REVIEW ARTICLE

Comparative Efficacy and Safety of Monoclonal Antibodies and Janus Kinase Inhibitors in Moderate-to-severe Atopic Dermatitis: A Systematic Review and Meta-analysis

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The aim of this study was to compare the efficacies of systemic treatments with dupilumab, tralokinumab and Janus kinase inhibitors for moderate-to-severe atopic dermatitis. A systematic review following Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines was performed using Medline, EMBASE and Cochrane library. All randomized controlled trials investigating the efficacy of systemic treatments for moderate-to-severe atopic dermatitis in adults were included. Primary outcomes were the proportion of patients with atopic dermatitis achieving 50%, 75%, and 90% improvement in Eczema Area and Severity Index (EASI) score after dupilumab, tralokinumab or Janus kinase inhibitors. Nineteen studies totalling 6,444 patients were included. In monotherapy studies, upadacitinib 30 mg once daily had the numerically highest efficacy regarding EASI-50, EASI-75 and EASI-90. In combination therapy studies with topical corticosteroids, dupilumab 300 mg once every other week had highest efficacy regarding EASI-50, and abrocitinib 200 mg once daily had the highest score regarding EASI-75 and EASI-90. Analysis provided evidence that dupilumab, tralokinumab and Janus kinase inhibitors all had an acceptable efficacy profile and resulted in clinically relevant improvements in EASI score. Furthermore, upadacitinib and abrocitinib seem to have great potential to treat patients with atopic dermatitis. However, further studies are needed to determine the long-term efficacy of Janus kinase inhibitors in adults with moderate-to-severe atopic dermatitis.

Key words: atopic dermatitis; systemic; biological.

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SIGNIFICANCE

Atopic dermatitis can, in most cases, be adequately controlled with topical treatments alone or in combination with phototherapy. However, in moderate-to-severe atopic dermatitis, systemic therapy may be needed for adequate disease control. Dupilumab, tralokinumab and Janus kinase inhibitors are some of the newly developed systemic treatments. The aim of this review was to investigate the efficacy of these treatments, which is an urgent need to implement evidence-based practice guidelines, to ensure the best possible patient care. This study suggests that patients who have moderate-to-severe atopic dermatitis that is unresponsive to topical therapies may benefit from treatment with dupilumab, tralokinumab, or Janus kinase inhibitors.

Atopic dermatitis (AD) is a chronic relapsing and remitting skin disease, affecting up to 20% of children and 10% of adults in high-income countries (1, 2). AD is clinically characterized by intense itching, recurrent eczematous lesions and a heterogeneous clinical presentation (3). Approximately 60% of cases of AD manifest in childhood, but AD can start at any age (4). Intensified pruritus, skin pain, sleep disturbance, infection risk and reduced quality of life have all been associated with worsening of AD (4–7).

Regarding treatment of AD, the strategy is based heavily on current disease severity. Severity of AD can be divided into 3 groups: mild, moderate, and severe. Mild and moderate AD can usually be managed with a combination of moisturizing creams, topical corticosteroids (TCS) or calcineurin inhibitors and phototherapy. Approximately 2% of patients have recalcitrant AD, which does not respond to this regimen, and require a variety of systemic immunosuppressive or antimicrobial treatments in combination or sequentially (8, 9). Generally, most common immunpsuppressors (methotrexate, azathioprine and mycophenolate mofetil) are used as off-label drugs in treatment of moderate-to-severe AD, when conventional treatment with TCS or phototherapy fails. Systemic corticosteroids can be used as treatment for acute exacerbations, but they are not recommended for long-term treatment in AD due to side-effects (10–12). Cyclosporine is the only approved treatment in some countries for severe AD, but serious side-effects, such as dose-dependent nephrotoxicity and hypertension, limit the use of cyclosporine in the long term (10). An unmet need for treatment of moderate-to-severe AD therefore exists.

Now, and in recent years, treatments with monoclonal antibodies including dupilumab, tralokinumab, and Janus kinase (JAK) inhibitors are being developed. Dupilumab is a subcutaneously (SC) administrated antibody, directed against the interleukin (IL)-4 receptor antagonist that blocks IL-4 and IL-13 (13–22). Tralokinumab is an IL-

13 antibody (23–25). In addition, oral JAK inhibitors are becoming available, i.e. abrocitinib (JAK1), upadacitinib (JAK1), baricitinib (JAK 1/2) and tofacitinib (JAK 1/3) (26–32). Abrocitinib, upadacitinib and baricitinib are for oral use, while tofacitinib may be used both orally and topically (the last one as off-label).

These treatments all appear to have great potential for treatment of AD in randomized controlled trials (RCTs) against placebo. However, a lack of head-to-head (HTH) trials, as well as variability in AD study designs and outcome measures, make it difficult to compare the efficacy of these new drugs. The aim of this systematic review was to compare the efficacy of monoclonal antibodies, including dupilumab, tralokinumab, and JAK inhibitors, in patients with moderate and severe AD.

