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Review article

Efficacy and safety of abrocitinib and upadacitinib versus dupilumab in adults with moderate-to-severe atopic dermatitis: A systematic review and meta-analysis

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ABSTRACT

Background: The sparsity of head-to-head trials for medications used as in atopic dermatitis (AD) treatment makes therapy options difficult.
Objective: To better compare the efficacy and safety of abrocitinib and upadacitinib with dupilumab in patients with moderate-to-severe AD.
Methods: We systematically searched MEDLINE, EMBASE, and the Cochrane Library database for head-to-head trials.
Results: Three studies with 2256 patients were included. The analysis revealed that improvement of EASI-75 was rapidly registered with abrocitinib/upadacitinib as compared to the dupilumab, even as early as week 2 of treatment. The proportions of patients who reached the endpoint of EASI-75 at week 12 and end of therapy were also higher in the abrocitinib/upadacitinib group. Significant improvement in EASI-90 scores was demonstrated with abrocitinib/upadacitinib at week 2 and at all subsequent time points. The administration of abrocitinib/upadacitinib provided a faster onset of IGA response at week 2. The differences in IGA response remained significant at week 12 and end of therapy. Compared with dupilumab, a larger proportion of patients treated with abrocitinib/upadacitinib achieved early itch relief at 2 weeks. Better results were found later during treatment, in between the 12 weeks to the end of study in abrocitinib/upadacitinib group. The only observed significant result of adverse events were severe adverse events between the abrocitinib/upadacitinib group ($n = 40$) and the dupilumab group ($n = 24$) ($p = 0.043$). TEAEs of any causality that led to treatment discontinuation and serious adverse events have not shown special risks in the patients treated with abrocitinib/upadacitinib.
Conclusions: This study demonstrated that *anti*-JAK therapy, particularly abrocitinib and upadacitinib, exhibited superiority over dupilumab in achieving fast relief of disease signs with an acceptable safety profile in patients with moderate-to-severe atopic dermatitis.

1. Introduction

Atopic dermatitis (AD) is a chronic, inflammatory skin disease associated with itch, pain, anxiety, depression, and increased health care utilization [1,2]. Most patients suffer from physical symptoms and mental trauma. AD is a life-long disorder which requires

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long-term treatment, and reliable evidence on the discovery of benefit-to-harm ratio of drugs is needed to make better clinical choices [3]. Therapeutic goals include achieving fast disease control and maintaining remission [4,5]. To date, topical therapies have been deemed the mainstay in AD management [6]. Systemic therapies are employed when topical treatments are not effective enough. These therapies encompass phototherapy, immunosuppressant therapies, Janus kinase (JAK) inhibitors and biological therapies [7,8]. Research in recent years in AD has mainly focus on systemic therapies and obtained encouraging results in rapid improvement of disease.

Among the systemic treatments that can be prescribed today, two types of novel agents are attractive and have been approved in many countries to alleviate the symptoms of AD [9–11]: JAK inhibitors, such as baricitinib (*anti*-JAK1/2), abrocitinib (*anti*-JAK1), and upadacitinib (*anti*-JAK1), and anti-interleukin (IL) signalling antibody, such as dupilumab (*anti*-IL-4Rα), tralokinumab (*anti*-IL-13), and nemolizumab (*anti*-IL-31 Rα). Evidences have demonstrated that abrocitinib, a small molecule JAK inhibitor, has yielded beneficial responses in adolescents and adults who received abrocitinib once a day in doses of 200 mg or 100 mg in inducing early reductions of itch and symptom [12–14]. Dupilumab, a humanized monoclonal antibody against the IL-4 receptor α, provided superior efficacy and safety in patients with AD [15–17]. There is a dilemma in treatment options. A physician's choice to start one or the other may be affected by the efficacy and safety profile of the drugs. Head-to-head studies of systemic therapies should help physicians further understand the potential role of these agents in clinical practice. However, the sparsity of head-to-head trials for these medications makes direct comparisons of efficacy and safety difficult.

Therefore, for the first time, we incorporated the results of three recent head-to-head studies for the treatment of patients with moderate-to-severe AD to better assess the efficacy and safety of abrocitinib and upadacitinib versus dupilumab.

2. Methods

2.1. Search strategy

A comprehensive literature search was retrieved in the following databases: Medline (from 1950 to September 2022), Embase (from 1950 to September 2022), Cochrane Library (from 1950 to September 2022) and Clinical Trials.gov with related keywords of "Janus kinase inhibitor", "Janus kinase 1 inhibitor", "abrocitinib", "upadacitinib", "IL-4 receptor-α antibody", "dupilumab", "atopic dermatitis", "randomized controlled trial", "RCT" and "randomized study". Articles published in English were searched and included. This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [18].

2.2. Study selection, inclusion, and exclusion criteria

We included all RCTs that enrolled patients with moderate-to-severe AD and investigated therapeutic effects of abrocitinib or upadacitinib compared to dupilumab. The inclusion criteria of studies were defined as follows: (1) abrocitinib or upadacitinib compared to dupilumab; (2) patients with moderate-to-severe atopic dermatitis; (3) at least one reported outcome or more; (4) RCT. The exclusion criteria were the following: (1) animal studies, reviews or experimental studies; (2) case reports, observational studies or case-control studies; (3) non-English studies; (4) duplicate publication.

2.3. Data extraction and quality of evidence

Firstly, two authors independently screened titles, abstracts, and full texts. Subsequently, they extracted data related to the following: (1) patient characteristics including: age, disease duration, disease severity, eczema area and severity index (EASI) score, the percent of body surface area affected, peak pruritus numerical rating scale (*P*P-NRS) score, dermatology life quality index (DLQI) score, and investigator's global assessment (IGA) grade numer; (2) study design including: study period and country, design and phase, total number of participants and inclusion criteria; (3) treatment details including: dose, route, and regimen; (4) short-term (2 weeks) and long-term ($\geq$16 weeks) time points efficacy outcome measures including: EASI 75 and 90 responses, IGA response, *P*P-NRS score; (5) safety outcomes including: TEAEs of any causality that led to treatment discontinuation, serious and severe adverse events, death, nausea, headache, dermatitis, atopic, nasopharyngitis, upper respiratory tract infection. A third reviewer checked and confirmed the accuracy of the above data. We assessed the quality of the included trials using the Cochrane's risk of bias tool [19].

