

SYSTEMATIC REVIEW

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

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Abstract

Background Current systemic treatments for atopic dermatitis (AD) offer limited efficacy and are often restricted by safety concerns. Biologics may address the unmet need for improved AD therapeutics.

Objective The aim of this study was to evaluate the efficacy and safety of biologic agents in AD.

Methods A systematic review and meta-analysis of studies evaluating AD patients treated with biologics was performed. The primary outcome was the Eczema Area and Severity Index (EASI)-75 response, while secondary outcomes were SCORing Atopic Dermatitis (SCORAD)-75, EASI-50, SCORAD-50, Investigator Global Assessment 0/1 responses, change in responses from baseline, and adverse events.

Results We included 13 randomized controlled trials (RCTs) and 10 observational studies evaluating nine biologics. High-quality evidence was available for dupilumab, nemolizumab and ustekinumab. Pooling five studies, at weeks 12–16 dupilumab 300 mg every week to every 2 weeks achieved EASI-75 responses of 55%, superior to placebo [relative risk (RR) 3.3, 95% confidence interval (CI) 2.9–3.6]. Nemolizumab had similar EASI-75

responses as placebo, but significantly improved pruritus. In online reports, lebrikizumab demonstrated superior EASI-50 responses versus placebo (RR 1.3, 95% CI 1.04–1.7), while tralokinumab had superior SCORAD-50 responses versus placebo, with borderline significance (RR 1.7, 95% CI 0.97–3.1). In two RCTs each, omalizumab and ustekinumab were comparable with placebo, while antithymic stromal lymphopoietin receptor, infliximab, and rituximab lacked adequate evidence of efficacy. All medications had a comparable safety profile to placebo.

Limitations Lack of RCTs and the use of variable outcome measures limited conclusions.

Conclusion Dupilumab is currently the only biologic with robust evidence of efficacy in AD. Nemolizumab, lebrikizumab, and tralokinumab show promise but further data are needed. Longer follow-up and larger studies will establish their safety profile.

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Key Points

There is an unmet need for better treatments for atopic dermatitis (AD).

In this systematic review of biologic therapies, we found that dupilumab is well-established for treating AD, while nemolizumab, lebrikizumab, and tralokinumab show promise.

Biologics are emerging as efficacious treatments for AD, with T-helper 2-blocking drugs showing the most efficacy. Safety was favorable for all agents but long-term data are lacking.

1 Introduction

Atopic dermatitis (AD) is a common chronic pruritic inflammatory skin disorder [1, 2]. Although most patients have mild disease that can be controlled with topical agents, a subset of patients have severe disease requiring systemic therapy [3]. A commonly used systemic treatment is cyclosporine, a broad-range immunosuppressive agent that, although efficacious in improving the signs and symptom of AD, is limited to short-term use due to side effects associated with long-term use, particularly nephrotoxicity and malignancy. Other treatments are immunomodulatory agents such as methotrexate, mycophenolate mofetil and azathioprine, which, in small studies, have been shown to provide limited efficacy (approximately 40% improvement in clinical scores) and have potential significant side effects such as hepatotoxicity [4, 5]. Because of the limitations of the current treatment armamentarium, there remains an unmet need for safe and effective systemic therapeutics.

The pathogenesis of AD centers around barrier dysfunction and disturbed immunologic pathways, with dysregulated immune responses in several axes, including T-helper (Th) 2, Th17, Th22 and Th1 [6]. The significant progress made in delineating the aberrant immune pathways in AD has led to reports on the use of biologic therapies that target specific elements in disease pathogenesis, with the potential for an improved safety profile [7]. This new era in AD treatment led to the recent US FDA [8] approval of dupilumab for treating AD [9, 10], the first biologic approved for this indication.

In this systematic review and meta-analysis we aimed to update and expand on previous reviews [11–13] and assess the efficacy of all available biologic therapies for the treatment of AD via the use of validated AD severity scores.

2 Methods

2.1 Search Strategy

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14], and was registered with the PROSPERO international prospective register (CRD42017056878). We conducted our search, 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 were manually scanned for additional results. We included grey literature (e.g. conference abstracts, web pages) to avoid publication bias, and added a post hoc search of reviews submitted to the FDA for drug registration to verify no studies were lacking [15]. The search strategy is shown in the electronic supplementary material.

2.2 Study Selection and Data Extraction

We included English-language studies of all designs, studying patients of all ages with a physician diagnosis of AD and of at least 8 weeks' duration. Due to an expected low number of studies using validated diagnostic criteria, we allowed permissive criteria. Studies that did not report change in at least one outcome or evaluated drugs discontinued from the market (e.g. efalizumab) were excluded, as were case series with fewer than five patients due to the risk of publication bias. Two reviewers (IS and OR) independently screened titles and abstracts, followed by the full text of articles considered potentially eligible. The proportion of patients with an improvement from baseline of at least 75% on the Eczema Area and Severity Index (EASI)-75 was selected as our primary outcome because it was a key endpoint in many of the available RCTs [13, 16]. Secondary outcomes were 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. The first author (IS) extracted data into an electronic form, and the second author (OR) checked extracted data. These reviewers independently assessed risk of bias via the Cochrane Risk of Bias Tool [17] and the Newcastle Ottawa Quality Assessment Scale [18] for RCT and observational studies, respectively. Disagreement was resolved by discussion with a third reviewer (YAL). Publication bias was not assessed owing to the small number of studies per agent [19].

2.3 Data Analysis and Synthesis

We calculated the relative risks (RRs) and 95% confidence intervals (CIs) for dichotomous data, and RRs were pooled using statistical software (Comprehensive Meta-Analysis, version 3.0; Meta-Analysis@Meta-Analysis.com). Analyses were performed using a random effects model because we expected considerable clinical heterogeneity. Heterogeneity was assessed by visually examining the forest plot for non-overlapping CIs and via the Chi-square test, with $p < 0.1$ indicating statistical significance and $I^2 > 50\%$ indicating substantial heterogeneity.

To estimate the efficacy of case series outcomes, when RCTs using the same outcome measure were available, we pooled their placebo responses for comparison [20].

3 Results

Our search yielded 2135 citations, with 23 studies eligible for review after the exclusion process (Fig. 1). No study was excluded due to language restrictions. The eligible studies included 13 randomized controlled trials (RCTs) and 10 observational studies, with a total of 3773 patients [13, 16, 21–40, 43]. Baseline characteristics of the included studies are presented in Table 1, and efficacy outcomes and

adverse events are presented in Table 2. Dupilumab, omalizumab and ustekinumab were the most studied biologics, evaluated by five (RCTs), 10 (two RCTs, eight observational) and two (RCTs) studies, respectively. Six other agents were evaluated in one study each [nemolizumab, lebrikizumab, tralokinumab, antithymic stromal lymphopoietin receptor (TSLPR), infliximab and rituximab]. All patients were older than 18 years of age, except for omalizumab studies, which included children. Baseline disease severity was categorized based on EASI scores (mild, ≤ 7 ; moderate, 7.1–21; severe, 21.1–50; very severe, > 50) [41], SCORAD scores (mild, ≤ 25 ; moderate, 25.1–49.9; severe, ≥ 50), objective SCORAD scores (mild, ≤ 23.9 ; moderate, 24–37.9; severe, ≥ 38) [42], and baseline

Fig. 1 Systematic literature search according to the PRISMA guidelines. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses

