Relative efficacy of systemic treatments for atopic dermatitis

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Background: Systemic medications are often required for severe atopic dermatitis (AD) refractory to topical therapies. Biologic medications are a recent advancement in the field and a comparison with standard systemic approaches would be beneficial.

Objective: To compare efficacies of systemic therapies for the treatment of AD.

Methods: A systematic literature review was performed using Medline, Ovid, and Embase. Randomized controlled trials looking at the efficacy of systemic treatments for AD in adults and children were included.

Results: A total of 41 studies met criteria and were included in our final analysis. Consistent improvements in Eczema Area and Severity Index and Scoring Atopic Dermatitis were reported with dupilumab and cyclosporine. Phase 2 clinical trials for lebrikizumab and tralokinumab were effective and would benefit from phase 3 trials. No study reported efficacy of biologic medications in pediatric patients; however, cyclosporine improved clinical severity by the greatest amount in this group.

Limitations: A lack of well controlled comparison studies make direct comparisons between the treatments difficult.

Conclusion: For treatment of severe AD, the strongest evidence currently exists for dupilumab and cyclosporine at improving clinical disease severity. Further research is required to determine long-term safety and efficacy of biologic medications. (J Am Acad Dermatol 2019;80:411-6.)

Key words: adults; atopic dermatitis; biologic treatment; children; cyclosporine; dupilumab; efficacy; lebrikizumab; systemic treatment; tralokinumab.

Atopic dermatitis (AD) is a chronic eczematous skin condition associated with significant pruritus affecting patients' quality of life. Topical corticosteroid therapies remain the mainstay of treatment in mild disease.[1] Topical calcineurin inhibitors and phototherapy are sometimes efficacious when corticosteroids fail to adequately control the disease.[2,3] These skin-directed regimens are often incompletely effective, and patients require systemic treatment.

Short courses of oral corticosteroids have been used in severe cases where immediate responses are desired; however, long-term oral corticosteroids are not suitable for a chronic disease.[4] The affect on daily life of individuals with AD is large, and systemic therapies that both reduce severity of disease and

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improve quality of life are needed.[5] Recently, biologic medications targeting cellular pathways of AD have been developed. Comparison of the efficacy of these new treatments will enable the physician to better select appropriate therapies.

A lack of head-to-head trials makes it difficult to compare the efficacy of systemic AD treatments. The hurdle is exacerbated by the variability in study design and outcome measures that have been used in AD trials. Nevertheless, the purpose of this systematic analysis is to identify systemic therapies that have been used in or are being developed for the treatment of atopic dermatitis and determine, as best we can, which therapies appear to be most effective at improving disease severity and quality of life.

CAPSULE SUMMARY

- Systemic treatments are common for severe atopic dermatitis, and biologic medications represent recent advances in the field.
- Dupilumab and cyclosporine are both effective at improving clinical severity of atopic dermatitis, as are newer biologic medications lebrikizumab and tralokinumab. Long-term efficacy and safety results are needed for biologic medications.

METHODS

Search strategy

We conducted a systematic literature search for clinical studies using Medline (PubMed), Ovid, and Embase to identify systemic treatments used in the management of atopic dermatitis and pruritus using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplemental Fig 1; available at http://www.jaad.org).[6] We searched for all studies published during January 1990-July 2018 using a combination of terms related to systemic treatments of atopic dermatitis. After this comprehensive search, 4781 studies were identified.

Abstracts from all studies were obtained and read independently by 2 authors (Mr Seger and Mr Wechter) to assess the articles for eligibility using the following inclusion criteria: (1) full-text reports; (2) randomized controlled trials (RCTs); (3) studies involving patients with clinically diagnosed moderate-to-severe atopic dermatitis criteria as described by Hanifin and Rajka[7]; (4) studies involving the use of systemic treatments; and (5) studies that included information on treatment efficacy with validated measures as an outcome measure. Studies published in languages other than English and whose outcome did not report severity or quality of life measures were excluded. Many studies allow concurrent use of topical corticosteroids and oral antihistamines. Therefore, the concurrent use of topical corticosteroids and antihistamines was not criteria for exclusion except in instances when patients were given these therapies for the explicit purpose of the study design.