2.4. Statistical analysis

The dichotomous data were pooled as risk ratio (RR) and 95% confidence interval (95% CI) using Mantel–Haenszel method. We used the fixed-effect model when the pooled data are homogenous; otherwise, random-effects model was used. I^2 statistic was applied to check heterogeneity among included studies. Statistical significance was indicated by 2-sided $p < 0.05$. We used Stata 16.0 software to perform meta-analysis.

3. Results

3.1. Study selection and baseline characteristics

A total of 125 articles were identified. After reviewing titles, abstracts and the full texts, 123 records were excluded. Ultimately, 3

studies with 2256 patients with moderate-to-severe atopic dermatitis were included [14,20,21]. The flow of screening process is shown in Fig. 1. In these three studies, two compared abrocitinib with dupilumab, and one compared upadacitinib with dupilumab. All patients had moderate-to-severe AD. Abrocitinib and upadacitinib are administered orally once daily, while dupilumab is administered subcutaneously every other week (Table 1). The mean age of included patients ranged from 35 to 38 years with at least 20 years disease duration. The studies were conducted between 2021 and 2022. Patients were randomized into 4 arms of abrocitinib 200 mg, 100 mg, dupilumab and placebo in one study and 2 arms of abrocitinib 200 mg and dupilumab (Table 1). The duration of treatment in one study was 16 weeks, one was 24 weeks and one was 26 weeks (Table 1). At baseline of these studies, the mean EASI score was ranged from 28 to 30, the mean IGA score was at least 3 points on a severity scale of 0–4, the averaged *P*P-NRS score was 7 on a scale of 0–10, and the mean body surface area involvement was 40–50% (Table 2). Baseline characteristics of each study were shown in Tables 1 and 2

3.2. Quality assessment

The risk of bias of trials was performed by the Cochrane risk of bias tool, including sequence generation, allocation concealment, performance bias, detection bias, incomplete outcome data, selective reporting, and other possible sources of bias. All studies were at low risk of bias in overall judgment and the assessment of the risk of bias is depicted in Fig. 2.

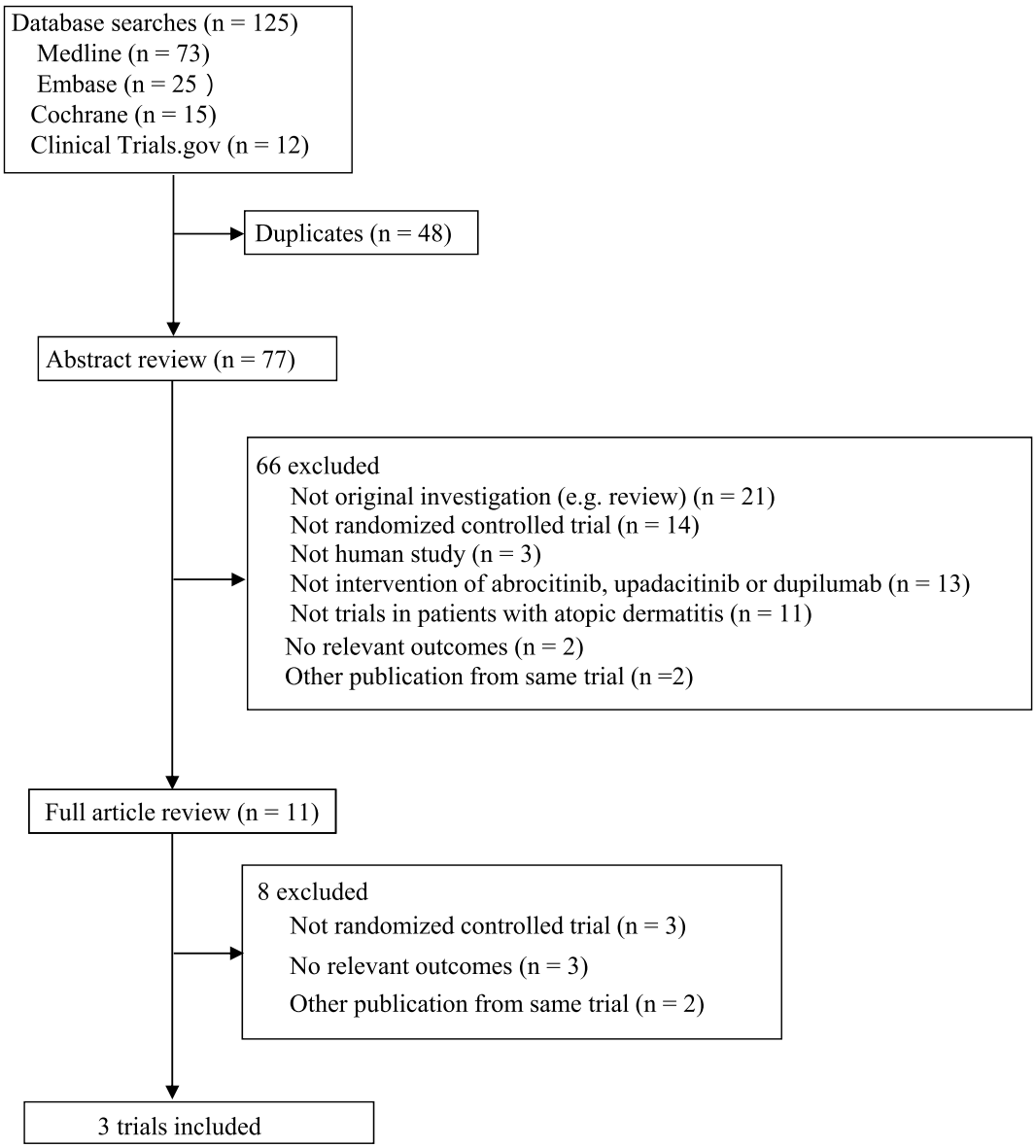

Fig. 1. Process for identifying studies eligible for the meta-analysis.

Table 1
Characteristics of studies included in the meta-analysis.

