Gemeinsamer Bundesausschuss

# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

# und

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

# und

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

## Vorgang: 2022-B-238 Baricitinib

Stand: Oktober 2022

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

**Baricitinib**

**Behandlung der mittelschweren bis schweren atopischen Dermatitis bei Kindern und Jugendlichen von 2 bis 17 Jahren**

| **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. | Aufzählung, wenn dies in Betracht gezogen wird, sonst „nicht angezeigt“ |
| Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen | – NB-UVB<br>– UVA (die UVA1 ist hiervon ausgenommen, da ausgeschlossen) |
| 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**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet**<br>(Text aus Fachinformation) |
|---|---|
| Zu bewertendes Arzneimittel: | |
| Baricitinib<br><br><br>***Hinweis*** | Geplantes Anwendungsgebiet laut Beratungsanforderung:<br>*Behandlung der mittelschweren bis schweren atopischen Dermatitis bei Kindern und Jugendlichen zwischen 2 und 18 Jahren, die auf eine topische Therapie unzureichend angesprochen haben oder eine Unverträglichkeit gegen eine entsprechende Behandlung aufweisen.*<br>***Aufgrund der großen Menge an Wirkstoffen im Anwendungsgebiet werden hier einzelne Arzneimittel exemplarisch aufgeführt*** |
| **TOPISCHE THERAPIEN** | |
| **Glukokortikoide Klasse 1:** | |
| Prednisolon<br>D07AA03<br>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<br>D07AA02<br>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<br>D07AB02<br>z.B. Laticort® Creme 0,1 % | Zur Behandlung entzündlicher Hautkrankheiten, bei denen mittelstark wirksame, topisch anzuwendende Glucocorticoide angezeigt sind.<br>Creme: insbesondere bei akuten und subakuten Formen, in intertriginösen Arealen und beim fettigen Hauttyp.<br>Salbe: insbesondere bei subakuten bis chronischen Formen. |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| Clobetasonbutyrat 0,5 mg<br>D07AB01<br>z.B. Emovate®<br>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<br>D07AB09<br>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<br>D07AC18<br>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<br>D07AC 14<br>Advantan® 0,1 % Creme | Zur Behandlung des endogenen Ekzems (atopische Dermatitis, Neurodermitis), Kontaktekzems, degenerativen Ekzems und des nummulären Ekzems. |
| Amcinonid<br>D07AC11<br>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<br>D07AC13<br>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:** | |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| Clobetasol-propionat<br>D07AD01<br>z.B. Clobetasol acis®<br>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<br>D11AH01<br>Protopic® 0.03%<br>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<br>D11AH02<br>Elidel® 10 mg/g<br>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<br>D11AH05<br>Dupixent® | 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.<br>Dupixent wird angewendet zur Behandlung von schwerer atopischer Dermatitis bei Kindern von 6 bis 11 Jahre, die für eine systemische Therapie in Betracht kommen. |
| Upadacitinib<br>L04AA44<br>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. |
| Ciclosporin<br>L04AD01<br>z.B. Ciclosporin dura | Ciclosporin dura ist indiziert bei Patienten mit schwerer atopischer Dermatitis, falls eine systemische Therapie erforderlich ist. |
| **Systemische Glucokortikoide** | |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| Methylprednisolon<br>H02AB04<br>Methylprednisolon 4 mg, 8mg, 16 mg, 32 mg Tabletten;<br>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<br>H02AB08<br>Volon® 4, 8, 12 mg Tabletten | Orale Anfangsbehandlung ausgedehnter, schwerer akuter, auf Glukokortikoide ansprechender Hautkrankheiten wie:<br>Allergische Dermatosen (z. B. akute Urtikaria, Kontaktdermatitis, Arzneimittelexanthem), atopisches Ekzem (akute Exazerbationen bzw. großflächige nässende Ekzeme), Pemphigus vulgaris. |
| **Antihistaminika** | |
| z.B.Cetirizin-dihydrochlorid<br>R06A E07<br>Cetirizin beta®<br>Filmtablette | Zur Behandlung von Krankheitssymptomen bei allergischen Erkrankungen wie<br>– 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: 2022-B-238 (Baricitinib)

| | |
|---|---|
| Auftrag von: | Abt. AM |
| Bearbeitet von: | Abt. FB Med |
| Datum: | 25. Oktober 2022 |

# Inhaltsverzeichnis

# Abkürzungsverzeichnis

| | |
|---|---|
| (c)DLQI | (Children's) Dermatology Life Quality Index |
| AD | atopic dermatitis |
| ADIS | Atopic Dermatitis Itch Scale |
| AE | atopic eczema |
| AWMF | Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften |
| AZA | Azathioprine |
| BSA | affected Body Surface Area |
| CSA | Ciclosporin A |
| DDG | Deutsche Dermatologische Gesellschaft |
| DLQI | Dermatology Life Quality Index |
| EAACI | The European Academy of Allergy and Clinical Immunology |
| EASI | Eczema Area and Severity Index |
| EC-MPS | entericcoated mycophenolate sodium |
| ECP | extracorporeal photopheresis |
| EDI | Eczema Disability Index |
| ETFAD | European Task Force Atopic dermatitis |
| GDG | guideline development group |
| GIN | Guidelines International Network |
| GISS | Global Individual Sign Score |
| GoR | Grade of Recommendations |
| HADS | Hospital Anxiety and Depression Scale |
| HCP | health care practitioner |
| HR | Hazard Ratio |
| IGA | Investigator Global Assessment |
| IVIG | intravenous immunoglobulins |
| KI | Konfidenzintervall |
| LoE | Level of Evidence |
| MTX | Methotrexate |
| NICE | National Institute for Health and Care Excellence |
| NRS | pruritus numeric rating scale |
| OR | Odds Ratio |
| PGA | Patient Global Assessment |
| PGE | Physicians global evaluation |
| POEM | Patient-Oriented Eczema Measure |

| | |
|---|---|
| QoLIAD | Quality of Life Index for Atopic Dermatitis |
| RR | Relatives Risiko |
| SCORAD | Scoring Atopic Dermatitis |
| SIGN | Scottish Intercollegiate Guidelines Network |
| TCI | Topical calcineurin inhibitors |
| TCS | topische Glukokortikoide |
| TRIP | Turn Research into Practice Database |
| UKSIP | United Kingdom Sickness Impact Profile |
| WHO | World Health Organization |

# 1 Indikation

Behandlung der mittelschweren bis schweren atopischen Dermatitis bei Kindern und Jugendlichen zwischen 2 und 18 Jahren, die auf eine topische Therapie unzureichend angesprochen haben oder eine Unverträglichkeit gegen eine entsprechende Behandlung aufweisen.

*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 folgende am 23.09.2022. 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 960 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 25 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

# 3 Ergebnisse

## 3.1 Cochrane Reviews

**Ferguson L et al., 2018 [9].**

Leukotriene receptor antagonists for eczema.

**Fragestellung**

„To assess the possible benefits and harms of leukotriene receptor antagonists for eczema."

**Methodik**

Population:

- adults and children with established eczema

Intervention:

- systemic (oral or intravenous) LTRAs alone or in combination with other (topical or systemic) treatments in the acute or chronic (maintenance) phase of eczema

Komparator:

- other treatments alone (all topical or systemic treatment, including corticosteroids, topical calcineurin inhibitors, immunomodulators, and alternative medicines) or placebo

Endpunkte:

- Primary outcomes:
  1. Change in disease severity assessed by SCORAD (SCORing of Atopic Dermatitis) severity index, EASI (Eczema Area and Severity Index), SASSAD (Six Area, Six Sign Atopic Dermatitis) severity score, IGA (Investigator's Global Assessment), or any validated scoring system for eczema in the short and long term. A reduction in the score using these validated scoring systems equates to an improvement of the participant's eczema.
  2. Effect of long-term control, such as time to relapse of 'flare' in the maintenance (flare-free) phase.
  3. All adverse events, including allergic reactions and impact on quality of life and skin.
- Secondary outcomes
  1. Requirement for any topical or systemic corticosteroids, i.e. LTRA permits the lowering or minimising of the dose of corticosteroids needed, thus sparing some of the undesirable side effects of corticosteroids.
  2. Reduction of pruritus.
  3. Improvement in quality of life with any validated scoring system.
  4. Need for emollient use.

Recherche/Suchzeitraum:

- Up to 7 September 2017 in Cochrane Skin Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL) (2017, Issue 8), the Cochrane Library, MEDLINE via Ovid (from 1946), Embase via Ovid (from 1974), Global Resource for EczemA Trials (GREAT) (Centre of Evidence Based Dermatology (www.greatdatabase.org.uk)), ISI Web of Science (from 1945)
- Several trial regisitries up to 7 September 2017

Qualitätsbewertung der Studien:

- 'Risk of bias' using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions

**Ergebnisse**

Anzahl eingeschlossener Studien:

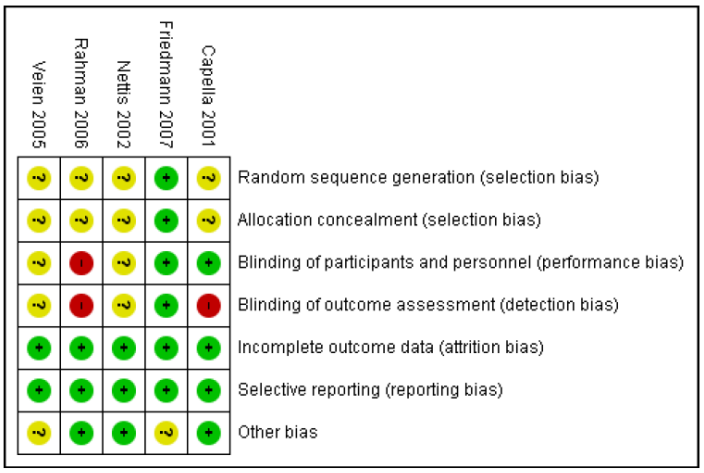
- 5 RCT (involving a total of 202 participants)
- sample sizes ranged from 20 to 60 participants
- All studies used montelukast 10 mg for adults (age 14 years and above) or 5 mg for children (age 6 years to 14 years) in tablet form taken orally as the LTRA intervention; three studies compared this with placebo (Friedmann 2007; Nettis 2002; Veien 2005), and two studies compared this with conventional treatment (Capella 2001; Rahman 2006).
- Conventional treatment included oral antihistamine and topical corticosteroid in both Capella 2001 and Rahman 2006, but Capella 2001 also included oral antibiotics (clarithromycin) in the conventional treatment arm.
- Two of the three studies using a placebo tablet did not allow participants in either arm to use topical corticosteroids.
- The intervention periods varied: 4 weeks in 2 studies (Rahman 2006; Veien 2005), 6 weeks in 2 studies (Capella 2001; Nettis 2002), and 8 weeks in 1 study (Friedmann 2007).

Charakteristika der Population:

- A physician's diagnosis of eczema was compulsory
- Participants of one study included children aged six years and above (Rahman 2006).
- The remaining studies did not include children; the age range in these studies was from 16 to 70 years
- One study included only men (Nettis 2002), with the remaining studies including both genders.
- Study participants were diagnosed with moderate-to-severe eczema in four studies (Capella 2001; Nettis 2002; Rahman 2006; Veien 2005), and only moderate eczema in one study (Friedmann 2007).
- With regard to coexisting asthma, one study reported that 15 of 32 participants had allergic asthma (Capella 2001).

Qualität der Studien:

- 3 studies double-blind trials; one trial single-blind; one open-label trial
- We judged three studies as at unclear risk of bias (Friedmann 2007; Nettis 2002; Veien 2005), and two studies as at high risk of bias (Capella 2001; Rahman 2006).




Studienergebnisse:

*Montelukast versus placebo*

- i) Primary outcome 1: change in disease severity in the short term and long term
  - All three studies for the comparison montelukast versus placebo assessed this outcome, for 4 weeks in Veien 2005, 6 weeks in Nettis 2002, and 8 weeks in Friedmann 2007.
  - Veien 2005 reported using the modified EASI (Eczema Area and Severity Index) score, which they calculated as the sum of the pruritus scores (0 to 3) and the EASI score. The modified EASI decreased from 8.9 to 6.8 in the montelukast group (n = 25) and from 9.5 to 7.6 in the placebo group (n = 28) (no standard deviations (SDs) provided). The difference between the groups was not significant (P = 0.46, confidence interval not stated)
- ii) Primary outcome 2: effect of long-term control
  - We defined three months or more as long term. We found no data evaluating this outcome, as the longest included study was of only eight weeks' duration.
- iii) Primary outcome 3: adverse events All three studies reported on this outcome (total of 131 followed participants).
  - We judged the quality of evidence for the outcome adverse events as low, downgrading due to imprecision (small sample size and low event rate) and indirectness because only participants with moderate-to-severe eczema were included. Additionally, these were treatment studies, and as such not specifically designed to detect this outcome.

*Montelukast versus conventional treatment*

- i) Primary outcome 1: change in disease severity in the short term and long term
  - Two of the five included studies used this comparison (involving 63 participants). Treatment with montelukast was compared with conventional treatment for four weeks in the Rahman 2006 study and six weeks in the Capella 2001 study.
  - Rahman 2006 showed that the SCORAD score (mean ± SD) decreased for the montelukast group from 52.70 ± 15.95 to 37.41 ± 6.04 at 4 weeks (P = 0.003), but the score only changed from 53.31 ± 15.17 to 48.58 ± 14.37 (P = 0.088) in the conventional treatment group.
  - The mean difference in improvement in disease severity between groups was 10.57 (95% CI 4.58 to 16.56, P < 0.001, n = 31), in favour of the montelukast group.

  - In the other study, no standard deviation was provided; therefore, we were unable to pool the data from this study with that of Rahman 2006 without having to make serious assumptions about the exact P value and true standard deviation.
  - We judged the quality of evidence for this outcome as very low, downgrading due to risk of bias, indirectness, and imprecision because outcome assessors were not blinded, and the sample size of each study was small.
- ii) Primary outcome 2: effect of long-term control
  - We defined three months or more as long term. We found no data evaluating this outcome
- iii) Primary outcome 3: adverse events
  - We judged the quality of evidence on adverse events as low, downgrading due to imprecision and indirectness because only 63 participants were evaluated, […].
  - Neither of the studies reported any adverse effects in the montelukast group (32 participants) (Capella 2001; Rahman 2006)

**Anmerkung/Fazit der Autorinnen und Autoren**

The findings of this review are limited to montelukast. There was a lack of evidence addressing the review question, and the quality of the available evidence for most of the measured outcomes was low. Some primary and secondary outcomes were not addressed at all, including long-term control.

We found no evidence of a difference between montelukast (10 mg) and placebo on disease severity, pruritus improvement, and topical corticosteroid use. Very low-quality evidence means we are uncertain of the effect of montelukast (10 mg) compared with conventional treatment on disease severity. Participants in only one study reported adverse events, which were mainly mild (low-quality evidence).

There is no evidence that LTRA is an effective treatment for eczema. Serious limitations were that all studies focused on montelukast and only included people with moderate-to-severe eczema, who were mainly adults; and that each outcome was evaluated with a small sample size, if at all.

Further large randomised controlled trials, with a longer treatment duration, of adults and children who have eczema of all severities may help to evaluate the effect of all types of LTRA, especially on eczema maintenance.

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**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:

- People of all ages with a clinical diagnosis of eczema, identified as 'atopic eczema' or 'eczema', made by a dermatologist or a physician.

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
  - Mean change in patient-assessed symptoms of eczema, as measured by a standardised or validated eczema symptoms score
  - Proportion of participants reporting adverse effects and serious adverse events throughout the study period
- Secondary outcomes
  - Mean change in physician-assessed clinical signs, as measured by a standardised or validated eczema signs score
  - Mean change in quality of life, as measured by a standardised or validated quality of life measure
  - 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:

- 36 references referring to a total of 25 RCTs

Interventions:

- 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).