A total of 102 abstracts were identified and full-text versions of each were read in full. Initially, 45 studies were identified as meeting criteria. Four additional studies were excluded for multiple reasons. In 1 study, psoralen was used as a bath treatment rather than an ingested medication; therefore, this was a more skin-directed therapy.[8] In another study, during the lead-in period before the start of treatment, high-dose cyclosporine was used, likely affecting pretreatment and posttreatment efficacy scores,[9] and 2 studies were long-term follow-up studies of an RCT included in our study.[10,11]

Data reporting

Outcome measures were calculated as the difference between pretreatment and posttreatment disease severity and quality of life. For crossover studies and studies in which the medication or dosing regimen used was altered throughout the study, results were reported before the crossover event to maintain consistency.

RESULTS

We included 41 RCTs in the final analysis, reporting on a total of 4938 patients and 17 different medications (Supplemental Table I; available at http://www.jaad.org).[12-52] The most frequently reported therapy was cyclosporine (15 studies),[12-26] followed by montelukast (4 studies),[27-30] azathioprine (3 studies), and methotrexate (3 studies).[24,26,31-33] Two studies reported on interferon λ and thymopentin,[34-37] and a single study each reported on flunisolide, pimecrolimus, prednisolone, and oral psoralen plus ultraviolet A light.[23,38-40] Biologics were tested in 12 studies.[41-52] All patients had a history of chronic AD refractory to topical treatments (Supplemental Table I). With the exception of methotrexate (1 time a week) and psoralen plus ultraviolet A light (3 times a week), daily use was required.[24,26,33,35] In addition, biologic drugs were administered from once every 4 weeks to as frequent as 4 times per week.[41,42,45,47-49,52] Treatment duration ranged from 2 weeks (oral corticosteroids) to 1 year (cyclosporine and dupilumab).[17,23,38,43]

In adults, the largest improvements in clinical severity were seen with cyclosporine and

Abbreviations used:

AD:	atopic dermatitis
DLQI:	Dermatology Life Quality Index
EASI:	Eczema Area and Severity Index
IL:	interleukin
RCT:	randomized controlled trial
SASSAD:	Six Area, Six Sign Atopic Dermatitis
SCORAD:	Scoring Atopic Dermatitis

dupilumab. Eight weeks of cyclosporine improved Six Area, Six Sign Atopic Dermatitis (SASSAD) scores by 68%-69% with high-dose treatment (4-4.5 mg/kg 2x/day) and by 44% with low-dose treatment (2.5 mg/kg/d).[18,26] Moreover, 5 mg/kg/d cyclosporine improved Scoring Atopic Dermatitis (SCORAD) scores by 56% at week 24.[26] In phase 3 trials, the interleukin (IL) 4 receptor antagonist dupilumab improved Eczema Area and Severity Index (EASI) scores 76% at week 16 (Table I).[41,42,44] One year of dupilumab treatment reduced SCORAD 66%.[43] Biologic drugs targeting IL-13 are also effective. In a pair of phase 2 clinical trials, lebrikizumab and tralokinumab improved EASI scores by 59%-71% and 55%-58%, respectively.[45,50] There are no placebo-controlled studies evaluating methotrexate for the treatment of AD; however, after 12 and 24 weeks in nonplacebo-controlled studies, methotrexate treatment reduced SCORAD scores by 40%-48%.[26,33] Studies evaluating azathioprine had SASSAD reductions of 26%-37% at week 12.[31,32] Montelukast, mepolizumab, and omalizumab did not improve clinical severity.[27,29,46,49]

In addition to improving disease severity, dupilumab improved quality of life. Dupilumab improved Dermatology Life Quality Index (DLQI) scores by 9.1 points at 16 weeks[43] and 10.9 points at 1 year.[43] After subtracting the improvement with placebo, DLQI score reduction was 6.5 at week 16 with dupilumab and 3.5 at week 12 with tralokinumab.[42,50] The phase 2 trial of lebrikizumab similarly showed improved DLQI scores by 34%-43% in adults with moderate-to-severe AD.[45] Patient-reported pruritus improved by 34%-53% with 300 mg biweekly dupilumab compared with 41% with lebrikizumab every 4 weeks.[43,45] In a phase 2 clinical trial for nemolizumab, a monoclonal antibody targeting IL-31, the DLQI scores improved by 34%-45% and also the patient-reported pruritus scores improved by as much as 63%.[47]

Although we identified no placebo-controlled study evaluating cyclosporine for the treatment of AD and reporting DLQI scores, in nonplacebo-controlled studies, low-dose cyclosporine treatment (2.5 mg/kg/d) improved DLQI scores by 5.5 points at week 8.[26] Increasing cyclosporine dose to 5 mg/kg/d for an additional 16 weeks improved DLQI scores by 73% of pretrial values (8.7-point reduction).[26] Azathioprine improved DLQI scored by 5.9 points (61% reduction) when dosing was based on thiopurine methyltransferase levels.[32]

