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Short-term efficacy and safety of biologics and Janus kinase inhibitors for patients with atopic dermatitis: A systematic review and meta-analysis

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ABSTRACT

Background: In recent years, biologics targeting key cytokines and Janus kinase (JAK) inhibitors have demonstrated favorable efficacy and safety outcomes for atopic dermatitis (AD) therapy. To evaluate the short-term efficacy and safety of AD therapy involving biologics, JAK inhibitors, and their combination with topical corticosteroids (TCS) for patients with AD, we conducted this systematic review and meta-analysis. Using eligible randomized clinical trials (RCTs) of 12 or 16 weeks of treatment with systemic medications and 4 weeks of topical treatment for AD.

Methods: PubMed, Web of Science, ScienceDirect, and the Cochrane Library were searched from inception up to October 25, 2023. English-language randomized clinical trials (RCTs) of 12 or 16 weeks of treatment with systemic medications and 4 weeks of topical treatment for AD were included. Titles, abstracts, and articles were screened in duplicate. Of 7261 citations, 37 studies were included. The data were analyzed using Review Manager 5.4 and the outcomes were measured by the Eczema Area and Severity Index (EASI), Investigator Global Assessment (IGA), the pruritus Numerical Rating Scale (NRS), as well as instances of adverse events (AE), and serious AE (SAE), which were presented as risk ratio (RR) with a 95 % confidence interval (CI). The efficacy of the biological therapies was analyzed with the percentage of patients who have achieved EASI 75, EASI 90, IGA 0/1 and pruritus NRS4, while the safety of treatments was evaluated in terms of the number of patients who had ≥1 AE and who had at least one SAE.

Results: A total of 37 studies with 43 cohorts that examined 9 medications and placebo and involved 18172 participants were included. Compared with the placebo, all biologics and JAK inhibitors were associated with a higher response rate in efficacy outcomes, while systematic administration was presented by dupilumab 200 mg subcutaneously every 2 weeks with superior improvement in EASI 90 (RR 9.50, 95 % CI 2.31–39.03) and IGA0/1 (RR 17.00, 95 % CI

Abbreviations: AD, atopic dermatitis; AE, adverse events; CI, confidence interval; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; IL, interleukin; JAK, janus kinase; NRS, numerical rating scale; RR, risk ratio; SAE, serious adverse events; TCS, topical corticosteroids.

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2.33–123.78), upadacitinib 30 mg once daily in EASI 75 (RR 5.14, 95 % CI 4.20–6.31) and Pruritus NRS4 (RR 5.73, 95 % CI 4.44–7.39), and external use was presented by ruxolitinib 1.5 % twice daily orally in EASI 75 (RR 4.14, 95 % CI 3.06–5.61) and Pruritus NRS4 (RR 4.08, 95 % CI 2.86–5.81), and most of doses led to a better safety profile. Most doses of baricitinib, dupilumab, tralokinumab, and upadacitinib in combination with TCS demonstrated good efficacy as compared with the control groups (placebo + TCS). However, patients receiving baricitinib at a dosage of 2 mg daily (RR 1.23, 95 % CI 1.02–1.49) and 4 mg daily (RR 1.39, 95 % CI 1.22–1.58) in combination with TCS, exhibited a higher incidence of one or more SAE as compared with those taking placebo + TCS.

Conclusion: Our research has revealed that ruxolitinib and dupilumab are effective and safe treatments for mild to moderate AD and moderate to severe AD, respectively. Additionally, the combination of dupilumab and TCS demonstrates greater efficacy and safety compared to baricitinib, tralokinumab, and upadacitinib with TCS as a background treatment for moderate to severe AD. We suggest that the use of topical JAK inhibitors could be a potential alternative to TCS when used in combination with systemic medications, as a novel approach to treat AD. Insufficient different data sources caused by partial interventions were only mentioned in a few articles and low event rates in safety analyses may lead to the results being biased. Further studies directly comparing existing and novel treatments are needed and will be included in forthcoming updates of this review. Our findings could form a useful foundation for developing a new generation of treatment guidelines for AD.

1. Introduction

Also known as atopic eczema, atopic dermatitis (AD) is a chronic inflammatory skin disease with increasing prevalence. It affects 5–30 % of the pediatric population and 1–10 % of the adult population worldwide [1]. AD is mainly characterized by intense itching, skin barrier function alteration, and immune system dysfunction towards a Th2 response, which is associated with multiple triggers and complex pathophysiological mechanisms [2]. Presently, treatments for AD comprise topical therapy, phototherapy, and systemic immunotherapy. Traditional topical corticosteroids (TCS) or in conjunction with topical calcineurin inhibitors (TCI) are the first-line treatment for AD [3]. Possible adverse reactions of TCS include skin atrophy, telangiectasia, hypopigmentation, etc., and those of TCI comprise burning sensation, pruritus at the application site and a possible link to malignancies, although solid evidence of increased TCI-related lymphoma or other malignancies risk or photocarcinogenicity is lacking [3,4]. Reducing skin inflammation with minimal adverse effects, narrow band ultraviolet B (NB-UVB) phototherapy is a second-line treatment for moderate to severe AD, and ultraviolet A phototherapy could be used in the acute phase. However, the high frequency of treatment and the need for specialized equipment associated with phototherapy inconveniences patients and results in low acceptance [3,5]. When standard therapy proves ineffective, systemic immunotherapy agents, such as cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, and others, may be an off-label option. However, strict adherence to indications and contraindications is necessary, alongside close monitoring of adverse reactions, including liver and kidney function damage and elevated blood pressure [4,5]. All the above-mentioned treatments have a number of problems, such as limited efficacy in treating moderate to severe AD, severe side effects, or inconvenient use, so that they cannot fully cover all disease types and patient groups. Therefore, an increasing number of novel agents have been developed for the treatment of AD and have shown good efficacy in recent years.

As an inflammation predominantly driven by Th2 cells, the pathophysiological mechanism and clinical manifestation of AD are closely related to the inflammatory mediators released by Th2 cells. Accordingly, biological agents targeting these cytokines are promising options for the treatment of AD. Interleukin (IL)-4 and IL-13 are associated with elevated immunoglobulin E (IgE) and eosinophilic responses in atopy. IL-4 plays a critical role in the differentiation of naive $CD4^+$ T cells into Th2, and IL-13 enhances neuronal itch in human sensory neurons in multiple itch pathways [6]. Dupilumab, an antibody directed against the IL-4 receptor α (IL-4Rα) subunit shared with IL-13, was the first biologic approved by the US Food and Drug Administration (FDA) in 2016 for the treatment of patients aged ≥6 years with moderate to severe AD, and was also the first biologic approved in the US for children aged 6 months to 5 years with moderate to severe AD in June 2022, with encouraging results [7,8]. Other drugs targeting IL-13 alone have been extensively studied with varying degrees of efficacy, such as tralokinumab, which was approved in the EU in June 2021 and in the US in December 2021 for the treatment of moderate to severe AD in adults [9]. Lebrikizumab, which is being tested in phase III trials, was granted fast-track designation by the FDA for patients aged ≥12 years with moderate to severe AD [10–12]. IL-31 exerts direct pruritogenic effects and influences the inflammatory response and epidermal barrier disruption in AD. Nemolizumab, a humanized monoclonal antibody that targets the IL-31 receptor A and has relieved pruritus and skin symptoms in multiple clinical trials [13,14], was approved in Japan on March 28, 2022 for the treatment of AD-associated pruritus in patients aged >13 years only when existing treatment was insufficiently effective [15].

In addition to the aforementioned biologics, Janus kinase (JAK) inhibitors have recently shown remarkable efficacy in the treatment of dermatologic diseases [1]. JAK is a receptor-associated tyrosine kinase that is important in type I and type II cytokine signaling and regulates downstream signaling. Accumulating evidence demonstrated that a dysregulated JAK–STAT pathway is a key driver in AD. The JAK family is composed of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), which are predominantly involved in the inflammatory and innate immune responses, erythropoiesis and thrombopoiesis, lymphocyte proliferation and immune homeostasis,

Table 1
Characteristics of the studies and baseline population included.