Study ID	Phase	Study period	No. Of participants	Age	Atopic dermatitis severity	Interventions	Duration of treatment
Bieber 2021 (JADE-COMPARE)	Phase III	Oct 2018 to Aug 2019	837	≥18 years	Patients with moderateto-severe atopic dermatitis	Oral abrocitinib, 100 mg and 200 mg once daily, Subcutaneously Dupilumab every other week, Placebo.	16 weeks
Reich 2022 (JADE DARE)	Phase III	Jun 2020 to Dec 2020	727	≥18 years	Patients with moderateto-severe atopic dermatitis	The abrocitinib group received abrocitinib 200 mg (two 100 mg tablets) administered orally once per day from day 1 to week 26. The dupilumab group received dupilumab 300 mg administered by subcutaneous injection every 2 weeks (loading dose of 600 mg at baseline [two injections of 300 mg], with last injection at week 24).	26 weeks
Blauvelt 2021 (Heads Up)	phase 3 b	Feb 2019 to Dec 2020	692	≥18 years	Patients with moderateto-severe atopic dermatitis	Patients were randomized 1:1 to receive 30 mg of upadacitinib administered orally once daily until week 24 or 300 mg of dupilumab administered as a subcutaneous injection every 2 weeks after a loading dose of 600 mg, starting at week 2 and until week 22.	24 weeks

Table 2
Baseline characteristics of the enrolled patients in the included RCTs.

Study ID	Age	Disease duration (years), mean SD)	Eczema area and severity index (EASI) score, mean (SD)	Investigator's global assessment (IGA) grade number, moderate (grade 3) and severe (grade 4)	Pruritus numeric rating scale (NRS) score, mean (SD)	Body surface area affected, % mean (SD)	Dermatology life quality index (DLQI) score, mean (SD)
Bieber 2021 (JADE-COMPARE)	37.7 ± 14.7/ 37.1 ± 14.6	22.7 ± 15.8/22.8 ± 14.8	30.9 ± 12.8/30.4 ± 12.0	253,173/162,80	7.4 ± 1.6/7.3 ± 1.7	48.5 ± 23.1/46.5 ± 22.1	15.7 ± 6.6/15.6 ± 6.7
Reich 2022	36.6 (14.6)/ 35.5 (13.3)		28.1 (11.5)/28.1 (11.9)	216,146/220,145	7.4 (1.6)/7.4 (1.6)	42.5 (19.9)/42.6 (21.3)	14.0 (6.8)/14.2 (6.3)
Blauvelt 2021 (Heads Up)	36.6 (14.61)/ 36.9 (14.09)	23.5 (14.7)/25.0 (14.8)	30.8 (12.5)/28.8 (11.5)	171,173/174,174	7.4 (1.6)/7.5 (1.7)	48.2 (24.0)/44.4 (22.8)	

3.3. EASI-75 and 90 responses

EASI quantifies severity of AD based on severity of lesion clinical signs and % of BSA affected. EASI-75 score is defined as at least a 75% reduction from baseline in EASI response. Three studies provided EASI-75 score after treatment. The analysis revealed that improvement of EASI-75 was rapidly registered with abrocitinib/upadacitinib as compared to the dupilumab, even as early as week 2 of treatment (2 weeks, RR 1.92; 95% CI: 1.64 to 2.26, $p < 0.001$, Fig. 3). The proportions of patients who reached the endpoint of EASI-75 at week 12 and end of therapy were also higher in the abrocitinib/upadacitinib group than in the dupilumab group (12 weeks, RR 1.14; 95% CI: 1.03 to 1.26, $p = 0.009$; end of therapy, RR 1.12; 95% CI: 1.04 to 1.20, $p = 0.002$, Fig. 3).

EASI-90 score is defined as at least a 90% reduction from baseline in EASI response. Three studies provided EASI-90 score after treatment. Significant improvement in EASI-90 scores was demonstrated with abrocitinib/upadacitinib versus dupilumab at week 2 and at all subsequent time points (2 weeks, RR 2.04; 95% CI: 1.54 to 2.69; 12 weeks, RR 1.60; 95% CI: 1.40 to 1.84; end of therapy, RR 1.32; 95% CI: 1.20 to 1.45; $p < 0.001$ for all comparisons, Fig. 4).

3.4. IGA grade

The severity of AD was assessed using the IGA, which ranges from worst (4 point) to the best (0 points). Two studies with 1564 patients provided the data of IGA score. According to the results, the daily oral administration of abrocitinib/upadacitinib provided a faster onset of IGA response at week 2 (2 weeks, RR 2.57; 95% CI: 1.79 to 3.70, $p < 0.001$). The differences in IGA response remained significant at week 12 (12 weeks, RR 1.39; 95% CI: 1.22 to 1.59, $p < 0.001$) and end of therapy (end of therapy, RR 1.13; 95% CI: 1.01 to 1.27; $p = 0.035$, Fig. 5).

3.5. PP-NRS4

*P*P-NRS assessed the severity of pruritus due to AD, which ranges from worst (10 point) to the best (0 points). *P*P-NRS4 is defined as achieving a 4 point or higher improvement in *P*P-NRS. Compared with dupilumab, a larger proportion of patients treated with abrocitinib/upadacitinib achieved early itch relief at 2 weeks (2 weeks, RR 1.87; 95% CI: 1.60 to 2.20, $p < 0.001$, Fig. 6). Better results were found later during treatment, in between the 12 weeks to the end of study in abrocitinib/upadacitinib group, as compared to the dupilumab group (12 weeks, RR 1.10; 95% CI: 1.01 to 1.21; $p = 0.033$; end of therapy, RR 1.20; 95% CI: 1.11 to 1.30; $p < 0.001$, Fig. 6).

