Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-256 Dupilumab

Stand: Januar 2019

I. Zweckmäßige Vergleichstherapie: Kriterien der VerfO	
Dupilumab (2018-B-256) **Zur Behandlung der 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.	Topisch: Glukokortikosteroide der Klassen 2 bis 4 Pimecrolimus (moderates atopisches Ekzem) Tacrolimus (moderate und schwere atopisches Ekzeme) Systemisch: Ciclosporin A (schwere atopische Dermatitis) systemische Glukokortikoide (für schwere Ekzeme) Dupilumab Antihistaminika
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)
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; Beschluss über die Nutzenbewertung nach § 35a SGB V vom 17. Mai 2018
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	⇨ *siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff ATC-Code Handelsname	**Anwendungsgebiet**
Zu prüfendes Arzneimittel:	
Dupilumab D11AH05 Dupixent®	Dupixent® wird angewendet zur Behandlung von mittelschwerer bis schwerer atopischer Dermatitis bei Patienten ab 12 Jahren, die für eine systemische Therapie in Betracht kommen.
Hinweis	***Aufgrund der großen Menge an Wirkstoffen im Anwendungsgebiet werden hier einzelne Arzneimittel exemplarisch aufgeführt***
TOPISCHE THERAPIEN	
Glukokortikoide Klasse 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 hartnackigen Hauterkrankungen, die mit einem starker wirkenden Corticoid anbehandelt worden sind. - bei Säuglingen und Kleinkindern zur lokalen Corticoidbehandlung, z. B. Windelekzem oder endogenem Ekzem. Aus FI 4.4.: Bei Kindern unter 12 Jahren sollte eine kontinuierliche Langzeitbehandlung mit topischen Corticoiden möglichst vermieden werden
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 fur akute bis subchronische sowie nassende Dermatosen ohne keratotische Veränderungen.

Glukokortikoide Klasse 3:	
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. Aus FI 4.4: Bei Säuglingen darf Prednicarbat acis nur bei zwingender Indikation angewendet werden, da die Gefahr systemischer Effekte durch Glucocorticoidresorption (z. B. Wachstumsverzögerung) erhöht ist. Ist eine Behandlung mit Prednicarbat acis unvermeidlich, so muss die Anwendung auf die für den Behandlungserfolg unbedingt notwendige Menge begrenzt werden.
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. Aus FI 4.2.: Advantan® 0,1 % Creme wird nicht empfohlen für die Anwendung bei Kindern unter 3 Jahren aufgrund des Fehlens von Daten zur Unbedenklichkeit. Es gibt keine Erfahrungen bei Kindern unter 3 Jahren.
z.B. Amcinonid D07AC11 z.B. Amciderm® Fettsalbe, Salbe, Creme, Lotio und Emulsion zur Anwendung auf der Haut	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. Aus FI 4.2: *Kinder unter 2 Jahren:* Amciderm enthält ein stark wirksames Glukokortikoid. Wegen der ausgeprägten Empfindlichkeit der kindlichen Haut mit dem Risiko systemischer Glukokortikoidwirkungen nach Resorption wird die Anwendung von Amciderm bei Säuglingen und Kleinkindern unter 2 Jahren nicht empfohlen.
z.B. Mometasonfuroat	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.

D07AC z.B. ECURAL® Fettcreme, 1 mg/g Creme ECURAL® Salbe, 1 mg/g Salbe	Aus 4.2. der Fachinformation: Die Anwendung von Fettcreme und Salbe bei Kindern sollte über einen möglichst kurzen Behandlungszeitraum bei geringstmöglicher Dosierung, die noch therapeutische Wirksamkeit gewährleistet, erfolgen. Die Anwendungsdauer betragt für Kinder über 2 Jahre (bei Fettcreme) bzw. für Kinder über 6 Jahre (bei Salbe) maximal 3 Wochen. Bei Kindern sollte Fettcreme und Salbe nur klein flächig (< 10 % der Korperoberfläche) angewendet werden. Aus FI 4.3: ECURAL Fettcreme sollte nicht bei Kindern unter 2 Jahren, ECURAL Salbe und ECURAL Losung nicht bei Kindern unter 6 Jahren angewendet werden, da keine ausreichenden klinischen Erfahrungen vorliegen.
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. Aus 4.3 der FI: BetaGalen ist bei Kindern nicht angezeigt.
Glukokortikoide Klasse 4:	
z.B. Clobetasolpropionat 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 zur Anwendung auf der Haut	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. Aus 4.4 der Fachinformation: Clobetasol sollte bei älteren Patienten nicht grossflächig angewendet werden.
z.B. Betamethason	Chronische oder nicht akut verlaufende trockene Dermatosen, die auf eine äußerliche Therapie mit stark wirksamen Kortikosteroiden ansprechen, z. B. Schuppenflechte (Psoriasis vulgaris), chronische Ekzeme bzw. allergische Hautentzündungen (u. a. Berufsekzeme),

D07XC01 Betamethason Hexal comp 0,64 mg/30 mg pro g Salbe	Knötchenflechte (Lichen ruber planus), Fischschuppenkrankheit (Ichthyosis). Aus 4.4 der Fachinformation: Allgemein ist bei der Behandlung von Kindern mit Betamethason HEXAL® comp erhöhte Vorsicht geboten.
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. Aus FI 4.2.: Bei Kindern von 2 bis 16 Jahren sollte nur Protopic 0,03 % Salbe angewendet werden. Protopic Salbe sollte bei Kindern unter 2 Jahren nicht angewendet werden, bis weitere Daten vorliegen.
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 moglich 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	
Ciclosporin Weichkapseln L04AD01 25, 50 und 100 mg Weichkapseln Ciclosporin 100	Ciclosporin Pro ist indiziert bei Patienten mit schwerer atopischer Dermatitis, falls eine systemische Therapie erforderlich ist. Aus 4.4 der Fachinformation: Abgesehen von der Behandlung von nephrotischem Syndrom liegen keine entsprechenden Erfahrungen mit Ciclosporin bei Kindern vor. Eine Anwendung bei Kindern unter 16 Jahren ausserhalb der Transplantationsindikationen mit Ausnahme des nephrotischen Syndroms kann daher nicht empfohlen werden. Ältere Patienten (65 und älter) sollten nur bei Vorliegen einer mit Behinderungen verbundenen atopischen Dermatitis behandelt werden. Die Dosis für einen älteren Patienten sollte mit Vorsicht gewählt werden.

mg/ml Lösung zum Einnehmen Einnehmen z.B. Ciclosporin Pro	
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 Aus FI 4.4: Die Anwendung der Filmtabletten ist bei Kindern unter 6 Jahren nicht empfohlen, da diese Formulierung keine geeignete Dosisanpassung ermöglicht.

Quellen: AMIS Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2018-B-256 (Dupilumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	19. November 2018

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Abkürzungsverzeichnis

AD	Atopic dermatitis
AE	Adverse events
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BSA	Body Surface Area
CAM	Complementary and alternative medicine
CI	Konvidenzintervall
DAHTA	DAHTA Datenbank
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HADS	Hospital Anxiety and Depression Scale
HR	Hazard Ratio
IGA	Investigator's Global Assessment
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
POEM	Patient-Oriented Eczema Measure
RR	Relatives Risiko
SCORAD	SCOring Atopic Dermatitis
SIGN	Scottish Intercollegiate Guidelines Network
SMD	standardized mean difference
SoR	Strength of Recommendation
TCI	Topical calcineurin inhibitors

TCS	topical corticosteroids
TRIP	Turn Research into Practice Database
WHO	World Health Organization
WMD	weighted mean difference

1 Indikation

Behandlung der mittelschweren bis schweren Atopischen Dermatitis bei Kindern ab 2 Jahren und Erwachsenen, die auf eine topische Therapie unzureichend angesprochen haben oder eine Unverträglichkeit gegen eine entsprechende Behandlung aufweisen.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *atopische Dermatitis* durchgeführt. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, SIGN, TRIP, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien.

Die Erstrecherche wurde am 07.05.2018 durchgeführt, die Folgerecherche am 13.11.2018. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherche übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt.

Die Recherchen ergaben insgesamt 609 Quellen, die in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Es wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen und nur die Quellen der letzten 5 Jahre berücksichtigt. 22 Quellen wurden in die synoptische Evidenz-Übersicht aufgenommen

3 Ergebnisse

3.1 IQWiG Berichte/G-BA Beschlüsse

G-BA, 2018 [10].

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.

Siehe auch IQWiG, 2018 [12].

Anwendungsgebiet

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 (UVA[1] /NB-UVB[2])
- 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, 2016 [7].

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 21.12.2016

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 mittelschwerem 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 Be-handlungsoptionen, 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 Makrolidimmun-suppressiva. 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.

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.

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

Da keine Erfahrungen bei Kindern unter zwei Jahren vorliegen, ist hier eine Behandlung nicht indiziert.

Kombinationsbehandlungen von Tacrolimus

- mit systemischen oder topischen wirkstoffhaltigen Arzneimitteln sind nicht untersucht und von daher unwirtschaftlich
- mit gleichzeitigem Einsatz von Lichttherapien sind wegen eines nicht auszuschließenden photokanzerogenen Risikos nicht angezeigt

---

G-BA, 2018 [8].

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 [9]

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.

3.2 Cochrane Reviews

Cury Martins J et al., 2015 [3].

Topical tacrolimus for atopic dermatitis

Fragestellung

To assess the efficacy and safety of topical tacrolimus for moderate and severe atopic dermatitis compared with other active treatments.

Methodik

Population:

- People with moderate to severe atopic dermatitis who a physician had diagnosed, with no restrictions on age, sex, or ethnicity

Intervention:

- Topical tacrolimus at any dose, course duration, and follow-up time

Komparator:

- other active treatments. We only considered including a placebo (vehicle) group in more complex comparisons of combined treatment approaches, e.g., topical corticosteroids alongside tacrolimus versus either tacrolimus plus placebo or topi-cal corticosteroids plus placebo.

Endpunkt:

- Primäre Endpunkte:
  - Physician's assessment of global response of improvement
  - Participant's self-assessment of global response of improvement
  - Occurence and severity of adverse effects
- Sekundäre Endpunkte:
  - Improvement of disease assessed by a validated or objective
  - measure, such as the following:
  - affected Body Surface Area (BSA);
  - Eczema Area and Severity Index (EASI);
  - relapse (over a period of up to one year); or
  - quality of life.

Recherche/Suchzeitraum:

- bis 3. Juni 2015

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

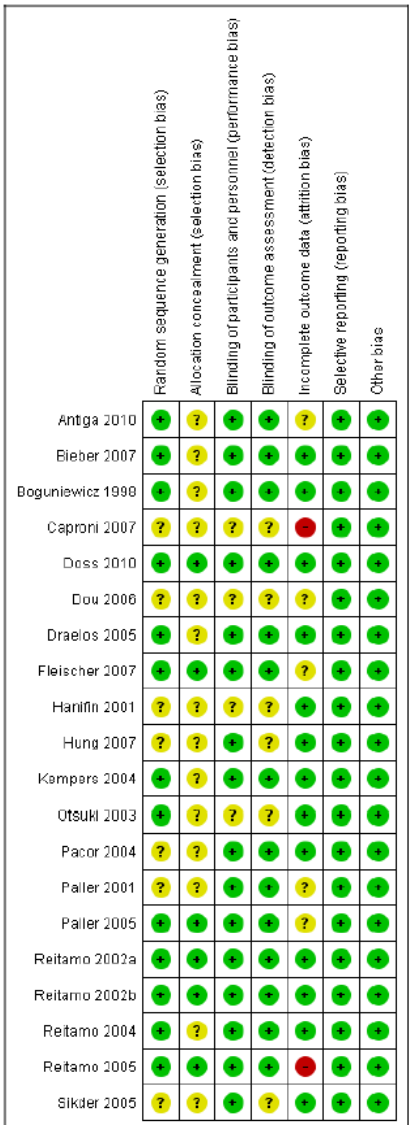
Ergebnisse

Anzahl eingeschlossener Studien: 20

Charakteristika der Population:

- Seventeen of the studies included participants with moderate or severe atopic dermatitis
- Eight studies included only adult participants (> = 16 or 18 years)
- 10 studies included only paediatric participants (6 months to 18 years)
- Two studies included both adults and paediatric participants with ages ranging from 9 months to 45 years

Qualität der Studien:



Studienergebnisse:

- Tacrolimus 0.1% compared with corticosteroids
  - Wirksamkeit: Mit Ausnahme von einer Studie (siehe Grafik) zeigte sich ein stat. signifikanter Vorteil für Tacrolimus im Vergleich zu Hydrokortisonen hinsichtlich des

Physician's assessment of global response of improvement, clear or excellent tacrolimus 0.1% versus hydrocortisone butyrate.

- Adverse effects: Es zeigte sich ein stat. signifikanter Nachteil für Tacrolimus im Vergleich zu Hydrokortisonen bei Betrachtung aller Vergleiche.

Patient or population: people with atopic dermatitis
Settings: outpatients, Europe and Canada
Intervention: tacrolimus 0.1%
Comparison: corticosteroids

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Corticosteroids	Tacrolimus 0.1%				
Physician's assessment of global response of improvement, clear or excellent - tacrolimus 0.1% versus hydrocortisone acetate 0.1%: 3 weeks Follow-up: mean 3 weeks	**Study population**		**RR 3.09** (2.14 to 4.45)	371 (1 study)	⊕⊕⊕○ **moderate**[1]	-
	157 per 1000	**484 per 1000** (335 to 698)				
	Moderate					
	157 per 1000	**485 per 1000** (336 to 699)				
Physician's assessment of global response of improvement, clear or excellent - tacrolimus 0.1% versus hydrocortisone butyrate: 3 weeks Follow-up: mean 3 weeks	**Study population**		**RR 0.95** (0.78 to 1.16)	377 (1 study)	⊕⊕○○ **low**[1, 2]	-
	516 per 1000	**490 per 1000** (403 to 599)				
	Moderate					
	516 per 1000	**490 per 1000** (402 to 599)				
Physician's assessment of global response of improvement, clear or excellent - tacrolimus 0.1% versus hydrocortisone acetate and butyrate 0.1%: short term (6 months) Follow-up: 6 months	**Study population**		**RR 1.32** (1.17 to 1.49)	972 (1 study)	⊕⊕○○ **moderate**[1]	-
	464 per 1000	**612 per 1000** (543 to 691)				
	Moderate					
	464 per 1000	**612 per 1000** (543 to 691)				
Adverse effects: burning - tacrolimus 0.1% versus hydrocortisone acetate 0.1%: 3 weeks Follow-up: mean 3 weeks	**Study population**		**RR 2.91** (1.6 to 5.28)	371 (1 study)	⊕⊕⊕○ **moderate**[1]	-
	70 per 1000	**204 per 1000** (112 to 371)				
	Moderate					
	70 per 1000	**204 per 1000** (112 to 370)				
Adverse effects: burning - tacrolimus 0.1% versus hydrocortisone butyrate: 3 weeks Follow-up: mean 3 weeks	**Study population**		**RR 4.59** (3.1 to 6.78)	377 (1 study)	⊕⊕⊕○ **moderate**[1]	-
	129 per 1000	**592 per 1000** (400 to 875)				
	Moderate					
	129 per 1000	**592 per 1000** (400 to 875)				
Adverse effects: burning - tacrolimus 0.1% versus hydrocortisone acetate and butyrate 0.1%: 6 months Follow-up: 6 months	**Study population**		**RR 3.79** (2.99 to 4.81)	972 (1 study)	⊕⊕⊕○ **moderate**[1]	-

	138 per 1000	**524 per 1000** (413 to 664)				
	Moderate					
	138 per 1000	**524 per 1000** (413 to 664)				
Participant's self-assessment of global response of improvement Follow-up: mean 6 months	**Study population**		**RR 1.21** (1.13 to 1.29)	974 (1 study)	⊕⊕◯◯ **low**[1, 3]	-
	718 per 1000	**868 per 1000** (811 to 926)				
	Moderate					
	718 per 1000	**869 per 1000** (811 to 926)				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades 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.

[1]Downgraded one level due to publication bias because only one study was identified and publication bias was strongly suspected.
[2]Downgraded one level due to Imprecision: sample size falls below the optimal information size; 95% CI of the estimated effect includes both no effect and appreciable benefit.
[3]Downgraded one level due to Imprecision: sample size falls below the optimal information size.

- Tacrolimus 0.1% versus pimecrolimus 1%
  - Wirksamkeit: Mit Ausnahme von einer Studie (siehe Grafik) zeigte sich ein stat. signifikanter Vorteil für Tacrolimus 0.1% im Vergleich zu Pimecrolimus 1% bei Betrachtung aller Vergleiche hinsichtlich des Physician's assessment of global response of improvement, clear or excellent: 13 days.
  - Adverse effects: Es zeigte sich kein stat. signifikanter Unterschied.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Physician's assessment of global response of improvement, clear or excellent	3	543	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.35, 2.42]
1.1 13 days	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [0.19, 19.13]
1.2 6 weeks	2	506	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.34, 2.42]
2 Adverse effects - 6 weeks	2	506	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.47, 1.71]

- Tacrolimus 0.03% versus steroids
  - Wirksamkeit: Bei 2 der 4 Vergleichen zeigte sich ein stat. signifikanter Vorteil für Tacrolimus im Vergleich zu Steroiden hinsichtlich des Endpunkts *Physician's assessment of global response of improvement* . Bei 2 Vergleichen zeigte sich kein stat. signifikanter Unterschied.
  - Hinsichtlich des *Participant's self-assessment of global response of improvement* zeigte sich kein stat. signifikanter Unterschied.
  - Adverse effects: Bei 6 Vergleichen zeigte sich ein stat. signifikanter Nachteil für Tacrolimus im Vergleich zu Steroiden. Bei 3 Vergleichen zeigte sich kein stat. signifikanter Unterschied.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Physician's assessment of global response of improvement, clear or excellent	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Tacrolimus 0.03% 1x/day versus hydrocortisone acetate 1% 2x/day	1	411	Risk Ratio (M-H, Random, 95% CI)	2.05 [1.36, 3.08]
1.2 Tacrolimus 0.03% 2x/day versus hydrocortisone acetate 1% 2x/day	2	790	Risk Ratio (M-H, Random, 95% CI)	2.58 [1.96, 3.38]
1.3 Tacrolimus 0.03% 2x/day versus steroids moderate potency 2x/day	2	409	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.13, 1.57]
1.4 Tacrolimus 0.03% 2x/day versus methylprednisolone 0.03% 1x/day	1	265	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.85, 1.19]
2 Participants's assessment of global response of improvement better or much better	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Tacrolimus 0.03 1x/day versus hydrocortisone acetate 1% 2x/day	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Tacrolimus 0.03% 2x/day versus hydrocortisone acetate 1% 2x/day	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Tacrolimus 0.03% 2x/day versus fluticasone 0.005% 2x/day	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Adverse effects: burning	5	1883	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [1.96, 3.14]
3.1 Tacrolimus 0.03% versus hydrocortisone acetate 1%	2	998	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.36, 2.57]
3.2 Tacrolimus 0.03% versus steroids moderate potency	3	885	Risk Ratio (M-H, Fixed, 95% CI)	3.52 [2.45, 5.06]
4 Adverse effects: pruritus	5	1883	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.17, 1.95]
4.1 Tacrolimus 0.03% versus hydrocortisone acetate 1%	2	998	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.00, 1.88]
4.2 Tacrolimus 0.03% versus steroids of moderate potency	3	885	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [1.18, 2.80]
5 Adverse effects: skin infection	4	1643	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.69, 1.66]
5.1 Tacrolimus 0.03% versus hydrocortisone acetate 1%	2	788	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.49, 1.79]
5.2 Tacrolimus 0.03% versus steroids of moderate potency	2	855	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.65, 2.18]

- Tacrolimus 0.03% versus tacrolimus 0.1%
  - Wirksamkeit: Es zeigte sich ein stat. signifikanter Nachteil für Tacrolimus 0.03% im Vergleich zu Tacrolimus 0.1% bei Betrachtung aller Vergleiche hinsichtlich des *Physician's assessment of global response of improvement*.
  - Adverse effects: Es zeigte sich kein stat. signifikanter Unterschied.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Physician's assessment of global response of improvement, clear or excellent	6	1640	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.72, 0.92]
1.1 3 weeks	4	985	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.71, 0.96]
1.2 12 weeks	2	655	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.64, 0.99]
2 Adverse effects	4	986	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.86, 1.06]

- Tacrolimus 0.03% versus pimecrolimus 1%
  - Wirksamkeit: Es zeigte sich ein stat. signifikanter Vorteil für Tacrolimus 0.03% im Vergleich zu Pimecrolimus 1% bei Betrachtung aller Vergleiche hinsichtlich des *Physician's assessment of global response of improvement*.