A)

Agent	First author	Publication year	Journal	Week of evaluation of response, wk
Dupilumab	Beck	2014	NEJM	12
	Blauvelt	2017	Lancet	16
	Bruin-Weller	2018	BJD	16
	Guttman	2019	JACI	16
	Paller	2020	JAAD	16
	Simpson	2020	JAMA Dermatol	16
	Simpson	2016	NEJM	16
	Thaci	2016	Lancet	16
	Zhao	2021	BJD	16
Lebrikizmab	Silverberg	2023	NEJM	16
	Simpson	2023	JAMA Dermatol	16
	Simpson	2018	JAAD	12
Tralokinumab	Gutermuth	2022	BJD	16
	Paller	2023	JAMA Dermatol	16
	Silverberg	2021	BJD	16
	Wollenberg	2021	BJD	16
	Wollenberg	2019	JACI	12
Nemolizumab	Kabashima	2020	NEJM	16
Abrocitinib	Bieber	2021	NEJM	16
	Eichenfield	2021	JAMA Dermatol	12
	Gooderham	2019	JAMA Dermatol	12
	Silverberg	2020	JAMA Dermatol	12
	Simpson	2020	Lancet	12
Baricitinib	Bieber	2022	BJD	16
	Guttman	2019	JAAD	16
	Reich	2020	JAMA Dermatol	16
	Simpson	2021	JAAD	16
	Simpson	2020	BJD	16
	Torrelo	2023	BJD	16
Upadacitinib	Guttman	2021	Lancet	16
	Katoh	2022	JAAD Int	16
	Reich	2021	Lancet	16
Delgocitinib	Nakagawa	2021	JAAD	4
	Nakagawa	2020	JAAD	4
	Nakagawa	2019	JACI	4
Ruxolitinib	Kim	2020	JACI	4
	Papp	2021	JAAD	4

B)

Study	Trial name	Treatment	Dosing, schedule, route	Total, n	Males, n (%)	Age, y (Mean)	Disease duration, y (Mean)	Basal EASI score (Mean)	IGA 4, n (%)	Basal pruritus NRS score (Mean)
Beck, NEJM, 2014		Placebo	sc	54	27 (50)	39.4	NR	30.8	NR	5.8
		Dupilumab	300 mg qw sc	55	31 (56)	33.7	NR	28.4	NR	6.1
Blauvelt, Lancet, 2017		Placebo + TCS	sc	315	193 (61)	Median: 34.0	Median: 26.0	Median: 29.6	147 (47)	7.6
		Dupilumab + TCS	300 mg q2w sc	106	62 (58)	Median: 40.5	Median: 28.0	Median: 30.9	53 (50)	7.7
		Dupilumab + TCS	300 mg qw sc	319	191 (60)	Median: 34.0	Median: 26.0	Median: 29.0	147 (46)	7.4
Bruin-Weller, BJD, 2018		Placebo + TCS	sc	108	68 (63)	Median: 37.5	Median: 28.5	Median: 31.7	52 (48.1)	6.9
		Dupilumab + TCS	300 mg q2w sc	107	65 (61)	Median: 38.0	Median: 29.0	Median: 31.6	50 (46.7)	7
		Dupilumab + TCS	300 mg qw sc	110	66 (60)	Median: 38.0	Median: 32.0	Median: 31.1	52 (47.3)	6.4
Guttman, JACI, 2019		Placebo	sc	27	14 (51.9)	Median: 43.0	Median: 38.0	Median: 34.0	14 (51.9)	Median: 8
		Dupilumab	200 mg qw sc	27	16 (59.3)	Median: 35.0	Median: 25.0	Median: 30.0	13 (48.1)	Median: 8
Paller, JAAD, 2020		Placebo + TCS	sc	123	61 (49.6)	8.3	7.2	39	NR	7.7
		Dupilumab + TCS	300 mg q4w sc	122	57 (46.7)	8.5	7.4	37.4	NR	7.8

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Table 1 (*continued*)

B)

Study	Trial name	Treatment	Dosing, schedule, route	Total, n	Males, n (%)	Age, y (Mean)	Disease duration, y (Mean)	Basal EASI score (Mean)	IGA 4, n (%)	Basal pruritus NRS score (Mean)
Simpson, JAMA Dermatol, 2020		Placebo	sc	85	53 (62.4)	14.5	12.3	35.5	46 (54.1)	7.7
		Dupilumab	300 mg q4w sc	166	52 (61.9)	14.4	11.9	35.8	46 (54.8)	7.5
Simpson, NEJM, 2016	SOLO-1	Placebo	sc	224	119 (53)	Median: 39.0	Median: 28.0	31.8	110 (49)	7.7
		Dupilumab	300 mg q2w sc	224	130 (58)	Median: 38.0	Median: 26.0	30.4	108 (48)	7.6
		Dupilumab	300 mg qw sc	223	143 (64)	Median: 39.0	Median: 26.0	29.8	106 (48)	7.7
	SOLO-2	Placebo	sc	236	132 (56)	Median: 35.0	Median: 26.0	30.5	115 (49)	7.7
		Dupilumab	300 mg q2w sc	233	137 (59)	Median: 34.0	Median: 24.5	28.6	115 (49)	7.8
		Dupilumab	300 mg qw sc	239	139 (58)	Median: 35.0	Median: 24.0	29	112 (47)	7.8
Thaci, Lancet, 2016		Placebo	sc	61	40 (66)	37.2	29.8	32.9	29 (48)	6.34
		Dupilumab	100 mg q4w sc	65	34 (52)	36.3	27.9	32.2	31 (48)	6.71
		Dupilumab	300 mg q4w sc	65	40 (62)	36.8	26.5	29.4	28 (43)	6.84
		Dupilumab	200 mg q2w sc	61	36 (59)	35.8	25.2	32.9	30 (49)	6.98
		Dupilumab	300 mg q2w sc	64	41 (64)	39.4	30.5	33.8	30 (47)	6.74
		Dupilumab	300 mg qw sc	63	43 (68)	36.2	27.9	30.1	31 (49)	6.54
Zhao, BJD, 2021		Placebo	sc	83	60 (72.3)	Median: 26.0	Median: 12.0	Median: 31.0	46 (55)	8
		Dupilumab	300 mg q2w sc	82	58 (70.7)	Median: 28.0	Median: 13.0	Median: 30.3	47 (57)	8
Silverberg, NEJM, 2023	Advocate1	Placebo	sc	141	68 (48.2)	34.2	23.8	31.0	58 (41.1)	7.3
		Lebrikizmab	250 mg q2w sc	283	142 (50.2)	36.1	22.0	28.8	113 (39.9)	7.2
	Advocate2	Placebo	sc	146	71 (48.6)	35.3	20.1	29.6	51 (34.9)	7.2
		Lebrikizmab	250 mg q2w sc	281	145 (51.6)	36.6	20.8	29.7	106 (37.7)	7.1
Simpson, JAMA Dermatol, 2023		Placebo + TCS	sc	66	33 (50.0)	36.7	21.2	26.4	18 (27.3)	6.8
		Lebrikizmab + TCS	250 mg q2w sc	145	75 (51.7)	37.6	21.0	27.7	47 (32.4)	7.3
Simpson, JAAD, 2018		Placebo + TCS	sc	53	36 (67.9)	38.7	NR	23.6	11 (21)	NR
		Lebrikizmab + TCS	125 mg SD sc	52	34 (65.4)	34.9	NR	24.6	10 (19)	NR
		Lebrikizmab + TCS	250 mg SD sc	53	31 (58.5)	34.4	NR	26.3	15 (28)	NR
		Lebrikizmab + TCS	125 mg q4w sc	51	35 (68.6)	36.6	NR	26.9	11 (22)	NR
Gutermuth, BJD, 2022		Placebo + TCS	sc	137	83 (60.6)	Median: 34.0	Median: 26.0	29.1	NR	7.5
		Tralokinumab + TCS	300 mg q2w sc	140	82 (58.6)	Median: 33.0	Median: 33.0	28.6	NR	7.4
Paller, JAMA Dermatol, 2023		Placebo	sc	94	51 (54.3)	Median: 14.0	Median: 13.0	27.2	43 (45.7)	7.6
		Tralokinumab	150 mg q2w sc	98	51 (52.0)	Median: 15.0	Median: 13.0	28.9	44 (44.9)	7.5
		Tralokinumab	300 mg q2w sc	97	47 (48.5)	Median: 15.0	Median: 13.0	28.0	48 (49.5)	8.1
Silverberg, BJD, 2021		Placebo + TCS	sc	127	84 (66.1)	Median: 34.0	Median: 26.0	Meidan: 26.5	60 (47.2)	8

