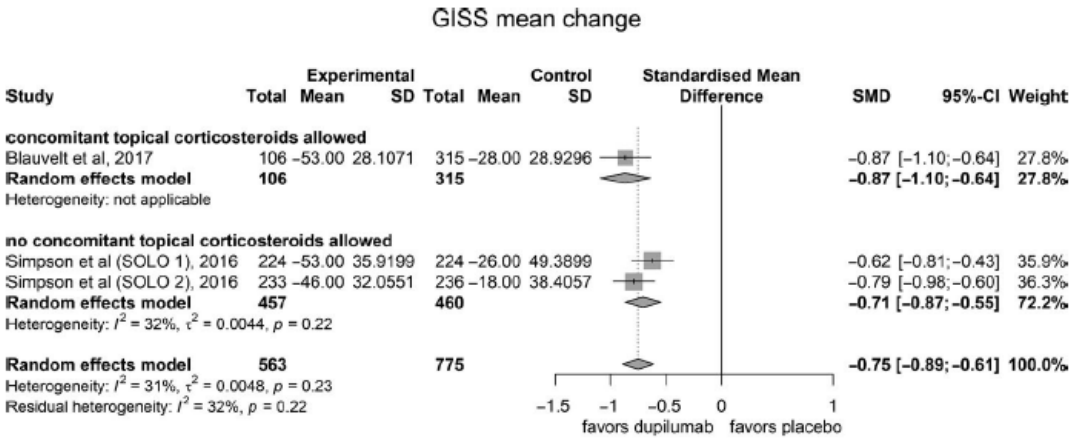


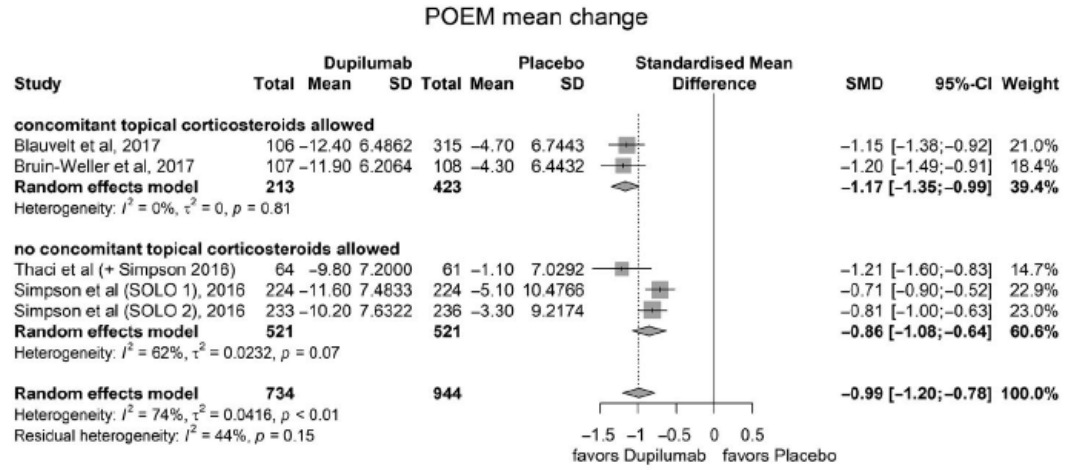
SCORAD mean change

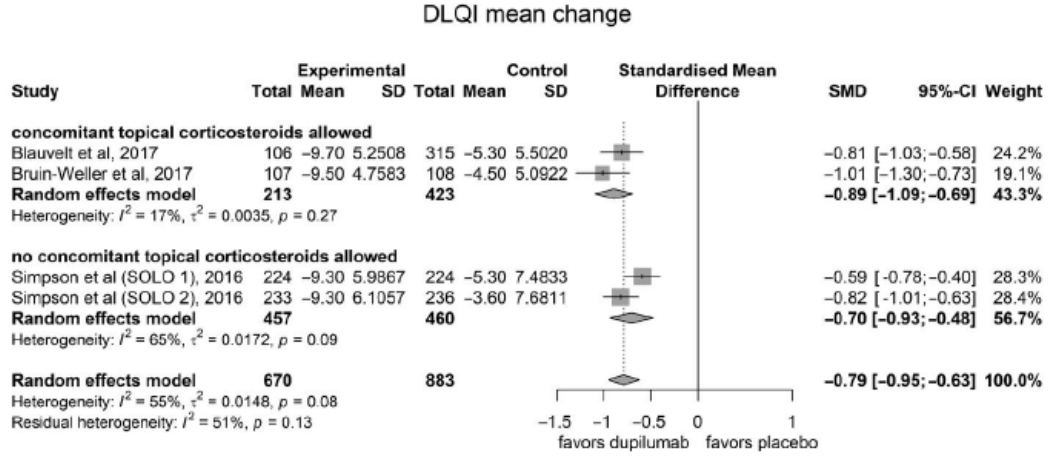


NRS pruritus mean change









Anmerkung/Fazit der Autoren

Many treatments evaluated in this systematic review are well established in practice (AZA, CSA, corticosteroids, dupilumab, MTX), but there remains uncertainty regarding first- and second- line therapy. Robust trial evidence was elaborated for AZA, baricitinib, CSA and dupilumab. However, there remains uncertainty for AZA, baricitinib and CSA as a consequence of lower trial quality, less number of included patients and/or trials in the meta- analyses, compared to dupilumab. Furthermore, more biologics and small molecules for AD such as JAK inhibitors, which include baricitinib and upadacitinib, fulfilled the inclusion criteria of this systematic review. These biologics are already approved for other indications in Europe (there are two licensed and available) and will most likely be approved

also for AD in the near future. The treatment spectrum will continuously expand; recommendations for treatment will have even greater relevance. In this regard, a timely update will be planned as soon as new developments will be available. EAACI's forthcoming atopic dermatitis guidelines will combine the findings from this systematic review with expert opinion and other evidence to suggest practical implications for health professionals and patients according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Zhang Y et al., 2022 [29].

The efficacy and safety of IL-13 inhibitors in atopic dermatitis: A systematic review and meta-analysis

Fragestellung

To assess the efficacy and safety of IL-13 inhibitors in moderate to severe AD

Methodik

Population:

- individuals with moderate to severe AD who did not receiving lebrikizumab or tralokinumab before

Intervention:

- IL-13 inhibitors

Komparator:

- control/placebo

Endpunkte:

- disease severity, quality of life and adverse events

Recherche/Suchzeitraum:

- PubMed, Embase, Cochrane Central Register of Controlled Trials were searched from its inception to November 9th, 2021

Qualitätsbewertung der Studien:

- Cochrane Collaboration's assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- n=7 RCTs (N=2946)

Charakteristika der Population/Studien:

- n=2 Studien (Lebrikizumab)
- n=5 Studien (Tralokinumab)
- All the included studies used subcutaneous placebo as the comparator, and treatment duration varied from 12 weeks to 16 weeks.

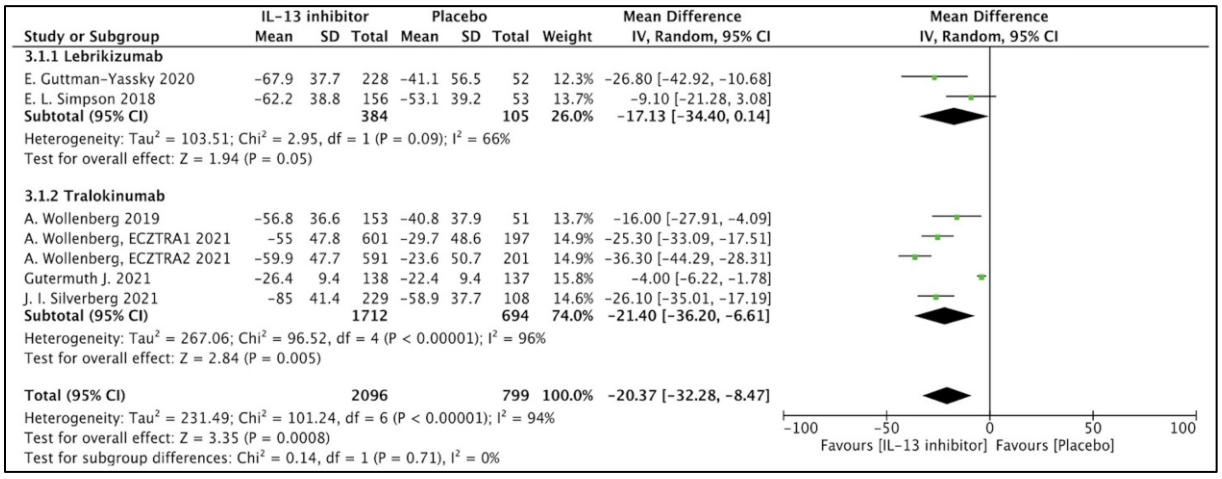
Study(year)	Clinical trial identified	Severity of AD	Participant characteristics						Treatment	Dosage/frequency	Duration of treatment	Outcomes
			Treatment group			Placebo group						
			No. of participants/no. of males	Age (y)	Race (%)	No. of participants/no. of males	Age (y)	Race (%)				
E. Guttman-Yassky et al. (2020) (18)	NCT 03443024	Moderate to severe	228/86	38.7 ± 17.3	White (52.2) Black or African American (33.8) American Indian or Alaskan native (1.3) Asian (9.2) Multiple or other (3.5)	52/28	42.2 ± 18.2	White (50.0) Black or African American (30.8) American Indian or Alaskan native (0.0) Asian (11.5) Multiple or other (7.7)	Lebrikizumab (125mg Q4W, 250mg Q4W or 250 mg Q2W) or placebo	16 wk	EASI%, EASI-75, NRS improvement>4, DLQI
E. L. Simpson et al. (2018) (21)	NCT 02340234	Moderate to severe	156/100	35.3 ± 12.4	White (73.7) Asian (23.7) Other (25.6)	53/36	38.7 ± 13.2	White (66.0) Asian (30.2) Other (3.8)	Lebrikizumab (125mg SD, 250mg SD or 125 mg Q4W) or placebo	12 wk	EASI%, EASI-75, IGA 0/1
J. I. Silverberg et al. (2021) (19)	NCT 03363854	Moderate to severe	253/125	37.0 (28.0-52.-0)	White (80.2) Black or African American (9.1) Asian (6.7) Native Hawaiian or other Pacific Islanfer (0.4) Other (3.6)	127/84	34.0 (24.0-50.0)	White (66.9) Black or African American (9.4) Asian (18.9) Native Hawaiian or other Pacific Islanfer (0.8) Other (3.9)	Tralokinumab (300mg Q2W+TCS) or placebo	16 wk	EASI%, EASI-75, IGA 0/1, NRS improvement>4, DLQI
A. Wollenberg et al. ECZTRA1 (2021) (22)	NCT 03131648	Moderate to severe	603/351	37.0 (27.0-48.0)	White (70.6) Black (6.8) Asian (19.9) Other or missing data (2.7)	199/123	37.0 (26.0-49.0)	White (69.4) Black (9.0) Asian (20.1) Other or missing data (1.5)	Tralokinumab (300mg Q2W) or placebo	16 wk	EASI%, EASI-75, IGA 0/1, NRS improvement>4, DLQI
A. Wollenberg et al. ECZTRA2 (2021) (22)	NCT 03160885	Moderate to severe	593/359	34.0 (25.0-48.0)	White (63.1) Black (7.3) Asian (26.0) Other or missing data (3.7)	201/114	30.0 (23.0-46.0)	White (61.2) Black (8.5) Asian (25.9) Other or missing data (4.5)	Tralokinumab (300mg Q2W) or placebo	16 wk	EASI%, EASI-75, IGA 0/1, NRS improvement>4, DLQI
A. Wollenberg et al. (2019) (23)	NCT 02347176	Moderate to severe	153/88	37.3 ± 14.5	Asian (22.9) Black or African American (13.7) White (61.4) Other (0.7)	51/22	39.4 ± 14.5	Asian (19.6) Black or African American (15.7) White (60.8) Other (1.9)	Tralokinumab (45, 150 or 300mg Q2W) or placebo	12 wk	EASI%, IGA 0/1, DLQI
Gutermuth J. et al. (2021) (24)	NCT 03761537	Severe	140/82	33.0 (25.5-47.0)	White (97.9) Black or African American (0) Asian (0) Other (2.1)	137/83	34.0 (26.0-45.0)	White (98.5) Black or African American (0.7) Asian (0.7) Other (0)	Tralokinumab (300 mg Q2W+TCS or placebo)	16 wk	EASI%, EASI-75, NRS improvement>4, DLQI

Qualität der Studien:

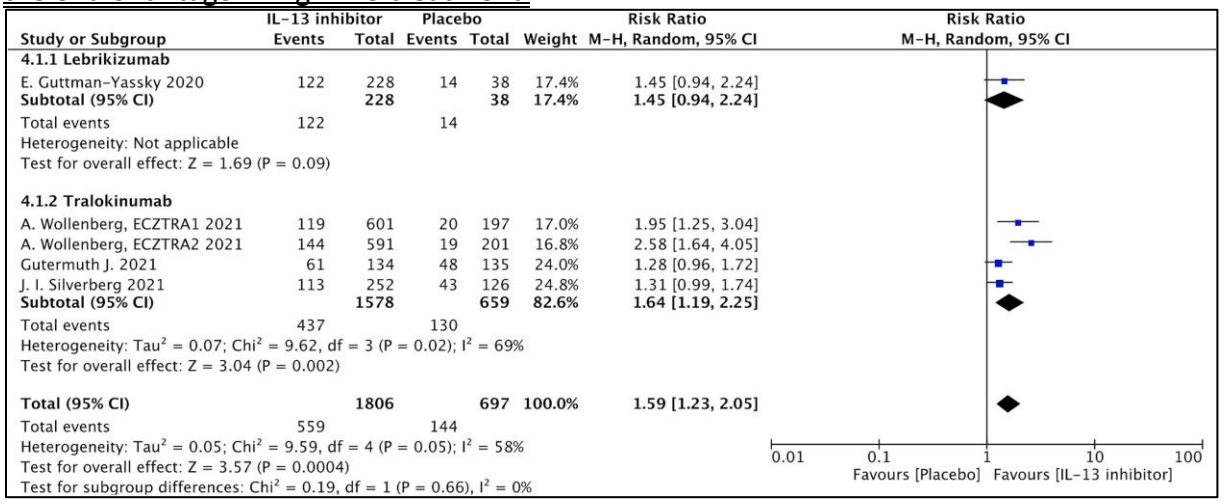
- high quality in all included RCTs. Only 1 study (21) did not report the detailed description of random sequence generation, allocation concealment, blinding of participants and health care personnel, and blinding of outcome assessment.

Studienergebnisse:

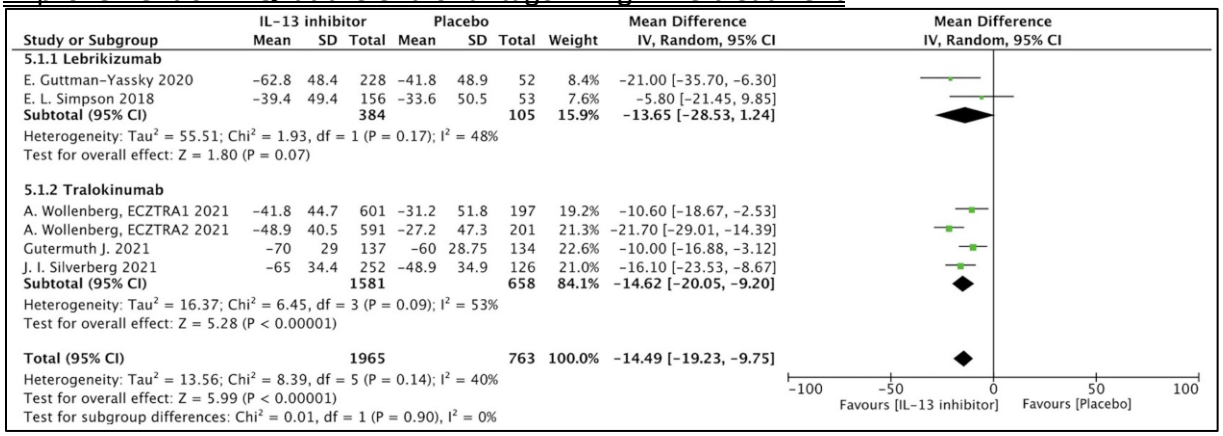
Percentage improvement of EASI score at the end of antagonizing IL-13 treatment.



Proportion of patients achieving NRS score with more than 4-points daily improvement at the end of antagonizing IL-13 treatment.



Improvement of DLQI at the end of antagonizing IL-13 treatment



Anmerkung/Fazit der Autoren

In summary, antagonizing IL-13 with either lebrikizumab or tralokinumab could significantly reduce the disease severity and improve the quality of life, thus providing a promising alternative option for AD. More powered studies would be warranted to evaluate the long-term and durable clinical response of IL-13 inhibitors, and to identify certain patients who were more likely to respond to IL-13 inhibitors, thus enabling more efficient management of Th2-mediated AD compared with currently available biologics.

Kommentare zum Review

- *Ausschließlich Placebovergleiche.*
- *Relevant hier nur der Wirkstoff Tralokinumab*
- *Keine Differenzierung nach Schweregrad der atop. Dermatitis*

Zhang D et al., 2022 [28].

Efficacy of abrocitinib for atopic dermatitis: a meta-analysis of randomized controlled trials

Siehe auch folgende systematische Reviews zur Behandlung der atopischen Dermatitis:

- Meher BR et al. 2021 [13]. Efficacy and safety of abrocitinib for the treatment of moderate-to-severe atopic dermatitis: a metaanalysis of randomized clinical trials

Fragestellung

to explore the efficacy of abrocitinib for patients with atopic dermatitis.