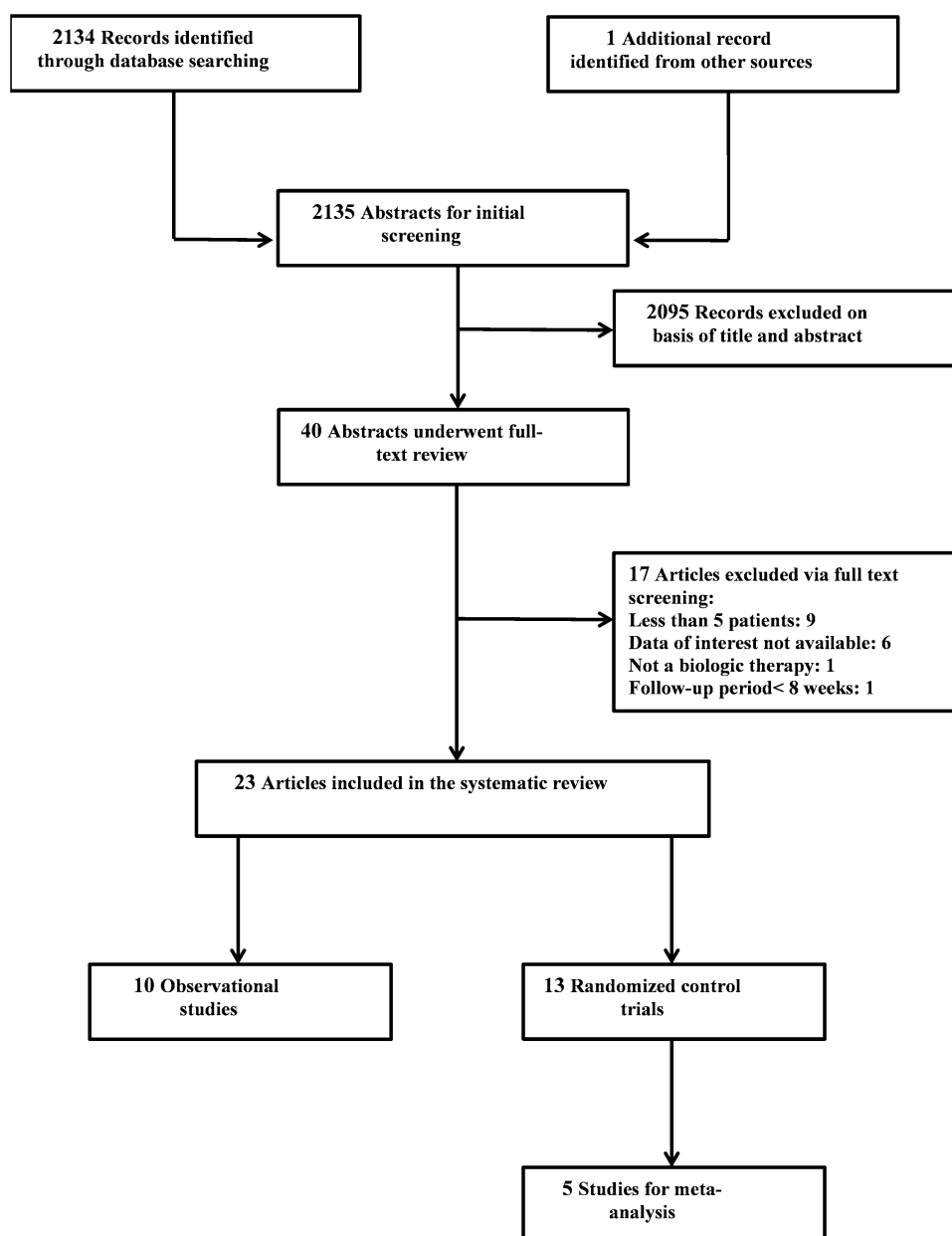


Table 1 Baseline characteristics and quality assessment of the included studies

Publication (country) [subgroup]	Design	Intervention (N, verum vs. controls)	Treatment duration (weeks)	Age (years), mean $\pm$ SD or range	Adults/ children	Female (%)	Baseline severity EASI	Baseline severity SCORAD [C/O] ^a	Baseline IGA $\geq$ moderate (%)	Concomitant treatment	Overall risk of bias across studies	Remarks
<i>Dupilumab</i>												
Simpson et al., 2016 [16] (North America, Europe, Asia)	RCT Phase III	SOLO 1 Dupilumab 300 mg every other week (224) vs. p (224)	16	Median (IQR) 38 (28–48) vs. 39 (27–51) (47%)	A	94 (42%) vs. 106 (47%)	Severe vs. severe	Severe vs. severe [C]	100 vs. 100%	Only topical emollients	Low	
[I]												
[III]												
[III]		SOLO 1 Dupilumab 300 mg every week (223) vs. p (224)	16	Median (IQR) 39 (27–51) vs. 39 (27–51) (47%)	A	81 (36%) vs. 106 (47%)	Severe vs. severe	Severe vs. severe [C]	100 vs. 100%	Only topical emollients		
[IV]		SOLO 2 Dupilumab 300 mg every other week (233) vs. p (236)	16	Median (IQR) 34 (25–46) vs. 35 (25–47) (44%)	A	96 (41%) vs. 104 (44%)	Severe vs. severe	Severe vs. severe [C]	100 vs. 100%	Only topical emollients		
[IV]		SOLO 2 Dupilumab 300 mg every week (239) vs. p (236)	16	Median (IQR) 35 (25–46) vs. 35 (25–47) (44%)	A	100 (42%) vs. 104 (44%)	Severe vs. severe	Severe vs. severe [C]	100 vs. 100%	Only topical emollients		
Thaçi et al., 2016 [22] (North America, Europe, Asia)	RCT Phase IIb	Dupilumab 100 mg every 4 weeks (65) vs. p (61)	16	37 (19–66) vs. 37 (18–69)	A	31 (48%) vs. 21 (34%)	Severe vs. severe	Severe vs. severe [C]	100 vs. 100%	Only topical emollients		
[I]												
[III]												
[III]		Dupilumab 200 mg every other week (61) vs. p (61)	16	36 (18–75) vs. 37 (18–69)	A	25 (41%) vs. 21 (34%)	Severe vs. severe	Severe vs. severe [C]	100 vs. 100%	Only topical emollients		
[IV]		Dupilumab 300 mg every other week (64) vs. p (61)	16	39 (21–68) vs. 37 (18–69)	A	23 (36%) vs. 21 (34%)	Severe vs. severe	Severe vs. severe [C]	100 vs. 100%	Only topical emollients		
[IV]		Dupilumab 300 mg every week (63) vs. p (61)	16	36 (19–66) vs. 37 (18–69)	A	20 (32%) vs. 21 (34%)	Severe vs. severe	Severe vs. severe [C]	100 vs. 100%	Only topical emollients		

Table 1 continued

Publication (country) [subgroup]	Design	Intervention (N, verum vs. controls)	Treatment duration (weeks)	Age (years), mean $\pm$ SD or range	Adults/ children	Female (%)	Baseline severity EASI	Baseline severity SCORAD [C/O] ^a	Baseline IGA $\geq$ moderate (%)	Concomitant treatment	Overall risk of bias across studies	Remarks
Beck et al., 2014 [21] (Europe)	RCT Phase I	Dupilumab 300 mg every week (55) vs. p (54)	12	34 $\pm$ 1 vs. 39 $\pm$ 2	A	24 (44%) vs. 27 (50%)	Severe vs. severe [C]	Severe vs. severe [C]	100 vs. 100%	Only topical emollients		
Blauvelt et al., 2016 [23] (USA)	RCT Phase II	Dupilumab 300 mg every week (97) vs. p (97)	16	NA	A	NA	NA	NA	100% vs. 100%	TCSs/calcineurin inhibitors or low-dose SCSs		Oral abstract from 2016 congress
Blauvelt et al., 2017 [13] (USA) [I]	RCT Phase III	Dupilumab 300 mg every other week (106) vs. p (315)	52	41 (28–49) vs. 34 (25–45)	A	44 (42%) vs. 122 (39%)	Severe vs. severe [C]	Severe vs. severe [C]	100 vs. 100%	TCSs/calcineurin inhibitors		
[II]		Dupilumab 300 mg every week (319) vs. p (315)	52	34 (26–45) vs. 34 (25–45)	A	128 (40%) vs. 122 (39%)	Severe vs. severe [C]	Severe vs. severe [C]	100 vs. 100%	TCSs/calcineurin inhibitors		
<i>Nemolizumab</i>												
Ruzicka et al., 2017 [39] (USA) [I]	RCT Phase II	Nemolizumab 0.1 mg/kg every 4 weeks (53) vs. p (53)	12	34 $\pm$ 10 vs. 37 $\pm$ 13	A	25 (47%) vs. 28 (53%)	Severe vs. severe	NA	100%	Emollients and rescue TCSs after week 4	Low	
[II]		Nemolizumab 0.5 mg/kg every 4 weeks (54) vs. p (53)	12	34 $\pm$ 12 vs. 37 $\pm$ 13	A	32 (59%) vs. 28 (53%)	Severe vs. severe	NA	100%	Emollients and rescue TCSs after week 4		
[III]		Nemolizumab 2 mg/kg every 4 weeks (52) vs. p (53)	12	34 $\pm$ 12 vs. 37 $\pm$ 13	A	21 (40%) vs. 28 (53%)	Severe vs. severe	NA	100%	Emollients and rescue TCSs after week 4		
[IV]		Nemolizumab 2 mg/kg every 8 weeks (52) vs. p (53)	12	36 $\pm$ 14 vs. 37 $\pm$ 13	A	23 (44%) vs. 28 (53%)	Severe vs. severe	NA	100%	Emollients and rescue TCSs after week 4		
<i>Lebrikizumab</i>												
Clinical trial 2016 [NCT02340234] [27]	RCT Phase II	Lebrikizumab 125 mg once (52) vs. p (53)	12	NA	A	NA	NA	NA	NA	TCSs	Unclear	Short online report of trial results
		Lebrikizumab 250 mg once (53) vs. p (53)	12	NA	A	NA	NA	NA	NA	TCSs		

