Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

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

Vorgang: 2021-B-183z Abrocitinib

Stand: Mai 2021

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Zur Behandlung der mittelschweren bis schweren atopischen Dermatitis	
Kriterien gemäß 5. Kapitel § 6 Absatz 3 Satz 2 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	<u>Topisch:</u> Glukokortikosteroide der Klassen 1 bis 4 Pimecrolimus (moderates atopisches Ekzem) Tacrolimus (moderate und schwere atopische Ekzeme) <u>Systemisch:</u> Ciclosporin A (schwere atopische Dermatitis) systemische Glukokortikoide (für schwere Ekzeme) Dupilumab Antihistaminika Baricitinib
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	- NB-UVB - UVA (die UVA1 ist hiervon ausgenommen, da ausgeschlossen) - Balnephototherapie
Als Vergleichstherapie sollen bevorzugt Arzneimittel-anwendungen oder nicht-medikamentöse Behandlungen herangezogen werden, deren patientenrelevanter Nutzen durch den Gemeinsamen Bundesausschuss bereits festgestellt ist.	– *Therapiehinweise zu Tacrolimus (Beschluss vom 04.09.2003) und Pimecrolimus (Beschluss vom 04.09.2003)* – Dupilumab; Beschlüsse über die Nutzenbewertung nach § 35a SGB V vom 17. Mai 2018 und 20. Februar 2020 – Baricitinib; Beschluss über die Nutzenbewertung nach§ 35a SGB V vom 6. Mai 2021
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	⇨ *siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet**
Abrocitinib N/N	Geplantes Anwendungsgebiet: Behandlung von Patienten ≥ 12 Jahren mit mittelschwerer bis schwerer atopischer Dermatitis mit unzureichendem Ansprechen auf die topische Therapie oder fehlender Eignung für solche Therapien.
Hinweis	***Aufgrund der großen Menge an Wirkstoffen im Anwendungsgebiet werden hier einzelne Arzneimittel exemplarisch aufgeführt***
TOPISCHE THERAPIEN	
Glukokortikoide Klasse 1:	
z.B. Prednisolon D07AA03 Prednisolon Creme LAW	Zur Behandlung subakuter und akuter gering ausgeprägter entzündlicher Hauterkrankungen, die auf eine äußerliche Behandlung mit schwach wirksamen Corticosteroiden ansprechen.
z.B. Hydrocortison D07AA02 Hydrocortison Heumann 1 % Creme	Zur Behandlung von entzündlichen Hauterkrankungen, bei denen schwach wirksame, topisch anzuwendende Glucocorticosteroide angezeigt sind.
Glukokortikoide Klasse 2:	
z.B. Hydrocortison-17-butyrat D07AB02 Laticort® Creme 0,1 % Laticort® Salbe 0,1 %	Zur Behandlung entzündlicher Hautkrankheiten, bei denen mittelstark wirksame, topisch anzuwendende Glucocorticoide angezeigt sind Creme: insbesondere bei akuten und subakuten Formen, in intertriginösen Arealen und beim fettigen Hauttyp. Salbe: insbesondere bei subakuten bis chronischen Formen.

z.B. Clobetasonbutyrat 0,5 mg D07AB01 Emovate® Crème	- Leichte Formen von Ekzemen, seborrhoischer Dermatitis und andere leichte Hauterkrankungen, die auf eine lokale Corticoidbehandlung ansprechen. - Weiterbehandlung von hartnäckigen Hauterkrankungen, die mit einem starker wirkenden Corticoid anbehandelt worden sind. - Bei Säuglingen und Kleinkindern zur lokalen Corticoidbehandlung, z. B. Windelekzem oder endogenem Ekzem.
z.B. Triamcinolon D07AB09 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.
z.B. Prednicarbart D07AC18 Prednicarbat acis® Creme, 2,5mg/g Prednicarbat acis® Fettsalbe, 2,5mg/g Salbe Prednicarbat acis® Salbe, 2,5mg/g Creme	Entzündliche Hauterkrankungen, bei denen eine äußerliche Behandlung mit mittelstark wirksamen Glucocorticoiden angezeigt ist, wie z. B. mäßig stark ausgeprägtes Ekzem.
Glukokortikoide Klasse 3:	
z.B. Methylprednisolon aceponat D07AC 14 Advantan® 0,1 % Creme	Zur Behandlung des endogenen Ekzems (atopische Dermatitis, Neurodermitis), Kontaktekzems, degenerativen Ekzems und des nummulären Ekzems.
z.B. Amcinonid D07AC11 z.B. Amciderm® Fettsalbe, Salbe, Creme, Lotio und Emulsion zur	Fettsalbe und Salbe: Hauterkrankungen, die auf stark wirksame Kortikoide ansprechen wie z.B. toxische Ekzeme, allergische Kontaktekzeme, atopisches Ekzem (Neurodermitis), Psoriasis vulgaris, Lichen ruber. Creme und Lotio: Hauterkrankungen, die auf stark wirksame Kortikoide ansprechen wie z.B. toxische Ekzeme, allergische Kontaktekzeme, seborrhoische Ekzeme, atopisches Ekzem (Neurodermitis), Lichen ruber.

Anwendung auf der Haut	
z.B. Mometasonfuroat D07AC z.B. ECURAL® Fettcreme, 1 mg/g Creme ECURAL® Salbe, 1 mg/g Salbe	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.
z.B. Betamethasonvalerat D07AC01 z.B.Betagalen® Salbe,Creme, Lotio, Lösung (0,1%)	Salbe,Creme, Lotio: Zur Behandlung von entzündlichen Hauterkrankungen, die sich durch Rötung, Bläschen, Schuppung, Juckreiz manifestieren können und auf eine äußerliche Behandlung mit Corticosteroiden ansprechen sowie einer Therapie mit stark wirksamen Corticosteroiden bedürfen. Lösung: Zur Behandlung von entzündlichen Hauterkrankungen, die sich durch Rötung, Bläschen, Juckreiz, Schuppung (z.B. Psoriasis capitis) manifestieren können und auf eine äußerliche Behandlung mit Corticosteroiden ansprechen sowie einer Therapie mit stark wirksamen Corticosteroiden bedürfen.
Glukokortikoide Klasse 4:	
Clobetasol-propionat D07AD01 Clobetasol acis® Creme, 0,5 mg/g Clobetasol acis® Fettsalbe, 0,5 mg/g Salbe Clobetasol acis® Salbe, 0,5 mg/g Clobetasol acis® Crinale, 0,5 mg/g Lösung	Creme/Salbe/Fettsalbe: Zur Behandlung lokalisierter therapieresistenter Plaques von entzündlichen Hauterkrankungen bei denen die symptomatische Anwendung topischer Glukokortikoide mit sehr starker Wirkung angezeigt ist. Lösung: Zur Behandlung lokalisierter therapieresistenter Plaques von entzündlichen Hauterkrankungen an behaarten Körperregionen, bei denen die symptomatische Anwendung topischer Glukokortikoide mit sehr starker Wirkung angezeigt ist.

zur Anwendung auf der Haut	
Calcineurinhemmer	
z.B. Tacrolimus 0.03% D11AH01 Protopic® 0,03 % Salbe	Behandlung des mittelschweren bis schweren atopischen Ekzems (Ekzemschub) bei Erwachsenen ab 16 Jahren, die auf herkömmliche Therapien wie z. B. topische Kortikosteroide nicht ausreichend ansprechen oder diese nicht vertragen. Als Erhaltungstherapie. Behandlung des mittelschweren bis schweren atopischen Ekzems (Ekzemschub) bei Kindern ab 2 Jahren, die nicht ausreichend auf eine herkömmliche Therapie wie z. B. topische Kortikosteroide angesprochen haben. Als Erhaltungstherapie.
z.B. Tacrolimus 0.1% D11AH01 Protopic® 0,1 % Salbe	Behandlung des mittelschweren bis schweren atopischen Ekzems bei Erwachsenen ab 16 Jahre, die auf herkömmliche Therapien wie z. B. topische Kortikosteroide nicht ausreichend ansprechen oder diese nicht vertragen.
z.B. Pimecrolimus D11AH02 Elidel® 10 mg/g Creme	Behandlung von Patienten ab 2 Jahren 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	
Ciclosporin Weichkapseln L04AD01 25, 50 und 100 mg Weichkapseln Ciclosporin 100 mg/ml Lösung zum Einnehmen z.B. Ciclosporin Pro	Ciclosporin Pro ist indiziert bei Patienten mit schwerer atopischer Dermatitis, falls eine systemische Therapie erforderlich ist.
Dupilumab D11AH05	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.

Dupixent®	
Baricitinib L04AA37 Olimiant®	Olumiant ist angezeigt zur Behandlung von mittelschwerer bis schwerer atopischer Dermatitis bei erwachsenen Patienten, die für eine systemische Therapie infrage kommen.
Systemische Glucokortikoide	
z.B. Methylprednisolon H02AB04 Methylprednisolon 4 mg, 8mg, 16 mg, 32 mg Tabletten 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.
z.B. Triamcinolon H02AB08 Volon® 4, 8, 12 mg Tabletten	Orale Anfangsbehandlung ausgedehnter, schwerer akuter, auf Glukokortikoide ansprechender Hautkrankheiten wie: allergische Dermatosen (z. B. akute Urtikaria, Kontaktdermatitis, Arzneimittelexanthem), atopisches Ekzem (akute Exazerbationen bzw. großflächige nässende Ekzeme), Pemphigus vulgaris.
Antihistaminika	
z.B.Cetirizin-dihydrochlorid R06A E07 Cetirizin beta® Filmtablette	Zur Behandlung von Krankheitssymptomen bei allergischen Erkrankungen wie – Juckreiz bei chronischer Nesselsucht (Urtikaria) und bei atopischer Dermatitis (Neurodermitis) mit Beschwerden wie Rötung der Haut

Quellen: AMIce Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2021-B-183z (Abrocitinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	6. Mai 2021

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
EASI	Eczema Area and Severity Index
EC-MPS	entericcoated mycophenolate sodium
ECP	extracorporeal photopheresis
EDI	Eczema Disability Index
ETFAD	European Task Force Atopic dermatitis
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GISS	Global Individual Sign Score
GoR	Grade of Recommendations
HADS	Hospital Anxiety and Depression Scale
HR	Hazard Ratio
IGA	Investigator Global Assessment
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
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 atopischen Dermatitis bei Erwachsenen und Jugendlichen ab 12 Jahren.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *atopische Dermatitis* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 15.01.2021 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 664 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 24 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse

G-BA, 2020 [12].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Baricitinib (neues Anwendungsgebiet: mittelschwere bis schwere atopische Dermatitis) vom 06. Mai 2021

Neues Anwendungsgebiet (laut Zulassung vom 19. Oktober 2020):

Olumiant ist angezeigt zur Behandlung von mittelschwerer bis schwerer atopischer Dermatitis bei erwachsenen Patienten, die für eine systemische Therapie infrage kommen.

Erwachsene Patienten mit mittelschwerer bis schwerer atopischer Dermatitis, die für eine kontinuierliche systemische Therapie infrage kommen

Zweckmäßige Vergleichstherapie:

- Dupilumab (ggf. in Kombination mit topischen Glukokortikoiden (TCS) und/oder topischen Calcineurininhibitoren (TCI))

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Baricitinib gegenüber Dupilumab:

- Ein Zusatznutzen ist nicht belegt.

G-BA, 2020 [8].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Richtlinie Methoden vertragsärztliche Versorgung (MVV-RL): Balneophototherapie bei atopischem Ekzem vom 20. März 2020.

Fazit

Der Gemeinsame Bundesausschuss (G-BA) hat der in seiner Sitzung am 20. März 2020 beschlossen, die Richtlinie des Gemeinsamen Bundesausschusses zu Untersuchungs- und Behandlungsmethoden vertragsärztlichen Versorgung (Richtlinie Methoden vertragsärztliche Versorgung), in der Fassung vom 17. Januar 2006 (BAnz 2006 S. 1523), zuletzt geändert am T. Monat JJJJ (BAnz AT TT.MM.JJJJ V), wie folgt zu ändern:

(…)

3. Der neue § 2 wird wie folgt geändert:

d) Folgender Absatz 2 wird angefügt:

„Die Photosoletherapie gemäß § 1 Absatz 2 darf bei Patientinnen und Patienten mit mittelschwerem bis schwerem atopischen Ekzem angewendet werden. Von einem mittelschweren Ekzem wird in der Regel bei einem SCORAD-Score größer 25 ausgegangen.“

e) Folgender Absatz 3 wird angefügt:

„Die Indikationsstellung bei Patientinnen und Patienten unter 18 Jahren darf nur nach sorgfältiger Prüfung der zur Verfügung stehenden Therapieoptionen erfolgen.“

(…)

G-BA, 2020 [16].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Dupilumab (neues Anwendungsgebiet: atopische Dermatitis, Jugendliche ab 12 bis < 18 Jahre) vom 20. Februar 2020

Neues Anwendungsgebiet (laut Zulassung vom 1. August 2019)

Dupixent wird angewendet zur Behandlung von mittelschwerer bis schwerer atopischer Dermatitis (AD) bei Jugendlichen ab 12 bis < 18 Jahren, die für eine systemische Therapie in Betracht kommen.

Zweckmäßige Vergleichstherapie

Ein patientenindividuell optimiertes Therapieregime aus topischer und systemischer Therapie in Abhängigkeit der Ausprägung der Erkrankung und unter Berücksichtigung der Vortherapie, unter Berücksichtigung folgender Therapien:

- topische Glukokortikoide der Klassen 2 bis 4
- Tacrolimus (topisch)
- Ciclosporin

Der jeweilige Zulassungsstatus der Arzneimittel ist zu berücksichtigen.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Dupilumab gegenüber der zweckmäßigen Vergleichstherapie)

Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen.

G-BA, 2018 [15].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 17. Mai 2018 – Dupilumab.

Anwendungsgebiet (laut Zulassung vom 26.09.2017)

Dupixent wird angewendet zur Behandlung von mittelschwerer bis schwerer atopischer Dermatitis (AD) bei erwachsenen Patienten, die für eine systemische Therapie in Betracht kommen.

Zweckmäßige Vergleichstherapie

Ein patientenindividuell optimiertes Therapieregime in Abhängigkeit der Ausprägung der Erkrankung und unter Berücksichtigung der Vortherapie, unter Berücksichtigung folgender Therapien:

- topische Glukokortikoide (TCS) der Klassen 2 bis 4
- Tacrolimus (topisch)
- UV-Therapie (UVA1 /NB-UVB2)
- systemische Glukokortikoide (nur kurzfristig im Rahmen einer Schubtherapie)
- Ciclosporin

Der jeweilige Zulassungsstatus der Arzneimittel ist zu berücksichtigen.

[1] UVA1 ist hiervon nicht umfasst, da ausgeschlossen

[2] Schmalband-UVB (311 nm)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Hinweis für einen beträchtlichen Zusatznutzen

G-BA, 2020 [14].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage IV zum Abschnitt H der Arzneimittel-Richtlinie; Verordnungseinschränkungen und -ausschlüsse in der Arzneimittelversorgung; Therapiehinweise gemäß § 92 Abs. 2 Satz 7 SGB V i. V. m. § 17 AM-RL zur wirtschaftlichen Verordnungsweise von Arzneimitteln; letzte Änderung in Kraft getreten am 27.06.2020

Pimecrolimus

(z. B. Elidel ®)
Beschluss vom: 04.09.2003
In Kraft getreten am: 07.01.2004
BAnz. Nr. 2 vom 06.01.2004, S. 68

Indikation

Pimecrolimus ist zugelassen bei Patienten ab 2 Jahren mit leichtem bis mittelschwerem atopischen Ekzems zur

- Kurzzeitbehandlung von Anzeichen und Symptomen
- intermittierenden Langzeitbehandlung, um das Auftreten von akuten Ekzemschüben zu verhindern.

Die Behandlung erfolgt zweimal täglich bis zur vollständigen Abheilung und sollte dann abgesetzt werden. Nach Unterbrechung beziehungsweise bei Langzeittherapie sollte die Behandlung beim ersten Wiederauftreten der Symptome erneut begonnen werden, um das Auftreten weiterer Krankheitsschübe zu verhindern.

Neben dem Wirkstoff sind folgende Hilfsstoffe enthalten: mittelkettige Triglyceride,

(Z)-Octadec-9-en-1-ol, Propylenglycol, Stearylalkohol, Cetylalkohol, Glycerol-mono/dispeisefettsäureester, Natriumcetylstearylsulfat, Benzylalkohol, Citronensäure, Natriumhydroxid und gereinigtes Wasser.

Pimecrolimus sollte nur von Ärzten verschrieben werden, die Erfahrung in der topischen Behandlung des atopischen Ekzems haben.

Empfehlungen zur wirtschaftlichen Verordnungsweise

Der Einsatz als First-Line-Therapie ist unwirtschaftlich.

Angesicht des fehlenden Nachweises einer Überlegenheit gegenüber schwach wirksamen topischen Steroiden und fehlender hinreichend aussagekräftiger placebokontrollierter Studien bei Erwachsenen ist die Anwendung nur wirtschaftlich bei leichtem bis mittelschwe-rem atopischen Ekzem

- bei Erwachsenen, die auf herkömmliche Therapie nicht ausreichend ansprechen oder diese nicht vertragen, sowie
- bei Kindern ab 2 Jahren, die nicht ausreichend auf die herkömmliche Therapie angesprochen haben.

Insgesamt dürfte dies nur auf wenige Patienten zutreffen, dies gilt auch für den Einsatz als Second-Line-Behandlung.