Methodik

Population:

- patients with atopic dermatitis

Intervention:

- abrocitinib at the dose of 200 mg once daily

Komparator:

- placebo

Endpunkte:

- Primary outcomes were IGA response and EASI-75.
- Secondary outcomes included EASI-90, NRS response, adverse events and serious adverse events.

Recherche/Suchzeitraum:

- (inception to June 2021): PubMed, Embase, Web of Science, EBSCO, and Cochrane Library databases

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- n=6 (N=9329

Charakteristika der Population/Studien:

Table 1. Characteristics of included studies

Author	Abrocitinib group						Control group						Jadad scores
	Number	Age [years]	Female (*n*)	Duration of atopic dermatitis [years]	EASI score	Methods	Number	Age [years]	Female (*n*)	Duration of atopic dermatitis [years]	EASI score	Methods	
Bieber 2021	226	38.8 ±14.5	122	23.4 ±15.6	32.1 ±13.1	200 mg of abrocitinib orally once daily for 12 weeks	131	37.4 ±15.2	54	21.4 ±14.4	31.0 ±12.6	Placebo	4
Simpson 2020	154	33.0 ±17.4	73	22.7 ±14.5	30.6 ±14.1	200 mg of abrocitinib once daily for 12 weeks	77	31.5 ±14.4	28	22.5 ±14.4	28.7 ±12.5	Placebo	4
Silverberg 2020	155	33.5 ±14.7	67	20.5 ±14.8	29.0 ±12.4	200 mg of abrocitinib once daily for 12 weeks	78	33.4 ±13.8	31	21.7 ±14.3	28.0 ±10.2	Placebo	5
Gooderham 2019	55	38.7 ±17.6	27	19.6 (1.9–68.8), median (range)	24.6 ±13.5	200 mg of abrocitinib once daily for 12 weeks	56	42.6 ±15.1	35	25.6 (1.1–67.1), median (range)	25.4 ±12.9	Placebo	5

Qualität der Studien:

- siehe Abbildung Charakteristika der Population/Studien

Studienergebnisse:

Primary outcomes: IGA response and EASI-75

- These outcome data were analyzed with the randomeffects model, and compared to the control group, for atopic dermatitis, abrocitinib results in a significantly higher IGA response (OR = 6.60; 95% CI: 4.41–9.87; $p < 0.00001$) with no heterogeneity among the studies ($I2 = 0\%$, heterogeneity $p = 0.54$) (Figure 2) and EASI-75 (OR = 9.19; 95% CI: 6.20–13.61; $p < 0.00001$) with low heterogeneity among the studies ($I2 = 19\%$, heterogeneity $p = 0.29$)

Secondary outcomes

- In comparison with the control group for atopic dermatitis, abrocitinib is associated with substantially improved EASI-90 (OR = 10.50; 95% CI: 5.54–19.93; p < 0.0001; Figure 4), NRS response (OR = 6.99; 95% CI: 4.43–11.01; p < 0.00001; Figure 5) and adverse events (OR = 1.76; 95% CI: 1.23–2.52; p = 0.002; Figure 6), but no obvious impact on serious adverse events was revealed (OR = 0.53; 95% CI: 0.20–1.44; p = 0.22)

Anmerkung/Fazit der Autoren

Our meta-analysis included four RCTs and 932 patients with atopic dermatitis. The results showed that abrocitinib at the dose of 200 mg once daily promoted a significant improvement in IGA response, EASI-75, EASI-90 and NRS response compared to placebo. Abrocitinib, a small-molecule JAK1 inhibitor, can be administered orally once daily, and promotes the treatment efficacy through inhibiting signaling of interleukin-4, interleukin-13, and other cytokines involved in the pathogenesis of atopic dermatitis [24]. Abrocitinib was reported to be less likely to stimulate an immunogenic response than biologic treatment

Kommentare zum Review

Die Qualitätsbewertung der Primärliteratur wurde anhand der [z. B. Jadad-Skala] vorgenommen. Diese Bewertung ermöglicht keine umfassende Einschätzung des Verzerrungspotenzials.

- *Keine Angaben zum Schweregrad der atop. Dermatitis*
- *Ausschließlich Placebovergleiche*

Wang B et al., 2022 [23].

Efficacy and safety of baricitinib for the treatment of moderate-to-severe atopic dermatitis: A systematic review and meta-analysis of randomized clinical trials

Fragestellung

We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) reporting the efficacy and safety of baricitinib.

Methodik

Population:

- Patients with moderate-to-severe AD

Intervention:

- Baricitinib with or without topical corticosteroids.

Komparator:

- placebo

Endpunkte:

- Eczema Area and Severity Index (EASI), and Validated Investigator's Global Assessment of atopic dermatitis (vIGA-AD) score, Safety

Recherche/Suchzeitraum:

- databases of PubMed, Web of Science, Embase and the Cochrane Library for studies evaluating the efficacy and safety of baricitinib in the treatment of moderate-to-severe AD from inception to 26 July 2021

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool for randomised trials (RoB 2)

Ergebnisse

Anzahl eingeschlossener Studien:

- n= 6 RCTs (n=2595), davon eine Phase-2 Studie

Charakteristika der Population/Studien:

TABLE 1 Characteristics of included studies

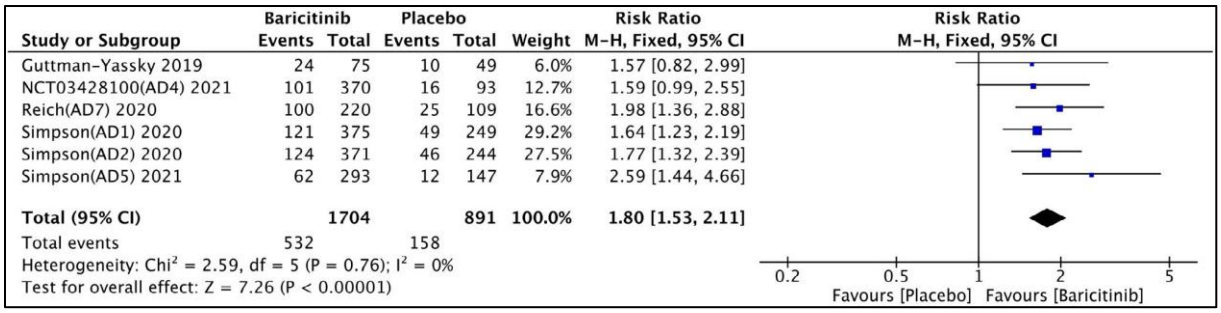
Study	Study design	Intervention	No. of patients	No. of women (%)	Age, years, mean (SD)	Disease duration, years, mean (SD)	Timepoints of outcomes assessment	Outcomes
Guttman-Yassky et al., 2019	Phase II RCT	Placebo plus TCS	49	25 (51%)	35 (28.0–48.0)[a]	17.7 (7.3-29.5)[a]	Week 16	EASI75, EASI90, IGA-Response, TEAEs
		Baricitinib 2 mg plus TCS	37	15 (41%)	42 (26.0–52.0)[a]	26.4 (18.3-40.5)[a]		
		Baricitinib 4 mg plus TCS	38	16 (42%)	32.5 (26.0–48.0)[a]	22.0 (6.4-30.7)[a]		
Simpson et al., 2020 (AD1)	Phase III RCT	Placebo (TCS as rescue)	249	101 (40.6%)	35 (12.6)	26 (15.5)	Week 16	EASI75, EASI90, IGA-Response, SCORAD75, Itch NRS improvement, TEAEs
		Baricitinib 1 mg (TCS as rescue)	127	49 (38.6%)	36 (12.4)	27 (14.9)		
		Baricitinib 2 mg (TCS as rescue)	123	41 (33.3%)	35 (13.7)	25 (14.6)		
		Baricitinib 4 mg (TCS as rescue)	125	42 (33.6%)	37 (12.9)	25 (14.9)		
Simpson et al., 2020 (AD2)	Phase III RCT	Placebo (TCS as rescue)	244	90 (36.9%)	35 (13.0)	25 (13.9)	Week 16	EASI75, EASI90, IGA-Response, SCORAD75, Itch NRS improvement, TEAEs
		Baricitinib 1 mg (TCS as rescue)	125	45 (36.0%)	33 (10.0)	24 (12.7)		
		Baricitinib 2 mg (TCS as rescue)	123	58 (47.2%)	36 (13.2)	24 (13.8)		
		Baricitinib 4 mg (TCS as rescue)	123	41 (33.3%)	34 (14.1)	23 (14.8)		
Simpson et al., 2021 (AD5)	Phase III RCT	Placebo	147	67 (46%)	39 (17)	23 (17)	Week 16	EASI75, EASI90, IGA-Response, SCORAD75, Itch NRS improvement, TEAEs
		Baricitinib 1 mg	147	72 (49%)	40 (17)	24 (17)		
		Baricitinib 2 mg	146	77 (53%)	40 (15)	24 (16)		
Reich et al., 2020 (AD7)	Phase III RCT	Placebo with TCS	109	38 (35%)	33.7 (13.2)	22.0 (12.2)	Week 16	EASI75, EASI90, IGA-Response, SCORAD75, Itch NRS improvement, TEAEs
		Baricitinib 2 mg with TCS	109	39 (36%)	33.8 (12.8)	24.6 (14.8)		
		Baricitinib 4 mg with TCS	111	36 (32%)	33.9 (11.4)	25.5 (13.2)		
NCT03428100, 2021 (AD4)	Phase III RCT	Placebo with TCS	93	44 (47.3%)	38.7 (13.6)	Not reported	Week 16	EASI75, EASI90, IGA-Response, SCORAD75, Itch NRS improvement
		Baricitinib 1 mg with TCS	93	35 (37.6%)	38.9 (14.0)	Not reported		
		Baricitinib 2 mg with TCS	185	52 (28.1%)	37.3 (13.6)	Not reported		
		Baricitinib 4 mg with TCS	92	35 (38.0%)	38.7 (13.3)	Not reported		

[a]Data are presented as median (interquartile range, IQR).

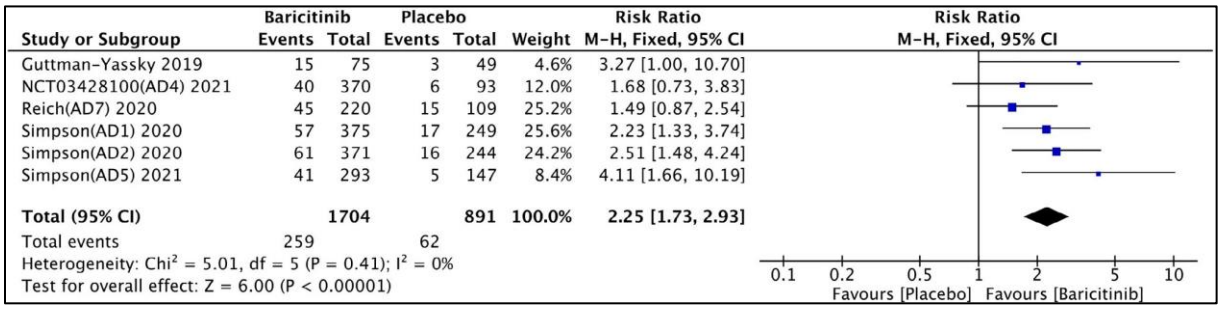
Qualität der Studien:

Studienergebnisse:

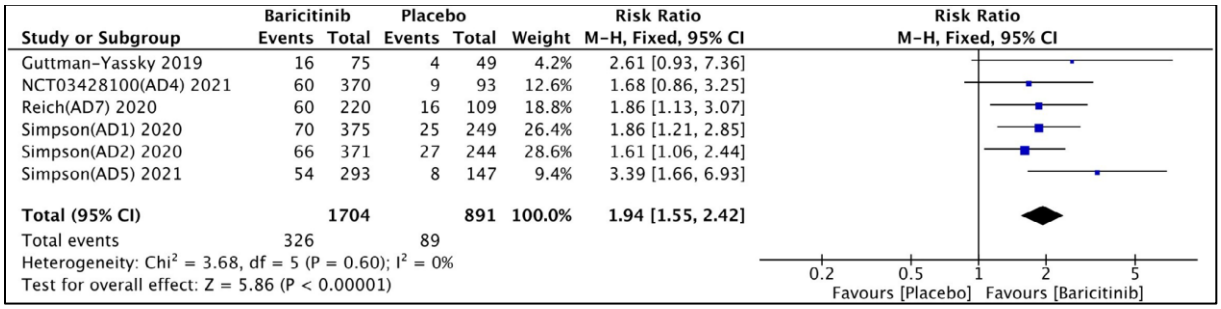
Proportion of patients achieving EASI75



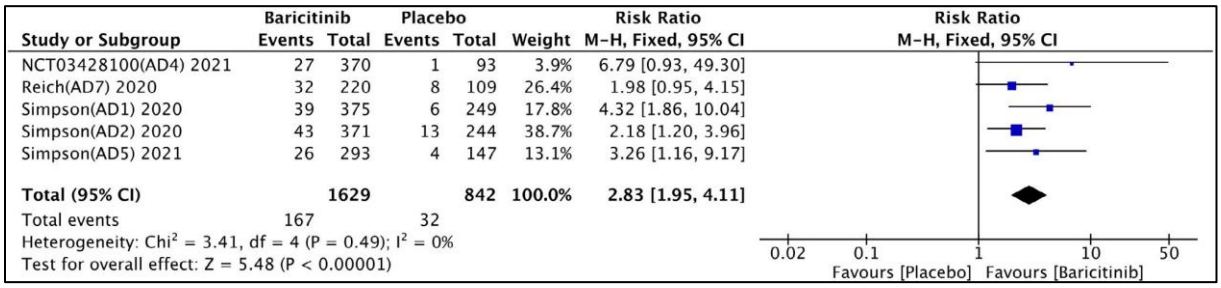
Proportion of patients achieving EASI90



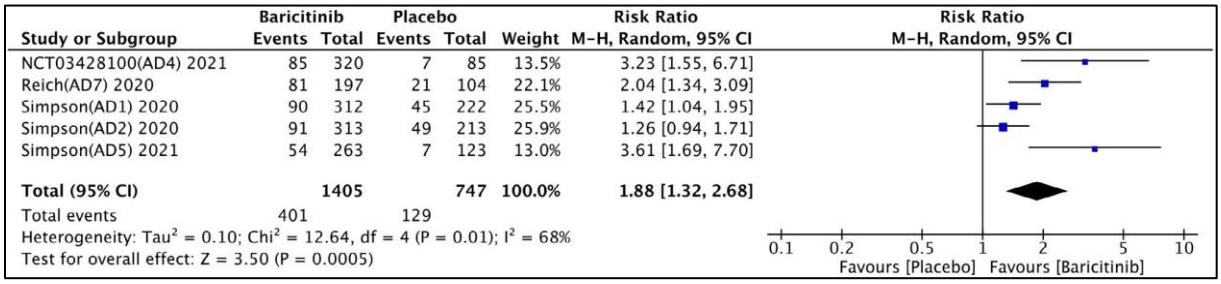
Proportion of patients achieving IGA-Response



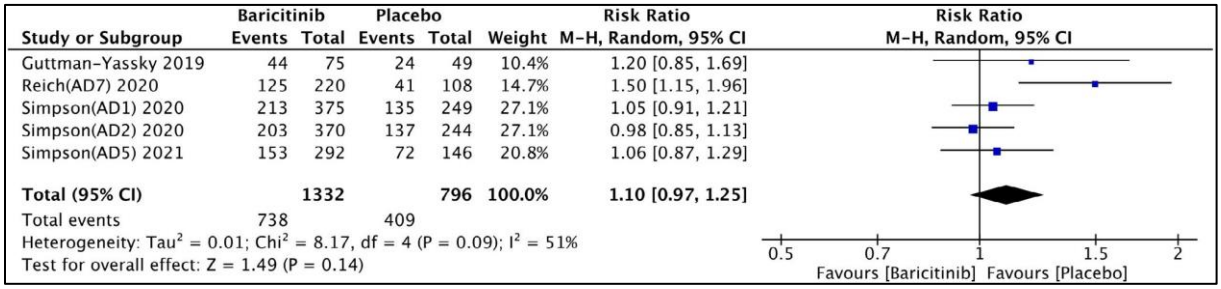
Proportion of patients achieving SCORAD75



Proportion of patients achieving Itch NRS improvement



Proportion of patients with any treatment-emergent adverse effects (TEAEs)



Anmerkung/Fazit der Autoren

Baricitinib has promising efficacy for moderate-to-severe AD with favourable safety files that has the potential to improve the well-being and quality of life for AD patients. However, more studies are needed to further identify the long-term efficacy, safety, and the most effective dosage, and to compare baricitinib with other active agents for providing definitive evidence about the drug.

Kommentare zum Review

- *ausschließlich Placebovergleiche*

Agache I et al., 2021 [2].

Efficacy and safety of dupilumab for moderate-to-severe atopic dermatitis: A systematic review for the EAACI biologicals guidelines.

Siehe auch folgende systematische Reviews mit vergleichbaren Ergebnissen:

- Shih, Y-C et al., 2022 [18]. Efficacy and Safety of Multiple Dupilumab Dose Regimens in Patients with Moderate-To-Severe Atopic Dermatitis: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

Fragestellung

This systematic review evaluates the efficacy, safety and economic impact of dupilumab compared to standard of care for uncontrolled moderate-to-severe atopic dermatitis (AD).