Six studies specifically examined treatment efficacy in pediatric populations (under the age of 18 years, Table II).[17,22,24,30,38,48] No placebo-controlled study was found on the evaluation of cyclosporine for the treatment of AD in children; however, in a nonplacebo-controlled study, cyclosporine improved SASSAD scores by 46% at week 12 and 56% at 1 year.[17] Moreover, there was no difference in SCORAD scores between children treated with methotrexate or cyclosporine at week 12.[24] In a 2-week placebo-controlled trial, flunisolide improved total clinical severity scores by 54%.[38] Omalizumab did not improve AD clinical severity.[48]

DISCUSSION

For patients suffering from AD refractory to conventional topical therapies, several systemic treatments exist that could provide relief. These medications are generally well-tolerated, and for those with potential toxicities, dosing strategies and criteria for monitoring have improved long-term safety. The most frequently used systemic treatments in severe AD are oral corticosteroids, but they are not suitable for long-term maintenance therapy.[1,23]

Of the reviewed systemic treatments, dupilumab has the strongest supporting evidence. The Food and Drug Administration—recommended dose of 300 mg dupilumab biweekly with combination topical corticosteroids resulted in the largest overall improvement in both clinical severity and quality of life after 1 year of treatment.[43] Furthermore, the dupilumab biweekly dosing schedule might improve adherence compared with once daily cyclosporine and azathioprine.[17,32,43] Beyond dupilumab, nonbiologic systemic treatments, including cyclosporine, were also effective at improving AD disease severity. To more directly compare medication efficacy, a standardized controlled trial comparing biologic and nonbiologic systemic therapies is needed.[12,39,45,50] Omalizumab was the only biologic therapy we found that was tested in pediatric patients, and it did not improve disease severity.[48] Dupilumab for AD in the pediatric population is currently under investigation.[53]

One limitation of AD literature is nonuniform reporting of outcome data. Disease severity metrics include but are not limited to SCORAD, SASSAD, and EASI.[54] Likewise, multiple quality-of-life indexes

Table I. Drug efficacy in adult placebo-controlled trials

	Biologic medications				Nonbiologic systemic medications			
	Dupilumab		Lebrikizumab	Tralokinumab	Azathioprine	Cyclosporine	Pimecrolimus	Thymopentin
	300 mg Q2W		125 mg Q4W	300 mg Q2W	1.0-2.5 mg/d	5 mg/kg/d	30 mg BID	50 mg/d
Scoring system	1 year	16 weeks	12 weeks	12 weeks	12 weeks	8 weeks	12 weeks	6-12 weeks
EASI	32.5	38.6	17.4	16.8	NR	NR	27.0	NR
EASI 50	49.0	44.5	20.1	21.5	NR	NR	NR	NR
EASI 75	43.0	38.8	20.9	27.0	NR	NR	NR	NR
DLQI	5.3	5.2	NR	3.5	1.4	NR	NR	NR
SASSAD	NR	NR	NR	NR	17.0	42.0	NR	NR
SCORAD	32.1	32.0	18.1	16.2	NR	NR	NR	NR

Values reported as therapeutic group percentage change from baseline minus the placebo group percentage change from baseline. DLQI reported as raw numerical change from baseline in the therapeutic group minus raw placebo group change from baseline. For dupilumab, Food and Drug Administration–approved dosing reported. For all other medications, most efficacious medication dose reported.
BID, Two times per day; *EASI*, Eczema Area and Severity Index; *EASI 50*, ≥50% improvement of Eczema Area and Severity Index from baseline; *EASI ≥75*, 75% improvement of Eczema Area and Severity Index from baseline; *DLQI*, Dermatology Life Quality Index; *NR*, not reported; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *SASSAD*, Six Area, Six Sign Atopic Dermatitis; *SCORAD*, Scoring Atopic Dermatitis.