<u>Charakteristika der Population:</u>

- 3285 participants
- 8 studies (participants = 1941) investigated children (aged 0 to 12 years) or adolescents (aged 12 to 18 years), or both
  - Cambazard 2001: 1 to 5 year old children
  - Diepgen 2002: infants (1 to 2 years of age)
  - Iikura 1992: elementary school children
  - Jung 1989: 3 to 6 year old children
  - LaRosa 1994: 6 to 12 year old children
  - Leon 1989: Ketotifen group: Age: mean = 5.95 years; SD = 3.41; Placebo group: M = 5.92 years; SD = 2.70
  - Munday 2002: Age: median: 7 years (range 1 to 12 years)
  - Simons 2007: Levocetirizine group: Age: M = 19.3 months; Placebo: M = 19.4 months
- Seventeen studies (participants = 1325) conducted with adults
- 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).

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:*

- LaRosa 1994 reported the results of a long-term intervention (eight weeks; n = 23) conducted in children six to 12 years of age. Investigators compared 5 mg cetirizine for children ≤ 30 kg and 10 mg for children > 30 kg versus placebo.
- Primary outcome 1. Mean change in patient-assessed symptoms of eczema
  - Cetirizine showed a significant advantage over placebo at week 8 ($Chi^2$ 4.55; $P < 0.05$) with regard to pruritus assessed by a diary, which favours the intervention group.
  - Results as presented not reproducible, no data could be extracted for analysis
  - Quality of evidence downgraded by two levels to low: one level for limitations in design due to unclear judgement for all other domains apart from the domain incomplete outcome data (low risk), and one level due to imprecision (small sample size).
- Primary outcome 2. Proportion of participants reporting adverse: effects and serious adverse events throughout the study period
  - Investigators observed no adverse events and provided no study data for analysis
  - Quality of evidence downgraded by two levels to low: one level for limitations in design due to unclear judgement for all other domains apart from the domain

incomplete outcome data (low risk), and one level due to imprecision (small sample size).

- Secondary outcome 1. Mean change in physician-assessed clinical signs
  - No significant differences between groups observed
  - No data from this study available for analysis
  - Quality of evidence downgraded by two levels to low: one level for limitations in design due to unclear judgement for all other domains apart from the domain incomplete outcome data (low risk), and one level due to imprecision (small sample size).
- Secondary outcome 3. Number of eczema flares
  - Investigators measured the use of concomitant therapy
  - 18% in the active treatment group and 82% in the placebo group reported use of concomitant therapy (disodium cromoglycate, procaterol, steroids); Chi² test: P < 0.01; RR 0.22, 95% CI 0.06 to 0.80; P= 0.02; participants = 22)
  - Quality of evidence downgraded by two levels to low: one level for limitations in design due to unclear judgement for all other domains apart from the domain incomplete outcome data (low risk), and one level due to imprecision (small sample size)

*Chlorpheniramine maleate BP (2 to 4 mg/d (age dependent) or twice that amount) versus placebo*

- Munday 2002 reported the results of an intermediate-term (one month) intervention
- Primary outcome 1. Mean change in patient-assessed symptoms of eczema
  - Participants rated the severity of pruritus (ranked) as none, minimal, mild, or moderate between days 1 and 29
  - No significant differences (P = 0.745 based on the Cochran-Mantel-Haenzsel test) between intervention and placebo groups (stratified for age groups and controlling for baseline differences) in severity of night-time pruritus
  - Quality of evidence downgraded by one level from high to moderate for limitations in design due to serious risk of bias (most domains judged as having unclear risk of bias)
- Primary outcome 2. Proportion of participants reporting adverse effects and serious adverse events throughout the study period
  - No significant differences between groups (RR 0.95, 95% CI 0.49 to 1.82; P = 0.87; participants = 151).
  - Quality of evidence downgraded by one level from high to moderate for limitations in design due to serious risk of bias (most domains judged as having unclear risk of bias)
- Secondary outcome 1. Mean change in physician-assessed clinical signs
  - Investigators presented this outcome as a composite score consisting of five symptoms (erythema, excoriation, dryness, lichenification, exudation and crusting).
  - No significant differences between groups at day 1 (P = 0.479), day 15 (P =0.33), or day 29 (P = 0.53). No data were available for analysis.
  - Quality of evidence downgraded by one level from high to moderate for limitations in design due to serious risk of bias (most domains judged as having unclear risk of bias)
- Secondary outcome 3. Number of eczema flares

- Assessed as the amount of 1% hydrocortisone in grams used and analysed data separately for age groups one to five years and six to 12 years
- No significant differences between intervention and placebo groups, neither in the age group one to five years (MD -1.30, 95% CI -5.96 to 3.36; P = 0.58; participants = 61) nor in the age group six to 12 years (MD 1.60, 95% CI -2.53 to 5.73; P = 0.45; participants = 90)
- Quality of evidence downgraded by two levels from high to low due to serious risk of bias (most domains judged as having unclear risk of bias) with serious imprecision (wide CI due to small sample size or high variability in outcome measurements).

*Ketotifen versus placebo:*

- Leon 1989 investigated a long-term intervention (nine weeks) of ketotifen (2 mg/d) in a small sample of children (n = 20).
- Primary outcome 1. Mean change in patient-assessed symptoms of eczema
  - Intensity of day and night pruritus assessed on a scale from 0 to 3 (absent = 0, mild = 1, moderate = 2, intense = 3
  - Study authors stated that differences in both daytime and night-time pruritus between visit 1 and week 9 were not significant for the placebo group but showed significant improvement for the ketotifen group (P = 0.01 for nighttime and P = 0.005 for daytime pruritus comparisons). However, investigators carried out no comparison between groups, and as we could extract no data from the study, no inference could be made about whether ketotifen has an effect on pruritus over placebo.
  - Quality of evidence downgraded by two levels from high to low due to serious risk of bias (most domains judged as having unclear risk of bias) and imprecision (small sample size).

**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*

- Es konnten keine Subgruppenanalysen (z.B. nach Alter) durchgeführt werden
- Ergebnisse lediglich auf Ebene einzelner, kleiner Primärstudien.
- 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 [15].**

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:

- We considered 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**

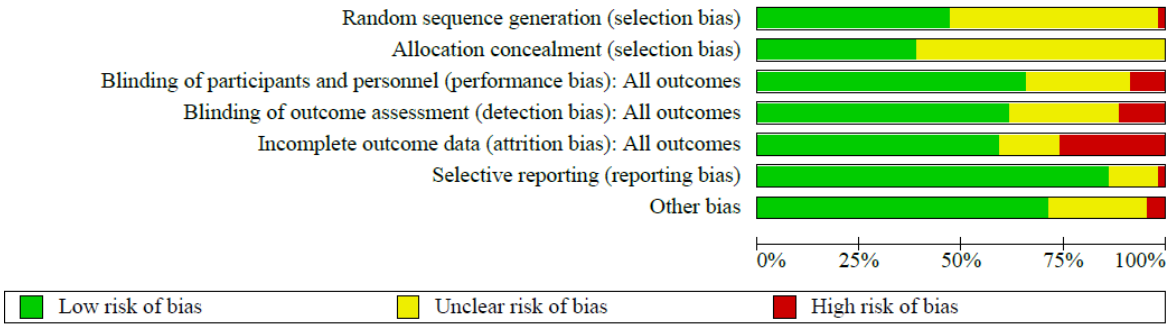
Anzahl eingeschlossener Studien:

- This review included 74 trials. A total of 8177 participants were randomised to different interventions.

Charakteristika der Population:

- The mean or median age in included trials ranged from 2 to 84 years, with an overall mean or median age of 32 years. Seven of 74 trials determined the effects of systemic treatment in children with reported overall mean or median age ranging from 3.6 to 14.5 years
- Trials included more men (54.7%; 3824 participants) than women. Age and gender were unreported for 419 and 902 participants (10 and 20 studies), respectively.
- All trials included participants with moderate to severe eczema. However, most of the studies (46/74; 62%) included participant with moderate to severe eczema without separately reporting outcomes for moderate or severe disease. Twenty-eight trials (28/74; 38%) included only participants with severe eczema. Only 30 studies (40%) provided information on the duration of the participants' condition. Among those reported, the average duration of disease was 23 years (SD 8.4 years), with a range of 1 to 37 years.
- Of all the included trials, 60 trials provided a co-intervention, mainly consisting of emollients or topical corticosteroids, or both (81.1%).
- The total duration of included trials ranged from 2 weeks for prednisolone to 60 months for methotrexate (MTX), whereas treatment duration varied from a single dose (CIM331, KPL-716) to 60 months of treatment (MTX).
- Most of the included trials were placebo-controlled (48/74; 65%), 34% were head-to-head studies (15% assessed effects of different doses of the same drug), and 1% were multi-armed studies with both an active comparator and placebo.

Qualität der Studien:




Studienergebnisse:

**Proportion of participants who achieved 75% improvement in EASI (EASI75) during short-term follow-up (< 16 weeks)**

**Direct evidence**

**Summary of findings 1. Summary of findings for EASI75 during short-term follow-up**

**Estimates of effects, confidence intervals, and certainty of evidence for the proportion of participants who achieved EASI75 with any systemic intervention compared with placebo in the short term (≤ 16 weeks)**

**Patient or population:** patients with moderate to severe eczema

**Intervention:** dupilumab, tralokinumab, tezepelumab, GBR830, lebrikizumab, ustekinumab, ASN002

**Comparison:** placebo

**Outcome:** achieving 75% improvement in Eczema Area and Severity Index (EASI75); range of follow-up between 4 weeks and 16 weeks

**Settings:** all participants were recruited from a hospital setting

**Network geometry plots:** Figure 4

| **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 |

CI: confidence interval; EASI: Eczema Area and Severity Index (EASI75 = proportion of participants who achieved 75% improvement in EASI score); RR: risk ratio; SUCRA: surface under the cumulative ranking (SUCRA was expressed as a percentage between 0 (when a treatment is certain to be the worst) and 100% (when a treatment is certain to be the best)).

**GRADE Working Group grades of evidence (or certainty of evidence).**
**High quality:** further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** we are very uncertain about the estimate.

## 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.

- 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).

## Proportion of participants who achieve 75% improvement in EASI (EASI75) during long-term follow-up

**Summary of findings 2. Summary of findings for EASI75 during long-term follow-up**

**Estimates of effects, confidence intervals, and certainty of evidence for the proportion of participants who achieved EASI75 with any systemic intervention compared with placebo in the long term (> 16 weeks)**

**Patient or population:** patients with moderate to severe eczema

**Intervention:** dupilumab and ustekinumab

**Comparison:** placebo

**Outcome:** achieving 75% improvement in Eczema Area and Severity Index (EASI75); range of follow-up between 6 months and 13 months

**Settings:** all participants were recruited from a hospital setting

**Network geometry plots:** Figure 4

| **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 during shortterm follow-up (< 16 weeks)

### Direct evidence

**Summary of findings 3. Summary of findings for POEM scores during short-term follow-up**

**Estimates of effects, confidence intervals, and certainty of evidence for Patient-Oriented Eczema Measure (POEM) scores with any systemic intervention compared with placebo in the short term (≤ 16 weeks)**

**Patient or population:** patients with moderate to severe eczema

**Intervention:** dupilumab

**Comparison:** placebo

**Outcome:** change in POEM scores; time of follow-up 16 weeks

**Settings:** all participants were recruited from a hospital setting

**Network geometry plots:** Figure 4

| **Total studies: 6 RCTs**<br>**Total participants:** 2680 | **Relative effect** (95% CI) | **Anticipated absolute effect** (95% CI) | | | **Certainty of evidence** (CiNEMA) | **SUCRA** |
|---|---|---|---|---|---|---|
| | | ***Without* intervention** | ***With* intervention** | **Difference** | | |
| Dupilumab<br>(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 |

## Proportion of participants experiencing serious adverse events (SAEs) during short-term follow-up (< 16 weeks)

### Direct evidence

**Summary of findings 4. Summary of findings for patients with SAEs during short-term follow-up**

**Estimates of effects, confidence intervals, and certainty of evidence for serious adverse events (SAEs) with any systemic intervention compared with placebo in the short term (≤ 16 weeks)**

**Patient or population:** patients with moderate to severe eczema

**Intervention:** dupilumab, tralokinumab, tezepelumab, apremilast, baricitinib, lebrikizumab, PF-04965842, QAW039, Timapiprant

**Comparison:** placebo

**Outcome:** serious adverse events (SAEs); range of follow-up between 1 month and 16 weeks

**Settings:** all participants were recruited from a hospital setting

**Network geometry plots:** Figure 4

| **Total studies: 17 RCTs**<br>**Total participants:** 3972 | **Relative effect (95% CI)** | **Anticipated absolute effect** (95% CI) | | | **Certainty of evidence** (CiNEMA) | **SUCRA** |
|---|---|---|---|---|---|---|
| | | ***Without* intervention** | ***With* intervention** | **Difference** | | |
| QAW039<br>(1 RCT; 76 participants) | **RR 0.09**<br>(0.01 to 0.76)<br>Network estimate | 54 per 1000 | 5 per 1000 | 49 more per 1000<br>(13 more to 53 more) | **Moderate**<br>confidence in estimate due to some concern of within-study bias | 94.2 |
| Dupilumab<br>(9 RCTs; 1663 participants) | **RR 0.37**<br>(0.23 to 0.59)<br>Network estimate | 54 per 1000 | 20 per 1000 | 34 more per 1000<br>(22 more to 44 more) | **Low**<br>confidence in estimate due to major concern of within-study bias | 75.5 |
| Timapiprant<br>(1 RCT; 70 participants) | **RR 0.34**<br>(0.07 to 1.62)<br>Network estimate | 54 per 1000 | 18 per 1000 | 36 more per 1000<br>(33 fewer to 50 more) | **Low**<br>confidence in estimate due to major concern of imprecision | 74 |
| Tezepelumab<br>(1 RCT; 56 participants) | **RR 0.65**<br>(0.11 to 3.77)<br>Network estimate | 54 per 1000 | 35 per 1000 | 19 more per 1000<br>(149 fewer to 48 more) | **Low**<br>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 |

**Network meta-analysis**

- 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.

**Anmerkung/Fazit der Autoren**

Our study aimed to assess the efficacy and safety of different types of systemic immunosuppressive treatments for moderate to severe eczema. We analysed 74 trials including 8177 participants with eczema, comparing 29 systemic immunosuppressive treatments with placebo or other systemic immunosuppressive treatments.

Our primary outcome measures were proportions of participants who achieved 75% improvement in Eczema Area and Severity Index scores (EASI75) and improvement in Patient-Oriented Eczema Measure (POEM) scores; safety outcomes consisted of the proportions of serious adverse events (SAEs) and any infection; however, no more than 19 studies assessed any of the primary outcomes.

Our findings are presented separately for short-term (N 16 weeks) and long-term (> 16 weeks) follow-up and pertain to moderate to severe atopic eczema. However, follow-up was mainly short term, with only three studies following up with participants for longer than a year. Ciclosporin was the most investigated systemic treatment (24 trials), followed by dupilumab (12 studies).

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.

**Implications for practice**

With high certainty of available evidence, we conclude that dupilumab is the most effective of the biological treatments used to treat people with moderate to severe eczema, based on short-term NMA of EASI75 and POEM. Dupilumab is safer than other agents based on short-term safety data (N 16 weeks).

It is not currently possible to confidently rank the efficacy and safety of conventional immunosuppressive treatments for moderate to severe eczema compared with newer treatments such as biological agents for our primary efficacy and safety outcomes due to limited data.

Based on NMA, when compared to placebo, dupilumab increases the proportion of participants who achieve EASI75 and improves POEM score in the short term (high-certainty evidence). We are uncertain of the effect of dupilumab on EASI75 in the long term due to very low-certainty evidence. In addition, lack of long-term outcome data after cessation of immunosuppressive treatment renders difficulty in drawing conclusion on the long-term efficacy of any systemic treatment.