3.6. Adverse events

The most frequent reported side effects were listed in Table 3, which were mild and non-lethal. The adverse effects reported in ≥5% of patients were nausea, conjunctivitis, nasopharyngitis, upper respiratory tract infection, headache, acne, herpes zoster, dermatitis

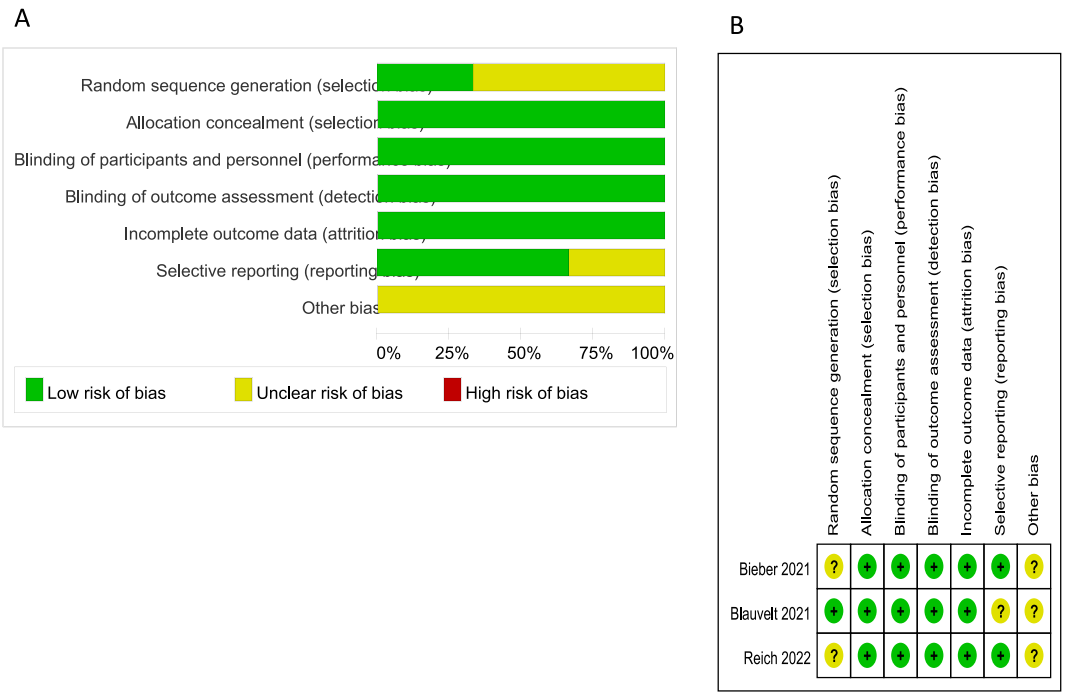

Fig. 2. Risk of bias graph (A) and risk of bias summary (B).

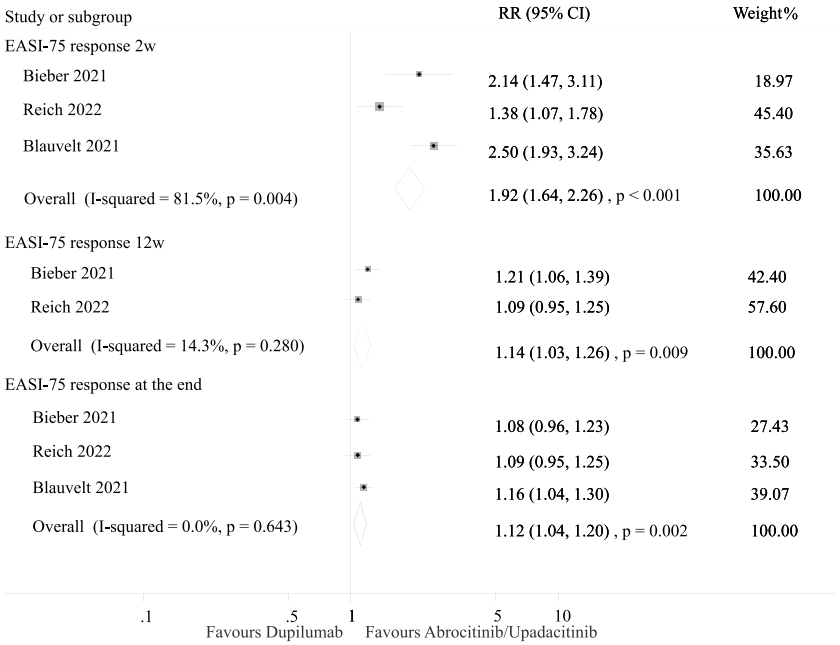

Fig. 3. Forest plot of EASI-75 response at week 2, week 12 and end of therapy.

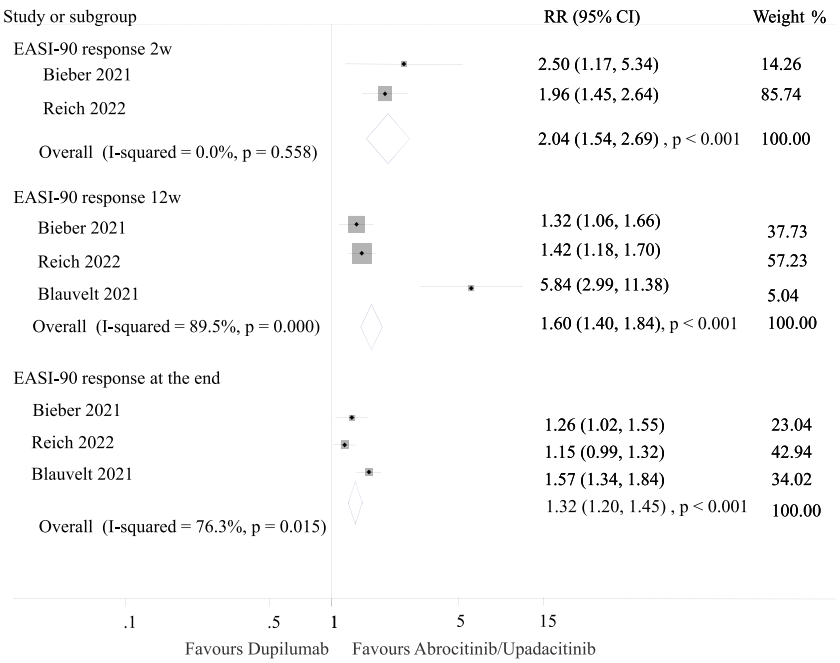

Fig. 4. Forest plot of EASI-90 response at week 2, week 12 and end of therapy.