Table 1 continued

Publication (country) [subgroup]	Design	Intervention (N, verum vs. controls)	Treatment duration (weeks)	Age (years), mean $\pm$ SD or range	Adults/ children	Female (%)	Baseline severity EASI	Baseline severity SCORAD [C/O] ^a	Baseline IGA $\geq$ moderate (%)	Concomitant treatment	Overall risk of bias across studies	Remarks
Tralokinumab												
Clinical trial 2017 [NCT02347176] [43]	RCT Phase II	Lebrikizumab 125 mg at weeks 0, 4, 8, 12 (51) vs. p (53)	12	NA	A	NA	NA	NA	NA	TCSs		
		Tralokinumab 45 mg every other week (50) vs. p (51)	12	39 $\pm$ 15 vs. 39 $\pm$ 15	A	21 (42%) vs. 29 (57%)	NA	NA	100 vs. 100%	TCSs	Unclear	Trial results reported in ClinicalTrials.gov
		Tralokinumab 150 mg every other week (51) vs. p (51)	12	37 $\pm$ 14 vs. 39 $\pm$ 15	A	25 (49%) vs. 29 (57%)	NA	NA	100 vs. 100%	TCSs		
		Tralokinumab 300 mg every other week (52) vs. p (51)	12	36 $\pm$ 15 vs. 39 $\pm$ 15	A	19 (37%) vs. 29 (57%)	NA	NA	100 vs. 100%	TCSs		
Omalizumab												
Iyengar et al. [33] (USA)	RCT	Omalizumab 150–375 mg every 2–4 weeks (4) vs. p (4)	24	7 vs. 16	C	NA	NA	Severe vs. severe [C]	NA	None	High	Baseline IgE, mean $\pm$ SD: 1065 $\pm$ 587 vs. 1070 $\pm$ 746 IU/ml
Heil et al. [35] (Austria)	RCT	Omalizumab 0.016 mg/kg/IgE every 4 weeks (13) vs. p (7)	16	Median 30 (18–47) vs. 26 (18–43)	A	8 (62%) vs. 6 (86%)	NA	NA	85 vs. 57%	TCSs		Baseline IgE, mean $\pm$ SD: 373 $\pm$ 205 vs. 118 $\pm$ 48 IU/ml
Hotze et al. [37] (Germany)	Obs	Omalizumab 150–300 mg every 2 weeks (20)	28	46 $\pm$ 16	A	11 (55%)	NA	Moderate [C]	NA	TCSs		Baseline IgE, mean $\pm$ SD: 936 $\pm$ 5 IU/ml
Kim et al. [30] (Korea)	Obs	Omalizumab 300 mg every 2 weeks (10)	16	26 $\pm$ 6	A	4 (40%)	NA	Severe [O]	NA	Only topical emollients		Baseline IgE mainly (<i>n</i> = 6) equal or above 5000 IU/ml
Ramírez del Pozo et al. [38] (Mexico)	Obs	Omalizumab (11)	43	12–52	A + C	10 (91%)	NA	Severe [C]	NA	NA		
Sheinkopf et al. [32] (USA)	Obs	Omalizumab 150–300 mg every 2–4 weeks (21)	39	43 (14–64)	A + C	12 (57%)	NA	NA	57%	TCSs	High	Baseline IgE, mean $\pm$ SD: 1520 $\pm$ 2416 IU/ml
Belloni et al. [34] (Germany)	Obs	Omalizumab 150 mg every 2 weeks (11)	20	NA	A	NA	NA	NA	NA	TCSs		Baseline IgE >1000 IU/ml

Table 1 continued

Publication (country) [subgroup]	Design	Intervention (N, verum vs. controls)	Treatment duration (weeks)	Age (years), mean $\pm$ SD or range	Adults/ children	Female (%)	Baseline severity EASI	Baseline severity SCORAD [C/O] ^a	Baseline IGA $\geq$ moderate (%)	Concomitant treatment	Overall risk of bias across studies	Remarks
Vigo et al. [31] (USA)	Obs	Omaliuzumab [max 375 mg] every 2 weeks (7)	13	32 (7–58)	A + C	6 (86%)	NA	NA	86%	NA		Baseline IgE, mean $\pm$ SD: 1063 $\pm$ 558 IU/ml
Lacombe et al. [29] (Canada)	Obs	Omaliuzumab 225–375 mg every 2 weeks (7)	51	11 (6–19)	C	3 (43%)	NA	Severe [C]	NA	TCS		Baseline IgE, mean $\pm$ SD: 16,007 $\pm$ 9806 IU/l
Zink et al. [36] (Germany)	Obs	Omaliuzumab 450 mg every 2 weeks (10)	25	44 (26–65)	A	2 (20%)	NA	Severe [C]	NA	Low-potency TCSs		Few days prior to omalizumab administration, patients were treated with immunoadsorption IgE [after immunoadsorption], mean $\pm$ SD: 4927 $\pm$ 4243 IU/ml
<i>Ustekinumab</i>												
Saeki et al. [40] (Japan) [I]	RCT Phase II	Ustekinumab 45 mg at weeks 0, 4 (24) vs. p (27)	12	Median 39 (25–57) vs. 30 (20–57)	A	7 (29%) vs. 8 (30%)	Severe vs. severe	NA	100%	TCSs/calceineurin inhibitors	Low	
[II]		Ustekinumab 90 mg at weeks 0, 4 (28) vs. p (27)	12	Median 34 (20–50) vs. 30 (20–57)	A	9 (32%) vs. 8 (30%)	Severe vs. severe	NA	100%	TCSs/calceineurin inhibitors		
Khattari et al. [25] (USA)	RCT Phase II (weeks 0–16)	Ustekinumab 45/90 mg at weeks 0, 4 (16) vs. p (16)	16	37 (18–60) vs. 40 (19–66)	A	6 (38%) vs. 6 (38%)	NA	Severe vs. severe [O]	NA	TCSs		
[Crossover]	(Weeks 16–40)	Ustekinumab 45/90 mg at weeks 16, 20, 32 (12) ^b vs. p [previously ustekinumab-treated] (14) ^c	16	NA ^d	A	NA ^d	NA	NA ^d	NA	TCSs		
<i>MK-8226-003 (anti-TSLPR)</i>												
Clinical trial 2016 [NCT01732510] [28]	RCT Phase Ib	MK-8226 0.3 mg/kg every 2 weeks (9) vs. p (8)	12	49 $\pm$ 12 vs. 38 $\pm$ 14	A	4 (44%) vs. 5 (63%)	NA	NA	NA	NA	Unclear	Trial results reported in ClinicalTrials.gov
		MK-8226 1 mg/kg every 2 weeks (9) vs. p (8)	12	31 $\pm$ 13 vs. 38 $\pm$ 14	A	2 (22%) vs. 5 (63%)	NA	NA	NA	NA		

Table 1 continued

Publication (country) [subgroup]	Design	Intervention (N, verum vs. controls)	Treatment duration (weeks)	Age (years), mean $\pm$ SD or range	Adults/ children	Female (%)	Baseline severity EASI	Baseline severity SCORAD [C/O] ^a	Baseline IGA $\geq$ moderate (%)	Concomitant treatment	Overall risk of bias across studies	Remarks
<i>Infliximab</i> Jacobi et al. [26] (Germany)	Obs	MK-8226 3 mg/kg every 2 weeks (8) vs. p (8)	12	42 $\pm$ 13 vs. 38 $\pm$ 14	A	4 (50%) vs. 5 (63%)	NA	NA	NA	NA		
		MK-8226 10 mg/kg every 2 weeks (10) vs. p (8)	12	35 $\pm$ 10 vs. 38 $\pm$ 14	A	6 (60%) vs. 5 (63%)	NA	NA	NA	NA		
<i>Rituximab</i> Simon et al. [24] (Swiss)	Obs	Rituximab 1000 mg 2 weeks apart (6)	24 follow-up	39 (19–63)	A	4 (67%)	Severe	NA	NA	TCSs	High	

A adults (over 18 years), C combined, EASI Eczema Area and Severity Index, IGA Investigator Global Assessment, IgE immunoglobulin E, IQR interquartile range, max maximum, NA not available, O objective, Obs observational, p placebo, RCT randomized controlled trial, SCORAD SCOring Atopic Dermatitis, SCSSs systemic corticosteroids, SD standard deviation, TCSs topical corticosteroids

^aA combined score of investigator-reported disease severity and affected body surface area (objective) and patient-reported symptoms (subjective). Scores range from 0 to 103

^b4/16 patients withdrawn due to lack of efficacy or protocol violation

^c2/16 patients withdrawn due to disease worsening or time constraints

^dUpdated data after patients were withdrawn were unavailable

^ePatients were followed for an overall-period of 46 weeks. As most patients dropped out during weeks 10–46, we made efficacy analysis at week 10