Based on NMA, when compared to placebo, tralokinumab may increase the proportion of patients who achieve EASI75 in the short term. Studies evaluating tralokinumab did not assess this outcome in the long term (low-certainty evidence).

Due to very low-certainty evidence, we are not certain of the effect of ustekinumab on the proportion of participants achieving EASI75 in the short or long term. This is based on NMA and comparison of ustekinumab to placebo.

Due to low- or very low-certainty evidence, we cannot be sure how other immunosuppressive agents for which our key outcomes were assessed affect the proportion of patients achieving short-term EASI75. These agents were compared against placebo.

The only immunosuppressive agent used to assess improvement in POEM score in the short term was dupilumab. Dupilumab and ustekinumab were the only immunosuppressive agents for which EASI75 was evaluated in the long term.

Based on low- to moderate-certainty evidence, QAW039 and dupilumab show a lower proportion of participants with SAEs assessed in the short term when compared with placebo. However, no difference is seen in the proportion of participants with SAEs assessed in the short term when other immunosuppressive agents are compared to placebo (low- to very low-certainty evidence).

Based on low- or very low-certainty evidence, we found no evidence of a difference in risk of any infection (measured in the short or long term) or in the proportion of participants with SAEs assessed in the long term when immunosuppressive agents were compared with placebo.

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

## 3.2 Systematische Reviews

**Kritsanaviparkporn, C. et al., 2021 [11].**

Efficacy of moisturizers in paediatric atopic dermatitis: A systematic review and meta-analysis of randomised controlled trials.

**Fragestellung**

to investigate the knowledge gap regarding the efficacy of moisturizer in young patients.

**Methodik**

Population:

- participants age ≤15 years old with atopic dermatitis

Intervention:

- any type of topical moisturizer

Komparator:

- no moisturizer treatment
  - Cointervention such as cleansing gel, bodywash, topical corticosteroid, topical calcineurin inhibitor, antibiotics or antihistamine were allowed if both groups were administered the same agent

Endpunkte:

- time to flare in days after the disease has been controlled with moisturizer therapy, risk of relapse after each month of latency and rate of remission (defined as flare-free period of greater or equal to three months), alleviation of global disease severity, individual signs and symptoms and improvement in quality of life

Recherche/Suchzeitraum:

- Embase, Ovid Medline, Web of Science, Cochrane Database of Controlled Trials (CENTRAL), CINAHL, GREAT and DARE for relevant randomised controlled trials from inception to July 31, 2020

Qualitätsbewertung der Studien:

- GRADE approach

**Ergebnisse**

Anzahl eingeschlossener Studien:

- Six trials were included (intervention n= 436; control n= 312)

## Charakteristika der Population:

**Table 1:Characteristics of studies included for quantitative analyses**

| Author and year | Study design | Study duration (months) | Number (intervention, control) | Baseline characteristics | | Treatment Arms | | | | Conflict of interest |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Age (mean years) | Gender, M (%) | Intervention | | Placebo/ vehicle | Cointervention in both groups | |
| | | | | | | Description | Regimen | | | |
| Giordano-Labadie *et al.*, 2006. France | Multicentre, open label, | 2 | 37, 39 | 3.92 | NR | Exomega milk® | Twice daily over whole body | None | Cleansing bar (A-Derma®) | None declared |
| Grimalt *et al.*, 2007. France | Multicentre, open label, | 1.5 | 91, 82 | 5.96 | 50.3 | Exomega milk® | Twice daily over whole body | None | Hygiene product (not specified) | Pierre Fabre |
| Weber *et al.*, 2015. Germany | Single centre, open label, | 6 | 21,24 | 3.55 | 53.3 | Eucerin® Eczema Relief Body Crème | Once daily over whole body | None | Hypoallergenic Cleanser (by Beiersdorf Inc. Wilton, CT) | None declared |
| Bianchi *et al.*, 2016. Italy | Multicentre, open label, | 1 | 28, 27 | 2.5 | NR | Avène Xeracalm balm | Twice daily over whole body | None | Hygeine product (Trixera) | Pierre Fabre |
| Ma *et al.*, 2017. China | Single centre, single blinded, | 3 | 32, 32 | 5.4 | 42.1 | Cetaphil® Restoraderm ® moisturizer | Twice daily over whole body | None | Cetaphil® Restoraderm® body wash | Galderma R&D |
| Tiplica *et al.*, 2017. Romania | Multicentre, Open label, Three arms | 3 | Arm 1:111, Arm 2: 116, Control:108 | 4.10 | 48.1 | Arm 1: Dexeryl® Arm 2: Atopiclair® | Arm 1: Twice daily over whole body Arm 2: Three times daily on affected or previous affected skin | None | None | Pierre Fabre |

## Qualität der Studien:

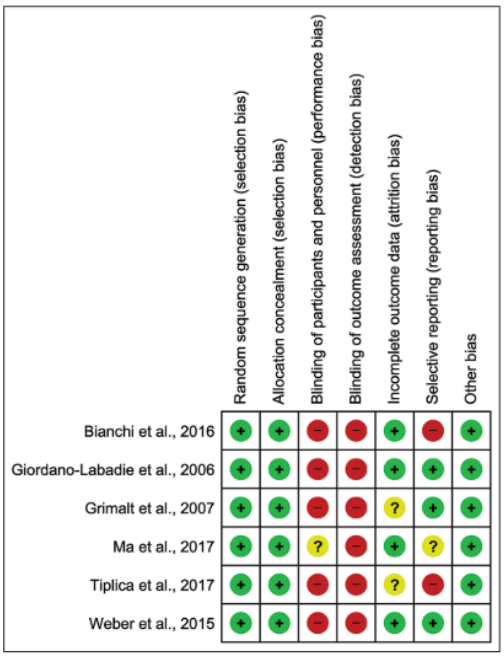



**Figure 2:**Risk of bias summary: review authors' judgments about each risk of bias item for each included study

## Studienergebnisse:

- Moisturizer use extended time to flare by 13.52 days (95% confidence interval 0.05–26.99, $I^2$ 88%).

- Greater reduction in risk of relapse was observed during the first month of latency (pooled risk ratio 0.47, 95% confidence interval 0.31–0.72, $I^2$ 28%) compared to the second and third months (pooled risk ratio 0.65, 95% confidence interval 0.47–0.91, I2 35% and pooled risk ratio 0.63, 95% confidence interval 0.47–0.83, I2 33%, respectively).
- Treated patients were 2.68 times more likely to experience a three–six months remission (95% confidence interval1.18–6.09, I2 56%).
- Moisturizer minimally improved disease severity and quality of life.

**Fazit der Autoren**

Moisturizers are effective at prolonging remission and reducing risk of relapse but may have limited efficacy in improving disease severity and quality of life in paediatric atopic dermatitis. Despite our findings, high quality randomised controlled trials with standardised designs are warranted to confirm the effectiveness of moisturizers in the young.

**Agache I et al., 2021 [3].**
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:

- Snast I et al., 2018 [19]. Are Biologics Efficacious in Atopic Dermatitis? A Systematic Review and Meta-Analysis

**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:

- The SR for the efficacy and safety included seven RCTs

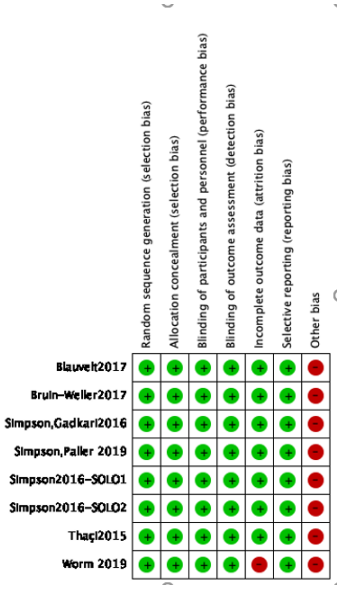
Population

| Author, Year, trial number, and name | Study design (Number of subjects included) | Age (years) Placebo vs. Dupilumab | Population | Intervention | Control | Follow up |
|---|---|---|---|---|---|---|
| Blauvelt 2017<br>NCT02260986<br>LIBERTY AD CHRONOS | Multicenter<br>RCT<br>(N=421) | Mean (95% CI)<br>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<br>NCT01859988<br>TROPOS | Multicenter<br>RCT<br>(N=125) | Mean (SD)<br>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<br>Simpson, Eric 2017<br>NCT02277743<br>SOLO 1 | Multicenter<br>RCT<br>(N=448) | Median (IQR)<br>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<br>Simpson,Eric 2017<br>NCT02277769<br>SOLO 2 | Multicenter<br>RCT<br>(N=469) | Median age (IQR)<br>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<br>NCT02755649<br>LIBERTY AD CAFE | Multicenter<br>RCT<br>(N=215) | Median (IQR)<br>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<br>NCT03054428<br>LIBERTY AD ADOL | Multicenter<br>RCT<br>(N= 167) | Mean (SD)<br>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<br>NCT02395133<br>LIBERTY AD SOLO-CONTINUE | Multicenter<br>RCT<br>(N= 252) | median (IQR)<br>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;

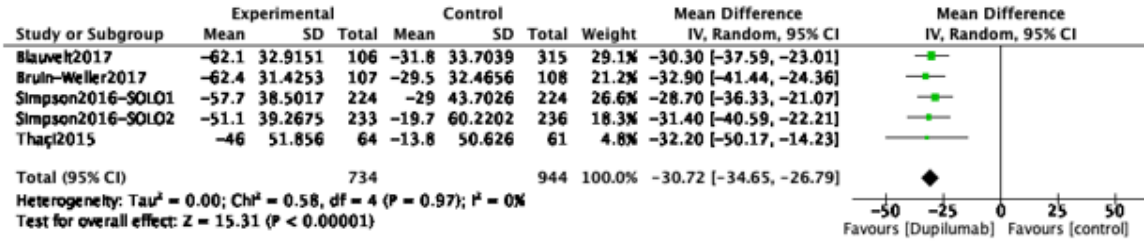
- The RCTs included in the SR evaluated 1678 adults and 167 adolescents with moderate-to-severe AD inadequately controlled by topical treatment. Follow-up under treatment ranged from 16 weeks36,37,39,40 to 1 year.38 One RCT recruited responders from SOLO trials and continued the intervention for another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

Qualität der Studien:



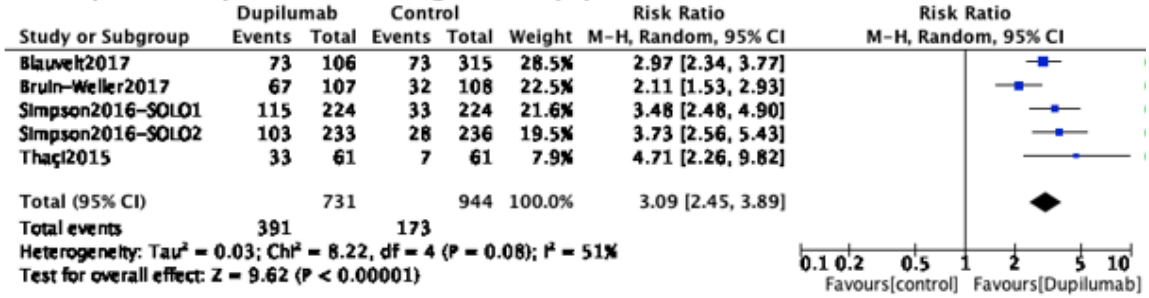

Studienergebnisse:

Scoring Atopic Dermatitis (SCORAD) score

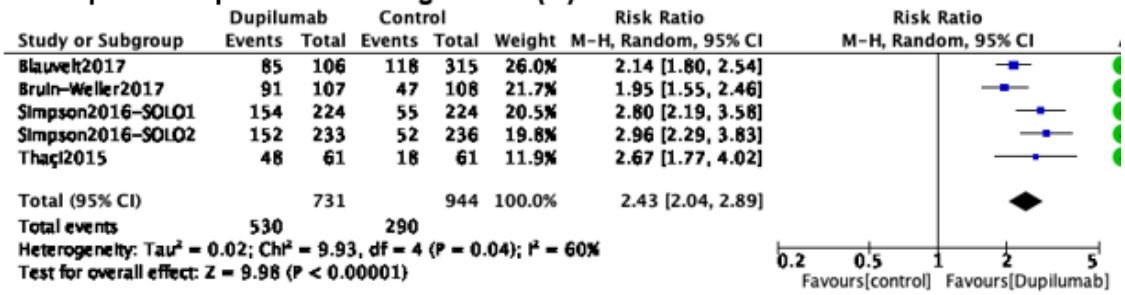



- Eczema Area and Severity Index (EASI)

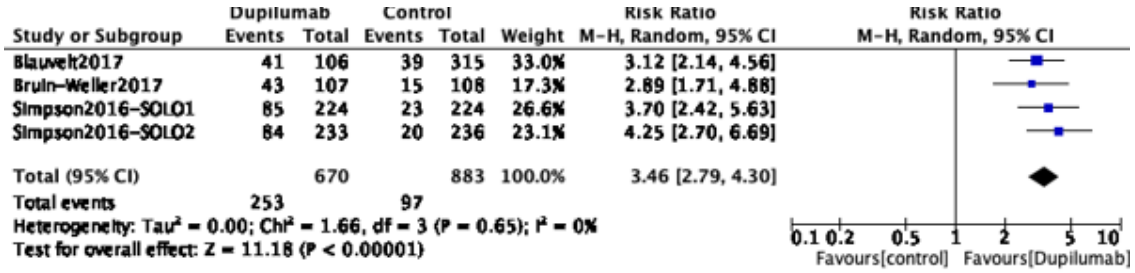
**2.1 Proportion of patients achieving EASI-75 (%)**



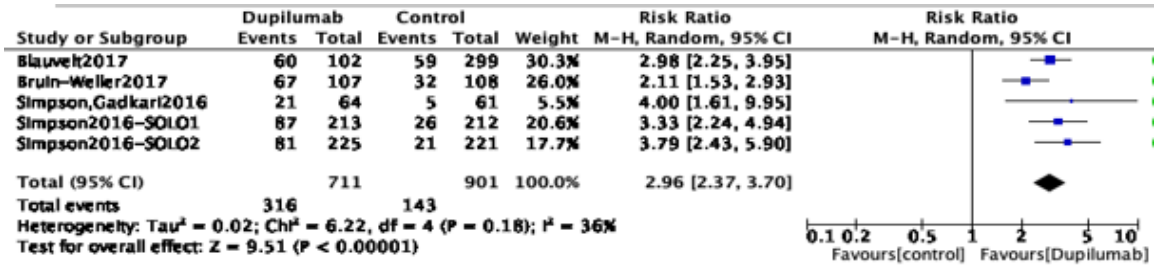

**2.2 Proportion of patients achieving EASI-50 (%)**



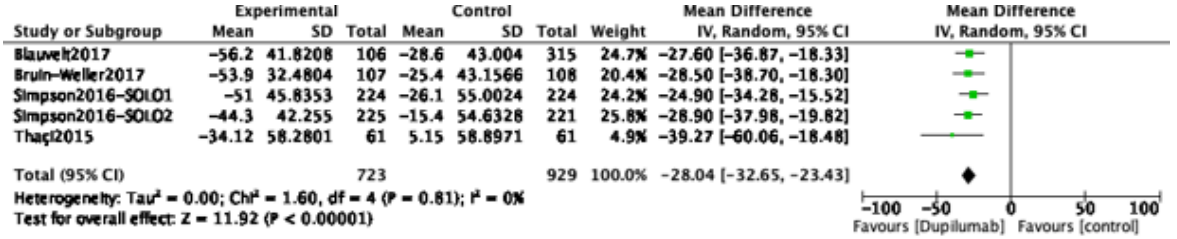

- IGA score achieved 0/1 and reduction of ≥2 points from baseline



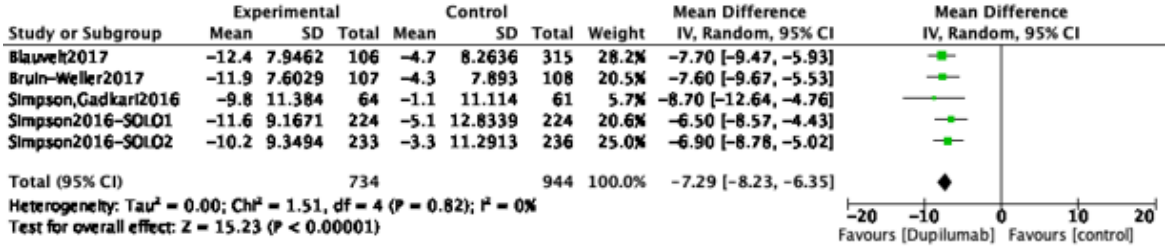

- Pruritus
  - Improvement in peak score on numerical rating scale (NRS) for pruritus ≥ 4 points