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Table 1 (*continued*)

B)

Study	Trial name	Treatment	Dosing, schedule, route	Total, n	Males, n (%)	Age, y (Mean)	Disease duration, y (Mean)	Basal EASI score (Mean)	IGA 4, n (%)	Basal pruritus NRS score (Mean)
		Tralokinumab + TCS	300 mg q2w sc	253	125 (49.4)	Median: 37.0	Median: 27.0	Median: 24.7	116 (45.8)	8
Wollenberg, BJD, 2021	ECZTRA-1	Placebo	sc	199	123 (61.8)	Median: 37.0	Median: 28.0	Meidan: 30.3	102 (51.3)	7.9
		Tralokinumab	300 mg q2w sc	603	351 (58.2)	Median: 37.0	Median: 27.0	Median: 28.2	305 (50.6)	7.9
	ECZTRA-2	Placebo	sc	201	114 (56.7)	Median: 30.0	Median: 25.0	Median: 29.6	101 (50.2)	8.1
		Tralokinumab	300 mg q2w sc	593	359 (60.5)	Median: 34.0	Median: 25.5	Median: 28.2	286 (48.2)	8
Wollenberg, JACI, 2019		Placebo + TCS	sc	51	22 (43.1)	39.4	NR	26.4	20 (39.2)	NR
		Tralokinumab + TCS	45 mg q2w sc	50	28 (58.0)	39.1	NR	24.8	18 (36.0)	NR
		Tralokinumab + TCS	150 mg q2w sc	51	26 (51.0)	37.1	NR	27.1	20 (39.2)	NR
		Tralokinumab + TCS	300 mg q2w sc	52	33 (63.5)	35.7	NR	27.3	23 (44.2)	NR
Kabashima, NEJM, 2020		Placebo + TCS	sc	72	48 (67)	Median: 40.5	28.9	22.7	27 (38)	NR
		Nemolizumab + TCS	60 mg q4w sc	143	93 (65)	Median: 39.0	30.3	24.2	61 (43)	NR
Bieber, NEJM, 2021		Placebo	PO	131	77 (58.8)	37.4	21.4	31	43 (32.8)	7.3
		Abrocitinib	100 mg qd PO	238	120 (50.4)	37.3	22.7	30.3	85 (35.7)	7.1
		Abrocitinib	200 mg qd PO	226	104 (46.0)	38.8	23.4	32.1	88 (38.9)	7.6
		Dupilumab	300 mg q2w sc	242	108 (44.6)	37.1	22.8	30.4	80 (33.1)	7.3
Eichenfield, JAMA Dermatol, 2021		Placebo	PO	96	44 (45.8)	Median: 14.0	10.5	29.2	39 (40.6)	7.2
		Abrocitinib	100 mg qd PO	95	45 (47.4)	Median: 16.0	9.8	31	38 (40.0)	7
		Abrocitinib	200 mg qd PO	94	56 (59.6)	Median: 15.0	9.7	29.5	33 (35.1)	6.8
Gooderham, JAMA Dermatol, 2019		Placebo	PO	56	21 (37.5)	42.6	Median: 25.6	25.4	21 (38.2)	7.6
		Abrocitinib	10 mg qd PO	49	21 (42.9)	44.3	Median: 30.2	28.1	22 (44.9)	7.6
		Abrocitinib	30 mg qd PO	51	22 (43.1)	37.6	Median: 20.5	22.1	22 (44.0)	7.6
		Abrocitinib	100 mg qd PO	56	31 (55.4)	41.1	Median: 23.8	26.7	26 (47.3)	7.4
		Abrocitinib	200 mg qd PO	55	28 (50.9)	38.7	Median: 19.6	24.6	20 (37.0)	6.9
Silverberg, JAMA Dermatol, 2020		Placebo	PO	78	47 (60.3)	33.4	21.7	28	26 (33.3)	6.7
		Abrocitinib	100 mg qd PO	158	94 (59.5)	37.4	21.1	28.4	51 (32.3)	7.1
		Abrocitinib	200 mg qd PO	155	88 (56.8)	33.5	20.5	29	49 (31.6)	7
Simpson, Lancet, 2020		Placebo	PO	77	49 (64)	31.5	22.5	28.7	31 (40)	7
		Abrocitinib	100 mg qd PO	156	90 (58)	32.6	24.9	31.3	64 (41)	6.9
		Abrocitinib	200 mg qd PO	154	82 (53)	33	22.7	30.6	63 (41)	7.1
Bieber, BJD, 2022		Placebo + TCS	PO	93	49 (53)	38.7	27.2	30.9	50 (54)	NR
		Baricitinib + TCS	1 mg qd PO	93	58 (62)	38.9	25.1	34.3	47 (51)	NR
		Baricitinib + TCS	2 mg qd PO	185	133 (72)	37.3	25.3	30.6	93 (51)	NR

(*continued on next page*)

Table 1 (*continued*)

B)

Study	Trial name	Treatment	Dosing, schedule, route	Total, n	Males, n (%)	Age, y (Mean)	Disease duration, y (Mean)	Basal EASI score (Mean)	IGA 4, n (%)	Basal pruritus NRS score (Mean)
		Baricitinib + TCS	4 mg qd PO	92	57 (62)	38.7	27.5	32.7	47 (51)	NR
Guttman, JAAD, 2019		Placebo + TCS	PO	49	24 (49)	Median: 35.0	Median: 17.7	Median: 22.1	NR	Median: 7
		Baricitinib + TCS	2 mg qd PO	37	22 (59)	Median: 42.0	Median: 26.4	Median: 22.1	NR	Median: 6
		Baricitinib + TCS	4 mg qd PO	38	22 (58)	Median: 32.5	Median: 22.0	Meidan: 19.5	NR	Median: 6.5
Reich, JAMA Dermatol, 2020		Placebo + TCS	PO	109	71 (65)	33.7	22	28.5	48 (44)	7.4
		Baricitinib + TCS	2 mg qd PO	109	70 (64)	33.8	24.6	29.3	50 (46)	7
		Baricitinib + TCS	4 mg qd PO	111	75 (68)	33.9	25.5	30.9	50 (45)	7
Simpson, JAAD, 2021		Placebo	PO	147	80 (54)	39	23	27	61 (41)	7
		Baricitinib	1 mg qd PO	147	75 (51)	40	24	27.7	62 (42)	7.2
		Baricitinib	2 mg qd PO	146	69 (47)	40	24	26.6	61 (42)	7.3
Simpson, BJD, 2020	BREEZE-AD-1	Placebo	PO	249	148 (59.4)	35	26	32	NR	6.7
		Baricitinib	1 mg qd PO	127	78 (61.4)	36	27	29	NR	6.1
		Baricitinib	2 mg qd PO	123	82 (66.7)	35	25	31	NR	6.4
		Baricitinib	4 mg qd PO	125	83 (66.4)	37	25	32	NR	6.5
	BREEZE-AD-2	Placebo	PO	244	154 (63.1)	35	25	33	NR	6.8
		Baricitinib	1 mg qd PO	125	80 (64.0)	33	24	33	NR	6.4
		Baricitinib	2 mg qd PO	123	65 (53)	36	24	35	NR	6.6
		Baricitinib	4 mg qd PO	123	82 (67)	34	23	33	NR	6.6
Torrelo, BJD, 2023		Placebo	PO	122	58 (47.5)	11.8	9.2	27.0	48 (39.3)	4.9
		Baricitinib	1 mg qd PO	121	59 (48.8)	12.4	9.8	26.6	45 (37.5)	5.7
		Baricitinib	2 mg qd PO	120	57 (47.5)	11.8	9.4	26.8	46 (38.3)	5.7
		Baricitinib	4 mg qd PO	120	67 (55.8)	11.9	9.0	25.3	45 (37.5)	5.7
Guttman, Lancet, 2021	Measure Up 1	Placebo	PO	281	144 (51)	34.3	21.3	28.8	125 (44.5)	7.3
		Upadacitinib	15 mg qd PO	281	157 (56)	34.1	20.5	30.6	127 (45.2)	7.2
		Upadacitinib	30 mg qd PO	285	155 (54)	33.6	20.4	29	131 (46.0)	7.3
	Measure Up 2	Placebo	PO	278	154 (55)	33.4	21.1	29.1	153 (55.0)	7.3
		Upadacitinib	15 mg qd PO	276	155 (56)	33.3	18.8	28.6	150 (54.3)	7.2
		Upadacitinib	30 mg qd PO	282	162 (57)	34.1	20.8	29.7	156 (55.3)	7.3
Katoh, JAAD Int, 2022		Placebo + TCS	PO	90	74 (82.2)	36.3	24.7	34.4	43 (47.8)	6.8
		Upadacitinib + TCS	15 mg qd PO	91	68 (74.7)	35.9	23	34.2	44 (48.4)	6.7
		Upadacitinib + TCS	30 mg qd PO	91	69 (75.8)	34.7	20.7	36.1	43 (47.3)	7
Reich, Lancet, 2021		Placebo + TCS	PO	304	178 (59)	34.3	24.3	30.3	162 (54)	7.1
		Upadacitinib + TCS	15 mg qd PO	300	179 (60)	32.5	22.9	29.2	157 (52)	7.1