Table 2 Efficacy outcomes of included studies

Publication (country) [subgroup]	Intervention (N, verum vs. controls)	Change from baseline EASI (%)	EASI-50 (Pro, RR [95% CI])	EASI-75 (Pro, RR [95% CI])	SCORAD-50 (Pro, RR [95% CI])	SCORAD-75 (Pro, RR [95% CI]) ^b	IGA 0/1 (Pro, RR [95% CI]) ^b	Change from baseline SCORAD (%) [C/O]	Participants AE (Pro, RR [95% CI])	Participants SAE (Pro, RR [95% CI])	Patients withdrawn due to AE (Pro, RR [95% CI])	Comment
<i>Dupilumab</i>												
Simpson et al. [16] (North America, Europe, Asia) [I]	SOLO 1	–72 ± 3	154/224 vs. 55/224, 2.8 [2.2–3.6]	115/224 vs. 33/224, 3.5 [2.5–4.9]	NA	NA	85/224 vs. 23/224, 3.7 [2.4–5.6]	–58 ± 2 vs. –29 ± 3 [C]	167/229 vs. 145/222, 1.1 [1–1.3]	7/229 vs. 11/222, 0.6 [0.2–1.6]	4/229 vs. 2/222, 1.9 [0.4–10.5]	
	Dupilumab 300 mg every other week (224) vs. p (224)											
	SOLO 1	–72 ± 3	136/223 vs. 55/224, 2.5 [1.9–3.2]	117/223 vs. 33/224, 3.6 [2.5–5]	NA	NA	83/223 vs. 23/224, 3.6 [2.4–5.5]	–57 ± 2 vs. –29 ± 3 [C]	150/218 vs. 145/222, 1.1 [0.9–1.2]	2/218 vs. 11/222, 0.2 [0–0.8]	4/218 vs. 2/222, 2 [0.4–11]	
[III]	Dupilumab 300 mg every week (223) vs. p (224)											
	SOLO 2	–67 ± 3	152/233 vs. 52/236, 3 [2.3–3.8]	103/233 vs. 28/236, 3.7 [2.6–5.43]	NA	NA	84/233 vs. 20/236, 4.3 [2.7–6.7]	–51 ± 2 vs. –20 ± 3 [C]	154/236 vs. 168/234, 0.9 [0.8–1]	4/236 vs. 13/234, 0.3 [0.1–2]	2/236 vs. 5/234, 0.4 [0.1–2]	
	Dupilumab 300 mg every other week (233) vs. p (236)											
[IV]	SOLO 2	–69 ± 3	146/239 vs. 52/236, 2.8 [2.1–3.6]	115/239 vs. 28/236, 4.1 [2.8–5.9]	NA	NA	87/239 vs. 20/236, 4.3 [2.7–6.8]	–54 ± 2 vs. –20 ± 3 [C]	157/237 vs. 168/234, 0.9 [0.8–1]	8/237 vs. 13/234, 0.6 [0.3–1.4]	3/237 vs. 5/234, 0.6 [0.1–2.5]	
	Dupilumab 300 mg every week (239) vs. p (236)											
	SOLO 2	–69 ± 3	146/239 vs. 52/236, 2.8 [2.1–3.6]	115/239 vs. 28/236, 4.1 [2.8–5.9]	NA	NA	87/239 vs. 20/236, 4.3 [2.7–6.8]	–54 ± 2 vs. –20 ± 3 [C]	157/237 vs. 168/234, 0.9 [0.8–1]	8/237 vs. 13/234, 0.6 [0.3–1.4]	3/237 vs. 5/234, 0.6 [0.1–2.5]	
Thaçi et al. [22] (North America, Europe, Asia) [I]	Dupilumab 100 mg every 4 weeks (65) vs. p (61)											
	SOLO 1	–45 ± 5	29/65 vs. 18/61, 1.5 [0.9–2.4]	19/65 vs. 7/61, 2.6 [1.2–5.6] ^a	NA	NA	8/65 vs. 1/61, 7.51 [1–58]	–27 ± 4 vs. –14 ± 4 [C]	53/65 vs. 49/61, 1.02 [0.9–1.2]	5/65 vs. 4/61, 1.2 [0.3–4.2]	10/65 vs. 3/61, 2.4 [0.8–7.1]	
	Dupilumab 300 mg every 4 weeks (65) vs. p (61)											
[III]	SOLO 1	–64 ± 5	46/65 vs. 18/61, 2.4 [1.6–3.6]	32/65 vs. 7/61, 4.3 [2.1–9] ^a	NA	NA	14/65 vs. 1/61, 13.14 [1.8–96.9]	–49 ± 4 vs. –14 ± 4 [C]	56/65 vs. 49/61, 1.1 [0.9–1.3]	3/65 vs. 4/61, 0.7 [0.2–3]	3/65 vs. 3/61, 0.9 [0.2–4.5]	
	Dupilumab 300 mg every 4 weeks (65) vs. p (61)											
	SOLO 1	–65 ± 5	38/61 vs. 18/61, 2.1 [1.4–3.3]	34/61 vs. 7/61, 4.9 [2.3–10.1] ^a	NA	NA	17/61 vs. 1/61, 17 [2.3–124]	–46 ± 4 vs. –14 ± 4 [C]	46/61 vs. 49/61, 0.9 [0.8–1.1]	1/61 vs. 4/61, 0.3 [0–2.2]	1/61 vs. 3/61, 0.3 [0–3.1]	
[III]	Dupilumab 200 mg every other week (61) vs. p (61)											
	SOLO 1	–65 ± 5	38/61 vs. 18/61, 2.1 [1.4–3.3]	34/61 vs. 7/61, 4.9 [2.3–10.1] ^a	NA	NA	17/61 vs. 1/61, 17 [2.3–124]	–46 ± 4 vs. –14 ± 4 [C]	46/61 vs. 49/61, 0.9 [0.8–1.1]	1/61 vs. 4/61, 0.3 [0–2.2]	1/61 vs. 3/61, 0.3 [0–3.1]	
	Dupilumab 200 mg every other week (61) vs. p (61)											

Table 2 continued

Publication (country) [subgroup]	Intervention (N, verum vs. controls)	Change from baseline EASI (%)	EASI-50 (Pro, RR [95% CI])	EASI-75 (Pro, RR [95% CI])	SCORAD-50 (Pro, RR [95% CI])	SCORAD-75 (Pro, RR [95% CI]) ^b	IGA 0/1 (Pro, RR [95% CI]) ^b	Change from baseline SCORAD (%) [C/O]	Participants AE (Pro, RR [95% CI])	Participants SAE (Pro, RR [95% CI])	Patients withdrawn due to AE (Pro, RR [95% CI])	Comment
[IV]	Dupilumab 300 mg every other week (64) vs. p (61)	-68 ± 5 vs.	50/64 vs.	34/64 vs.	NA	NA	19/64 vs.	-51 ± 4 vs.	50/64 vs.	2/64 vs.	2/64 vs.	
		-18 ± 5	18/61, 2.7 [1.8-4]	7/61, 4.6 [2.2-9.7] ^a			1/61, 18.1 [2.5-131]	-14 ± 4 [C]	49/61, 1 [0.8-1.2]	4/61, 0.5 [0.1-2.5]	3/61, 0.6 [0.1-3.7]	
[V]	Dupilumab 300 mg every week (63) vs. p (61)	-74 ± 5 vs.	52/63 vs.	38/63 vs.	NA	NA	21/63 vs.	-57 ± 4 vs.	53/63 vs.	1/63 vs.	1/63 vs.	
		-18 ± 5	18/61, 2.8 [1.9-4.2]	7/61, 5.3 [2.6-10.9] ^a			1/61, 20 [2.8-147]	-14 ± 4 [C]	49/61, 1.1 [0.9-1.2]	4/61, 0.2 [0-2.1]	3/61, 0.3 [0-3]	
Beck et al. [21] (Europe)	Dupilumab 300 mg every week (55) vs. p (54)	-74 ± 4 vs.	47/55 vs.	34/55 vs.	NA	NA	22/55 vs.	NA	42/55 vs.	1/55 vs.	1/55 vs.	
		-23 ± 7	19/54, 2.4 [1.7-3.5]	8/54, 4.2 [2.1-8.2]			4/54, 5.4 [2-14.6]		43/54, 1 [0.8-1.2]	7/54, 0.1 [0-1.1]	3/54, 0.3 [0-3.1]	
Blauvelt et al. [23] (USA)	Dupilumab 300 mg every week (97) vs. p (97)	NA	70/97 vs.	52/97 vs.	NA	NA	43/97 vs.	NA	54/97 vs.	3/97 vs.	NA	Patients were permitted use of topical and low-dose systemic corticosteroids
			31/97, 2.3 [1.7-3.1]	19/97, 2.7 [1.8-4.3]			10/97, 4.3 [2.3-8]		60/97, 0.9 [0.7-1.1]	0/97, 7 [0.4-133]		
Blauvelt et al. [13] (USA)	Dupilumab 300 mg every other week (106) vs. p (315)	Week 16 -77 ± 4 vs.	Week 16 85/106 vs.	Week 16 73/106 vs.	NA	NA	Week 16 41/106 vs.	Week 16 -62 ± 3 vs.	Week 52 97/110 vs.	Week 52 4/110 vs.	Week 52 2/110 vs.	
		-43 ± 2	118/315, 2.1 [2.3-3.8]	73/315, 3 [2.3-3.8]			39/315, 3.1 [1-1.1]	-32 ± 2 [C]	266/315, 1 [1-1.1]	16/315, 0.7 [0.2-2.1]	24/315, 0.2 [0-1]	
[II]	Dupilumab 300 mg every week (319) vs. p (315)	Week 52 -78 ± 4 vs.	Week 52 70/89 vs.	Week 52 58/89 vs.	NA	NA	Week 52 32/89 vs.	Week 52 -66 ± 3 vs.	Week 52 33/264, 2.9 [1.9-4.4]	Week 52 33/264, 2.9 [1.9-4.4]	Week 52 33/264, 2.9 [1.9-4.4]	
		-46 ± 3	79/264, 2.6 [2.1-3.3]	57/264, 3 [2.3-4]			33/264, 2.9 [1.9-4.4]	-34 ± 2 [C]				
[III]	Dupilumab 300 mg every week (319) vs. p (315)	Week 16 -77 ± 2 vs.	Week 16 249/319 vs.	Week 16 204/319 vs.	NA	NA	Week 16 125/319 vs.	Week 16 -63 ± 2 vs.	Week 52 261/315 vs.	Week 52 9/315 vs.	Week 52 9/315 vs.	
		-43 ± 2	118/315, 2.1 [2.2-3.4]	73/315, 2.8 [2.2-3.4]			39/315, 4 [2.9-5.5]	-32 ± 2 [C]	266/315, 1 [0.9-1.1]	16/315, 0.6 [0.3-1.3]	24/315, 0.4 [0.2-0.8]	
[III]	Dupilumab 300 mg every week (319) vs. p (315)	Week 52 -80 ± 3 vs.	Week 52 189/270 vs.	Week 52 173/270 vs.	NA	NA	Week 52 108/270 vs.	Week 52 -66 ± 2 vs.	Week 52 33/264, 3.2 [2.3-4.5]	Week 52 33/264, 3.2 [2.3-4.5]	Week 52 33/264, 3.2 [2.3-4.5]	
		-46 ± 3	79/264, 2.3 [1.9-2.9]	57/264, 3 [2.3-3.8]			33/264, 2.3 [1.9-2.9]	-34 ± 2 [C]				