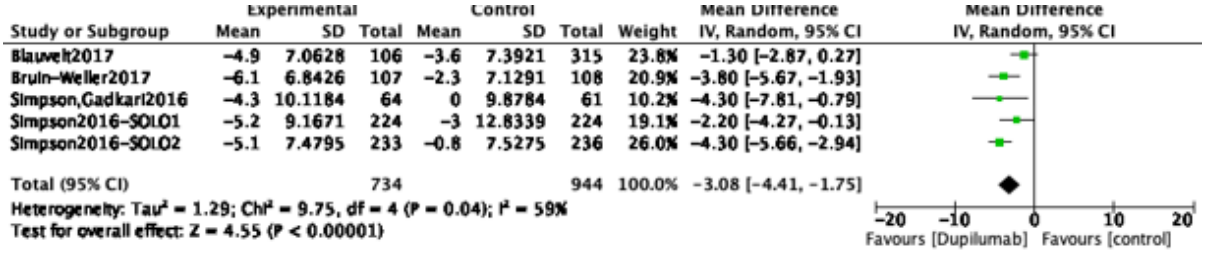

  - Peak pruritus NRS score (LS mean % change from baseline)



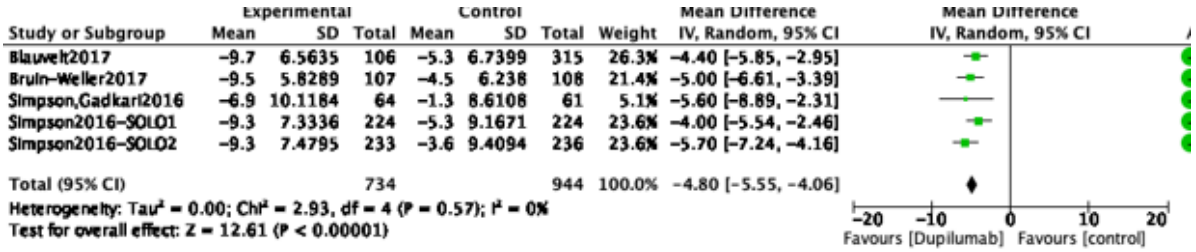

- Patient-Oriented Eczema Measure



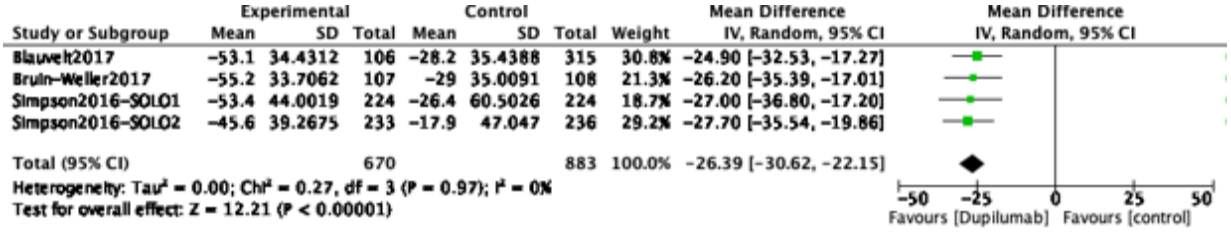

- Hospital Anxiety and Depression Scale (HADS)



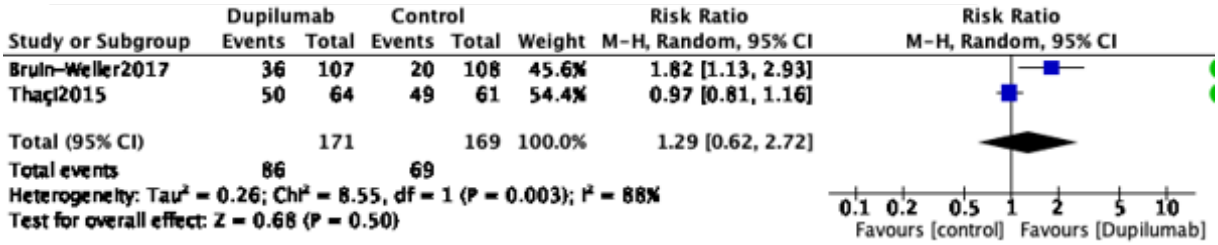

- Quality of life measured by Dermatology Life Quality Index (DLQI)




- Global Individual Signs Score (GISS)




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




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

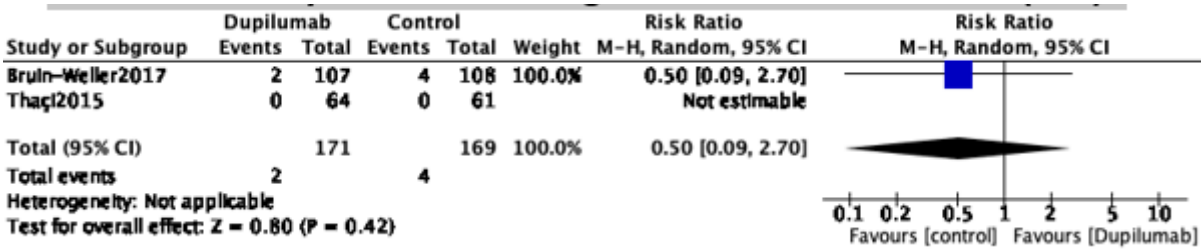



TABLE 3 Summary of evidence for the outcomes of interest. Adult atopic dermatitis population: Dupilumab efficacy and safety compared to standard of care

| 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<br>Assessed with least square (LS) mean % change from baseline | 1678 (5 RCTs)[1,2,3,4]<br>16-52 wk | ⨁⨁⨁⨁ HIGH[5,a,b] | – | – | MD - 30.72% (−34.65 to −26.79)[d] |
| EASI-75<br>Assessed with proportion of patients achieving EASI-75 (%) | 1675 (5 RCTs)[1,2,3,4]<br>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<br>Assessed with improvement in peak score on NRS for pruritus ≥ 4 points | 1612 (5 RCTs)[1,2,4,5]<br>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)<br>Assessed with number of patients reporting AEs | 340 (2 RCTs)[2,3]<br>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)<br>Assessed with number of patients reporting AAEs | 340 (2 RCTs)[2,3]<br>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<br>Assessed with number of patients who received any rescue therapy | 1406 (4 RCTs)[1,2,4]<br>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)<br>Assessed with: LS mean change from baseline | 1678 (5 RCTs)[1,2,4,5]<br>16-52 wk | ⨁⨁⨁⨁ HIGH[6,11,b,g] | – | – | MD −7.29 points (−8.23 to −6.35)[i] |
| Pain<br>Assessed with proportion of patients with no problem of the EQ-5D item 4 (pain/discomfort) | 215 (1 RCT)<br>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)<br>Assessed with the LS mean change from baseline | 1678 (5 RCTs)[1,2,4,5]<br>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)<br>Assessed with: LS mean change from baseline<br>Scale from 0 to 30 | 1678 (5 RCTs)[1,2,4,5]<br>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.

**Abędź N & Pawliczak R, 2019 [1].**

Efficacy and safety of topical calcineurin inhibitors for the treatment of atopic dermatitis: meta-analysis of randomized clinical trials.

**Fragestellung**

This review aimed at determination if TCI are a superior alternative for TCS and comparison of these two therapies in terms of their efficacy and safety.

**Methodik**

Population:

- people diagnosed with AD

Intervention/Komparator:

- TCI vs. TCS treatments

Endpunkte:

- physician's global assessment of improvement, occurrence of AEs, affected Body Surface Area (BSA), Eczema Area and Severity Index (EASI) and modified EASI (mEASI)

Recherche/Suchzeitraum:

- up to 22 February 2018

Qualitätsbewertung der Studien:

- Cochrane approcha / GRADE

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 14 studies / A total number of 7376 participants were included into analysis

Charakteristika der Population:

| Study | Therapy | N | Duration [weeks] | Location | Age of participants |
|---|---|---|---|---|---|
| Bieber 2007 [26] | Tacrolimus 0.03% | 136 | 3 | Multi-centre | Children |
| | Methylprednisolone aceponate 0.1% | 129 | | | |
| Doss 2009 [2] | Tacrolimus 0.1% | 288 | 3 | Multi-centre | Adults |
| | Fluticasone 0.005% | 280 | | | |
| Doss 2010 [24] | Tacrolimus 0.03% | 240 | 6 | Multi-centre | Children |
| | Fluticasone 0.005% | 239 | | | |
| Hofman 2006 [18] | Tacrolimus 0.03% | 121 | 28 | Multi-centre | Children |
| | Hydrocortisone acetate 0.1% and hydrocortisone butyrate 1% | 111 | | | |
| Luger 2001 [25] | Pimecrolimus 1% | 45 | 3 | Multi-centre | Adults |
| | Betamethasone valerate 0.1% | 42 | | | |
| Luger 2004 [23] | Pimecrolimus 1% | 328 | 52 | Multi-centre | Adults |
| | Triamcinolone acetonide 0.1% and hydrocortisone acetate 1% | 330 | | | |
| Mandelin 2010 [22] | Tacrolimus 0.1% | 40 | 52 | Single-centre | Adults |
| | Hydrocortisone butyrate 0.1% and hydrocortisone acetate 1% | 40 | | | |
| Neumann 2008 [27] | Tacrolimus 0.1% | 20 | 87 | Single-centre | Adults |
| | corticosteroids regimen | 20 | | | |
| Reitamo 2002a [26] | Tacrolimus 0.03% or Tacrolimus 0.1% | 189/186 | 3 | Multi-centre | Adults |
| | Hydrocortisone acetate 1% | 185 | | | |
| Reitamo 2002b [15] | Tacrolimus 0.03% or Tacrolimus 0.1% | 193/191 | 3 | Multi-centre | Children |
| | Hydrocortisone butyrate 0.1% | 186 | | | |
| Reitamo 2004 [17] | Tacrolimus 0.03% | 210 | 3 | Multi-centre | Children |
| | Hydrocortisone acetate 1% | 207 | | | |
| Reitamo 2005 [19] | Tacrolimus 0.1% | 487 | 26 | Multi-centre | Adults |
| | Hydrocortisone butyrate 0.1% and hydrocortisone acetate 1% | 485 | | | |
| Sigurgeirsson 2015 [20] | Pimecrolimus 1% | 1205 | 260 | Multi-centre | Children |
| | Hydrocortisone acetate 1% and hydrocortisone butyrate 0.1% | 1213 | | | |
| Sikder 2005 [21] | Tacrolimus 0.03% | 15 | 4 | Multi-centre | Children |
| | Clobetasone butyrate 0.05% | 15 | | | |

Qualität der Studien:

- The methodological quality of 14 trials, based on risk of bias assessment, was good. All studies were free of other sources of bias and did not report their outcomes selectively. Eleven out of 14 trials were investigator-blinded ones, in 12 blinding of participants or personnel were described. Only two studies did not mention any operation to deal with incomplete outcome data. Random sequence generation was not described in one trial. Allocation concealment was not reported in majority of trials. Quality of evidence questions the results of current review. Main outcomes evaluating the efficacy were assessed to provide very low quality of evidence assessed using GRADE score. Adverse events (skin burning or pruritus) outcomes were estimated to have moderate quality.

Studienergebnisse:

- Calcineurin inhibitors were significantly more effective than various potency TCS, neither least potent to lower mid-strength nor mid-strength to potent TCS (RR = 1.24, 95% CI: 1.06–1.44).
- The major AEs were skin burning and pruritus, their incidence was higher in TCI treatment (RR = 3.32, 95% CI: 2.90–3.80; RR = 1.59, 95% CI: 1.34–1.80)
  - (…) Surprisingly, despite age-dependent treatment recommendations, no substantial differences between children and adults were observed in this review. Only one study [17] incorporating children and two incorporating adults [16, 23] revealed TCI treatment to be significantly more effective than TCS only. (…)

**Anmerkung/Fazit der Autoren**

TCI treatment might be slightly more efficient than AD treatment. Contrarily they are associated with more incidences of AEs, such as skin burning or pruritus. Albeit, standardized recommendations for reporting outcomes and interventions should be developed to ease the analysis of a subject in question. Another issue, which impedes the analysis, is still too small number of long-term trials. Along with a greater number of existing trials, more variables, like age of participants, followup time or drug potency, could be accommodated into meta-analysis. Complex analysis, incorporating these variables simultaneously, would provide credible safety and efficacy data, and consequently novel guidance for AD therapy.

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**Drucker AM et al., [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 [20]. 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 [18]. 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 [17]. 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 [14]. 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.

**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:

- The 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. The 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:

- We ultimately included 39 trials with 6360 patients

Charakteristika der Population:

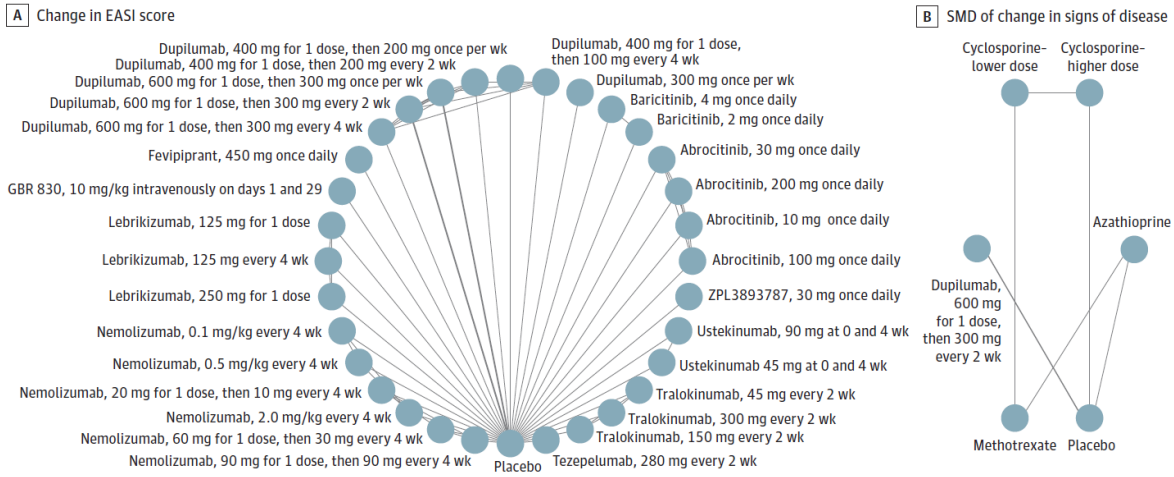
- The included studies evaluated 20 different systemic immunomodulatory therapies and most comparisons were with placebo
- Mean sample size per group was 60 (range, 4-319), the mean proportion of females per trial group was 45%, and the mean or median age in trial groups ranged between 6 and 44 years. 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 39RCTs 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.