MATERIALS AND METHODS

A systematic literature search was conducted for clinical studies, using Medline (Pubmed), EMBASE and Cochrane library to identify systemic drugs used in treatment of AD. This was investigated using the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines (33). Two authors (F.S. and M.H.) independently searched the medical databases Pubmed, EMBASE, and Cochrane library using the following search terms: (atopic dermatitis) AND (upadacitinib OR rinvoq OR ABT-494) OR (baricitinib OR LY3009104) OR (olumiant OR baricitinib) OR (dupilumab OR dupixent OR REGN668 OR SAR231893) OR (abrocitinib OR PF-04965842) OR (tralokinumab OR ct-354) OR (tofacitinib OR xeljanz) OR (Janus kinase inhibitor) OR (JAK inhibitor). Furthermore, studies were identified by screening reference lists of key articles and review articles.

Inclusion and exclusion criteria

Inclusion criteria were clinical trials in English that investigated at least 10 adult patients with AD in each treatment group, who were treated with monoclonal antibodies including dupilumab, tralokinumab, or JAK inhibitors. Only phase II and III trials were included. Trials that did not include any placebo group, or did not provide detailed information about the proportion of patients achieving 50%, 75% and 90% improvement in Eczema Area and Severity Index (EASI) score, were excluded. Furthermore, trials that investigated topical treatment with monoclonal and JAK inhibitors were also excluded.

Primary outcomes were the proportion of patients achieving 50%, 75% and 90% improvement in EASI score. Studies were included only if data fulfilling EASI50, EASI-75 and EASI-90 could be extracted directly from the tables or the manuscript of the relevant studies. Secondary outcomes included mean percentage reduction in EASI score from baseline until evaluation of the efficacy, and mean percentage reduction in scores for the Dermatology Life Quality Index (DLQI), Patient-Oriented Eczema Measure (POEM), Pruritus Numerical Rating Scale (NRS), Pruritus Visual Analog Scale (VAS), and proportion of patients achieving an Investigator Global Assessment (IGA) score of 0 or 1 reflecting clear or mild AD.

Data extraction

After inclusion of all relevant studies, the same authors independently performed data extraction. Studies were screened according to title and abstract. After all relevant studies were included, the duplicate studies were removed. The extraction data listed in tables included the name of the first author, year of publication, phase and name of clinical trial, medication and dose, number of randomized patients, mean EASI score at the beginning, age of patients, control group, information about concurrent topical treatment allowed, AD severity and information about prior treatments/ washout (Table SI). Data regarding fulfilling EASI-50, EASI-75 and EASI-90 was extracted directly from the tables of the manuscripts of the relevant studies (Table SII). If data were provided only by graphs, Engauge Digitizer Software (Engauge Digitizer (markummitchell.github.io), assessed 1 July 2021) was used to read out the data.

Statistical analysis

Efficacy outcomes were grouped based on doses and weeks of treatment with the relevant treatments. When statistically appropriate (same treatment agent, period of treatment and dose), meta-analyses were conducted using random-effects models by using Review Manger version 5.4 (https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman) assessed 26 November 2021). One outcome measure was used for meta-analyses: the risk difference (RD) for binary outcomes, both with 95% confidence interval (95% CI). The RD of 0.2 means that the risk of event in focus is 20 percentage points more likely in the experimental group than in the control group. For each outcome scale, a separate meta-analysis was performed. In the case of every treatment agent, subgroup analyses were performed depending on whether TCS were allowed (Figs S1–S6).

RESULTS

The database search resulted in 1,614 non-duplicate studies (**Fig. 1**). Most studies originated as multinational studies conducted in several continents, including Europe, North America, Australia, Asia, or Latin America (15–17, 23–31). Five studies originated from North America (14, 20–22, 32) and 2 studies from Europe (18, 19). All included patients had moderate-to-severe AD.

Regarding dupilumab, the dose was either 200 or 300 mg once a week (QW) or once every other week (Q2W) in 9 studies (14–22). The dose of tralokinumab was either 45, 150, 300 mg Q2W, or once every 4 weeks (Q4W) in 3 studies (23–25). For abrocitinib, the dose was either 10, 30, 100 or 200 mg once daily in 2 studies (22, 26), for baricitinib either 1, 2 or 4 mg once daily in 4 studies (27, 29, 30, 32), and for updacitinib either 7.5 or 15 mg in 1 study (28), or 30 mg once daily in 2 studies (28, 31). Concomitant TCS was allowed or recommended in 10 studies (17, 19, 20, 22–24, 27, 29, 30, 32) and not allowed in 9 studies (14–16, 18, 21, 25, 26, 28, 31). For further details on each study, see Table SI.