Methodik

Population:

- patients (≥12 years or older) with confirmed diagnosis of moderate-to-severe AD

Intervention:

- dupilumab

Komparator:

- standard of care or the best standard of care

Endpunkt:

- SCORAD 75; EASI 50 or 75; and pruritus and safety (drug-related adverse events (AE) and drug-related serious AE (SAE)); IGA, resource utilization, rescue medication use, pain, sleep disturbance, symptoms of anxiety and depression, and quality of life (QoL)

Recherche/Suchzeitraum:

- MEDLINE (via PubMed, February 2020); (b) Cochrane Controlled Trials Register (via The Cochrane Library, February 2020); and (c) EMBASE (via Ovid, February 2020).

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- n=7 RCTs (N=1845 subjects >12 years)

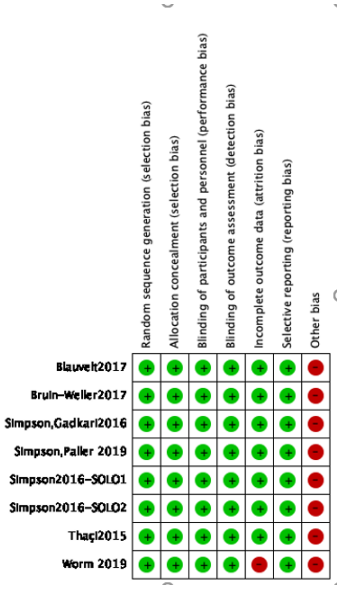
Population

Author, Year, trial number, and name	Study design (Number of subjects included)	Age (years) Placebo vs. Dupilumab	Population	Intervention	Control	Follow up
Blauvelt 2017 NCT02260986 LIBERTY AD CHRONOS	Multicenter RCT (N=421)	Mean (95% CI) 34.0 (25.0–45.0) vs. 40.5 (28.0–49.0)	>18 years, moderate-to-severe AD and inadequate response to topical corticosteroids (TCS)	Dupilumab 300 (q2w), (loading dose, 600mg) +TCS	Matching placebo +TCS	52weeks
Thaçi 2015, Simpson 2016 NCT01859988 TROPOS	Multicenter RCT (N=125)	Mean (SD) 37.2 (13.1) vs. 39.4 (12.1)	>18 years, moderate-to-severe AD not adequately controlled by topical treatments, or for whom systemic treatment was inadvisable.	Dupilumab 300 (q2w), (loading dose, 600mg).	Matching placebo	16 weeks
Simpson 2016 Simpson, Eric 2017 NCT02277743 SOLO 1	Multicenter RCT (N=448)	Median (IQR) 39.0 (27.0–50.5) vs. 38.0 (27.5–48.0)	>18 years with moderate-to-severe AD whose disease was inadequately controlled by topical treatment	Dupilumab 300 (q2w), (loading dose, 600mg).	Matching placebo	16 weeks
Simpson 2016 Simpson,Eric 2017 NCT02277769 SOLO 2	Multicenter RCT (N=469)	Median age (IQR) 35.0 (25.0–47.0) vs. 34.0 (25.0–46.0)	>18 years with moderate-to-severe AD whose disease was inadequately controlled by topical treatment	Dupilumab 300 (q2w), (loading dose, 600mg) +TCS	Matching placebo +TCS	16 weeks
De Bruin-Weller, 2017 NCT02755649 LIBERTY AD CAFE	Multicenter RCT (N=215)	Median (IQR) 37.5 (29.0–49.0) vs. 38.0 (25.0–47.0)	≥18 years with AD with inadequate response to/intolerance of Ciclosporin (CsA), or for whom continuation of systemic treatment was inadvisable.	Dupilumab 300 (q2w), (loading dose, 600mg) + TCS	Matching placebo +TCS	16 weeks
Simpson, Paller 2019 NCT03054428 LIBERTY AD ADOL	Multicenter RCT (N= 167)	Mean (SD) 14.5 (1.8) vs. 14.5 (1.7)	≥12 to <18 years with moderate to severe AD inadequately controlled by topical treatment or for whom systemic treatment was inadvisable.	Dupilumab 300 (q2w), (loading dose, 600mg)/ Dupilumab 200 (q2w), (loading dose, 400mg)	Matching placebo	16 weeks
Worm 2019 NCT02395133 LIBERTY AD SOLO-CONTINUE	Multicenter RCT (N= 252)	median (IQR) 37 (27.0-46.0) vs. 36 (26.0-48.0)	Dupilumab-treated patients (q2w/qw) who had achieved an Investigator's Global Assessment (IGA) score of 0 or 1 or 75%or greater improvement in EASI-75 at week 16 in SOLO studies	Dupilumab (q2w/qw) 300mg, with loading dose of 600mg	Matching placebo	36 weeks

Worm 2019 reported a combined effect for patients received dupilumab 300mg, q2w and qw; SD: Standard deviation; IQR: Interquartile range; TCS: Topical corticosteroids; q2w: every 2 weeks; qw: every week;

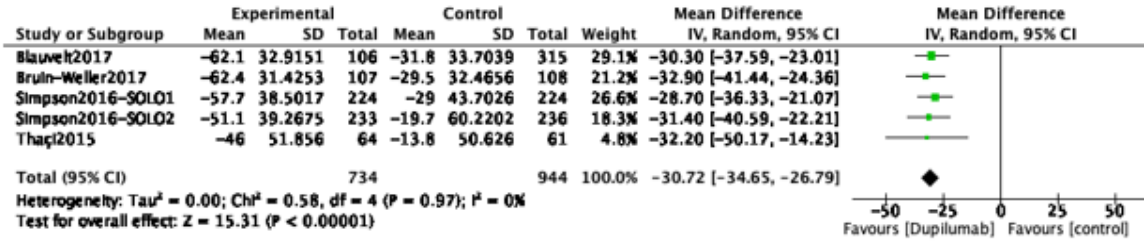
- The RCTs included in the SR evaluated 1678 adults and 167 adolescents with moderate-to-severe AD inadequately controlled by topical treatment. Follow-up under treatment ranged from 16 weeks36,37,39,40 to 1 year.38 One RCT recruited responders from SOLO trials and continued the intervention for another 36 weeks.41 In all trials evaluated, only regulatory-approved doses were considered.

Qualität der Studien:



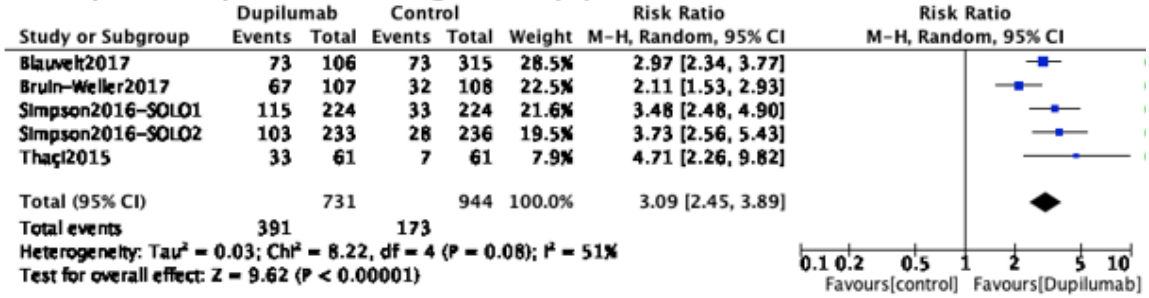
Studienergebnisse:

Scoring Atopic Dermatitis (SCORAD) score

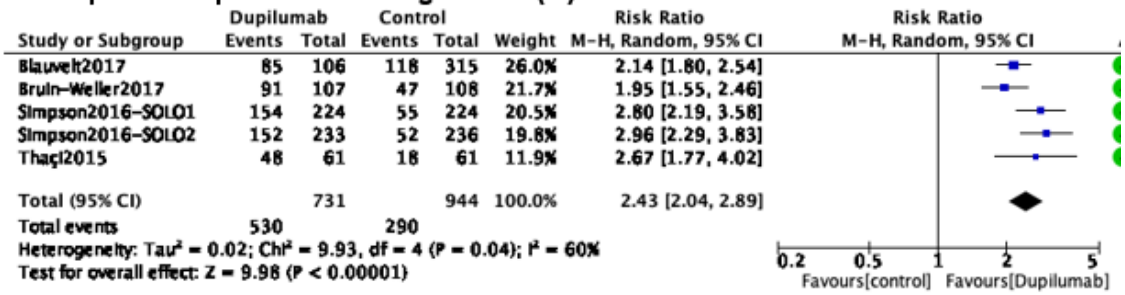


- Eczema Area and Severity Index (EASI)

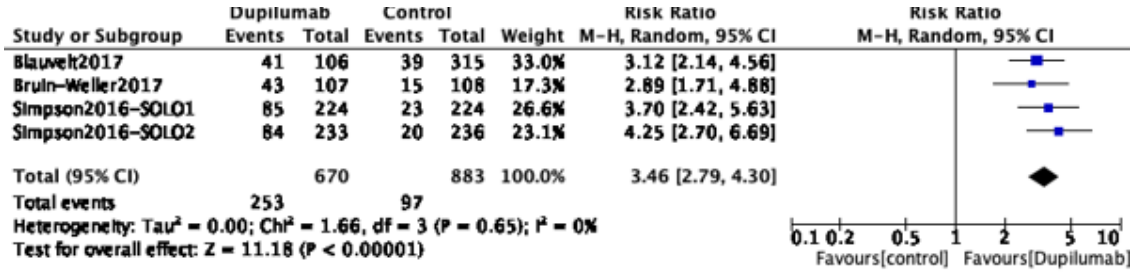
2.1 Proportion of patients achieving EASI-75 (%)



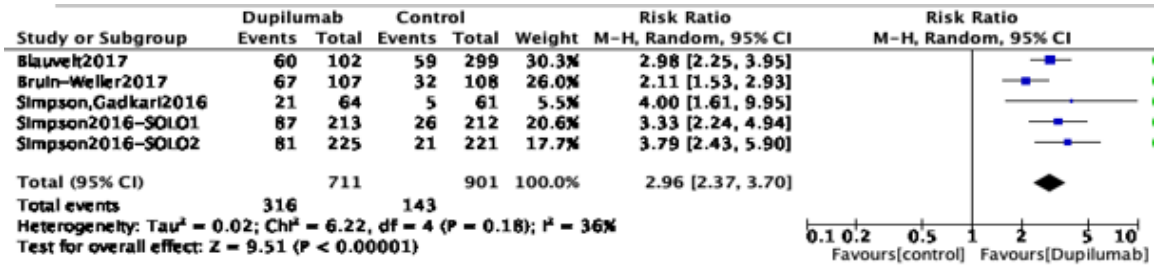
2.2 Proportion of patients achieving EASI-50 (%)



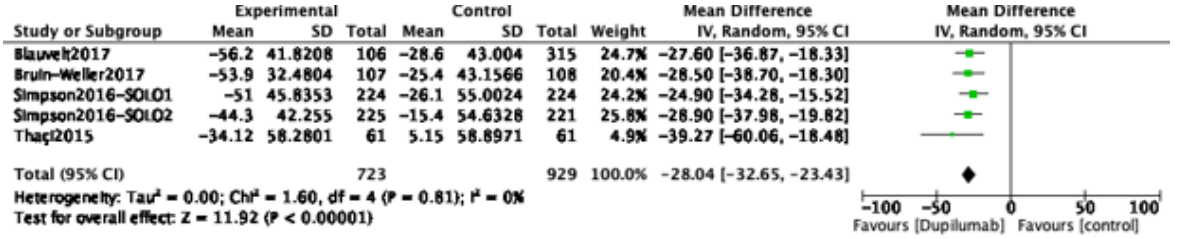
- IGA score achieved 0/1 and reduction of ≥2 points from baseline



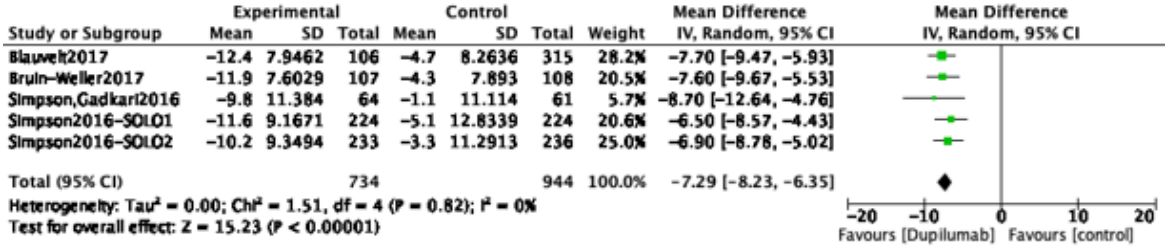
- Pruritus
  - Improvement in peak score on numerical rating scale (NRS) for pruritus ≥ 4 points



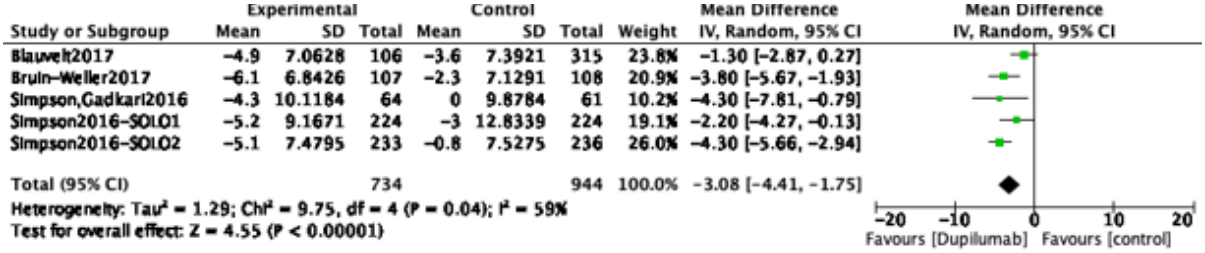
  - Peak pruritus NRS score (LS mean % change from baseline)



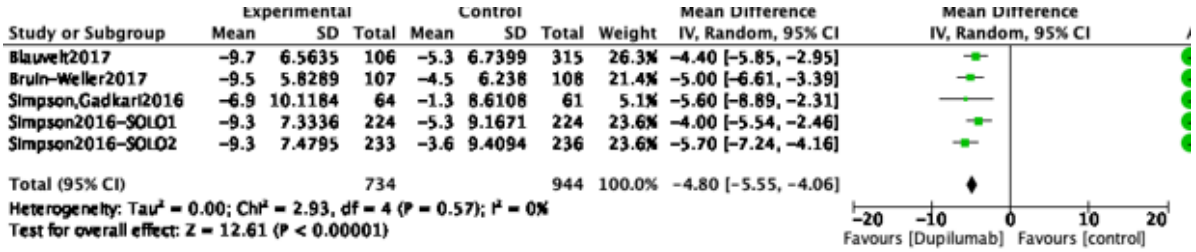
- Patient-Oriented Eczema Measure



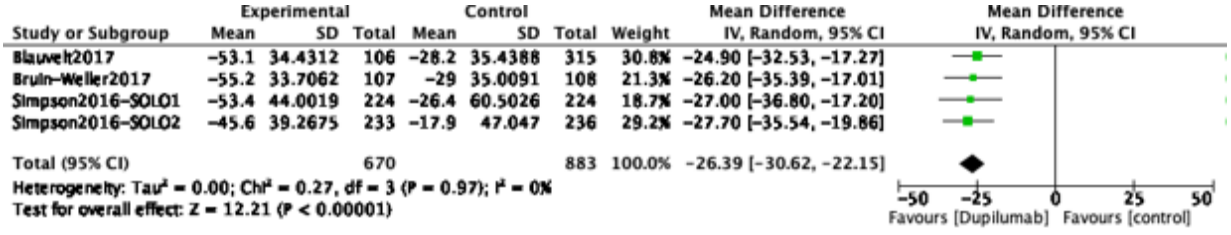
- Hospital Anxiety and Depression Scale (HADS)



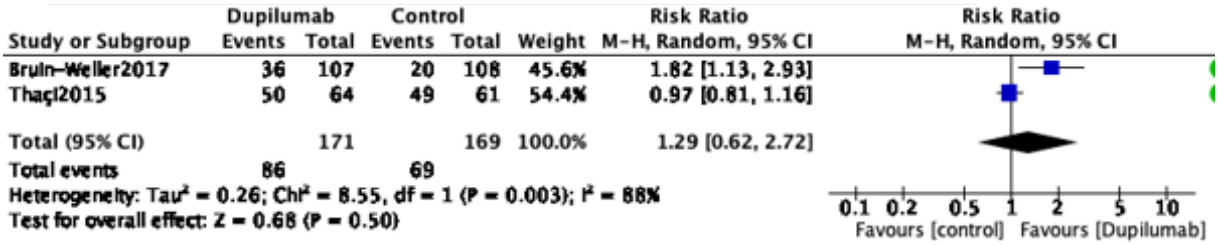
- Quality of life measured by Dermatology Life Quality Index (DLQI)



- Global Individual Signs Score (GISS)



- Safety
  - Patients with any treatment-emergent adverse events (AE)



  - Patients with any treatment-emergent Severe adverse events (SAE)