- Adverse effects: Es zeigte sich kein stat. signifikanter Unterschied.

Patient or population: people with atopic dermatitis
Settings: outpatients, USA
Intervention: tacrolimus 0.03% versus pimecrolimus 1%

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Tacrolimus 0.03% versus pimecrolimus 1%				
Physician's assessment of global response of improvement Follow-up: mean 6 weeks	Study population		RR 1.42 (1.02 to 1.98)	139 (1 study)	⊕⊕◯◯ low[1, 2]	-
	429 per 1000	609 per 1000 (437 to 849)				
	Moderate					
	429 per 1000	609 per 1000 (438 to 849)				
Adverse effects - application site reaction Follow-up: mean 6 weeks	Study population		RR 1.07 (0.6 to 1.91)	141 (1 study)	⊕⊕◯◯ low[2, 3]	-
	239 per 1000	256 per 1000 (144 to 457)				
	Moderate					
	239 per 1000	256 per 1000 (143 to 456)				
Adverse effects - burning Follow-up: mean 6 weeks	Study population		RR 0.87 (0.43 to 1.75)	141 (1 study)	⊕⊕◯◯ low[2, 3]	-
	197 per 1000	172 per 1000 (85 to 345)				
	Moderate					
	197 per 1000	171 per 1000 (85 to 345)				
Adverse effects - itching Follow-up: mean 6 weeks	Study population		RR 2.37 (0.96 to 5.81)	141 (1 study)	⊕⊕◯◯ low[2, 3]	-
	85 per 1000	200 per 1000 (81 to 491)				
	Moderate					
	85 per 1000	201 per 1000 (82 to 494)				
Adverse effects - erythema Follow-up: mean 6 weeks	Study population		RR 2.2 (0.89 to 5.46)	141 (1 study)	⊕⊕◯◯ low[2, 3]	-
	85 per 1000	186 per 1000 (75 to 461)				
	Moderate					
	85 per 1000	187 per 1000 (76 to 464)				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades 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.

[1]Downgraded one level due to imprecision: sample size is smaller than the optimal information size.
[2]Downgraded one level due to publication bias because only one study was identified and publication bias was strongly suspected.
[3]Downgraded one level due to imprecision: 95% CI of the estimate of summary effect includes both no effect and appreciable harm.

- Tacrolimus 0.1% versus ciclosporin
  - Wirksamkeit: Mit Ausnahme des Follow-up-Zeitpunkts 42 Tage (siehe Grafik) zeigte sich ein stat. signifikanter Vorteil für Tacrolimus 0.03 im Vergleich zu Ciclosporin hinsichtlich des Endpunkts *SCORAD score*.
  - Adverse effects: Es zeigte sich kein stat. signifikanter Unterschied.

Review: Topical tacrolimus for atopic dermatitis

Comparison: 6 Tacrolimus 0.1% versus ciclosporin

Outcome: 2 SCORAD

Study or subgroup	Tacrolimus 0.1% N	Ciclosporin N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 14 days					
Pacor 2004	15	15	-12.6 (3.1)		-12.60 [-18.68, -6.52]
2 21 days					
Pacor 2004	15	15	-11.6 (3.1)		-11.60 [-17.68, -5.52]
3 28 days					
Pacor 2004	15	15	-18.7 (3.1)		-18.70 [-24.78, -12.62]
4 35 days					
Pacor 2004	15	15	-10.1 (3.1)		-10.10 [-16.18, -4.02]
5 42 days					
Pacor 2004	15	15	-1.3 (3.1)		-1.30 [-7.38, 4.78]

Tacrolimus 0.1% versus ciclosporin for atopic dermatitis

Patient or population: people with atopic dermatitis
Settings: outpatients, Italy
Intervention: tacrolimus 0.1% versus ciclosporin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Tacrolimus 0.1% versus ciclosporin				
Adverse effects Follow-up: mean 6 weeks	**Study population**		**RR 1** (0.31 to 3.28)	30 (1 study)	⊕○○○ **very low**[1, 2, 3]	-
	267 per 1000	**267 per 1000** (83 to 875)				
	Moderate					
	267 per 1000	**267 per 1000** (83 to 876)				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades 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.

[1]Downgraded one level due to risk of bias: randomisation and allocation concealment procedures were unclear.
[2]Downgraded one level due to imprecision: sample size is smaller than optimal information size; 95% CI of the estimate of summary effect includes both no effect and appreciable benefit and harm.

[3]Downgraded one level due to publication bias because only one study was identified and publication bias was strongly suspected.

Anmerkung/Fazit der Autoren

Tacrolimus 0.1% was better than low-potency corticosteroids, pimecrolimus 1%, and tacrolimus 0.03%. Results were equivocal when comparing both dose formulations to moderate-to-potent corticosteroids. Tacrolimus 0.03% was superior to mild corticosteroids and pimecrolimus. Both tacrolimus formulations seemed to be safe, and no evidence was found to support the possible increased risk of malignancies or skin atrophy with their use. The reliability and strength of the evidence was limited by the lack of data; thus, findings of this review should be interpreted with caution.

Kommentare zum Review

- Keine Angaben zur Vorbehandlung der Patienten vorhanden.
- Daten von Kindern und Erwachsenen wurden kombiniert.

3.3 Systematische Reviews

Wang FP et al., 2018 [21].

Dupilumab treatment in moderate-to-severe atopic dermatitis: A systematic review and meta-analysis

Fragestellung

to assess the overall efficacy and safety of dupilumab treatment in AD.

Methodik

Population:

- adults (age ≥18 years) with moderate-to severe AD at least 3 years before the screening visit; Investigator's Global Assessment (IGA, scores range from 0 to 4, with higher scores indicating more severe disease) score of 3 (moderate) or 4 (severe); Eczema Area and Severity Index (EASI) score 12 or higher at screening and baseline visits; body surface area (BSA) affected of more than 10%; documented history within 6 months before screening of inadequate response to topical treatments.

Intervention:

- dupilumab 300 mg once weekly (qw) and 300 mg every 2 weeks (q2w)

Komparator:

- placebo

Endpunkte:

- EASI,
- IGA,
- pruritus numeric rating scale (NRS)
- percent BSA affected with AD,
- Dermatology Life Quality Index (DLQI)
- adverse events

Recherche/Suchzeitraum:

- systematic literature review search using the PubMed, Embase, the Cochrane Library, and the Chinese Biological Medicine (CBM), published up to September 5, 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

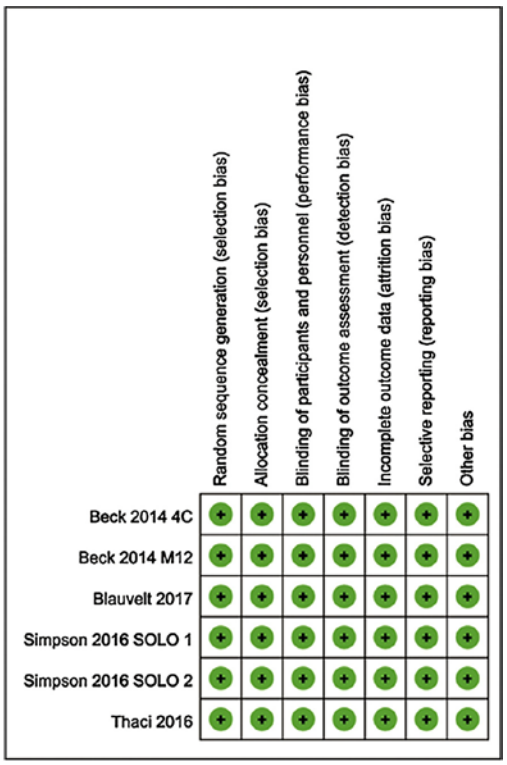
- 6 trials

Charakteristika der Population:

- treatment groups received dupilumab monotherapy in four trials [18,20], while in the rest trials received combination therapy with topical corticosteroids

Qualität der Studien:

- All studies had a low risk of bias. All used random sequence generation by means of central interactive voice response system and allocation concealment. All the trials were described as being double-blinded and reported complete outcome data.
- all the included trials were funded by pharmaceutical company (Sanofi and Regeneron Pharmaceuticals).



Studienergebnisse:

- Meta-analysis demonstrated significant improvement in efficacy of dupilumab for the treatment of AD in all measures of clinical indexes.
  - o significant reduction in EASI score (SMD = -0.89, 95% CI: -1.0 to -0.78, P < 0.001, moderate heterogeneity (I^2 = 45%, P = 0.06), N (Dupilumab)=1481, N (Placebo)=1634
  - o higher proportion of patients achieved IGA response (IGA 0/1) in dupilumab treatment groups (RR = 3.82; 95% CI: 3.23 to 4.51; P < 0.001), minimal heterogeneity (I^2 = 16%, P = 0.3), N (Dupilumab)=1481, N(Placebo)=1634
  - o greater improvement versus placebo in percentage of BSA (SMD = -0.83, 95% CI: -0.90 to -0.75, P < 0.001), heterogeneity not statistically significant (I^2 = 9%, P = 0.36), N(Dupilumab)=1481, N(Placebo)=1634
  - o dupilumab significantly improved pruritus NRS scores (SMD = -0.81, 95% CI: -0.96 to -0.66, P < 0.001), high level of heterogeneity (I^2 = 71%, P < 0.001), N (Dupilumab)=1481, N (Placebo)=1634

- dupilumab were associated with significant increase in DLQI scores (SMD = -0.78, 95% CI: -0.89 to -0.66, P < 0.001), significant heterogeneity (I^2 = 53%, P = 0.04), N (Dupilumab)=1405, N (Placebo)=1570

- safety
  - overall incidence of adverse events was similar in dupilumab-treated(42%) and placebo-treated (43%) patients (RR = 1.0; 95% CI: 0.96 to 1.04; P = 0.83), heterogeneity (I^2 = 11%, P = 0.34), N (Dupilumab)=1548, N (Placebo)=1728
  - most common adverse events were nasopharyngitis, exacerbation of atopic dermatitis, headache, and upper respiratory tract infection

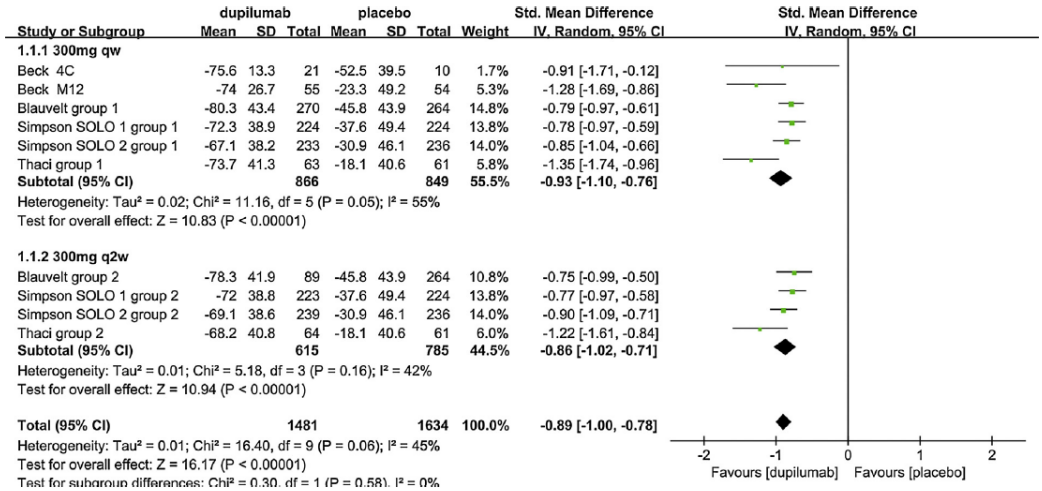


Fig. 2. Forest plot of the effect of dupilumab treatment on EASI scores verse placebo. SD = standard derivation, IV = Inverse Variance, CI = confidence interval, Std. Mean Difference = standardized mean difference.

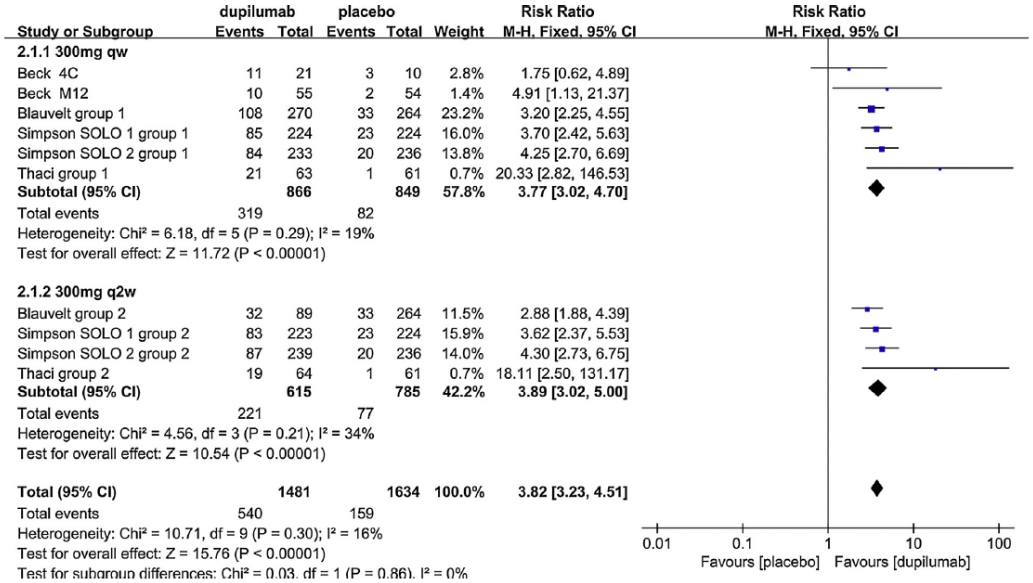


Fig. 3. Forest plot of the effect of dupilumab treatment on proportion of patients achieving IGA response (IGA 0/1) verse placebo. Fixed-effects model. M-H = Mantel-Haenszel, CI = confidence interval.

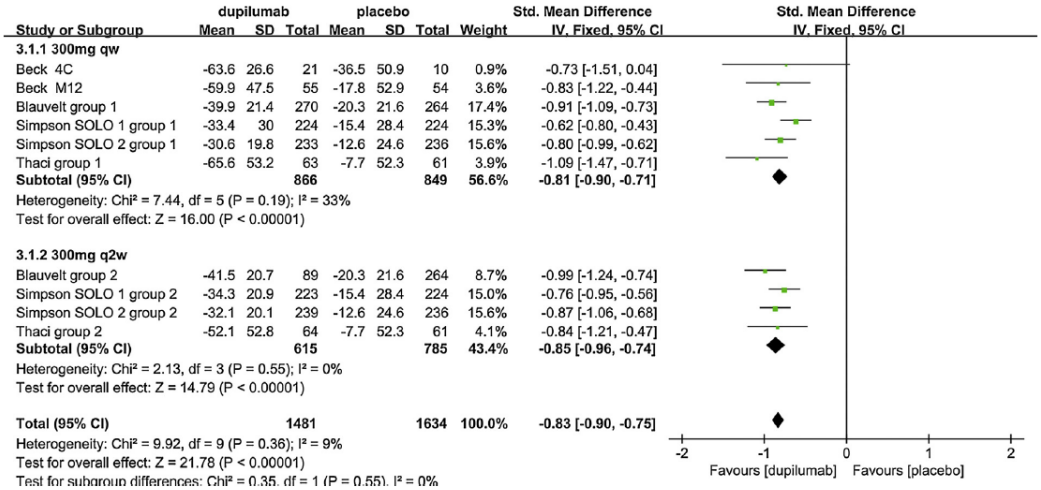


Fig. 4. Forest plot of the effect of dupilumab treatment on percentage of BSA affected verse placebo. SD = standard derivation, IV = Inverse Variance, CI = confidence interval, Std. Mean Difference = standardized mean difference.

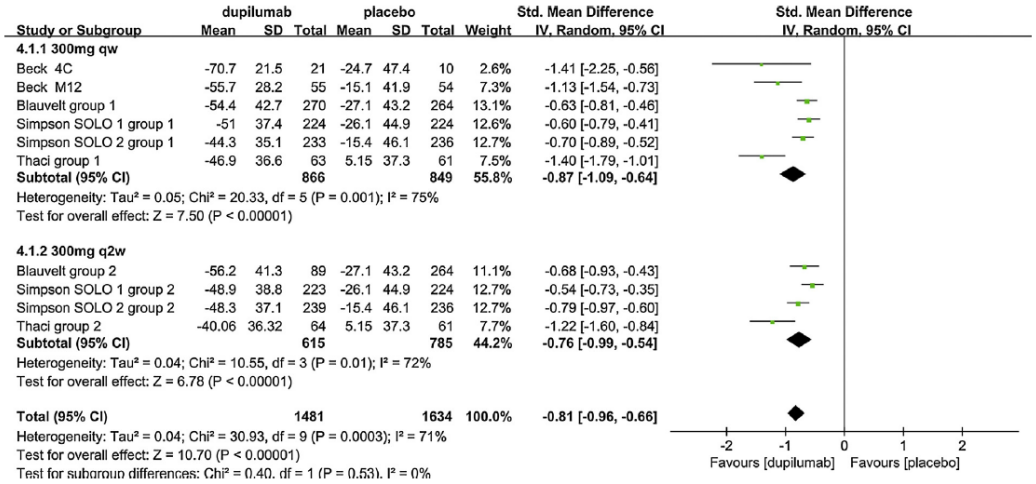


Fig. 5. The effect of dupilumab versus placebo on pruritus NRS score. SD = standard derivation, IV = Inverse Variance, CI = confidence interval, Std. Mean Difference = standardized mean difference.

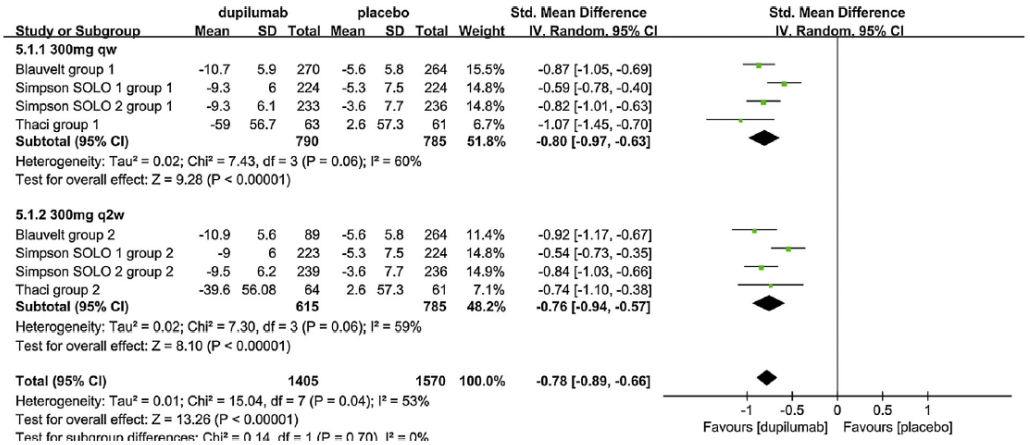


Fig. 6. The effect of dupilumab versus placebo on DLQI. SD = standard derivation, IV = Inverse Variance, CI = confidence interval. Std. Mean Difference = standardized mean difference.