(*continued on next page*)

Table 1 (*continued*)

B)

Study	Trial name	Treatment	Dosing, schedule, route	Total, n	Males, n (%)	Age, y (Mean)	Disease duration, y (Mean)	Basal EASI score (Mean)	IGA 4, n (%)	Basal pruritus NRS score (Mean)
		Upadacitinib + TCS	30 mg qd PO	297	190 (64)	35.5	23.1	29.7	157 (53)	7.4
Nakagawa, JAAD, 2021		Placebo	ext	68	31 (45.6)	8.3	6.2	NR	14 (20.6)	NR
		Delgocitinib	0.25 % bid ext	69	39 (56.5)	8.2	5.8	NR	16 (23.2)	NR
Nakagawa, JAAD, 2020		Placebo	ext	52	34 (65.4)	32.3	24.8	NR	16 (30.8)	NR
		Delgocitinib	0.5 % bid ext	106	64 (60.4)	31.4	24.7	NR	33 (31.1)	NR
Nakagawa, JACI, 2019		Placebo	ext	35	18 (51.4)	8.6	6.4	NR	2 (5.7)	NR
		Delgocitinib	0.25 % bid ext	34	22 (64.7)	8.4	6.1	NR	1 (2.9)	NR
		Delgocitinib	0.5 % bid ext	34	18 (52.9)	8.5	6.6	NR	1 (2.9)	NR
Kim, JACI, 2020		Placebo	ext	52	20 (38.5)	Meidan: 31.5	Median: 19.5	8.6	NR	6
		Ruxolitinib	0.15 % qd ext	51	25 (49.0)	Meidan: 38.0	Median: 22.3	8.2	NR	6.1
		Ruxolitinib	0.5 % qd ext	51	24 (47.1)	Meidan: 37.0	Median: 19.8	8.5	NR	6.2
		Ruxolitinib	1.5 % qd ext	52	21 (40.4)	Meidan: 37.0	Median: 20.2	8.4	NR	6.2
		Ruxolitinib	1.5 % bid ext	50	26 (52.0)	Meidan: 35.5	Median: 21.2	8.4	NR	5.9
Papp, JAAD, 2021	TRuE-AD1	Placebo	ext	126	47 (37.3)	Meidan: 31.5	17.9	7.4	NR	5.1
		Ruxolitinib	0.75 % bid ext	252	98 (38.9)	Meidan: 34.0	14.1	8.2	NR	5.1
		Ruxolitinib	1.5 % bid ext	253	95 (37.5)	Meidan: 30.0	16	7.9	NR	5.2
	TRuE-AD2	Placebo	ext	124	44 (35.5)	Meidan: 37.5	15.9	8.2	NR	5.1
		Ruxolitinib	0.75 % bid ext	248	98 (39.5)	Meidan: 33.0	15.9	8.1	NR	5.2
		Ruxolitinib	1.5 % bid ext	246	96 (39.0)	Meidan: 32.0	16.6	7.8	NR	4.9

Abbreviations: bid: twice a day; EASI: Eczema Area and Severity Index; ext: usus externus; IGA: Investigator Global Assessment; NRS: Numerical Rating Scale; NR: not reported; PO: Per Oral; q4w: every 4 weeks; q2w: every 2 weeks; qw: every week; qd: every day; sc: subcutaneous; SD: single dose; TCS: topical corticosteroids.

and antiviral response, respectively [16]. The first-generation JAK1 and JAK2 inhibitors include baricitinib, the first JAK inhibitor approved in Europe in 2020 for treating moderate to severe AD in adults, and ruxolitinib, 1.5 % cream of which was approved by the US FDA in 2021 for short-term, non-continuous chronic treatment of mild to moderate AD in patients aged >12 years when other topical prescription therapies fail to control the disease or are not advisable. Second-generation agents have greater selectivity for JAK1, such as abrocitinib and upadacitinib, which were recently approved in the US and China for treating moderate to severe AD refractory to other systemic treatments [16,17]. In addition, delgocitinib, which is suitable for topical application, is being investigated and has been approved in Japan for the treatment of moderate to severe 16 CE Most JAK inhibitors, both oral and topical, have demonstrated satisfactory efficacy in phase II and III clinical trials [18–32].

Considering that there are no current available direct comparisons of the abovementioned drugs, we conducted this meta-analysis to compare the efficacy and safety of biologic agents and JAK inhibitors in the treatment of AD to provide suggestions for the use of drugs in the clinical treatment of AD. We also evaluated the efficacy and safety of biologics or JAK inhibitors with background topical corticosteroid in the treatment of AD.

2. Methods

2.1. Literature search

A systematic literature search was conducted in PubMed, Web of Science, ScienceDirect, and the Cochrane Library from inception up to October 25, 2023. Based on existing reviews [33,34] and current clinical experience for novel therapeutic approaches of AD, the

following search terms were used: “atopic dermatitis” or “atopic eczema” and “dupilumab” or “lebrikizumab” or “tralokinumab” or “nemolizumab” or “tofacitinib” or “baricitinib” or “abrocitinib” or “upadacitinib” or “ruxolitinib” or “delgocitinib”. All of the drugs searched above are monoclonal antibodies or small molecules which are commonly tested so far. The detailed search strategies are presented in eTable 1 in the Supplement. Regarding language restriction, only studies published in English were included.

The inclusion criteria were: (1) randomized double-blind placebo-controlled clinical trials in children and adults with a diagnosis of AD who had not previously undergone treatment involving biologics or JAK inhibitors, without age or gender restrictions, and (2) reporting at least one of the primary outcomes of interest at 12/16 weeks for systemic therapy or at 4 weeks for topical therapy. The titles and abstracts were reviewed and the full texts were obtained and rechecked to exclude the articles that did not meet the inclusion criteria by two independent screeners (Qianyu Chen and Lian Cui), and any citation approved by either of the two individuals can be included in the selection. Any discrepancies were also solved by discussion between the 2 screeners. Based on the inclusion criteria, trials that used tofacitinib were excluded as tofacitinib was rarely studied and the outcomes of interest were not clearly reported [35, 36]. Although patient age was not restricted, younger pediatric patients were systematically administered weight-based medications such as dupilumab; however, different doses were combined for statistical analysis to compare with the control group, and therefore results for which specific doses could not be distinguished were not included. The studies were distributed to the co-authors for detailed assessment and data extraction using standardized data extraction tools. Ethical approval was not required as this systematic review and meta-analysis does not involve direct human participation.

2.2. Data extraction

Data retrieved by two co-authors (Qianyu Chen and Lian Cui) from the studies included the first author’s name, year of publication, journal title, participants’ demographics and baseline characteristics, intervention and control conditions, outcomes and times of outcome measurement, and information necessary to assess the risk of bias. The Cochrane risk of bias tool [37] was used to critically appraise the included studies, which were independently evaluated by two of the previously mentioned authors. Partially missing efficacy data were obtained by referring to the ClinicalTrials.gov website (https://clinicaltrials.gov/) and any inconsistencies were resolved through discussion between the two co-authors or by inviting the judgment of a third co-author (Yifan Hu).