Table 2 continued

Publication (country) [subgroup]	Intervention (N, verum vs. controls)	Change from baseline EASI (%)	EASI-50 (Pro, RR [95% CI])	EASI-75 (Pro, RR [95% CI])	SCORAD- 50 (Pro, RR [95% CI])	SCORAD- 75 (Pro, RR [95% CI]) ^b	IGA 0/1 (Pro, RR [95% CI]) ^b	Change from baseline SCORAD (%) [C/O]	Participants AE (Pro, RR [95% CI])	Participants SAE (Pro, RR [95% CI])	Patients withdrawn due to AE (Pro, RR [95% CI])	Comment
<i>Nemolizumab</i>												
Ruzica et al. [39] (USA)	Nemolizumab 0.1 mg/kg every 4 weeks (53) vs. p (53)	-30 ± 6 ^b vs. -37 ± 6	20/45 ^b vs. 16/43, 1.2 [0.7–2]	15/45 ^b vs. 8/43, 1.8 [0.9–3.8]	10/39 ^b vs. 6/39, 1.7 [0.7–4.1]	1/39 ^b vs. 1/39, 1 [0.1–15]	NA	-35 ± 4 ^b vs. -24 ± 4 [C]	38/53 vs. 36/53, 1.1 [0.8–1.4]	1/53 vs. 1/53, 1 [0.1–16]	5/53 vs. 1/53, 5 [0.6–41]	
	Nemolizumab 0.5 mg/kg every 4 weeks (54) vs. p (53)	-44 ± 6 ^b vs. -37 ± 6	24/46 ^b vs. 16/43, 1.4 [0.9–2.3]	17/46 ^b vs. 8/43, 2 [1–4.1]	15/40 ^b vs. 6/39, 2.4 [1.1–5.6]	8/40 ^b vs. 1/39, 7.8 [1–59]	NA	-39 ± 2 ^b vs. -24 ± 4 [C]	36/54 vs. 36/53, 1 [0.8–1.3]	0/54 vs. 1/53, 0.3 [0–7.9]	3/54 vs. 1/53, 2.9 [0.3–27]	
	Nemolizumab 2 mg/kg every 4 weeks (52) vs. p (53)	-46 ± 6 ^b vs. -37 ± 6	21/46 ^b vs. 16/43, 1.2 [0.7–2]	10/46 ^b vs. 8/43, 1.2 [0.5–2.7]	15/41 ^b vs. 6/39, 2.4 [1–5.5]	7/41 ^b vs. 1/39, 6.6 [0.9–52]	NA	-41 ± 4 ^b vs. -24 ± 4 [C]	40/52 vs. 36/53, 1.1 [0.9–1.4]	3/52 vs. 1/53, 3.1 [0.3–28]	4/52 vs. 1/53, 4.1 [0.5–35]	
	Nemolizumab 2 mg/kg every 8 weeks (52) vs. p (53)	NA	NA	NA	NA	NA	NA	NA	37/52 vs. 36/53, 1.1 [0.8–1.4]	2/52 vs. 1/53, 1 [0.1–16]	3/52 vs. 1/53, 3.1 [0.3–28]	
<i>Lebrikizumab</i>												
Clinical trial 2016 [NCT02340234] [27]	Lebrikizumab 125 mg once (52) vs. p (53)	NA	36/52 vs. 33/53, 1.1 [0.8–1.5]	NA	18/52 vs. 14/53, 1.3 [0.7–2.4]	NA	NA	NA	NA	NA	NA	Herpes infections occurred in 2–6% of patients receiving lebrikizumab
	Lebrikizumab 250 mg once (53) vs. p (53)	NA	37/53 vs. 33/53, 1.1 [0.9–1.5]	NA	25/53 vs. 14/53, 1.8 [1.1–3]	NA	NA	NA	NA	NA	NA	
	Lebrikizumab 125 mg at weeks 0, 4, 8, 12 (51) vs. p (53)	NA	42/51 vs. 33/53, 1.3 [1.04–1.7]	NA	26/51 vs. 14/53, 1.9 [1.1–3.3]	NA	NA	NA	NA	NA	NA	

Table 2 continued

Publication (country) [subgroup]	Intervention (N, verum vs. controls)	Change from baseline EASI (%)	EASI-50 (Pro, RR [95% CI])	EASI-75 (Pro, RR [95% CI])	SCORAD-50 (Pro, RR [95% CI])	SCORAD-75 (Pro, RR [95% CI]) ^h	IGA 0/1 (Pro, RR [95% CI]) ^h	Change from baseline SCORAD (%) [C/O]	Participants AE (Pro, RR [95% CI])	Participants SAE (Pro, RR [95% CI])	Patients withdrawn due to AE (Pro, RR [95% CI])	Comment
<i>Tralokinumab</i>												
Clinical trial 2017 [NCT02347176] [43]	Tralokinumab 45 mg every other week (50) vs. p (51)	AMD -3 (95% CI -7 to 1)	29/45 vs. 25/41, 1.1 [0.8-1.5] [24]	NA	16/45 vs. 11/41, 1.3 [0.7-2.5]	NA	6/50 vs. 6/50, 1 [0.3-2.9]	Absolute change -22 ± 2 vs. -17 ± 2 [C]	23/50 vs. 17/51, 1.4 [0.8-2.3]	3/50 vs. 2/51, 1.5 [0.3-8.8]	NA	
	Tralokinumab 150 mg every other week (51) vs. p (51)	AMD -4 (95% CI -8 to -1)	34/47 vs. 25/41, 1.2 [0.9-1.6] [24]	NA	22/47 vs. 11/41, 1.7 [0.97-3.1]	NA	10/51 vs. 6/50, 1.6 [0.6-4.2]	Absolute change -26 ± 2 vs. -17 ± 2 [C]	23/51 vs. 17/51, 1.4 [0.8-2.2]	2/51 vs. 2/51, 1 [0.1-6.8]	NA	
	Tralokinumab 300 mg every other week (52) vs. p (51)	AMD -5 (95% CI -9 to -1)	36/48 vs. 25/41, 1.2 [0.9-1.7] [24]	NA	21/48 vs. 11/41, 1.6 [0.9-3]	NA	13/51 vs. 6/50, 2.1 [0.9-5.1]	Absolute change -27 ± 2 vs. -17 ± 2 [C]	22/52 vs. 17/51, 1.3 [0.8-2.1]	0/52 vs. 2/51, 0.2 [0-4]	NA	
<i>Omalizumab</i>												
Iyengar et al., 2013 [33] (USA)	Omalizumab 150-375 mg every 2-4 weeks (4) vs. p (4)	NA	NA	NA	1/4 vs. 3/4 ^e , 0.3 [0-2]	0/4 vs. 2/4 ^e , 0.2 [0-3.2]	NA	-26 ± 15 vs. -71 ± 20 [C]	NA	None	None	
Hotze et al. [37] (Germany)	Omalizumab 150-300 mg every 2 weeks (20)	NA	NA	NA	4/20 ^f	NA	NA	-12 [C]	NA	NA	None	7/20 patients experienced disease exacerbation
Kim et al. [30] (Korea)	Omalizumab 300 mg every 2 weeks (10)	NA	NA	NA	2/10	NA	NA	-25 [O]	None	None	None	
Ramírez del Pozo et al. [38] (Mexico)	Omalizumab (11)	NA	NA	NA	NA	NA	NA	-56 [C]	None	None	None	Patients experienced improvement in quality of life

Table 2 continued

Publication (country) [subgroup]	Intervention (N, verum vs. controls)	Change from baseline EASI (%)	EASI-50 (Pro, RR [95% CI])	EASI-75 (Pro, RR [95% CI])	SCORAD-50 (Pro, RR [95% CI])	SCORAD-75 (Pro, RR [95% CI]) ^h	IGA 0/1 (Pro, RR [95% CI]) ^h	Change from baseline SCORAD (%) [C/O]	Participants AE (Pro, RR [95% CI])	Participants SAE (Pro, RR [95% CI])	Patients withdrawn due to AE (Pro, RR [95% CI])	Comment
Heil et al. [35] (Austria)	Dupilumab 0.016 mg/kg/IgE every 4 weeks (13) vs. p (7)	NA	NA	NA	NA	NA	4/13 vs. 4/7, 0.5 [0.2–1.5]	NA	10/13 vs. 4/7, 1.4 [0.7–2.7]	None	None	Under omalizumab, patients had improvement in immediate/delayed skin tests
Sheinkopf et al. [32] (USA)	Omalizumab 150–300 mg every 2–4 weeks (21)	NA	NA	NA	NA	NA	20/21 ^c	NA	NA	None	None	
Belloni et al. [34] (Germany)	Omalizumab 150 mg every 2 weeks (11)	NA	NA	NA	2/11	1/11	NA	–17 ± 42 [C]	None	None	None	2/11 patients experienced disease exacerbation
Vigo et al. [31] (USA)	Omalizumab (max 375 mg) every 2 weeks (7)	NA	NA	NA	NA	NA	3/7	NA	NA	NA	NA	5/7 patients completed 6 months of treatment, with 4/5 achieving IGA ≤1
Lacombe et al. [29] (Canada)	Omalizumab 225–375 mg every 2 weeks (7)	NA	NA	NA	6/7	1/7	NA	–59 ± 12 [C]	None	None	None	
Zink et al. [36] (Germany)	Omalizumab 450 mg every 2 weeks (10)	NA	NA	NA	3/10	None	NA	–49 ± 20 ^d [C]	4/10	None	None	Two and one patients dropped out due to exacerbation and lack of compliance, respectively
<i>Ustekinumab</i>												
Saeiki et al. [40] (Japan) [I]	Ustekinumab 45 mg at weeks 0, 4 (24) vs. p (27)	–38 ± 7 vs. –38 ± 7	9/24 vs. 11/27, 0.9 [0.5–1.8]	2/24 vs. 4/27, 0.6 [0.1–2.8]	NA	NA	0/24 vs. 0/27, 1.1 [0–54]	NA	18/24 vs. 20/27, 1 [0.7–1.4]	None	None	