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**Siegels D et al., 2020 [16].**

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))<br>▪ Patient-reported symptoms score (eg mean change in Patient Oriented Eczema Measure (POEM))<br>▪ 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)<br>▪ Incidence rate of serious adverse events (SAE) | ▪ Investigator Global Assessment (IGA)<br>▪ Patient Global Assessment (PGA) | ▪ Total withdrawal rates<br>▪ Withdrawal due to AE<br>▪ 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:

- In summary, we included 51 articles that reported on 50 RCTs and 6681 patients from evidence-based clinical practice guidelines, systematic reviews and systematic literature search of RCTs
- 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.

Charakteristika der Population:

- 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.

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:

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] nonvalidated severity scores and VAS pruritus[34,36,53,57] VAS sleeplessness[34,53] EDI and UKSIP[31] | Wahlgren et al, 1990[57] | Short-term (10 days) | Adults |
| | | | | Sowden et al, 1991[34] | Short-term (8 weeks) | Mixed (≥17 years) |
| | | | | Salek et al, 1993[31] | Short-term (8 weeks) | Mixed (≥17 years) |
| | | | | 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] 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 |
| | | | 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[81] | Koppelhus et al, 2014[81] | 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] | Zonneveld et al, 1999[58] | Long-term (52 weeks) | Adults |
| | | | | Czech et al, 2000[21] | Short-term (8 weeks) | Adults |
| | | | DLQI, VAS pruritus and VAS sleeplessness equally effective[21] | | | |
| | | | 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] | Kwon et al, 2013[82] | Short-term (2 weeks) | Mixed (≥12 years) |
| | | | | Jin et al, 2015[79] | Short-term (8 weeks) | Mixed (≥7 years) |
| | | | SCORAD superior with concomitant glucosamine[79] EASI equally effective with "topical agents"[80] | 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] | Beck et al, 2014[19] | Short-term (4 and 12 weeks) | Adults |
| | | | EASI[19,35,47,56,71,73,78,85,86,88] | Thaci et al, 2016[35] Simpson et al, 2016[56] | Short-term (16 weeks) | Adults |
| | | | SCORAD[35,47,56,73,78,85] | Simpson et al, 2016[86] | Short-term (16 weeks) | Adults |
| | | | POEM[35,47,56,71,73,78,85] | Blauvelt et al, 2017[47] | Short- and long-term (16 and 52 weeks) | Adults |
| | | | NRS pruritus[19,35,47,56,71,73,78,85] | Bruin-Weller et al, 2017[73] | Short-term (16 weeks) | Adults |
| | | | DLQI[35,47,56,73] | Blauvelt et al, 2018[71] | Short-term (16 weeks) | Adults |
| | | | cDLQI[85] | Tsianikas et al, 2018[87] | Short-term (12 weeks) | Adults |
| | | | QoLIAD[87] | Guttmann-Yassky et al, 2019[78] | Short-term (16 weeks) | Adults |
| | | | IGA[19] | Simpson et al, 2020[85] | Short-term (16 weeks) | Adolescents |
| | | | GISS[47,56,73,78] | 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

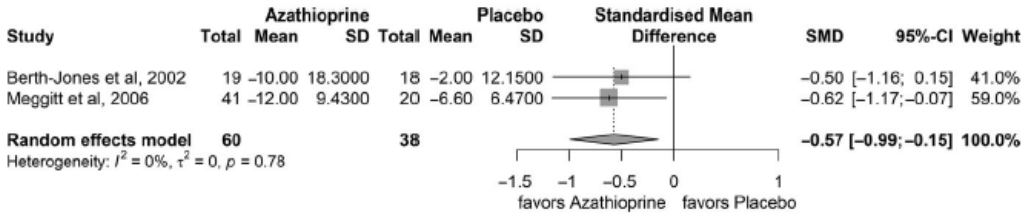
| Treatment | Total n | Number of RCTs | Reported safety | Reference, year | Safety assessment timepoint[a] | Age[b] |
|---|---|---|---|---|---|---|
| Apremilast | 185 | 1 | Cumulative incidence rate of AEs: 70% for apremilast 40mg twice daily, 62% for apremilast 20mg twice daily, 47% for placebo[83]<br>Cumulative incidence rate of SAEs: 5% for apremilast 40mg twice daily, 2% for apremilast 20mg twice daily, 0% for placebo[83]<br>Most common AEs for apremilast: diarrhoea, nausea, headache, nasopharyngitis, upper respiratory tract infection, abdominal discomfort, dyspepsia[83]<br>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]<br>Cumulative incidence rate of SAEs: 0%-10% for AZA, 0% for comparator[28,33]<br>Most common AEs for AZA: myelosuppression, hepatotoxicity, diarrhoea, infections/infestations, gastrointestinal adverse events/nausea/abdominal pain/diarrhoea, headache[20,28,33,74]<br>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]<br>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]<br>Most common AEs for baricitinib: acne, nasopharyngitis, upper respiratory tract inflammation, elevated blood creatine phosphokinase levels and headache[76,84]<br>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]<br>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]<br>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]<br>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]<br>Cumulative incidence rate of SAEs: SAEs occurred in one trial (10% for prednisolone, 0% for comparator CSA)[32]<br>Most common AEs for corticosteroids: not AEs reported[26,32,45]<br>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]<br>Cumulative incidence rate of SAEs: 0%-8% for dupilumab, 0%-13% for placebo[19,35,47,56,71,73,78,85]<br>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]<br>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]<br>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]<br>Cumulative incidence rate of SAEs: not reported[48,50]<br>Most common AEs for IFN-γ: headache, myalgia, chill, constitutional symptoms, disease flare, granulocytopenia, fever, LDH elevation[48,50]<br>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]<br>Cumulative incidence rate of SAEs: 0% for IVIG, 0% for comparator[30,46]<br>Most common AEs for IVIG: fever, chill, headache, nausea, vomiting[30,46,51]<br>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]<br>Cumulative incidence rate of SAEs: not reported[29]<br>Most common AEs for Mepolizumab: ´mild side effects´[29]<br>Most common SAEs for Mepolizumab: no SAEs reported[29] | Oldoff et al, 2005[29] | Short-term (4 weeks) | Adults |

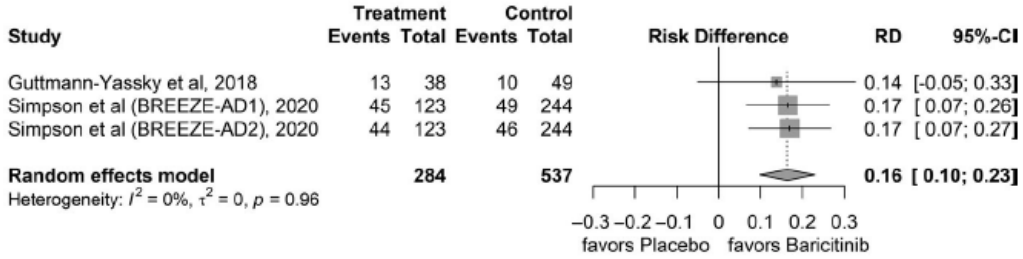
| | | | | | | |
|---|---|---|---|---|---|---|
| Methotrexate (MTX) | 179 | 3 | Cumulative incidence rate of AEs: 82 and 100% for MTX, 79 and 100% for comparators[33,75]<br>Cumulative incidence rate of SAEs: 0% for MTX, 0%-2% for comparators[33,75]<br>Most common AEs for MTX: elevation of liver enzymes, gastrointestinal issues, infections, neuromuscular disorders, lymphocytopenia[33,75]<br>Most common SAEs for MTX: no SAEs reported[22,33,74,75] | Schram et al, 2011[33]<br>Gerbens et al, 2018[74]<br>El-Khalawany et al, 2013[22]<br>Goujon et al, 2017[75] | Long-term (24 weeks)<br>Long-term (5 years)<br>Short-term (12 weeks)<br>Long-term (24 weeks) | Adults<br>Adults<br>Mixed (8-14 years)<br>Adults |
| Omalizumab | 91 | 3 | Cumulative incidence rate of AEs: 77%-94% for omalizumab, 57%-100% for placebo[27,72]<br>Cumulative incidence rate of SAEs: 0%-19% for omalizumab, 0%-19% for placebo[27,49,72]<br>Most common AEs for omalizumab: vertigo, headache, nausea, abdominal pain, allergic reactions, aggravated eczema[27,49,72]<br>Most common SAEs for omalizumab: anaphylaxis (one patient with history of idiopathic anaphylaxis)[72] | Chan et al, 2020[72]<br>Iyengar et al, 2013[49]<br>Heil et al, 2010[27] | Long-term (24 weeks)<br>Long-term (24 weeks)<br>Short-term (16 weeks) | Mixed (4-19 years)<br>Mixed (4-22 years)<br>Mixed (≥12 years) |
| Upadacitinib | 167 | 1 | Cumulative incidence rate of AEs: 74%-79% for upadacitinib, 61% for placebo[77]<br>Cumulative incidence rate of SAEs: 0%-5% for upadacitinib, 2% for placebo[77]<br>Most common AEs for upadacitinib: upper respiratory tract infection, acne, AD worsening[77]<br>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]<br>Cumulative incidence rate of SAEs: 0% for ustekinumab, 0% for placebo[52,55]<br>Most common AEs for ustekinumab: nasopharyngitis, contact dermatitis, worsening of skin infection (eczema herpeticatum)[52,55]<br>Most common SAEs for ustekinumab: no SAEs occurred[52,55] | Khattri et al, 2017[52]<br>Saeki et al, 2017[55] | Long-term (24 weeks)<br>Long-term (24 weeks) | Adults<br>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.

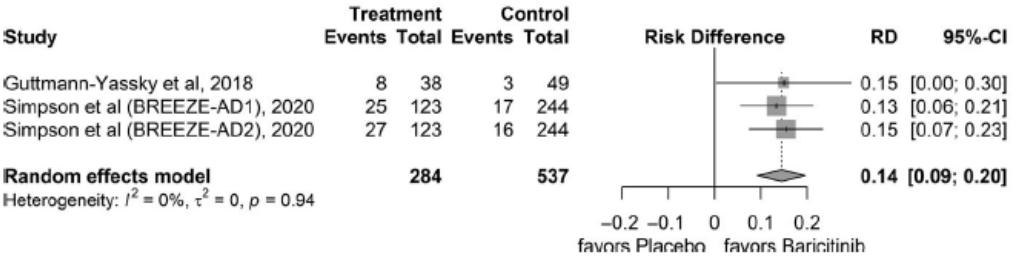
SASSAD Azathioprine at 12 weeks



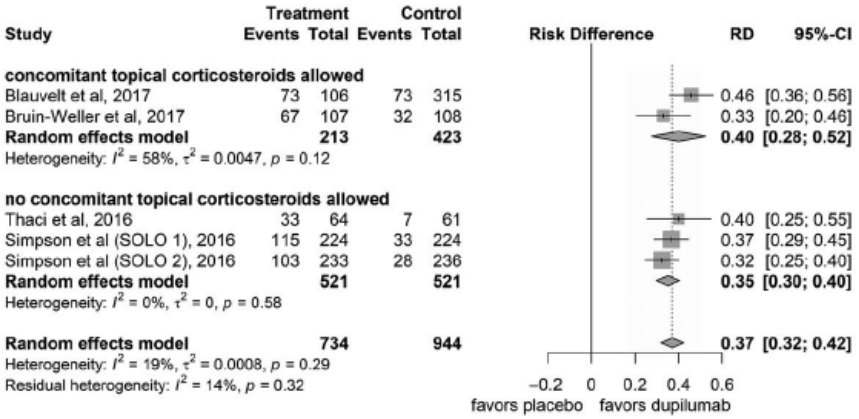

EASI-75 Baricitinib 4 mg every day (topical corticosteroids allowed)



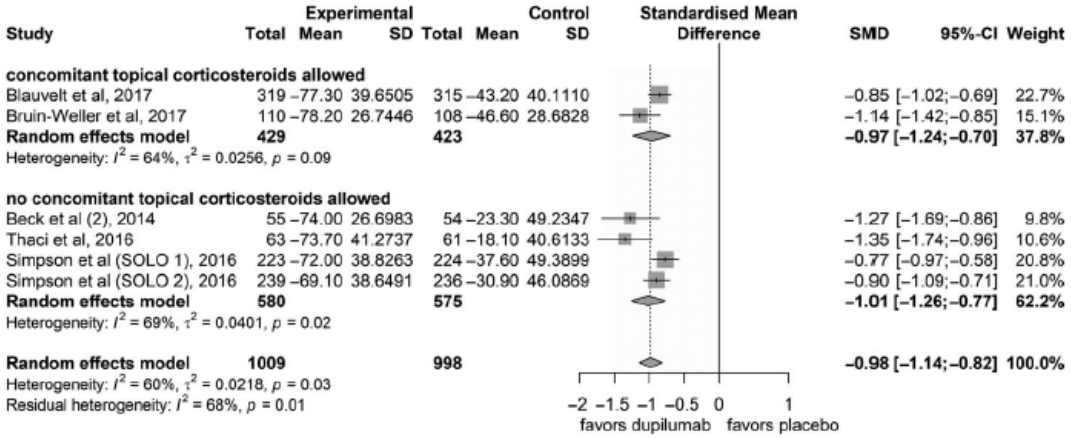

EASI-90 Baricitinib 4 mg every day (topical corticosteroids allowed)