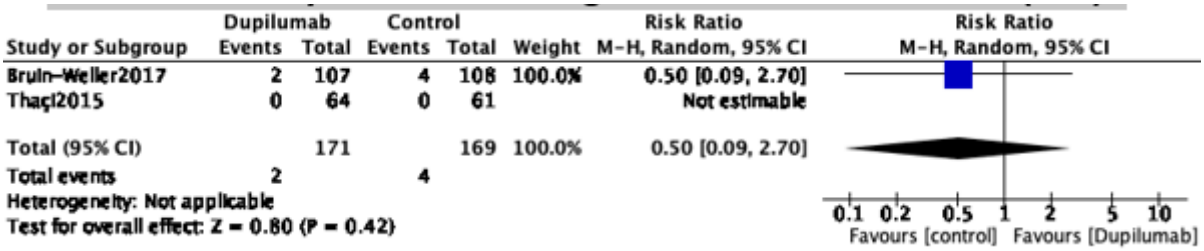


TABLE 3 Summary of evidence for the outcomes of interest. Adult atopic dermatitis population: Dupilumab efficacy and safety compared to standard of care

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)p	Anticipated absolute effects: Risk with Standard of care	Anticipated absolute effects: Risk difference with Dupilumab
SCORAD Assessed with least square (LS) mean % change from baseline	1678 (5 RCTs)[1,2,3,4] 16-52 wk	⨁⨁⨁⨁ HIGH[5,a,b]	–	–	MD - 30.72% (−34.65 to −26.79)[d]
EASI-75 Assessed with proportion of patients achieving EASI-75 (%)	1675 (5 RCTs)[1,2,3,4] 16-52 wk	⨁⨁⨁⨁ HIGH[6,7,b,d,e]	RR 3.09 (2.45 to 3.89)	183 per 1000	+383 per 1,000 (+266 to +530)
Pruritus Assessed with improvement in peak score on NRS for pruritus ≥ 4 points	1612 (5 RCTs)[1,2,4,5] 16-52 wk	⨁⨁⨁⨁ HIGH[9,10,b,f]	RR 2.96 (2.37 to 3.70)	159 per 1000	+311 per 1,000 (+217 to +429)
Treatment-related adverse events (AEs) Assessed with number of patients reporting AEs	340 (2 RCTs)[2,3] 16 wk	⨁⨁◯◯ LOW[b,m,n]	RR 1.29 (0.62 to 2.72)	408 per 1000	+118 per 1,000 (−155 to +702)
Treatment-related severe adverse events (SAE) Assessed with number of patients reporting AAEs	340 (2 RCTs)[2,3] 16 wk	⨁◯◯◯ VERY LOW[b]	RR 0.50 (0.09 to 2.70)	per 1000	-12 per 1,000 (−22 to +40)
Rescue medication use Assessed with number of patients who received any rescue therapy	1406 (4 RCTs)[1,2,4] 16-52 wk	⨁⨁⨁⨁ HIGH[b]	RR 0.36 (0.28 to 0.46)	422 per 1000	-270 per 1,000 (−304 to −228)
Sleep disturbance—Patient-Oriented Eczema Measure (POEM) Assessed with: LS mean change from baseline	1678 (5 RCTs)[1,2,4,5] 16-52 wk	⨁⨁⨁⨁ HIGH[6,11,b,g]	–	–	MD −7.29 points (−8.23 to −6.35)[i]
Pain Assessed with proportion of patients with no problem of the EQ-5D item 4 (pain/discomfort)	215 (1 RCT) 16 wk	⨁⨁⨁⨁ HIGH[b]	RR 1.89 (1.44 to 2.49)	370 per 1000	+330 per 1,000 (+163 to +552)
Symptoms of anxiety and depression Hospital Anxiety and Depression Scale (HADS) (HADS) Assessed with the LS mean change from baseline	1678 (5 RCTs)[1,2,4,5] 16-52 wk	⨁⨁⨁⨁ HIGH[b]	–	–	MD - 3.08 points (−4.41 to −1.75)[12,j]
Quality of life measured with Dermatology Life Quality Index (DLQI) Assessed with: LS mean change from baseline Scale from 0 to 30	1678 (5 RCTs)[1,2,4,5] 16-52 wk	⨁⨁⨁⨁ HIGH[b,j]	–	–	MD - 4.8 points (−5.55 to −4.06)[l,m]

Anmerkung/Fazit der Autoren

Agache et al.: The current systematic review showed that dupilumab as add-on treatment for moderate-to-severe AD in adults and adolescents significantly reduces short-term (16 weeks) AD symptoms, severity, use of rescue medication, and improves quality of life. For adults, there is good evidence for long-term efficacy (52 weeks). Dupilumab may increase short-term drug-related AE. The evidence for severe drug-related AE is very uncertain. All RCTs were mainly powered for efficacy and less powered to show rare adverse events which are now frequently reported in the postmarketing literature.

This SR is the most up to date review on the effectiveness, safety and economic impact on dupilumab in AD. Similar to previous SRs, the current analysis reinforces the short-term (16 weeks) efficacy of dupilumab in improving SCORAD, EASI, IGA, pruritus and quality of life.49-51 In addition, the current SR provides evidence for long-term (52 weeks) benefit in adults.

49. Wang F-P, Tang X-J, Wei C-Q, et al. Dupilumab treatment in moderate- to-severe atopic dermatitis: a systematic review and meta-analysis. J Dermatol Sci. 2018;90(2):190-198.
50. Snast I, Reiter O, Hodak E, et al. Are biologics efficacious in atopic dermatitis? A systematic review and meta-analysis. Am J Clin Dermatol. 2018;19(2):145-165.
51. Drucker AM, Ellis AG, Bohdanowicz M, et al. Systemic immunomodulatory treatments for patients with atopic dermatitis: a systematic review and network meta-analysis. JAMA Dermatol. 2020;156(6):1-10.

Dupilumab demonstrated a significant short-term benefit for the adults and adolescents with uncontrolled moderate-to-severe atopic dermatitis, by improving symptoms and disease severity, reducing the use of rescue medications and improving the quality of life. For adults, there is evidence for long-term benefit. Thresholds for cost-effectiveness are probably acceptable for some high-income countries; however, dupilumab might not be equally cost-effective in countries with limited resources.

Although short-term safety data showed no visible increase of AE, more accurate AE reporting is warranted in RCTs for both adult and adolescent population, combined with long-term safety evaluation using observational and effectiveness studies and registries. There are several ongoing open-label studies53,54 and registries55 evaluating the long-term safety and efficacy of dupilumab in atopic dermatitis that are likely to be informative in formulating recommendations.

Xu et al.: Our pooled analysis demonstrated that dupilumab significantly improved the signs and symptoms of atopic dermatitis, including pruritus, quality of life, and psychological symptoms, as compared with placebo. All dosage regimens of dupilumab contributed to better clinical results compared with placebo and showed a placebo-like safety profile. Analyses of different dupilumab doses demonstrated that the overall efficacy results of dupilumab 300 mg every week and dupilumab 300 mg every other week were similar.

The results showed that incidence of adverse events was similar in dupilumab-treated patients and placebo-treated patients. Dupilumab had a placebo-like safety profile, was well tolerated and most adverse events reported were mild or moderate. Interestingly, dupilumab treatments showed even slightly lower rates of severe adverse events and treatment discontinuation due to adverse event than placebo treatments. Dupilumab improved atopic signs and symptoms with acceptable safety.

Our results indicated that the administration of 300 mg every week and 300 mg every 2 weeks had parallel efficacy in reducing EASI, BSA score, and NRS score in patients with moderate-to-severe atopic dermatitis, as well as the rate of IGA response. As to treatment duration, patients receiving dupilumab for 12 weeks achieved the best clinical outcomes. Week 52 results were similar to week 16, demonstrating that dupilumab had a satisfactory long-term efficacy, though only the latest released LEBERTY AD trial investigated the long term efficacy and safety of dupilumab with topical corticosteroids versus placebo with topical corticosteroids.

Koskeridis F et al., 2022 [10].

Treatment With Dupilumab in Patients with Atopic Dermatitis: Systematic Review and Meta-Analysis

Fragestellung

In this study, we conducted a systematic review and meta-analysis on the currently available randomized evidence to evaluate the safety and efficacy of dupilumab for the treatment of patients with moderate-to-severe AD across all age groups.

Methodik

Population:

- patients with atopic dermatitis or eczema in any age

Intervention:

- dupilumab

Komparator:

- Placebo

Endpunkte:

- Eczema Area and Severity Index (EASI), Scoring Atopic Dermatitis (SCORAD), pruritus Numerical Rating Scale (pNRS), Patient-Oriented Eczema Measure (POEM), Investigator's Global Assessment (IGA), Dermatology Life Quality Index (DLQI), Body Surface Area (BSA) to assess the efficacy and the overall number of Adverse Events (AE) and the overall number of Severe Adverse Events (SAEs) to assess dupilumab safety

Recherche/Suchzeitraum:

- PubMed and CENTRAL up to February 3, 2022

Qualitätsbewertung der Studien:

- Cochrane collaboration's tool

Ergebnisse

Anzahl eingeschlossener Studien:

- n=14 RCTs (N=4435)

Charakteristika der Population/Studien:

- The age of the population was exclusively adults (>18 years) in 12 studies, adolescents (12-17 years) in one study and children (6-11 years) in another study

Qualität der Studien:

- Most studies were of high methodological quality; two studies were found to have some concerns on the assessment of the outcome as it was not clear if the outcome assessors were blinded regarding the intervention received by patients

Studienergebnisse:

Figure 1. Forest plot of the meta-analysis for the number of patients succeeding a reduction of at least 75% in Eczema Area Severity Index score (EASI-75%). Three estimates were generated: overall, subgroup adults only and subgroup adolescents/children only.

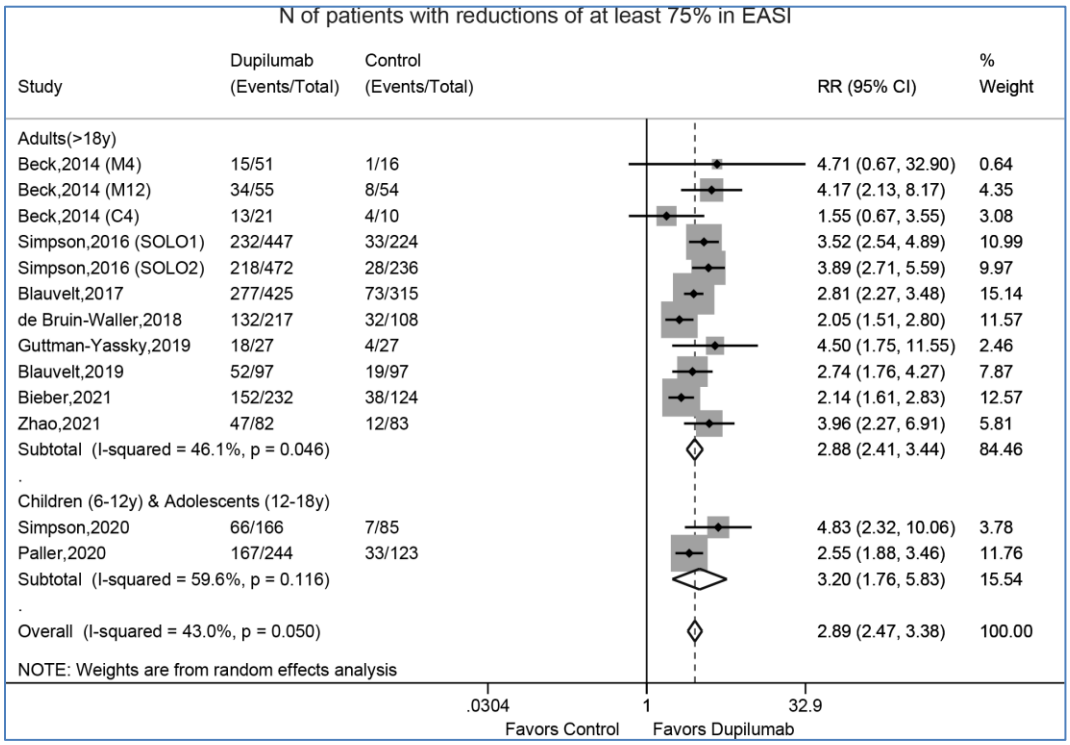
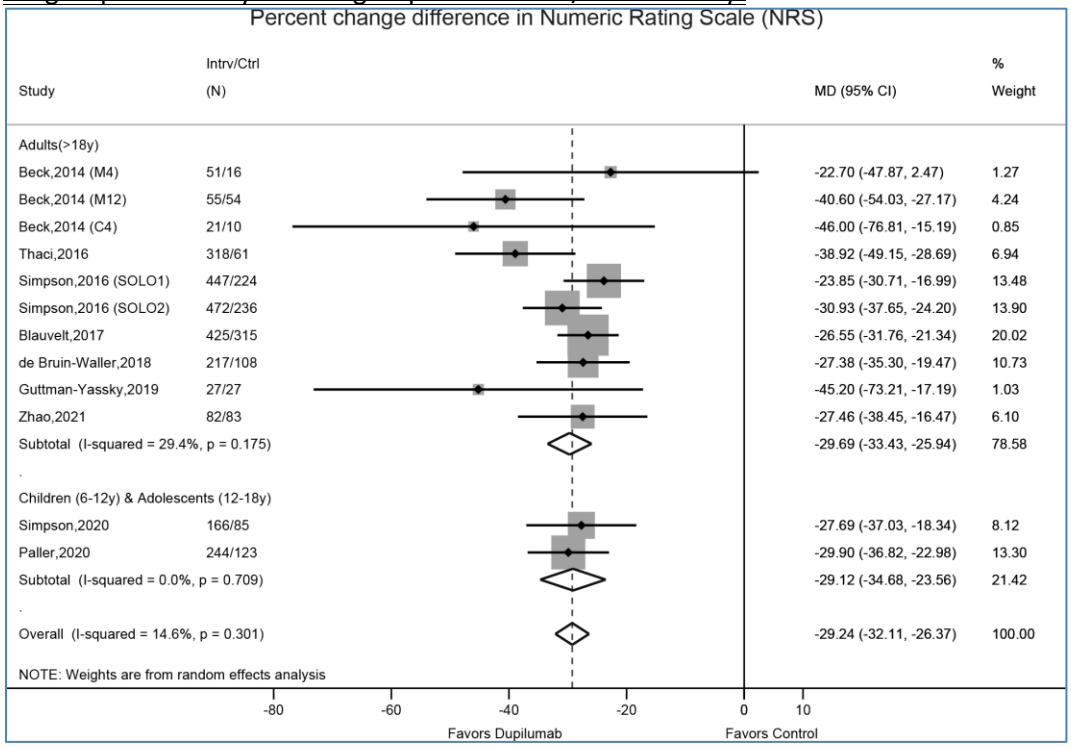
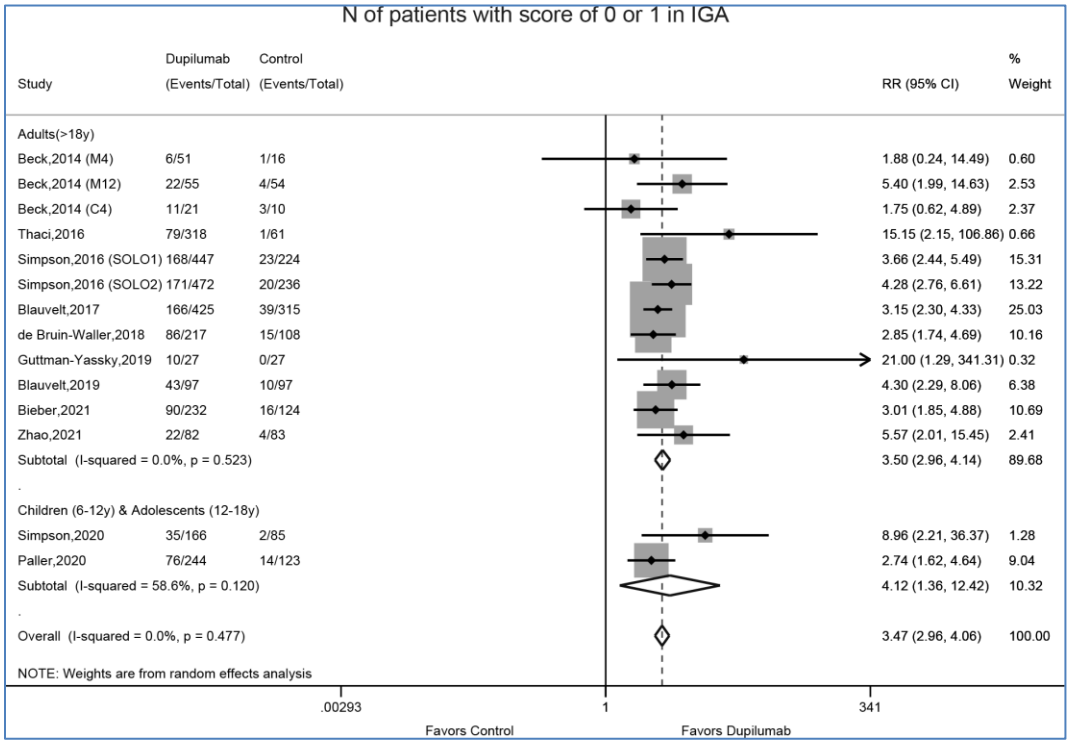


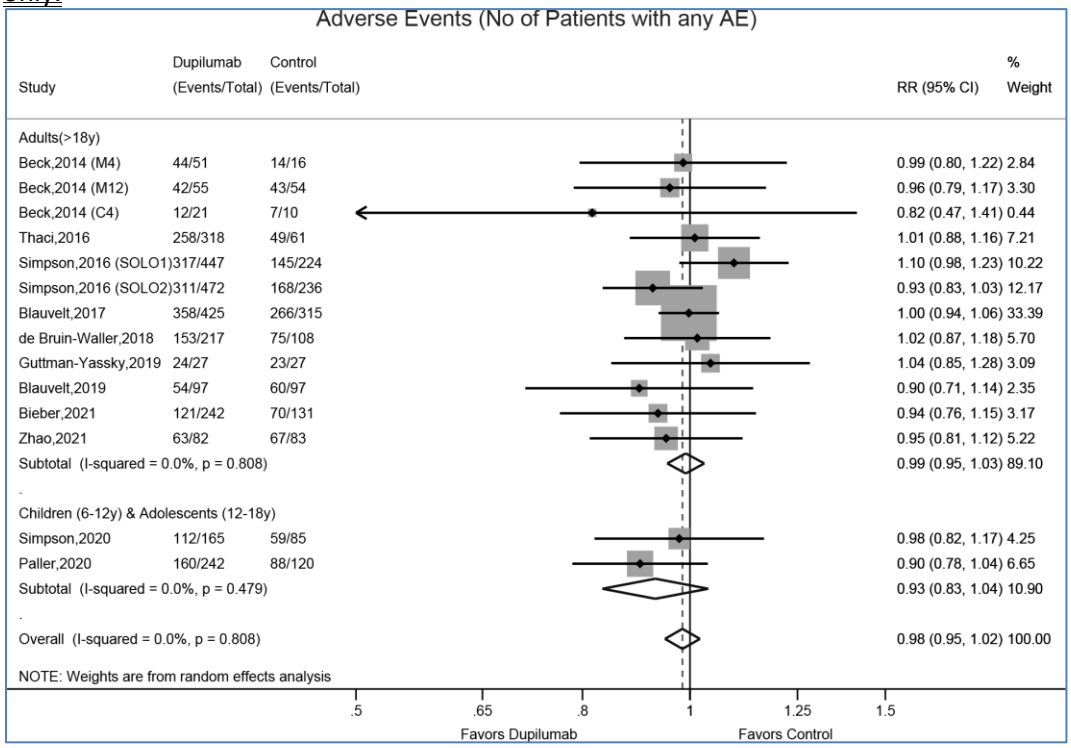
Figure 2. Forest plot of the meta-analysis for the percent change difference between groups after intervention in the pruritus Numeric Rating Scale (pNRS). Three estimates were generated: Overall, subgroup adults only and subgroup adolescents/children only.