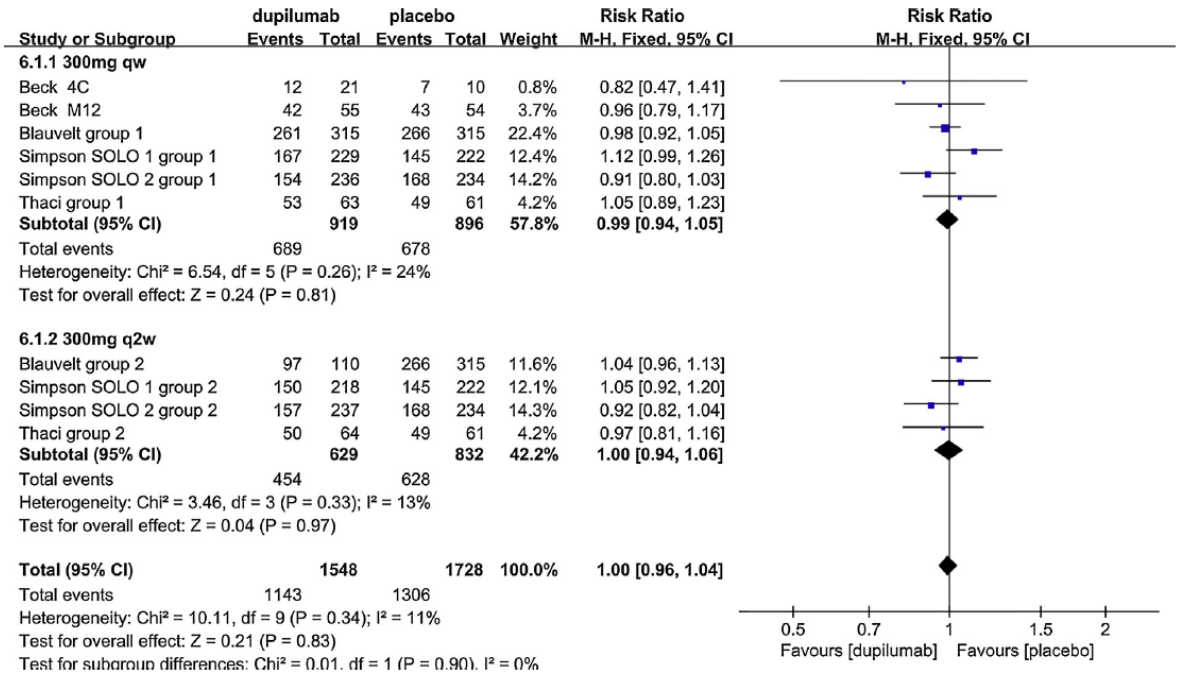


Fig. 7. Forest plot of the effect of dupilumab treatment on adverse events verse placebo. M–H = Mantel–Haenszel, CI = confidence interval.

Anmerkung/Fazit der Autoren

Both dose regimens of dupilumab were found to improve all the evaluated measures of moderate-to-severe AD in adults, including EASI, IGA, BSA, pruritus NRS scores and DLQI scores, with acceptable safety. In addition, our findings suggested that the 300 mg qw and 300 mg q2 w dosage nearly provided the similar benefits for patients.

Snast I et al., 2018 [20].

Are Biologics Efficacious in Atopic Dermatitis? A Systematic Review and Meta-Analysis.

Fragestellung

to evaluate the efficacy and safety of biologic agents in AD.

Methodik

Population:

- patients of all ages with a physician diagnosis of AD and of at least 8 weeks' duration

Intervention:

- all available biologic therapies for the treatment of AD (extraction of results on dupilumab only)

Komparator:

- no restriction

Endpunkt:

- Primary outcome: proportion of patients with an improvement from baseline of at least 75% on the Eczema Area and Severity Index (EASI)-75
- Secondary outcomes: SCOring Atopic Dermatitis (SCORAD)-75 response, a clear or almost clear Investigator Global Assessment (IGA) response (IGA 0/1), EASI-50 and SCORAD-50 responses, score change from baseline, and adverse events.

Recherche/Suchzeitraum:

- Without date limits, in May 2017 using PubMed, the ongoing trials registry of the US National Institutes of Health (http://www.clinicaltrials.gov), the Cochrane Central Register of Controlled Trials, and the Global Resource for EczemA Trials (GREAT) database (Centre of Evidence-Based Dermatology; http://www.greatdatabase.org.uk). reference lists from key trials, grey literature (e.g. conference abstracts, web pages), post hoc search of reviews submitted to the FDA for drug registration

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool for RCTs and Newcastle Ottawa Quality Assessment Scale for observational studies

Ergebnisse

Anzahl eingeschlossener Studien:

- 23 studies (13 randomized controlled trials (RCTs) and 10 observational studies)
- On dupilumab: 5 RCTs (one phase I, two phase II, two phase III)

Charakteristika der Population:

- Only two studies allowed concomitant topical corticosteroids (TCSs).

Qualität der Studien:

- Low risk of bias for all studies on dupilumab.

Studienergebnisse:

- pooled RRs of dupilumab 300 mg every week to every 2 weeks versus placebo were 3.3 for EASI-75 (95% CI 2.9–3.6, p<0.001, I2 = 0%) and 3.7 for IGA 0/1 (95% CI 3.2–4.3, p<0.001, I2 = 0%)
- risk for at least one adverse event was similar between dupilumab and placebo (RR 1.0 (95% CI 1.0-1.0, p=0.91, I^2=13%)
- The risks for at least one severe adverse event (RR 0.5 (95% CI 0.3-0.7), p<0.001, I^2=0%) and withdrawal due to adverse events (RR 0.43 (95% CI 0.28-0.68), p<0.001, I^2=0%) were favorable in the dupilumab arm

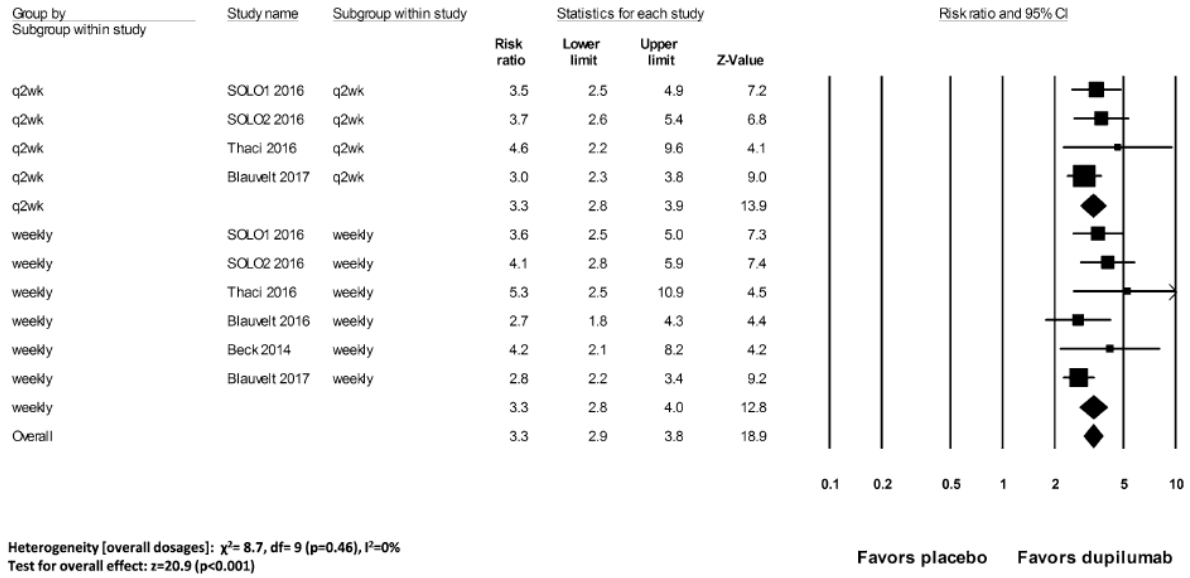


Fig. 2 Forest plot: dupilumab versus placebo—EASI-75 at weeks 12–16. *CI* confidence interval, *q2wk* every 2 weeks, *df* degrees of freedom, *EASI* Eczema Area and Severity Index

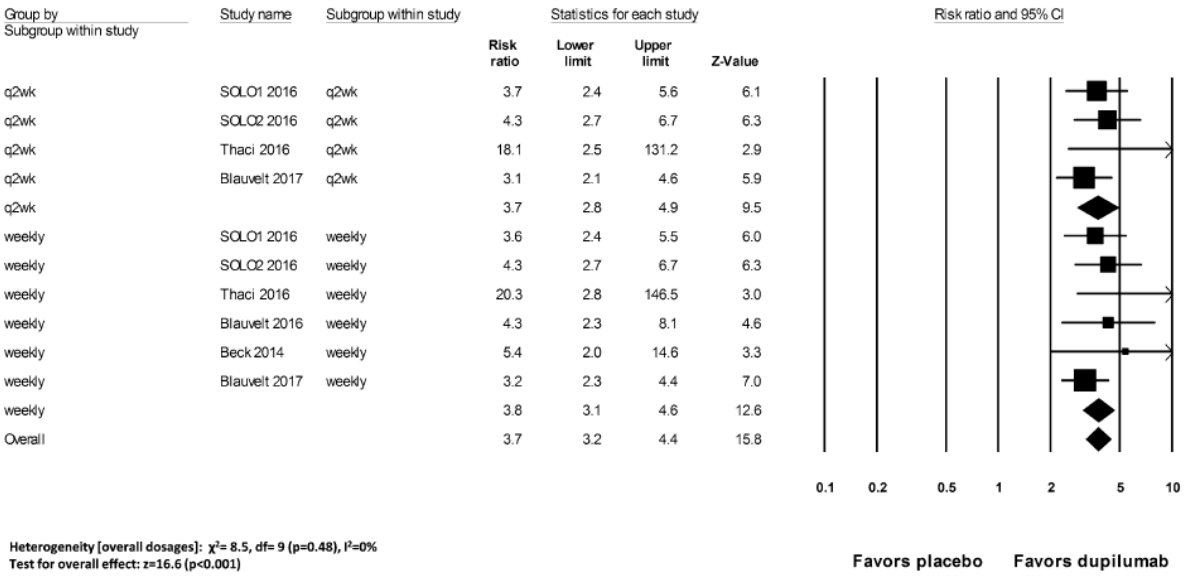


Fig. 3 Forest plot: dupilumab versus placebo—IGA 0/1 at weeks 12–16. *CI* confidence interval, *q2wk* every 2 weeks, *df* degrees of freedom, *IGA* Investigator Global Assessment

Anmerkung/Fazit der Autoren

Based on the current available data, dupilumab is the only biologic to provide a significant clinical effect in alleviating signs of moderate to severe AD, based on high-quality studies.

Kommentar zum Review:

- Daten zu Erwachsen und Kinder kombiniert. Keine Subgruppenanalysen

Ou Z et al., 2018 [17].

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:

- comprehensive searches of the 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 trials

Charakteristika der Population:

- All patients were adults (≥18 years old), had an Investigator's Global Assessment (IGA) score of ≥3, affected body surface area of ≥10%, and a diagnosis of AD for ≥3 years.

Qualität der Studien:

- All the studies included in this work were randomised trials with details on the method of randomisation. Blinding of participants, investigators, and outcome assessor was considered adequate in all studies. Four of the studies had a high risk of selective reporting because they only provided the conclusions, but no details, for some adverse events.

Studienergebnisse:

- Skin infection
  - incidence of skin infection was 6.7% (120/1790) in the dupilumab group and 13.3% (121/912) in the placebo group (RR 0.54, 95% CI 0.42–0.69, p < 0.00001, $p\chi^2$= 0.62, I^2 = 0%;
- Herpes virus infection
  - in 102/1663 (6.1%) of the participants treated with dupilumab and 43/832 (5.2%) of the participants treated with a placebo (RR 1.21, 95% CI 0.84–1.74, p = 0.30, $p\chi^2$ =0.32, I^2 =15%)
- Upper respiratory tract infections (subgroup analysis according to the interval between the end of the study and the end of assessment)
  - interval of 16 weeks: lower incidence of upper respiratory tract infections in the dupilumab group than in the placebo group (23/318 = 7.2% and 11/ 61 = 18.0%, respectively; RR 0.40, 95% CI 0.21–0.78, p = 0.007, only one study)
  - no interval: incidence of upper respiration tract infections was similar in the dupilumab group and placebo group in this subgroup (87/ 1345 = 6.5% and 42/771 =5.4%, respectively; RR 1.34, 95% CI 0.94–1.91, p = 0.11, $p\chi^2$= 0.81, I^2= 0%)
  - combined: similar incidence of upper respiratory infections in the dupilumab group and the placebo group (110/1663 = 6.6% and 53/832 = 6.4%, respectively; RR 1.03, 95% CI 0.53–2.01, p = 0.94, pχ2 =0.01, I^2 =71%)
- Nasopharyngitis
  - reported in 261/1663 (15.7%) of the participants treated with dupilumab and in 116/832 (13.9%) of the participants treated with a placebo (RR 1.06, 95% CI 0.87–1.31, p =0.55, $p\chi^2$= 0.71, I^2 =0%)
- Conjunctivitis
  - reported in 133/1663 (8.0%) of the participants treated with dupilumab, but in only 30/832 (3.6%) of the participants treated with a placebo (RR 2.64, 95% CI 1.79–3.89, p < 0.0001, $p\chi^2$= 0.46, I^2 = 0%)
- Urinary tract infection
  - reported in 25/1238 (2.0%) of the participants treated with dupilumab and in 12/517 (2.3%) of the participants treated with a placebo (RR 0.58, 95% CI 0.28–1.19, p = 0.14, pχ2= 0.42, I^2 = 0%)
- exacerbation of AD (subgroup analysis according to the interval between the end of each study and the end of

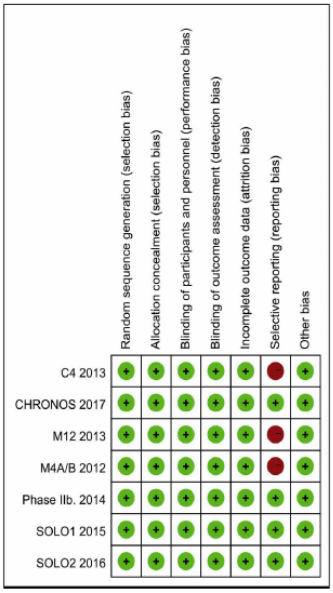


Fig. 2. Risk-of-bias summary. Our judgment of each risk-of-bias item for each included study.

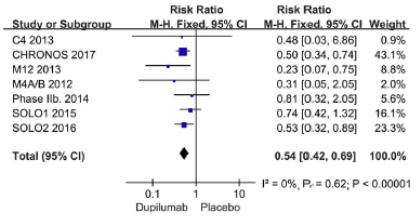


Fig. 3. Meta-analysis (pooled data) of studies of skin infections in patients treated with dupilumab or a placebo. CI, confidence interval.

assessment)

- interval of 16 weeks: no difference between dupilumab and placebo groups (54/318 = 17.0% and 11/61 = 18.0%, respectively; RR 0.94, 95% CI 0.52–1.69, p = 0.84)
- no interval: incidence of AD exacerbation was lower in the dupilumab group than in the placebo group (193/1345 =14.3% and 292/771 = 37.9%, respectively; RR 0.39, 95% CI 0.33–0.46, p < 0.00001, $p\chi^2$= 0.73, I^2 = 0%)
- combined: incidence of AD exacerbation was lower in the dupilumab group than in the placebo group (193/1345 =14.3% and 292/771 = 37.9%, respectively; RR 0.39, 95% CI 0.33–0.46, p < 0.00001, $p\chi^2$= 0.73, I^2 = 0%)

- injection site reactions
  - 221/1663 (13.2%) of the participants treated with dupilumab and 54/832 (6.5%) of the participants treated with a placebo (RR 2.24, 95% CI 1.68–2.99 p < 0.0001, $p\chi^2$= 0.99, I^2= 0%)

Table 2
Infrequent adverse events and those reported in only one study.

Events	Dupilumab group n (incidence)	Placebo group n (incidence)	RR	95%CI	*p* value
Bacterial infection	25(7.9%)	7(11.5%)	0.69	0.31–1.51	0.35
Viral infection	17(5.3%)	6(9.8%)	0.54	0.22–1.32	0.18
Dermatitis and eczama	63(19.8%)	12(19.7%)	1.01	0.58–1.75	0.98
Nausea and vomiting symptoms	10(3.1%)	4(6.6%)	0.48	0.16–1.48	0.20
Musculoskeletal and connective tissue pain and disorder	15(4.7%)	5(8.2%)	0.58	0.22–1.52	0.27
Back pain	9(2.8%)	5(8.2%)	0.35	0.12–0.99	0.05
Sinusitis	23(1.7%)	15(1.9%)	0.68	0.10–4.68	0.70
Influenza	19(1.4%)	19(2.5%)	0.68	0.36–1.28	0.23
Asthma	7(1.6%)	19(6.0%)	0.27	0.12–0.64	0.003

RR, risk ratio; CI, confidence interval.

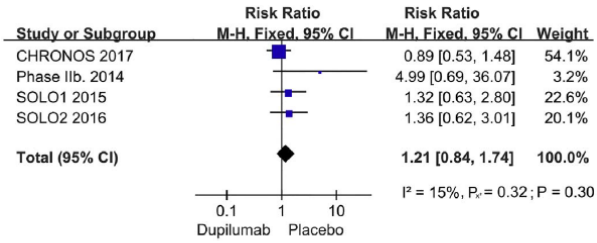


Fig. 4. Meta-analysis (pooled data) of studies of herpes virus infections in patients treated with dupilumab or a placebo. CI, confidence interval.

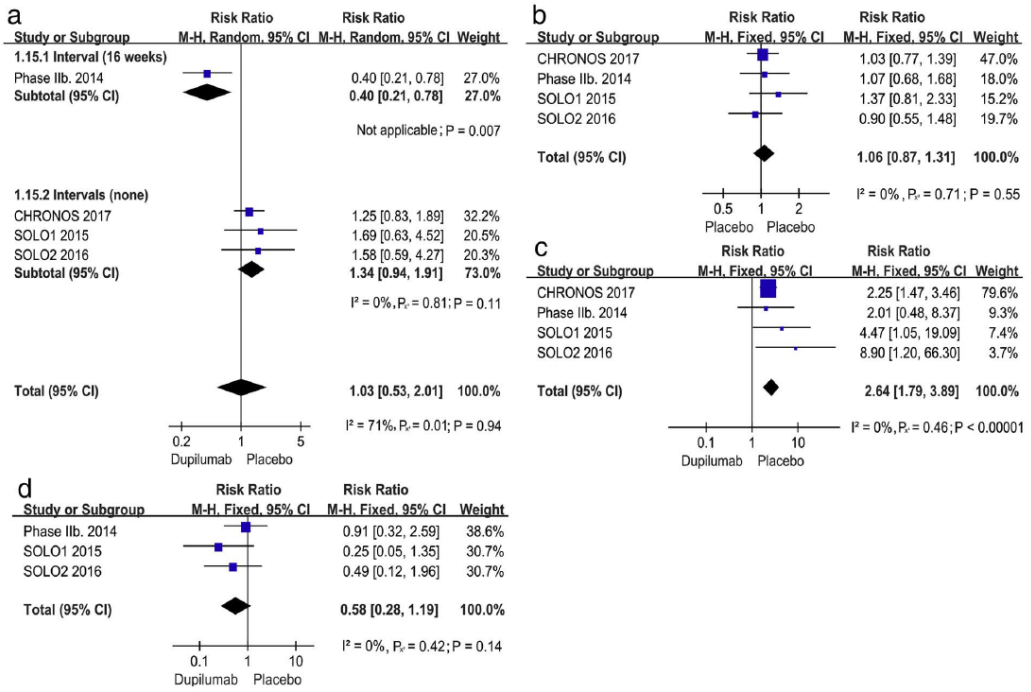


Fig. 5s. Meta-analysis (pooled data) of studies of non-skin infections in patients treated with dupilumab or a placebo. (a) Upper respiratory tract infection; (b) nasopharyngitis; (c) conjunctivitis; (d) urinary tract infection. CI, confidence interval.