Die bisherigen verblindeten, placebovergleichenden Studien gingen nicht über sechs Wochen hinaus, sodass eine abschließende Beurteilung der unterschiedlichen Behandlungsoptionen, insbesondere zu Langzeitnebenwirkungen, zurzeit nicht möglich ist.

Pimecrolimus ist mittelstark bis stark wirksamen Glukokortikoiden unterlegen. Ob es eine vergleichbare Wirksamkeit zu schwach wirksamen Kortikosteroiden hat, ist nicht belegt. Direkt vergleichende Untersuchungen zu schwach wirksamen Steroiden fehlen. Der Stellenwert der Behandlung mit Pimecrolimus, insbesondere im direktem Vergleich zum optimierten Einsatz von schwach wirksamen Glukokortikoiden, auch im Wechsel mit wirkstofffreien Mitteln in der erscheinungsarmen Zeit, ist unklar.

Ein kortisonsparender Effekt zu einem solchen Therapieregime ist nicht belegt.

Es fehlen zurzeit direkt vergleichende Studien zu anderen topischen Makrolidimmunsuppressiva. Aufgrund der jetzigen Datenlage wird angenommen, dass Pimecrolimus eher weniger wirksam als Tacrolimus ist.

Pimecrolimus ist nur zugelassen für Kinder ab 2 Jahren, bei jüngeren traten vermehrt Nebenwirkungen auf. Der Einsatz ist daher nicht vertretbar und somit unwirtschaftlich.

Kombinationsbehandlungen von Pimecrolimus

- mit systemischen oder wirkstoffhaltigen topischen Arzneimitteln sind nicht untersucht. Die Wirksamkeit ist nicht belegt und von daher ist der Einsatz unwirtschaftlich.
- mit gleichzeitigem Einsatz von Lichttherapien sind wegen eines nicht auszuschließenden photokanzerogenen Risikos nicht angezeigt.

Tacrolimus

(zum Beispiel Protopic®)
Beschluss vom: 04.09.2003
In Kraft getreten am: 07.01.2004
BAnz. 2004 Nr. 2 vom 06.01.2004, S. 68

Indikation

Tacrolimus ist zugelassen zur Behandlung des mittelschweren bis schweren atopischen Ekzems bei Erwachsenen, die auf herkömmliche Therapie nicht ausreichend ansprechen oder diese nicht vertragen, sowie bei Kindern ab 2 Jahren, die nicht ausreichend auf die herkömmliche Therapie angesprochen haben.

Es kann zur Kurzzeitbehandlung und intermittierenden Langzeitbehandlung angewendet werden.

Die Behandlung erfolgt zweimal täglich bis zu drei Wochen und wird dann auf einmal täglich reduziert und bis zur Abheilung fortgeführt, danach abgesetzt. Bei Kindern ist nur die Wirkstärke 0,03 % indiziert. Bei Erwachsenen (ab 16 Jahren) sollte mit der 0,1 % Salbe begonnen werden bei zweimal täglicher Anwendung für eine Dauer von bis zu drei Wochen. Danach sollte die Stärke auf 0,03 % bei zweimal täglicher Anwendung reduziert werden. Wenn der klinische Zustand es erlaubt, sollte versucht werden, die Anwendungshäufigkeit zu verringern.

Ist nach zweiwöchiger Behandlung keine Besserung zu erkennen, sind andere Therapiemöglichkeiten in Betracht zu ziehen.

Neben dem Wirkstoff sind folgende Hilfsstoffe enthalten: weißes Vaselin, dickflüssiges Paraffin, Propylencarbonat, gebleichtes Wachs und Hartparaffin.

Tacrolimus darf nur von Dermatologen beziehungsweise Ärzten mit umfangreicher Erfahrung in der Behandlung des atopischen Ekzems mit immunmodulierenden Therapien verschrieben werden.

Empfehlungen zur wirtschaftlichen Verordnungsweise

Tacrolimus ist nur zugelassen zur Behandlung des mittelschweren bis schweren atopischen Ekzems

- bei Erwachsenen, die auf herkömmliche Therapie nicht ausreichend ansprechen oder diese nicht vertragen, sowie
- bei Kindern ab 2 Jahren, die nicht ausreichend auf die herkömmliche Therapie angesprochen haben.

Die zur Zulassung führenden vergleichenden Studien haben solche Patienten nicht explizit eingeschlossen. Insgesamt dürfte dies nur auf wenige Patienten zutreffen.

Der Einsatz als First-Line-Therapie ist unwirtschaftlich.

In den direkt vergleichenden Untersuchungen traten mehr lokale Nebenwirkungen unter Tacrolimus-Salbe und auch unter der Salbengrundlage allein als unter Kortikosteroidbehandlung auf. Die bisherigen vergleichenden Studien gingen nicht über drei Wochen hinaus, sodass eine abschließende Beurteilung insbesondere zu Langzeitnebenwirkungen der unterschiedlichen Behandlungsoptionen zurzeit nicht möglich ist.

Der Stellenwert der Behandlung mit Tacrolimus, insbesondere im direktem Vergleich zum optimierten Einsatz von topischen Glukokortikoiden, auch im Wechsel mit wirkstofffreien Mitteln in der erscheinungsarmen Zeit, ist unklar. Tacrolimus scheint eine vergleichbare Wirksamkeit wie mittelstark bis stark wirksame Glukokortikoide zu haben.

Vergleichende Untersuchungen zu topischen Glukokortikoiden wurden durchgeführt. Bei Kindern war Tacrolimus dem schwach wirksamen 1 % Hydrocortisonacetat in zwei Studien überlegen. Allerdings wird die Wahl des schwach wirksamen Referenzsteroids wegen dessen begrenzter Wirksamkeit als nicht optimal angesehen. Im Vergleich zu einem mittelstarken Kortikosteroid (0,1 % Hydrocortisonbutyrat) ergab sich bei Erwachsenen kein signifikanter Unterschied der Wirksamkeit. In zwei vergleichenden japanischen Studien der Phase III mit insgesamt 329 Patienten war die Wirksamkeit von 0,1 % Tacrolimus dem stark wirksamen topischen Kortikosteroid (0,12 % Betamethasonvalerat) vergleichbar und dem mittelstark wirksamen 0,1% Alcometasondipropionat überlegen.

Unter Tacrolimus und auch unter der Salbengrundlage allein traten mehr lokale Nebenwirkungen auf als unter Kortikosteroiden.

Das Wiederauftreten der Erkrankung war bisher nicht Ziel von Untersuchungen. In den US-amerikanischen Studien kam es bei ungefähr der Hälfte der Patienten zwei Wochen nach Absetzen der Therapie zu einem erneuten Schub. In den europäischen Untersuchungen hielt eine moderate Verbesserung bei etwa der Hälfte der Patienten zwei Wochen nach Absetzen an.

G-BA, 2018 [11].

Beschluss des Gemeinsamen Bundesausschusses über die Wiederaufnahme des Bewertungsverfahrens gemäß §135 Abs. 1 SGB V: Synchrone Balneophototherapie bei atopischem Ekzem

Siehe auch G-BA, 2018 [13].

Fazit/Ergebnis:

Der Gemeinsame Bundesausschuss (G-BA) hat in seiner Sitzung am 15. Februar 2018 folgenden Beschluss gefasst:

I. Das Bewertungsverfahren gemäß § 135 Absatz 1 SGB V über die synchrone Balneophototherapie bei atopischem Ekzem, zu dem die Beschlussfassung mit Beschluss vom 13. März 2008 ausgesetzt wurde (siehe Anlage III Nummer 2 der Richtlinie Methoden vertragsärztliche Versorgung), wird wiederaufgenommen.

II. Der Unterausschuss Methodenbewertung wird mit der Fortsetzung der Bewertung der synchronen Balneophototherapie bei atopischem Ekzem nach I. unter Zugrundelegung des Zeitplans (siehe Anlage) beauftragt.

III. Der Unterausschuss Methodenbewertung kann das Institut für Wirtschaftlichkeit und Qualität im Gesundheitswesen gemäß § 139a Absatz 3 Nummer 1 SGB V mit der Durchführung der Recherche, Darstellung und Bewertung des aktuellen medizinischen Wissenstandes der synchronen Balneophototherapie bei atopischem Ekzem beauftragen.

G-BA, 2003 [9].

Bekanntmachung des Bundesausschusses der Ärzte und Krankenkassen über eine Änderung der Richtlinien über die Verordnung von Arzneimitteln der vertragsärztlichen Versorgung (Arzneimittel-Richtlinien) vom 4. September 2003: Therapiehinweis nach Nr. 14 der Arzneimittel-Richtlinien; Pimecrolimus zur topischen Behandlung

Indikation

Pimecrolimus ist zugelassen bei Patienten ab 2 Jahren mit leichtem bis mittelschwerem atopischen Ekzems zur

- Kurzzeitbehandlung von Anzeichen und Symptomen,
- intermittierenden Langzeitbehandlung, um das Auftreten von akuten Ekzemschüben zu verhindern.

Die Behandlung erfolgt zweimal täglich bis zur vollständigen Abheilung und sollte dann abgesetzt werden. Nach Unterbrechung beziehungsweise bei Langzeittherapie sollte die Behandlung beim ersten Wiederauftreten der Symptome erneut begonnen werden, um das Auftreten weiterer Krankheitsschübe zu verhindern.

Neben dem Wirkstoff sind folgende Hilfsstoffe enthalten: mittelkettige Triglyceride, (Z)-Octadec-9-en-1-ol, Propylenglycol, Stearylalkohol, Cetylalkohol, Glycerolmono/dispeisefettsäureester, Natriumcetylstearylsulfat, Benzylalkohol, Citronensäure, Natriumhydroxid und gereinigtes Wasser.

Pimecrolimus sollte nur von Ärzten verschrieben werden, die Erfahrung in der topischen Behandlung des atopischen Ekzems haben.

Wirksamkeit

Es wurden drei placebokontrollierte Hauptstudien zum Beleg der Wirksamkeit durchgeführt, die alle über sechs Wochen eine Doppelblindphase enthielten und eine sich anschließende 20-wöchige Phase, in der offen behandelt wurde. Endpunkt aller drei Studien war die Gesamtbewertung durch den Prüfarzt (IGA = Investigator Global Assessment) nach sechs Wochen. In allen Studien wurde Pimecrolimus 1% zweimal täglich gegen die Cremegrundlage getestet. Es erfolgte jeweils eine 2:1-Randomisierung.

In zwei Studien wurden Patienten in identischen Designs im Alter von 2 bis 17 Jahren behandelt. Der primäre Endpunkt zeigte eine statistisch-signifikante Überlegenheit gegenüber Cremegrundlage an dem prädefinierten Endpunkt in einer Studie, während dies in der anderen Studie nicht erreicht wurde. Die kombinierte Auswertung, die auch publiziert wurde, zeigt eine signifikante Überlegenheit von Pimecrolimus gegenüber Placebo.

Die dritte Studie wurde in fast identischem Design bei Kindern im Alter von 3 bis 21 Monaten durchgeführt. Auch hier zeigte sich eine statistisch signifikante Überlegenheit gegenüber der Cremegrundlage. Allerdings näherte sich der Anteil der Kleinkinder, die in der Verumgruppe in der Doppelblindphase unter Nebenwirkungen litten, dem Niveau statistisch signifikant (p=0,052). In der sich anschließenden offenen Phase blieb die Rate der Nebenwirkungen unter Pimecrolimus 1% weitgehend konstant (79,5%), während die Kinder, die von Cremegrundlage auf Pimecrolimus umgestellt wurden, eine deutliche Zunahme an Nebenwirkungen erlitten. Signifikant häufiger waren Fieber (31,7% versus 12,7%), Durchfall (8,1% versus 0%) und Otitis media (4,1% versus 0%). Gehäuft traten auch Infektionen des oberen Respirationstraktes auf (Differenz 9,3%), Nasopharynx-Infektionen (6,7%), Gastroenteritis (4,1%) etc. Beispielhaft kann hier die Inzidenz der Otitis media aufgeführt werden. Während der Doppelblindphase

lag sie bei 0% in der Gruppe der Kinder, die mit Cremegrundlage behandelt wurden. Nach Umstellung auf Pimecrolimus in der offenen Phase stieg sie auf 7,1% an. In der Behandlungsgruppe, die durchgängig mit Pimecrolimus behandelt wurde, stieg sie von 4,1% auf 9,4%, sodass angenommen werden kann, dass das Risiko mit der Dauer der Behandlung ansteigt.

Die gepoolte Analyse aller drei Studien erreichte statistische Überlegenheit am 43. Tag ($p<0,001$), als 160 Patienten (41%) der mit Pimecrolimus behandelten Patienten erfolgreich behandelt waren im Vergleich zu lediglich 40 (20,1%) der mit Placebo behandelten.

Die drei Hauptstudien wurden einer gemeinsamen Subgruppenanalyse unterzogen. Hierbei zeigte sich eine Überlegenheit von Pimecrolimus 1% in allen Subgruppen bis auf einen TBSA von >60% (total body surface area).

Eine vergleichbare placebokontrollierte Studie wurde bei Erwachsenen nicht durchgeführt.

In einer sechsarmigen Studie an Erwachsenen wurden vier Wirkstärken Pimecrolimus versus Cremegrundlage versus ein stark wirksames Kortikosteroid (0,1% Betamethasonvalerat) an 260 Patienten über drei Wochen geprüft. Betamethason war in dieser Dosisfindungsstudie wirksamer als Pimecrolimus.

In einer doppelblind randomisierten, 12-monatigen Studie an Erwachsenen wurde bei 658 Patienten Pimecrolimus im Vergleich zu einem mittelstark wirksamen Kortikosteroid (Triamcinolonacetonid 0,1%) beziehungsweise für Gesicht, Nacken und intertrigeniöse Areale mit einem schwach wirksamen Kortikosteroid (Hydrocortisonacetat 1%) verglichen. In dieser multizentrischen Studie mit 1:1-Randomisierung war zu allen Beobachtungszeitpunkten das Kortikosteroid statistisch signifikant Pimecrolimus überlegen. Entsprechend unterbrachen Patienten unter Kortikosteroiden deutlich seltener die Therapie als unter Pimecrolimus (8,2% versus 36,3%).

Zudem sprachen die Patienten, die mit topischen Kortikosteroiden behandelt wurden, deutlich schneller auf die Therapie an.

In einer randomisierten und multizentrischen, doppelblind placebokontrollierten (Cremegrundlage) Studie mit einer Randomisierung von 2:1 wurde in beiden Therapiearmen beim Schub die Studienmedikation zusammen mit blinden Emollentien verabreicht. Bei einem Schub wurde mit Kortikosteroiden behandelt. Im Anschluss daran wurde wiederum über sieben Tage mit Pimecrolimus beziehungsweise Placebo therapiert. Primärer Endpunkt der Studie war die Schubrate nach sechs Monaten (Schub wurde definiert als IGA von 4 oder 5 sowie einer Second-Line-Kortikoid-Therapie innerhalb von drei Tagen nach klinischer Visite). Die Studie wurde über insgesamt 12 Monate fortgeführt. Eingeschlossen wurden Patienten im Alter von 2 bis 18 Jahren. Die Anzahl der Patienten, die keinerlei Schübe erlitten, war nach sechs Monaten fast doppelt so hoch wie in der placebokontrollierten Gruppe (61% versus 34,2%). Dies veränderte sich nicht wesentlich nach 12 Monaten (50,8% versus 28,3%). Die Anzahl der Patienten, die Schübe erlitten, unterschied sich in den zwei Armen nach sechs Monaten nicht wesentlich, einen Schub erlitten in beiden Armen 10,1% der Patienten, zwei Schübe unter Pimecrolimus 2,5% und unter Placebo 5,1% und mehr als zwei Schübe 1,9% beziehungsweise 2,5%. Die Aussagekraft der Studie wird eingeschränkt dadurch, dass schwach, mittelstark und stark wirksame Glukokortikosteroide eingesetzt wurden und häufig das Protokoll verletzt wurde, insgesamt 53,6% Protokollverletzungen in der Gruppe, die Pimecrolimus erhielten, und 58,6% der Patienten, die Placebo erhielten. Ganz wesentlicher Mangel der Studie ist der verpflichtende Gebrauch von Pimecrolimus oder Placebo über sieben Tage nach der Behandlung des Schubs mit topischen Kortikosteroiden, der dazu führt, dass die mit Pimecrolimus behandelte Gruppe insgesamt sieben Tage länger eine aktive

Arzneimitteltherapie im Vergleich zu Placebo erhält. Unter diesen Aspekten ist die Studie nicht in der Lage, für sich in Anspruch zu nehmen, nachweisen zu können, dass Pimecrolimus die Anzahl der Schübe bei atopischer Dermatitis im Vergleich zur „Standardbehandlung“ zu vermindern oder insbesondere auch eine Reduktion des Gebrauchs von topischen Kortikosteroiden zu induzieren vermag. Im Studiendesign vergleichbare Studien wurden bei Kindern im Alter von 3 bis 23 Monaten und Erwachsenen durchgeführt. Auf sie trifft die gleiche Kritik zu.

Risiken — ggf. Vorsichtsmaßnahmen

Die am häufigsten vorkommenden Nebenwirkungen waren Reaktionen am Anwendungsort, die von zirka 19% der mit Elidel® behandelten Patienten und von zirka 16% der Patienten der Kontrollgruppe berichtet wurden. Diese Reaktionen traten vor allem zu Beginn der Behandlung auf, sie waren schwach bis mäßig stark und von kurzer Dauer.