2.3. Comparators and outcomes

The comparators for the base case analysis included the aforementioned drugs used as monotherapy or in combination with first-line topical agents (corticosteroids and calcineurin inhibitors).

In this analysis, the primary outcomes of interest were: (1) $\geq$75 % and $\geq$90 % improvement in the Eczema Area and Severity Index score from baseline (EASI 75 and EASI 90, respectively); (2) Investigator Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) with $\geq$2 steps improvement from baseline or achievement of an IGA response as defined in the studies (collectively referred to as “IGA 0/1”). Secondary outcomes were the achievement of a pruritus Numerical Rating Scale (NRS) response with $\geq$4-point improvement from baseline (collectively referred to as “pruritus NRS4”) and the occurrence of adverse events (AE) (including treatment-emergent AE) and serious AE (SAE) (including serious treatment-emergent AE).

As one of the only AD-specific physician outcome measures, the EASI assesses the extent and severity of disease and is sufficiently validated to be used in clinical trials as well as in the clinic. The IGA is often used to assess overall severity because it is easy to use in the clinic and is considered a gold standard clinical assessment that is often used to validate other outcome measures [38]. The global Harmonizing Outcome Measures for Eczema (HOME) supported itch intensity as a core symptom of AD, and the patient-reported pruritus NRS can accurately reflect the presence and intensity of itch. Therefore, EASI, IGA and pruritus NRS were selected to evaluate the therapeutic effects of the drugs.

AE was defined as the manifestation or worsening of any adverse sign, symptom, or medical condition occurring after the signing of the informed consent form, even if the event was unrelated to the study treatments. SAE was defined as any event that resulted in a fatal or life-threatening situation, persistent or significant disability or incapacity, congenital anomaly or birth defect in the participant’s children, and hospitalization or prolongation of existing hospitalization.

2.4. Statistical analysis

Datawere analyzed using Review Manager 5.4 (The Cochrane Collaboration, 2020) and the outcomes were presented as the risk ratio (RR) with 95 % confidence interval (CI). Data without significant heterogeneity were analyzed using the fixed model (Mantel–Haenszel) while data with significant heterogeneity were analyzed using the random-effects model (DerSimonian and Laird). The I^2 statistic was calculated to quantify the proportion of the total variation due to heterogeneity, where $I^2 > 50$ % was considered to indicate significant heterogeneity among the studies. The fixed-effects model was used when the effects were assumed to be homogeneous, and the random-effects model was used when there was significant heterogeneity. The combined statistical results were evaluated using the *U* test (z-test). For each comparison model, a funnel plot was carried out to examine the publishing bias. The efficacy of the biologic therapies was analyzed using the EASI 75, EASI 90, IGA 0/1, and pruritus NRS4, while the safety of the biologics was evaluated according to the number of patients with $\geq$1 AE and at least 1 SAE. Considering that TCS in combination therapy may confound the efficacy and safety outcomes of biologics and JAK inhibitors, the studies included in this meta-analysis were divided into only placebo-controlled trials (monotherapy) and trials with placebo + TCS as the control groups (combination therapy) for further analysis.

3. Results

3.1. Search results and study characteristics

A total of 5028 non-duplicate records were retrieved from the database search; 4812 records were excluded after their titles and abstracts were screened and 172 records were excluded during the full-text article review. Thirty-seven articles screened for eligibility met our inclusion criteria and were included in this meta-analysis [7,10–13,18–32,38–54]. Fig. 1 illustrates the flowchart for screening in the study along with a comparison of the screeners' work using Cohen's kappa metric.

The selected studies were all randomized double-blind placebo-controlled clinical trials published between 2014 and 2023 and involved 18172 participants. Five articles treated patients with topical ointments (two JAK inhibitor creams) [20–23,28], whereas patients in the remaining studies were all treated with systemic therapies, such as oral or subcutaneous injections (biologic agents targeting IL-4, IL-13, or IL-31, n = 18; oral JAK inhibitors, n = 14). 14 studies with 4895 participants used placebo + TCS as the control group [10–13,19,25,29,38,39,41,48–51], and the remaining trials used placebo only as a control. All studies included in this meta-analysis had similar baseline characteristics and inclusion criteria. Table 1 summarizes the main characteristics of the trials included in this analysis, and Table 2 outlines the range of application and targets for all the included drugs.

3.2. Risk of bias assessment and heterogeneity investigation

The risk of bias assessment showed that the quality of the studies was moderate-high (Fig. 2). eFig. 1 in the Supplement presents a detailed assessment of the risk of bias. One or more treatment groups of two included studies did not present specific data on all outcomes, including some prespecified outcomes, thus introducing a risk of attrition bias [12,28].

The analysis of heterogeneity between the different studies showed that there was significant heterogeneity in the efficacy outcomes, as we compared different doses of different drugs in a group therefore this result was inevitable and a random effects model was employed. Conversely, the overwhelming majority of safety outcomes exhibited significant homogeneity, with I^2 values of 0 or close to 0, and were analyzed using a fixed-effects model.

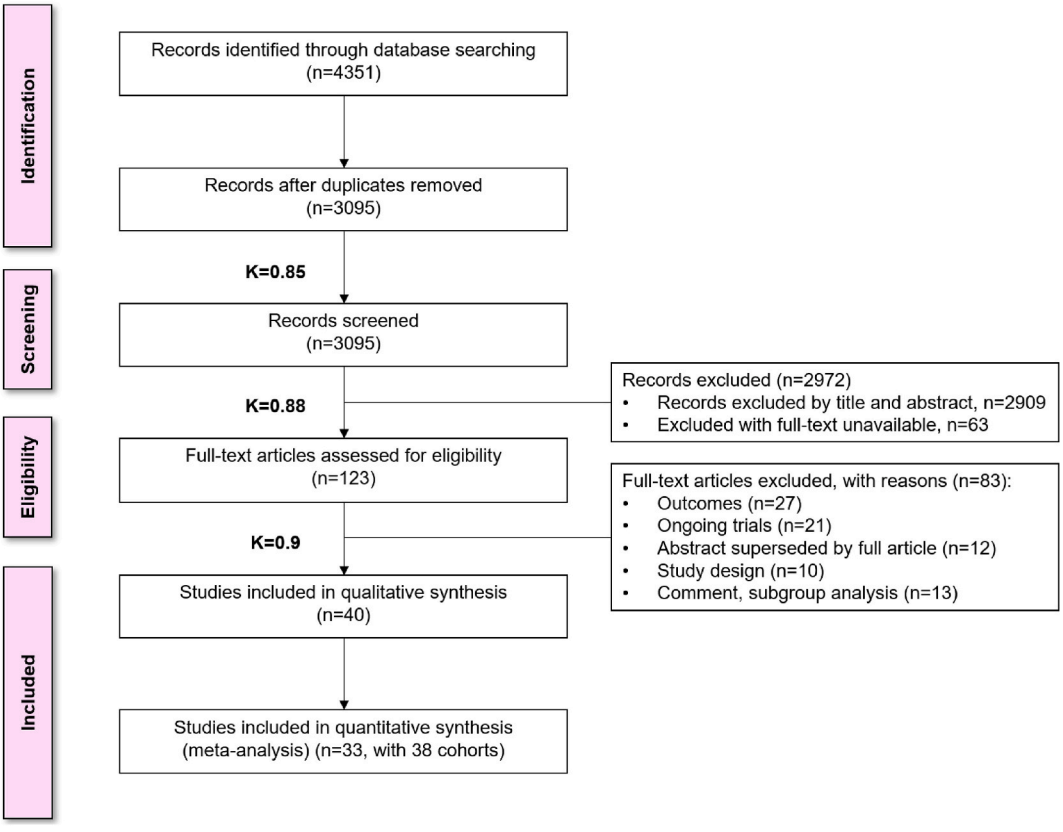

Fig. 1. Flowchart of the Identification, inclusion, and Exclusion of studies.

Table 2
Applications and targets of included drugs.