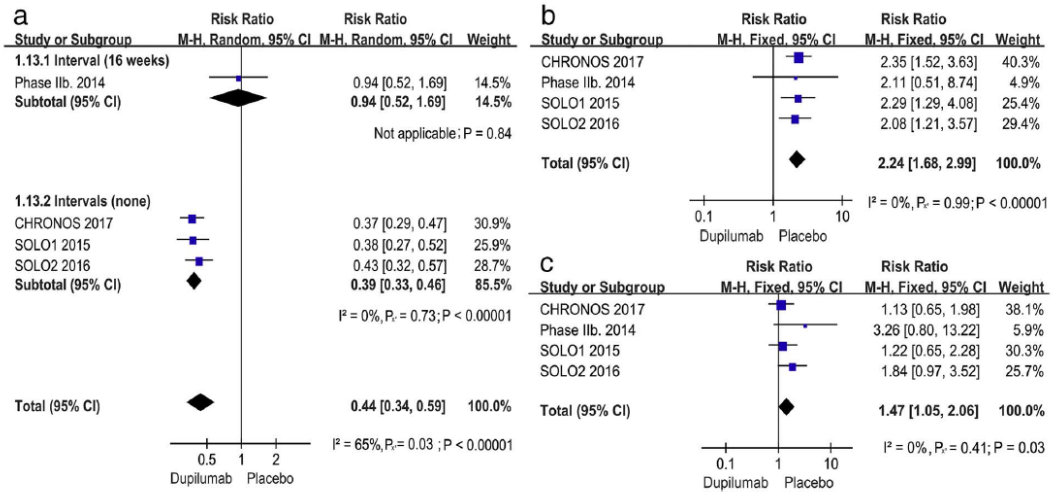


Fig. 6s. Meta-analysis (pooled data) of studies of other adverse effects in patients treated with dupilumab or a placebo. (a) Exacerbation of atopic dermatitis; (b) injection-site reaction; (c) headache. CI, confidence interval.

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.

Fleming P et al., 2018 [6].

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:

- searched 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

Qualität der Studien:

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

Supplemental Table I. Risk for bias assessment

Study ID	Adequate generation of a random sequence	Adequate allocation concealment	Adequate blinding of participants	Adequate blinding of treaters	Adequate blinding of outcome assessors	Complete outcome data	Complete reporting	Other bias
Study A in Beck et al[8]	Yes	Yes	Yes	Yes	Yes	Yes	No	None identified
Study C in Beck et al[8]	Yes	Yes	Yes	Yes	Yes	Yes	No	None identified
Study D in Beck et al[8]	Yes	Yes	Yes	Yes	Yes	Yes	No	None identified
Thaçi et al[12]	Yes	Yes	Yes	Yes	Yes	Yes	No	None identified
SOLO 1 in Simpson et al[10]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	None identified
SOLO 2 in Simpson et al[10]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	None identified
Blauvelt et al[13]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	None identified

ID, Identifier.

- All included studies were industry sponsored.

Studienergebnisse:

- skin infections
  - Dupilumab 120/1790, Placebo 121/912; **RR, 0.54; 95% CI, 0.42-0.70**, I^2=0%, P_{het}=0.62
- herpes infections
  - Dupilumab 102/1663, Placebo 43/832; RR, **1.16; 95% CI, 0.78-1.74,** I^2=12%, P_{het}=0.34
- eczema herpeticum
  - Dupilumab 7/1790, Placebo 11/912; **OR, 0.34; 95% CI, 0.14-0.84**, I2=0%, P_{het}=0.90
  - Dupilumab was no longer associated with lower risk for eczema herpeticum when excluding RCTs with concomitant topical corticosteroid use or RCTs with a duration other than 16 weeks, primarily because of exclusion of the 1-year RCT.
- overall infection
  - RR, 0.98; 95% CI, 0.83-1.16

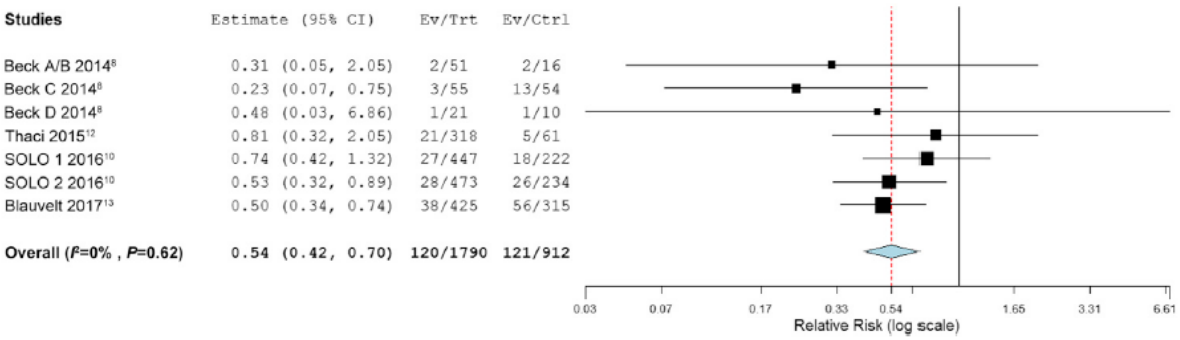


Fig 2. Forest plot for the relative risk for skin infections for all doses of dupilumab compared with placebo. *CI*, Confidence interval; *Ctrl*, control; *Ev*, event; *Trt*, treatment.

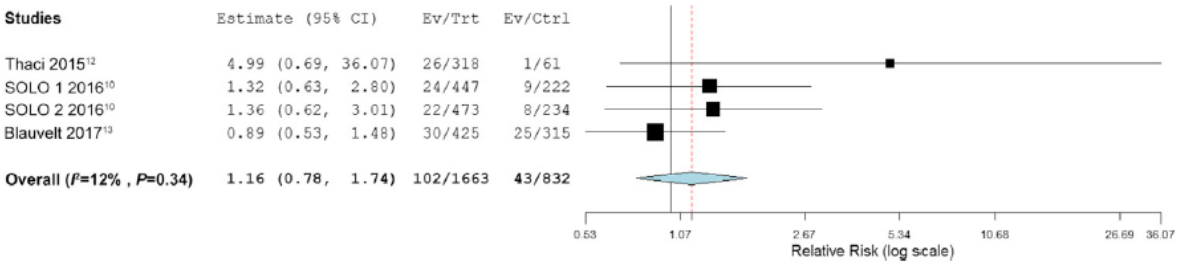


Fig 3. Forest plot for the relative risk for herpesvirus infections for all doses of dupilumab compared with placebo. *CI*, Confidence interval; *Ctrl*, control; *Ev*, event; *Trt*, treatment.

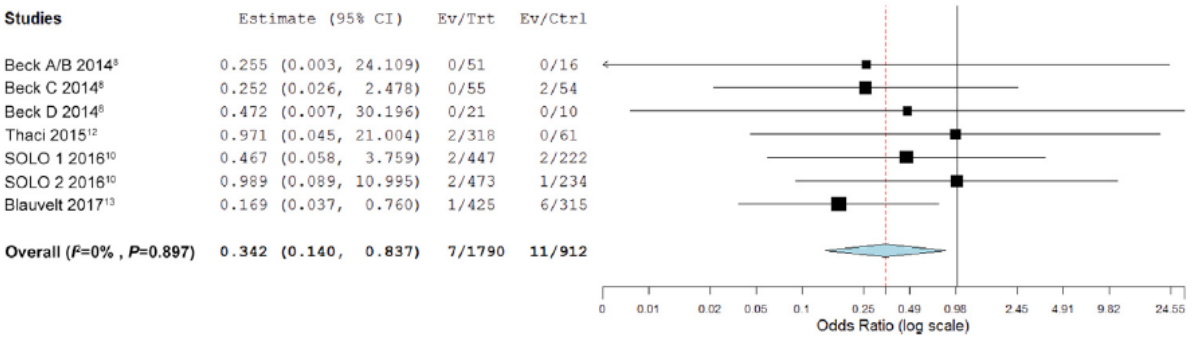


Fig 4. Forest plot for the odds ratio of eczema herpeticum for all doses of dupilumab compared with placebo. *CI*, Confidence interval; *Ctrl*, control; *Ev*, event; *Trt*, treatment.

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.

Xu X et al., 2017 [22].

Efficacy and safety of dupilumab for the treatment of moderate-to-severe atopic dermatitis in adults

Siehe auch **Han Y et al., 2017 [11].**

Fragestellung

summarize the efficacy, safety, and influence on quality of life of dupilumab for the treatment of moderate-to-severe atopic dermatitis in adults

Methodik

Population:

- adults with moderate to-severe atopic dermatitis, which meant a score of 3 (moderate) or 4 (severe) according to the Investigator's Global Assessment (IGA, scores range from 0 to 4, with higher scores indicating more severe disease); chronic atopic dermatitis for at least 3 years before recruitment; inadequate response to topical treatment

Intervention:

- dupilumab

Komparator:

- placebo

Endpunkt:

- IGA response (IGA score of 0 or 1 and an improvement of 2 points or more from baseline score),
- EASI,

- NRS score,
- BSA
- incidence of adverse events, severe adverse events, discontinuation due to adverse events
- Dermatology Life Quality Index (DLQI
- Patient-Oriented Eczema Measure (POEM)
- Hospital Anxiety and Depression Scale (HADS)

Recherche/Suchzeitraum:

- comprehensive search in databases including Pubmed, Embase, and the Cochrane Library for eligible articles published between January 1st, 2000 and July 15th, 2017 (English publications only).

Qualitätsbewertung der Studien:

- The Cochrane Reviewer's Handbook 5.1 was used to assess the risks of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias in the RCTs included in meta-analysis [28]. Trial with high-risk components of less than 2 was considered to have a low risk of bias.

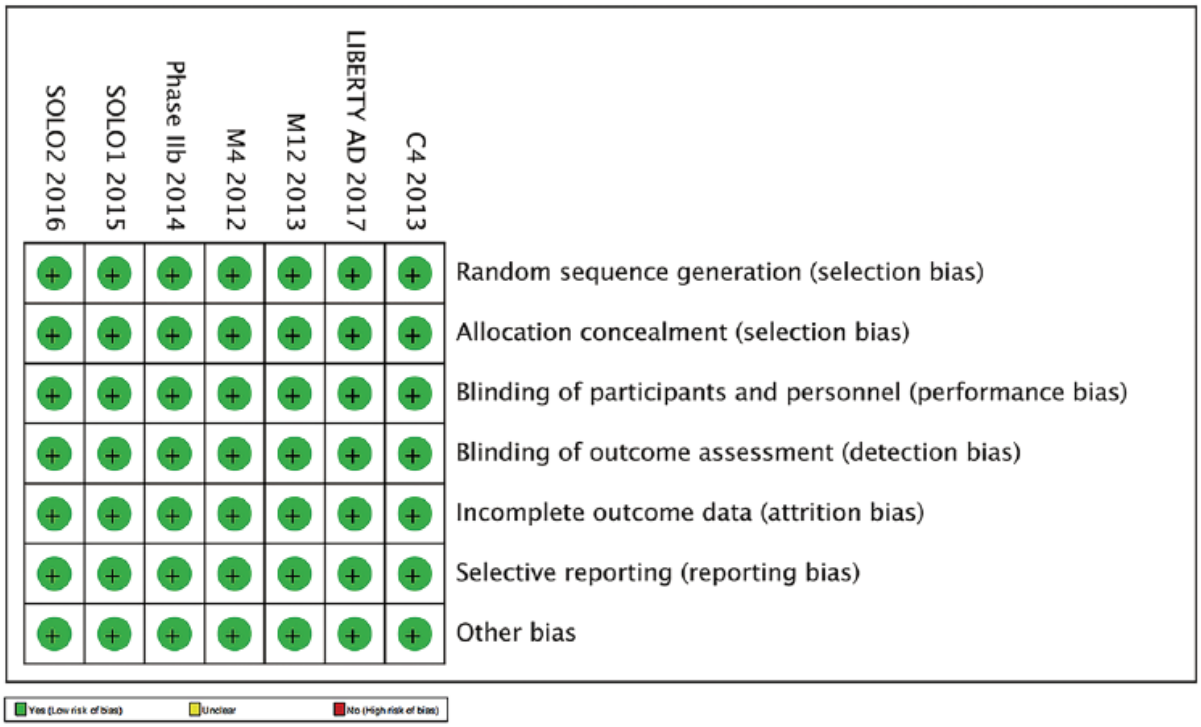
Ergebnisse

Anzahl eingeschlossener Studien:

- 7 RCTs

Qualität der Studien:

- All the 7 included RCTs showed a low risk of bias.



Studienergebnisse:

Table 2: Meta-analysis of the RCTs comparing efficacy and safety between the dupilumab and placebo groups

Variables	No.*	No. treat/con	IGA response RR (95% CI)	EASI WMD (95% CI)	NRS WMD (95% CI)	BSA WMD (95% CI)	AE RR (95% CI)	Discontinuation due to AE, RR (95%CI)
All doses	14	1789/916	3.95 (3.37–4.63)	–10.56 (–11.37 to –9.74)	–2.22 (–2.52 to –1.93)	–11.55 (–14.08 to –9.02)	1.00 (0.96–1.03)	0.70 (0.48–1.03)
300mg qw	4	844/399	3.77 (3.02–4.71)	–10.29 (–11.49 to –9.09)	–2.24 (–2.80 to –1.69)	–8.83 (–12.36 to –5.30)	0.99 (0.93–1.04)	0.52 (0.29–0.96)
300mg q2w	4	627/399	3.93 (3.08–5.01)	–10.65 (–12.02 to –9.28)	–2.12 (–2.49 to –1.75)	–8.98 (–12.77 to –5.18)	1.01 (0.95–1.08)	0.69 (0.32–1.48)
Other doses	6	318/118	5.45 (2.90–10.27)	–11.04 (–12.93 to –9.15)	–2.23 (–2.90 to –1.56)	–17.90 (–22.12 to –13.68)	0.99 (0.91–1.07)	1.04 (0.55–1.98)
Time point								
4 wk	2	72/26	1.78 (0.24–14.49)	–8.76 (–12.64 to –4.87)	–2.99 (–3.57 to –2.41)	–12.59 (–19.74 to –5.43)	0.93 (0.75–1.16)	0.14 (0.01–1.24)
12 wk	6	373/115	12.27 (5.76–26.15)	–12.94 (–14.75 to –11.14)	–2.38 (–2.72 to –2.05)	–21.86 (–25.61 to –18.11)	1.00 (0.93–1.08)	1.17 (0.64–2.15)
16 wk	4	919/460	3.95 (3.17–4.91)	–10.00 (–11.21 to –8.79)	–2.00 (–2.26 to –1.73)	–6.28 (–7.45 to –5.10)	0.99 (0.93–1.06)	2.20 (0.77–6.31)
52 wk	2	359/264	3.09 (2.35–4.07)	–10.09 (–11.77 to –8.40)	–2.08 (–2.52 to –1.63)	–10.72 (–12.34 to –9.10)	1.07 (1.01–1.13)	0.33 (0.17–0.62)

Treat, treatment; con, control; IGA, Investigator's Global Assessment; RR, relative risk; EASI, Eczema Area Severity Index; WMD, weighted mean difference; NRS, numerical rating scale; BSA, body surface area; AE, adverse event; qw, every week; q2w, every other week; wk, week.
*Number of comparisons.

- IGA score of 0 or 1 and an improvement of 2 points or more from the baseline score
  - 34.2% (611/1789) patients treated with dupilumab and 9.7% (89/916) patients receiving placebo (P < 0.001)
- Across all RCTs, 2034 of 2705 randomized patients experienced at least one adverse events, with approximately equal incidence in dupilumab-treated (75.0%, 1342/1789) and placebo-treated (75.5%, 692/916) patients.
- Severe adverse event
  - uncommon in both dupilumab treatment group (2.0%, 36/1789) and control group (4.0%, 37/916).
- most common adverse events in most trials were exacerbations of atopic dermatitis, infection, and injection site reactions.
- Patients treated with dupilumab had a slightly lower risk of severe adverse events (RR, 0.45; 95% CI, 0.23–0.93) as compared with patients treated with placebo.
- In patients receiving dupilumab, 2.5% (43/1746) discontinued because of adverse events, while 3.9% (72/1863) patients receiving placebo discontinued due to adverse events (RR, 0.70; 95% CI, 0.48–1.03, I^2=31.7%)
- dupilumab improved DLQI scores significantly compared with placebo (WMD, –5.16; 95% CI, –5.95 to –4.37, I^2=65.2%)
- dupilumab was significantly more effective in ameliorating anxiety or depression measured by Hospital Anxiety and Depression Scale (HADS) (WMD, –2.88; 95%CI, –3.37 to –2.38, I^2=85.8%) and improving sleep quality measured by POEM (WMD, –7.31; 95% CI, –7.89 to –6.73, I^2=13.4%) when compared with placebo or topical topical corticosteroids alone

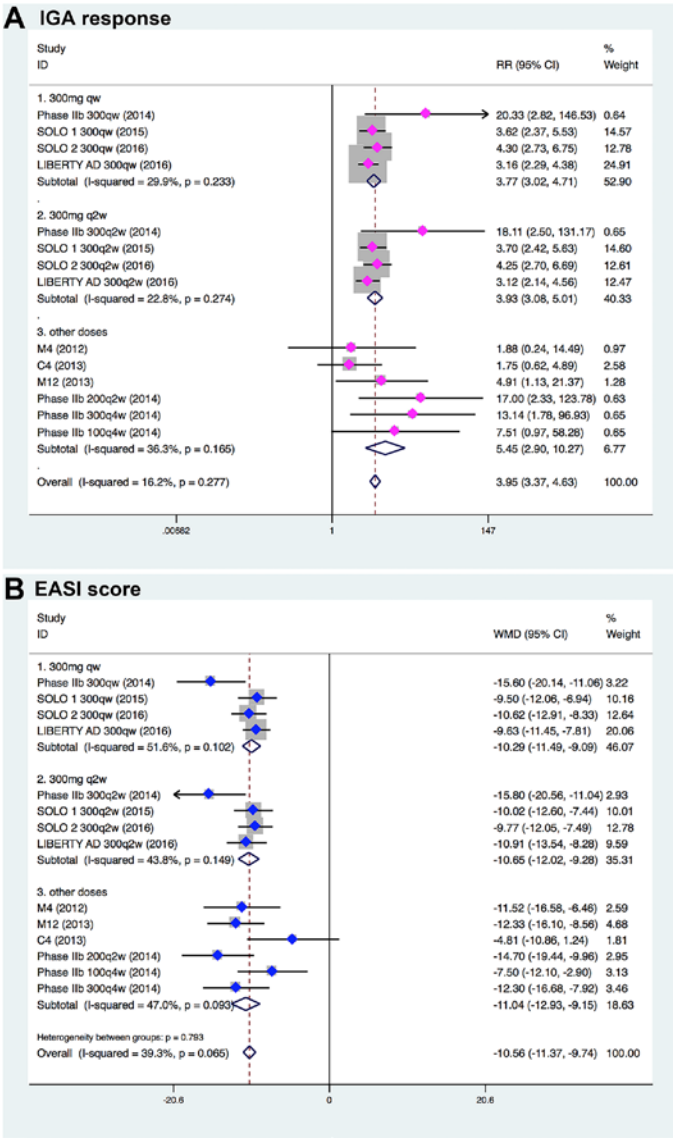


Figure 3: Meta-analysis of the RCTs comparing efficacy outcomes between the dupilumab- and placebo-treated groups. (A) Rates of IGA response. (B) EASI score. Horizontal lines represent 95% CI. Diamonds represent the meta-analysis summary effect estimate; blue dots represent the WMD, and magenta dots represent the RR.