In klinischen Untersuchungen kam es in 0,9% zu Lymphadenopathien. In der Mehrzahl waren sie auf Infektionen zurückzuführen, die unter einer angemessenen Antibiotikabehandlung abklangen. Patienten, die eine Lymphadenopathie entwickeln, sollten überwacht werden, um sicherzustellen, dass die Lymphadenopathie abklingt. Die Ätiologie ist zu klären. Kann die Krankheitsursache nicht eindeutig ermittelt werden oder liegt eine akute infektiöse Mononukleose vor, so ist die Unterbrechung der Behandlung mit Pimecrolimus in Erwägung zu ziehen.

Bei Patienten mit ausgedehnter atopischer Dermatitis wird empfohlen, Impfungen während behandlungsfreier Intervalle durchzuführen. Pimecrolimus sollte nicht gleichzeitig mit topischen Kortikosteroiden oder anderen topischen antiinflammatorischen Produkten appliziert werden. Es gibt keine Erfahrungen zur gleichzeitigen Anwendung von immunosuppressiven Therapien bei atopischem Ekzem, wie Azathioprin oder Ciclosporin.

Gemäß US-amerikanischer Fachinformation zeigte sich in Photokanzerogenitätsstudien beim Tier eine Verkürzung der Zeitspanne bis zum Auftreten von Tumorformationen durch die Cremegrundlage. Da die Relevanz dieser Daten für den Menschen nicht bekannt ist, sollten während der Behandlung mit Pimecrolimus-Creme ausgedehnte Bestrahlungen der Haut mit ultraviolettem Licht, wie beispielsweise in Solarien, oder die Therapie mit PUVA, UVA oder UVB vermieden werden. Der Arzt sollte die Patienten auf angemessene Sonnenschutzmaßnahmen hinweisen, wie eine Minimierung der Aufenthaltszeit in der Sonne, Benutzung von Sonnenschutzprodukten und Bedeckung der Haut mit entsprechender Kleidung.

Bei Kindern unter zwei Jahren traten, wie dargestellt, vermehrt Nebenwirkungen auf. Die Anwendung von Pimecrolimus bei Kindern unter 2 Jahren wird nicht empfohlen.

Eine Behandlung mit Pimecrolimus kann mit einem erhöhten Risiko für eine Herpes-simplex-Infektion oder Eczema herpeticum einhergehen (erkennbar an einer schnellen Ausbreitung von bläschenartigen und erosiven Läsionen). Bei Vorhandensein einer Herpes- simplex-Infektion sollte an der betroffenen Stelle die Behandlung nicht fortgesetzt werden, bis die virale Infektion abgeklungen ist. Obwohl bei Patienten, die mit Pimecrolimus behandelt wurden, bakterielle Autoinfektionen seltener waren als bei Patienten, die mit Placebo behandelt wurden, kann bei Patienten mit schwerem atopischen Ekzem das Risiko für bakterielle Hautinfektionen (Impetigo) während der Behandlung mit Elidel® erhöht sein. Pimecrolimus darf nicht auf Bereiche aufgetragen werden, die von akuten viralen Hautinfektionen betroffen sind (Herpes simplex, Windpocken).

Die Anwendung in der Schwangerschaft und Stillzeit sowie bei Patienten mit genetisch bedingten Schädigungen der Epidermisschranke (z. B. Netherton-Syndrom) und

generalisierter Erythrodermie wird nicht empfohlen. Kontakt mit Augen und Schleimhäuten ist zu vermeiden, das Gleiche gilt für Okklusionsverbände.

G-BA, 2003 [10].

Bekanntmachung des Bundesausschusses der Ärzte und Krankenkassen über eine Änderung der Richtlinien über die Verordnung von Arzneimitteln der vertragsärztlichen Versorgung (Arzneimittel-Richtlinien) vom 4. September 2003: Therapiehinweis nach Nr. 14 der Arzneimittel-Richtlinien; Tacrolimus zur topischen Behandlung

Indikation

Tacrolimus ist zugelassen zur Behandlung des mittelschweren bis schweren atopischen Ekzems bei Erwachsenen, die auf herkömmliche Therapie nicht ausreichend ansprechen oder diese nicht vertragen, sowie bei Kindern ab 2 Jahren, die nicht ausreichend auf die herkömmliche Therapie angesprochen haben.

Es kann zur Kurzzeitbehandlung und intermittierenden Langzeitbehandlung angewendet werden.

Die Behandlung erfolgt zweimal täglich bis zu drei Wochen und wird dann auf einmal täglich reduziert und bis zur Abheilung fortgeführt, danach abgesetzt. Bei Kindern ist nur die Wirkstärke 0,03% indiziert. Bei Erwachsenen (ab 16 Jahren) sollte mit der 0,1% Salbe begonnen werden bei zweimal täglicher Anwendung für eine Dauer von bis zu drei Wochen. Danach sollte die Stärke auf 0,03% bei zweimal täglicher Anwendung reduziert werden. Wenn der klinische Zustand es erlaubt, sollte versucht werden, die Anwendungshäufigkeit zu verringern.

Ist nach zweiwöchiger Behandlung keine Besserung zu erkennen, sind andere Therapiemöglichkeiten in Betracht zu ziehen.

Neben dem Wirkstoff sind folgende Hilfsstoffe enthalten: weißes Vaselin, dickflüssiges Paraffin, Propylencarbonat, gebleichtes Wachs und Hartparaffin.

Tacrolimus darf nur von Dermatologen beziehungsweise Ärzten mit umfangreicher Erfahrung in der Behandlung des atopischen Ekzems mit immunmodulierenden Therapien verschrieben werden.

Wirksamkeit

Die Wirksamkeit wurde in fünf maßgeblichen Phase-III-Studien geprüft, die in Europa und Amerika durchgeführt wurden. Bei den eingeschlossenen Patienten war im Durchschnitt ein Drittel der Körperoberfläche erkrankt und ungefähr die Hälfte der Patienten litten unter einer schweren Erkrankung.

Die Behandlung mit Tacrolimus-Salbe zeigte im Vergleich zur Salbengrundlage in direkt vergleichenden Studien über eine Behandlungsdauer von drei bis zwölf Wochen signifikant bessere Ergebnisse. Ungefähr drei- bis viermal mehr Patienten sprachen auf Tacrolimus versus Salbengrundlage an (Salbengrundlage 7—8%, 0,03% Tacrolimus zirka 35%, 0,1% Tacrolimus zirka 40%).

Vergleichende Untersuchungen zu topischen Glukokortikoiden wurden durchgeführt. Bei Kindern war Tacrolimus dem schwach wirksamen 1% Hydrocortisonacetat in zwei Studien überlegen. Allerdings wird die Wahl des schwach wirksamen Referenzsteroids wegen dessen begrenzter Wirksamkeit als nicht optimal angesehen. Im Vergleich zu einem mittelstarken Kortikosteroid (0,1% Hydrocortisonbutyrat) ergab sich bei Erwachsenen kein signifikanter

Unterschied der Wirksamkeit. In zwei vergleichenden japanischen Studien der Phase III mit insgesamt 329 Patienten war die Wirksamkeit von 0,1% Tacrolimus dem stark wirksamen topischen Kortikosteroid (0,12% Betamethasonvalerat) vergleichbar und dem mittelstark wirksamen 0,1% Alcometasondipropionat überlegen.

Unter Tacrolimus und auch unter der Salbengrundlage allein traten mehr lokale Nebenwirkungen auf als unter Kortikosteroiden.

Das Wiederauftreten der Erkrankung war bisher nicht Ziel von Untersuchungen. In den US-amerikanischen Studien kam es bei ungefähr der Hälfte der Patienten zwei Wochen nach Absetzen der Therapie zu einem erneuten Schub. In den europäischen Untersuchungen hielt eine moderate Verbesserung bei etwa der Hälfte der Patienten zwei Wochen nach Absetzen an.

Risiken — ggf. Vorsichtsmaßnahmen

Bei 50% aller Patienten traten Nebenwirkungen in Form von Hautreizungen verschiedener Art im behandelten Bereich auf. Brennen, Jucken und Hautrötung traten sehr häufig auf und verschwanden in der Regel innerhalb einer Woche. Erhöhte Empfindlichkeit in der Haut und Prickeln sowie Hyperästhesie wurden ebenso wie lokale Unverträglichkeit gegenüber Alkohol häufig beobachtet. Unter den häufigen Nebenwirkungen finden sich auch Follikulitis, Akne und Herpes simplex (Herpes, Fieberbläschen, Eczema herpeticatum [Kaposi varicelliforme Eruption]).

In klinischen Untersuchungen kam es in 0,8% zu Lymphadenopathien. In der Mehrzahl handelte es sich um Infektionen, die unter einer angemessenen Antibiotikabehandlung abklangen. Bei transplantierten, mit Immunsuppressiva behandelten Patienten ist das Risiko der Entstehung eines Lymphoms erhöht; daher sind mit Tacrolimus behandelte Patienten, die eine Lymphadenopathie entwickeln, zu überwachen, um sicherzustellen, dass die Lymphadenopathie abklingt. Die Ätiologie ist zu klären. Kann die Krankheitsursache nicht eindeutig ermittelt werden oder liegt eine infektiöse Mononukleose vor, so ist die Unterbrechung der Behandlung mit Tacrolimus in Erwägung zu ziehen.

Die Auswirkungen der Behandlung auf das sich entwickelnde Immunsystem bei Kindern ist nicht bekannt. Impfungen sollten nicht während der Behandlung mit Tacrolimus verabreicht werden. Bei abgeschwächten Lebendimpfstoffen (z. B. gegen Masern, Mumps, Röteln oder Kinderlähmung) beträgt die Karenzzeit 28 Tage, bei inaktivierten Impfstoffen (z. B. gegen Tetanus, Diphtherie, Keuchhusten oder Grippe) 14 Tage.

In einer Photokanzerogenitätsstudie wurden haarlose Albinomäuse chronisch mit Tacrolimus-Salbe und UV-Bestrahlung behandelt. Die mit Tacrolimus-Salbe behandelten Tiere zeigten eine statistisch signifikante Verkürzung der Zeitspanne bis zum Auftreten von Hauttumoren (Plattenepithelkarzinome) und eine erhöhte Anzahl von Tumoren. Inwieweit diese Befunde auf den Menschen übertragbar sind, ist unbekannt. Nach der Fachinformation des Herstellers sollte während der Behandlung mit Tacrolimus-Salbe die Haut möglichst nicht dem Sonnenlicht ausgesetzt werden. Die Anwendung von ultraviolettem (UV) Licht in Solarien sowie die Therapie mit UVB oder UVA in Kombination mit Psoralenen (PUVA) sollte vermieden werden. Der Arzt muss die Patienten über geeignete Lichtschutzmaßnahmen beraten (z. B. Vermeidung von Aufenthalt in der Sonne, Anwendung von Lichtschutzmitteln und Abdeckung der Haut mit entsprechender Kleidung).

Ob eine Behandlungsdauer von mehr als zwei Jahren mit dem Risiko einer lokalen, eventuell zu Infektionen oder kutanen Malignomen führenden Immunsuppression verbunden ist, ist nicht bekannt.

Hautpflegemittel dürfen innerhalb von zwei Stunden vor beziehungsweise nach Applikation von Tacrolimus nicht im gleichen Hautbereich angewendet werden. Über die gleichzeitige Verwendung anderer topischer Präparate und systemischer Steroide oder Immunsuppressiva liegen keine Erfahrungen vor. Die gleichzeitige systemische Verabreichung von CYP3A4-Hemmern (z. B. Erythromycin, Itraconazol, Ketoconazol und Diltiazem) bei Patienten mit ausgedehnter und/oder erythrodermischer Erkrankung sollte mit Vorsicht erfolgen.

Die Anwendung in der Schwangerschaft und Stillzeit sowie bei Patienten mit genetisch bedingten Schädigungen der Epidermisschranke (z. B. Netherton-Syndrom) und generalisierter Erythrodermie wird nicht empfohlen. Das Gleiche gilt für Okklusivverbände. Der Kontakt mit Augen und Schleimhaut ist zu vermeiden. Die Salbe darf auf infizierten Hautstellen nicht angewendet werden.

3.2 Cochrane Reviews

Ferguson L et al., 2018 [6].

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:

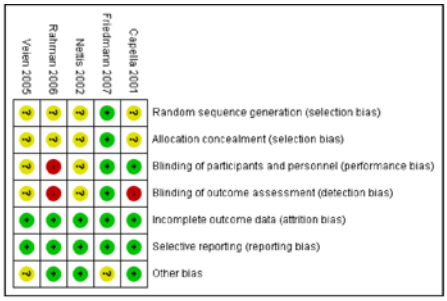
- 5 RCT (involving a total of 202 participants)
- sample sizes ranged from 20 to 60 participants
- All studies used montelukast 10 mg for adults (age 14 years and above) or 5 mg for children (age 6 years to 14 years) in tablet form taken orally as the LTRA intervention; three studies compared this with 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.

Kommentare zum Review

- Die Studiendauern sind mit 4-8 Wochen sehr kurz.

Matterne U et al., 2019 [17].

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).

Charakteristika der Population:

- 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

- 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 [20].

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

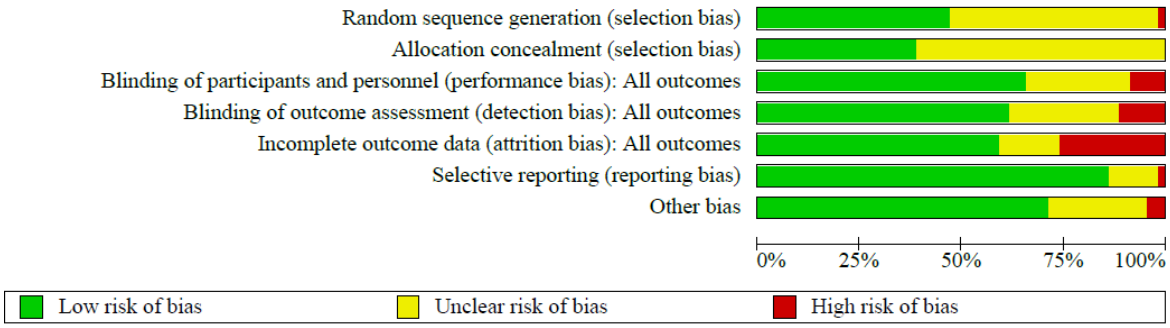
Anzahl eingeschlossener Studien:

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

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

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.

3.3 Systematische Reviews

Agache I et al., 2021 [2].

Efficacy and safety of dupilumab for moderate-to-severe atopic dermatitis: A systematic review for the EAACI biologicals guidelines.
Siehe auch folgende systematische Reviews mit vergleichbaren Ergebnissen:

- Xu et al., 2017 [24]. Efficacy and safety of dupilumab for the treatment of moderate-to-severe atopic dermatitis in adults
- Snast I et al., 2018 [22]. Are Biologics Efficacious in Atopic Dermatitis? A Systematic Review and Meta-Analysis
- Wang FP et al., 2018 [23]. Dupilumab treatment in moderate-to-severe 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

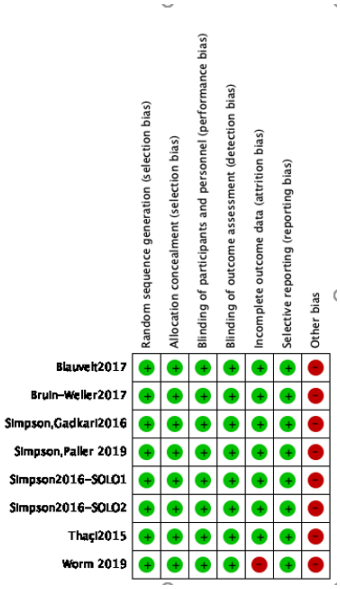
Population

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

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

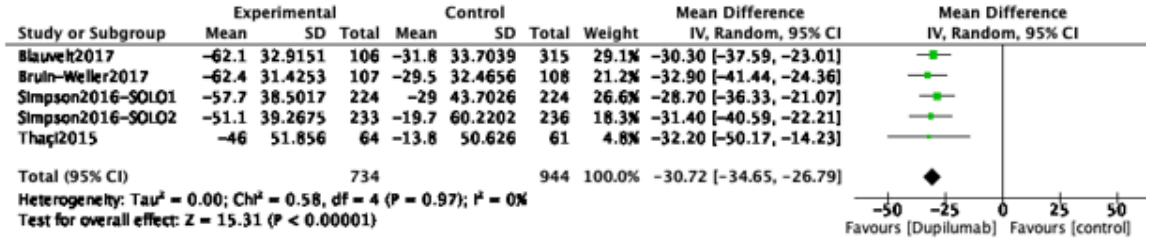
- The RCTs included in the SR evaluated 1678 adults and 167 adolescents with moderate-to-severe AD inadequately controlled by topical treatment. Follow-up under treatment ranged from 16 weeks36,37,39,40 to 1 year.38 One RCT recruited responders from SOLO trials and continued the intervention for another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

Qualität der Studien:



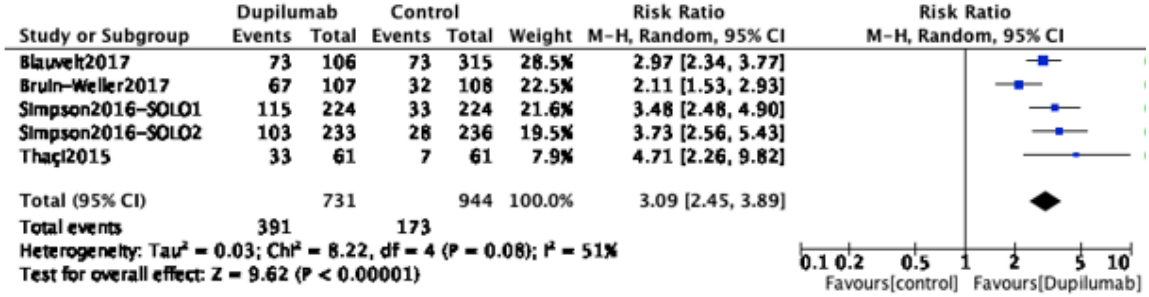
Studienergebnisse:

Scoring Atopic Dermatitis (SCORAD) score

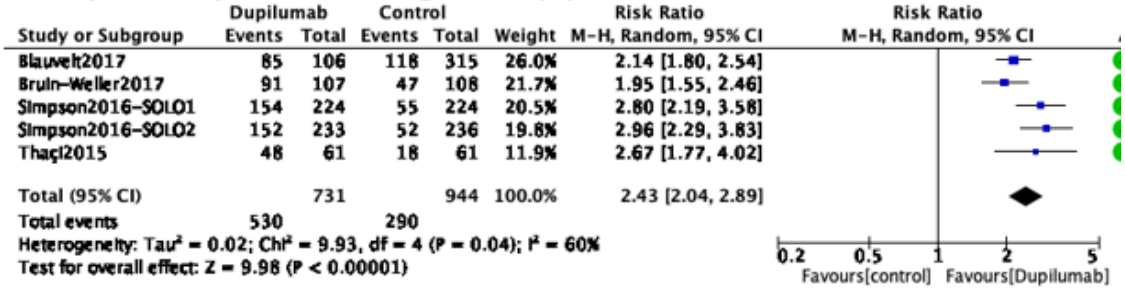


- Eczema Area and Severity Index (EASI)

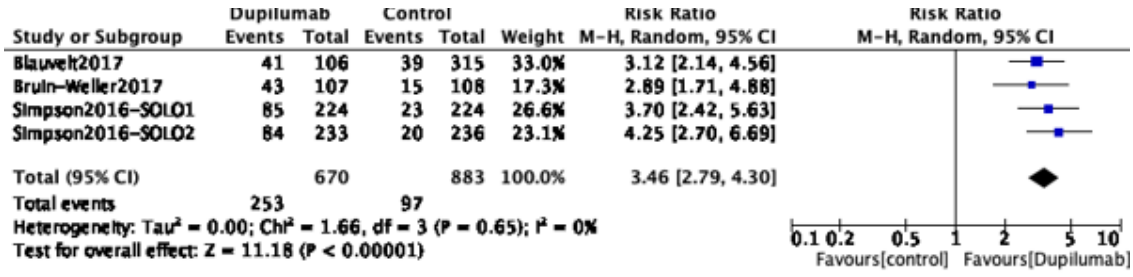
2.1 Proportion of patients achieving EASI-75 (%)



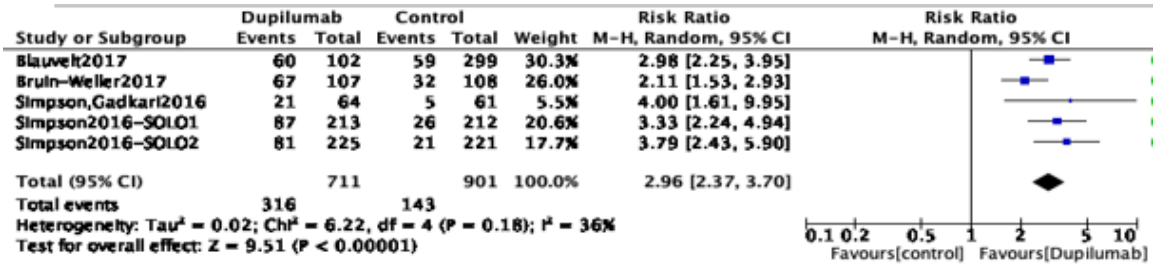
2.2 Proportion of patients achieving EASI-50 (%)



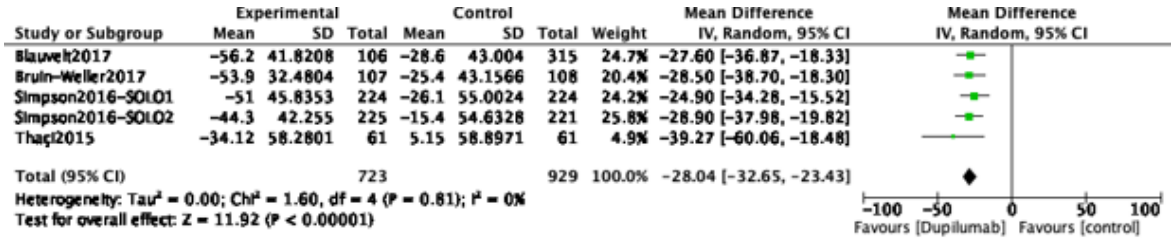
- IGA score achieved 0/1 and reduction of ≥2 points from baseline



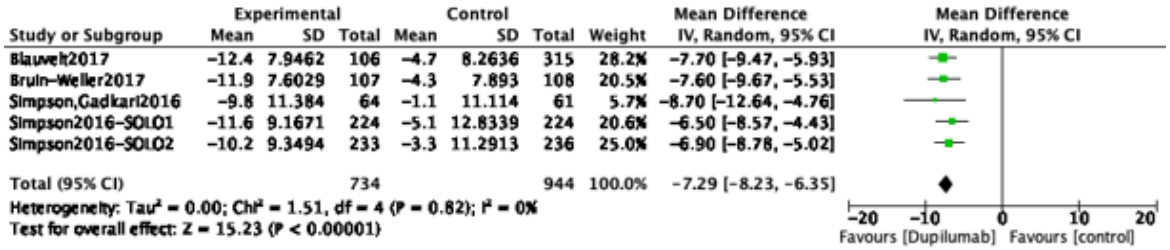
- Pruritus
  - Improvement in peak score on numerical rating scale (NRS) for pruritus ≥ 4 points



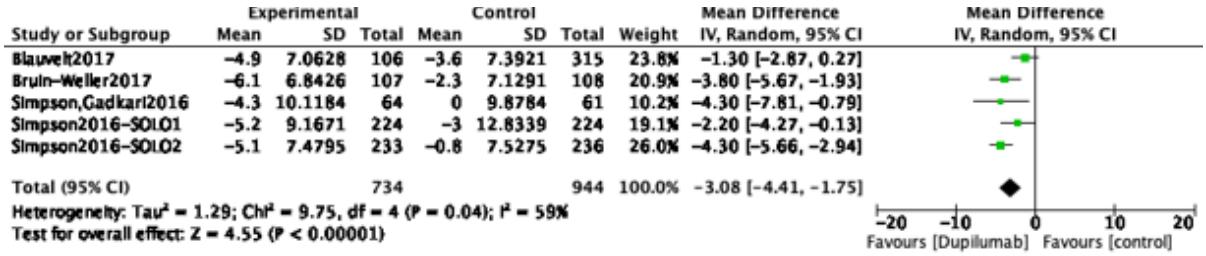
  - Peak pruritus NRS score (LS mean % change from baseline)



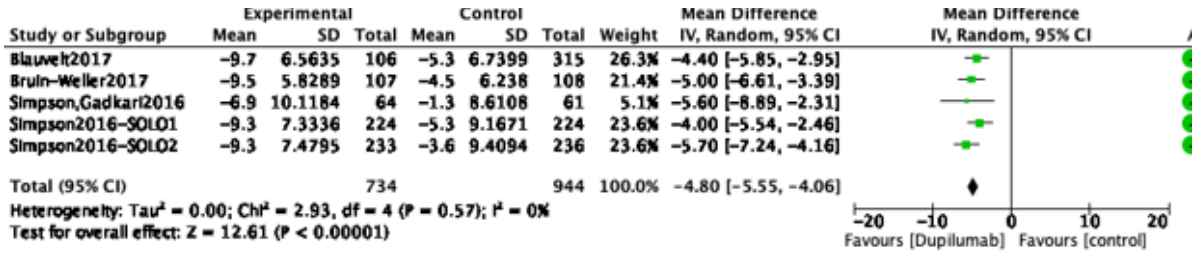
- Patient-Oriented Eczema Measure



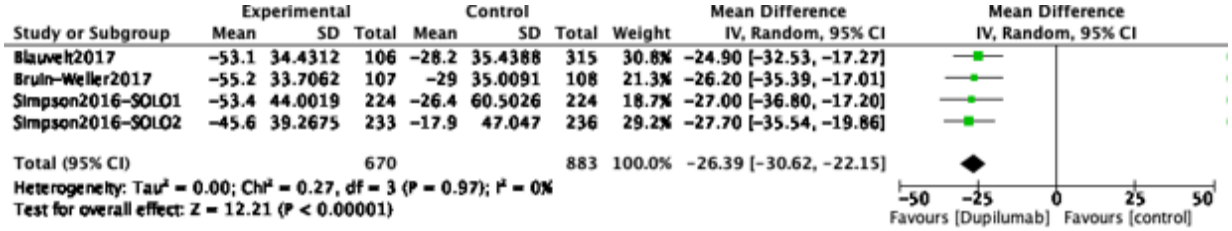
- Hospital Anxiety and Depression Scale (HADS)



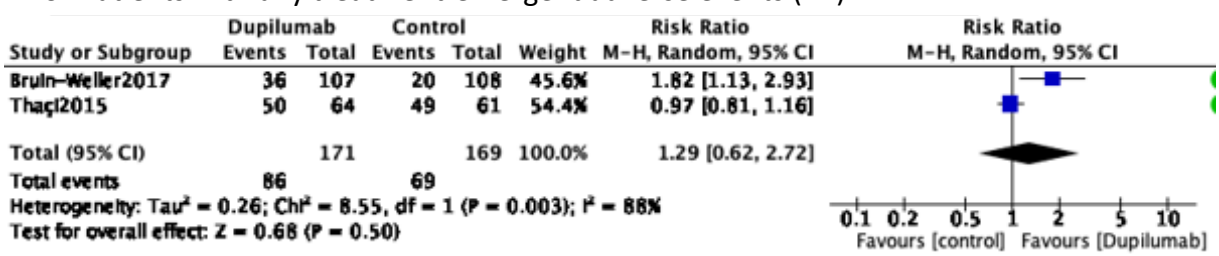
- Quality of life measured by Dermatology Life Quality Index (DLQI)



- Global Individual Signs Score (GISS)



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



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

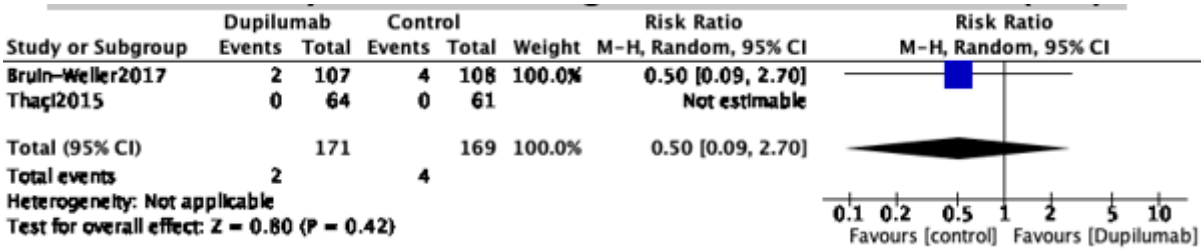


TABLE 3 Summary of evidence for the outcomes of interest. Adult atopic dermatitis population: Dupilumab efficacy and safety compared to standard of care

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

Anmerkung/Fazit der Autoren

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

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

49. Wang F-P, Tang X-J, Wei C-Q, et al. Dupilumab treatment in moderate- to-severe atopic dermatitis: a systematic review and meta-analysis. J Dermatol Sci. 2018;90(2):190-198.

50. Snast I, Reiter O, Hodak E, et al. Are biologics efficacious in atopic dermatitis? A systematic review and meta-analysis. Am J Clin Dermatol. 2018;19(2):145-165.

51. Drucker AM, Ellis AG, Bohdanowicz M, et al. Systemic immunomodulatory treatments for patients with atopic dermatitis: a systematic review and network meta-analysis. JAMA Dermatol. 2020;156(6):1-10.

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

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

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

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

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

Fleming P et al., 2018 [7].

Risk of infection in patients with atopic dermatitis treated with dupilumab: a meta-analysis of randomized controlled trials.

Fragestellung

To determine the impact of dupilumab on rates of skin and other infections in patients with moderate-to-severe AD

Methodik

Population:

- patients with AD

Intervention:

- dupilumab

Komparator:

- placebo

Endpunkt:

- skin infection
- overall herpetic infections [of any organ system]
- eczema herpeticum
- overall infections or infestation of any organ system

Recherche/Suchzeitraum:

- PubMed on October 6, 2016, update on June 15, 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs with 2706 adult participants

Charakteristika der Population:

- moderate-to-severe AD

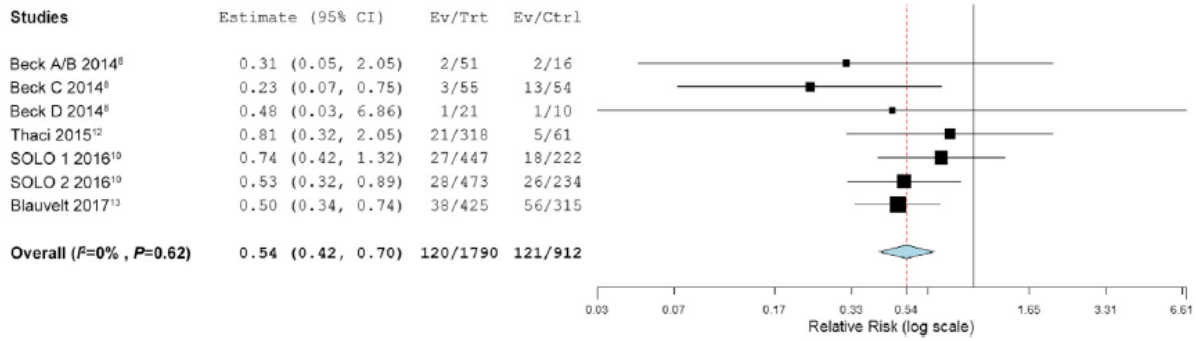
Study ID	Study design and duration	TCS use	Intervention arms	No. randomized
Studies A and B in Beck et al, 2014[8]	Phase 1 RCT (Combined US and global study) with 4-wk follow-up	Not individually reported	Placebo	16
			Dupilumab, 75 mg (n = 8), 150 mg (n = 22), or 300 mg (n = 21) qwk	51
Study C in Beck et al, 2014[8]	Phase 2a RCT with 12-wk follow-up	Not individually reported	Placebo	54
			Dupilumab, 300 mg qwk	55
Study D in Beck et al, 2014[8]	Phase 2a RCT with 4-wk follow-up	Yes	Placebo + TCS	10
			Dupilumab, 300 mg qwk + TCS	21
Thaçi et al, 2015[12]	Phase 2b RCT dose-finding study of dupilumab with 16-wk follow-up	Not individually reported (counted as non-responders with other therapies)	Placebo	61
			Dupilumab, 300 mg q2wk	64
			Dupilumab, 300 mg qwk	63
			Dupilumab, 200 mg q2wk	62
			Dupilumab, 300 mg q4wk	65
			Dupilumab, 100 mg q4wk	65
SOLO 1 in Simpson et al, 2016[10]	Phase 3 RCT with 16-wk follow-up	Not individually reported	Placebo	224
			Dupilumab, 300 mg q2wk	224
			Dupilumab, 300 mg qwk	223
SOLO 2 in Simpson et al, 2016[10]	Phase 3 RCT with 16-wk follow-up	Not individually reported	Placebo	236
			Dupilumab, 300 mg q2wk	233
			Dupilumab, 300 mg qwk	239
Blauvelt et al, 2017[13]	Phase 3 RCT with 1 y follow-up	Yes	Placebo + TCS	315
			Dupilumab, 300 mg q2wk + TCS	106
			Dupilumab, 300 mg qwk + TCS	319

<u>Qualität der Studien:</u>

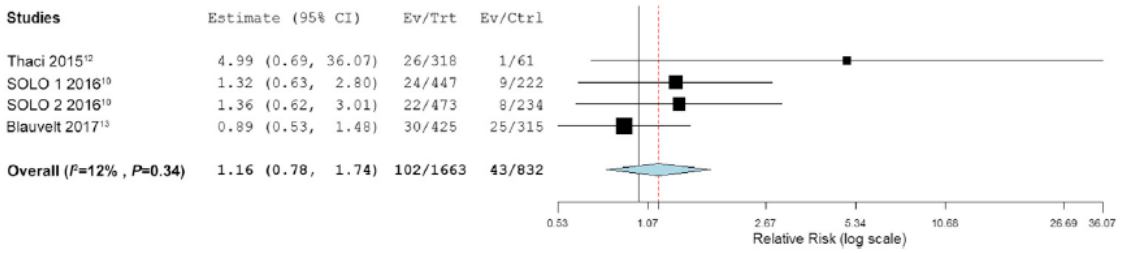
- All studies were considered to be generally at low risk for bias.