atopic, thrombocytopenia, blood CPK level increased. The analysis revealed that abrocitinib/upadacitinib was associated with higher incidence of nausea (RR 6.45; 95% CI: 3.71 to 11.18), acne (RR 5.21; 95% CI: 3.31 to 8.22) and blood CPK level increased (RR 2.27; 95% CI: 1.007 to 4.85), and with lower incidence of conjunctivitis (RR 0.19; 95% CI: 0.09 to 0.39) and nasopharyngitis (RR 0.54; 95% CI: 0.38 to 0.79) than dupilumab. There was no significant difference in other adverse effects reported in ≥5% of patients between these two group (all $p > 0.05$ for all comparisons). TEAEs of any causality that led to treatment discontinuation, serious and severe adverse events were report in Fig. 7. The only observed significant result of adverse events were severe adverse events between the abrocitinib/upadacitinib group (n = 40) and the dupilumab group (n = 24) (RR, 1.67; 95% CI: 1.017–2.741, p = 0.043). TEAEs of any causality that led to treatment discontinuation and serious adverse events have not shown special risks in the patients treated with

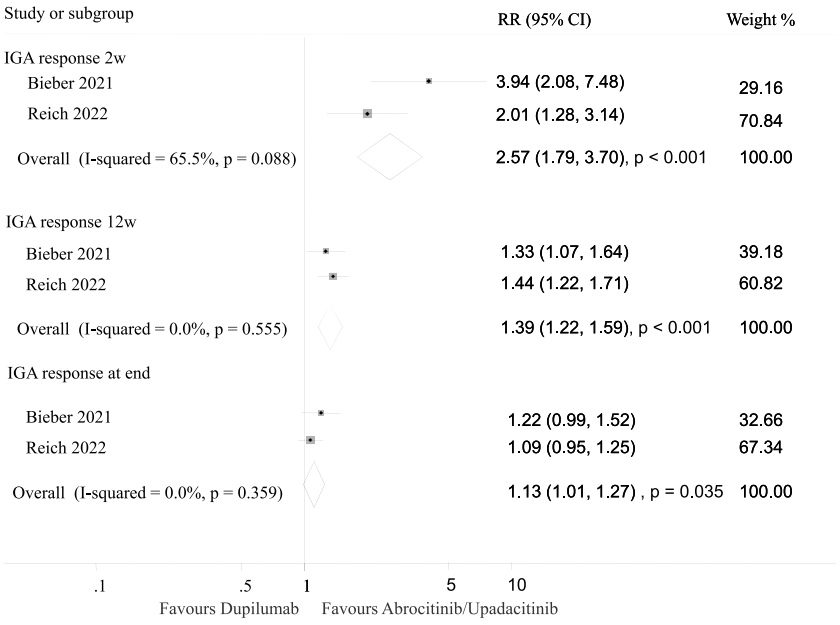

Fig. 5. Forest plot of IGA response at week 2, week 12 and end of therapy.

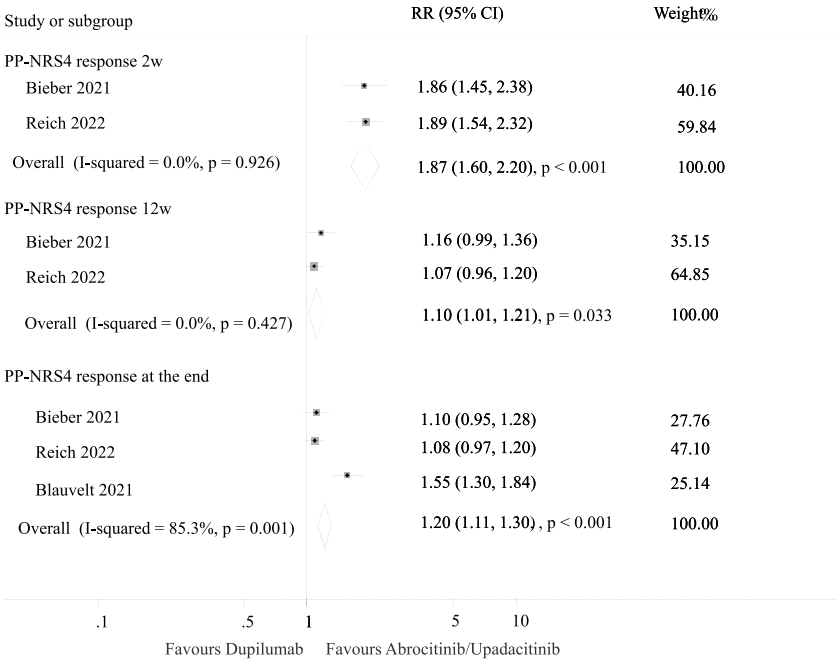

Fig. 6. Forest plot of *P*P-NRS4 response at week 2, week 12 and end of therapy.

abrocitinib/upadacitinib (all $p > 0.05$ for all comparisons).

4. Discussion

As JAK inhibitor (such as abrocitinib and upadacitinib) and anti-interleukin-receptor antibody (dupilumab) for atopic dermatitis approved by United States, European Union, and other countries, head-to-head studies done by comparing the efficacy and safety of these two types of novel systemic therapy agents will provide useful evidence for specialists in having treatment options. To the best of our knowledge, this is the first meta-analysis to compare the efficacy and safety of JAK inhibitor and *anti*-IL-4 receptor antibody in the

Table 3
Adverse event reported in ≥5% of patients with moderate-to-severe atopic dermatitis treated with abrocitinib, upadacitinib or Dupilumab.

	Abrocitinib/Upadacitinib (n/936)	Dupilumab (n/951)	RR	95% CI	P value
Nausea	95	15	6.45	3.705 to 11.175	<0.001
Conjunctivitis	8	44	0.185	0.087 to 0.394	<0.001
Nasopharyngitis	45	84	0.544	0.375 to 0.790	0.001
Upper respiratory tract infection	31	22	1.432	0.823 to 2.491	0.202
Headache	76	58	1.331	0.935 to 1.896	0.112
Acne	118	23	5.212	3.305 to 8.222	<0.001
Herpes zoster	4	0			0.061
Thrombocytopenia	2	0			0.246
Dermatitis atopic	24	29	0.841	0.486 to 1.455	0.535
Blood CPK level increased	23	10	2.337	1.106 to 4.937	0.022