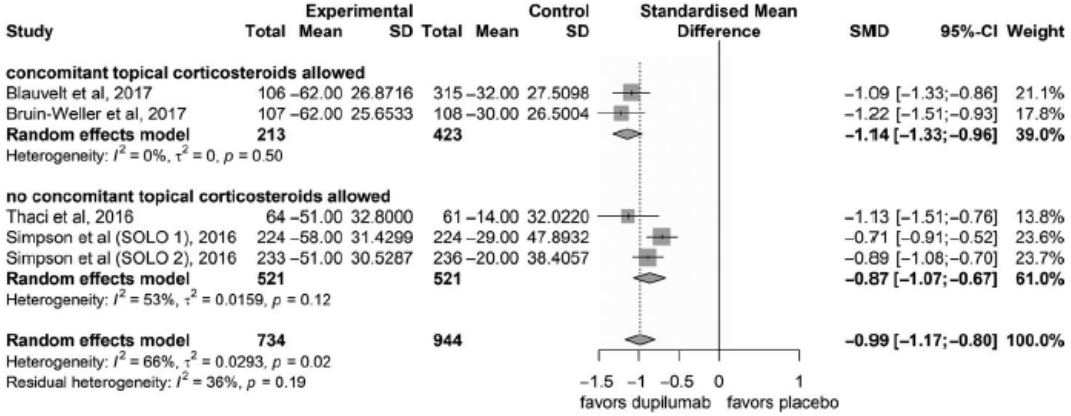

EASI-75 response



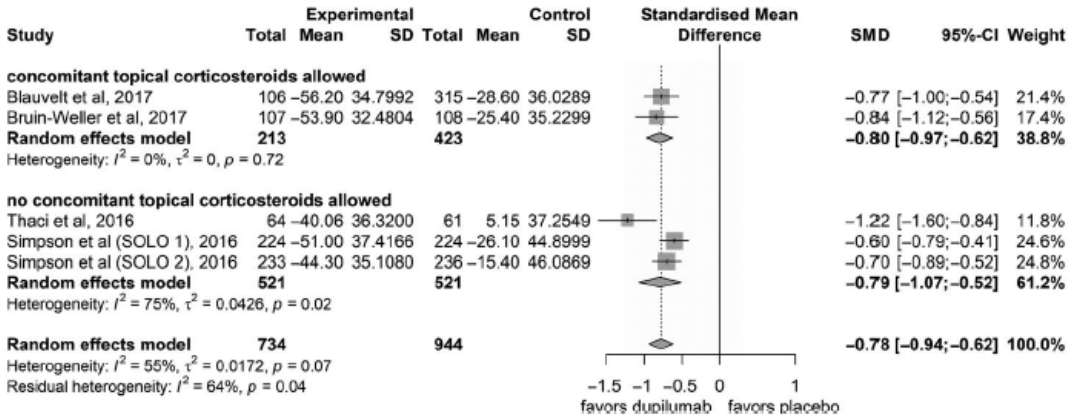
EASI dupilumab 300 mg two every weeks



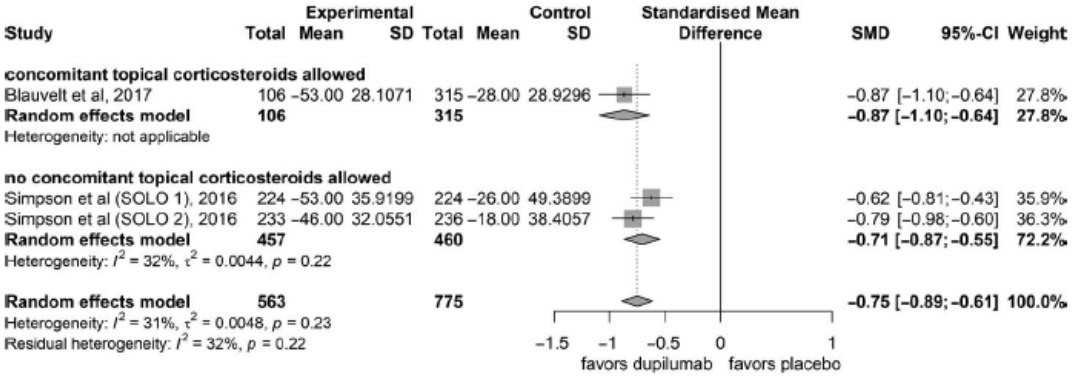

SCORAD mean change



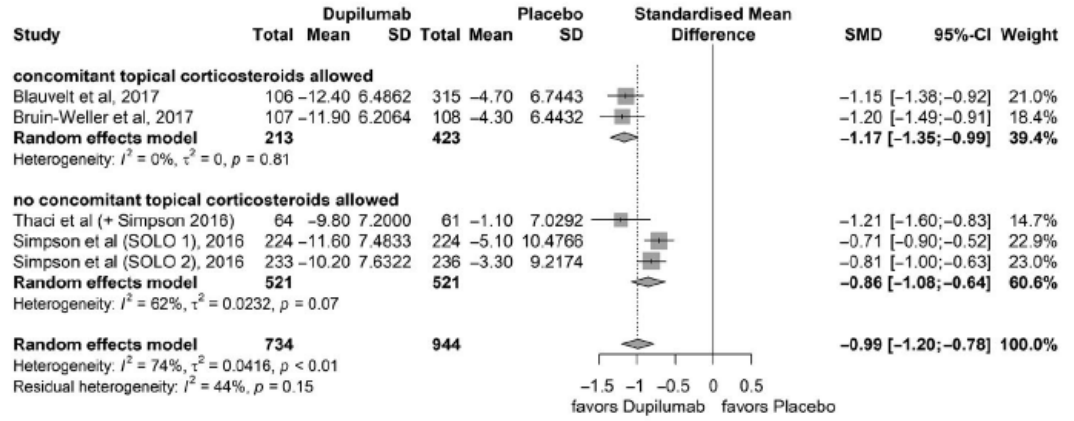

NRS pruritus mean change



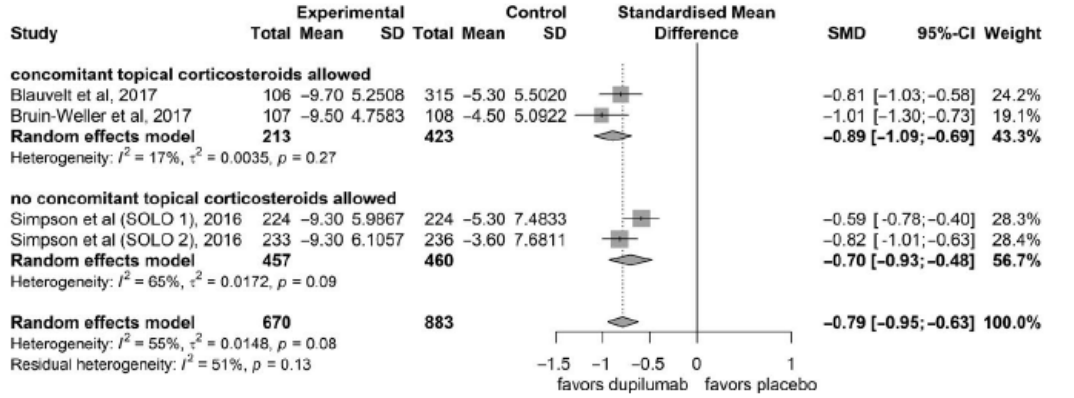
GISS mean change




POEM mean change




DLQI mean change




**Anmerkung/Fazit der Autoren**

This systematic review has identified, critically appraised and summarized 51 publications, including 50 RCTs referring to 13 different systemic treatments for moderate-to-severe AD. The most robust, replicated high-quality trial evidence, was identified for dupilumab (up to one year in adults). Furthermore, robust trial evidence was revealed for AZA, baricitinib and CSA. Only for these four treatments, meta-analyses could be calculated. However, there are limitations for AZA, baricitinib and CSA compared to dupilumab due to lower trial quality, less number of included trials and/or patients. In total, 37 of the included publications are concerned with these treatments. Importantly, the majority of all trial patients were included in the dupilumab trials (dupilumab n = 3529; total n = 6681). Although the first impression may be that 50 trials on 13 interventions form a robust evidence base, we have to conclude that except for dupilumab vs. placebo in adults, a lot of uncertainty still exists regarding the safety and efficacy and safety of all other interventions for patients with moderate-to-severe AD. The main reasons for this are significant limitations in trial design, outcome choice and reporting of trials leading to a situation in which many trials have a high risk of bias, and in which trials cannot be compared. Therefore, evidence-based clinical decision making for patients with moderate-to-severe AD remains, for now, a significant challenge for the EAACI guideline on systemic therapy in atopic dermatitis (in preparation). Given the extensive ongoing clinical trial activity in AD, this space will change rapidly. AD currently has high scientific reference, as new papers are continuously published, such as the systematic review with a network meta-analysis on systemic immunomodulatory therapy of Drucker et al.

**CONCLUSIONS**

This systematic review will be part of the first evidence-based guideline on systemic therapy for AD in Europe, which is intended toprovide recommendations based on higher standards than previous published guidelines for AD.38,39,41-43

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).

## 3.3 Leitlinien

**Agache I et al. 2021 [2].**

*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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76. Worm M, Simpson EL, Thaci D, et al. Efficacy and safety of multiple dupilumab dose regimens after initial successful treatment in patients with atopic dermatitis: a randomized clinical trial. JAMA Dermatol. 2019;156(2):131-143.

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80. Kridin K, Renert-Yuval Y, Guttman-Yassky E, Cohen AD. Alopecia Areata Is Associated with Atopic Diathesis: Results from a Population-Based Study of 51,561 Patients. J Allergy Clin Immunol Pract. 2020;8(4):1323-1328.

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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**

Grundlage der Leitlinie

- 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<br>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<br>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<br>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<br>Extrapolated evidence from studies rated as 2++ |
| D | Evidence level 3 or 4, or<br>Extrapolated evidence from studies rated as 2+, or<br>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.

107 Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2007; 21:606–19.

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

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**Goulden V et al., 2022 [10].**

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.

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**NICE, 2007 [13].**

*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<br>• Mild potency topical corticosteroids |
| Moderate atopic eczema | • Emollients<br>• Moderate potency topical corticosteroids<br>• Topical calcineurin inhibitors<br>• Bandages |
| Severe atopic eczema | • Emollients<br>• Potent topical corticosteroids<br>• Topical calcineurin inhibitors<br>• Bandages<br>• Phototherapy<br>• 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).

**Werfel, T. et al., 2020 [21].**

*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]
- 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)

Verfügbare Biologika ohne Zulassung zur Therapie bei Neurodermitis

**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)

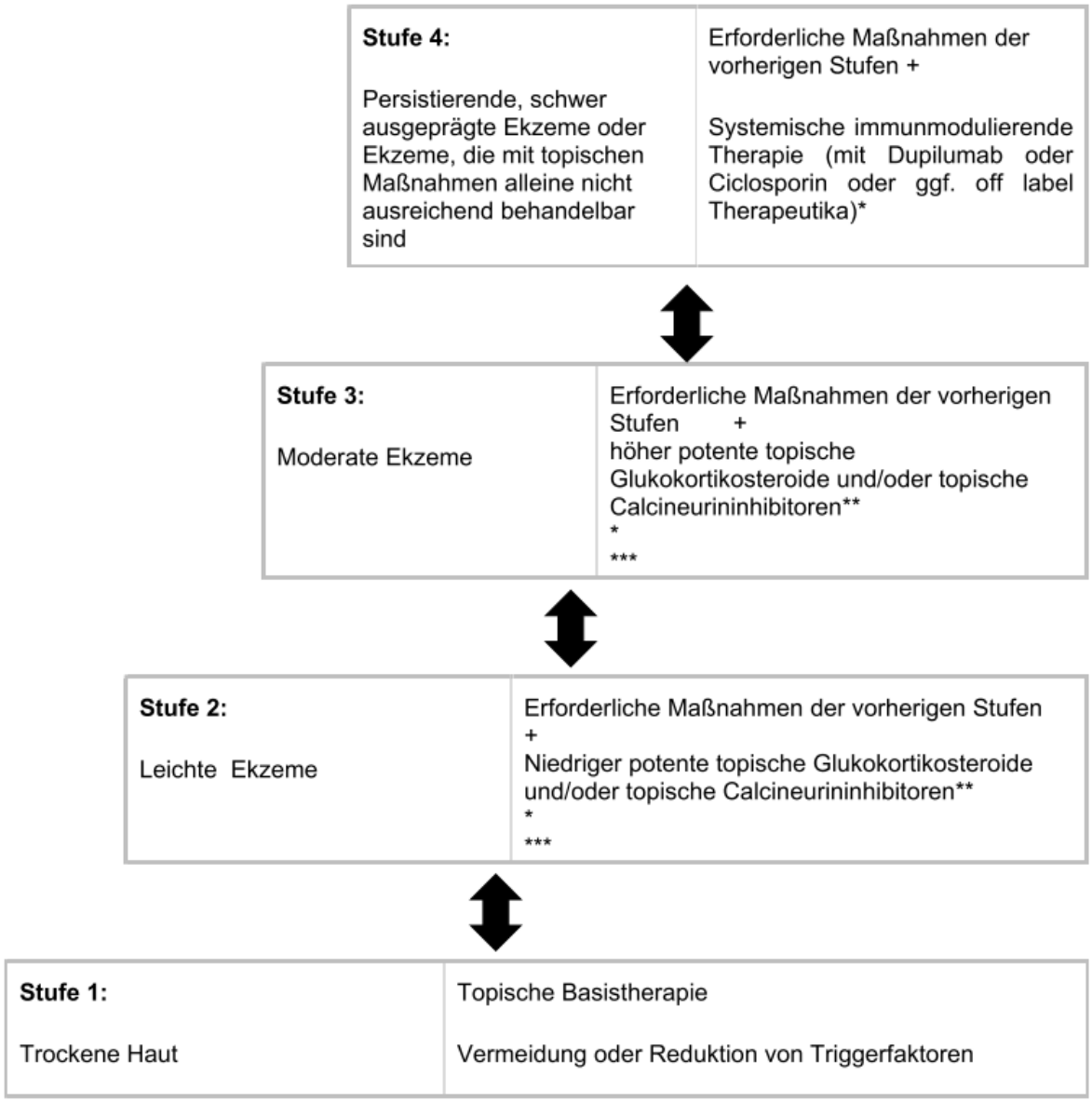



**Abbildung 1: Stufentherapie der Neurodermitis**

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.

**Wollenberg A et al., 2022 [8,24,25].**

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

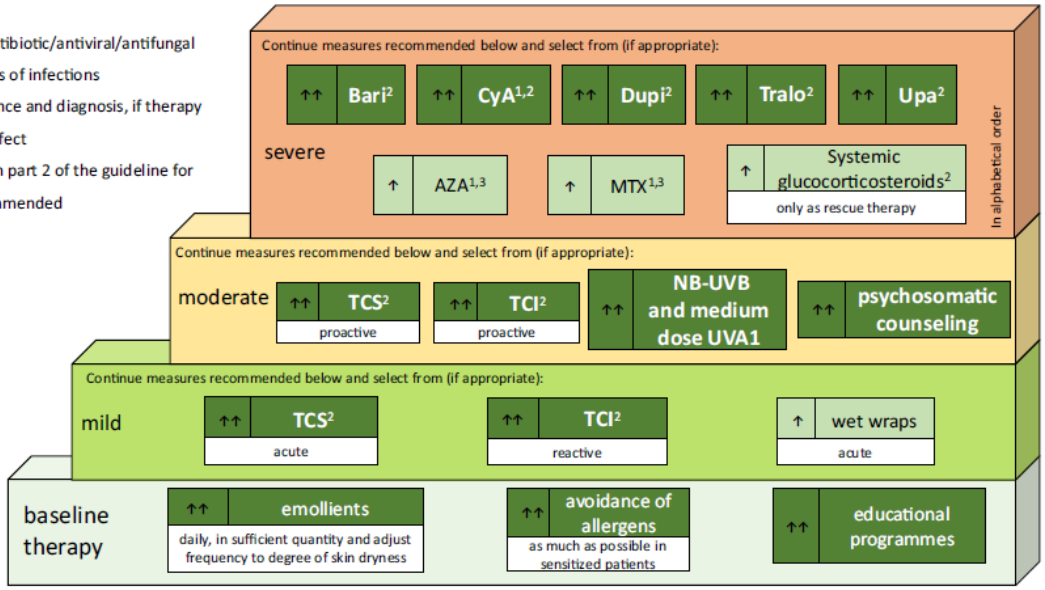
GoR

**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



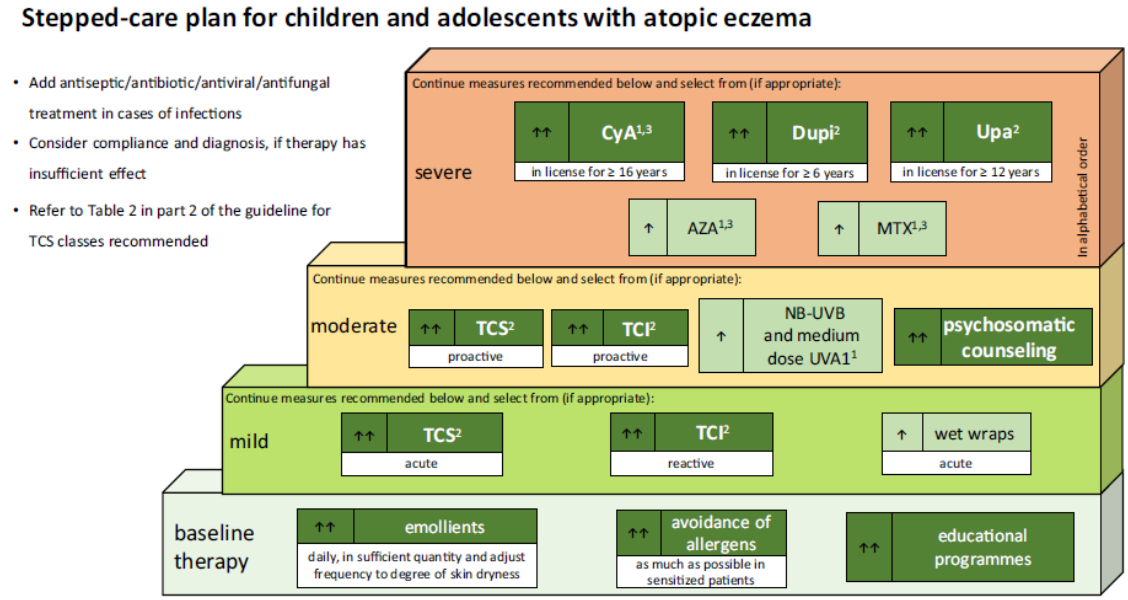

[1] refer to guideline text for restrictions, [2] licensed indication, [3] off-label treatment
↑↑ (dark green) strong recommendation for the use of an intervention / ↑ (light green) weak recommendation for the use of an intervention
For definitions of disease severity, acute, reactive, proactive see 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