<u>Studienergebnisse:</u>

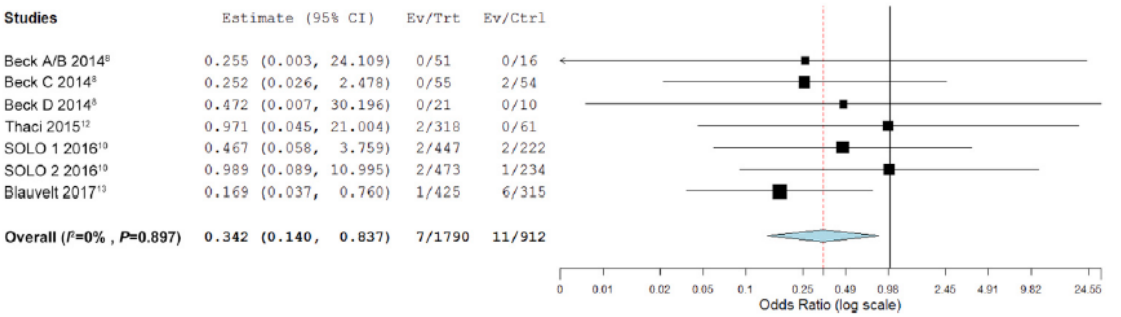
- skin infections



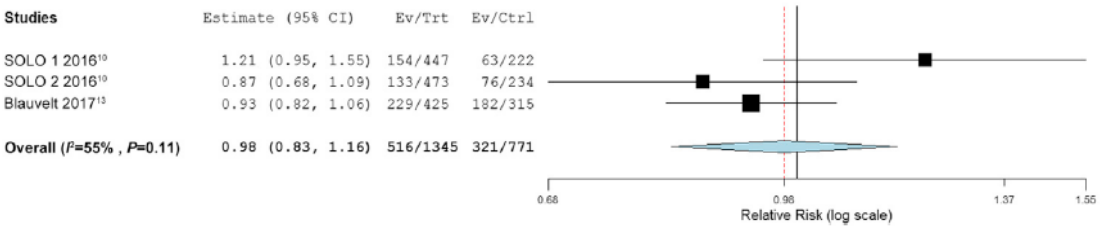
- Herpes Virus infections



- eczema herpeticum



- overall infections



Anmerkung/Fazit der Autoren

Dupilumab was associated with decreased skin infections and eczema herpeticum in our meta-analysis of 8 placebo-controlled RCTs. We did not find an association between dupilumab and overall herpesvirus infections or infections and infestations. The mechanism underlying dupilumab's effects on skin infections is uncertain but is likely related to improvement in AD severity.

Kommentare zum Review

- Keine Subgruppenanalysen zum Schweregrad

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.

Ou Z et al., 2018 [19].

Adverse events of dupilumab in adults with moderate-to-severe atopic dermatitis: a meta-analysis

Fragestellung

To assess the influence of dupilumab on adverse events in adults with moderate-to-severe AD.

Methodik

Population:

- patients diagnosed with AD & Investigator's Global Assessment score of patients must have been 3 or higher at screening and baseline;

Intervention:

- dupilumab

Komparator:

- placebo

Endpunkt:

- adverse events

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, Web of Science and the Cochrane Library from inception to December 2017

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Risk of Bias tool

Ergebnisse

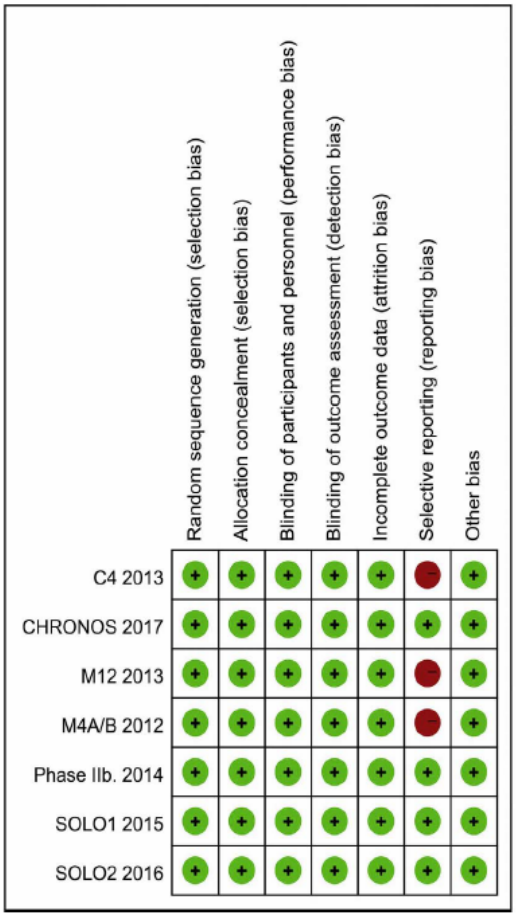
Anzahl eingeschlossener Studien:

- 8 RCTs

Charakteristika der Population:

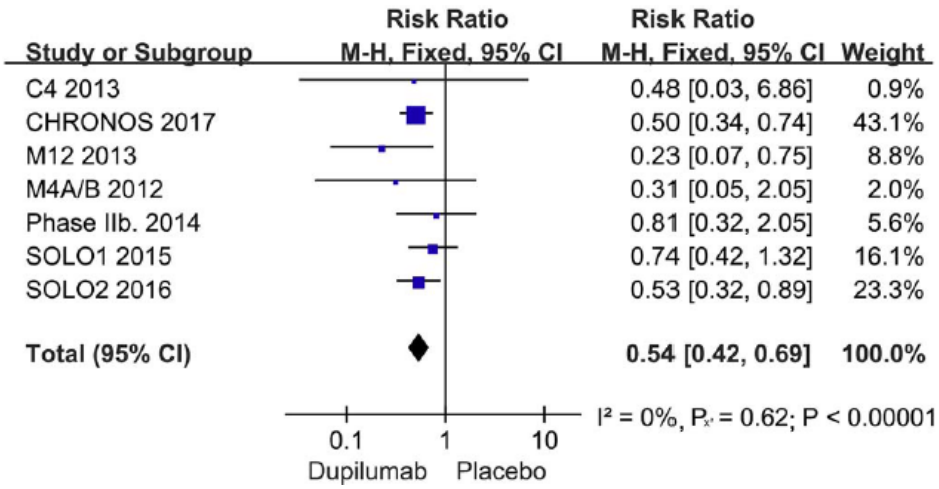
Reference (study, year)	Patients	Outcomes	Intervention (patients)	Control
Beck et al. 2014 (M4A, 2012)	30 adults (≥ 18 y, 58.2% male) with IGA ≥ 3, BSA ≥ 10%	Skin infection	Dupilumab:75 mg qw (8), 150 mg qw (8), 300 mg qw (8) for 4 weeks	Placebo
Beck et al. 2014 (M4B, 2012)	37 adults (≥ 18 y, 58.2% male) with IGA ≥ 3, BSA ≥ 10%	Skin infection	Dupilumab:150 mg qw (14), 300 mg qw (13) for 4 weeks	Placebo
Beck et al. 2014 (M12, 2013)	109 adults (≥ 18 y, 53.2% male) with IGA ≥ 3, BSA ≥ 10%	Skin infection	Dupilumab: 300 mg qw (55) for 12 weeks	Placebo
Beck et al. 2014 (C4, 2013)	31 adults (≥ 18 y, 41.9% male) with IGA ≥ 3, BSA ≥ 10%	Skin infection	Dupilumab + TGC:300 mg qw (21) for 4 weeks	Placebo + TGC
Thaci et al. 2015 (Phase IIb, 2014)	379 adults (≥ 18 y, 61.7% male) with IGA ≥ 3, BSA ≥ 10%	Infections[b]; exacerbation of AD; injection-site reaction; headache	Dupilumab: 300 mg qw (63), 300 mg q2w (64), 200 mg q2w (61), 300 mg q4w (65), 100 mg q4w (65) for 16 weeks	Placebo
Simpson et al. 2016 (SOLO 1, 2015)	671 adults[a] (≥ 18 y, 58.1% male) with IGA ≥ 3, BSA ≥ 10%	Infections[b]; exacerbation of AD; injection-site reaction; headache	Dupilumab: 300 mg qw (218), 300 mg q2w (229) for 16 weeks	Placebo
Simpson et al. 2016 (SOLO 2, 2016)	708 adults[a] (≥ 18 y, 57.6% male) with IGA ≥ 3, BSA ≥ 10%	Infections[b]; exacerbation of AD; injection-site reaction; headache	Dupilumab: 300 mg qw (237), 300 mg q2w (236) for 16 weeks	Placebo
Blauvelt et al. 2017 (CHRONOS, 2016)	740 adults[a] (≥ 18 y, 60.0% male) with IGA ≥ 3, BSA ≥ 10%	Infections[b] except urinary tract infection; exacerbation of AD; injection-site reaction; headache	Dupilumab + TGC: 300 mg qw (315), 300 mg q2w (110) for 52 weeks	Placebo + TGC

Qualität der Studien:

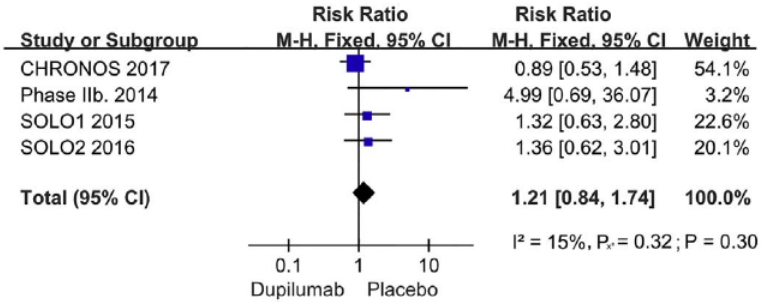


Studienergebnisse:

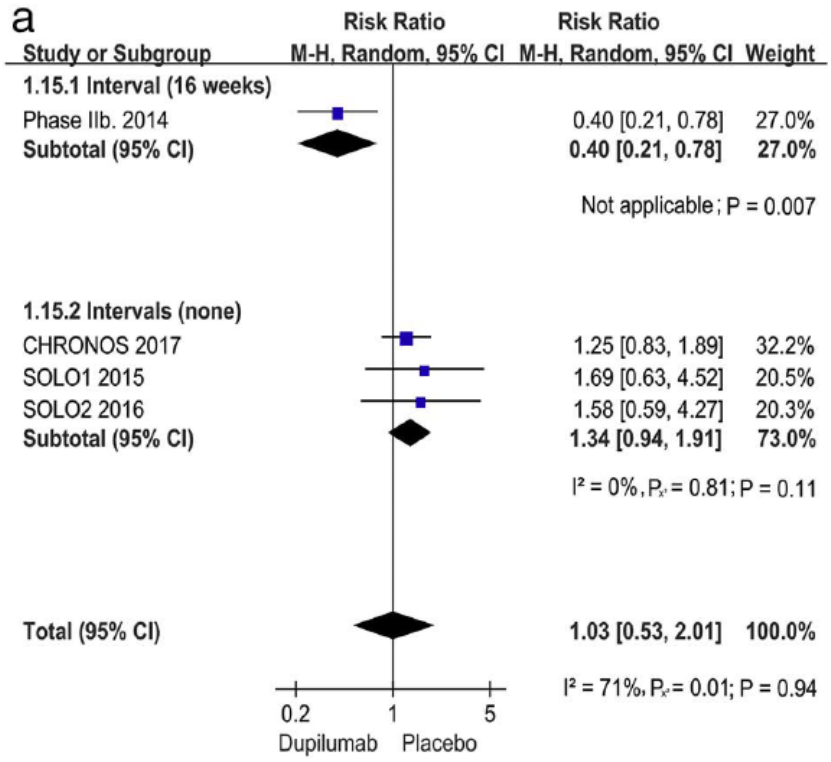
- skin infections



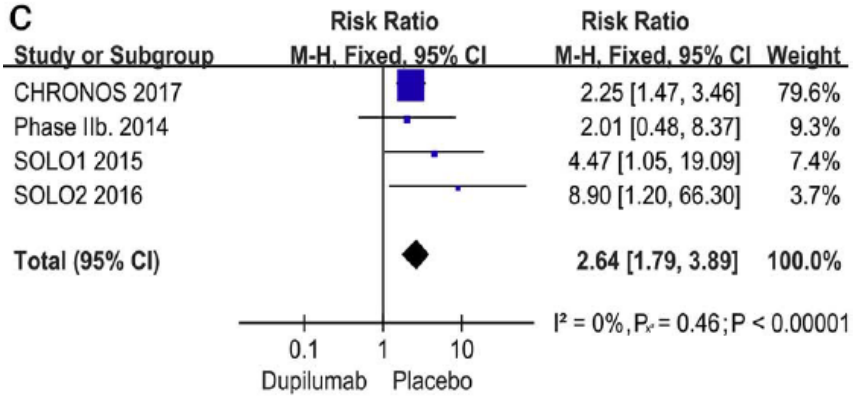
- herpes virus infections



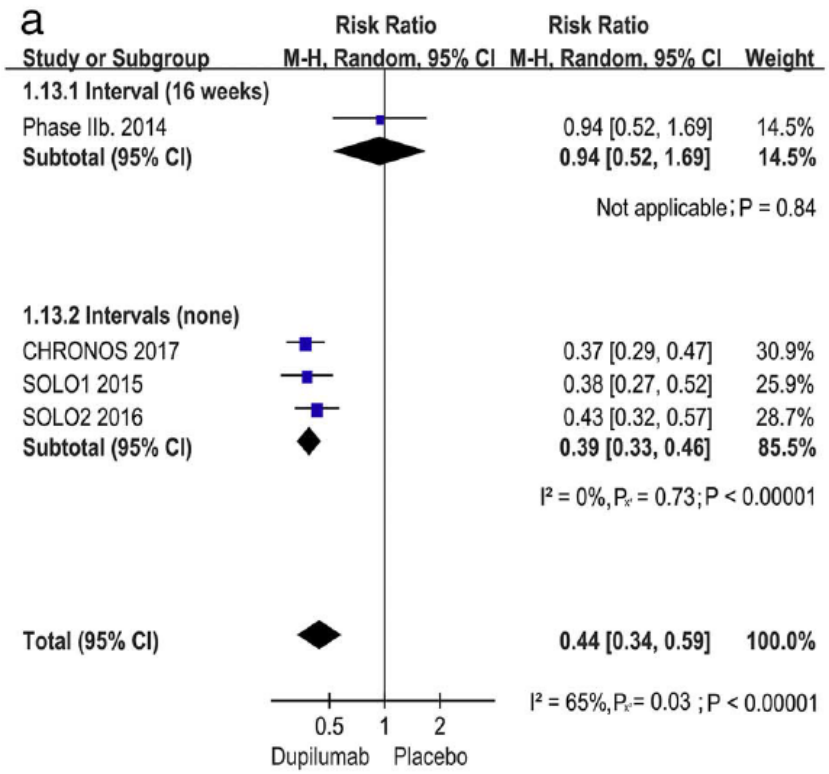
- Upper respiratory tract infection



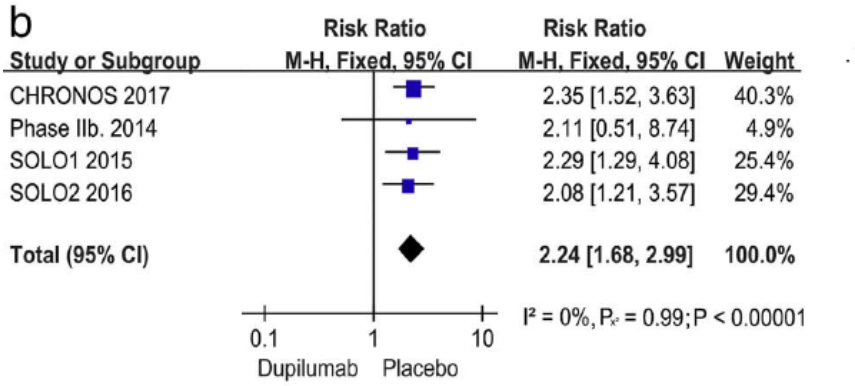
- Conjunctivitis



- Exacerbation of atopic dermatitis



- injection-site reaction



- Nasopharyngitis, urinary tract infection, headache
  - Kein signifikanter Unterschied

Anmerkung/Fazit der Autoren

In this study, we have found dupilumab to have few side effects, even decreasing the risk of skin infection and the exacerbation of AD in adults with moderate-to-severe AD. In summary, dupilumab possesses many significant advantages over current therapies for patients with moderate-to-severe AD. However, the long-term safety and effect on the most commonly affected population, children, need to be explored in future clinical research.

Kommentare zum Review

- Keine Subgruppenanalysen zum Schweregrad

Drucker AM et al., 2020 [5].

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

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.

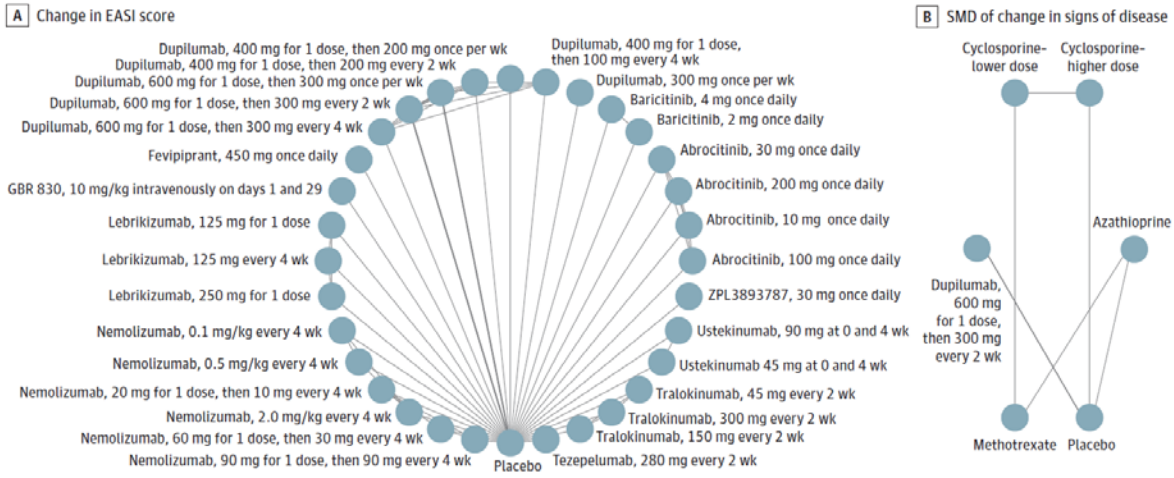
- Very few studies (n = 6) included outcomes beyond 16 weeks, and network meta-analyses were therefore limited to short-term outcomes

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.