Range of application	Category	Drug
Systemic	Anti-IL-4/IL-13	Dupilumab
	Anti-IL-13	Lebrikizumab
		Tralokinumab
	Anti-IL-31	Nemolizumab
	Oral JAKi	Abrocitinib
		Baricitinib
		Upadacitinib
Topical	Topical JAKi	Delgocitinib
		Ruxolitinib

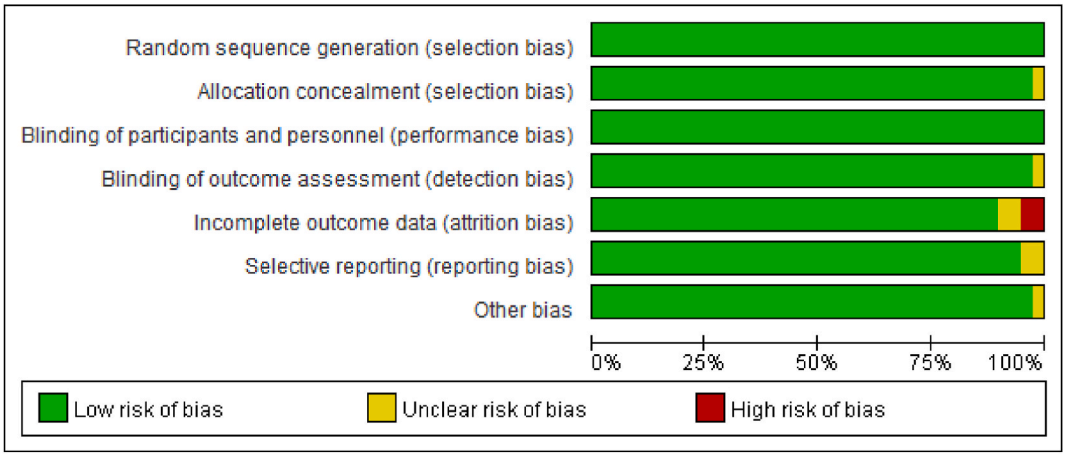

Fig. 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

4. Outcomes

4.1. Monotherapy

In EASI 75, the systemic drug upadacitinib [30 mg once daily (qd)] (RR 5.14, 95 % CI 4.20–6.31, $P < 0.00001$) had the highest probability of response among the systemic drugs as compared to placebo, followed by dupilumab [200 mg every 2 weeks (q2w)] (RR 4.86, 95 % CI 2.34–10.10, $P < 0.0001$), dupilumab [200 mg every week (qw)] (RR 4.50, 95 % CI 1.75–11.55, $P = 0.002$), tralokinumab [150 mg q2w] (RR 4.48, 95 % CI 1.96–10.32, $P = 0.0004$), and dupilumab [300 mg every 4 weeks (q4w)] (RR 4.45, 95 % CI 2.62–7.56, $P < 0.00001$). Among the topical creams, ruxolitinib [1.5 % twice daily (bid)] (RR 4.14, 95 % CI 3.06–5.41, $P < 0.00001$) performed the best.

The EASI 90 yielded highly similar results. Among the systemic medicine treatment groups, the highest numerical efficacy was observed for dupilumab 200 mg qw (RR 19.00, 95 % CI 1.16–310.94, $P = 0.04$), dupilumab 200 mg q2w (RR 9.50, 95 % CI 2.31–39.03, $P = 0.002$), upadacitinib 30 mg qd (RR 9.13, 95 % CI 6.67–12.50, $P < 0.00001$), and dupilumab 300 mg q4w (RR 8.50, 95 % CI 3.10–23.31, $P < 0.0001$). Among the seven topical interventions, ruxolitinib 0.75 % bid (RR 8.59, 95 % CI 4.28–17.23, $P < 0.00001$) and ruxolitinib 1.5 % bid (RR 7.91, 95 % CI 3.54–17.69, $P < 0.00001$) showed better efficacy.

A higher percentage of patients achieved a higher IGA response with systemic dupilumab 200 mg qw (RR 21.00, 95 % CI 1.29–341.31, $P = 0.03$), dupilumab 200 mg q2w (RR 17.00, 95 % CI 2.33–123.78, $P = 0.005$), dupilumab 300 mg q4w (RR 9.16, 95 % CI 2.84–29.54, $P = 0.0002$), upadacitinib 30 mg qd (RR 8.63, 95 % CI 6.27–11.88, $P < 0.00001$), dupilumab 100 mg q4w (RR 7.51, 95 % CI 0.97–58.28, $P = 0.05$), and topical delgocitinib 0.25 % bid (RR 8.02, 95 % CI 1.02–62.93, $P = 0.05$). It is worth mentioning that some of the medications did not reach statistical significance with RR CI values that were close to or included 1.

In the systemic treatment groups, the likelihood of achieving a pruritus NRS4 response was highest in patients treated with tralokinumab [150 mg q2w] (RR 6.95, 95 % CI 2.15–22.41, $P = 0.001$), followed by those on upadacitinib 30 mg qd (RR 5.73, 95 % CI 4.44–7.39, $P < 0.00001$), dupilumab 300 mg q4w (RR 5.57, 95 % CI 2.00–15.46, $P = 0.001$), upadacitinib 15 mg qd (RR 4.51, 95 % CI 3.47–5.85, $P < 0.00001$), dupilumab 300 mg qw (RR 3.65, 95 % CI 2.72–4.90, $P < 0.00001$), and tralokinumab [300 mg q2w] (RR 3.60, 95 % CI 1.15–11.31, $P = 0.003$). In the topical cream treatment groups, patients treated with ruxolitinib 1.5 % bid (RR 4.08, 95 % CI 2.86–5.81, $P < 0.00001$) were more likely to achieve a pruritus NRS4 response.

Overall, most of the studies reported a significant change in efficacy between the intervention and control groups. Among them, systemic dupilumab and upadacitinib and topical ruxolitinib performed particularly well in the efficacy outcomes evaluated. The

optimal doses of the three drugs were dupilumab 200 mg qw or q2w, upadacitinib 30 mg qd, and ruxolitinib 1.5 % bid. Fig. 3A and eFig. 2 in the Supplement provide more detailed data on the efficacy of monotherapy.

The risk of experiencing an AE or SAE in most of the treatment groups compared to the control groups was not statistically significantly different, and the RR values were close to 1. Therefore, the included drugs demonstrated good safety. Notably, in the systemic treatment groups, abrocitinib 200 mg qd (RR 1.23, 95 % CI 1.11–1.37, $P = 0.0002$) had the highest risk for presenting ≥1 AE, followed by upadacitinib 30 mg qd (RR 1.21, 95 % CI 1.10–1.33, $P < 0.0001$). Dupilumab 200 mg qw (RR 7.00, 95 % CI 0.38–129.34, $P = 0.19$) and dupilumab 100 mg q4w (RR 1.17, 95 % CI 0.33–4.17, $P = 0.81$) presented relatively higher risk of ≥1 SAE while lebrilizumab [250 mg q2w] (RR 0.17, 95 % CI 0.01–4.15, $P = 0.28$) and dupilumab 200 mg q2w (RR 0.25, 95 % CI 0.03–2.17, $P = 0.21$) presented a lower risk. Regarding the two topical medications, various ruxolitinib interventions typically exhibited better safety than delgocitinib, especially ruxolitinib 0.5 % qd (RR 0.66, 95 % CI 0.34–1.27, $P = 0.21$), which presented the lowest risk of AE occurrence, followed by ruxolitinib 1.5 % bid (RR 0.79, 95 % CI 0.64–0.98, $P = 0.0002$). Fig. 3B presents the pooled safety data and eFig. 3 in the Supplement contains more details.

4.2. Combination therapy

The TCS combination therapy trials included 16 interventions with six systemic medicines (dupilumab 300 mg q4w, 300 mg q2w, and 300 mg qw; lebrikizumab 125 mg single dose [SD], 250 mg SD, 125 mg q4w, 250 mg q2w; tralokinumab 45 mg q2w, 150 mg q2w, 300 mg q2w; nemolizumab 60 mg q4w; baricitinib 1 mg qd, 2 mg qd, 4 mg qd; upadacitinib 15 mg qd and 30 mg qd). Placebo + TCS was used as the control group.