Forest plot of the meta-analysis or the number of patients succeeding a score less or equal to 1 in Investigator's Global Assessment (IGA) after intervention. Three estimates were generated: overall, subgroup adults only and subgroup adolescents/children only.



Forest plot of the meta-analysis for the number of patients presented any Adverse Events (AE). Three estimates were generated: overall, subgroup adults only and subgroup adolescents/children only.



Anmerkung/Fazit der Autoren

In conclusion, this meta-analysis indicated that treatment with dupilumab improves the symptoms and quality of life of patients with moderate-to-severe AD with a safety profile comparable to placebo. Importantly, our findings support the efficacy and safety of dupilumab in the management of patients in all age groups. However, additional studies should be conducted in children, as the present evidence derived from a limited number of studies and thus, it may not be sufficient to produce robust results and lead to safe conclusion.

Kommentare zum Review

- *Keine Angaben zum Schweregrad der atop. Dermatitis*
- *Ausschließlich Placebovergleiche*

Wu S et al., 2022 [27].

Efficacy and safety of dupilumab in the treatment of moderate-to-severe atopic dermatitis: a meta-analysis of randomized controlled trials.

Fragestellung

We conducted this meta-analysis to evaluate the efficacy and safety of dupilumab in patients with moderate-to-severe AD.

Methodik

Population:

- Patients diagnosed with moderate-to-severe AD

Intervention:

- Dupilumab

Komparator:

- Placebo or any other treatment

Endpunkte:

- Investigator's Global Assessment response (IGA), Eczema Area and Severity Index (EASI), the pruritus numeric rating scale (NRS), percent BSA affected with AD, Dermatology Life Quality Index (DLQI) and adverse events

Recherche/Suchzeitraum:

- Articles published between 1975 and March 2021 (PubMed, Web of Science, and Embase)

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool for assessing risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- n=11 RCTs (n=4094)

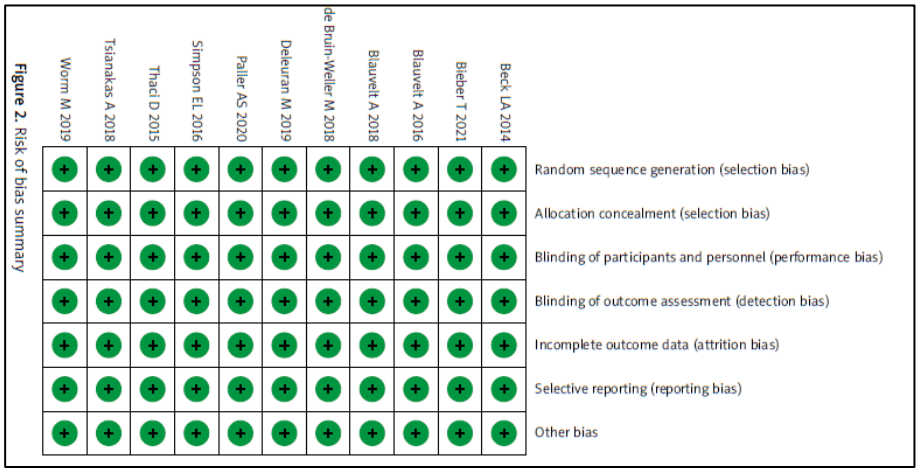
Charakteristika der Population/Studien:

Table 1. Baseline characteristics of patients in the trials included in the meta-analysis

Study	Country	Treatment regimen	Dosing	No. of patients	Treatment duration
Paller AS [26]	China	Dupilumab	300 mg q4w, 200/300 mg q2w	84	16 weeks
		Placebo		85	
Simpson EL [27]	USA	Dupilumab	300 mg qw, 300 mg q2w	447	16 weeks
		Placebo		224	
Blauvelt A [28]	USA	Dupilumab + TCS	300 mg qw, 300 mg q2w	425	52 weeks
		Placebo + TCS		315	
Blauvelt A [29]	USA	Dupilumab	300 mg qw	97	16 weeks
		Placebo		97	
de Bruin-Weller M [30]	Netherlands	Dupilumab + TCS	300 mg qw, 300 mg q2w	217	16 weeks
		Placebo + TCS		108	
Deleuran M [31]	Denmark	Dupilumab	300 mg qw	249	76 weeks
		Placebo		398	
Worm M [32]	Germany	Dupilumab	300 mg qw/q2w, 300 mg q4w, 300 mg q8w	339	36 weeks
		Placebo		83	
Tsianakas A [33]	Germany	Dupilumab	300 mg qw	32	12 weeks
		Placebo		32	
Beck LA [34]	USA	Dupilumab	300 mg qw	55	16 weeks
		Placebo		54	
Thaci D [35]	Germany	Dupilumab + TCS	300 mg qw, 300 mg, q2w, 300 mg q4w, 200 mg qw, 200 mg q2w, 100 mg q4w	318	16 weeks
		Placebo + TCS		61	
Bieber T	Germany	Dupilumab	200 mg q2w	243	12 weeks
		Placebo		131	

SD – standard deviation.

Qualität der Studien:



Studienergebnisse:

- Pooled estimate showed that dupilumab significantly improved the mean change in the Eczema Area and Severity Index (EASI) score (SMD = –10.90, 95% CI: –12.13, –9.68; p<0.001), percentage of body surface area (BSA) affected (SMD = –10.87, 95% CI: –13.04, –8.70; p<0.001), pruritus numeric rating scale (NRS) scores (SMD = –9.29, 95% CI: –

10.34, –8.25; p<0.001), and Dermatology Life Quality Index (DLQI) scores (SMD = –9.66, 95% CI: –11.50, –7.82; p<0.001).

- In addition, dupilumab was associated with a significantly higher Investigator's Global Assessment (IGA) response (RR = 3.57, 95% CI: 2.53, 5.03; p<0.001). The overall incidence of adverse events was comparable between dupilumab and other treatments (RR = 1.00, 95% CI: 0.96, 1.03; p=0.832). However, the injection-site reaction, headache and conjunctivitis were more frequently seen in patients treated with dupilumab.

Anmerkung/Fazit der Autoren

Our findings provided evidence that dupilumab was an effectively targeted biologic therapy in the treatment of patients with moderate-to-severe AD because it ameliorated the signs and symptoms of AD and improved health-related quality of life. Moreover, its safety was acceptable. Considering the potential limitations in this study, more large-scale RCTs are needed to verify our findings.

Ayen-Rodríguez A et al., 2022 [3].

Long-Term Effectiveness and Safety of Biologic and Small Molecule Drugs for Moderate to Severe Atopic Dermatitis: A Systematic Review

Fragestellung

The long-term efficacy and safety of biological and JAK inhibitors in moderate to severe atopic dermatitis, currently approved by the EMA (Dupilumab, Tralokinumab, Baricitinib, Abrocitinib and Upadacitinib)

Methodik

Population:

- adult population (over 18 years of age) with moderate to severe atopic dermatitis
- Drugs with RCTs including both adults and adolescents (≥ 12 years) were also included

Intervention:

- k.A.

Komparator:

- k.A.

Endpunkte:

- The two primary outcomes analyzed were: (a) the number of patients achieving at least a 75% reduction from baseline on the EASI scale (EASI 75) at 48–60 weeks; and (b) the number of patients who reached IGA 0 (fully cleared patients) or IGA 1 (almost cleared patients).
- Secondary outcomes included the number of patients who achieved (a) a reduction in at least 90% from baseline on the EASI scale (EASI 90) at 48–60 weeks; (b) an improvement of at least 4 points on the NRS itch scale; (c) the number of patients who experienced at least one AE; (d) the number of patients who experienced at least one SAE.

Recherche/Suchzeitraum:

- three databases (MEDLINE and EMBASE and the Cochrane Central Register), veröffentlicht zwischen Jan. 2000 bis April 2022

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Assessment Tool (ROB-2)

Ergebnisse

Anzahl eingeschlossener Studien:

- N=7 RCTs

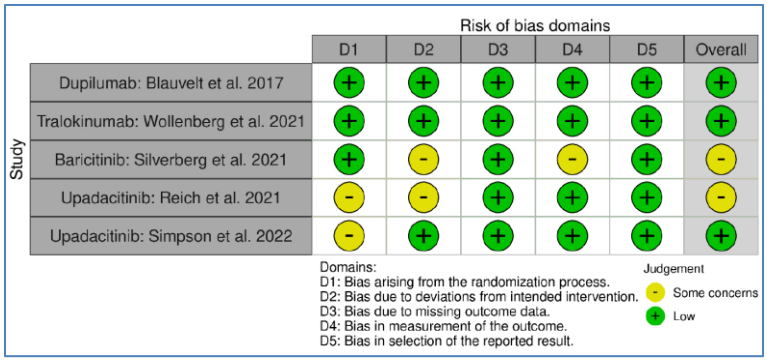
Charakteristika der Population/Studien:

- Among the selected RCTs, three evaluated the use of Upadacitinib and two evaluated tralokinumab, while dupilumab and baricitinib were evaluated in a single RCT, respectively.

Publication Data			Study Design			Study Arm Baseline Characteristics										
Study ID	Year	Phase	Agent	Dosing, Schedule, Route	*n*	Males *n* (%)	Age Mean/Median	Adolescent (12–17 Years) *n* (%)	Race (White) *n* (%)	Disease Duration Years Mean/Median	Basal EASI Score Mean/Median	Basal BSA % Mean/Median	Basal SCORAD Score Mean/Median	Weekly WP-NRS Score Mean/Median	vIGA-AD Score = 4 *n* (%)	DLQI Score Mean/Median
LIBERTY AD CHRONOS * [10]	2017	3	Placebo + TCS	QW sc	315	193 (61.3)	34.0 (25.0–45.0)	0	208 (66.0)	26.0 (17.0–38.0)	29.6 (22.2–40.8)	55.0 (40.0–75.0)	64.1 (55.9–76.1)	7.6 (6.3–8.6)	147 (46.6)	14.0 (9.0–20.0)
			Dupilumab + TCS	300 mg Q2W sc	106	62 (58.5)	40.5 (28.0–49.0)	0	74 (69.8)	28.0 (20.0–44.0)	30.9 (22.3–41.6)	58.8 (43.5–78.5)	69.7 (60.4–79.8)	7.7 (6.6–8.5)	53 (50.0)	13.5 (8.0–20.0)
			Dupilumab + TCS	300 mg QW sc	319	191 (59.9)	34.0 (26.0–45.0)	0	208 (65.2)	26.0 (18.0–39.0)	29.0 (21.6–40.7)	52.0 (36.0–71.5)	65.3 (55.2–76.3)	7.4 (6.0–8.6)	147 (46.1)	14.0 (8.0–20.0)
ECZTRA-1 * [11]	2020	3	Placebo	Q2W sc	199	123 (61.8)	37.0 (26.0–49.0)	0	138 (69.3)	28.0 (18.0–41.0)	30.3 (22.0–41.5)	52.5 (31.0–77.0)	70.8 (63.8–81.0)	7.9 (6.9–8.7)	102 (51.3)	16.0 (13.0–22.0)
			Tralokinumab	300 mg Q2W sc	603	351 (58.2)	37.0 (27.0–48.0)	0	426 (70.6)	27.0 (19.0–38.0)	28.2 (21.3–40.0)	50.0 (33.0–70.0)	69.2 (61.5–79.1)	7.9 (6.7–8.9)	305 (50.6)	17.0 (12.0–22.0)
ECZTRA-2 * [11]	2020	3	Placebo	Q2W sc	201	114 (56.7)	30.0 (23.0–46.0)	0	123 (61.2)	25.0 (18.0–36.0	29.6 (20.6–41.4)	50.0 (31.0–74.0)	69.9 (61.9–79.1)	8.1 (7.1–9.0)	101 (50.2)	18.0 (12.5–24.0)
			Tralokinumab	300 mg Q2W sc	593	359 (60.5)	34.0 (25.0–48.0)	0	374 (63.1)	25.5 (17.0–39.0)	28.2 (19.8–40.8)	50.0 (31.0–74.0)	69.5 (60.5–79.1)	8.0 (7.0–9.0)	286 (48.2)	18.0 (13.0–23.0)
BREEZE-AD3 ** [12]	2021	3	Baricitinib	2 mg QD oral	54	28 (51.9)	32.8 (12.7)	0	45 (83.3)	19.2 (11.8)	24.9 (8.7)	NR	62.2 (12.0)	6.1 (2.2)	18 (33.3)	NR
			Baricitinib	4 mg QD oral	70	42 (60.0)	36.7 (15.5)	0	47 (67.1)	23.2 (16.8)	28.1 (10.6)	NR	63.4 (12.3)	6.5 (2.1)	22 (31.4)	NR
AD Up **, *** [13]	2021	3	Placebo	QD oral	304	178 (58.6)	34.3 (12–75)	40 (13.2)	225 (74.0)	24.3 (15.2)	30.3 (13.0)	48.6 (23.1)	NR	7.1 (1.6)	163 (53.6)	16.3 (7.0)
			Upadacitinib + TCS	15 mg QD oral	300	179 (59.7)	32.5 (13–74)	39 (13.0	204 (68.0)	22.9 (13.9)	29.2 (11.8)	46.7 (21.6)	NR	7.1 (1.8)	157 (52.3)	16.4 (7.2)
			Upadacitinib + TCS	30 mg QD oral	297	190 (64.0)	35.5 (12–72)	37 (12.5)	218 (73.4)	23.1 (16.1)	29.7 (11.8)	48.5 (23.1)	NR	7.4 (1.6)	157 (52.9)	17.1 (7.0)
Measure Up 1 **, *** [14]	2022	3	Placebo	QD oral	281 [244]	144 (51.2)	34.4 (12–75)	40 (14.2)	182 (64.8)	21.3 (15.3)	28.8 (12.6)	45.7 (21.6)	66.1 (12.9)	7.3 (1.7)	122 (44.5)	17.0 (6.8)
			Upadacitinib + TCS	15 mg QD oral	281	157 (55.9)	34.1 (12–74)	42 (14.9)	182 (64.8)	20.5 (15.9)	30.6 (12.8)	48.5 (22.2)	68.2 (12.6)	7.2 (1.6)	127 (45.2)	16.2 (7.0)
			Upadacitinib + TCS	30 mg QD oral	285	155 (54.4)	33.6 (12–75)	42 (14.7)	191 (67.0)	20.4 (14.3)	29.0 (11.1)	47.0 (22.0)	67.3 (12.5)	7.3 (1.5)	131 (46.0)	16.4 (7.0)
Measure Up 2 **, *** [14]	2022	3	Placebo	QD oral	278 [241]	154 (55.4)	33.4 (13–71)	36 (12.9)	195 (70.1)	21.1 (13.6)	29.1 (12.1)	47.6 (22.7)	67.9 (12.1)	7.3 (1.6)	153 (55.0)	17.1 (7.2)
			Upadacitinib + TCS	15 mg QD oral	276	155 (56.2)	33.3 (12–74)	33 (12.0)	184 (66.7)	18.8 (13.3)	28.6 (11.7)	45.1 (22.4)	66.6 (12.5)	7.2 (1.6)	150 (54.3)	16.9 (7.0)
			Upadacitinib + TCS	30 mg QD oral	282	162 (57.4)	34.1 (12–75)	35 (12.4)	198 (70.2)	20.8 (14.3)	29.7 (12.2)	47.0 (23.2)	66.7 (13.0)	7.3 (1.6)	156 (55.3)	16.7 (6.9)

Table 2 Data are expressed as *n* (%), median (IQR = interquartile range) * or mean (SD = standard deviation) ** or mean (range) ***. Every 2 weeks, QD = once daily, sc = subcutaneous administration. NR = not reported. EASI = Eczema Area and Severity Index. BSA = body surface area. SCORAD = Scoring Atopic Dermatitis. WP-NRS = Worst Pruritus Numerical Rating Scale. vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis. DLQI = Dermatology Life Quality Index. Note that the number of patients in the placebo group at the start of the trials in Measure Up 1 (*n* = 281) and Measure Up 2 (*n* = 241) is different from the final sample used to assess efficacy and safety (244 and 241, respectively). However, the baseline patient characteristics listed in this table refer to the baseline sample of each study.