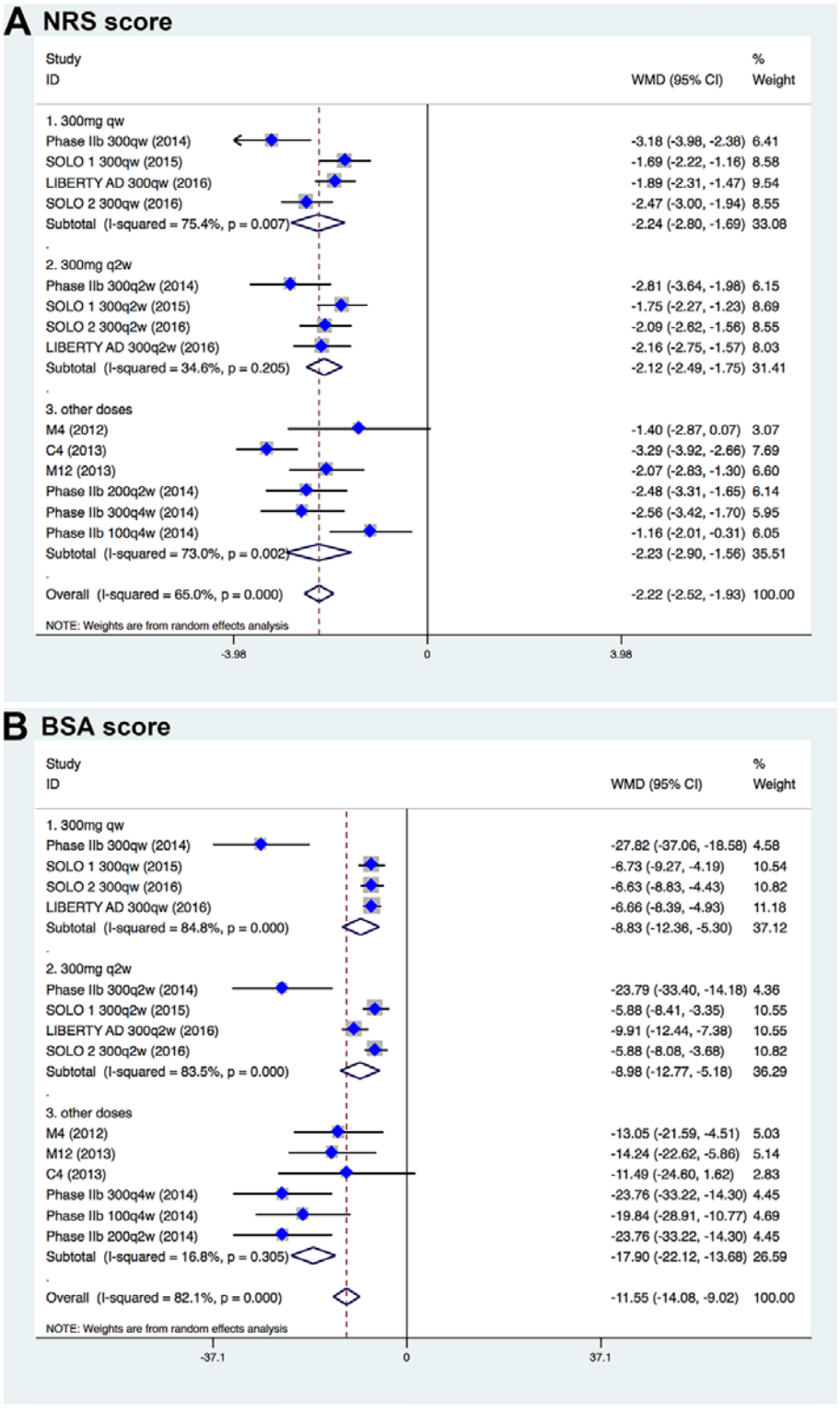


Figure 4: Forest plots for NRS score (A) and BSA score (B) between dupilumab- and placebo-treated patients with moderate-to-severe atopic dermatitis.

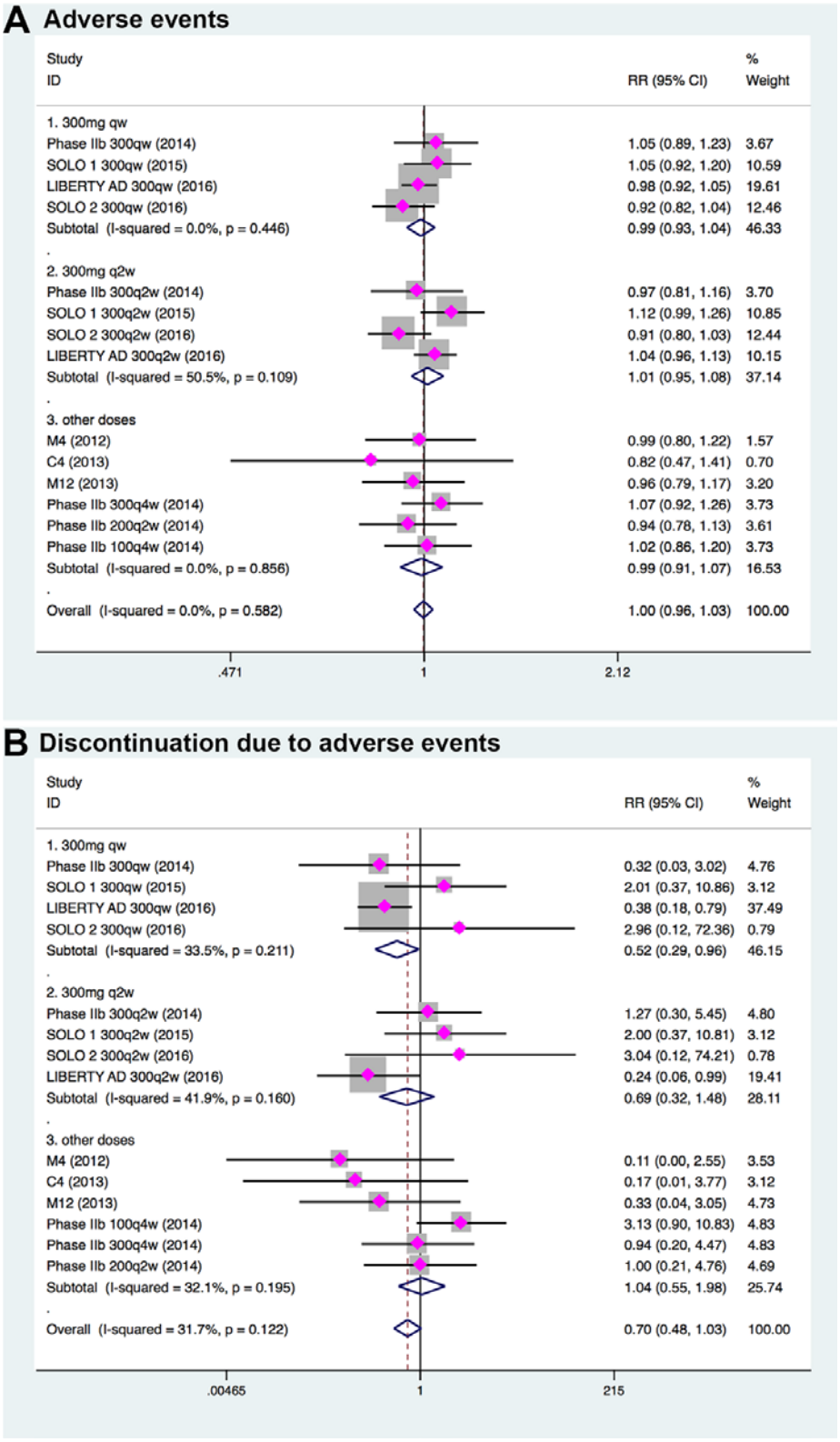


Figure 5: Comparison of incidence of at least 1 adverse event (A) and treatment discontinuation due to adverse events (B) in patients receiving dupilumab treatment and patients treated with placebo.

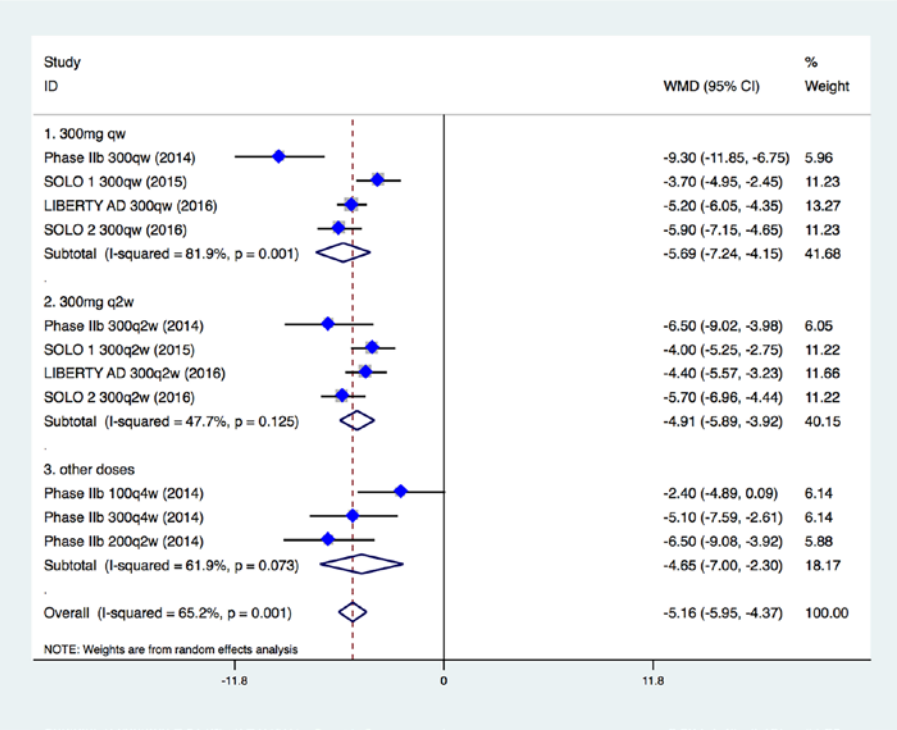


Figure 6: Influence of different dupilumab doses on patients' quality of life (DLQI).

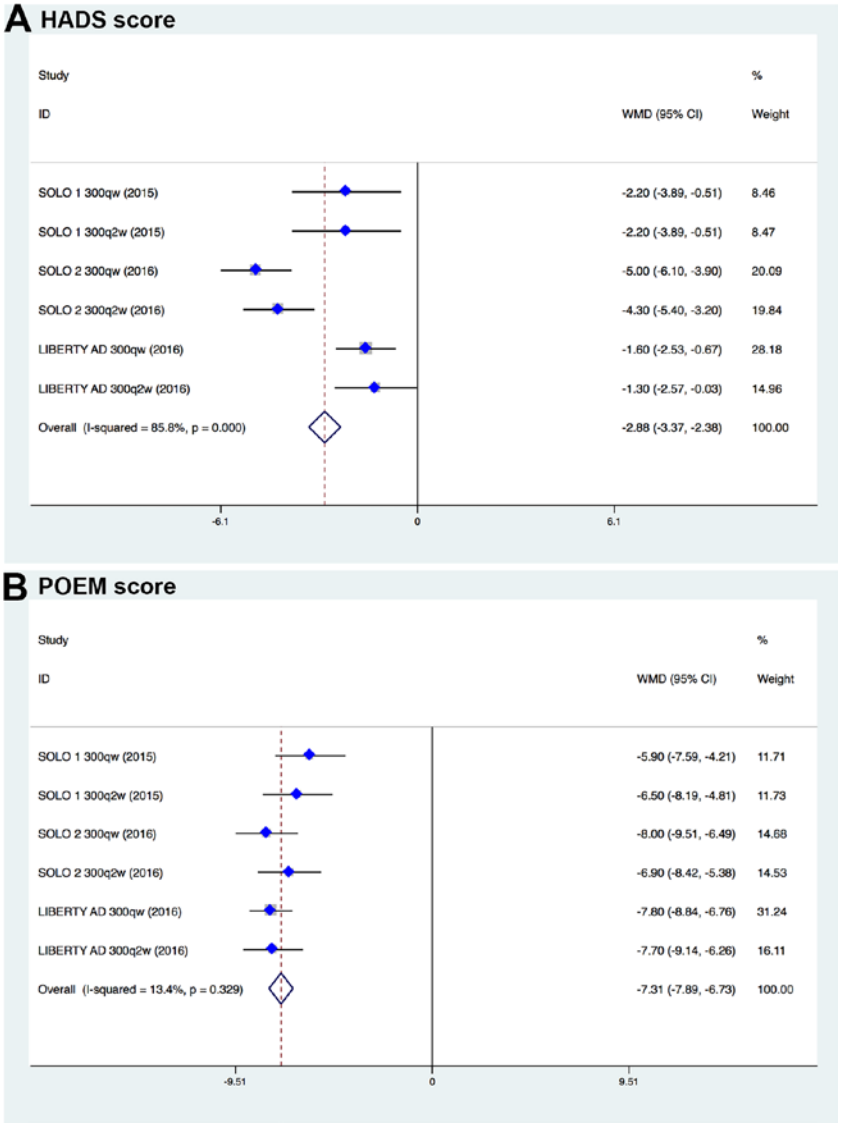


Figure 7: Meta-analysis of improved HADS score and POEM score in dupilumab- and placebo-treated patients with moderate-to-severe atopic dermatitis.

Anmerkung/Fazit der Autoren

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.

To conclude, dupilumab is effective and safe for the treatment of moderate-to-severe atopic dermatitis in adults. The benefit-to-risk profile of this meta-analysis supports the role of dupilumab as a primary targeted biologic therapy in patients with moderate-to-severe atopic dermatitis that are inadequately controlled with topical medications.

Nankervis H et al., 2017 [14].

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

- enthält auch Ergebnisse zu leichten bis mittelschwerer AD
- Abkürzung AE für atopic eczema und nicht wie sonst üblich für adverse event

- Keine seperaten Analysen zu Kindern vs. Erwachsenen. Studien z.T. gemischt (siehe Ergebnisteil)

Canadian Agency for Drugs and Technologies in Health (CADTH), 2017 [2].

Pimecrolimus for the Treatment of Adults with Atopic Dermatitis, Seborrheic Dermatitis, or Psoriasis: a Review of Clinical and Cost-Effectiveness

Fragestellung

1. What is the clinical effectiveness of pimecrolimus for the treatment of adults with atopic dermatitis?

Methodik

Population:

- Adults requiring treatment of atopic dermatitis

Intervention:

- Pimecrolimus

Komparator:

- Other active comparators, placebo

Endpunkt:

- Clinical effectiveness, clinical benefit and harm,

Recherche/Suchzeitraum:

- A limited literature search was conducted on key resources including PubMed, EMBASE via Ovid, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2012 and August 18, 2017.

Qualitätsbewertung der Studien:

- The included systematic reviews were critically appraised using AMSTAR, and randomized studies were critically appraised using Downs and Black checklist. Summary scores were not calculated for the included studies. Rather, a review of the strengths and limitations of each included study were described.

Ergebnisse

Anzahl eingeschlossener Studien:

- 2 Systematische Reviews, 1 RCT

Charakteristika der Population:

- Adult patients

Qualität der Studien:

SR

Strengths	Limitations
Nankervis, 2016.[11]	
• Pre-specified and published protocol. • The objective was stated. • The inclusion criteria were stated. • The exclusion criteria were stated. • Multiple databases were searched (Electronic databases including MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Skin Group Specialised Register, Latin American and Caribbean Health Sciences Literature (LILACS), Allied and Complementary Medicine Database (AMED) and Cumulative Index to Nursing and Allied Health Literature (CINAHL). • Flow chart of study selection was provided. • List of included studies was provided. • List of excluded studies was provided. • Article selection was done in duplicate. • Data extraction was done in duplicate. • Quality assessment was done using the Cochrane Collaboration risk-of-bias tool. • Characteristics of the individual studies were provided. • Authors declared no conflicts of interest.	• Lack of inclusion of grey literature. • Meta-analyses were not conducted. • Publication bias was not explored.
Frankel, 2012[10]	
• The objective was stated. • The exclusion criteria were stated. • List of included studies was provided. • Characteristics of the individual studies were provided.	• Lack of a pre-specified and published protocol. • Lack of inclusion of grey literature. • The inclusion criteria were not explicit. • Multiple databases were not searched • Flow chart of study selection was not provided. • List of excluded studies was not provided. • Article selection was not described. • Data extraction methods were not described.
	• Quality assessment of included studies was not conducted. • Meta-analyses were not conducted. • Publication bias was not explored. • Authors did not include a declaration of conflicts of interest.

RCT:

Bauer, 2012[12]	
• The objective was stated. • The inclusion and exclusion criteria were stated. • Patient characteristics, intervention and outcomes were reported. • Power analysis was conducted a priori. • Randomization sequence generated by permutated-block of 4. • Double- blind study. • No withdrawals or loss to follow-up. • Analysis conducted on ITT population. • Statistical significance was reported. • Of the six authors, two had no conflict of interest.	• Randomization procedure not well described. • Allocation concealment and blinding procedure was not well described. • One of the authors is an employee at the manufacturer and three were paid lecturers by the manufacturer. • The study was funded by the manufacturer.

Studienergebnisse:

- Pruritus Reduction
  - one systematic review indicated that pimecrolimus was statistically superior ($p < 0.003$) to vehicle (placebo) in reducing pruritus (on a scale of 0–3), where the severity score in pimecrolimus was reduced 0.9 while it increased 0.3 in vehicle.
  - The same systematic review also reported that there were marked differences in the severity of symptoms in one trial that compared pimecrolimus to betamethasone in favour of betamethoasone (no statistical comparison was conducted).

- Eczema Area Severity Index
  - triamcinolone acetate was statistically significantly better in reducing the disease severity at all time points reported during one year.
  - the proportion of patients rated as moderately clear or better was statistically significantly higher in the triamcinolone acetate group compared to pimecrolimus.
  - Tacrolimus was also reported in one systematic review to be statistically significantly better at 6 weeks than primecrolimus as measured through the EASI.
- Investigator Global Assessment
  - Based on the assessment of the overall disease severity using IGA, one included RCT assessing maintenance therapy using primecrolimus compared to vehicle failed to show any statistically significant differences.
- Severity and Life Quality Indices
  - Other outcomes including the hand eczema severity index, patient severity index, dermatology life quality index, and transepidermal water loss were reported in the included RCT, all of these outcomes show no statistically significant difference between pincrolimus and vehicle treated patients.

Main Study Findings	Author's Conclusion
Systematic Reviews	
Nankervis, 2016[11]	
• In one trial, pimecrolimus showed statistically significant reduction in the first signs and symptoms of a flare or recurrence compared to vehicle. also • Three trials showed significant difference over vehicle in the proportion of participants' assessment that their eczema is "completely or well controlled". • Four trials indicated a significant reduction in flares at six months • One trial reported triamcinolone and hydrocortisone to be significantly more effective than pimecrolimus in reducing disease severity as measured through EASI, but no difference in remission or time to first recurrence. • Another trial also showed betamethasone to be better in improving the EASI score over pimecrolimus • A third trial showed no difference in the measured outcome between pimecrolimus and emollient foam group. • Three trials indicate a statistically superior reduction in the severity measured by EASI in tacrolimus compared to pimecrolimus	• "There is strong evidence that using a calcineurin inhibitor confers clinically relevant benefits compared with a placebo" (pg. 39). • The evidence base for the efficacy of pimecrolimus compared with topical corticosteroids is still weak" pg. 41). • "Although pimecrolimus and tacrolimus have now been compared 'head to head' in several trials, it is important to remember that they are licensed for different ranges of severity of eczema. Pimecrolimus is not licensed for severe eczema as evidence has shown that it is not as potent as tacrolimus (0.1%)" (pg. 44).
Frankel, 2012.[10]	
• Two RCT showed greater improvements in topical corticosteroids treated patients than pimecrolimus treated patients • Two economic analysis reports found that the overall cost for tacrolimus is slightly lower then pimecrolimus ($US 501.27 vs $US546.14) • One economic analysis indicated that topical corticosteroids were more cost effective than first or second-line pimecrolimus	"The available clinical trials data do not suggest an efficacy advantage for topical calcineurin inhibitors over topical corticosteroids in adults with AD "atopic dermatitis" of the trunk and extremities, and there is not yet adequate evidence to support topical calcineurin inhibitors as first-line therapy for adult AD" (pg. 114).