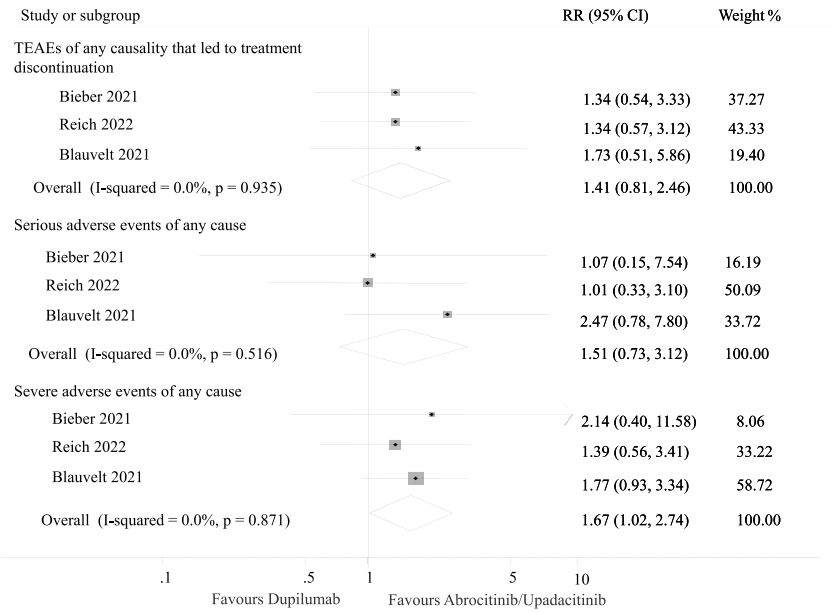

Fig. 7. Forest plot of the treatment emergent adverse events, serious and severe adverse events.

treatment of adult patients with moderate-to-severe AD. Three head-to-head studies with 2256 patients were included. According to the results, it was confirmed that compared to *anti*-IL-4 receptor antibody, dupilumab, JAK inhibitor, including abrocitinib and upadacitinib demonstrated a faster improvement in EASI-75 and 90 response, IGA response and *P*P-NRS4 at week 2. And patients treated with abrocitinib/upadacitinib continued to show numerically better efficacy outcomes when compared to dupilumab in week 12 and end-of-study. Among adverse events, rate of severe adverse events of any cause was higher for patients treated with abrocitinib/upadacitinib than those treated with dupilumab. While there was no significant difference in serious adverse events and TEAEs of any causality that led to treatment discontinuation between these two groups. Accordingly, the results supported the potential use of JAK1 inhibitors, especially abrocitinib and upadacitinib, in moderate-to-severe AD patients who need rapid itch relief and high amounts of skin improvement.

The pathophysiology of AD was involved in disruption of the epidermal skin barrier and infiltration of Th2 cells [22,23]. Th2 cells have the ability to release a wide range of cytokines, including IL-4, IL-13, IL-31 into the skin, and then activating downstream JAK pathways. In recent years, medications of novel systemic therapies are being investigated for the use in patients with moderate-to-severe AD. *Anti*-IL-4-receptor α mono-clonal antibody is a small molecular compound that inhibits the intracellular transduction of the signal derived from the cell's cytokine receptors [24]. Janus kinase-1 (JAK) inhibitors target the type 2 inflammation pathway and inhibit both IL-4 and IL-13 signal transduction [25,26]. The results from numerous studies have shown that abrocitinib, upadacitinib, and dupilumab could provide high levels of skin clearance and itch improvement in adolescents and adults with moderate-to-severe AD [14,16,27]. These agents have been approved by many countries for use in patients with moderate-to-severe AD. Recently, the efficacy between abrocitinib, upadacitinib, and dupilumab was compared. JADE COMPARE, a 16-week and phase 3 study, has yielded better responses in patients who received doses of 200 mg of oral abrocitinib daily, improving EASI-75 and 90 response, IGA response and *P*P-NRS4 response and resulting in significantly greater reductions in signs and itch of moderate-to-severe AD than dupilumab [14]. Heads Up, a 24-week and phase 3 study, compared the efficacy and safety of upadacitinib with dupilumab in adults with moderate to severe AD and demonstrated upadacitinib provided more rapid skin improvement and itch

relief compared with dupilumab [21]. In current meta-analysis including 3 RCTs, EASI-75 and 90 responses have a 1.92-fold and 2.04-fold increase in patients with abrocitinib/upadacitinib compared with dupilumab at week 2. The proportion of patients achieving an early IGA response and itch reduction (*P*P-NRS4) at week 2 showed advantages of abrocitinib/upadacitinib over dupilumab. The skin-improvement and itch relief were sustained at week 12 and end of study, although between-group differences decreased over time. Given the existing evidence, the therapeutic benefits could be quickly found in AD patients who treated with abrocitinib/upadacitinib for a short time period. A likely explanation for the difference in efficacy is that JAK inhibitors was not only blocking upstream JAK signalling pathways but also having a modulatory effect on downstream cytokines signalling involved in AD pathogenesis, whereas the effect of dupilumab is mostly restricted to cytokines signalling (eg, IL-4 and IL-13) [28]. The true benefit of JAK inhibitors, such as abrocitinib and upadacitinib, need to be assessed in long-term clinical trials or real-world studies so that they can be prescribed to patients as the first chose in patients who need fast relief of AD signs and itch.

The life-long AD course requires obtaining the best benefit-to-risk ratio of abrocitinib and upadacitinib. Safety is a vital concern of *anti*-JAK therapy in patients suffering from moderate-to-severe AD. Compared with subcutaneous dupilumab, oral abrocitinib and upadacitinib were more likely to be accepted. The results in our systematic review and meta-analysis showed that patients who were taking abrocitinib/upadacitinib had a higher rate of severe advere events than those who were taking dupilumab. Severe adverse events mainly include events that prevent normal everyday activities. However, no significant difference in serious adverse events and TEAEs of any causality that led to treatment discontinuation between these two groups. As for the commonly reported adverse events, patients treated with abrocitinib/upadacitinib had increased risk of nausea, acne and increased blood CPK level, and decreased risk of conjunctivitis and nasopharyngitis. Most of these adverse effects are mild or moderate, and manageable. In general, patients with AD have a good tolerance to abrocitinib and upadacitinib. In patients opting to start abrocitinib or upadacitinib, clinical and laboratory monitoring is essential to avoid the possible adverse events.