Qualität der Studien:



Studienergebnisse:

- Regarding efficacy, the best results are obtained with Upadacitinib 30 mg (84.7% (77.3–92.1)) at 52 weeks, slightly improving its results when TCS is added (84.9% (80.3–89.5)). These results are replicated in the measurement of vIGA 0/1 for Updacitinib 30 mg + TCS, where 65.5% (55.7–75.2) of patients maintain it at 52 weeks.
- Of the four drugs, no long-term safety results have been reported for baricitinib. In relation to the safety findings, there were no significant differences in the dropout rates for this reason in the remaining three drugs.

- In all the included studies, the treatment response has been evaluated by determining the EASI75 and IGA0/1. Upadacitinib and dupilumab provided clinically superior efficacy on both parameters. Concomitant use of TCS was allowed in these RCTs. In the SR and NMA carried out, the best efficacy data (EASI75, 52w) are obtained by Upadacitinib 30 mg + TCS, being the main combination that we would use in real clinical practice. These results are confirmed in the percentage of patients who reach and maintain vIGA 0/1 at 52 weeks. Dupilumab and Tralokinumab data are also highly satisfactory.

Anmerkung/Fazit der Autoren

Today, different therapeutic options for AD patients can be prescribed. Individualizing the treatment allows for better therapeutic consistency, in addition to being cost-efficient to avoid primary therapeutic failures. The results of the present SR may provide us with a useful basis for the preparation of management guidelines for the use of new generation therapies in moderate to severe atopic dermatitis.

Kommentare zum Review

- *Keine separate Auswertung nach Alter*

3.3 Leitlinien

Agache I et al. 2021 [1].

The European Academy of Allergy and Clinical Immunology (EAACI)

EAACI Biologicals Guidelines – dupilumab for children and adults with moderate-to-severe atopic dermatitis.

Leitlinienorganisation/Fragestellung

- "The current EAACI guideline for the use of dupilumab in AD is focussed only on treatment with dupilumab for AD. It does not address any topics related to AD diagnosis, concurrent treatment or monitoring adherence."
- "The EAACI Guideline for the use of dupilumab in AD is not intended to impose a standard of care. Instead, it provides the framework for rational decisions for the use of dupilumab in AD by HCPs, patients, third-party payers, institutional review committees and other stakeholders."

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft zu
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft nicht zu (Darlegung von Interessenskonflikten erwähnt, Daten sind allerdings nicht verfügbar)
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu
- Regelmäßige Überprüfung der Aktualität gesichert: trifft zu

Recherche/Suchzeitraum:

- Kein Datum benannt, aktuellste Quelle aus dem Jahr 2020

LoE/ GoR

- A strong recommendation was made in favour of an intervention when the GDG was certain that the desirable consequences outweighed the undesirable consequences.
- A conditional recommendation was provided if there were reasons for uncertainty on the benefit-risk profile, especially for low or very low quality of evidence. The underlying values and preferences played a key role in formulating recommendations.
- As the key target audience of this EAACI Guideline are HCPs and the patients they treat, the perspective chosen when formulating recommendations was mainly that of the HCPs and of the patient, although the health systems perspective was also evaluated, as per WHO recommendations for guidelines development.62 Recommendations are formulated separate by outcome.
- The recommendations formulated in this guideline should be used following the GRADE interpretation
- Where no evidence was available the GDG formulated expert-based recommendations.

Sonstige methodische Hinweise

- For the purpose of the SR[49] that informed the recommendations, the AD population was defined as patients (≥12 years or older) with confirmed diagnosis of moderate-to-severe AD. Moderate-to-severe disease was defined as an Investigator´s Global Assessment (IGA) score of three or higher at baseline or an Eczema Area and Severity Index (EASI) score of 12 or higher at baseline.
- For the recommendations, the population was defined as in the clinical trials that informed the regulatory approval.

Empfehlungen

Box 1 **Recommendation for dupilumab treatment in adults and in the paediatric population 12–17 years old with uncontrolled atopic dermatitis**

1. Dupilumab is recommended in adults and in the paediatric population 12–17 years old with atopic dermatitis* to:	Reduce disease activity as reflected by SCORAD, EASI, IGA	Strong recommendation
	Reduce rescue** and background*** medication	Strong recommendation
	Improve quality of life	Strong recommendation
2. Dupilumab has demonstrated a good safety profile however drug-related AEs should be periodically monitored		Conditional recommendation

*population: moderate-to-severe AD not adequately controlled with topical prescription therapies or when those therapies are not advisable

**Rescue refers to 'on demand'

**Background medication includes systemic and topical treatment

Accumulating experience with dupilumab treatment for AD confirmed its effectiveness and safety, by reducing AD severity, reliever and background medication, and improving QoL, both in the paediatric population 12–17 years old and in adults.[68-77]

Box 3 **Recommendation for dupilumab in adults and 12–17 years old patients with both AD associated with other T2 allergic diseases or other co-morbidities**

Dupilumab may be of particular benefit in adults and 12–17 years old patients with both AD associated with other T2 diseases (asthma, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis)	Conditional recommendation, expert opinion based

The GDG evaluated the evidence for dupilumab efficacy in AD associated with other T2 diseases or other co-morbidities not included in the SR (Table S2) and formulated a conditional recommendation, expert opinion based on the efficacy of dupilumab in patients with AD and other T2 co-morbidities (Box 3). Emerging evidence on the associations between AD and alopecia areata,[79-81] may also need to be considered, when considering treatments for patients with both

Referenzen:

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Berth-Jones J et al., 2019 [4].

British Association of Dermatologists

British Association of Dermatologists guidelines for the safe and effective prescribing of oral ciclosporin in dermatology 2018

Leitlinienorganisation/Fragestellung

„[…] to provide up-to-date, evidence-based recommendations for the safe and effective use of oral ciclosporin in the field of dermatology. The document aims to

- Offer an appraisal of all relevant literature since 1970 focusing on any key developments
- Address important, practical clinical questions relating to the primary guideline objective
- Provide guideline recommendations with some health economic implications, where appropriate
- Discuss potential developments and future directions".

Methodik

<u>Grundlage der Leitlinie</u>

- Leitlinie einer dermatologischen Fachgesellschaft, dadurch kein repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; Umgang mit dargelegten Interessenkonflikten jedoch unklar;
- Systematische Suche dargelegt, systematische Auswahl und Bewertung erwähnt, aber keine Details beschrieben;

- Keine Beschreibung von Konsensusprozessen; externes Begutachtungsverfahren dargelegt: Leitlinie wurde vor Veröffentlichung durch die folgenden Fachgesellschaften begutachtet:
- British Dermatological Nursing Group, Primary Care Dermatological Society, Psoriasis and Psoriatic Arthritis Alliance, Psoriasis Association, Becet's Syndrome Society and National Eczema Society
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Weder Gültigkeit, noch Verfahren zur Überwachung und Aktualisierung beschrieben.

Recherche/Suchzeitraum:

- PubMed, MEDLINE and Embase databases from January 1970 to February 2018
- Ohne Datum: Royal College of Physicians guidelines database, CINAHL and the Cochrane Library

LoE/ GoR

Levels of evidence

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

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

Strength of recommendation

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

RCT, randomized controlled trial; NICE, National Institute for Health and Care Excellence.

Empfehlungen

Severe atopic dermatitis

Ciclosporin is a highly effective treatment for severe AD (level of evidence 1+; strength of recommendation A).

- A systematic review confirmed that 11 studies on the use of ciclosporin in AD consistently demonstrated efficacy.[106]
- An additional review of 15 studies and a meta-analysis of 12 studies (which partially shared authorship with the aforementioned systematic review) concluded, somewhat more cautiously, that short-term use of ciclosporin can decrease the severity of atopic eczema in patients whose condition cannot be adequately controlled with conventional therapies. However, there was some evidence of publication bias, so these findings should be interpreted with caution. The effectiveness of ciclosporin is similar in adults

and children; however, tolerability may be better in children. There was insufficient data to evaluate the long-term effectiveness and safety of ciclosporin in patients with atopic eczema.[107]

106 Schmitt J, Schakel K, Schmitt N, Meurer M. Systemic treatment of severe atopic eczema: a systematic review. Acta Derm Venereol 2007; 87:100–11.

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8.1 Children

- Ciclosporin can be used in children. Trials in AD show that it is effective and relatively well tolerated by children aged 2 years and older in short courses of 6 weeks, 6 to 12 weeks, and for periods of up to 1 year.142,144 (Level of evidence 1+; strength of recommendation A.)

  Case reports about the use of ciclosporin in childhood psoriasis indicate that results are favourable.353–356 Ciclosporin has also been effective in several cases of generalized pustular psoriasis in children.357–364

Goulden V et al., 2022 [9].

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

Zielsetzung/Fragestellung

The overall objective of the guideline is to provide up-to-date, evidence-based recommendations for the use of narrowband ultraviolet B (NB-UVB) phototherapy in adults, young people and children.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium; trifft zu.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; trifft zu.
- Systematische Suche, Auswahl und Bewertung der Evidenz; trifft zu.
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt; trifft zu.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; trifft zu.
- Regelmäßige Überprüfung der Aktualität gesichert. scheduled for 2027.

Recherche/Suchzeitraum:

- A systematic literature search of the PubMed, MEDLINE, Embase, Cochrane and AMED databases was conducted to identify key articles on NB-UVB to 18 February 2021.
- An additional targeted literature search (for randomized controlled trials and systematic reviews) was conducted on 29 March 2022; no new publications were identified that would have materially affected the recommendations

LoE/ 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

Empfehlungen: Eczema

- R16 (↑↑) Offer NB-UVB as first-line phototherapy to people with eczema who have an inadequate response to topical therapy alone, prior to offering systemic immunosuppression or immunomodulation therapies, including PUVA.
- R17 (GPP) Emollients and, if necessary, short-term intermittent topical corticosteroids should continue to be used during a course of phototherapy for eczema.
- R18 (GPP) Stabilize severe, acute flares of eczema prior to commencing NB-UVB therapy by optimizing topical therapy, the use of systemic corticosteroids and/or antibiotics as appropriate.
- R19 (GPP) Consider adding NB-UVB to methotrexate or another suitable systemic immunomodulatory medication (avoid with ciclosporin, mycophenolate, azathioprine and tacrolimus) as a short-term rescue therapy to control flares, if eczema is normally well controlled on these treatments.

NICE, 2007 [14,15].

National Institute for Health and Care Excellence (NICE)

Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years.

Zielsetzung/Fragestellung

This guideline covers diagnosing and managing atopic eczema in children under 12.

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:

- Last Update: 02.03.2021

LoE/GoR

- Methodenreport beschreibt systematische Evidenzaufbereitung und Konsensusprozesse (je nach Bedarf fomal oder informal) - eigene Checklisten - Anwendung von GRADE - GoR schlagen sich in den Formulierungen wider ""To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations." Interventionen werden mittels GRADE-Methodik bewertet und in SoF-Tabellen dargestellt.

Recommendations

Stepped approach to management

- 1.5.1.1 Healthcare professionals should use a stepped approach for managing atopic eczema in children. This means tailoring the treatment step to the severity of the atopic eczema. Emollients should form the basis of atopic eczema management and should always be used, even when the atopic eczema is clear. Management can then be stepped up or down, according to the severity of symptoms, with the addition of the other treatments listed in table 2.

Table 2 Stepped treatment options

Mild atopic eczema	• Emollients • Mild potency topical corticosteroids
Moderate atopic eczema	• Emollients • Moderate potency topical corticosteroids • Topical calcineurin inhibitors • Bandages
Severe atopic eczema	• Emollients • Potent topical corticosteroids • Topical calcineurin inhibitors • Bandages • Phototherapy • Systemic therapy

- 1.5.1.3 Treatment for flares of atopic eczema in children should be started as soon as signs and symptoms appear and continued for approximately 48 hours after symptoms subside.

Emollients

- 1.5.1.4 Healthcare professionals should offer children with atopic eczema a choice of unperfumed emollients to use every day for moisturising, washing and bathing. This should be suited to the child's needs and preferences, and may include a combination of products or one product for all purposes. Leave-on emollients should be prescribed in large quantities (250 g to 500 g weekly) and easily available to use at nursery, pre-school or school.
- 1.5.1.5 Healthcare professionals should inform children with atopic eczema and their parents or carers that they should use emollients in larger amounts and more often than

other treatments. Emollients should be used on the whole body both when the atopic eczema is clear and while using all other treatments.

- 1.5.1.6 Healthcare professionals should inform children with atopic eczema and their parents or carers that they should use emollients and/or emollient wash products instead of soaps and detergent-based wash products.
- 1.5.1.7 Healthcare professionals should advise parents or carers of children aged under 12 months with atopic eczema to use emollients and/or emollient wash products instead of shampoos for the child. If shampoo is used for older children with atopic eczema it should be unperfumed and ideally labelled as being suitable for eczema; washing the hair in bath water should be avoided.
- 1.5.1.8 Healthcare professionals should show children with atopic eczema and their parents or carers how to apply emollients, including how to smooth emollients onto the skin rather than rubbing them in.
- 1.5.1.9 Healthcare professionals should offer an alternative emollient if a particular emollient causes irritation or is not acceptable to a child with atopic eczema.
- 1.5.1.10 Healthcare professionals should review repeat prescriptions of individual products and combinations of products with children with atopic eczema and their parents or carers at least once a year to ensure that therapy remains optimal.
- 1.5.1.11 Where emollients (excluding bath emollients) and other topical products are used at the same time of day to treat atopic eczema in children, the different products should ideally be applied one at a time with several minutes between applications where practical. The preferences of the child and parents or carers should determine which product should be applied first.

Topical corticosteroids

- 1.5.1.12 Healthcare professionals should discuss the benefits and harms of treatment with topical corticosteroids with children with atopic eczema and their parents or carers, emphasising that the benefits outweigh possible harms when they are applied correctly.
- 1.5.1.13 The potency of topical corticosteroids should be tailored to the severity of the child's atopic eczema, which may vary according to body site. They should be used as follows:
  - use mild potency for mild atopic eczema
  - use moderate potency for moderate atopic eczema
  - **use potent for severe atopic eczema**
  - use mild potency for the face and neck, except for short-term (3 to 5 days) use of moderate potency for severe flares
  - use moderate or potent preparations for short periods only (7 to 14 days) for flares in vulnerable sites such as axillae and groin
  - do not use very potent preparations in children without specialist dermatological advice.
- 1.5.1.15 It is recommended that where more than 1 alternative topical corticosteroid is considered clinically appropriate within a potency class, the drug with the lowest acquisition cost should be prescribed, taking into account pack size and frequency of application.
- 1.5.1.16 Healthcare professionals should inform children with atopic eczema and their parents or carers that they should only apply topical corticosteroids to areas of active atopic eczema (or eczema that has been active within the past 48 hours – see recommendation 1.5.1.3), which may include areas of broken skin.

- 1.5.1.17 Healthcare professionals should exclude secondary bacterial or viral infection if a mild or moderately potent topical corticosteroid has not controlled the atopic eczema within 7 to 14 days. In children aged 12 months or over, potent topical corticosteroids should then be used for as short a time as possible and in any case for no longer than 14 days. They should not be used on the face or neck. If this treatment does not control the atopic eczema, the diagnosis should be reviewed and the child referred for specialist dermatological advice.
- 1.5.1.18 Potent topical corticosteroids should not be used in children aged under 12 months without specialist dermatological supervision.
- 1.5.1.20 Healthcare professionals should consider treating problem areas of atopic eczema with topical corticosteroids for 2 consecutive days per week to prevent flares, instead of treating flares as they arise, in children with frequent flares (2 or 3 per month), once the eczema has been controlled. This strategy should be reviewed within 3 months to 6 months to assess effectiveness.
- 1.5.1.21 A different topical corticosteroid of the same potency should be considered as an alternative to stepping up treatment if tachyphylaxis to a topical corticosteroid is suspected in children with atopic eczema.

Topical calcineurin inhibitors

- 1.5.1.22 Topical tacrolimus and pimecrolimus are not recommended for the treatment of mild atopic eczema or as first-line treatments for atopic eczema of any severity.
- 1.5.1.23 Topical tacrolimus is recommended, within its licensed indications, as an option for the second-line treatment of moderate to severe atopic eczema in adults and children aged 2 years and older that has not been controlled by topical corticosteroids (see recommendation 1.5.1.25), where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.
- 1.5.1.24 Pimecrolimus is recommended, within its licensed indications, as an option for the second-line treatment of moderate atopic eczema on the face and neck in children aged 2 years to 16 years that has not been controlled by topical corticosteroids (see recommendation 1.5.1.25), where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.
- 1.5.1.25 For the purposes of this guidance, atopic eczema that has not been controlled by topical corticosteroids refers to disease that has not shown a satisfactory clinical response to adequate use of the maximum strength and potency that is appropriate for the patient's age and the area being treated.
- 1.5.1.26 It is recommended that treatment with tacrolimus or pimecrolimus be initiated only by physicians (including general practitioners) with a special interest and experience in dermatology, and only after careful discussion with the patient about the potential risks and benefits of all appropriate second-line treatment options.
- 1.5.1.27 Healthcare professionals should explain to children with atopic eczema and their parents or carers that they should only apply topical calcineurin inhibitors to areas of active atopic eczema, which may include areas of broken skin.
- 1.5.1.28 Topical calcineurin inhibitors should not be used under occlusion (bandages and dressings) for treating atopic eczema in children without specialist dermatological advice.
- 1.5.1.29 For facial atopic eczema in children that requires long-term or frequent use of mild topical corticosteroids, consider stepping up treatment to topical calcineurin inhibitors.