Table II. Drug efficacy in pediatric clinical trials

Drug	Duration	Dose	Disease severity reduction, % (scoring system)	*P* value
Cyclosporine	1 year	5 mg/kg/d	56 (Six Area, Six Sign Atopic Dermatitis)	<.001*
	12 weeks	2.5-5 mg/kg/d	35-44 (Scoring Atopic Dermatitis); 46 (Six Area, Six Sign Atopic Dermatitis)	<.001*; NS†
Flunisolide	2 weeks	7.5 mg/wk	54 (Total clinical severity)	<.001‡
Methotrexate	12 weeks	640-1200 μg	49 (Scoring Atopic Dermatitis)	NS†
Montelukast	4 weeks	Not specified	42 (Six Area, Six Sign Atopic Dermatitis)	<.05*‡§
Omalizumab	24 weeks	150-375 mg Q2-4W	26 (Scoring Atopic Dermatitis)	NR

NS, Not significant; *Q2-4W*, every 2-4 weeks.
*Compared with baseline.
†No difference between methotrexate and cyclosporine.
‡Compared with placebo.
§NS with crossover group.

exist for AD.[54] Metric standardization would enable more accurate comparisons between treatments. Another limitation of these studies is inflated placebo efficacy, which might be a result of eligibility creep rather than true improvement in disease severity.[55] Last, biologic medications are relatively new and direct comparisons are difficult between phase 2 and phase 3 studies, many of which are still ongoing. Future research comparing these biologic medications after phase 3 trials, once they are complete, can provide an update on the comparative efficacy of these therapies.

Systemic treatments are effective options for patients with refractory AD. Of these treatments, both biologic and systemic treatments such as cyclosporine are effective at improving disease severity and quality of life, and decisions on which medication to use should be made on a case-by-case basis. Future investigation into novel biologic agents that exploit AD pathophysiology could lead to even more effective treatments.

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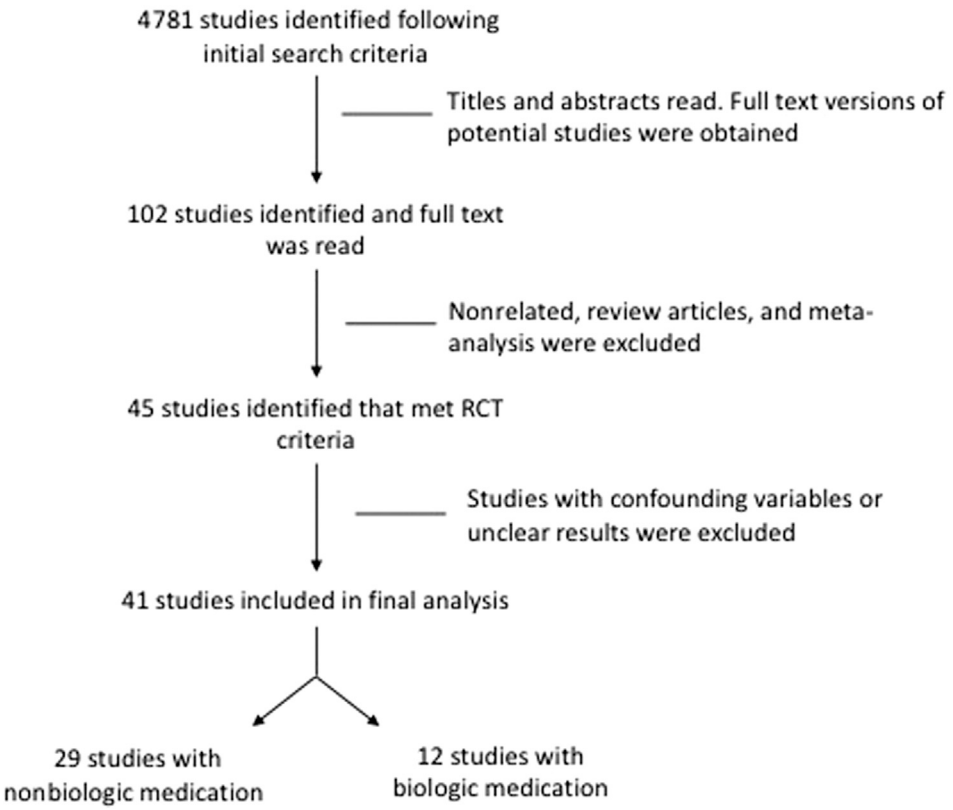

Supplemental Fig 1. Study flow chart. *RCT*, Randomized controlled trial.