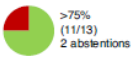
| Symbols | Implications (adapted from GRADE [1]) |
|---|---|
| ↑↑ | We believe that all or almost all informed people would make that choice. |
| ↑ | We believe that most informed people would make that choice, but a substantial number would not. |
| 0 | We cannot make a recommendation. |
| ↓ | We believe 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 [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: 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%<br>Tacrolimus 0.03% | Pimecrolimus 1% |
| **For further information see background text** | class I not suitable for long-term proactive treatment;<br>long-term proactive treatment only class II | acute flare;<br>proactive treatment with TCS class III<br>class IV not for long term daily treatment or head and neck;<br>class IV not recommended for proactive treatment either | acute flare;<br>long-term proactive treatment;<br>especially in face, intertriginous sites, anogenital area | acute flare;<br>especially in face, intertriginous sites, anogenital area |
| **Most important side effects** | skin atrophy<br>telangiectasia<br>striae distensae<br>ecchymosis<br>hypertrichosis<br>perioral dermatitis | skin atrophy<br>telangiectasia<br>striae distensae<br>ecchymosis<br>hypertrichosis<br>perioral dermatitis<br>corticosteroid addiction syndrome<br>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 [18])** |
|---|---|
| ↑↑ | 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] 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] 1 Abstention

## Empfehlungen: Anti-inflammatory treatment

| | | |
|---|---|---|
| **We recommend** the use of topical corticosteroids (TCS) as anti-inflammatory agents.<br>**We recommend** the use of topical calcineurin inhibitors (TCI) as anti-inflammatory agents. | ↑↑ | >75%<br>  <br>(24/26)<br>Expert consensus |
| **We suggest** using anti-inflammatory topical agents according to the fingertip unit rule. | ↑ | >75%<br>  <br>(23/26)<br>Expert consensus |
| **We suggest** the use of wet wraps with diluted (see background text) or low potency topical corticosteroid in acute AE. | ↑ | >50%<br>  <br>(14/22)<br>Expert consensus |
| **We recommend** TCS in AE especially for treatment of acute flares.<br>**We recommend** to note and adequately address patients concerns or fears about corticosteroid side effects.<br>**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<br>  <br>(23/23)<br>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<br>  <br>(23/23)<br>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<br>  <br>(22/22)<br>Expert consensus |

## Empfehlungen: Phototherapy and photochemotherapy

| | | |
|---|---|---|
| **We recommend** narrowband UVB and medium-dose UVA1 for AE patients with moderate-to-severe AE. | ↑↑ | >95%<br>  <br>(24/25)<br>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%<br>  <br>(24/25)[1]<br>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<br>  <br>(25/25)<br>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<br>  <br>(25/25)<br>Expert consensus |
| **We suggest** co-treatment with topical emollients during phototherapy. | ↑ | 100% agreement<br>  <br>(25/25)<br>Expert consensus |
| **We recommend against** the use of prolonged or repeated treatment cycles and maintenance regimens with all phototherapy modalities. | ↓↓ | 100% agreement<br>  <br>(24/24)<br>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<br>  <br>(25/25)<br>Expert consensus |

**Wollenberg, A. et al., 2018 [22,23].**

Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I & part II.

**Zielsetzung/Fragestellung**

- The first part covers methods, patient perspective, general measures and avoidance strategies, basic emollient treatment and bathing, dietary intervention, topical anti-inflammatory therapy, phototherapy and antipruritic therapy
- The second part of the guideline covers antimicrobial therapy, systemic treatment, allergen-specific immunotherapy, complementary medicine, psychosomatic counselling and educational interventions

**Methodik**

*Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz zur systemischen Therapie bei Kindern mit schwerer AD.*

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: nein → This is a consensus-based S2k guideline
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- by March 2017

LoE/GoR

**Table 1** Grades of evidence

| |
|---|
| 1a) Meta-analysis of randomized clinical trials (RCT) |
| 1b) Single RCTs |
| 2a) Systematic review of cohort studies |
| 2b) Single cohort studies and RCTs of limited quality |
| 3a) Systematic review of case–control studies |
| 3b) Single case–control study |
| 4) Case series, case cohort studies or cohort studies of limited quality |
| Recommendations (see Table 2) were classified based on the grade of evidence. |

**Table 2** Classification of strength of recommendation

| Recommendation strength | Evidence grade |
|---|---|
| A | 1a, 1b |
| B | 2a, 2b, 3a, 3b |
| C | 4 |
| D | Expert opinion |

**Table 3** Language of recommendations

| Wording in standard situations | Free text explanation |
|---|---|
| **Must be used** | This intervention should be done in all patients, unless there is a real good reason not to do it |
| **Should be used** | Most expert physicians would do it this way, but some would prefer other possible action |
| **May be used** | It would be correct to do this intervention, but it would also be correct not to do it; the choice depends largely on the specific situation |
| **Is possible** | Most expert physicians would do something else, but it would not be wrong to do it |
| **May be used in selected patients only** | This intervention is not adequate for most patients, but for some patients, there may be a reason to do it |
| **Is not recommended** | Most expert physicians would not choose this intervention, but some specific situation may justify its use |
| **Must not be used** | This intervention is inadequate in most situations |

Sonstige methodische Hinweise

- This is an update of the 2012 guideline on atopic dermatitis. The former, first version of this guideline had been based on the evidence-based national guideline from Germany, the HTA report, as well as the position paper of the ETFAD, which were compared and assessed. The former committee had decided that all these documents fulfilled enough criteria to be used as the base of the first version of the European Guidelines on Treatment of Atopic Eczema.

## Recommendations

**(b) Treatment recommendation for atopic eczema: children**

- For every phase, *additional* therapeutic options should be considered
- Add antiseptics / antibiotics in cases of superinfection
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to guideline text for restrictions, especially for treatment marked with [1]
- Licensed indication are marked with [2], off-label treatment options are marked with [3]

| | |
|---|---|
| **SEVERE: SCORAD >50 / or persistent eczema** | Hospitalization, systemic immunosuppression: cyclosporine A [3], methotrexate [3], azathioprin [3], mycophenolate mofetil [1,3] |
| **MODERATE: SCORAD 25-50 / or recurrent eczema** | Proactive therapy with topical tacrolimus [2] or class II or III topical glucocorticosteroids [3], wet wrap therapy, UV therapy (UVB 311 nm) [1], psychosomatic counseling, climate therapy |
| **MILD: SCORAD <25 / or transient eczema** | Reactive therapy with topical glucocorticosteroids class II [2] or depending on local cofactors: topical calcineurin inhibitors [2], antiseptics incl. silver, silver coated textiles |
| **BASELINE: Basic therapy** | Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests) |

**Table 4** Topical drugs for treatment of atopic eczema

| | TCS class II | TCS class III | Tacrolimus | Pimecrolimus |
|---|---|---|---|---|
| Overall recommendation | default treatment | short-term flare treatment | long-term maintenance | children, facial lesions |
| Most important side-effects | Skin atrophy<br>Telangiectasia<br>Striae distensae | Skin atrophy<br>Telangiectasia<br>Striae distensae | Initial burning/stinging | Initial burning/stinging |
| Suitable for long-term treatment | Sometimes | No | Yes | Yes |
| Suitable for proactive therapy | Yes† | Yes† | Yes‡ | No |
| Suitable for children >2 years of age | Yes | Sometimes, see text | Yes‡ | Yes‡ |
| Suitable for babies <2 years of age | Yes | Diluted use | Yes† | Yes† |
| Suitable during pregnancy | Yes | Yes | Possible with strict indication† | Possible with strict indication† |
| Suitable during lactation | Yes | Yes | Possible with strict indication† | Possible with strict indication† |

†Off label use; ‡Licensed use.

**Table 4** Systemic drugs for treatment of severe atopic eczema

| | Cyclosporine | Methotrexate | Azathioprine | Mycophenolic acid | Corticosteroids | Dupilumab |
|---|---|---|---|---|---|---|
| Overall recommendation | ++ acute flare intervention | ++ long-term maintenance | Can be used long term | ++ little toxicity | Outdated‡ | Long-term maintenance |
| Time to respond (weeks)§ | 2 | 8–12 | 8–12 | 8–12 | 1–2 | 4–6 |
| Time to relapse (weeks) | <2 | >12 | >12 | >12 | <2 | >8 |
| Most important side-effects | Serum creatinine ↑ blood pressure ↑ | Haematological liver enzymes ↑ gastrointestinal | Haematological liver enzymes ↑ gastro-intestinal | Haematological skin infections gastro-intestinal | Cushing's osteoporosis diabetes | Conjunctivitis |
| Starting dose adult | 4–5 mg/kg/day‡ | 5–15 mg/week | 50 mg/day‡ | MMF 1–2 g/day (EC-MPA 1.44 g/day) | 0.2–0.5 mg/kg/day | 600 mg loading dose |
| Maintenance dose adult | 2.5–3 mg/kg/day | Most often 15/week; can increase to max 25 mg/week | 2–3 mg/kg/day† | MMF 2–3 g/day (EC-MPA 1.44 g/day) | Not for maintenance‡ | 300 mg/2 weeks |
| Starting dose children | 5 mg/kg/day | 10–15 mg/m$^2$/week | 25–50 mg/day | MMF 20–50 mg/kg/day | 0.2–0.5 mg/kg/day | No data yet |
| Maintenance dose children | 2.5–3 mg/kg/day | Increase 2.5–5 mg/week, decrease 2.5 mg/week to effective/lowest effective dose | 2–3 mg/kg/day† | Increase daily total dose by 500 mg every 2–4 weeks up to 30–50 mg/kg/day | Not for maintenance‡ | No data yet |
| Pregnancy | Possible | Teratogenic, absolutely contraindicated | Conflicting data, possible with strict indication | Teratogenic, absolutely contraindicated | Possible | No data yet |
| Fathering | Possible | Little information, conflicting data, contra-indicated | Little information, possible with strict indication | Conflicting data | Possible | No data yet |

†TPMT heterozygote 1–1.5 mg/kg/day. ‡See full text. §Time to reach most of expected full response.
EC-MPS, enteric-coated mycophenolic sodium; MMF, mycophenolate mofetil.

# 4 Detaillierte Darstellung der Recherchestrategie

**Cochrane Library - Cochrane Database of Systematic Reviews (Issue 09 of 12, September 2022) am 22.09.2022**

| # | 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 Sep 2017 to present, in Cochrane Reviews |

**Systematic Reviews in PubMed am 22.09.2022**

verwendete Suchfilter:
*Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.*

| # | 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 (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] |

| # | Suchfrage |
|---|---|
| | OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab])))))) |
| 6 | (#5) AND ("2017/09/01"[PDAT] : "3000"[PDAT]) |
| 7 | (#6) NOT "The Cochrane database of systematic reviews"[Journal] |
| 8 | (#7) NOT (retracted publication [pt] OR retraction of publication [pt]) |

**Leitlinien in PubMed am 22.09.2022**

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 ("2017/09/01"[PDAT] : "3000"[PDAT]) |
| 7 | (#6) NOT (retracted publication [pt] OR retraction of publication [pt]) |

**Iterative Handsuche nach grauer Literatur, abgeschlossen am 23.09.2022**

- 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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# Anhang

*Abbildung 1: Abbildungsbeschriftung*

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

**2022-B-238**

**Kontaktdaten**

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

Stand: 11.10.2022

Indikation gemäß Beratungsantrag

Behandlung der mittelschweren bis schweren atopischen Dermatitis bei Kindern und Jugendlichen zwischen 2 und 18 Jahren, die auf eine topische Therapie unzureichend angesprochen haben oder eine Unverträglichkeit gegen eine entsprechende Behandlung aufweisen.

**Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?**

Die Therapie der atopischen Dermatitis richtet sich nach der Schwere und dem Ausmaß der Krankheit (Stufentherapie). Die Therapie beinhaltet grundsätzlich unabhängig von der Ausprägung und dem Stadium eine lokale Behandlung der Haut (u. a. mit Harnstoff oder Glycerin) als Basistherapie und eine Reduktion von möglichen Provokationsfaktoren (1-2). Die Basistherapie (Hautpflege) mit Pflegesalben, Pflegecremes und Pflegelotionen sowie Badeölen verhindert ein Austrocknen der Haut. Diese Therapie der Hautpflege muss regelmäßig bei atopischer Dermatitis, auch bei systemischer Therapie, angewendet werden.

Die spezifische Therapie erfolgt zur Entzündungshemmung mit topischen Kortikosteroiden (Hydrocortison, Prednicarbat oder Methylprednisolon) oder mit topischen Calcineurininhibitoren (Tacrolimus, Pimecrolimus). Behandelt werden die befallenen Hautareale und nicht selten wird eine Intervalltherapie nach Abheilung der Läsionen angeschlossen (1-2). Kürzlich wurde Pimecrolimus (Elidel® 10 mg/g Creme) auch für Kinder ab drei Monaten bis zwei Jahren zugelassen, wenn eine Behandlung mit topischen Kortikosteroiden entweder nicht angebracht oder nicht möglich ist (3).

**Krankheitsspezifische entzündungshemmende systemische Therapie**

Eine systemische antiinflammatorische Therapie kann bei schwer betroffenen Patienten mit atopischer Dermatitis angezeigt sein; bei Erwachsenen werden etwa 10 % aller Patienten zeitweilig systemisch behandelt, bei Kindern wurde die Indikation zur systemischen antiinflammatorischen Therapie bisher nur ausnahmsweise gestellt (2).

Die Kurzzeittherapie mit oralen Kortikosteroiden (von drei Tagen bis zu drei Wochen) kann in begründeten Fällen zur Unterbrechung eines akuten Schubes bei schweren Formen einer atopischen Dermatitis eingesetzt werden. Wegen des ungünstigen Nebenwirkungsprofils wird eine längerfristige Therapie über diesen Zeitraum hinaus mit systemischen Kortikosteroiden nicht empfohlen (1-2). Nicht unproblematisch ist ein gewisser Rebound-Effekt nach Beendigung der systemischen Therapie mit Kortikosteroiden.

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Zur systemischen Therapie bei schweren Verlaufsformen gibt es für Kinder und Jugendliche ab sechs Jahren seit kurzer Zeit mit Dupilumab einen neuen, zugelassenen Wirkstoff. Für Kinder im Alter von sechs Monaten bis fünf Jahren ist aber nur eine Kurzzeittherapie mit Kortikosteroiden (z. B. Prednisolon) in der Indikation schwere atopische Dermatitis zugelassen:

**Prednisolon** (Prednisolon Stada® Tabletten) ist u. a. zugelassen zur Behandlung von Ekzemerkrankungen, z. B. atopisches Ekzem, bei Kindern, Jugendlichen und Erwachsenen (4). In der Behandlung eines schweren akuten Schubes wird Prednisolon 1–2 mg/kg pro Tag für wenige Tage empfohlen und dann ein Ausschleichen der Therapie.