Dry bandages and medicated dressings including wet wrap therapy

- 1.5.1.30 Occlusive medicated dressings and dry bandages should not be used to treat infected atopic eczema in children.
- 1.5.1.31 Localised medicated dressings or dry bandages can be used with emollients as a treatment for areas of chronic lichenified (localised skin thickening) atopic eczema in children.
- 1.5.1.32 Localised medicated dressings or dry bandages with emollients and topical corticosteroids can be used for short-term treatment of flares (7 to 14 days) or areas of chronic lichenified atopic eczema in children.
- 1.5.1.33 Whole-body (limbs and trunk) occlusive dressings (including wet wrap therapy) and whole-body dry bandages (including tubular bandages and garments) should not be used as first-line treatment for atopic eczema in children and should only be initiated by a healthcare professional trained in their use.
- 1.5.1.34 Whole-body (limbs and trunk) occlusive dressings (including wet wrap therapy) with topical corticosteroids should only be used to treat atopic eczema in children for 7 to 14 days (or for longer with specialist dermatological advice), but can be continued with emollients alone until the atopic eczema is controlled.

Antihistamines

- 1.5.1.35 Oral antihistamines should not be used routinely in the management of atopic eczema in children.
- 1.5.1.36 Healthcare professionals should offer a 1-month trial of a non-sedating antihistamine to children with severe atopic eczema or children with mild or moderate atopic eczema where there is severe itching or urticaria. Treatment can be continued, if successful, while symptoms persist, and should be reviewed every 3 months.
- 1.5.1.37 Healthcare professionals should offer a 7- to 14-day trial of an age-appropriate sedating antihistamine to children aged 6 months or over during an acute flare of atopic eczema if sleep disturbance has a significant impact on the child or parents or carers. This treatment can be repeated during subsequent flares if successful.

Phototherapy and systemic treatments

- 1.5.1.50 Healthcare professionals should consider phototherapy or systemic treatments for the treatment of severe atopic eczema in children when other management options have failed or are inappropriate and where there is a significant negative impact on quality of life. Treatment should be undertaken only under specialist dermatological supervision by staff who are experienced in dealing with children.
- 1.5.1.51 Phototherapy or systemic treatments should only be initiated in children with atopic eczema after assessment and documentation of severity of atopic eczema and quality of life (see recommendation 1.2.1.1).

Wollenberg A et al., 2022 [8,25,26].

European guideline (EuroGuiDerm) on atopic eczema: part I & part II

Zielsetzung/Fragestellung

This first part of the guideline includes general information on its scope and purpose, the health questions covered, target users and a methods section. It also provides guidance on which patients should be treated with systemic therapies, as well as recommendations and detailed information on each systemic drug.

Part two of the guideline will address avoidance of provocation factors, dietary interventions, immunotherapy, complementary medicine, educational interventions, occupational and psychodermatological aspects, patient perspective and considerations for paediatric, adolescent, pregnant and breastfeeding patients.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium; trifft zu.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; trifft zu.
- Systematische Suche, Auswahl und Bewertung der Evidenz; living systematic review by Drucker et al. was used.
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt; trifft zu.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; trifft zu.
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- living systematic review by Drucker et al. was used.; last update 2022

Drucker AM, Morra DE, Prieto-Merino D, Ellis AG, Yiu ZZN, Rochwerg B, et al. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. JAMA Dermatol. 2022;158; 523-532.

LoE

- Cochrane Risk of Bias tool

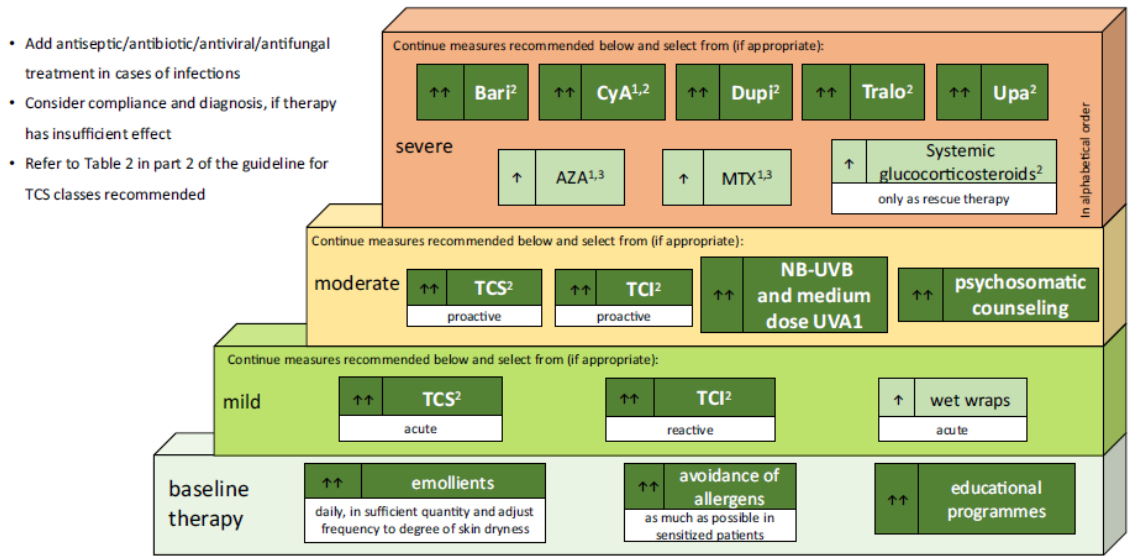
GoR

Table 3 Recommendation strengths – wording, symbols and interpretation and definition of certainty of evidence[6]

Strength	Wording	Symbols	Implications
Strong recommendation **for** the use of an intervention	'**We recommend . . .**'	↑↑	We believe that all or almost all informed people would make this choice.
Weak recommendation **for** the use of an intervention	'**We suggest . . .**'	↑	We believe that most informed people would make this choice, but a substantial number would not.
No recommendation with respect to an intervention	'**We cannot make a recommendation with respect to . . .**'	0	At the moment, a recommendation in favour of or against an intervention cannot be made due to certain reasons (e.g. no reliable evidence available, conflicting outcomes)
Weak recommendation **against** the use of an intervention	'**We suggest against . . .**'	↓	We believe that most informed people would make a choice against this intervention, but a substantial number would not.
Strong recommendation **against** the use of an intervention	'**We recommend against . . .**'	↓↓	We believe that all or almost all informed people would make a choice against this intervention.
High ⊗⊗⊗⊗: we are **very confident** that the true effect lies close to that of the estimate of the effect.			
Medium ⊗⊗⊗○: we are **moderately confident** in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.			
Low ⊗⊗○○: our **confidence in the effect estimate is limited: The true effect may be substantially different** from the estimate of the effect.			
Very low ⊗○○○: we have **very little confidence** in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.			

Empfehlungen: Erwachsene

Stepped-care plan for adults with atopic eczema



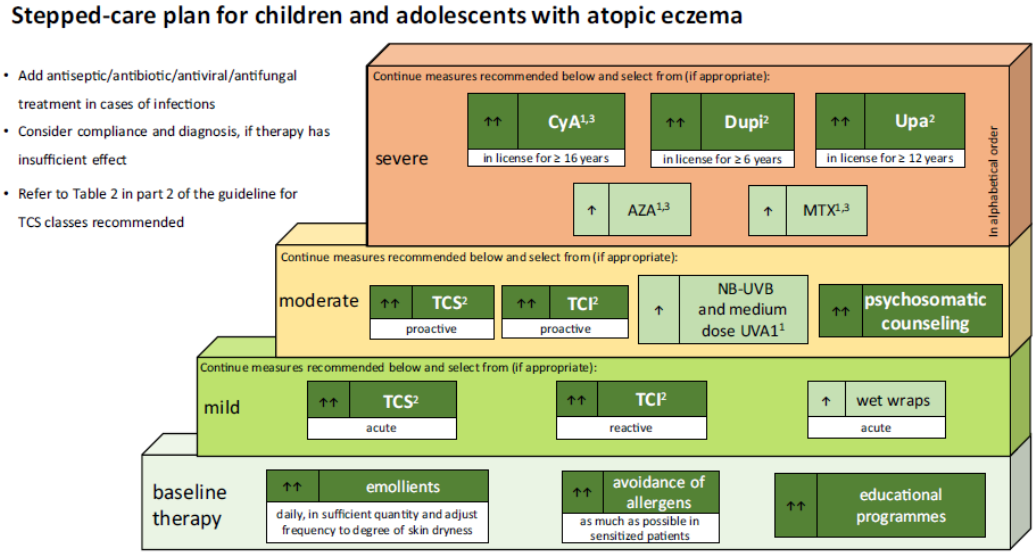
[1] refer to guideline text for restrictions, [2] licensed indication, [3] off-label treatment
↑↑ (dark green) strong recommendation for the use of an intervention / ↑ (light green) weak recommendation for the use of an intervention
For definitions of disease severity, acute, reactive, proactive see section 'VII' and section 'Introduction to systemic treatment' of the EuroGuiDerm Atopic Eczema Guideline
Abro= abrocitinib; AZA=azathioprine; Bari=baricitinib; CyA=ciclosporin; Dupi=dupilumab; MTX=methotrexate; TCI=topical calcineurin inhibitors; TCS= topical corticosteroids; Tralo=tralokinumab; Upa=upadacitinib; UVA1=ultraviolet A1; NB-UVB=narrow-band ultraviolet B

100% Agreement

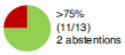
Symbols	Implications (adapted from GRADE [1])
↑↑	We believe that all or almost all informed people would make that choice.
↑	We believe that most informed people would make that choice, but a substantial number would not.
0	We cannot make a recommendation.
↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
↓↓	We believe that all or almost all informed people would make a choice against that choice.
	No recommendation.

Figure 1 Stepped-care plan for adults with AE.

Empfehlungen: Kinder und Jugendliche



[1] refer to guideline text for restrictions, [2] licensed indication, [3] off-label treatment
↑↑ (dark green) strong recommendation for the use of an intervention / ↑ (light green) weak recommendation for the use of an intervention
For definitions of disease severity, acute, reactive, proactive see section 'VII' and section 'Introduction to systemic treatment' of the EuroGuiDerm Atopic Eczema Guideline
AZA=azathioprine; CyA=ciclosporin; Dupi=dupilumab; MTX=methotrexate; TCI=topical calcineurin inhibitors; TCS= topical corticosteroids; Upa=upadacitinib; UVA1=ultraviolet A1; NB-UVB=narrow-band ultraviolet B



Symbols	Implications (adapted from GRADE [1])
↑↑	We believe that all or almost all informed people would make that choice.
↑	We believe that most informed people would make that choice, but a substantial number would not.
0	We cannot make a recommendation.
↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
↓↓	We believe that all or almost all informed people would make a choice against that choice.
	No recommendation.

Figure 2 Stepped-care plan for children and adolescents with AE.

Table 4 General recommendations for systemic drugs in adult AE patients who are candidates for systemic treatment (for details see corresponding chapter)

	Conventional systemic treatments			Biologics		JAK-inhibitors		Rescue therapy
	Ciclosporin	Methotrexate	Azathioprine	Dupilumab	Tralokinumab	Baricitinib	Upadacitinib	Systemic corticosteroids
Recommendation	↑↑	↑	↑	↑↑	↑↑	↑↑	↑↑	↑
Dose for adults[1]	licensed ≥ 16 years standard dosage adults: 2.5-5 mg/ kg per day in two single doses	off-label; commonly used dosage adults: initial dose: 5-15 mg/ per week; maximum dose: 25 mg/ week	off-label; commonly used dosage adults: 1-3 mg/kg per day	licensed ≥ 6 years; adults: initially 600 mg s.c. day 1 followed by 300 mg Q2W	licensed for adults; initially 600 mg s.c. day 1 followed by 300 mg Q2W; consider Q4W dosing at week 16 in those achieving clear or almost clear skin	licensed for adults; dosage adults: 4 mg per day, reduction to 2 mg per day possible, depending on treatment response	licensed ≥ 12 years; dosage adults: 15 or 30 mg per day based on individual patient presentation; age ≥ 65: 15 mg per day; the lowest effective dose for maintenance should be considered	general licence for adults and children; dosage maximum: 1 mg/kg per day
Time to response (weeks)[2]	1-2	8-12	8-12	4-6	4-8	1-2	1-2	1-2
Time to relapse (weeks, based on expert experience)[2]	<2	>12	>12	>8	>8	<2	<2	<2
Monitoring	complete blood count, renal and liver profile, blood pressure,	complete blood count, renal and liver profile, PIIINP if available, screen for chronic infections	complete blood count, renal and liver profile, TPMT activity if available, screen for chronic infections	not required	not required	complete blood count, lipid profile, liver profile	complete blood count, lipid profile, liver profile	not required for short-term treatment, consider blood glucose and testing for adrenal gland suppression with high doses/ longer-term treatment
Selection of most relevant adverse events	serum creatinine↑, blood pressure ↑	nausea, fatigue, liver enzymes ↑, myelotoxicity	gastrointestinal disturbances, idiosyncratic hypersensitivity reactions, hepatotoxicity, myelotoxicity	Conjunctivitis, upper respiratory tract infections, arthralgia	upper respiratory tract infections; conjunctitivitis	upper respiratory tract infections, increase in LDL cholesterol; thrombocytosis, nausea and abdominal pain herpes virus infections, acne	upper respiratory tract infections, acne; headache, anaemia and neutropenia, CK elevation, increase in LDL cholesterol, nausea and abdominal pain herpes virus infections	skin atrophy, weight gain, sleep disturbance, mood changes, hyperglycaemia or new onset diabetes, peptic ulcers/ gastritis, osteoporosis

Symbols	Implications (adapted from GRADE [1])
↑↑	We believe that all or almost all informed people would make that choice.
↑	We believe that most informed people would make that choice, but a substantial number would not.
0	We cannot make a recommendation.
↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
↓↓	We believe that all or almost all informed people would make a choice against that choice.
	No recommendation.

[1]SmPC, [2]expert experience, ↑ rise, AE- atopic eczema; GL – guideline, LDL – low density lipoprotein, PIIINP - Procollagen III N-Terminal Propeptide, TPMT – Thiopurine-S-Methyltransferase

Empfehlungen: Systemic drugs in special AE population

Table 1 General recommendations for systemic drugs in special AE patient populations (for details see corresponding chapter)

	Conventional systemic treatments			Biologics		JAK-inhibitors		Rescue therapy
	Ciclosporin	Methotrexate	Azathioprine	Dupilumab	Tralokinumab	Baricitinib	Upadacitinib	Systemic corticosteroids
Children and adolescents with AE who are candidates for systemic treatment	↑↑	↑	↑	↑↑			↑↑	
Dose for children	licensed for ≥ 16 years commonly used dosage children: 2.5-5 mg/kg per day in two single doses	off-label; commonly used dosage children: 0.3–0.4 mg/kg per week	off label; commonly used dosage children: 1-3 mg/ kg per day	licensed for ≥ 6 years; age 6-11: from 15kg <60kg, initially 300 mg s.c. day 1 &15 followed by 300 mg Q4W, when ≥60 kg, initially 600 mg s.c. day 1 followed by 300 mg Q2W age 12-17: <60 kg: initially 400 mg s.c. day 1 followed by 200 mg Q2W, when ≥60 kg: initially 600 mg s.c. day 1 followed by 300 mg Q2W	off-label	off-label	licensed for ≥ 12 years; age 12-17 (≥ 30 kg bw): 15 mg per day	general unspecific licence for children for steroid responsive skin disease dosage maximum: 1 mg/kg per day
Pregnancy (in candidates for systemic treatment)	↑	↓↓	↑	0		↓↓	↓↓	↑ prednisolone (0.5mg/ kg/d) *only* as rescue therapy for acute flares
Breastfeeding	↓	↓	↓	0		↓	↓	↑ prednisolone (0.5mg/ kg/d) *only* as rescue therapy for acute flares

[1] SmPC; Q2W - once every 2 weeks

Symbols	Implications (adapted from GRADE [1,2])
↑↑	We believe that all or almost all informed people would make this choice .
↑	We believe that most informed people would make this choice, but a substantial number would not.
0	We cannot make a recommendation.
↓	We believe that most informed people would make a choice against this intervention, but a substantial number would not.
↓↓	We believe that all or almost all informed people would make a choice against this intervention.
	No recommendation.