Supplemental Table I. Summary of included trials

Studies	Comparison	Design	Treatment duration	Inclusion criteria	Patient description (age, y)	N
Beck et al, 2014[41]	DUP vs PLC	Double-blind placebo-controlled RCT	12 weeks	Moderate-to-severe AD (IGA ≥3)	Adults (range 34-43)	207
Bemanian et al, 2005[22]	CYS vs IVIG	RCT	12 weeks	Severe AD (SCORAD >70)	Children (mean 12 in CYS, 6 in IVIG)	14
Berth-Jones et al, 2002[31]	AZA vs PLC	Double-blind placebo-controlled crossover RCT	12 weeks	Severe AD	Adults (range 17-73)	37
Blauvelt et al, 2017[43]	DUP vs PLC	Double-blind placebo-controlled RCT	1 year	Moderate-to-severe AD (IGA ≥3)	Adults (range 34-41)	740
Czech et al, 2000[19]	CYS	Double-blind RCT	8 weeks	Severe AD	Adults (range 18-63)	106
El-Khalawany et al, 2013[24]	CYS vs MTX	RCT	12 weeks	Severe AD	Children (range 7-14)	40
Friedman et al, 2007[29]	MONT vs PLC	Double-blind placebo-controlled RCT	8 weeks	Moderate AD (SASSAD 12-50)	Adults (range 16-60)	60
Goujon et al, 2018[26]	CYS vs MTX	RCT	8 weeks	Moderate-to-severe AD (SCORAD ≥15)	Adults (mean 33 CYS, 32 MTX)	97
Granlund et al, 2001[20]	CYS vs UVAB	Open RCT	8 weeks	Severe AD (7-9 Rajka and Langeland criteria)	Adults (mean 33 for both groups)	72
Hanifin et al, 1993[34]	IFN γ vs PLC	Double-blind placebo-controlled crossover RCT	12 weeks	Severe AD	Adults (mean 37 IFN, 28 placebo)	83
Harper et al, 2000[17]	CYS	Open RCT	12 weeks	Severe AD	Children (range 2-16)	40
Heil et al, 2010[49]	OMA vs PLC	Double-blind placebo-controlled RCT	16 weeks	Moderate-to-severe AD (IGA ≥2)	Adults (range 18-47)	20
Iyengar et al, 2013[48]	OMA vs PLC	Double-blind placebo-controlled RCT	24 weeks	Severe AD	Adults and children (range 4-22)	8
Jang et al, 2000[35]	IFN γ vs PLC	Placebo-controlled RCT	12 weeks	Severe AD (≥20% BSA)	Adults (mean 21)	51
Jin et al, 2015[25]	CYS + GLU	Double-blind placebo-controlled RCT	8 weeks	Severe AD (≥30 SCORAD)	Adults and children (range 9-49)	43
Khattri et al, 2017[51]	UST vs PLC	Double-blind placebo-controlled crossover RCT	16 weeks	Moderate-to-severe AD (SCORAD ≥15)	Adults (range 18-75)	33
La Rosa et al, 1995[38]	FLU vs PLC	Double-blind placebo-controlled crossover RCT	2 weeks	Severe AD	Children (range 2-6)	20
Leung et al, 1990[36]	THY vs PLC	Double-blind placebo-controlled crossover RCT	6 weeks	Chronic AD (severity score ≥6, BSA ≥20%)	Adults and children (range 2-66)	100
Meggitt et al, 2006[32]	AZA vs PLC	Double-blind placebo-controlled RCT	12 weeks	Moderate-to-severe AD	Adults (mean 30 AZA, 36 placebo)	63
Munro et al, 1994[14]	CYS vs PLC	Double-blind placebo-controlled crossover RCT	8 weeks	Severe AD	Adults (range 19-48)	24