Siegels D et al., 2020 [21].

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

Fragestellung

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

Methodik

Population:

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

Intervention:

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

Komparator:

- any

Endpunkte:

TABLE 2 Outcomes

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias 2.0 Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 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]	Wahlgren et al, 1990[57]	Short-term (10 days)	Adults
			nonvalidated severity scores and VAS pruritus[34,36,53,57]	Sowden et al, 1991[34]	Short-term (8 weeks)	Mixed (≥17 years)
			VAS sleeplessness[34,53]	Salek et al, 1993[31]	Short-term (8 weeks)	Mixed (≥17 years)
			EDI and UKSIP[31]	Munro et al, 1994[53]	Short-term (8 weeks)	Adults
				van Joost et al, 1994[36]	Short-term (6 weeks)	Mixed (≥17 years)
			CSA equally effective as MTX for: SCORAD[22,75]	El-Khalawany et al, 2013[22]	Short-term (12 weeks)	Mixed (8-14 years)
			EASI and DLQI[75]	Goujon et al, 2017[75]	Short- and long-term (12 and 24 weeks)	Adults
			CSA superior to UVAB phototherapy after 8 weeks (for SCORAD) and equally effective after 52 weeks (for SCORAD and EDI)[23]	Granlund et al, 2001[23]	Short- and long-term (8 and 52 weeks)	Adults
			CSA equally effective as tacrolimus ointment for: SCORAD, nonvalidated pruritus score and nonvalidated sleep score[54]	Pacor et al, 2004[54]	Short-term (6 weeks)	Mixed (≥13 years)
			CSA superior to IVIG for: SCORAD[46]	Bemanian et al, 2005[46]	Short-term (12 weeks)	Not reported (only "children" reported)
			CSA superior to prednisolone for: SCORAD[32]	Schmitt et al, 2010[32]	Short-term (12 weeks)	Adults
			CSA superior to ECP for: SCORAD and VAS pruritus[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:	Kwon et al, 2013[82]	Short-term (2 weeks)	Mixed (≥12 years)
			SCORAD equally effective with concomitant glucosamine[82]	Jin et al, 2015[79]	Short-term (8 weeks)	Mixed (≥7 years)
			SCORAD superior with concomitant glucosamine[79]	Kim et al, 2016[80]	Long-term (24 weeks)	Mixed (any age allowed)
			EASI equally effective with "topical agents"[80]			
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

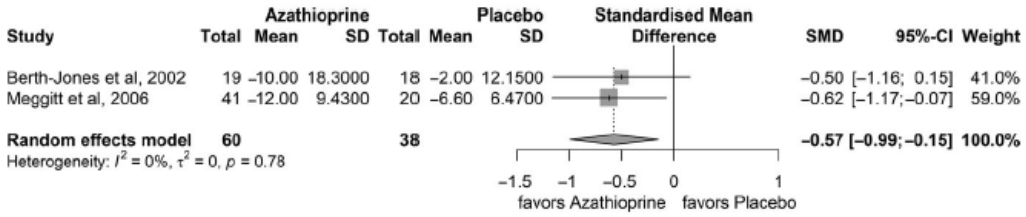
Treatment	Total n	Number of RCTs	Reported safety	Reference, year	Safety assessment timepoint[a]	Age[b]
Apremilast	185	1	Cumulative incidence rate of AEs: 70% for apremilast 40mg twice daily, 62% for apremilast 20mg twice daily, 47% for placebo[83] Cumulative incidence rate of SAEs: 5% for apremilast 40mg twice daily, 2% for apremilast 20mg twice daily, 0% for placebo[83] Most common AEs for apremilast: diarrhoea, nausea, headache, nasopharyngitis, upper respiratory tract infection, abdominal discomfort, dyspepsia[83] Most common SAEs for apremilast: cellulitis led to discontinuation of 40mg group (41)[83]	Simpson et al, 2018[83]	Long-term (24 weeks)	Adults
Azathioprine (AZA)	140	3	Cumulative incidence rate of AEs: 50%-100% for AZA, 11%-100% for comparator[20,28,33] Cumulative incidence rate of SAEs: 0%-10% for AZA, 0% for comparator[28,33] Most common AEs for AZA: myelosuppression, hepatotoxicity, diarrhoea, infections/infestations, gastrointestinal adverse events/nausea/abdominal pain/diarrhoea, headache[20,28,33,74] Most common SAEs for AZA: AZA hypersensitivity, abnormal transaminases, severe nausea[20,28,33,74]	Berth-Jones et al, 2002[20]	Long-term (24 weeks)	Mixed (≥16 years)
				Meggit et al, 2006[28]	Short-term (12 weeks)	Mixed (≥16 years)
				Schram et al, 2011[33]	Long-term (24 weeks)	Adults
				Gerbens et al, 2018[74]	Long-term (5 years)	Adults
Baricitinib	1363	3	Cumulative incidence rate of AEs: 54%-71% for baricitinib 4 mg/day, 46%-58% for baricitinib 2 mg/day, 49%-56% for placebo[76,84] Cumulative incidence rate of SAEs: 1%-3% for baricitinib 4 mg/day, 0%-2% for baricitinib 2 mg/day, 0%-4% for placebo[76,84] Most common AEs for baricitinib: acne, nasopharyngitis, upper respiratory tract inflammation, elevated blood creatine phosphokinase levels and headache[76,84] Most common SAEs for baricitinib: benign polyp[76,84]	Guttmann-Yassky et al, 2018[76]	Short-term (16 weeks)	Adults
				Simpson et al, 2020[84]	Short-term (16 weeks)	Adults

Ciclosporin A (CSA)	820	19	Cumulative incidence rate of AEs: range between 0%-100% for CSA and comparison groups[21,23,25,31,34,36,46,54,57,58,75,79-82] Cumulative incidence rate of SAEs: range between 0%-13% for CSA and comparison groups[21,23,24,31,32,34,36,46,54,57,58,75,79-82] Most common AEs for CSA: hypertension, nephrotoxicity, gastrointestinal symptoms, headache, hypertrichosis, upper respiratory tract infection, infections, fatigue, paraesthesia[21,23-25,31,32,34,36,46,54,57,58,75,79-82] Most common SAEs for CSA: severe headache, paraesthesia, abdominal pain, hypertension, nausea, upper respiratory tract infection[21,23-25,31,32,34,36,46,54,57,58,75,79-82]	Wahlgren et al, 1990[57]	Short-term (6 weeks)	Adults
				Sowden et al, 1991[34]	Short-term (16 weeks)	Mixed (≥17 years)
				Salek et al, 1993[31]	Short-term (16 weeks)	Mixed (≥17 years)
				Munro et al, 1994[53]	Short-term (16 weeks)	Adults
				van Joost et al, 1994[36]	Short-term (6 weeks)	Mixed (≥17 years)
				El-Khalawany et al, 2013[22]	Short-term (12 weeks)	Mixed (8-14 years)
				Goujon et al, 2017[75]	Long-term (24 weeks)	Adults
				Granlund et al, 2001[23]	Long-term (52 weeks)	Adults
				Pacor et al, 2004[54]	Short-term (6 weeks)	Mixed (≥13 years)
				Bemanian et al, 2005[46]	Short-term (12 weeks)	Not reported (only "children" reported)
				Schmitt et al, 2010[32]	Long-term (18 weeks)	Adults
				Koppelhus et al, 2014[81]	Short-term (16 weeks)	Adults
				Haeck et al, 2011[24]	Long-term (30 weeks)	Adults
				Zonneveld et al, 1999[58]	Long-term (52 weeks)	Adults
				Czech et al, 2000[21]	Short-term (12 weeks)	Adults
				Zurbriggen et al, 1999[37]	Short-term (16 weeks)	Adults
				Harper et al, 2000[25]	Long-term (52 weeks)	Mixed (3-16 years)
				Kwon et al, 2013[82]	Long-term (26 weeks)	Mixed (≥12 years)
				Jin et al, 2015[79]	Short-term (8 weeks)	Mixed (≥7 years)
				Kim et al, 2016[80]	Long-term (36 weeks)	Mixed (any age allowed)
Corticosteroids	85	3	Cumulative incidence rate of AEs: no AEs reported for corticosteroids and comparison groups[26,32,45] Cumulative incidence rate of SAEs: SAEs occurred in one trial (10% for prednisolone, 0% for comparator CSA)[32] Most common AEs for corticosteroids: not AEs reported[26,32,45] Most common SAEs for corticosteroids: SAEs occurred in one trial (exacerbation of AD with hospitalization)[32]	Heddle et al, 1984[26]	Short-term (12 weeks)	Mixed (3-14 years)
				La Rosa et al, 1995[45]	Short-term (5 weeks)	Children
				Schmitt et al, 2010[32]	Long-term (18 weeks)	Adults
Dupilumab	3529	11	Cumulative incidence rate of AEs: 56%-92% for dupilumab, 62%-88% for placebo[19,35,47,56,71,73,78,85] Cumulative incidence rate of SAEs: 0%-8% for dupilumab, 0%-13% for placebo[19,35,47,56,71,73,78,85] Most common AEs for dupilumab: conjunctivitis, (peri-)ocular clinical signs, nasopharyngitis, herpes virus infection, upper respiratory tract infection[19,35,47,56,71,73,78,85] Most common SAEs for dupilumab: respiratory disorder, Severe conjunctivitis[19,35,47,56,71,73,78,85]	Beck et al, 2014[19]	Short-term (4 and 12 weeks)	Adults
				Thaci et al, 2016[35] Simpson et al, 2016[56]	Long-term (32 weeks)	Adults
				Simpson et al, 2016[86]	Short-term (16 weeks)	Adults
				Blauvelt et al, 2017[47]	Long-term (52 weeks)	Adults
				Bruin-Weller et al, 2017[73]	Short-term (16 weeks)	Adults
				Blauvelt et al, 2018[71]	Long-term (32 weeks)	Adults
				Tsianikas et al, 2018[87]	-	Adults
				Guttmann-Yassky et al, 2019[78]	Long-term (32 weeks)	Adults
				Simpson et al, 2020[85]	Short-term (16 weeks)	Adolescents
				Worm et al, 2019[88]	Long-term (36 weeks)	Adults
Interferon-gamma (IFN-γ)	134	2	Cumulative incidence rate of AEs: not reported[48,50] Cumulative incidence rate of SAEs: not reported[48,50] Most common AEs for IFN-γ: headache, myalgia, chill, constitutional symptoms, disease flare, granulocytopenia, fever, LDH elevation[48,50] Most common SAEs for IFN-γ: disease flare, hepatic transaminase elevation[48,50]	Hanifin et al, 1993[48]	Short-term (12 weeks)	Mixed (≥2 years)
				Jang et al, 2000[50]	Short-term (12 weeks)	Mixed (≥15 years)
Intravenous immunoglobulins (IVIG)	64	3	Cumulative incidence rate of AEs: 17 and 33% for IVIG, 0 and 25% for comparators[46,51] Cumulative incidence rate of SAEs: 0% for IVIG, 0% for comparator[30,46] Most common AEs for IVIG: fever, chill, headache, nausea, vomiting[30,46,51] Most common SAEs for IVIG: severe headache, nausea, vomiting[30,46,51]	Jee et al, 2011[51]	Long-term (36 weeks)	Mixed (children ≥ 2 years reported)
				Bemanian et al, 2005[46]	Short-term (12 weeks)	Not reported (only "children" reported)
				Paul et al, 2002[30]	Short-term (90 days)	Adults
Mepolizumab	43	1	Cumulative incidence rate of AEs: not reported[29] Cumulative incidence rate of SAEs: not reported[29] Most common AEs for Mepolizumab: ´mild side effects´[29] Most common SAEs for Mepolizumab: no SAEs reported[29]	Oldoff et al, 2005[29]	Short-term (4 weeks)	Adults

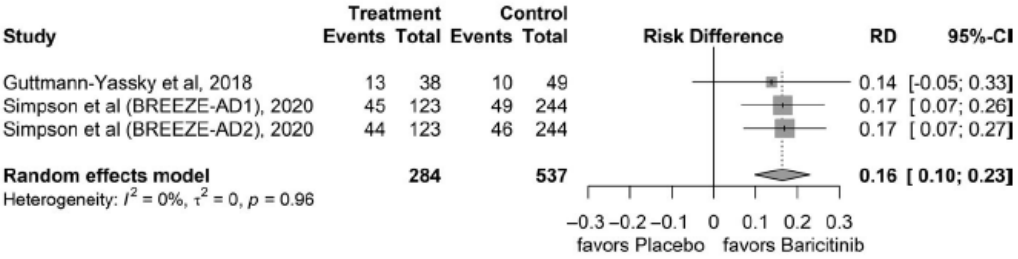
Methotrexate (MTX)	179	3	Cumulative incidence rate of AEs: 82 and 100% for MTX, 79 and 100% for comparators[33,75] Cumulative incidence rate of SAEs: 0% for MTX, 0%-2% for comparators[33,75] Most common AEs for MTX: elevation of liver enzymes, gastrointestinal issues, infections, neuromuscular disorders, lymphocytopenia[33,75] Most common SAEs for MTX: no SAEs reported[22,33,74,75]	Schram et al, 2011[33] Gerbens et al, 2018[74] El-Khalawany et al, 2013[22] Goujon et al, 2017[75]	Long-term (24 weeks) Long-term (5 years) Short-term (12 weeks) Long-term (24 weeks)	Adults Adults Mixed (8-14 years) Adults
Omalizumab	91	3	Cumulative incidence rate of AEs: 77%-94% for omalizumab, 57%-100% for placebo[27,72] Cumulative incidence rate of SAEs: 0%-19% for omalizumab, 0%-19% for placebo[27,49,72] Most common AEs for omalizumab: vertigo, headache, nausea, abdominal pain, allergic reactions, aggravated eczema[27,49,72] Most common SAEs for omalizumab: anaphylaxis (one patient with history of idiopathic anaphylaxis)[72]	Chan et al, 2020[72] Iyengar et al, 2013[49] Heil et al, 2010[27]	Long-term (24 weeks) Long-term (24 weeks) Short-term (16 weeks)	Mixed (4-19 years) Mixed (4-22 years) Mixed (≥12 years)
Upadacitinib	167	1	Cumulative incidence rate of AEs: 74%-79% for upadacitinib, 61% for placebo[77] Cumulative incidence rate of SAEs: 0%-5% for upadacitinib, 2% for placebo[77] Most common AEs for upadacitinib: upper respiratory tract infection, acne, AD worsening[77] Most common SAEs for upadacitinib: atrial fibrillation (multimorbid patient), pericoronitis (patient with history of tooth infections), exacerbation of AD in context with contact dermatitis (one patient), appendicitis (one patient)[77]	Guttmann-Yassky et al, 2019[77]	Short-term (16 weeks)	Adults
Ustekinumab	112	2	Cumulative incidence rate of AEs: 12%-75% for ustekinumab, 30%-74% for placebo[52,55] Cumulative incidence rate of SAEs: 0% for ustekinumab, 0% for placebo[52,55] Most common AEs for ustekinumab: nasopharyngitis, contact dermatitis, worsening of skin infection (eczema herpeticatum)[52,55] Most common SAEs for ustekinumab: no SAEs occurred[52,55]	Khattri et al, 2017[52] Saeki et al, 2017[55]	Long-term (24 weeks) Long-term (24 weeks)	Adults 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.