Empfehlungen: Topical drugs

Table 2 General recommendations for topical drugs for treatment of atopic eczema (for details see corresponding chapter)

Overall recommendation	**TCS ↑↑**		**TCI ↑↑**	
	TCS class I and II	TCS class III and IV	Tacrolimus 0.1% Tacrolimus 0.03%	Pimecrolimus 1%
For further information see background text	class I not suitable for long-term proactive treatment; long-term proactive treatment only class II	acute flare; proactive treatment with TCS class III class IV not for long term daily treatment or head and neck; class IV not recommended for proactive treatment either	acute flare; long-term proactive treatment; especially in face, intertriginous sites, anogenital area	acute flare; especially in face, intertriginous sites, anogenital area
Most important side effects	skin atrophy telangiectasia striae distensae ecchymosis hypertrichosis perioral dermatitis	skin atrophy telangiectasia striae distensae ecchymosis hypertrichosis perioral dermatitis corticosteroid addiction syndrome suppression of adrenal function	initial warmth, tingling or burning	initial warmth, tingling or burning
	TCI class II and III are off label for proactive treatment		in label for proactive treatment	not suitable for proactive treatment
Special considerations				
Suitable for **children > 2 to < 16** years of age	yes	yes	yes (0.03%)[2]	yes[2]
Suitable for **babies** < 2 years of age	yes	under specialist supervision	yes (0.03%)[1]	yes[2] (from the age of three months)
Suitable during **pregnancy**	yes	yes	yes (0.03% & 0.1%)[1]	yes[1]
Suitable during **breastfeeding**	yes	yes	yes (0.03% & 0.1%)[1]	yes[1]
Suitable for pruritus	yes	yes	yes (0.03% & 0.1%)	yes

[1] off label use [2] licensed use

Symbols	Implications (adapted from GRADE [188])
↑↑	We believe that all or almost all informed people would make this choice.
↑	We believe that most informed people would make this choice, but a substantial number would not.
0	We cannot make a recommendation.
↓	We believe that most informed people would make a choice against this intervention, but a substantial number would not.
↓↓	We believe that all or almost all informed people would make a choice against this intervention.
	No recommendation.

Empfehlungen: Basic emollients and moisturizers

We recommend gentle cleansing and bathing procedures especially in acutely inflamed or superinfected skin in patients with AE.	↑↑	100% agreement  (18/18) Expert consensus
We suggest bathing in moderately warm water over a short duration of time in patients with AE.	↑	>75%  (17/19) Expert consensus
We suggest against the use of alkaline soaps in patients with AE.	↓	100% agreement 
We suggest that patients with AE use body care products, for example gentle cleansers that do not contain potent irritants or relevant allergens.	↑	(19/19) Expert consensus
We recommend daily use of emollients, liberally and frequently for patients with AE, as basic treatment of the disturbed skin barrier function.	↑↑	>75%  (20/23) Expert consensus
We suggest using moisturizers with a hydrophilic formula in the summer and moisturizers with a higher lipid content in the winter in patients with AE.	↑	>75%  (15/18)[1] Expert consensus

[1] Abstention

We recommend to apply emollients immediately after bathing or showering and soft pat drying ('soak and seal technique').	↑↑	100% agreement  (19/19) Expert consensus
We recommend the use of emollients as background treatment to prevent flares and to reduce the symptoms of AE.	↑↑	>75%  (18/19)[1] Expert consensus

[1] Abstention

Empfehlungen: Anti-inflammatory treatment

We recommend the use of topical corticosteroids (TCS) as anti-inflammatory agents. **We recommend** the use of topical calcineurin inhibitors (TCI) as anti-inflammatory agents.	↑↑	>75%  (24/26) Expert consensus
We suggest using anti-inflammatory topical agents according to the fingertip unit rule.	↑	>75%  (23/26) Expert consensus
We suggest the use of wet wraps with diluted (see background text) or low potency topical corticosteroid in acute AE.	↑	>50%  (14/22) Expert consensus
We recommend TCS in AE especially for treatment of acute flares. **We recommend** to note and adequately address patients concerns or fears about corticosteroid side effects. **We recommend** using TCI particularly in skin areas with a risk of skin atrophy due to TCS application (face, intertriginous sites, anogenital area).	↑↑	100% agreement  (23/23) Expert consensus
We suggest initial treatment with topical corticosteroids before switching to a TCI to reduce the risk of skin stinging and burning.	↑	100% agreement  (23/23) Expert consensus
We recommend proactive therapy (e.g. twice weekly application) with a suitable TCS or a suitable TCI (see background text) to reduce the risk of relapse and for better disease control.	↑↑	100% agreement  (22/22) Expert consensus

Empfehlungen: Phototherapy and photochemotherapy

We recommend narrowband UVB and medium-dose UVA1 for AE patients with moderate-to-severe AE.	↑↑	>95%  (24/25) Expert consensus

We suggest the use of narrowband UVB or UVA1 in children and adolescents after the assessment of skin type (see background text), but frequent and/or protracted treatment cycles should be avoided.	↑	>95%  (24/25)[1] Expert consensus

[1] Abstention

We suggest that other phototherapy modalities (balneophototherapy, UVAB, BB-UVB, UVA) are to be considered as a second choice.	↑	100% agreement  (25/25) Expert consensus
We suggest that PUVA therapy is only used, when previous treatment cycles with other phototherapies were ineffective or when approved drug treatments are contraindicated, ineffective or have caused side effects.	↑	100% agreement  (25/25) Expert consensus
We suggest co-treatment with topical emollients during phototherapy.	↑	100% agreement  (25/25) Expert consensus
We recommend against the use of prolonged or repeated treatment cycles and maintenance regimens with all phototherapy modalities.	↓↓	100% agreement  (24/24) Expert consensus
We recommend against the use of all phototherapy modalities in patients with a history of skin cancer and with an increased risk of skin cancer (including photodamaged skin and those on systemic immunosuppressants (*see background text*)).	↓↓	100% agreement  (25/25) Expert consensus

Werfel, T. et al., 2020 [24].

Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) Organisation

Aktualisierung „Systemtherapie bei Neurodermitis“ zur Leitlinie Neurodermitis [atopisches Ekzem; atopische Dermatitis] Entwicklungsstufe: S2k.

Zielsetzung/Fragestellung

Systemtherapie bei Neurodermitis

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz zur systemischen Therapie bei Kindern mit schwerer AD und der Bedeutung für den deutschen Versorgungskontext, wird die Leitlinie ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium: Ja;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: Ja;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: Nein, Empfehlungen aus S2k Leitlinien enthalten keine schematische Angabe von Evidenz- und Empfehlungsgraden, da keine systematische Aufbereitung der Evidenz zugrunde liegt
- Regelmäßige Überprüfung der Aktualität gesichert: Ja

Recherche/Suchzeitraum:

- Aktualisierung der Leitlinie aus 2015. Siehe auch Siehe auch: Deutsche Dermatologische Gesellschaft (DDG), 2015 [5] – befindet sich aktuell in Revision
- Letztes Update: 02.2020

LoE/GoR

Positiv
wird empfohlen*
kann empfohlen werden
kann erwogen werden
Negativ
darf nicht erfolgen
wird nicht empfohlen

*Die Formulierung „muss“ wurde alternativ in Sonderfällen durch die Mandatsträger für als eindeutig und zwingend erforderlich erachtete Voraussetzungen und Maßnahmen konsentiert.

Empfehlungen

Orale Glukokortikosteroide

Therapieempfehlung

Die Kurzzeittherapie mit oralen Glukokortikosteroiden (das heißt wenige Wochen, Dosis ≤0.5 mg/kg Körpergewicht [KG] Prednisolonäquivalent) zur Unterbrechung des akuten Schubes kann vor allem bei der Therapie von erwachsenen Patienten, in Ausnahmefällen im Kindes- und Jugendalter, bei schweren Formen einer Neurodermitis in Kombination mit einem Therapiekonzept für die Anschlussbehandlung erwogen werden.

(starker Konsens)

Wegen der unerwünschten Arzneimittelwirkungen wird eine längerfristige Therapie der Neurodermitis mit systemischen Glukokortikosteroiden nicht empfohlen.

(starker Konsens)

Dupilumab

Therapieempfehlung

Der Einsatz von Dupilumab kann zur Therapie der chronischen, moderaten bis schweren Neurodermitis von Jugendlichen ab 12 Jahren und bei Erwachsenen, die mit topischen Medikamenten alleine nicht ausreichend behandelt werden können, empfohlen werden.

(starker Konsens)

Dupilumab kann auch zur Behandlung von Kindern unter 12 Jahren, die einen therapieresistenten, schweren Verlauf der Neurodermitis zeigen, als mögliche off-label-Therapieoption erwogen werden. Es stehen Expertenempfehlungen für die Dosierung im Kindesalter (≥ 6 Lebensmonate) zur Verfügung.

(Konsens)

Bei manifesten ekzematösen Läsionen wird die Therapie mit Dupilumab in Kombination mit einer topischen antientzündlichen Behandlung empfohlen.

(starker Konsens)

Ciclosporin

Therapieempfehlung

Der Einsatz von Ciclosporin A kann zur kurz- und mittelfristigen Therapie der chronischen, schweren Neurodermitis im Erwachsenenalter erwogen werden.

(starker Konsens)

Bei Einsatz von Ciclosporin bei der Indikation Neurodermitis ist das Verhältnis von zu erwartetem Nutzen zu Risiken vor dem Hintergrund therapeutischer Alternativen individuell zu prüfen.

(starker Konsens)

Es wird eine Anfangsdosis von 2,5 - 5 mg/kg KG/Tag in zwei Einzeldosen empfohlen.

(starker Konsens)

Es wird eine Induktionstherapie bei Neurodermitis empfohlen, wonach so lange mit einer wirksamen Dosis zwischen 2,5 – 5 mg/kg KG/Tag behandelt wird, bis eine weitgehende Besserung der Dermatose erreicht worden ist. Anschließend wird empfohlen, die Dosis schrittweise zu reduzieren. Nach Ansprechen kann eine Dosisreduktion auf die individuelle Erhaltungsdosis in zweiwöchigen Abständen (um 0,5-1,0 mg/kg KG/Tag) empfohlen werden.

(starker Konsens)

Vor Behandlungsbeginn müssen Untersuchungen vor allem hinsichtlich des Blutdrucks und der Nierenfunktion durchgeführt werden.

(starker Konsens)

Bei gutem Ansprechen wird eine Therapieunterbrechung nach 4-6 Monaten empfohlen.

(starker Konsens)

Eine Therapie bei schwer verlaufender Neurodermitis kann (bei guter Verträglichkeit) über einen längeren Zeitraum als 6 Monate erwogen werden.

(starker Konsens)

Ciclosporin kann auch zur Behandlung von Kindern und Jugendlichen, die einen therapieresistenten, schweren Verlauf der Neurodermitis zeigen, als Therpieoption erwogen werden (Off-Label-Use <16 Jahre).

(starker Konsens)

Aufgrund des erhöhten Hautkrebsrisikos soll eine Therapie mit Ciclosporin bei Neurodermitis nicht mit einer Phototherapie kombiniert werden.

(Konsens)

Während der Einnahme von Ciclosporin wird ein optimaler UV-Lichtschutz empfohlen.

(starker Konsens)

Für die Therapie der Neurodermitis nicht zugelassene antiinflammatorische Medikamente

- Azathioprin

Therapieempfehlung

Azathioprin kann (Off-Label-Use) zur Therapie der chronischen, schweren Neurodermitis erwogen werden, wenn Dupilumab oder Ciclosporin nicht wirksam oder kontraindiziert sind.

(Mehrheitliche Zustimmung*)

Die Bestimmung des Enzyms Thiopurinmethyltransferase (TPMT) vor Therapieeinleitung wird empfohlen, um eine Dosisanpassung ggf. vornehmen zu können, um das Risiko der Knochenmarkstoxizität zu verringern. Es wird in Abhängigkeit von der TPMT-Aktivität eine Dosis von 1-3mg/kg KG/Tag empfohlen.

(Konsens)

Unabhängig hiervon muss die Azathioprin-Dosis auf ein Viertel der normalen Dosis reduziert werden, wenn Xanthinoxidase-Inhibitoren wie Allopurinol, Oxipurinol oder Thiopurinol gleichzeitig eingesetzt werden.

(starker Konsens)

Eine Phototherapie unter Azathioprin wird nicht empfohlen.

(starker Konsens)

Unter Einnahme von Azathioprin wird ein optimaler UV-Lichtschutz empfohlen.

(starker Konsens)

* Einige Nicht-Zustimmende bewerteten den Einsatz von Azathioprin (Off-Label-Use) als gleichwertig gegenüber Ciclosporin (In-Label-Use).

- Mycophenolatmofetil

Therapieempfehlung

Im Einzelfall, kann Mycophenolatmofetil (Off-Label-Use) zur Therapie der chronischen, schweren Neurodermitis, insbesondere zur Erhaltungstherapie, erwogen werden.

(Konsens)

Mycophenolatmofetil ist kontraindiziert bei Frauen und Männern mit aktuellem Kinderwunsch. Bezüglich notwendiger Verhütungsmaßnahmen auch über 90 Tage nach Beendigung der Therapie hinaus wird auf die Empfehlungen der Fachinformation hingewiesen.

(starker Konsens)

- Methotrexat

Therapieempfehlung

Der Einsatz von Methotrexat (Off-Label-Use) kann zur langfristigen Therapie der chronischen, schweren Neurodermitis erwogen werden.

(starker Konsens)

<u>Verfügbare Biologika ohne Zulassung zur Therapie bei Neurodermitis</u>

Therapieempfehlung

Die Therapie der Neurodermitis mit Omalizumab wird nicht empfohlen.

(starker Konsens)

Therapieempfehlung

Die Therapie der Neurodermitis als alleinige Indikation für eine Behandlung mit Ustekinumab wird nicht empfohlen. Bei gleichzeitigem Vorliegen einer Psoriasis, Psoriasisarthritis, rheumatoiden Arthritis oder chronisch entzündlicher Darmerkrankung kann die Therapie mit Ustekinumab erwogen werden.

(starker Konsens)

Empfehlung

Die Therapie der Neurodermitis mit Rituximab und Tocilizumab wird nicht empfohlen.

(starker Konsens)

Empfehlung

Die Therapie der Neurodermitis mit Apremilast wird nicht empfohlen.

(starker Konsens)

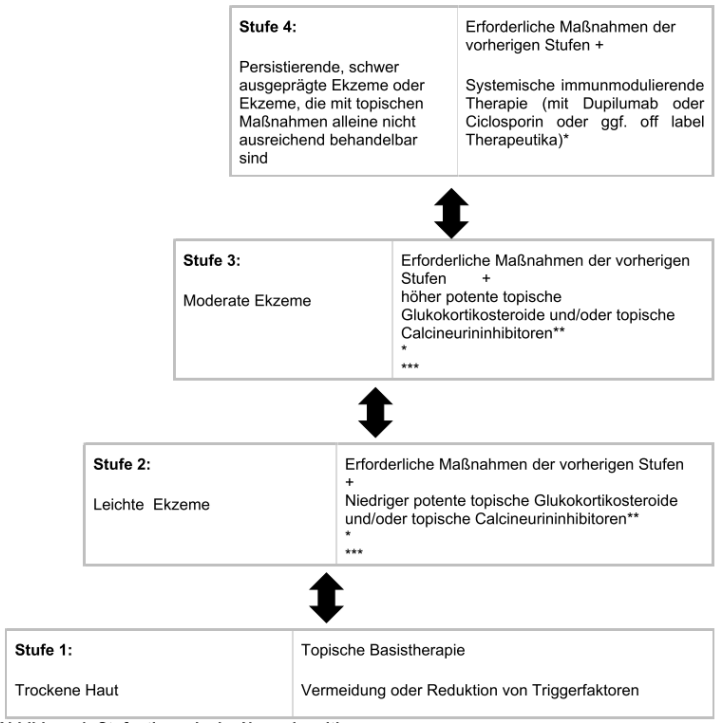


Abbildung 1: Stufentherapie der Neurodermitis

Je nach Schweregrad der Neurodermitis und/oder diagnostischer Fragestellung (zum Beispiel Provokationstestung mit Allergenen) wird eine ambulante, teilstationäre oder vollstationäre Behandlung empfohlen.

*Eine UV- Therapie ist häufig ab Stufe 2 unter Berücksichtigung der Altersbeschränkung (nicht im Kindesalter) indiziert. Cave: keine Kombination mit Ciclosporin A und topischen Calcineurininhibitoren

**First-line Therapie: In der Regel topische Glukokortikosteroide, bei Unverträglichkeit/Nichtwirksamkeit und an besonderen Lokalisationen (z.B. Gesicht, intertriginöse Hautareale, Genitalbereich, Capillitium bei Säuglingen) topische Calcineurininhibitoren

***Die zusätzliche Anwendung von antipruriginösen und antiseptischen Wirkstoffen kann erwogen werden.

Anmerkung: Abbildung 1 enthält aus Gründen der Übersichtlichkeit nicht alle Verfahren, die in dieser Leitlinie diskutiert werden.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 05 of 12, May 2023) am 17.05.2023

#	Suchfrage
1	[mh "Dermatitis, Atopic"]
2	((atopic OR infantile) AND (dermati* OR eczema*)):ti,ab,kw
3	(neurodermati* OR neurodermiti*):ti,ab,kw
4	#1 OR #2 OR #3
5	#4 with Cochrane Library publication date from May 2018 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 17.05.2023

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

#	Suchfrage
1	dermatitis, atopic[mh]
2	(atopic[tiab] OR infantile[tiab]) AND (dermati*[tiab] OR eczema*[tiab])
3	neurodermati*[tiab] OR neurodermiti*[tiab]
4	#1 OR #2 OR #3
5	(#4) 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

#	Suchfrage
	proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
6	(#5) AND ("2018/05/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 17.05.2023

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

#	Suchfrage
1	dermatitis, atopic[mh]
2	(atopic[tiab] OR infantile[tiab]) AND (dermati*[tiab] OR eczema*[tiab])
3	neurodermati*[tiab] OR neurodermiti*[tiab]
4	#1 OR #2 OR #3
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
6	(#5) AND ("2018/05/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 19.05.2023

- 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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