Table 2 continued

Publication (country) [subgroup]	Intervention (N, verum vs. controls)	Change from baseline EASI (%)	EASI-50 (Pro, RR [95% CI])	EASI-75 (Pro, RR [95% CI])	SCORAD-50 (Pro, RR [95% CI])	SCORAD-75 (Pro, RR [95% CI]) ^h	IGA 0/1 (Pro, RR [95% CI]) ^h	Change from baseline SCORAD (%) [C/O]	Participants AE (Pro, RR [95% CI])	Participants SAE (Pro, RR [95% CI])	Patients withdrawn due to AE (Pro, RR [95% CI])	Comment
[II]	Ustekinumab 90 mg at weeks 0, 4 (28) vs. p (27)	−40 ± 7 vs. −38 ± 7	10/28 vs. 11/27, 0.9 [0.5–1.7]	5/28 vs. 4/27, 1.2 [0.4–4]	NA	NA	0/27 vs. 0/27, 1 [0–49]	NA	16/28 vs. 20/27, 0.8 [0.5–1.1]	None	1/28 vs. 0/27, 2.9 [0.1–68]	
Khattari et al. [25] (USA)	Ustekinumab 45/90 mg at weeks 0, 4 (16) vs. p (16)	NA	NA	NA	5/16 vs. 3/16, 1.7 [0.5–5.8]	0/16 vs. 2/16, 0.3 [0–4]	NA	NA	NA ^g	None	None	
[Crossover]	Ustekinumab 45/90 mg at weeks 16, 20, 32 (12) vs. p [previously ustekinumab-treated] (14)	NA	NA	NA	8/14 vs. 8/12, 0.9 [0.5–1.6]	2/14 vs. 3/12, 0.6 [0.1–2.9]	NA	NA	NA ^g	None	None	
<i>MK-8226-003 (anti-TSLPR)</i>												
Clinical trial 2016 [NCT01732510] [28]	MK-8226 0.3 mg/kg every 2 weeks (9) vs. p (8)	Absolute change: −6 ± 6 vs. −0.4 ± 6	NA	NA	NA	NA	NA	NA	8/9 vs. 7/8, 1 [0.7–1.4]	NA	None	
	MK-8226 1 mg/kg every 2 weeks (9) vs. p (8)	Absolute change: −8 ± 9 vs. −0.4 ± 6	NA	NA	NA	NA	NA	NA	6/9 vs. 7/8, 0.8 [0.4–1.3]	NA	None	
	MK-8226 3 mg/kg every 2 weeks (8) vs. p (8)	Absolute change: −10 ± 7 vs. −0.4 ± 6	NA	NA	NA	NA	NA	NA	6/8 vs. 7/8, 0.9 [0.5–1.4]	NA	1/8 vs. 0/8, 3 [0.1–64]	
	MK-8226 10 mg/kg every 2 weeks (10) vs. p (8)	Absolute change: −8 ± 8 vs. −0.4 ± 6	NA	NA	NA	NA	NA	NA	7/10 vs. 7/8, 0.8 [0.5–1.3]	NA	None	
<i>Infliximab</i>												
Jacobi et al. [26] (Germany)	Infliximab 5 mg/kg at weeks 0, 2, 6 (9)	−24%	4/9	2/9	NA	NA	NA	NA	4/9	1/9	None	Three patients had disease exacerbation

Table 2 continued

Publication (country) [subgroup]	Intervention (N, verum vs. controls)	Change from baseline EASI (%)	EASI-50 (Pro, RR [95% CI])	EASI-75 (Pro, RR [95% CI])	SCORAD-50 (Pro, RR [95% CI])	SCORAD-75 (Pro, RR [95% CI]) ^b	IGA 0/1 (Pro, RR [95% CI]) ^b	Change from baseline SCORAD (%) [C/O]	Participants AE (Pro, RR [95% CI])	Participants SAE (Pro, RR [95% CI])	Patients withdrawn due to AE (Pro, RR [95% CI])	Comment
<i>Rituximab</i>												
Simon et al. [24] (Swiss)	Rituximab 1000 mg 2 weeks apart (6)	- 76% ^a	NA	NA	NA	NA	NA	NA	3/6	None	None	21 absolute EASI improvement from baseline ^a

AE adverse event, AMD absolute mean difference, C combined, CI confidence interval, EASI Eczema Area and Severity Index, IGA Investigator Global Assessment, IgE immunoglobulin E, max maximum, NA not available, O objective, P placebo, Pro proportions, RR relative risk, SAE serious adverse event, SCORAD SCORing Atopic Dermatitis, TSLPR thymic stromal lymphopoietin receptor

^aData were derived by graphical visualization. Numerical values were not available

^bIntention-to-treat population, including data after rescue therapy

^cCategorized as mild disease

^dMissing values of three patients dropping out were imputed by means of the last observation carried forward method

^eIn order to calculate SCORAD-50/75, SCORAD values of > 99 and < 5 were assigned a value of 100 and 4, respectively

^fDescribed as SCORAD reduction $\geq 50\%$

^gData regarding participants with adverse events were only available for the overall follow-up period of 40 weeks

^hOr equivalent to IGA 0 (clear) or 1 (almost clear)

IGA. Most patients had moderate to severe disease at baseline in the 20 studies that reported on this parameter. Eight studies reported on our primary outcome, whereas 15 reported secondary outcomes only. All the studies were published in peer-reviewed journals, except for the anti-TSLPR and tralokinumab studies, which were extracted from the ClinicalTrials.gov website, and the lebrikizumab study, which was extracted from an online report in a commercial dermatology news website. One dupilumab study was extracted from a conference abstract [23].

3.1 Risk of Bias

The dupilumab, nemolizumab and ustekinumab studies presented a low risk of bias. Studies succinctly described in abstracts and websites [23, 27, 28, 43] were designated an unclear risk of bias due to the lack of data, while the remaining studies yielded a high risk of bias [24, 26, 29–38] (for details see electronic supplementary Tables S1 and S2).

3.2 Dupilumab

Dupilumab is a monoclonal antibody directed against the shared α -subunit of the interleukin (IL)-4/13 receptor [9, 10]. Five RCTs (one phase I, two phase II, two phase III) investigated dupilumab in adults at doses ranging from 100 mg every 4 weeks to 300 mg every week for 12–52 weeks, in a total of 2801 patients [13, 16, 21–23]. Only two studies allowed concomitant topical corticosteroids (TCSs). At all doses except 100 mg every 4 weeks, dupilumab had superior efficacy compared with placebo. Of patients treated with dupilumab 300 mg every week to every 2 weeks, 55 and 38% achieved pooled EASI-75 and IGA 0/1 responses, respectively, at weeks 12–16. Results were maintained at week 52 [13]. In a meta-analysis, the 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, $p < 0.001$, $I^2 = 0\%$) and 3.7 for IGA 0/1 (95% CI 3.2–4.3, $p < 0.001$, $I^2 = 0\%$) (Figs. 2, 3). There was no difference in efficacy between the weekly and every other week 300 mg dose (electronic supplementary Fig. S4). The relative efficacy of dupilumab increased with the use of more rigorous outcomes (e.g. IGA 0/1, EASI-90) as the placebo response dropped more than the dupilumab response (Fig. 3 and electronic supplementary Fig. S1). After excluding one study from a conference abstract [23], the results remained (data not shown).

The risk for at least one adverse event was similar between dupilumab and placebo. Furthermore, the risks for at least one severe adverse event and withdrawal due to adverse events were favorable in the dupilumab arm (electronic supplementary Figs. S2–4).