The strength of this meta-analysis is its rigorous methodology. However, the limitations need to be considered. Firstly, the limited direct comparison between JAK inhibitors and *anti*-IL-4-receptor antibody prevented us from undertaking subgroup analysis to explore the potential of each drug class. Secondly, the positive results of EASI-75 and 90 responses, IGA response and *P*P-NRS4 in the abrocitinib/upadacitinib group should be interpreted with caution because concomitant topical anti-inflammatory therapies are permitted along with abrocitinib and upadacitinib. Thirdly, the measured outcomes were assessed with short duration, between 16 and 24 weeks. No long-term safety results have been reported in these studies. Therefore, more head-to-head RCTs with a longer follow-up period are needed to elucidate the efficacy and safety of *anti*-JAK therapy in patients with moderate-to-severe AD.

5. Conclusions

This study demonstrated that *anti*-JAK therapy, particularly abrocitinib and upadacitinib, exhibited superiority over dupilumab in achieving fast relief of disease signs and itch with an acceptable safety profile in patients with moderate-to-severe atopic dermatitis. Additional head-to-head comparisons are required to confirm the potential therapeutic efficacy of each drug class to achieve disease control.

Data availability statement

Data included in article/supp. Material/referenced in article.

Ethical statement

An ethics statement is not applicable because this study is based exclusively on published literature.

Authors' contributions

Qin Gao was the study leader and designed the study. Yanxia Zhao and Junling Zhang searched the papers and extracted the data. Yanxia Zhao and Qin Gao analyzed the results. Qin Gao drafted the manuscript. Qin Gao, Yanxia Zhao and Junling Zhang were responsible for manuscript editing, peer reviewing, and 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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References

[1] W.Y. Chen, S.C. Chen, S.Y. Hsu, Y.A. Lin, C.M. Shih, C.Y. Huang, K.H. Wang, A.W. Lee, Annoying psoriasis and atopic dermatitis: a narrative review, Int. J. Mol. Sci. 23 (9) (2022) 4898, https://doi.org/10.3390/ijms23094898.

[2] E. Niculet, C. Bobeica, I.A. Stefanopol, A.M. Pelin, A. Nechifor, C. Onisor, A.L. Tatu, Once-daily abrocitinib for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents aged 12 years and over: a short review of current clinical perspectives, Therapeut. Clin. Risk Manag. 18 (2022) 399–407, https://doi.org/10.2147/TCRM.S338661.

[3] H.A. Hadi, A.I. Tarmizi, K.A. Khalid, M. Gajdacs, A. Aslam, S. Jamshed, The epidemiology and global burden of atopic dermatitis: a narrative review, Life-Basel 11 (9) (2021) 936, https://doi.org/10.3390/life11090936.

[4] T. Bieber, Atopic dermatitis: an expanding therapeutic pipeline for a complex disease, Nat. Rev. Drug Discov. 21 (1) (2022) 21–40, https://doi.org/10.1038/s41573-021-00266-6.

[5] L. Pescitelli, E. Rosi, F. Ricceri, N. Pimpinelli, F. Prignano, Novel therapeutic approaches and targets for the treatment of atopic dermatitis, Curr. Pharmaceut. Biotechnol. 22 (1) (2021) 73–84, https://doi.org/10.2174/1389201021666200611112755.

[6] A. Diaz, E. Guttman-Yassky, Topical agents for the treatment of atopic dermatitis, Expet Rev. Clin. Immunol. 15 (4) (2019) 369–382, https://doi.org/10.1080/1744666X.2019.1564038.

[7] M. De Bruin-Weller, T. Biedermann, R. Bissonnette, M. Deleuran, P. Foley, G. Girolomoni, J. Hercogova, C.H. Hong, N. Katoh, A.E. Pink, M.A. Richard, S. Shumack, J.F. Silvestre, S. Weidinger, Treat-to-target in atopic dermatitis: an international consensus on a set of core decision points for systemic therapies, Acta Derm. Venereol. 101 (2) (2021), https://doi.org/10.2340/00015555-3751 adv402.

[8] U. Nygaard, C. Vestergaard, M. Deleuran, Emerging treatment options in atopic dermatitis: systemic therapies, Dermatology 233 (5) (2017) 344–357, https://doi.org/10.1159/000484406.

[9] P.O. Perche, M.K. Cook, S.R. Feldman, Abrocitinib: a new fda-approved drug for moderate-to-severe atopic dermatitis, Ann. Pharmacother. 57 (1) (2022), 286857993, https://doi.org/10.1177/10600280221096713.

[10] G. Radi, O. Simonetti, G. Rizzetto, F. Diotallevi, E. Molinelli, A. Offidani, Baricitinib: the first jak inhibitor approved in europe for the treatment of moderate to severe atopic dermatitis in adult patients, Healthcare 9 (11) (2021) 1575, https://doi.org/10.3390/healthcare9111575.

[11] A.K. Gupta, R.P. Love, W. Abramovits, K.D. Vincent, Dupixent(r) (dupilumab): a newly approved interleukin-4 receptor antagonist for the treatment of atopic dermatitis in pediatric patients, Skinmed 17 (2) (2019) 107–109.

[12] J.I. Silverberg, E.L. Simpson, J.P. Thyssen, M. Gooderham, G. Chan, C. Feeney, P. Biswas, H. Valdez, M. Dibonaventura, C. Nduaka, R. Rojo, Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis: a randomized clinical trial, Jama Dermatol 156 (8) (2020) 863–873, https://doi.org/10.1001/jamadermatol.2020.1406.

[13] M.J. Gooderham, S.B. Forman, R. Bissonnette, J.S. Beebe, W. Zhang, C. Banfield, L. Zhu, J. Papacharalambous, M.S. Vincent, E. Peeva, Efficacy and safety of oral janus kinase 1 inhibitor abrocitinib for patients with atopic dermatitis: a phase 2 randomized clinical trial, Jama Dermatol 155 (12) (2019) 1371–1379, https://doi.org/10.1001/jamadermatol.2019.2855.

[14] T. Bieber, E.L. Simpson, J.I. Silverberg, D. Thaci, C. Paul, A.E. Pink, Y. Kataoka, C.Y. Chu, M. Dibonaventura, R. Rojo, J. Antinew, I. Ionita, R. Sinclair, S. Forman, J. Zdybski, P. Biswas, B. Malhotra, F. Zhang, H. Valdez, Abrocitinib versus placebo or dupilumab for atopic dermatitis, N. Engl. J. Med. 384 (12) (2021) 1101–1112, https://doi.org/10.1056/NEJMoa2019380.