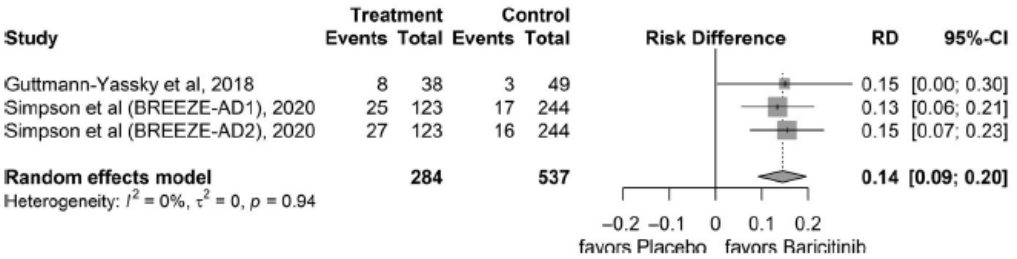
SASSAD Azathioprine at 12 weeks



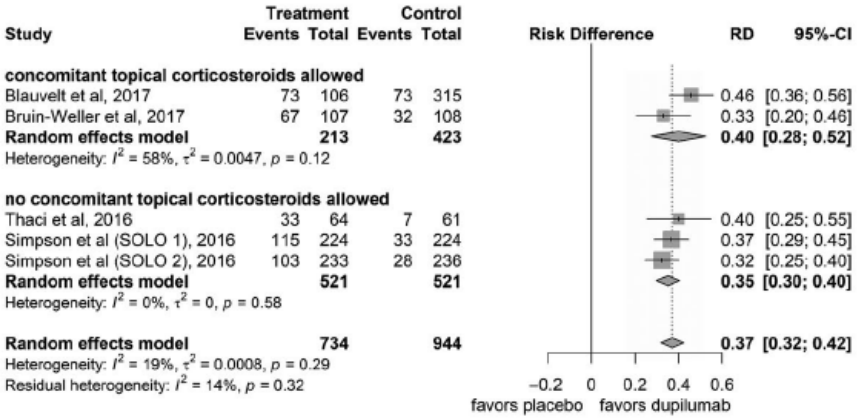
EASI-75 Baricitinib 4 mg every day (topical corticosteroids allowed)



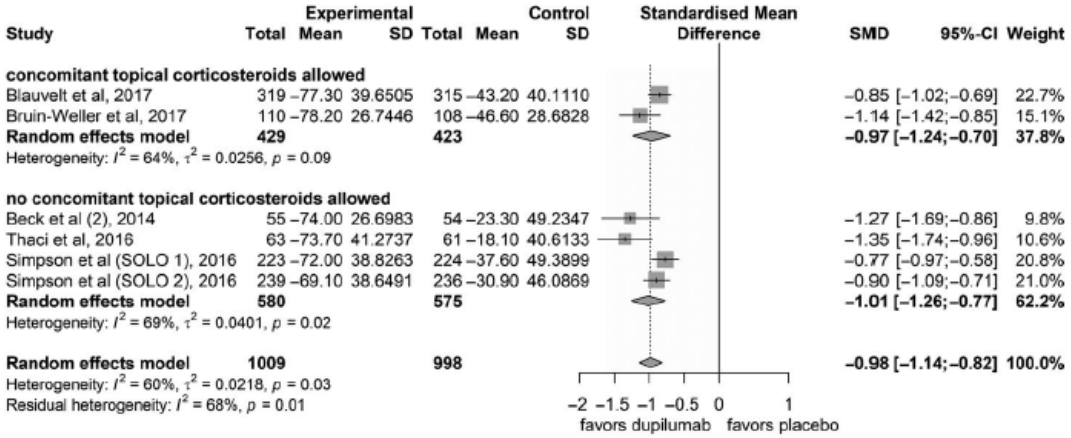
EASI-90 Baricitinib 4 mg every day (topical corticosteroids allowed)



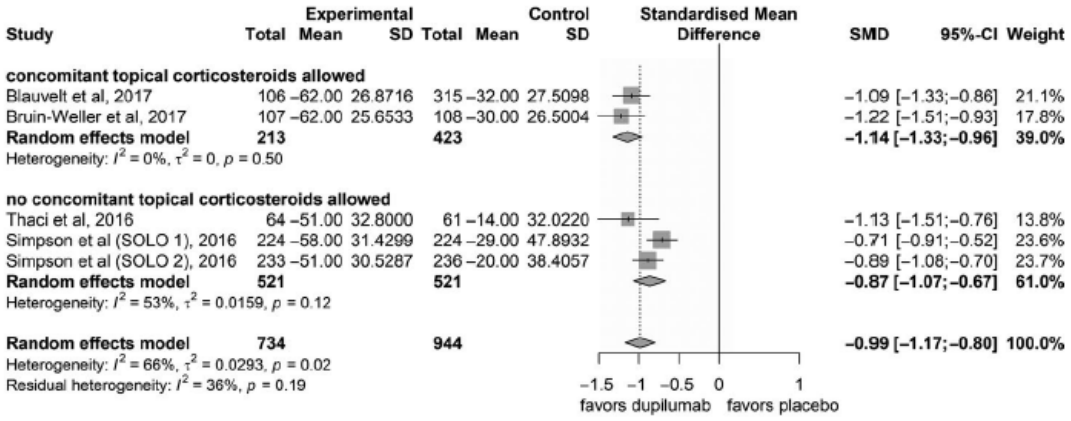
EASI-75 response



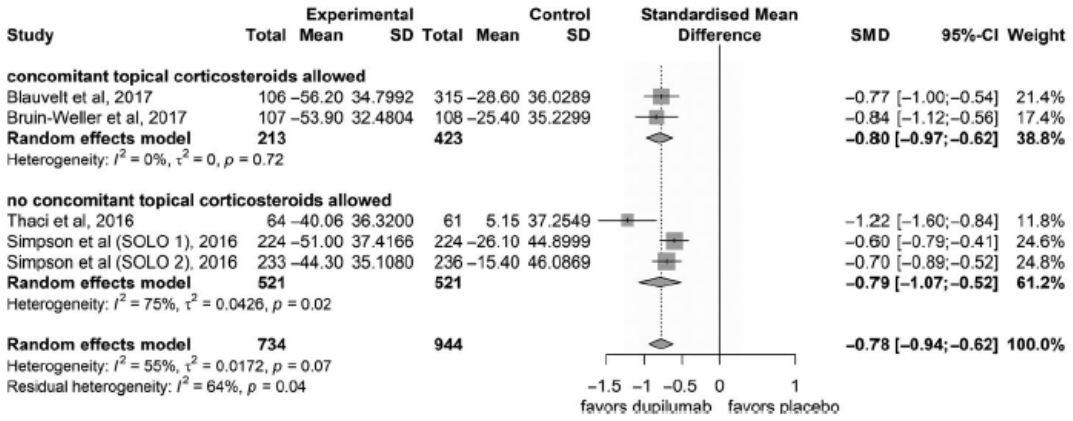
EASI dupilumab 300 mg two every weeks



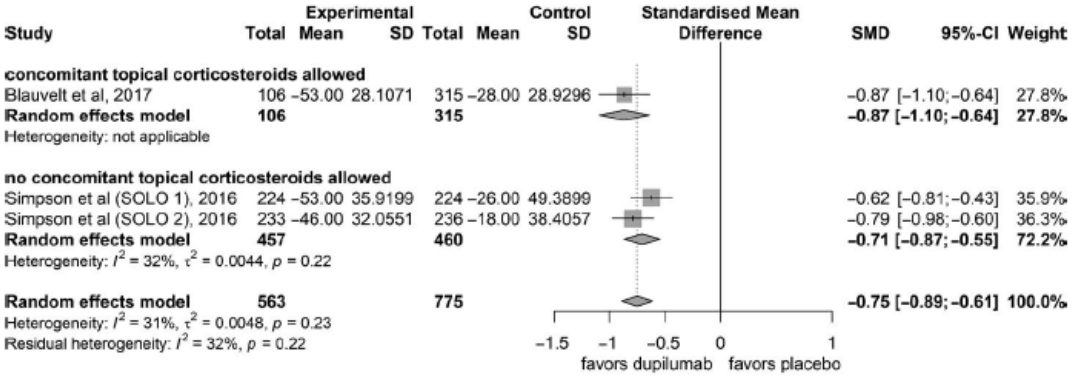
SCORAD mean change



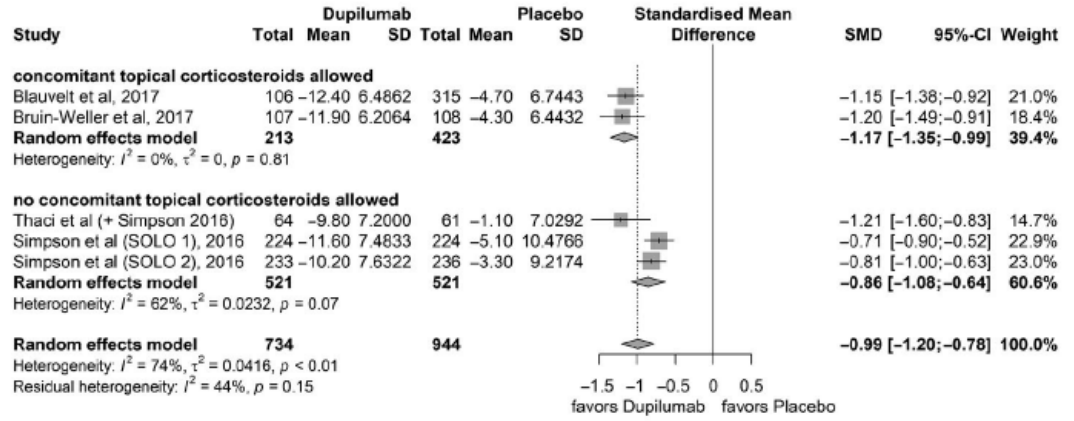
NRS pruritus mean change



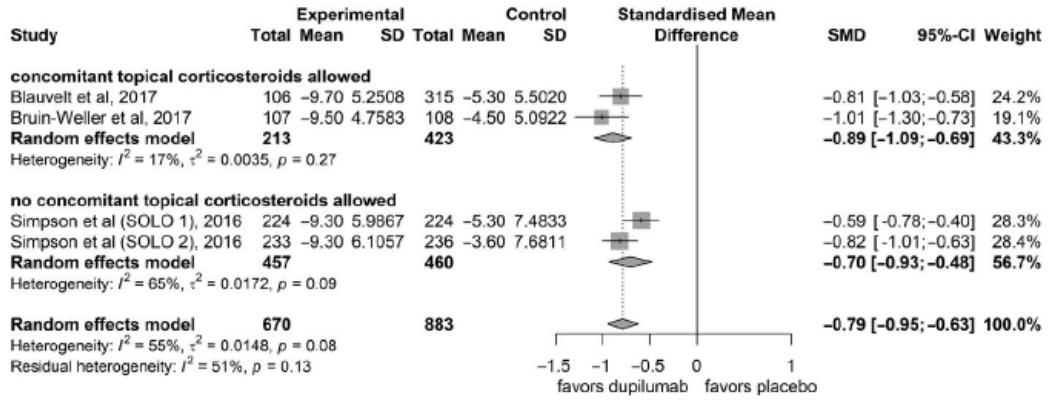
GISS mean change



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).97

Nankervis H et al., 2017 [18].

What is the evidence base for atopic eczema treatments? A summary of published randomized controlled trials.

Fragestellung

summarizing the evidence base for AE treatments for guideline writers, healthcare professionals and patients

Methodik

Population:

- participants (of any age) had AE, as diagnosed by a physician, or that met with diagnostic criteria (e.g. Hanifin and Rajka, U.K. working party or similar).

Intervention/ Komparator:

- any

Endpunkt:

- Changes in patient-rated symptoms such as itching (pruritus) or sleep loss
- Global severity, as rated by patients or their physician
- changes in AE severity rating
- scales, quality of life and adverse events (encompassing adverse events and adverse reactions depending on how these were reported in the original RCTs)

Recherche/Suchzeitraum:

- RCTs: searched the following electronic databases (search dates end of 1999 to 31 August 2013): Medline, Embase, CENTRAL, The Cochrane Skin Group Specialised Trials Register, Latin American and Caribbean Health Sciences database (LILACS); Allied and Complementary Medicine Database (AMED); Cumulative Index to Nursing and Allied Health Literature (CINAHL), http://www.controlled-trials.com
- Systematic reviews on AE treatments were searched up to December 2015 using PubMed, Embase, the Cochrane Library and NHS Evidence.

Qualitätsbewertung der Studien:

- Cochrane Collaboration's risk of bias assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 541 RCTs in total covering 92 different interventions for treating AE

Charakteristika der Population:

- Most of the trials were conducted in secondary care, and tended to include participants with either moderate-to-severe disease or mild-to-moderate disease. Very few RCTs included all severities of AE.

Qualität der Studien:

- Reporting was generally poor, with 'unclear' categories dominating the assessments; randomization method (2% high, 36% low and 62% unclear risk of bias), allocation concealment (3% high, 15% low and 82% unclear risk of bias) and blinding or masking of the intervention (15% high, 28% low, 57% unclear risk of bias). Only 22 of 287 studies (8%) were considered to be at low risk of bias for all three quality criteria (randomization, allocation concealment and blinding).

Studienergebnisse:

- Treatments with reasonable evidence of benefit for patients with atopic eczema (AE): 14 interventions, including the use of topical corticosteroids and topical calcineurin inhibitors, both for the treatment of active AE and as intermittent proactive (maintenance) therapy for the prevention of AE flares. Other interventions including Atopiclair emollient, ultraviolet light therapy, azathioprine and ciclosporin. All had reasonable evidence of benefit compared with placebo/vehicle.

Table 1 Treatments with reasonable evidence of benefit for patients with atopic eczema (AE)

Evidence of benefit: at least one good quality randomized controlled trial or a large body of evidence and a clinically useful finding. We defined a 'good quality' trial as well designed and well reported and with a magnitude of benefit deemed by the authors to be clinically relevant, and 'large body of evidence' as enough trials with consistent evidence of clinically relevant benefit, despite some limitations in reporting

Intervention and severity of AE	Population	Trials, n	Participants, n	Risk of bias	Systematic review(s)
Topical corticosteroids					
Corticosteroids (various strengths) are superior to vehicle for AE of all severities	Adults and children	23[21–42]	3857	Mostly unclear	None
Topical calcineurin inhibitors					
Pimecrolimus (1%) is superior to vehicle for mild-to-moderate AE	Mainly children	16[43–57]	3149	Mostly unclear	Chen (2011)[58] Number of included studies: 6 (< 18 years only) Meta-analysis: odds ratio (OR) 3·21, 95% confidence interval (CI) 2·48–4·14
Tacrolimus (0·03, 0·1, 0·3%) is superior to vehicle for moderate-to-severe AE	Adults and children	9[59–65]	2089	Mostly unclear	Chen (2011)[58] Number of included studies: 4 (< 18 years only) Meta-analysis: OR 4·56, 95% CI 2·80–7·44
Tacrolimus (0·03, 0·1%) is superior to hydrocortisone acetate (1%) for moderate-to-severe AE	Children	2[66,67]	1184	Unclear	Cury Martins (2015)[68] Number of included studies: 2 Tacrolimus 0·03%: relative risk (RR) 2·58, 95% CI 1·96–3·38 Number of included studies: 1 Tacrolimus 1%: RR 3·09, 95% CI 2·14–4·45
Tacrolimus (0·1%) superior to fluticasone propionate ointment (0·005%) for moderate-to-severe facial AE	Adults	1[69]	568	Mostly unclear	Not applicable
Tacrolimus (0·1, 0·03%) is superior to pimecrolimus (1%) for AE of all severities	Adults and children	5[70–72a]	1243	Mostly low	Cury Martins (2015)[68] Number of included studies: 3 Meta-analysis: RR 1·80, 95% CI 1·35–2·42

Proactive (maintenance) topical therapy for preventing flares					
Corticosteroids applied twice weekly are superior to vehicle for moderate-to-severe AE	Adults and children	4[73–76]	929	Mostly unclear	Schmitt (2011)[17] Number of included studies: 4 Meta-analysis: RR 0·46, 95% CI 0·38 –0·55
Tacrolimus (0·1, 0·03%) applied twice weekly is superior to vehicle for mild-to-severe AE	Adults and children	4[77–80]	741	Mostly unclear	Schmitt (2011)[17] Number of included studies: 3 Meta-analysis: RR 0·78, 95% CI 0·60 –1·00
Pimecrolimus (1%) applied twice weekly is superior to vehicle for AE of all severities	Mainly children	2[44,81]	251	Mostly low	None
Systemic therapies					
Ciclosporin superior to placebo for severe AE	Adults	4[82–85]	113	Mostly unclear	Schmitt (2007)[86] Number of included studies: 12 Meta-analysis: included non-RCTs
Azathioprine superior to placebo for moderate-to-severe AE	Adults	2[87,88]	100	Mostly low	Schram (2011)[89] Number of included studies: 2 Meta-analysis: not done

(continued)

Evidence of benefit: at least one good quality randomized controlled trial or a large body of evidence and a clinically useful finding. We defined a 'good quality' trial as well designed and well reported and with a magnitude of benefit deemed by the authors to be clinically relevant, and 'large body of evidence' as enough trials with consistent evidence of clinically relevant benefit, despite some limitations in reporting

Intervention and severity of AE	Population	Trials, n	Participants, n	Risk of bias	Systematic review(s)
Ultraviolet (UV) radiation therapy					
Narrowband-UVB superior to placebo (visible light) for moderate-to-severe AE	Adults	2[90,91]	116	Mostly unclear	Dogra (2015)[92] Number of included studies: 13 (included non-RCTs) Meta-analysis: not done Gambichler (2005)[93] Number of included studies: 3 (included non-RCTs) Meta-analysis: not done
Other					
Atopiclair® superior to vehicle for mild-to-moderate AE	Adults and children	4[94–98]	489	Mixed	None
Education superior to no education for moderate-to-severe AE	Mainly children	7[99–105]	1076	Mixed	Ersser (2014)[106] Number of included studies: 10 Meta-analysis: not done

[a]Please note, three studies were included within one paper.