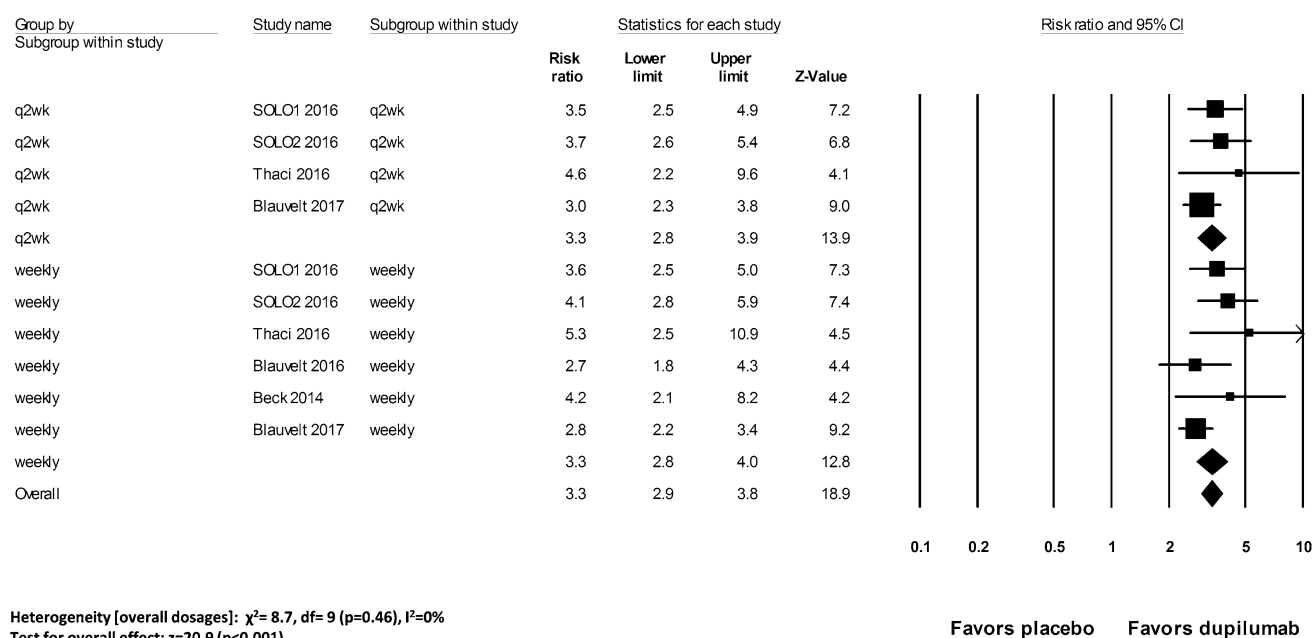


Fig. 2 Forest plot: dupilumab versus placebo—EASI-75 at weeks 12–16. *CI* confidence interval, *q2wk* every 2 weeks, *df* degrees of freedom, *EASI* Eczema Area and Severity Index

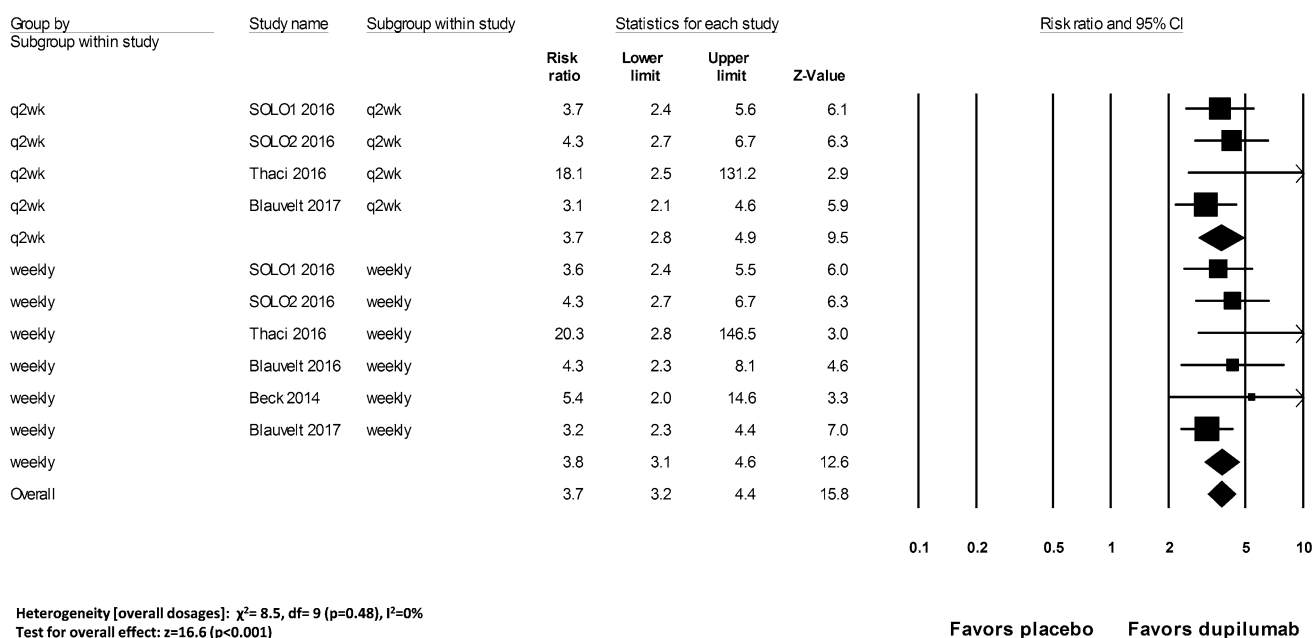


Fig. 3 Forest plot: dupilumab versus placebo—IGA 0/1 at weeks 12–16. *CI* confidence interval, *q2wk* every 2 weeks, *df* degrees of freedom, *IGA* Investigator Global Assessment

3.3 Nemolizumab

Nemolizumab is a monoclonal antibody against IL-31 receptor A [44]. One phase II RCT [39] evaluated three nemolizumab arms: 0.1 mg/kg (53 patients), 0.5 mg/kg (54 patients) and 2 mg/kg (52 patients) once every 4 weeks compared with placebo (53 patients) for 12 weeks. All

doses did not display superior EASI-75 or EASI-50 responses compared with placebo, although the 0.5 mg/kg dose had superior SCORAD-50 and SCORAD-75 responses, albeit with very wide CIs. The 2 mg/kg dose was similar to placebo for the same outcomes. There was no difference in adverse events or patients withdrawn due to adverse events.

3.4 Lebrikizumab

Lebrikizumab is a humanized monoclonal antibody targeting soluble IL-13. One phase II RCT [27] with partial results published online in a commercial dermatology news website evaluated three lebrikizumab arms of a single 125 mg dose (52 patients), a single 250 mg dose (51 patients) and 125 mg at weeks 0, 4, 8 and 12 compared with placebo (53 patients) for 12 weeks, with concomitant TCSs for all study arms. Only the repeated lebrikizumab dose achieved superior EASI-50 and SCORAD-50 responses versus placebo. Adverse events data were not available.

3.5 Tralokinumab

Tralokinumab is a human IL-13 neutralizing monoclonal antibody [45]. One phase II RCT [43] reported in the ClinicalTrials.gov website evaluated three tralokinumab dosing arms once every 2 weeks: 45 mg (50 patients), 150 mg (51 patients) and 300 mg (52 patients) compared with placebo (51 patients) for 12 weeks, with concomitant TCSs for all study arms. All doses did not display superior EASI-50 or SCORAD-50 responses compared with placebo, although the SCORAD-50 responses of the higher 150 and 300 mg doses showed a trend towards improved responses versus placebo. There was no difference in adverse events between study groups.

3.6 Omalizumab

Omalizumab is a recombinant humanized immunoglobulin (Ig) targeted against IgE [46]. Two RCTs [33, 35] and eight observational studies [29–32, 34, 36–38] evaluated omalizumab 150 mg every 4 weeks to 375 mg every 2 weeks for 16–51 weeks, among 125 patients. The baseline IgE levels varied significantly, ranging on average from 373 to 4927 IU/ml. Two small RCTs evaluated SCORAD-75 [33] and IGA 0/1 [35] in 17 patients treated with omalizumab compared with 11 controls. Both did not find superiority of drug to placebo at weeks 16–24. Six observational studies reported a mean reduction of $31 \pm 19\%$ in the SCORAD score in 69 patients treated with omalizumab, comparable with the mean placebo response observed in dupilumab trials (23% without TCSs, 32% with TCSs) (electronic supplementary Tables S3 and 4). Two other studies reported that 57% of seven patients achieved IGA 0/1, and 95% of 21 patients achieved a clear to mild IGA response [29–32, 34, 36–38].

Of the six studies describing adverse events, four found no adverse events [29, 30, 34, 38], one reported no difference between omalizumab and placebo (RR 1.4, 95% CI 0.7–2.7) [35], and one reported 4/10

participants with non-severe adverse events [36]. No participant had severe adverse events or withdrew due to adverse events.

3.7 Ustekinumab

Ustekinumab is an anti-IL-12/23 monoclonal antibody [47] evaluated in two phase II RCTs, with a total of 111 patients. The RCTs could not be pooled because they applied different outcome measurement instruments, but both did not show superiority to placebo in EASI-75 and SCORAD-75 responses [25, 40]. Both studies allowed concomitant TCSs, with a considerable effect in the placebo arm. No participants had severe adverse events, and only one study reported non-severe adverse events [40], which were comparable between ustekinumab 45/90 mg and placebo.

3.8 Antithymic Stromal Lymphopoietin Receptor (TSLPR), MK-8226-003

TSLP is a member of the hematopoietic cytokine family and partakes in the initiation of allergic inflammation in asthma and AD [48]. One phase Ib RCT [28] partially reported on the ClinicalTrials.gov website, evaluated four dosing arms of anti-TSLPR in a total of 36 patients, compared with eight patients receiving placebo for 12 weeks. Placebo versus drug analysis was provided for the 3 mg/kg every 2 weeks arm only, with anti-TSLPR leading to a larger improvement in mean baseline EASI (10 ± 7 vs. 0.4 ± 6 points, $p = 0.015$). A second part of the study evaluating the 3 mg/kg dose was not analyzed because the change from baseline EASI was inadequate in an interim futility analysis. The study was terminated early from a business perspective, and there was no difference in adverse events or patient withdrawals due to adverse events between the study arms.

3.9 Infliximab

Infliximab is a chimeric antibody that binds to free and membrane-bound tumor necrosis factor (TNF)- α [49]. One observational study [26] allowing concomitant TCSs evaluated nine patients treated with infliximab 5 mg/kg at weeks 0, 2 and 6 for 10 weeks. Four of nine (44%) and two of nine (22%) patients achieved EASI-50 and EASI-75 responses, respectively. Compared with the mean placebo responses of 575 patients from three RCTs investigating dupilumab with no TCSs (electronic supplementary Table S4), infliximab had similar EASI-50 (RR 1.8, 95% CI 0.8–3.7) and EASI-75 responses (RR 1.7, 95% CI 0.5–5.8) as the dupilumab placebo. Adverse events were observed in four of nine participants, one severe.