Patients treated with a combination of these drugs and TCS were more likely to achieve EASI 75, EASI 90, IGA 0/1, and pruritus NRS4 than those treated with TCS alone (Fig. 4A; eFig. 4 in the Supplement). The best EASI 75 and EASI 90 responses were achieved with upadacitinib 30 mg qd (RR 3.18, 95 % CI 2.44–4.14, $P < 0.00001$) and dupilumab 300 mg q4w (RR 5.71, 95 % CI 2.94–11.09, $P < 0.00001$), respectively. The largest difference in IGA 0/1 was observed for upadacitinib 30 mg qd (RR 5.62, 95 % CI 4.12–7.66, $P < 0.00001$). Dupilumab 300 mg q4w had the highest likehood of pruritus NRS4 response (RR 4.13, 95 % CI 2.49–6.85, $P < 0.00001$). Overall, dupilumab, tralokinumab, baricitinib, and upadacitinib with background TCS all demonstrated good efficacy as compared with TCS monotherapy, especially dupilumab and upadacitinib.

The combination therapy groups (Fig. 4B; eFig. 5 in the Supplement) demonstrated no statistically significant difference for AE as compared with the placebo + TCS groups, except for baricitinib 4 mg qd (RR 1.39, 95 % CI 1.22–1.58, $P = 0.0005$) and baricitinib 2 mg qd (RR 1.23, 95 % CI 1.02–1.49, $P = 0.03$). Numerically lower odds of SAE were observed with tralokinumab 300 mg q2w (RR 0.24, 95

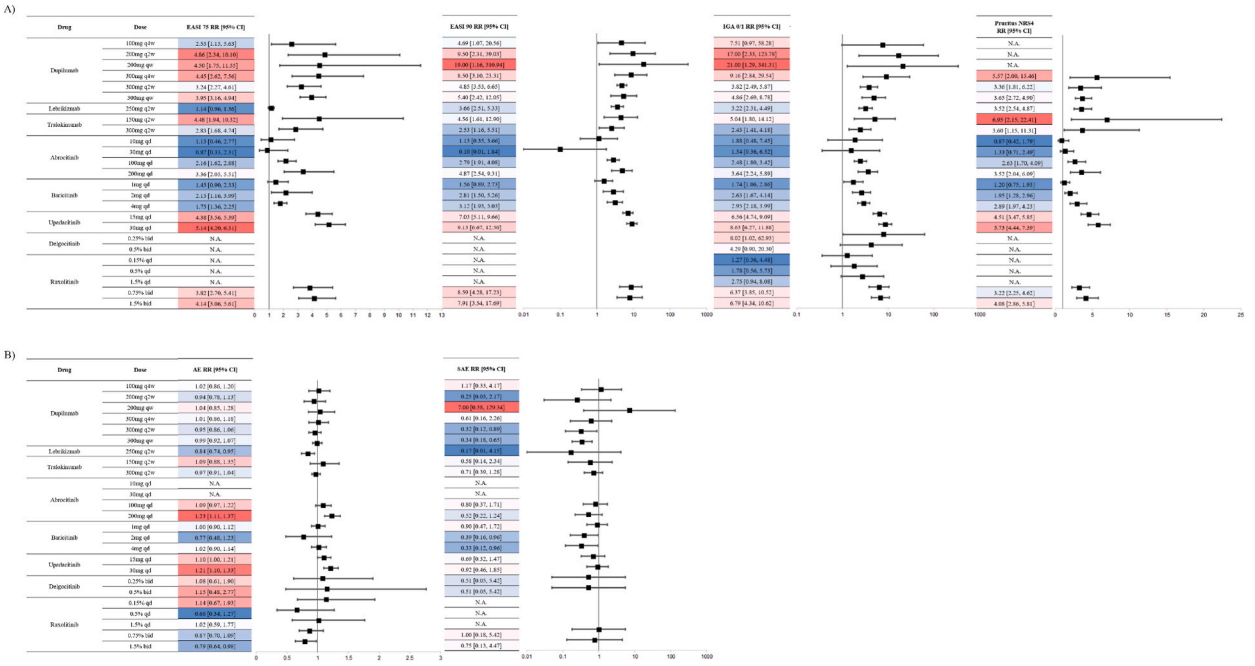

Fig. 3. Forest plots of meta-analysis results of monotherapy (pooled risk ratio versus placebo). (A) Pooled efficacy data. (B) Pooled safety data. AE: adverse event(s); bid: twice a day; CI: confidence interval; EASI: Eczema Area and Severity Index; IGA: Investigator Global Assessment; JAKi: Janus kinase inhibitor(s); N.A.: not applicable or not available; NRS: Numerical Rating Scale; q4w: every 4 weeks; q2w: every 2 weeks; qw: every week; qd: every day; RR: risk ratio; SAE: severe adverse event(s) Considering the different severity of AD in patients, the outcomes of systemic and topical medicaitons were ranked separately. Red indicates high rank and blue indicates low rank. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

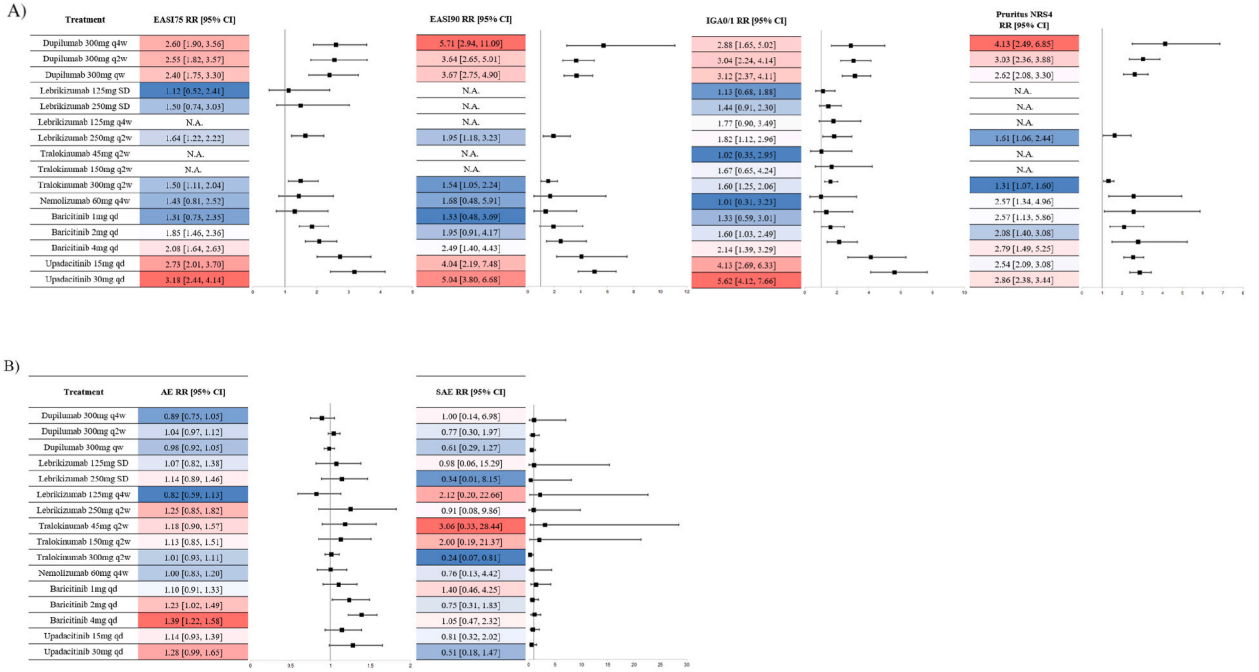

Fig. 4. Forest plots of meta-analysis results of monotherapy (pooled risk ratio versus placebo plus TCS). (A) Pooled efficacy data. (B) Pooled safety data. AE: severe adverse event(s); bid: twice a day; CI: confidence interval; EASI: Eczema Area and Severity Index; IGA: Investigator Global Assessment; JAKi: Janus kinase inhibitor(s); N.A.: not applicable or not available; NRS: Numerical Rating Scale; q4w: every 4 weeks; q2w: every 2 weeks; qw: every week; qd: every day; RR: risk ratio; SAE: severe adverse event(s); SD: single dose. Red indicates high rank and blue indicates low rank. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

% CI 0.07–0.81, $P = 0.02$), lebrikizumab 250 mg SD (RR 0.34, 95 % CI 0.01–8.15, $P = 0.51$), upadacitinib 30 mg qd (RR 0.51, 95 % CI 0.18–1.47, $P = 0.21$), and dupilumab 300 mg qw (RR 0.61, 95 % CI 0.29–1.27, $P = 0.19$). Baricitinib appeared to have reduced safety and other doses yielded similar odds to that of the control group.