Main Study Findings	Author's Conclusion
RCTs	
Bauer, 2012[12]	
• With regard to proportion of IGA patients who are relapse free, no difference was noted with vehicle (p = 0.406). • Similarly, HECSI, PSA, DLQI, and TEWL all showed no differences with vehicle.	"Pimecrolimus 1 % cream twice daily was not superior to vehicle in the sequential maintenance therapy of atopic hand dermatitis, but efficacy in moderate forms should be investigated in further studies" (pg. 426).

AD = atopic dermatitis; DLQI = dermatology life quality index; EASI = eczema area and sensitivity index; HECSI = hand eczema severity score; ICER = incremental cost-effectiveness ratio; IGA = investigator global assessment; NR = not reported; PSA = patient self-assessment; QALY = quality adjusted life year; RCT = randomized controlled trial; SD = standard deviation.

Anmerkung/Fazit der Autoren

Three systematic reviews and two RCTs comparing pimecrolimus to a variety of treatments in atopic dermatitis and seborrheic dermatitis suggested that pimecrolimus is superior to vehicle (placebo) in decreasing the severity of the symptoms of the disease. However, evidence from one RCT indicated that maintenance therapy with pimecrolimus was not statistically significantly different than vehicle. Evidence when comparing pimecrolimus to corticosteroid treatment can be conflicting: some studies suggest that pimecrolimus shows no statistically significant differences when compared to topical corticosteroids across some outcomes, but superior in other outcomes. Tacrolimus was reported to be superior to pimecrolimus in atopic dermatitis.

Kommentare zum Review

- Keine Angabe zum Schweregrad der Erkrankung
- Inhalte zu seborrheic dermatitis und Psoriasis nicht extrahiert

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Broeders JA et al., 2016 [1].

Systematic review and meta-analysis of randomized clinical trials (RCTs) comparing topical calcineurin inhibitors with topical corticosteroids for atopic dermatitis: A 15-year experience

Fragestellung

To bring the evidence base up to date and determine the therapy of choice for atopic dermatitis by comparing clinical outcome and costs of topical calcineurin inhibitors with corticosteroids.

Methodik

Population:

- Patients with atopic dermatitis (adults and children)

Intervention

- Calcineurin-Inhibitoren

Komparator:

- Kortikosteroide (topisch)

Endpunkt:

- Wirksamkeit: improvement of dermatitis and treatment success
- Sicherheit: adverse events, skin burning, pruritus, adverse events related to treatment, adverse events requiring treatment discontinuation, severe adverse events, atrophy, and skin infection.

Recherche/Suchzeitraum:

- Systematische Recherche bis 5. April 2015

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool, Jadad scoring system

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 RCTs

Charakteristika der Population:

- Most studies included patients with moderate to severe atopic dermatitis

Qualität der Studien:

- The trials had good methodological quality, with a mean Jadad score of 4 (range 2-5).

Table III. Risk of bias summary

	Sequence generation	Allocation concealment	Blinding observer	Blinding patient	Report loss follow-up	No other bias	Jadad score
Bieber et al[19]	No	No	Yes	Yes	Yes	Yes	4
Doss et al[20]	Yes	No	Yes	Yes	Yes	Yes	5
Doss et al[21]	Yes	No	Yes	Yes	Yes	Yes	5
Hofman et al[22]	No	No	Yes	Yes	Yes	Yes	4
Luger et al[23]	No	No	Yes	Yes	Yes	Yes	3
Luger et al[24]	No	No	Yes	Yes	Yes	Yes	3
Mandelin et al[25]	No	No	Yes	Yes	Yes	Yes	3
Reitamo et al[26]	Yes	No	Yes	Yes	Yes	Yes	4
Reitamo et al[27]	Yes	No	Yes	Yes	Yes	Yes	5
Reitamo et al[28]	No	No	Yes	Yes	Yes	Yes	3
Reitamo et al[29]	Yes	Yes	Yes	Yes	Yes	Yes	5
Sigurgeirsson et al[31]	Yes	No	No	No	Yes	Yes	3
Sikder et al[32]	No	No	No	No	Yes	Yes	2

Studienergebnisse:

- Improvement of dermatitis (basierend auf 11 Studien, 2070 vs. 1964 Patienten):
  - Es zeigte sich ein stat. signifikanter Vorteil für Calcineurin-Inhibitoren vs. Kortikosteroide: RR=1,18 (95%CI 1,04; 1,34)
- Treatment success (basierend auf 11 Studien, 2502 vs. 2439 Patienten):
  - Es zeigte sich ein stat. signifikanter Vorteil für Calcineurin-Inhibitoren vs. Kortikosteroide: RR=1,15 (95%CI 1,00; 1,31)
- Adverse events (basierend auf 12 Studien, 3487 vs. 3459 Patienten):
  - Es zeigte sich ein stat. signifikanter Nachteil für Calcineurin-Inhibitoren vs. Kortikosteroide: RR=1,28 (95%CI 1,05; 1.58)

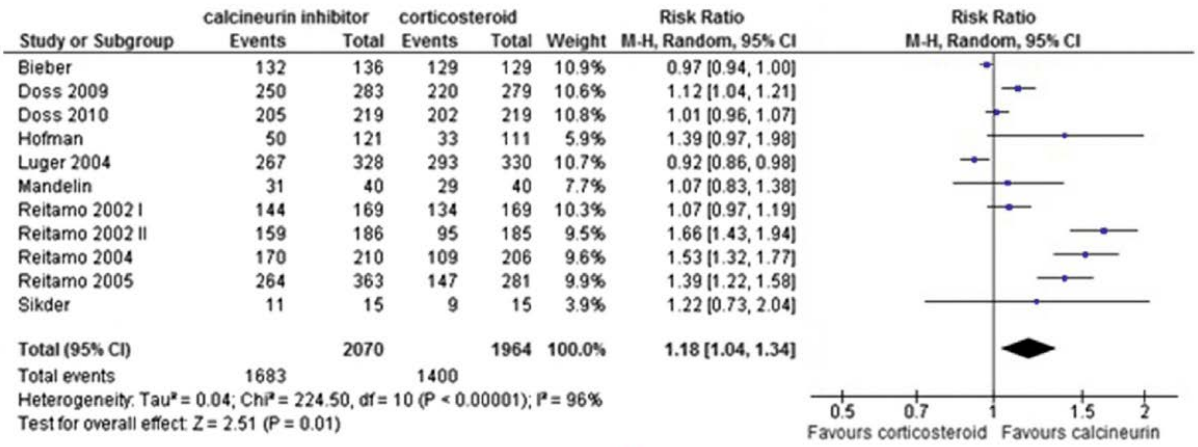

Fig 2. Improvement of dermatitis. Please see Table I for reference citations. *CI*, Confidence interval; *M-H*, Mantel-Haenszel.

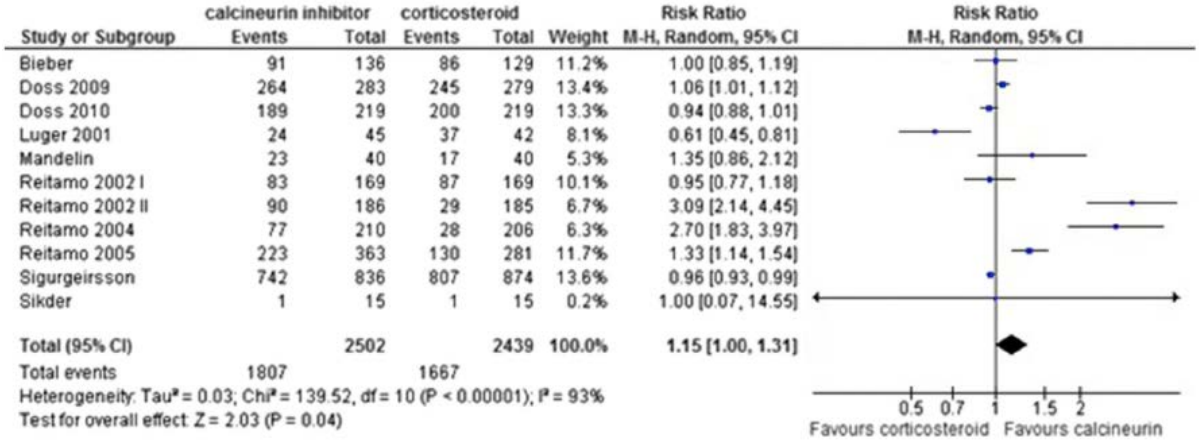

Fig 3. Treatment success. Please see Table I for reference citations. *CI*, Confidence interval; *M-H*, Mantel-Haenszel.

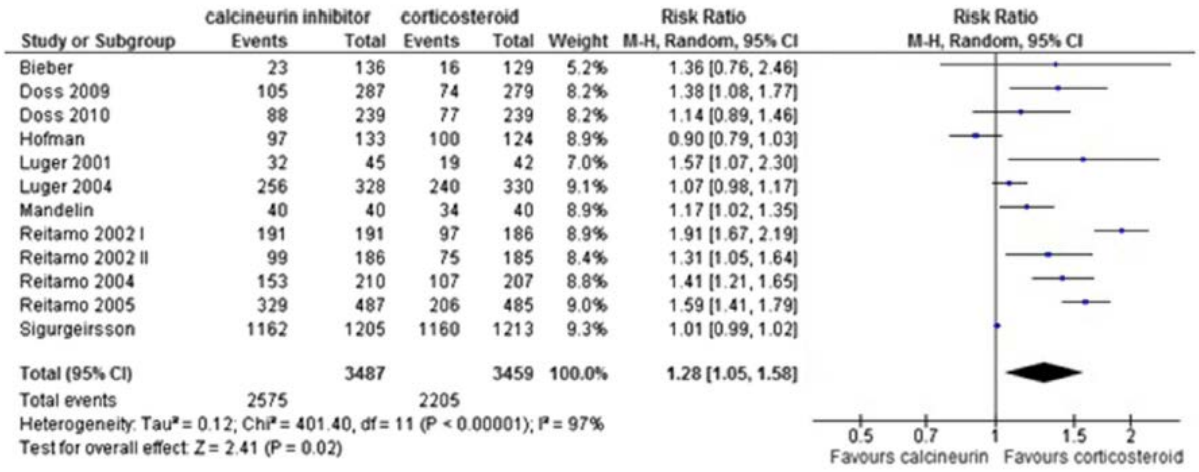

Fig 4. Adverse events. Please see Table I for reference citations. *CI*, Confidence interval; *M-H*, Mantel-Haenszel.

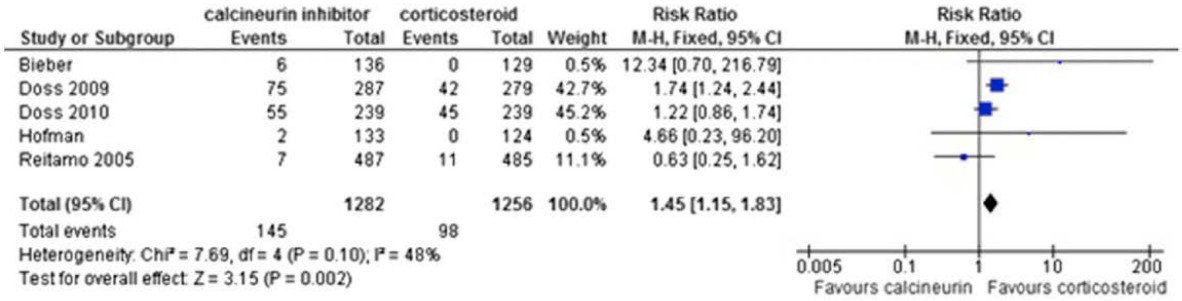

Fig 5. Adverse events related to treatment. Please see Table I for reference citations. *CI*, Confidence interval; *M-H*, Mantel-Haenszel.

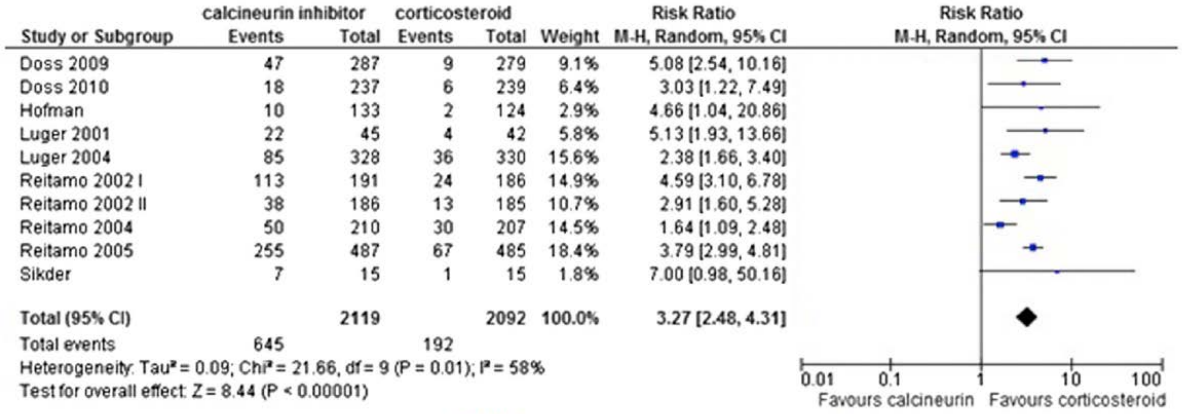

Fig 6. Skin burning. Please see Table I for reference citations. *CI*, Confidence interval; *M-H*, Mantel-Haenszel.

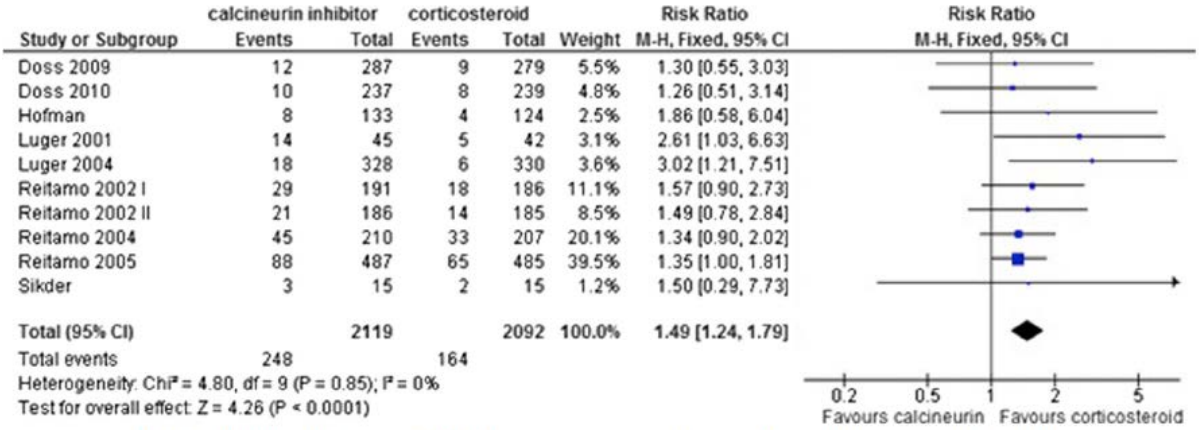

Fig 7. Pruritus. Please see Table I for reference citations. *CI*, Confidence interval; *M-H*, Mantel-Haenszel.

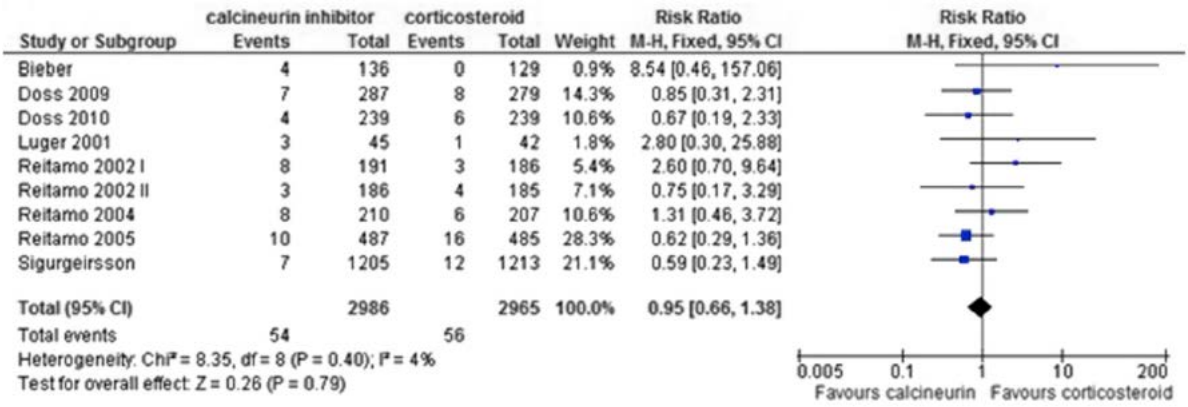

Fig 8. Adverse events requiring treatment discontinuation. Please see Table I for reference citations. *CI*, Confidence interval; *M-H*, Mantel-Haenszel.

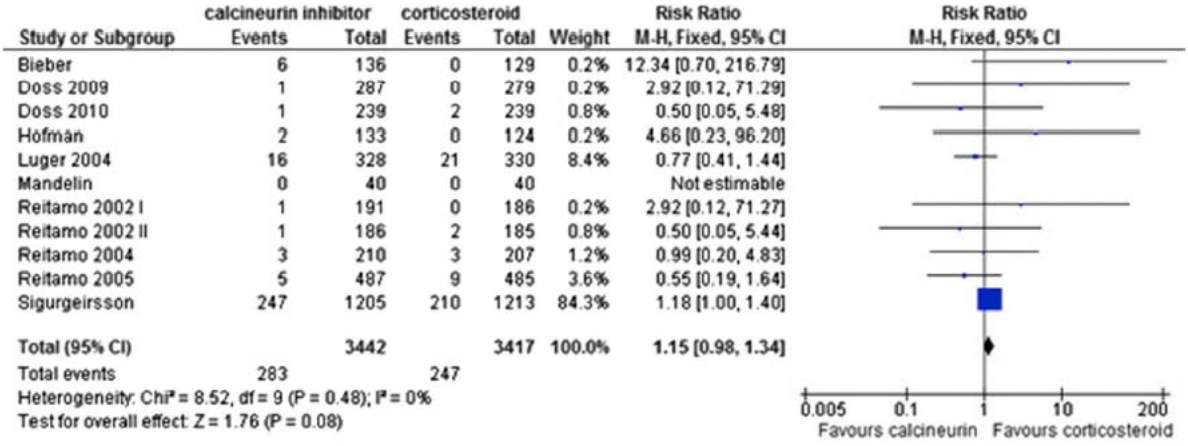

Fig 9. Severe adverse events. Please see Table I for reference citations. *CI*, Confidence interval; *M-H*, Mantel-Haenszel.