Continued

Supplemental Table I. Cont'd

Studies	Comparison	Design	Treatment duration	Inclusion criteria	Patient description (age, y)	N
Oldhoff et al, 2005[46]	MEPO vs PLC	Double-blind placebo-controlled RCT	2 weeks	Moderate-to-severe AD (SCORAD 20-40)	Adults (range 18-57)	40
Pacor et al, 2004[21]	CYS vs TACR	Double-blind placebo-controlled RCT	42 days	Moderate-to-severe AD	Adults and children (range 13-45)	30
Pei et al, 2001[30]	MONT vs PLC	Double-blind placebo-controlled crossover RCT	4 weeks	Moderate-to-severe AD	Children (range 6-16)	15
Rahman et al, 2006[28]	MONT vs PLC	Open RCT	4 weeks	Moderate-to-severe AD (SCORAD ≥30)	Adults and children (mean 20 ML, 18 placebo)	31
Ruzicka et al, 2017[47]	NEMO vs PLC	Double-blind placebo-controlled RCT	12 weeks	Moderate-to-severe AD (EASI ≥10, pruritus ≥50 mm, IGA ≥3)	Adults (range 18-65)	216
Saeki et al, 2017[52]	UST vs PLC	Double-blind placebo-controlled RCT	12 weeks	Moderate-to-severe AD (IGA ≥4, EASI ≥12)	Adults (range 20-65)	79
Salek et al, 1993[13]	CYS vs PLC	Double-blind placebo-controlled crossover RCT	8 weeks	Severe AD	Adults (range 17-56)	33
Schmitt et al, 2010[23]	CYS vs PRED	Double-blind RCT	6 weeks	Severe AD (SCORAD ≥40, DLQI ≥10)	Adults (range 18-55)	38
Schram et al, 2011[33]	AZA vs MTX	Single-blind RCT	12 weeks	Severe AD	Adults (mean 37 AZA, 43 MTX)	42
Simpson et al, 2016[44]	DUP vs PLC	Double-blind placebo-controlled RCT	16 weeks	Moderate-to-severe AD (IGA ≥3)	Adults (mean range 34-39)	1352
Simpson et al, 2018[45]	LEB vs PLC	Double-blind placebo-controlled RCT	12 weeks	Moderate-to-severe AD (EASI ≥14, IGA ≥3)	Adults (range 18-75)	209
Sowden el al, 1991[12]	CYS vs PLC	Double-blind placebo-controlled crossover RCT	8 weeks	Severe AD	Adults (range 16-58)	33
Stiller et al, 1994[37]	THY vs PLC	Double-blind placebo-controlled RCT	12 weeks	Severe AD (TCS ≥4)	Adults (mean 42 THY, 38 placebo)	39
Thaci et al, 2016[42]	DUP vs PLC	Double-blind placebo-controlled RCT	16 weeks	Moderate-to-severe AD (IGA ≥3)	Adults (range 18-69)	379
Tzaneva et al, 2010[40]	PUVA vs UVA	Single-blind crossover RCT	5 weeks	Severe AD (≥45 SCORAD)	Adults (mean 33)	40
van Joost et al, 1994[15]	CYS vs PLC	Double-blind placebo-controlled RCT	6 weeks	Severe AD	Adults (mean 32 CYS, 31 placebo)	46
Veien et al, 2005[27]	MONT vs PLC	Double-blind placebo-controlled RCT	4 weeks	Moderate-to-severe AD (BSA 5-35%, ≥4,5 Rajka and Langeland criteria)	Adults (range 16-70)	59

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Supplemental Table I. Cont'd

Studies	Comparison	Design	Treatment duration	Inclusion criteria	Patient description (age, y)	N
Wolff et al, 2005[39]	PIMC v PLC	Double-blind placebo-controlled RCT	12 weeks	Moderate-to-severe AD (IGA criteria)	Adults (range 18-65)	103
Wollenberg et al, 2018[50]	TRA vs PLC	Double-blind placebo-controlled RCT	12 weeks	Moderate-to-severe AD (IGA ≥3, SCORAD ≥25, BSA ≥10%)	Adults (range 18-75)	204
Zonneveld et al, 1996[16]	CYS	Open RCT	8 weeks	Severe AD	Adults (range 18-70)	78
Zurbriggen et al, 1999[18]	CYS	Double-blind crossover RCT	8 weeks	Severe AD	Adults (range 20-64)	14

AD, Atopic dermatitis; *AZA*, azathioprine; *BSA*, body surface area; *CYS*, cyclosporine; *DLQI*, Dermatology Life Quality Index; *DUP*, dupilumab; *EASI*, Eczema Area Severity Index; *FLU*, flunisolide; *GLU*, glucosamine; *IFN*, interferon; *IGA*, Investigator's Global Assessment; *IVIG*, intravenous immunoglobulin; *LEB*, lebrikizumab; *MEPO*, mepolizumab; *MONT*, montelukast; *MTX*, methotrexate; *NEMO*, nemolizumab; *OMA*, omalizumab; *PIMC*, oral pimecrolimus; *PLC*, placebo; *PRED*, prednisolone; *PUVA*, psoralen plus ultraviolet A; *RCT*, randomized controlled trail; *SASSAD*, Six Area, Six Sign Atopic Dermatitis; *SCORAD*, Scoring Atopic Dermatitis; *TACR*, topical tacrolimus; *TCS*, total clinical severity; *THY*, thymopentin; *TRA*, tralokinumab; *UST*, ustekinumab; *UVA*, ultraviolet A; *UVAB*, ultraviolet A and B.