[15] Y. Zhao, L. Wu, Q. Lu, X. Gao, X. Zhu, X. Yao, L. Li, W. Li, Y. Ding, Z. Song, L. Liu, N. Dang, C. Zhang, X. Liu, J. Gu, J. Wang, S. Geng, Q. Liu, Y. Guo, L. Dong, H. Su, L. Bai, J.T. O'Malley, J. Luo, E. Laws, L. Mannent, M. Ruddy, N. Amin, A. Bansal, T. Ota, M. Wang, J. Zhang, The efficacy and safety of dupilumab in Chinese patients with moderate-to-severe atopic dermatitis: a randomized, double-blind, placebo-controlled study, Br. J. Dermatol. 186 (4) (2022) 633–641, https://doi.org/10.1111/bjd.20690.

[16] E.L. Simpson, A.S. Paller, E.C. Siegfried, M. Boguniewicz, L. Sher, M.J. Gooderham, L.A. Beck, E. Guttman-Yassky, D. Pariser, A. Blauvelt, J. Weisman, B. Lockshin, T. Hultsch, Q. Zhang, M.A. Kamal, J.D. Davis, B. Akinlade, H. Staudinger, J.D. Hamilton, N. Graham, G. Pirozzi, A. Gadkari, L. Eckert, N. Stahl, G. D. Yancopoulos, M. Ruddy, A. Bansal, Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial, Jama Dermatol 156 (1) (2020) 44–56, https://doi.org/10.1001/jamadermatol.2019.3336.

[17] A.F. Alexis, M. Rendon, J.I. Silverberg, D.M. Pariser, B. Lockshin, C.E. Griffiths, J. Weisman, A. Wollenberg, Z. Chen, J.D. Davis, M. Li, L. Eckert, A. Gadkari, B. Shumel, A.B. Rossi, N.M. Graham, M. Ardeleanu, Efficacy of dupilumab in different racial subgroups of adults with moderate-to-severe atopic dermatitis in three randomized, placebo-controlled phase 3 trials, J. Drugs Dermatol. JDD 18 (8) (2019) 804–813.

[18] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the prisma statement, Int. J. Surg. 8 (5) (2010) 336–341, https://doi.org/10.1016/j.ijsu.2010.02.007.

[19] J.P. Higgins, D.G. Altman, P.C. Gotzsche, P. Juni, D. Moher, A.D. Oxman, J. Savovic, K.F. Schulz, L. Weeks, J.A. Sterne, The cochrane collaboration's tool for assessing risk of bias in randomised trials, BMJ 343 (2011), d5928, https://doi.org/10.1136/bmj.d5928.

[20] A. Blauvelt, H.D. Teixeira, E.L. Simpson, A. Costanzo, M. De Bruin-Weller, S. Barbarot, V.H. Prajapati, P. Lio, X. Hu, T. Wu, J. Liu, B. Ladizinski, A.D. Chu, K. Eyerich, Efficacy and safety of upadacitinib vs dupilumab in adults with moderate-to-severe atopic dermatitis: a randomized clinical trial, Jama Dermatol 157 (9) (2021) 1047–1055, https://doi.org/10.1001/jamadermatol.2021.3023.

[21] K. Reich, J.P. Thyssen, A. Blauvelt, K. Eyerich, W. Soong, Z.P. Rice, H.C. Hong, N. Katoh, F. Valenzuela, M. Dibonaventura, T.A. Bratt, F. Zhang, C. Clibborn, R. Rojo, H. Valdez, U. Kerkmann, Efficacy and safety of abrocitinib versus dupilumab in adults with moderate-to-severe atopic dermatitis: a randomised, double-blind, multicentre phase 3 trial, Lancet 400 (10348) (2022) 273–282, https://doi.org/10.1016/S0140-6736(22)01199-0.

[22] B.W. David, J.A. Tarbox, M.B. Tarbox, Atopic dermatitis: pathophysiology, Adv. Exp. Med. Biol. 1027 (2017) 21–37, https://doi.org/10.1007/978-3-319-64804-0_3.

[23] T. Nakahara, M. Kido-Nakahara, G. Tsuji, M. Furue, Basics and recent advances in the pathophysiology of atopic dermatitis, J. Dermatol. 48 (2) (2021) 130–139, https://doi.org/10.1111/1346-8138.15664.

[24] A. Tsianakas, T.A. Luger, The anti-il-4 receptor alpha antibody dupilumab: facing a new era in treating atopic dermatitis, Expet Opin. Biol. Ther. 15 (11) (2015) 1657–1660, https://doi.org/10.1517/14712598.2015.1095887.

[25] M.A. Rodrigues, T. Torres, Jak/stat inhibitors for the treatment of atopic dermatitis, J. Dermatol. Treat. 31 (1) (2020) 33–40, https://doi.org/10.1080/09546634.2019.1577549.

[26] A.M. Cartron, T.H. Nguyen, Y.S. Roh, M.M. Kwatra, S.G. Kwatra, Janus kinase inhibitors for atopic dermatitis: a promising treatment modality, Clin. Exp. Dermatol. 46 (5) (2021) 820–824, https://doi.org/10.1111/ced.14567.

[27] E. Guttman-Yassky, D. Thaci, A.L. Pangan, H.C. Hong, K.A. Papp, K. Reich, L.A. Beck, M.F. Mohamed, A.A. Othman, J.K. Anderson, Y. Gu, H.D. Teixeira, J. I. Silverberg, Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial, J. Allergy Clin. Immunol. 145 (3) (2020) 877–884, https://doi.org/10.1016/j.jaci.2019.11.025.

[28] T. Bieber, E.L. Simpson, J.I. Silverberg, D. Thaci, C. Paul, A.E. Pink, Y. Kataoka, C.Y. Chu, M. Dibonaventura, R. Rojo, J. Antinew, I. Ionita, R. Sinclair, S. Forman, J. Zdybski, P. Biswas, B. Malhotra, F. Zhang, H. Valdez, Comparing abrocitinib and dupilumab in the treatment of atopic dermatitis: a plain language summary, Immunotherapy 14 (1) (2022) 5–14, https://doi.org/10.2217/imt-2021-0224.