Table 3 Outcome data for dupilumab 300 mg every other week at weeks 12–16

Intervention	<i>N</i>	EASI-50 [<i>n/N</i> (%)]	EASI-75 [<i>n/N</i> (%)]	IGA 0/1 [<i>n/N</i> (%)]	EASI change from baseline (%)	SCORAD change from baseline (%)
<i>Concomitant topical emollients</i>						
Simpson et al. (SOLO 1) [16]	224	154/224 (69)	115/224 (51)	85/224 (38)	– 72	– 58
Simpson et al. (SOLO 2) [16]	233	152/233 (65)	103/233 (44)	84/233 (36)	– 67	– 51
Thaci et al. [22]	64	50/64 (78)	34/64 (53)	19/64 (30)	– 68	– 51
Sum (%)	521	356/521 (68)	252/521 (48)	188/521 (36)	– 69	– 54
<i>Concomitant topical corticosteroids</i>						
Blauvelt et al. [13]	106	85/106 (80)	73/106 (69)	41/106 (39)	– 77	– 62

EASI Eczema Area and Severity Index, IGA Investigator Global Assessment, NA not available, SCORAD SCORing Atopic Dermatitis

3.10 Rituximab

Rituximab is a chimeric anti-CD20 antibody [50]. One observational study [24] evaluated six patients followed up over 24 weeks who were receiving two 1000 mg infusions of rituximab, 2 weeks apart. Concomitant TCSs were allowed. On average, patients had a 21-point absolute reduction from baseline in EASI score. In all, three of six participants had non-severe adverse events.

4 Discussion

This systematic review and meta-analysis summarizes the up-to-date evidence on the efficacy of available biologic therapies in the treatment of AD. Twenty-three studies evaluating nine biologic agents were included [13, 16, 21–40, 43].

Only dupilumab showed favorable efficacy data in high-quality studies, with 55% of patients receiving 300 mg every 1 or 2 weeks reaching EASI-75 at weeks 12–16, 3.3-fold higher than placebo. These findings were consistent across the outcomes we explored, with no increase in adverse events (RR 1, 95% CI 0.9–1.1) or severe adverse events (RR 0.6, 95% CI 0.3–1.1) over 52 weeks of treatment compared with placebo. Adding TCSs to the study arms retained the superiority of dupilumab to placebo [13, 23]. Compared with available systemic non-biologic agents, dupilumab showed seemingly similar improvement from baseline in SCORAD scores compared with cyclosporine [54–62% (Table 3) vs. 42–88%] and superior responses compared with azathioprine (39%) and methotrexate (39%) [4]. As substantial heterogeneity exists in study and patient-level characteristics across trials, head-to-head studies are needed to draw reliable conclusions.

Nemolizumab, an anti IL-31 agent, was similar to placebo [39] across the majority of our assessed outcomes,

which focus on the investigator assessment of signs (e.g. erythema); however, the study achieved its primary outcome, i.e. reduction in pruritus, highlighting the role of IL-31 in AD pruritus [51]. Nemolizumab had a satisfactory short-term safety profile, comparable with placebo. Ongoing studies of large groups will help clarify the discrepancy between the beneficial effect of nemolizumab on pruritus and its limited effect on other aspects.

Data from a phase II RCT of lebrikizumab and tralokinumab, monoclonal antibodies that target IL-13 [52], were extracted from an online report [27] and the ClinicalTrials.gov website [43], respectively. The studies displayed borderline or limited efficacy advantage over placebo in EASI-50 and SCORAD-50 responses. The use of concomitant TCSs in both studies may have enhanced the placebo response more than the verum response, resulting in failure to demonstrate significant differences between the groups. Adopting more stringent outcomes (e.g. IGA 0/1) in future studies may be a way of mitigating the enhanced placebo response observed with TCSs. This is demonstrated in a dupilumab study that allowed concomitant TCSs and displayed higher dupilumab versus placebo RR for IGA 0/1 compared with EASI-50 responses [13]. Examination of the complete study data post peer review, including outcome data for stricter endpoints and a complete safety profile, is necessary to understand the role of IL-13-blocking antibodies in treating AD.

IgE represents a potential target in AD [53]. A recent systematic review on omalizumab in AD concluded that anti-IgE therapy can benefit patients with severe recalcitrant AD [11], but our findings argue differently. Two small RCTs did not find superiority of omalizumab to placebo [33, 35]. Additionally, six observational studies reported a decrease in mean SCORAD from baseline but this improvement was comparable to the placebo response from dupilumab studies [29, 30, 34, 36–38]. A possible explanation for the limited therapeutic effect is that IgE

Table 4 Biologic agents in the pipeline for AD

Drug	Mechanism	Phase and design	Company	Clinical trial number
XmAb7195	Anti-IgE	Phase I RCT: single-dose XmAb7195 vs. placebo	Xencor	NCT02148744
GBR 830	Anti-OX40	Phase IIa RCT: GBR 830 vs. placebo	Glenmark	NCT02683928
Tezepelumab/ MED19929	Anti-TSLPR	Phase IIa RCT: tezepelumab at weeks 0 and 10 vs. placebo	Amgen	NCT02525094
Ligelizumab/ QGE031	Anti-IgE	Phase II RCT: ligelizumab q2wk vs. placebo for 12 weeks	Novartis	NCT01552629
Fezakinumab/ILV-094	Anti-IL-22	Phase II RCT: fezakinumab q2wk vs. placebo for 10 weeks	Pfizer	NCT01941537
Nemolizumab	Anti-IL-31	Phase II RCT: nemolizumab low/medium/high-dose q4wk vs. placebo for 24 weeks	Galderma R&D	NCT03100344
Secukinumab	Anti-IL-17	Phase II RCT: secukinumab at weeks 0, 1, 2, 3, 4, and then q2wk vs. placebo for 12 weeks	Novartis	NCT02594098
Dupilumab	Anti-IL-4/13	Phase III RCT: dupilumab vs. placebo in children aged between 12 and 18 years	Regeneron/ Sanofi	NCT03054428
Omalizumab	Anti-IgE	Phase IV RCT: omalizumab q2wk–q4wk vs. placebo	Novartis/ Genentech	NCT02300701

AD atopic dermatitis, IgE immunoglobulin E, IL interleukin, *qxwk* every *x* weeks, RCT randomized controlled trial, TSLPR thymic stromal lymphopoietin receptor

production is a late event in AD pathogenesis, occurring downstream the skew toward Th2 [54]. Nonetheless, omalizumab has the advantage of being studied and well-tolerated in children [55], and, given that studies used different dosing and stratification by IgE levels, omalizumab may be effective in selected patients. A large phase IV RCT to clarify the role of omalizumab in severe pediatric AD has recently been published [56].

Ustekinumab was evaluated in two phase II RCTs [25, 40] and, although both studies used different outcome measurement instruments, they did not find superiority of drug to placebo at week 12. Both studies allowed the use of TCSs, which possibly augmented the placebo response more than the ustekinumab response, diminishing the difference between the groups. Ustekinumab blockage of the Th1 and Th17 axes may be effective in selected patients, e.g. in Asian patients who have a strong Th17 expression in lesional skin [57].

Despite initial promise, a study on anti-TSLPR agents did not demonstrate adequate effect in an interim analysis and was therefore terminated and never published. Two small case-series of infliximab [26] and rituximab [50] reported improvement in baseline EASI; however, without a comparator group and with both studies allowing concomitant TCSs, these results do not signify efficacy.

Our review has a few methodological limitations. First, we included grey literature, with limited data availability and reliability, but emphasized the data sources throughout the text. Second, given the small number of available RCTs, we included small-sized observational studies of low quality; however, because none had a control group,

we were required to compare their results with previous RCTs on different agents in order to draw any efficacy conclusions. As numerous RCTs are in the pipeline for AD (Table 4), future updates of this review should preferably be limited to RCTs [58]. Third, we were unable to conduct subgroup and sensitivity analyses because of the limited data and inconsistency across outcome measurements. Finally, we selected EASI-75 as our primary outcome due its relatively wide use in current AD trials; however, the measure of improvement in a score that is clinically important to patients with AD has not been investigated and defined. It is possible that other measures of change in outcomes such as EASI-90 will emerge as more significant. The EASI was also selected because it is the tool endorsed by the Harmonising Outcome Measures for Eczema (HOME) group for assessing clinical signs in AD trials [59]. Only eight RCTs reported on EASI-75, similar to the number of RCTs reporting on our secondary outcomes, highlighting the poor standardization of outcome measurement and the need for harmonizing outcomes in AD research [59].

5 Conclusions

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. Nemolizumab, lebrikizumab and tralokinumab may be efficacious, but further study is needed. Blocking the Th2 axis seems to be preferable to blockage of other

pathways, but it is possible that with appropriate patient stratification and mitigation of placebo responses other pathways will emerge. No major safety issues came to light in these studies; however, the majority of studies were short term and many were underpowered to capture less common or late side effects. Long-term follow-up is needed to clarify drug safety for these agents, and future high-quality RCTs with a longer follow-up period are warranted to consolidate our conclusions. Our findings support the notion that AD has a complex pathogenesis that cannot be accounted for by a single cytokine [57].

Compliance with ethical standards

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