- Treatments with evidence of no clinically useful benefit
  - 9 interventions including the use of topical corticosteroids containing an antibiotic for the treatment of AE that is not infected

Table 2 Treatments with reasonable evidence of no benefit for patients with atopic eczema (AE)

Evidence of no benefit: at least one good quality randomized controlled trial (RCT) or several less well reported RCTs that consistently failed to show a convincing benefit on overall disease activity. We defined a 'good quality' trial as well designed and well reported, and large enough to exclude a clinically useful benefit or several trials with no evidence of benefit to give confidence in there being no clinically relevant benefit, despite less clear reporting

Intervention and severity of AE	Population	Trials, n	Participants, n	Risk of bias	Systematic review(s)
Twice-daily vs. once-daily topical corticosteroids	Adults and children	3[34,107,108]	617	Mostly unclear	Green (2005)[109] Number of included studies: 10 Meta-analysis: not preformed (heterogeneity)
Antibiotic-containing corticosteroids vs. corticosteroids alone for mild-to-severe noninfected AE	Mainly unspecified	5[110–114]	352	Mostly unclear	Bath-Hextall (2010)[115] Number of included studies: 2 Meta-analysis: relative risk 0·52, 95% confidence interval (CI) 0·23–1·16
Probiotics for treating AE vs. placebo	Mainly children	20[116–135]	1513	Mostly unclear	Boyle (2009)[136] Number of included studies: 5 Meta-analysis: mean difference −0·90, 95% CI -2·84 to 1·04
Dietary supplements rich in linoleic acid (evening primrose oil and borage oil) vs. placebo	Mainly adults	23[137–159]	1448	Mostly unclear	Bamford (2013)[159] Number of included studies: 7 trials (evening primrose oil) Meta-analysis for evening primrose oil: mean difference −2·22, 95% CI −10·48 to 6·04 Number of included studies: 8 trials (borage oil) Meta-analysis for borage oil: not performed (heterogeneity)
Protease inhibitor SRD441 vs. vehicle for mild-to-moderate AE	Adults	1[160]	93	Mostly low	Systematic review not applicable
Emollient with furfuryl palmitate vs. emollient alone for mild-to-moderate AE	Children	1[161]	117	Low	Systematic review not applicable
Ion exchange water-softening devices vs. no water softening for moderate-to-severe AE	Children	1[162]	336	Low	Systematic review not applicable
Cipamfylline cream vs. vehicle	Adults	1[163]	103	Mostly low	Systematic review not applicable
Mycobacterium vaccae vaccine vs. no vaccine for moderate-to-severe AE	Mainly children	4[164–167]	372	Low	None

Anmerkung/Fazit der Autoren

When combined with RCTs from the previous review (n = 254), we found 'reasonable evidence of benefit' for corticosteroids, calcineurin inhibitors, Atopiclair, ciclosporin, azathioprine, ultraviolet radiation and education programmes. Interventions with reasonable evidence of 'no benefit' included some dietary interventions, ion exchange water softeners, multiple daily applications of topical corticosteroids and antibiotic-containing corticosteroids for noninfected AE. Many common treatments lack evidence of efficacy and warrant further evaluation. The evidence base for AE is still hampered by poor trial design and reporting.

Kommentare zum Review

- Abkürzung AE für atopic eczema und nicht wie sonst üblich für adverse event
- Keine Subgruppenanalysen zum Schweregrad oder Alter

3.4 Leitlinien

Berth-Jones J et al., 2019 [3].

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

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

Empfehlungen

Severe atopic dermatitis

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

- A systematic review confirmed that 11 studies on the use of ciclosporin in AD consistently demonstrated efficacy.[106]
- An additional review of 15 studies and a meta-analysis of 12 studies (which partially shared authorship with the aforementioned systematic review) concluded, somewhat more cautiously, that short-term use of ciclosporin can decrease the severity of atopic eczema in patients whose condition cannot be adequately controlled with conventional therapies. However, there was some evidence of publication bias, so these findings should be interpreted with caution. The effectiveness of ciclosporin is similar in adults and children; however, tolerability may be better in children. There was insufficient data to evaluate the long-term effectiveness and safety of ciclosporin in patients with atopic eczema.[107]

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

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

Damiani G et al., 2019 [4].

Italian guidelines for therapy of atopic dermatitis-Adapted from consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis)

Zielsetzung/Fragestellung

The present adaptation of the European guidelines (Ring et al., 2012a, 2012b; Wollenberg et al., 2018b) aims to adapt, enrich, and contextualize the current evidences toward important and relevant strategies for management of AD in Italy.

Methodik

Die Leitlinie entspricht nicht den methodischen Anforderungen an eine hochwertige evidenzbasierte Leitlinie. Aufgrund fehlender anderweitiger Leitlinienevidenz wurde sie trotzdem in die Synopse aufgenommen.

Grundlage der Leitlinie

- Gremienzusammensetzung unklar.
- Keine ausführliche Darlegung der Interessenkonflikte und finanzieller Unabhängigkeit. Am Ende des Dokuments gibt es ein COI Statement, wonach keine Interessenkonflikte bestehen.
- Systematische Suche der Evidenz wurde angegeben. Keine systematische Aufarbeitung der Qualität der Evidenz beschrieben.
- Konsensusprozesse nicht erklärt.
- Externes Begutachtungsverfahren beschrieben.
- Empfehlungen der Leitlinie sind nur zum Teil mit der zugrundeliegenden Evidenz im Hintergrundtext verbunden.
- Regelmäßige Überprüfung der Aktualität nicht angegeben.

Recherche/Suchzeitraum:

- papers published before May 2019 in PubMed, Embase, and Scopus

LoE und GoR

- Recommendation levels (A; B; C; D) were graded basing on the evidence levels (1–4):
  - A. Meta-analysis on randomized controlled trials (RCTs; 1a) or single RCT (1b).
  - B. Systematic review of cohort studies (2a) or single cohort study or RCTs of limited quality (2b) or systematic review of case control studies (3a) or single case–control study (3b).
  - C. Case series or case–control study or cohort study of limited quality (4).
  - D. Expert opinion (–).

Sonstige methodische Hinweise

- Die Leitlinie basiert auf der Europäischen Konsensusleitlinie von Wollenberg et al.:
  - Wollenberg et al., 2018. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children

Diese Leitlinie ist eine S2k Leitlinie und es wurde daher nicht systematisch recherchiert. In der vorliegenden italienischen Leitlinie wurde zusätzlich eine systematische Recherche durchgeführt, es ist aber unklar, wie die zusätzlichen Informationen in die bestehenden Empfehlungen integriert wurden.

Empfehlungen

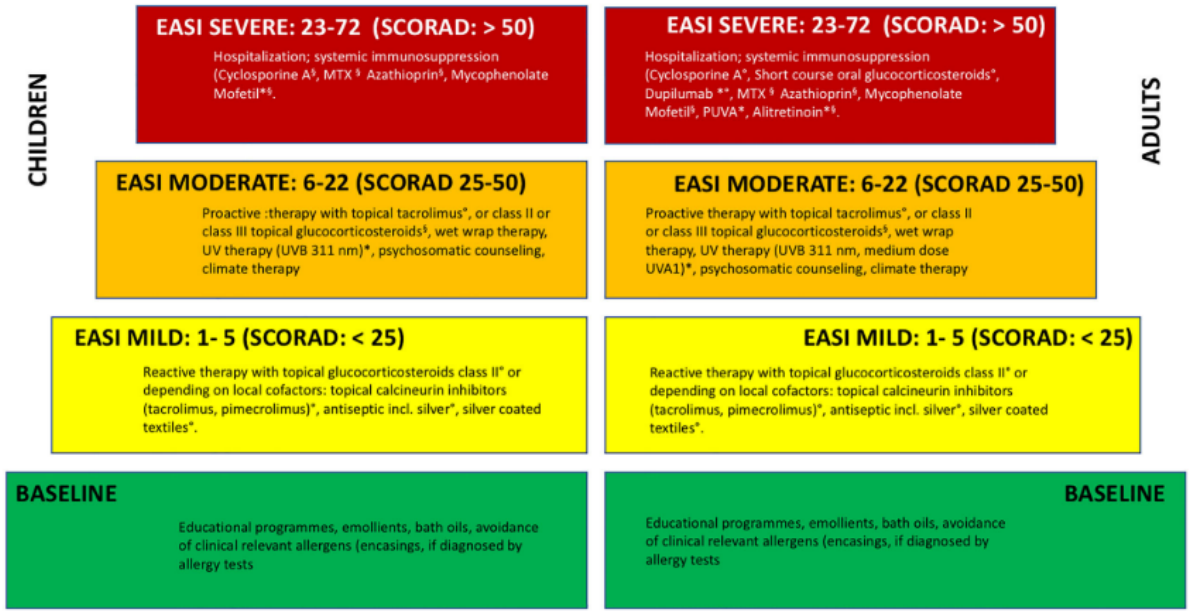


FIGURE 1 Therapeutic algorithm in children and adults based on Eczema Area and Severity Index (EASI). EASI mild: 1–5 points, EASI moderate: 6–22 points, EASI severe: 23–72 points. §, in-label treatment; °, contraindications to assess in Table 1; *, indication for atopic dermatitis

Source: Modified from Wollenberg et al., 2018a

5.2.1 | Topical corticosteroids (TCS)

The use of TCS in AD is recommended especially in the acute phase (D, –) and in patients with an improved risk/benefit ratio, such as the ones with infrequent relapses (D, –). Assessment of itch severity is used to evaluate response to treatment and dose-tapering is evaluable when itch is largely improved. To avoid steroid side effects (skin atrophy, teleangiectasia, spontaneous scars, striae distensae, and hypertrichosis), it is advisable to use steroids only during the acute flares. Potent TCS should not be used in sensitive skin areas (face, neck, folds). Only Group II TCS are suggested for long-term treatment (D,–), while Group III TCS require an appropriate dilution for children <2 years (D, –). Proactive therapy may reduce relapses (A, 1b), but is tested in RCTs only for a duration of 20 weeks (A, 1b). As already mentioned, an important issue in AD management is corticophobia: It needs to be recognized and addressed in order to avoid undertreatment and improve adherence (C, 4).

5.2.2 | TCI

TCI recommended for AD are tacrolimus and pimecrolimus. Currently, topical tacrolimus is available in Italy as ointment with two different concentrations 0.1% for adults and 0.03% for children, whereas pimecrolimus is available as 1% cream.

TCI have important anti-inflammatory properties in AD (D, –) and are indicated in sensitive skin areas such as face, anogenital, and intertriginous areas (A, 1b). TCI are indicated after the acute phase and should be considered after the flare is cleared by TCS (D, –).

Proactive therapy (twice/week) of tacrolimus is shown to reduce the time to relapses (A, 1b). Sun protection should be recommended during TCI use (D, –).

5.2.3 | Phototherapy

The following phototherapy sources are widely used in the treatment of AD:

- Narrow Band- Ultraviolet B (NB-UVB) emitting a maximum peak at 311–313 nm for chronic and moderate AD.
- Less frequently, UVA1 (340–400 nm) for more severe phase (Rodenbeck, Silverberg, & Silverberg, 2016).

In patients with pauci-lesional disease, there is the new option of employing excimer sources (monochromatic excimer light and laser at 308 nm); however, there is no recommendation for the treatment of AD patients (D, –).

Several pilot studies have demonstrated a moderate effectiveness of short wave of visible light at 380 nm (A, 1b).

Psoralen and ultraviolet A therapy is no more recommended for AD, neither in children nor in adults because of the long-term risk of malignancies. Caution is especially warranted in patients previously treated with systemic immunosuppressants (C, 4; Becker et al., 2011; Eustace, Dolman, Alsharqi, Sharpe, & Richard Parslew, 2017; Gamichler, Breuckman, Boms, Altmeyer, & Kreuter, 2005; Mavilia et al., 2008; Wollenschlager, Hermann, & Ockenfels, 2009).

NB-UVB has been considered for the treatment of mild-chronic forms of AD and it is administered three times a week using the same increments employed in the treatment of psoriasis (C, 4). The starting dose is chosen according to the skin phototype. NB-UVB is recommended for children as from the age of 10 years (B, 2b; Dittmar, Pflieger, Schopf, & Simon, 2001; Tzaneva, Seeber, Schwaiger, Honigsmann, & Tanew, 2001).

UVA1 is recommended for acute severe forms in adult patients. Following standard protocols, this source is delivered five times a week for a maximum period of 3 weeks. Some studies have suggested that a medium dose (60 J/cm2) could be as effective as a high dose (120 J/cm2); more recently, however, it has been shown that in dark skin types a high-dose protocol is more effective in treating severe forms in adult patients (C, 4; Pacifico et al., 2019).

Adjuvant use of emollients plus TCS should be considered especially in the initial phase of phototherapy in order to prevent acute flares (C, 4). Prepuberal patients may benefit from NB-UVB. Patients beyond the age of 11 years, may also benefit from UVA-1 (D, –).

5.3 | Systemic therapies

Systemic agents for AD may be divided into three main categories: immunosuppressants (Glucocorticosteroids, Cyclosporin A, Azatioprin (AZA), Methotrexate, Mycophenolate mofetil), biologics (Dupilumab) and others (antimicrobials). Immunosuppressants and biologics characteristics are summarized in Table 1. In the present document, agents cited anecdotally or without evidences are mentioned only if rated at least B.

5.3.1 | Oral glucocorticosteroids

The evidences for the use of oral glucocorticosteroids (OGCS) in AD are low grade. Short-term (up to 1 week) therapy with OGCS is moderately effective and the risk/benefit ratio is unfavorable. The indication for OGCS in children warrants even more caution. Long-term use of OGCS is strongly discouraged due to the plethora of side effects; short-term therapy (up to 1 week) may be considered an option, only exceptionally, for mild acute flares in AD

(recommended dose: 0.5 mg/kg; D, –). Long-term treatment with OGCS is not recommended (D, –).

5.3.2 | Cyclosporin a (Cyc-a)

Cyc-A treatment may be considered in chronic, severe cases of AD in adults in a continuous regimen for a duration of up to 2 years (A, 1a). Its use is off-label in children and adolescents, but it may be used in severe AD under careful monitoring of blood pressure and renal function (B, 2b). In adults, both short- and long-term may be effective (D, –). The starting dose should be 5 mg kg−1 day−1 divided in two administrations and the duration of the therapy must be guided by tolerance and efficacy (D, –). No routine check of cyclosporinemia is required (D, –). Once a clinical improved is achieved, a dose reduction should be planned, decreasing the dose by 1 mg kg−1 day−1 every 2 weeks (D, –). After 2 years of Cyc-A, clinicians should switch to another systemic therapy. A further cycle of Cyc-A can be considered, it should not be started 3–6 months from the end of the first Cyc-A cycle (D, –) have passed. Intermittent regimens may be constitute an option to decrease the long-term cumulative dosage (D, –).

Combination therapy with UV is not recommended due to Cyc-A photosensitization property (D, –). No evidences are available, but CyC-A should be paused 2 weeks before and started again 4–6 weeks after a vaccination (D, –).

5.3.3 | AZA

AZA may be used off-label both in adults (A, 1b) and children (C, 4) in case of nonresponse or loss of response, or even when other systemic therapies are counter indicated. Particular attention should be paid for thiopurine S-methyltransferase (TPMT) heterozygotic patients. Before starting AZA, TPMT screening is required due to the risk of bone marrow toxicity (A, 1b). The suggested dose range is 1–3 mg/kg bw/day (A, 1b), with 1–1.5 mg kg−1 day−1 as maintenance dose. The recommended initial dose amounts to 50 mg/day, a slow increase under control of full blood and liver function is possible (D, –). Pregnancy is a relative contraindication (D, –). Combination with UV is discouraged (D, –).

5.3.4 | Mycophenolate mofetil

Mycophenolate mofetil (MMF) is recommended for an off-label treatment, which should be considered after a failure of or Cyc-A therapy or when the latter is counter indicated. The dose must be not exceed 3 g/day in adults. Off-label treatment is possible also in children and adolescents.

Due to the teratogenic properties of the drug, when MMF is used an effective contraception should be employed both in women and men (B, 3a).

5.3.5 | Methotrexate

Methotrexate is considered for an off-label therapy in AD in both children and adults (C, 4), and the dosage are the same approved in psoriasis (D, –).

Due to the teratogenic properties of the drug, during the treatment and 6 months after withdrawal, an effective contraception should be employed in both women and men (B, 3a).

5.3.6 | Dupilumab (dup)

Dup is a fully human monoclonal antibody blocking the common alfachain receptor of IL-4 and IL-13. It was the first biologic drug approved in 2017 as first-line treatment for moderate–severe adult AD both in the United States and in Europe. It is so far the only approved biologic drug for AD. Its safety profile is good: Conjunctivitis is the only adverse

event more frequently described than placebo in CRTs. Dup is recommended as a disease-modifying drug for adult patients with moderate to severe AD when topical therapies are not effective enough and when systemic therapies are not advisable (A, 1a). Overall recommendation is for long-term maintenance treatment, as the response is maintained for at least 1 year of continuous treatment in the majority of patients (1b).

Daily topical emollients and topical anti-inflammatory drugs (TCS, TCI)—if needed—may be combined with DUP treatment (B, 2b).

5.3.7 | Antimicrobial therapy

Long-term topical antibiotics without clinically evident signs of bacterial infection should be avoided due to the sensitization and increase of bacterial resistance (B, 2b). However, patients with clinical signs of Staphylococcus aureus infection may benefit to short course antibiotic therapy (B, 2b).

Topical antiseptic drugs (such as antiseptic baths based on sodium hypochlorite 0.005%) may be considered, particularly in case of bacterial superinfection (C, 4) or treatment resistance (B, 2b). Topical or even systemic antifungal therapy should be evaluated in case of IgE sensitization to Malassezia spp. and/or in head and neck variant of AD (B, 2b). Prompt systemic antivirals are mandatory in case of eczema herpeticum (D, 4), and Varicella Zoster Virus vaccination remains mandatory for children with AD and their parents because they may trigger severe relapses (B, 2a).

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 01 of 12, January 2021) am 13.01.2021

#	Suchfrage
1	MeSH descriptor: [Dermatitis, Atopic] explode all trees
2	(atopic 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 Jan 2016 to present

Systematic Reviews in Medline (PubMed) am 13.01.2021

#	Suchfrage
1	dermatitis, atopic[mh]
2	atopic[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] 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 ("2016/01/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 13.01.2021

#	Suchfrage
1	dermatitis, atopic[mh]
2	atopic[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 ("2016/01/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

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