**Dupilumab** (Dupixent® 200 mg Injektionslösung in einer Fertigspritze/Fertigpen) ist u. a. zugelassen zur Behandlung der mittelschweren bis schweren atopischer Dermatitis bei Erwachsenen und Jugendlichen ab zwölf Jahren, die für eine systemische Therapie in Betracht kommen (5). Bei Kindern von sechs bis elf Jahren ist Dupilumab zugelassen zur Behandlung einer schweren atopischen Dermatitis, wenn sie für eine systemische Therapie in Betracht kommen (5). Die Dosierung von Dupilumab beträgt bei Erwachsenen 600 mg als Anfangsdosis (zwei Injektionen zu je 300 mg), gefolgt von 300 mg alle zwei Wochen als subkutane Injektion. Jugendliche (12 bis 17 Jahre) erhalten ab 60 kg Körpergewicht die gleiche Dosierung wie Erwachsene und unter 60 kg Körpergewicht 400 mg als Anfangsdosis und 200 mg als Erhaltungsdosis. Kinder (sechs bis elf Jahre) erhalten bei einem Körpergewicht 15 kg bis < 60 kg 300 mg (eine Injektion zu 300 mg) an Tag 1, gefolgt von weiteren 300 mg an Tag 15, sowie 300 mg alle vier Wochen. Bei Patienten mit einem Körpergewicht von 15 kg bis unter 60 kg kann nach Ermessen des Arztes die Dosierung auf 200 mg alle zwei Wochen erhöht werden.

Die Sicherheit von Dupilumab wurde in einer Studie an 250 Patienten im Alter von 12 bis 17 Jahren mit mittelschwerer bis schwerer atopischer Dermatitis (AD-1526) untersucht. Das bei diesen Patienten bis einschließlich Woche 16 beobachtete Sicherheitsprofil von Dupilumab war mit dem Sicherheitsprofil in Studien bei Erwachsenen mit atopischer Dermatitis vergleichbar (5). Die Wirksamkeit und Sicherheit von Dupilumab in Kombination mit topischen Kortikosteroiden bei Kindern wurden in einer multizentrischen, randomisierten, doppelblinden, placebokontrollierten Studie (AD-1652) mit 367 Patienten im Alter von sechs bis elf Jahren über 16 Wochen untersucht (6).

Mit Upadacitinib wurde kürzlich ein JAK-Kinaseinhibitor zur systemischen Therapie bei Jugendlichen ab zwei Jahren und Erwachsenen zugelassen:

**Upadacitinib** (Rinvoq® 15 mg Retardtabletten) ist u. a. zugelassen zur Behandlung der mittelschweren bis schweren atopischen Dermatitis bei Erwachsenen und Jugendlichen ab zwölf Jahren, die für eine systemische Therapie infrage kommen (7). Bei Jugendlichen mit einem Körpergewicht von mindestens 30 kg beträgt die empfohlene Dosis von Upadacitinib 15 mg einmal täglich. Upadacitinib kann mit oder ohne

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topische Kortikosteroide angewendet werden. Topische Calcineurininhibitoren können für empfindliche Bereiche wie Gesicht, Hals, intertriginöse und Genitalbereiche verwendet werden.

Insgesamt wurden 344 Jugendliche im Alter von 12 bis 17 Jahren mit mittelschwerer bis schwerer atopischer Dermatitis in den drei Phase-III-Studien randomisiert und erhielten entweder 15 mg (n = 114) bzw. 30 mg (n = 114) Upadacitinib oder ein entsprechendes Placebo (n = 116) als Monotherapie oder in Kombination mit topischen Kortikosteroiden (7;8). Die Wirksamkeit war bei Jugendlichen und Erwachsenen vergleichbar. Das Sicherheitsprofil bei Jugendlichen war in der Regel mit dem bei Erwachsenen vergleichbar, wobei die Raten einiger unerwünschter Ereignisse, u. a. Neutropenie und Herpes zoster, dosisabhängig höher waren.

In der aktualisierten Leitlinie „Systemtherapie bei Neurodermitis“ aus dem letzten Jahr (9) werden folgende Therapieempfehlungen gegeben: „Der Einsatz von Dupilumab kann zur Therapie der chronischen, moderaten bis schweren Neurodermitis von Jugendlichen ab zwölf 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 zwölf 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).“

Mittlerweile wurde im Jahre 2021 Dupilumab auch zur Behandlung der schweren atopischen Dermatitis bei Kindern ab sechs Jahren zugelassen, für die eine systemische Therapie in Betracht kommt. Es ist anzunehmen, dass nun ein starker Konsens der Anwendung von Dupilumab als systemisches Therapeutikum auch für Kinder ab sechs Jahre gefunden wird.

Mit der Zulassung von Dupilumab zur systemischen Therapie der schweren atopischen Dermatitis ab sechs Jahren ist dieser Wirkstoff klar als zweckmäßige Vergleichstherapie anzusehen. Für Jugendliche ab zwölf Jahren ist alternativ auch Upadacitinib als Vergleichstherapie möglich, obwohl in Deutschland in der Praxis noch wenig Erfahrung mit diesem Wirkstoff besteht.

Schwieriger ist eine Vergleichstherapie bei Kindern unter sechs Jahren festzulegen. Geeignet scheint eine patientenindividuell optimierte Therapie unter Gabe von topischen Glukokortikoiden und/oder topischen Calcineurininhibitoren (Tacrolimus, Pimecrolimus) zu sein, gegebenenfalls auch unter Durchführung einer Kurzzeittherapie mit oralen Glukokortikoiden bei schwerem schubförmigem Verlauf.

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Indikation gemäß Beratungsantrag

Behandlung der mittelschweren bis schweren atopischen Dermatitis bei Kindern und Jugendlichen zwischen 2 und 18 Jahren, die auf eine topische Therapie unzureichend angesprochen haben oder eine Unverträglichkeit gegen eine entsprechende Behandlung aufweisen.

In der europäischen Leitlinie aus dem Jahre 2018 zur atopischen Dermatitis wird für Kinder mit schwerer Verlaufsform als Therapieoption die systemische Gabe von Immunsuppressiva wie Ciclosporin, Methotrexat, Azathioprin und Mycophenolat zulassungsüberschreitend (Off-Label-Use) angegeben (10). Eine aktuelle europäische Leitlinie aus dem Jahr 2022 (EuroGuiDerm) zur systemischen Therapie empfiehlt für Kinder und Jugendliche mit schwerer atopischer Dermatitis zur systemischen Therapie Dupilumab (ab sechs Jahren zugelassen), Upadacitinib (ab zwölf Jahren zugelassen) und Ciclosporin (ab 16 Jahren zugelassen) (11).

**Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von mittelschwerer bis schwerer atopischen Dermatitis bei Kindern und Jugendlichen zwischen 2 und 18 Jahren, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Regelhaft muss die unterschiedliche Zulassung der zur Verfügung stehenden Wirkstoffe für eine systemische Therapie bei Kindern und Jugendlichen berücksichtigt werden. Dies ist in den Leitlinien nicht immer der Fall, da hierin auch eine Off-label-Anwendung empfohlen wird (9-11). Bisher war orales Ciclosporin eine akzeptierte Alternative bei schweren Verlaufsformen der atopischen Dermatitis, die auch bei Kindern und Jugendlichen eine systemische Therapie erforderte.

Bei 40 Kindern (2–16 Jahre) wurde Ciclosporin als repetitive Kurzzeittherapie mit einer kontinuierlichen Behandlung verglichen (12). Es fand sich eine signifikante Verbesserung von klinischem Score und Lebensqualität in beiden Gruppen ohne signifikante Unterschiede. Eine nachhaltigere Besserung wurde allerdings nur bei der kontinuierlichen Behandlung mit Ciclosporin beobachtet. Wenn eine längere systemische Therapie notwendig ist, wird auch bei Kindern orales Ciclosporin angewendet, das aber nur bei Erwachsenen in dieser Indikation zugelassen ist (13). Ciclosporin ist bei Kindern nach Transplantationen und beim nephrotischen Syndrom gut untersucht und in diesen Indikationen auch zugelassen. Durch Messung der Ciclosporin-Konzentration im Blut kann die Behandlung gut überwacht werden. Die empfohlene Off-label-Dosierung bei schwerer atopischer Dermatitis beträgt als Initialdosis 3–5 mg/kg/Tag in zwei Dosen über drei bis sechs Wochen. Die Erhaltungsdosis wird mit 2–5 mg/kg/Tag in zwei Dosen angegeben (14).

Heute stehen für Kinder und Jugendliche ab sechs Jahren mit Dupilumab und für Jugendliche ab zwölf Jahren mit Upadacitinib zwei neuere Wirkstoffe zur systemischen Therapie der schweren atopischen Dermatitis zur Verfügung. In Expertenempfehlungen wird Dupilumab auch schon für Kinder ab sechs Monaten erwähnt, obwohl die Datenlage dies nicht hergibt (9). Insgesamt ist zu erwarten, dass sich die

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Behandlung der atopischen Dermatitis mit den neueren Substanzen hin zu einer häufigeren Anwendung einer systemischen Therapie ändern wird.

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

**2022-B-238**

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**Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?**

Der aktuelle Behandlungsstandard in der o.g. Indikation besteht in der Verabreichung einer Systemtherapie mit dem Antikörper Dupilumab, der alters- und gewichtsadaptiert alle 14 Tage oder alle 30 Tage subkutan appliziert wird. Der Antikörper ist derzeit (Fachinformation September 2022) zugelassen zur Behandlung von mittelschwerer bis schwerer atopischer Dermatitis (AD) bei Erwachsenen und Jugendlichen ab 12 Jahren, die für eine systemische Therapie in Betracht kommen, sowie von schwerer atopischer Dermatitis bei Kindern von 6 bis 11 Jahren, die für eine systemische Therapie in Betracht kommen. Eine Zulassung für Säuglinge und Kleinkinder im Alter ≥ 6 Monate und <6 Jahren wird in Kürze erwartet, wobei davon auszugehen ist, dass dann hier ebenfalls ausschließlich die schwere atopische Dermatitis, wie für die Altersgruppe 6-11 Jahren, in der Indikation genannt wird.

Das bedeutet, dass für Kinder bis zu 12 Jahren mit nur mittelschwerer atopischer Dermatitis, die auf eine topische Therapie nur unzureichend angesprochen haben oder bei denen eine Unverträglichkeit gegen eine entsprechende Behandlung besteht, auf absehbare Zeit keine zugelassene systemische Medikation verordnet werden kann. Grundsätzlich ist für diese Altersgruppe zu fordern, aufgrund der Variationsbreite der individuellen Verläufe ggf. mit einer Spontanremission der atopischen Dermatitis länger als bei Jugendlichen und Erwachsenen topisch zu behandeln (standardmäßig mit topischen Glukokortikosteroiden der Klasse II und -wenn nicht ausreichend- der Klasse III sowie im Gesicht und in intertriginösen Hautarealen mit den topischen Immunmodulatoren Pimecrolimus oder Tacrolimus). Sprechen diese Therapien nicht an, ist die Anwendung von Dupilumab, in diesem Falle als Off-label-Verordnung, auch bei nur mittelschwerer atopischer Dermatitis der derzeitige Therapiestandard, wie u.a. aus aktuellen deutschen Registerdaten (TREATkids, unveröffentlicht) hervorgeht. In den USA wurde Dupilumab von der FDA zur Behandlung von Kindern in einem Alter von 6 Monaten bis 5 Jahren mit mittelschwerer bis schwerer atopischer Dermatitis zugelassen.

Dupilumab hat ein standardisiertes Zulassungsverfahren durchlaufen, in dem in kontrollierten Phase 3 Studien die Wirksamkeit in den Altersgruppen der Kinder und Jugendlichen ab 12 Jahren, der Kinder in der Altersgruppe 6-11 Jahren und der Kinder in der Altersgruppe von 6 Monaten bis 6 Jahren über 16 Wochen separat gezeigt wurde. Das Verträglichkeitsprofil war hier gut, als einzige häufigere Nebenwirkung traten in den genannten kontrollierten Studien okuläre und periokuläre Symptome (vor allem Blepharitis und Konjunktivitis) auf, die in der Regel einen milden Verlauf zeigten und topisch therapierbar waren.

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Für die Altersgruppe der Kinder und Jugendlichen ab 12 Jahren ist Upadacitinib in der Dosierung von 15 mg/Tag seit 2021 zur oralen Behandlung der der mittelschweren bis schweren atopischen Dermatitis zugelassen und kann seitdem als Behandlungsstandard in solchen Fällen angesehen werden, bei denen ein besonders schneller Wirkungseintritt gewünscht wird, bei denen wiederholte Injektionstherapien nicht möglich sind (z. B. bei Spritzenphobie) oder bei denen zuvor Unverträglichkeiten gegen Dupilumab aufgetreten sind.

Die Substanz hat ein Zulassungsverfahren durchlaufen und es wurde in Phase 3 Studien eine ausreichend große Zahl von Kindern und Jugendlichen ab 12 Jahren eingeschlossen, die mit Upadacitinib behandelt wurden. Die Substanz ist in der Regel gut verträglich, anders als bei Dupilumab sind allerdings das Auftreten von akneiformen Hautveränderungen sowie die Infektanfälligkeit erhöht, was sich u.a. im Auftreten von Hautinfektionen mit HerpesSimplex-Virus zeigt.

Der Antikörper Tralokinumab, derzeit zugelassen für die Behandlung der mittelschweren bis schweren atopischen Dermatitis bei Erwachsenen, wurde kürzlich von der EMA auch für die Altersgruppe 12-18 Jahre zugelassen. Die entsprechende Phase 3 Studie zur Wirksamkeit wurde bislang noch nicht als Vollpublikation vorgelegt. Es ist davon auszugehen, dass der Antikörper wie auch bei Erwachsenen hinsichtlich der Wirksamkeit zu Beginn der Behandlung etwas schwächer wirksam ist als Dupilumab, dann während des ersten Behandlungsjahres jedoch zu - auch zu einem Januskinase-Inhibitor - vergleichbaren Wirksamkeiten führt und in der Erhaltungsphase bei gutem Therapieansprechen wie bei Erwachsenen innerhalb der zugelassenen Indikation nach Woche 16 nur alle 4 Wochen appliziert werden muss, was für die Altersgruppe der Kinder und Jugendlichen vorteilhaft sein könnte. Das Sicherheits- und Verträglichkeitsprofil von Tralokinumab ist gut. In den publizierten Studien zu Erwachsenen traten – wie bei Dupilumab- als einzige häufigere Nebenwirkung okuläre und periokuläre Symptome (vor allem Blepharitis und Konjunktivitis) auf, die in der Regel einen milden Verlauf zeigten und topisch therapierbar waren.

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**Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von mittelschwerer bis schwerer atopischen Dermatitis bei Kindern und Jugendlichen zwischen 2 und 18 Jahren, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

**Dupilumab bei Kindern ab 2 Jahren und Jugendlichen**

Dupilumab soll bei AD in der Regel als Langzeittherapie eingesetzt werden.

Dupilumab soll bei Patienten mit AD, für die eine systemische Therapie in Frage kommt, bei gleichzeitig bestehendem Asthma bronchiale oder bei gleichzeitig bestehender chronischer Rhinosinusitis mit Nasenpolypen bevorzugt eingesetzt werden, für die ebenfalls Zulassungen vorliegen.

**Upadacitinib bei Kindern ab 12 Jahren und Jugendlichen:**

Die Behandlung der AD mit JAK-Inhibitoren ist für die Langzeittherapie zugelassen, sollte aber bei besonderen Verlaufsformen (z B bei wiederkehrenden, vornehmlich saisonalen Verschlechterungen der AD) auch als Intervalltherapie eingesetzt werden

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**.**JAK-Inhibitoren sollten nicht bei vorbekannten Infektionsrisiken (insbesondere von viralen Infekten) eingesetzt werden. JAK-Inhibitoren sollen nicht bei vorbekannten thromboembolischen Ereignissen oder genetisch bedingten, erhöhten Thromboserisiken eingesetzt werden. JAK-Inihibitoren sollten nicht bei vorbekannten malignen Vorerkrankungen eingesetzt werden.

Upadacitinib soll bei Patienten mit AD, für die eine systemische Therapie in Frage kommt, insbesondere auch bei gleichzeitig bestehender rheumatoider Arthritis, Psoriasis-Arthritis oder ankylosierender Spondylitis und Colitis ulcerosa bevorzugt eingesetzt werden