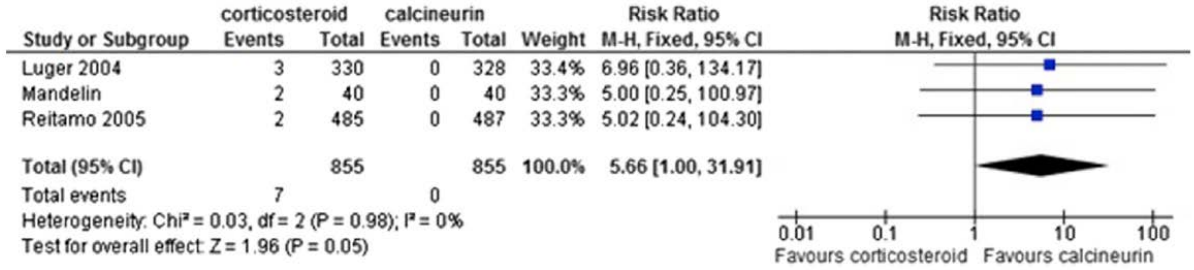

Fig 10. Atrophy. Please see Table I for reference citations. *CI*, Confidence interval; *M-H*, Mantel-Haenszel.

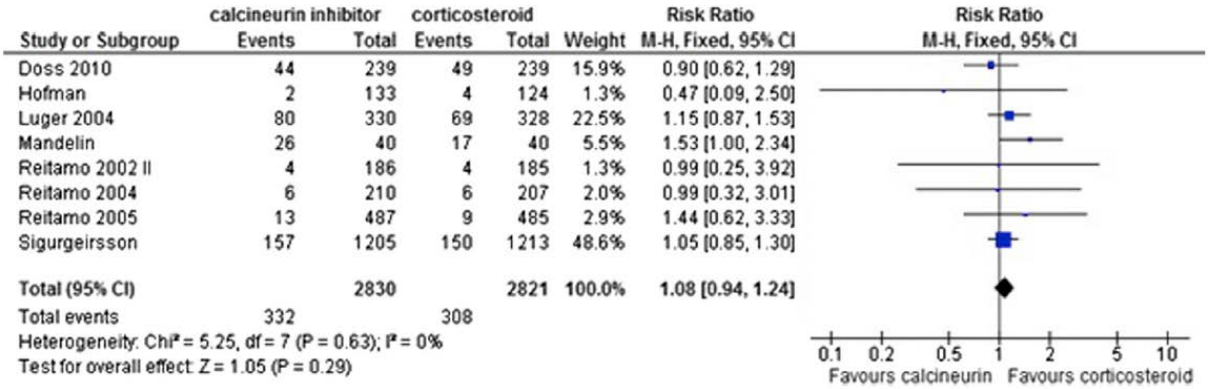

Fig 11. Skin infection. Please see Table I for reference citations. *CI*, Confidence interval; *M-H*, Mantel-Haenszel.

Anmerkung/Fazit der Autoren

[…] Calcineurin inhibitors and corticosteroids have similar efficacy. Calcineurin inhibitors are associated with higher costs and have more adverse events, such as skin burning and pruritus. These results provide level-1a support for the use of corticosteroids as the therapy of choice for atopic dermatitis.

[..] there was a statistical difference in treatment success and improvement of dermatitis in favor of calcineurin inhibitors, but this was not clinically significant compared with corticosteroids. It should however be noted that 8 of the available 12 RCTs compared calcineurin inhibitors with low-potency topical corticosteroids, which introduced a bias toward higher efficacy in the calcineurin inhibitor group.

Kommentare zum Review

- An 7 der 13 Studien nahmen Kinder teil (Alter: meist ab 2 Jahren, eine Studie mit Kindern ab 3 Monaten)
- Mit einer Ausnahme wurden alle Studien von pharmazeutischen Unternehmen gefördert.
- Art, Dauer und Dosierungen der Vorbehandlungen in den Studien mit 2. Linie unklar

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Perez-Ferriols A et al., 2015 [18].

Phototherapy in atopic dermatitis: a systematic review of the literature

Fragestellung

to evaluate, through a systematic review of the literature, the efficacy of the various modalities and regimens of phototherapy and photochemotherapy used in the treatment of patients with moderate to severe AD.

Methodik

Population:

- patients clinically diagnosed with atopic dermatitis, without any age limit

Intervention:

- all types of phototherapy as well as phototherapy in combination with psoralens (photochemotherapy)

Komparator:

- any

Endpunkt:

- all outcome measures, although measures of disease improvement or quality of life were preferred

Recherche/Suchzeitraum:

- We used the MEDLINE (via Ovid) and Embase databases and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify articles through the seventh week of 2013 (Embase) and through February 18, 2013 (MEDLINE and CENTRAL).

Qualitätsbewertung der Studien:

- Cochrane Collaboration's risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 21 RCTs

Charakteristika der Population:

- 2 studies included children and adolescents (32 patients)

Qualität der Studien:

- In general, the studies reviewed had a high risk of bias and relevant information was frequently missing.

Figure 2 Risk of bias.
+ indicates low risk of bias; ?, unknown risk of bias; –, high risk of bias; 1, generation of random allocation sequence (selection bias); 2, intervention allocation (selection bias); 3, masking of participants and personnel (performance bias); 4, masking of assessors (detection bias); 5, incomplete outcome data (attrition bias); 6, selective reporting (reporting bias); 7, other biases; BJD, *British Journal of Dermatology*.

Studienergebnisse:

- Classic Types of Phototherapy: UV-A, UV-B, and UV-AB
  - UV-B radiation was found to be more effective than visible light [24]
  - In an RCT[25] comparing UV-B to UV-AB, statistically significant differences in favor of UV-AB were observed for most variables.
  - In another RCT,[26] UV-A was found to be superior to UV-B in the total score and in the overall evaluation, but not in the pruritus score.
  - Two other studies[23] compared UVAB to UV-B and to UV-A, respectively, and found that UV-AB yielded the most favorable results.
- Narrowband UV-B
  - One RCT[30] found that NB UV-B was superior to UV-A and to visible light and that the results were maintained at 3 months.
- Studies Comparing Phototherapy to Other Treatments for Atopic Dermatitis
  - An RCT[14] compared 1% pimecrolimus cream to NB UV-B in patients between the ages of 5 and 17 years. Both interventions were beneficial, and concomitant use of both treatments was not found to be superior.
- Other Studies
  - One RCT[6] compared NB UV-B treatment and synchronous bathing in 10% Dead Sea salt solution----also known as synchronous balneophototherapy (sBPT)----to monotherapy with NB UV-B. sBPT yielded a greater reduction in SCORAD scores than NB UV-B as monotherapy and remained superior 1 month and 6 months after treatment.

Anmerkung/Fazit der Autoren

- There is evidence to support the use of NB UV-B and UV-A1 phototherapy in moderate to severe forms of AD. There is scant evidence to support the use of PUVA.
- It may be possible to find indications for modalities such as EL in the prurigo form of AD, FSL, and sBPT, but further studies are needed.
- Data on the use of phototherapy in childhood AD are limited, and therefore caution must be exercised when this technique is used in children.
- There is no evidence to support the use of phototherapy in pregnant women with AD.
- There are few data on the long-term effects of phototherapy in AD, including possible carcinogenic effects.
- We found no RCTs comparing the use of phototherapy to the use of oral corticosteroids.

Relevante Referenzen des SR:

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Lu et al., 2018 [13].

Complementary and alternative medicine for treatment of atopic eczema in children under 14 years old: a systematic review and meta-analysis of randomized controlled trials

Fragestellung

To evaluate the beneficial and harmful effects of CAM for children with AE under 14 years old.

Methodik

Population:

- children (< 14 years) diagnosed with AE

Intervention:

- CAM therapy alone

Komparator:

- combined with conventional medicine

Endpunkte:

- SCORAD index, symptoms and signs (siehe Ergebnisteil)

Recherche/Suchzeitraum:

- 12 Chinese and English databases from their inception to May 2018.

Qualitätsbewertung der Studien:

- Cochrane “Risk of bias” tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 24 randomized controlled trials involving 2233 children
- The trials tested 5 different types of CAM therapies, including probiotics, diet, biofilm, borage oil, and swimming

Qualität der Studien:

- unclear or high risk of bias in general

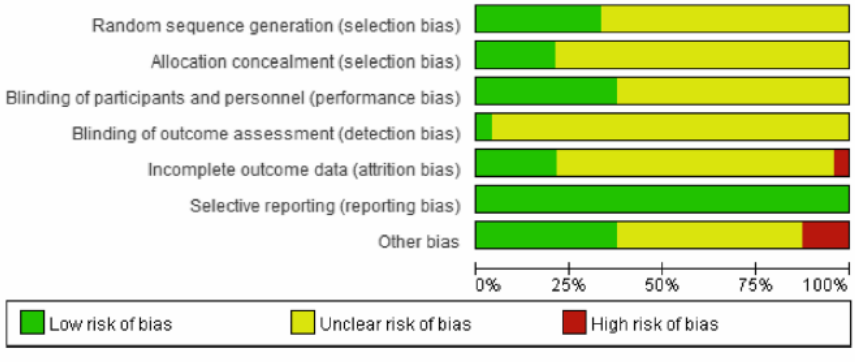

Fig. 2 Risk of bias graph

Studienergebnisse:

- Compared to placebo, probiotics showed improved effect for the SCORAD index (MD 9.01, 95% CI 7.12–10.90; n = 5).
- For symptoms and signs such as itching, skin lesions, CAM combined with usual care was more effective for symptom relief ≥95% (RR 1.47, 95% CI 1.30–1.68; n = 8), and for ≥50% symptoms improvement (RR 1.34, 1.25–1.45; n = 9) compared to usual care.
- There was no statistic significant difference between CAM and usual care on ≥95% improvement or ≥ 50% improvement of symptoms.
- However, swimming, diet and biofilm showed improvement of clinical symptoms compared with usual care.
- At follow-up of 8 weeks to 3 years, CAM alone or combined with usual care showed lower relapse rate (RR 0.38, 0.28–0.51, n = 2; RR 0.31, 0.24–0.40, n = 7; respectively) compared to usual care.
- Twelve out of 24 trials reported no occurrence of severe adverse events.

Anmerkung/Fazit der Autoren

Based on evidence from this systematic review we found some promising effect of CAM modalities on reducing symptoms and signs, and relapse of AE. However, it is still premature to recommend the therapy in clinical practice due to the limited number of trials and general low methodological quality of the included trials. Further rigorously double-blind, placebo-controlled trials are warranted to confirm efficacy of the CAM modalities for AE.

3.4 Leitlinien

American Academy of Dermatology, 2014 [5,19].

Guidelines of care for the management of atopic dermatitis:

section 2. Management and treatment of atopic dermatitis with topical therapies

section 3. Management and treatment with phototherapy and systemic agents

Fragestellung

This guideline addresses the management of **pediatric and adult** atopic dermatitis (AD; atopic eczema) of all severities.

Section 2: use of non-pharmacologic approaches (e.g, moisturizers, bathing practices, and wet wraps), and pharmacologic topical modalities, including corticosteroids, calcineurin inhibitors, antimicrobials, and antihistamines.

What are the efficacy, optimal dose, frequency of application, and adverse effects of the following agents used as monotherapy or in combination with other topical agents for the treatment of atopic dermatitis?

- Topical corticosteroids
- Topical calcineurin inhibitors
- Topical antimicrobials/antiseptics
- Topical antihistamines

Section 3: management of atopic dermatitis via phototherapy and systemic agents, including immunomodulators, antimicrobials, and antihistamines.

- Which immunomodulatory agents are efficacious and safe for the treatment of atopic dermatitis?
  - Cyclosporine A
  - Systemic steroids
  - Oral calcineurin inhibitors
- What is the efficacy of systemic antimicrobials and systemic antihistamines for the treatment of atopic dermatitis?
- What is the optimal dose, frequency of use, adverse effects, and efficacy of phototherapy and photochemotherapy for the treatment of atopic dermatitis?

Methodik

Grundlage der Leitlinie

- Update: Update und Erweiterung der vorherigen Version aus Mai 2004
- Systematische Evidenzsuche und -synthese, systematischer Begutachtungs-prozess
- work group of recognized AD experts:
  - identify clinical questions
  - developed recommendations based on evidence tables
  - CoI: completed, updated and reviewed for potential relevant conflicts of interest throughout guideline development. If a potential conflict was noted, the work group

member recused him or herself from discussion and drafting of recommendations pertinent to the topic area of the disclosed interest.

- opportunity for review and comment by the entire AAD membership and final review and approval by the AAD Board of Directors

Recherche/Suchzeitraum:

- Suchzeitraum: from November 2003 through November 2012 for clinical questions addressed in the previous version of this guideline published in 2004, and 1964 through 2012 for all newly identified clinical questions
- Durchsuchte Datenbanken (für das Update): PubMed, the Cochrane Library, and the Global Resources for Eczema Trials databases

LoE

Evidence was graded using a 3-point scale based on the quality of study methodology (e.g. randomized control trial, case-control, prospective / retrospective cohort, case series, etc.), and the overall focus of the study (i.e. diagnosis, treatment/prevention/screening, or prognosis) as follows:

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

GoR / Strength of Recommendation (SoR)

Clinical recommendations were developed based on the best available evidence tabled in the guideline. These are ranked as follows:

A. Recommendation based on consistent and good-quality patient-oriented evidence.

B. Recommendation based on inconsistent or limited-quality patient-oriented evidence.

C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence.

In those situations where documented evidence-based data is not available, we have utilized expert opinion to generate our clinical recommendations.

Sonstige methodische Hinweise

- Empfehlungen sind mit Literaturstellen verknüpft.
- Gültigkeit der Leitlinie: 5 Jahre
- keine getrennte Darstellung der Ergebnisse nach Therapielinien bzw für Kinder und Erwachsene

Empfehlungen: Management and treatment of atopic dermatitis with topical therapies

Übersicht der Empfehlungen zu topischen Kortikosteroiden und Calcineurin-Inhibitoren

Table III. Strength of recommendations for the use of topical therapies in the treatment of atopic dermatitis

Recommendation	Strength of recommendation	Level of evidence	References
Use of moisturizers	A	I	9-16,18-21,126
Bathing and bathing practices	C	III	23,24,26,28,30
Application of moisturizers after bathing	B	II	24,25
Limited use of nonsoap cleansers	C	III	27-30
Against use of bath additives, acidic spring water	C	III	31,32,127
Wet-wrap therapy	B	II	34-41
Use of TCS	A	I	42-46
Consideration of a variety of factors in TCS selection	C	III	49,128,129
Frequency of application	B	II	51-53
Proactive use of TCS for maintenance	B	II	54-56
Need for consideration of side effects with use	A	I	57,58,66
Need for monitoring for cutaneous side effects with potent TCS	B	III	57,58,66
Specific routine monitoring for systemic side effects with TCS not needed	C	III	57,58,62,66
Addressing fears with use	B	III	67-69
Use of TCI	A	I	70,76,81
Use as steroid-sparing agents	A	I	82,83
Off-label use of TCI in those age <2 y	A	I	76,89
Counseling on local reactions with TCI and the preceding use of TCS	B	II	81,85,96
Proactive use of TCI for maintenance	A	I	54,93-95
Concomitant TCS and TCI use	B	II	82,83,106-109
Informing patients regarding theoretical risk of cutaneous viral infections with use	C	III	82,98
Awareness of black-box warning of TCI	C	III	98-101
Routine monitoring of TCI blood levels not needed	A	I	102,103
Against routine use of topical antistaphylococcal treatments	A	I	110-112
Bleach baths and intranasal mupirocin for those with moderate to severe AD and clinical infection	B	II	113
Against use of topical antihistamines	B	II	42,115-117

AD, Atopic dermatitis; *TCI*, topical calcineurin inhibitors; *TCS*, topical corticosteroids.

Topical corticosteroids

- Topical corticosteroids are recommended for AD-affected individuals who have failed to respond to good skin care and regular use of emollients alone. (SoR A, LoE I)
- A variety of factors should be considered when choosing a particular topical corticosteroid for the treatment of AD, including patient age, areas of the body to which the medication will be applied, and other patient factors such as degree of xerosis, patient preference, and cost of medication. (SoR C, LoE III)
- Twice-daily application of corticosteroids is generally recommended for the treatment of AD; however, evidence suggests that once-daily application of some corticosteroids may be sufficient. (SoR B, LoE II)
- Proactive, intermittent use of topical corticosteroids as maintenance therapy (1-2 times/wk) on areas that commonly flare is recommended to help prevent relapses and is more effective than use of emollients alone. (SoR B, LoE II)
- The potential for both topical and systemic side effects, including possible hypothalamic-pituitary-adrenal axis suppression, should be considered, particularly in children with AD in whom corticosteroids are used. (SoR A, LoE I)

- Monitoring by physical examination for cutaneous side effects during long-term, potent steroid use is recommended. (SoR B, LoE III)
- No specific monitoring for systemic side effects is routinely recommended for patients with AD. (SoR C, LoE III)
- Patient fears of side effects associated with the use of topical corticosteroids for AD should be recognized and addressed to improve adherence and avoid undertreatment. (SoR B, LoE III)

Topical calcineurin inhibitors (TCI)

- TCI are recommended and effective for acute and chronic treatment, along with maintenance, in both adults and children with AD, and are particularly useful in selected clinical situations (siehe Box 1). (SoR A, LoE I)

Box 1. Clinical situations in which topical calcineurin inhibitors may be preferable to topical steroids

Recalcitrance to steroids
Sensitive areas (eg, face, anogenital, skin folds)
Steroid-induced atrophy
Long-term uninterrupted topical steroid use

- TCI are recommended for use on actively affected areas as a steroid-sparing agent for the treatment of AD. (SoR A, LoE I)
- For patients with AD < 2 years of age with mild to severe disease, off-label use of 0.03% tacrolimus or 1% pimecrolimus ointment can be recommended. (SoR A, LoE I)
- Pimecrolimus cream and tacrolimus ointment may cause skin burning and pruritus, especially when applied to acutely inflamed skin. Initial treatment of patients with AD using topical corticosteroids should be considered to minimize TCI application site reactions. Patients with AD should be counseled about the possibility of these reactions. (SoR B, LoE II)
- Proactive, intermittent use of TCI as maintenance therapy (2-3 times per week) on areas that commonly flare is recommended to help prevent relapses while reducing the need for topical corticosteroids, and is more effective than the use of emollients alone. (SoR A, LoE I)
- The concomitant use of a topical corticosteroid with a TCI may be recommended for the treatment of AD. (SoR B, LoE II)
- No consistent increases in the prevalence of cutaneous viral infections have been seen with continuous or intermittent use of TCI for up to 5 years; however, physicians should inform their patients of these theoretical cutaneous risks, given the lack of safety data for longer periods of time. (SoR C, LoE III)
- Clinicians should be aware of the black-box warning on the use of TCI for patients with AD and discuss as warranted. (SoR C, LoE III)
- Routine blood monitoring of tacrolimus and pimecrolimus levels in patients with AD who are applying these agents is not recommended at this time. (SoR A, LoE I)

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Empfehlungen: Management and treatment with phototherapy and systemic agents

Übersicht der Empfehlungen zu den ausgewählten Therapien

Recommendation	Strength of Recommendation	Level of Evidence	References
Phototherapy (all forms)	B	II	9-16, 19, 22-26
• Home phototherapy	C	III	27
Cyclosporine	B	I-II	34-43
Systemic steroids	B	II	4,35
Against use of systemic antihistamines	C	III	69-73
• Sedating	A	II	69-73
• Non-sedating			

Phototherapy

Phototherapy is a second line treatment, after failure of first-line treatment (emollients, topical steroids, and topical calcineurin inhibitors). Phototherapy can be used as maintenance therapy in patients with chronic disease.

Phototherapy treatment of all forms should be under the guidance and ongoing supervision of a physician knowledgeable in phototherapy techniques.

The light modality chosen should be guided by factors such as availability, cost, patient skin type, skin cancer history, patient use of photosensitizing medications, etc.

The dosing and scheduling of light should be based upon minimal erythema dose (MED) and/or Fitzpatrick skin type.

Home phototherapy under the direction of a physician may be considered for patients who are unable to receive phototherapy in an office setting.