5. Discussion

Our analysis was based on the data from 37 articles with a total of 18172 participants. In this review, we compared the efficacy and safety of 4 types of biologic drugs and 5 types of JAK inhibitors in trials that were placebo-controlled or placebo + TCS controlled for the treatment of AD at any severity level, and included common AD treatment drugs that were proven effective in clinical trials.

Based on the findings of the above meta-analysis, it appears that dubilumab and udatinib seem to be highly effective in treating AD, followed by ruxolitinib, as reflected by the EASI, IGA, and Pruritus NRS scores. As a Th2-predominant inflammation, AD is driven by epidermal barrier dysfunction, pruritus, the skin microbiome, and abnormal immune activation [55]. Several cytokines, such as interferon gamma (IFN-γ), IL-4, IL-13, IL-22, and IL-31 were associated with AD signaling pathway transduction. Among them, IL-4 and IL-13 are typical type 2 cytokines mediating Th2 inflammation [55,56]. Moreover, the JAK–STAT pathway is prominent in various signal transduction pathways that mediate the inflammatory processes. These cytokines can be involved in AD signaling through the JAK transduction pathway. Numerous clinical trials have confirmed that inhibition of these key cytokines and pathways successfully reduces the symptoms and severity of AD. Dupilumab is a fully human IgG4 monoclonal antibody directed against the IL-4Rα subunit of IL-4 and IL-13 receptors to block both the IL-4 and IL-13 signaling pathways [55], while upadacitinib and ruxolitinib are highly selective JAK inhibitors targeting only JAK1 or both JAK1 and JAK2 respectively, which are responsible for itching and proliferation of the hematopoietic stem cell lineage, respectively [57]. This may explain why dupilumab, upadacitinib and ruxolitinib all appeared to show superior efficacy in multiple clinical trials in AD patients.

It is worth mentioning that the patients treated with dupilumab, upadacitinib, or ruxolitinib had different AD severity and different treatment durations. In the included trials, dupilumab and upadacitinib were commonly used to treat patients with moderate to severe AD for 12 or 16 weeks, whereas ruxolitinib was used for patients with mild to moderate AD for only 4 weeks. Our research indicates that the optimal treatment dose of dupilumab, upadacitinib, and ruxolitinib all seemed to yield good efficacy outcomes with little difference in the RR, but the treatment duration of the ruxolitinib group was four times shorter than that of the dupilumab and upadacitinib groups. Therefore, it appears that 1.5 % ruxolitinib is a better option for patients with mild to moderate AD and we expect that ruxolitinib may also demonstrate good efficacy and safety for treating moderate to severe AD, which requires further exploration. Although both dupilumab and upadacitinib have shown favorable efficacy, we recommend the former for patients with moderate-to-severe AD because dupilumab appears to have a better safety profile and upadacitinib possibly has a slightly higher risk of ≥1 AE than

placebo based on current results. Furthermore, dupilumab requires less frequent administration and may be preferred by more patients.

In addition to the effects of various AD treatment drugs in placebo-controlled trials, this meta-analysis also evaluated the efficacy and safety of their combined application with TCS in TCS treatment-controlled studies. Our findings suggest that baricitinib, dupilumab, trastuzumab, and udatinib (+TCS) may show better efficacy than TCS monotherapy, especially dupilumab and udatinib, and most of them are not associated with an increased risk of AEs, and the probability of ≥1 SAE appears to be lower. This suggests that combination therapy using systemic drugs, such as dupilumab, and topical anti-inflammatory drugs, such as TCS, appears to be the preferred option for the treatment of AD patients, especially those with an inadequate response to first-line topical therapy, including TCS, to achieve better efficacy without the additional safety risks associated with the addition of a systemic drug. Moreover, many studies have shown that topical JAK inhibitors yield rapid and sustained antipruritic and anti-inflammatory effects without some common AE of long-term TCS use, such as striae, telangiectasia, skin bleaching, and skin atrophy [57]. Replacing corticosteroids with topical JAK inhibitors has the potential to be a long-term topical treatment option for AD. That is, combining systemic drugs, such as dupilumab, and topical JAK inhibitors, such as ruxolitinib cream, might be a good choice when treating AD. Unfortunately, very little attention has been paid to this combination therapy. Therefore, it would be of great interest to investigate the effects of combined applications of various drugs for the treatment of AD in future studies with in-depth understanding of these drugs.

At the same time, we also noted that the included studies covered a wide range of age groups, with 6 articles involving children or adolescents, and the involved medications such as dupilumab [41,43], tralokinumab [54], abrocitinib [27], baritinib [53], and delgocitinib [23]. In terms of safety, there shows little difference between the adolescent and adult groups due to the high safety of the drugs. The efficacy of these drugs also did not seem to differ much between the adolescent and adult groups and also because of the small number of articles, it did not significantly affect the overall results of the analyses, based on which we did not further refine the age breakdown for subgroup analyses in the results section.

Our meta-analysis review covered a significant patient cohort in a wide range of ages diagnosed with atopic dermatitis of all severities, whereas previous meta-analyses have concentrated on adult or adolescent patients, mainly in moderate to severe cases of AD. Besides, we included in the current several novel and promising kinds of drugs for the treatment of AD including biological agents and JAK inhibitors administered through both systemic and topical routes, to compare their efficacy and safety at the same time. Meanwhile we analyzed the efficacy and safety of the combination therapy of systemic administration and topical corticosteroid. We have incorporated a greater number of comparative effectiveness data outcomes than the majority of previous reviews. Nevertheless, our study has the following limitations: First, some interventions were only mentioned a small number of articles, which led to the results being biased as there were insufficient different data sources. Therefore, our review has publication bias. This may also be the reason why our analysis showed that the more effective dose for dupilumab was 200 mg qw or q2w, a result similar to the 2020 review by Drucker AM et al. [34], but different from the actual clinical dose for dupilumab 300 mg q2w. Moreover, most of the trials were placebo-controlled rather than direct comparisons, which limited our power to estimate heterogeneity and statistical incoherence. Furthermore, the meta-analysis was limited to the primary endpoints and the time points did not meet the optimal therapeutic efficacy of the clinical guidelines, which meant that the maximum clinical benefit could not be achieved. In addition, there was a time difference between the assessment time point and drug withdrawal. Because these drugs were designed for long-term use, the practical applicability of these findings may be limited. Finally, the drugs and their doses in most of the included trials did not take into account patients' body weight and racial differences, which means that the results are not consistent with actual clinical use.

6. Conclusions

Overall, dupilumab, upadacitinib, and ruxolitinib were the most effective treatments for AD in terms of the EASI 75, EASI 90, IGA 0/1, and pruritus NRS4. The specific doses were dupilumab 200 mg qw or q2w, upadacitinib 30 mg qd, and ruxolitinib 1.5 % bid. Almost all of the drugs analyzed in this study had a good safety profile, especially dupilumab 200 mg q2w and 300 mg qw or q2w. Compared with TCS alone, combination therapy of systemic medications such as baricitinib, dupilumab, tralokinumab, and upadacitinib with background TCS were more effective. However, baricitinib (+TCS) demonstrated reduced safety. Therefore, ruxolitinib 1.5 % bid is recommended for patients with mild to moderate AD. As upadacitinib 30 mg qd seems to increase the risk of presenting AE, we recommend dupilumab 200 mg q2w for treating moderate to severe AD. In treating moderate to severe AD, the effect of TCS treatment can be significantly improved by using dupilumab + TCS. In addition, we suggest exploring the potential of using topical JAK inhibitors, including ruxolitinib cream, as a viable substitute for TCS in conjunction with systemic medications. This presents a promising avenue for future research. These findings might provide a useful basis for preparing a new generation of treatment guidelines for AD.

Data availability statement

All data are already provided in the manuscript. For further if any may put a request to the corresponding author.

CRediT authorship contribution statement

Qianyu Chen: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Lian Cui:** Data curation, Investigation, Supervision, Writing – review & editing. **Yifan Hu:** Supervision, Writing – review & editing, Funding acquisition. **Zeyu Chen:** Conceptualization, Formal analysis, Methodology. **Yunlu Gao:** Funding acquisition, Methodology, Resources,

Supervision, Writing – review & editing. **Yuling Shi:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e22014.

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