Phototherapy as a treatment for children with AD unresponsive to multimodal topical measures is appropriate. The wavelength selection and treatment course should be individualized.

Hinweis: While it would be helpful to denote one or more forms of phototherapy as superior to all others, this is not possible given limited head-to-head trials and a lack of comprehensive comparative studies.

Systemic immunomodulatory agents

Systemic immunomodulatory agents are indicated for the subset of adult and pediatric patients in whom optimized topical regimens and/or phototherapy do not adequately control the signs and symptoms of disease.

Systemic immunomodulatory agents are indicated when the patient's skin disease has significant negative physical, emotional, or social impact.

All immunomodulatory agents should be adjusted to the minimal effective dose once response is attained and sustained. Adjunctive therapies should be continued in order to use the lowest dose and duration of systemic agent possible.

Insufficient data exists to firmly recommend optimal dosing, duration of therapy, and precise monitoring protocols for any systemic immunemodulating medication.

Treatment decisions should be based on each individual patient's AD status (current and historical), comorbidities, and preferences.

- **Cyclosporine**
  - Cyclosporine is effective and recommended as a treatment option for patients with AD refractory to conventional topical treatment **(SoR B, LoE I-II**)
  - Cyclosporine is an effective treatment for AD in the pediatric population, similar to adults. Both continuous long-term (up to twelve months) and intermittent short-term dosing schemes (three or six month courses) are efficacious.
- **Systemic steroids**
  - Systemic steroids should be avoided if possible for the treatment of AD. Their use should be exclusively reserved for acute, severe exacerbations and as a short-term bridge therapy to other systemic, steroid-sparing therapy. **(SoR B, LoE II**)
  - Systemic steroids are not recommended for children with AD unless they are required to manage comorbid conditions (such as asthma exacerbations), or are given as part of a short-term transition protocol to non-steroidal systemic immunomodulatory agents.
- **Systemic antihistamines**
  - There is insufficient evidence to recommend the general use of antihistamines as part of the treatment of atopic dermatitis.
  - Short-term, intermittent use of sedating antihistamines may be beneficial in the setting of sleep loss secondary to itch, but should not be substituted for management of atopic dermatitis with topical therapies.
  - Non-sedating antihistamines are not recommended as a routine treatment for atopic dermatitis in the absence of urticaria or other atopic conditions such as rhinoconjunctivitis.
  - The use of sedating antihistamines in school-age children may negatively affect school performance, warranting attention to dosage and scheduling.

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NICE, 2007 [16] & [15].

National Institute for Health and Care Excellence (NICE)

Atopic eczema in under 12s: diagnosis and management

Leitlinienorganisation/Fragestellung

This guideline covers diagnosing and managing atopic eczema in children under 12. It aims to improve care for children with atopic eczema by making detailed recommendations on treatment and specialist referral. The guideline also explains how healthcare professionals should assess the effect eczema has on quality of life, in addition to its physical severity.

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- This guideline was checked in July 2016. No new evidence was found that affects the recommendations in this guideline.

Treatment recommendations

Stepped approach to management

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

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

- Healthcare professionals should offer children with atopic eczema and their parents or carers information on how to recognise flares of atopic eczema (increased dryness, itching,

redness, swelling and general irritability). They should give clear instructions on how to manage flares according to the stepped-care plan, and prescribe treatments that allow children and their parents or carers to follow this plan.

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

Emollients

- Healthcare professionals should offer children with atopic eczema a choice of unperfumed emollients to use every day for moisturising, washing and bathing. This should be suited to the child's needs and preferences, and may include a combination of products or one product for all purposes. Leave-on emollients should be prescribed in large quantities (250–500 g weekly) and easily available to use at nursery, pre-school or school.
- Healthcare professionals should inform children with atopic eczema and their parents or carers that they should use emollients in larger amounts and more often than other treatments. Emollients should be used on the whole body both when the atopic eczema is clear and while using all other treatments.
- (…) Healthcare professionals should offer an alternative emollient if a particular emollient causes irritation or is not acceptable to a child with atopic eczema.

Topical corticosteroids

- Healthcare professionals should discuss the benefits and harms of treatment with topical corticosteroids with children with atopic eczema and their parents or carers, emphasising that the benefits outweigh possible harms when they are applied correctly.
- The potency of topical corticosteroids should be tailored to the severity of the child's atopic eczema, which may vary according to body site. They should be used as follows:
  - use mild potency for mild atopic eczema
  - use moderate potency for moderate atopic eczema
  - use potent for severe atopic eczema
  - use mild potency for the face and neck, except for short-term (3–5 days) use of moderate potency for severe flares
  - use moderate or potent preparations for short periods only (7–14 days) for flares in vulnerable sites such as axillae and groin
  - do not use very potent preparations in children without specialist dermatological advice.
- (…) It is recommended that where more than one alternative topical corticosteroid is considered clinically appropriate within a potency class, the drug with the lowest acquisition cost should be prescribed, taking into account pack size and frequency of application.
- (…) Potent topical corticosteroids should not be used in children aged under 12 months without specialist dermatological supervision.
- (…) A different topical corticosteroid of the same potency should be considered as an alternative to stepping up treatment if tachyphylaxis to a topical corticosteroid is suspected in children with atopic eczema.

Topical calcineurin inhibitors

- Topical tacrolimus and pimecrolimus are not recommended for the treatment of mild atopic eczema or as first-line treatments for atopic eczema of any severity.

- Topical tacrolimus is recommended, within its licensed indications, as an option for the second-line treatment of moderate to severe atopic eczema in adults and children aged 2 years and older that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.
- Pimecrolimus is recommended, within its licensed indications, as an option for the second-line treatment of moderate atopic eczema on the face and neck in children aged 2–16 years that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.

- (…) It is recommended that treatment with tacrolimus or pimecrolimus be initiated only by physicians (including general practitioners) with a special interest and experience in dermatology, and only after careful discussion with the patient about the potential risks and benefits of all appropriate second-line treatment options.
- For facial atopic eczema in children that requires long-term or frequent use of mild topical corticosteroids, consider stepping up treatment to topical calcineurin inhibitors.

Antihistamines

- Oral antihistamines should not be used routinely in the management of atopic eczema in children.

Phototherapy and systemic treatments

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

3.5 Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Deutsche Dermatologische Gesellschaft (DDG) , 2008 [4].

Leitlinie Neurodermitis (atopisches Ekzem; atopische Dermatitis)

Leitlinienorganisation/Fragestellung

Allgemeines Ziel der Leitlinie ist es, Dermatologen, Pädiatern, Allgemeinmedizinern sowie weiteren an der Behandlung der Neurodermitis beteiligten Ärzten in der Praxis und Klinik eine akzeptierte Entscheidungshilfe für die Auswahl sowie Durchführung einer geeigneten und suffizienten Therapie für Patienten mit Neurodermitis zur Verfügung zu stellen.

Die deutsche AWMF-Leitlinie „Neurodermitis“ wurde inhaltlich mit der entsprechenden Europäischen Leitlinie [3, 4] abgestimmt.

Methodik

Grundlage der Leitlinie

- Entwicklungsstufe: S2k → konsensbasiert
- Erstellungsdatum: 04/2008
- Letzte Überarbeitung: 03/2015
- Gültigkeitsdauer: verlängert bis 12/2018
- Nächste Überarbeitung geplant für: 05/2018
- Systematische Literatursuche und strukturierter Konsensprozess (Konsensuskonferenz unter Verwendung eines nominalen Gruppenprozesses oder Delphi-Verfahren)
- Update: Leitlinie ist eine Aktualisierung der 2008 publizierten AWMF-S2e-Leitlinie Neurodermitis.
- Offenlegung potentieller Interessenkonflikte

Recherche/Suchzeitraum:

- Suchzeitraum (Update): bis Januar 2014

LoE

- Keine Angabe

GoR

Tabelle 1 Empfehlungen wurden je nach Stärke wie folgt formuliert.

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

Sonstige methodische Hinweise

Diese deutsche Leitlinie ist der Entwicklungsstufe S2k zugeordnet und entspricht damit nicht den höchsten methodischen Anforderungen für Leitlinien. Sie wurde hier dennoch aufgrund ihrer Aktualität (letzte Aktualisierung 2015) und des geeigneten Versorgungskontextes ergänzend dargestellt.

Empfehlungen

Stufentherapie bei Neurodermitis

Es wird empfohlen, eine der klinischen Ausprägung angepasste Stufentherapie durchzuführen.

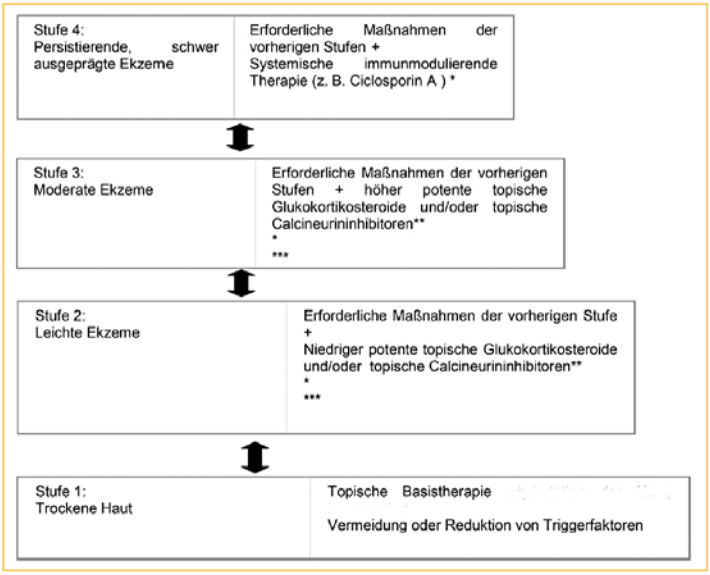

Abbildung 1 Stufentherapie der Neurodermitis. Die Abbildung enthält aus Gründen der Übersichtlichkeit nicht alle Verfahren, die in dieser Leitlinie diskutiert werden *Eine UV-Therapie ist häufig ab Stufe 2 unter Berücksichtigung der Altersbeschränkung (nicht im Kindesalter) indiziert. Cave: keine Kombination mit Ciclosporin A und topischen Calcineurininhibitoren. **First-Line-Therapie: in der Regel topische Glukokortikosteroide, bei Unverträglichkeit/Nichtwirksamkeit und an besonderen Lokalisationen (z. B. Gesicht, intertriginöse Hautareale, Genitalbereich, Kapillitium bei Säuglingen) topische Calcineurininhibitoren. ***Die zusätzliche Anwendung von antipruriginösen und antiseptischen Wirkstoffen kann erwogen werden.

Topische Therapie mit Glukokortikosteroiden

- Der Einsatz von topischen Glukokortikosteroiden unter Berücksichtigung des Nutzen-Nebenwirkungs-Profils zur antiinflammatorischen Therapie wird empfohlen.
- Die Behandlung mit topischen Glukokortikosteroiden wird in der Regel einmal täglich empfohlen, in Ausnahmefällen zweimal täglich. Außerdem wird eine Behandlung bis zur Abheilung der einzelnen Läsionen empfohlen.
- Eine dauerhafte tägliche Behandlung wird nicht empfohlen.
- Topische Glukokortikosteroide müssen hinsichtlich ihrer Wirkstärke gemäß dem lokalen Schweregrad, der Lokalisation und dem Patientenalter eingesetzt werden. Eine Steigerung der Wirkstärke bei unzureichender Wirkung wird empfohlen.
- Problembereiche für die Behandlung mit topischen Glukokortikosteroiden sind das Gesicht, der Hals, die intertriginösen Areale und das Skrotum, bei Säuglingen und Kleinkindern darüber hinaus aufgrund der erhöhten Resorption auch das Kapillitium. Die erhöhte Resorptionsgefahr unter okklusiven Verhältnissen (z. B. Windelbereich) sollte bedacht werden.
- Es wird empfohlen, topische Glukokortikosteroide in diesen Arealen nicht länger als auf wenige Tage befristet einzusetzen.

- Die individuelle Abklärung bei fehlendem Ansprechen der Neurodermitis auf topische Glukokortikosteroide wird empfohlen (verminderte Adhärenz, z. B. bei „Cortisonangst“, ungeeignetes Vehikel, Allergie gegen Glukokortikosteroide, fortbestehende Triggerung der Neurodermitis durch Schubfaktoren).
- Eine zeitlich begrenzte Intervalltherapie mit geeigneten topischen Glukokortikosteroiden (z. B. Fluticasonpropionat, Methylprednisolonaceponat) über die Phase der Abheilung hinaus wird empfohlen.
- Im Anschluss an die Akuttherapie kann eine proaktive mehrmonatige (in der Regel zunächst dreimonatige) intermittierende Nachbehandlung ein- bis zweimal pro Woche an zuvor erkrankten Arealen empfohlen werden.
- Insbesondere Säuglinge und Kleinkinder sind anfälliger in Bezug auf unerwünschte Wirkungen. Eine längere Anwendung potenterer Glukokortikosteroide (Klasse III) wird bei Säuglingen und Kleinkindern in der Regel nicht empfohlen. Die längerfristige Anwendung von Glukokortikosteroiden Klasse IV (Ausnahme: Hände, Füße) wird in allen Altersstufen nicht empfohlen.

Topische Calcineurinantagonisten

- Topische Calcineurininhibitoren werden vor allem dann empfohlen, wenn topische Glukokortikosteroide nicht einsetzbar sind oder über die Behandlungsdauer zu lokalen, irreversiblen unerwünschten Wirkungen führen können.
- Aufgrund des Profils unerwünschter Arzneimittelwirkungen von Glukokortikosteroiden können Calcineurininhi¬bitoren in „Problemarealen“ (z. B. Gesicht, intertriginöse Hautareale, Genitalbereich, Kapillitium bei Säuglingen) als First-Line-Therapie empfohlen werden.
- Die Beachtung der Altersbeschränkungen (Einsatz erst ab dem 3. Lebensjahr, Einsatz von 0,1 % Tacrolimus erst ab dem 17. Lebensjahr) wird empfohlen. Allerdings kann der Einsatz bei Säuglingen und Kleinkindern, insbesondere mit schweren, chronischen Gesichts-/Wangenekzemen, im Einzelfall empfohlen werden. In dieser Situation wird stets eine ausführliche Aufklärung der Eltern hinsichtlich der Anwendung außerhalb der Zulassung und des Nutzen-Nebenwirkungs-Profils empfohlen.
- Eine zeitlich begrenzte Intervalltherapie mit topischen Calcineurininhibitoren über die Phase der Abheilung hinaus wird empfohlen.
- Im Anschluss an die Akuttherapie kann eine proaktive mehrmonatige (in der Regel zunächst dreimonatige) intermittierende Nachbehandlung zweimal wöchentlich an zuvor erkrankten Arealen empfohlen werden.
- Ein wirksamer Sonnenschutz wird empfohlen.
- Beim Auftreten kutaner viraler Infektionen im Behandlungsareal wird hier eine Therapiepause empfohlen.
- Die Kombination von topischen Calcineurininhibitoren mit Phototherapie wird nicht empfohlen.

Antihistaminika

- Es gibt keine Evidenz für den Nutzen von H1-Antihistaminika zur Behandlung des Pruritus bei Neurodermitis. In Einzelfällen bei schweren, akuten Schüben können H1-Antihistaminika in Kombination mit anderen Therapiemaßnahmen eingesetzt werden.

- Ein Einsatz von topischen H1-Rezeptorantagonisten wird nicht empfohlen.
- H2-Antihistaminika werden nicht zur Therapie der Neurodermitis empfohlen.

Orale Glukokortikosteroide

- Die Kurzzeittherapie mit oralen Glukokortikosteroiden kann zur Unterbrechung des akuten Schubes vor allem bei der Therapie von erwachsenen Patienten mit schweren Formen einer Neurodermitis erwogen werden.
- Wegen der unerwünschten Arzneimittelwirkungen wird eine längerfristige Therapie der Neurodermitis mit systemischen Glukokortikosteroiden nicht empfohlen.

Ciclosporin

- Der Einsatz von Ciclosporin A kann zur Therapie der chronischen, schweren Neurodermitis im Erwachsenenalter empfohlen werden.
- Es wird eine Induktionstherapie bei Neurodermitis empfohlen, wonach so lange mit einer wirksamen Dosis zwischen 2,5–5 mg/kg KG/Tag behandelt wird, bis eine weitgehende Besserung der Dermatose erreicht worden ist. Anschließend wird empfohlen, die Dosis schrittweise zu reduzieren. Nach Ansprechen kann eine Dosisreduktion um 0,5–1,0 mg/kg KG/Tag auf die individuelle Erhaltungsdosis in zweiwöchigen Abständen empfohlen werden. Vor Behandlungsbeginn müssen eingehende Untersu¬chungen hinsichtlich des allgemeinen körperlichen und insbesondere des nephrologischen Status durchgeführt werden.
- Bei gutem Ansprechen wird eine Therapieunterbrechung nach 4–6 Monaten empfohlen.
- Eine Therapie bei schwer verlaufender Neurodermitis kann (bei guter Verträglichkeit) über einen längeren Zeitraum erwogen werden.
- Bei der Behandlung einer Neurodermitis mit Ciclosporin wird die Bestimmung der Ciclosporin-Tal-Blutspiegel nicht empfohlen.
- Ciclosporin kann auch zur Behandlung von Kindern und Jugendlichen, die einen therapieresistenten, sehr schweren Verlauf der Neurodermitis zeigen, als mögliche Off-Label-Therapieoption erwogen werden.
- Während der Behandlung mit Ciclosporin werden aufgrund des möglichen Ausbleibens eines Impferfolges, bzw. aufgrund möglicher Komplikationen, Schutzimpfungen mit Lebendimpfstoffen, nicht empfohlen. Für die Durchführung von Impfungen muss daher eine Therapiepause von zwei Wochen vor und vier bis sechs Wochen nach der Impfung eingehalten werden.
- Aufgrund des erhöhten Karzinogeneserisikos darf eine Kombination einer Therapie mit Ciclosporin A mit einer Phototherapie nicht durchgeführt werden.
- Während der Einnahme von Ciclosporin wird ein optimaler UV-Lichtschutz empfohlen.

Biologika: Die gegenwärtige Studienlage erlaubt keine Bewertung der Biologicals bei Neurodermitis.

Phototherapie: Die Phototherapie (UVA-1, UVB-Schmalband, UVB-Breitband, Balneo-Phototherapie) kann adjuvant in akuten Krankheitsphasen bei Neurodermitis bei Patienten ≥ 18 Jahren empfohlen werden. Bei Patienten > 12 Jahren kann eine Phototherapie erwogen werden.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2018) am 13.11.2018

#	Suchfrage
1	[mh "dermatitis, atopic"]
2	(atopic and dermati*):ti,ab,kw
3	((atopic or infant*) and (eczema*)):ti,ab,kw
4	(neurodermati* or neurodermiti*):ti,ab,kw
5	{OR #1-#4}
6	#5 with Cochrane Library publication date from Nov 2013 to Nov 2018, in Cochrane Reviews

SR, HTAs in Medline (PubMed) am 13.11.2018

#	Suchfrage
1	dermatitis, atopic[mh]
2	(atopic[tiab]) AND (dermati*[tiab])
3	(atopic[tiab] OR infant*[tiab]) AND (eczema*[tiab])
4	(neurodermati*[tiab]) OR (neurodermiti*[tiab])
5	#1 OR #2 OR #3 OR #4
6	(#5) AND ((Meta-Analysis[ptyp] OR systematic[sb] 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]))))
7	((#6) AND ("2013/11/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 13.11.2018

#	Suchfrage
1	dermatitis, atopic[mh]
2	(atopic[tiab]) AND (dermati*[tiab])
3	(atopic[tiab] OR infant*[tiab]) AND (eczema*[tiab])
4	(neurodermati*[tiab]) OR (neurodermiti*[tiab])
5	#1 OR #2 OR #3 OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
7	(((#6) AND ("2013/11/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]))

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