Meta-analysis; primary outcomes: EASI-50, EASI-75, EASI-90

Monotherapy. With respect to EASI-50 (7 studies, $n = 4,803$), upadacitinib 30 mg once daily and dupilumab 200 mg QW showed comparable results after 16 weeks of treatment (upadacitinib: RD 59%, 95% CI 42–76) (dupilumab: RD 56%, 95% CI 33–78). Abrocitinib 200

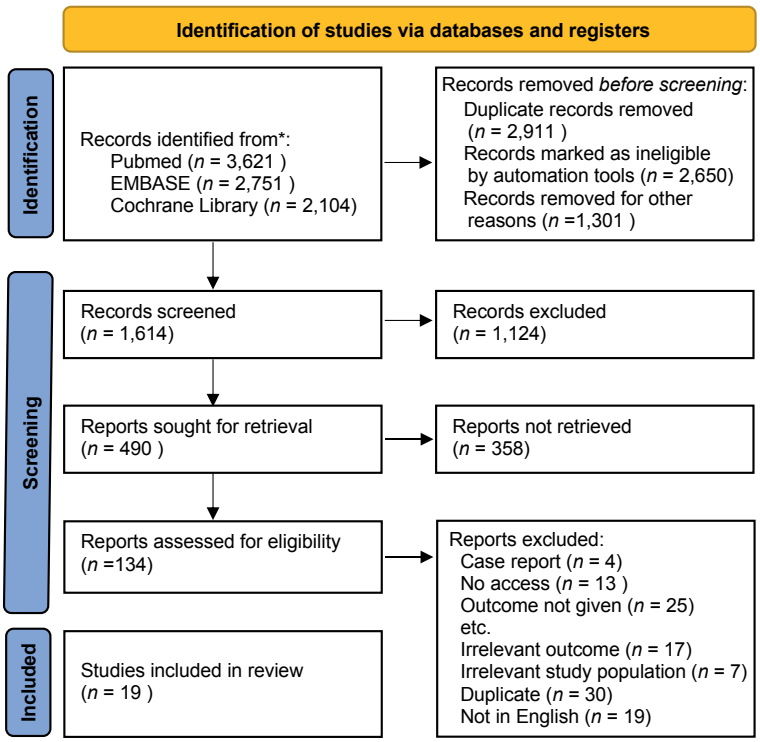

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

mg once daily after 16 weeks of treatment was almost as effective as dupilumab 300 mg QW after 12 weeks of treatment (abrocitinib: RD 52%, 95% subtotal CI 36–69) (dupilumab: RD 50%, CI 38–63). The response rates of upadacitinib dupilumab and abrocitinib, differed considerably with different dosages (Fig. S1).

With respect to EASI-75 (8 studies, $n=5495$), treatment with upadacitinib 30 mg once daily and dupilumab 200 mg QW once again showed comparable results compared with placebo groups (upadacitinib: RD 59%, 95% CI 43–76) (dupilumab: RD 52%, 95% CI 30–74) after 16 weeks of treatment. Similar trends were observed regarding treatment with abrocitinib 200 mg once daily (abrocitinib 200 mg: RD 49%, 95% CI 32–66) and dupilumab 200 mg Q2W (dupilumab 200 mg: RD 43%, 95% CI 28–57) both after 16 weeks of treatment) (Fig. S2).

With respect to EASI-90 (7 studies, $n=5,322$), treatment with upadacitinib 30 mg once daily after 16 weeks of treatment was superior compared with placebo group (RD 45%, 95% CI 29–61). Treatment with abrocitinib 200 mg once daily and dupilumab 200 mg QW showed comparable results (abrocitinib: RD 34%, 95% CI 18–50) (dupilumab RD 33%, 95% CI 15–52) after 16 weeks of treatment (Fig. S3).

Combination with TCS. With respect to EASI-50 (10 studies, $n=4,646$), treatment with dupilumab 300 mg Q2W and 300 mg QW after 16 weeks of treatment showed comparable results (300 mg Q2W: RD 42%, 95% 35–49) (300 mg QW: RD 41%, 95% CI 35–46). In second place, treatment with abrocitinib 200 mg once daily after 12 weeks of treatment also showed high efficacy compared with other treatments (abrocitinib 200 mg: RD 34%, 95% CI 24–43) (Fig. S4). No studies investigated upadacitinib in combination with TCS with respect to EASI-50.

With respect to EASI-75 (10 studies, $n=6,265$), treatment with abrocitinib 200 mg once daily after 12 weeks of treatment was superior to other treatments (RD 43%, 95% CI 33–53). In addition, treatment with dupilumab 300 mg Q2W and 300 mg QW after 16 weeks of treatment also showed comparable results (Q2W: RD 40%, 95% CI 28–52) (Q2 RD 37%, 95% CI 30–43) (Fig. S5). No studies investigated upadacitinib in combination with TCS with respect to EASI-75.

With respect to EASI-90 (8 studies, $n=5,765$), treatment with abrocitinib 200 mg once daily after 12 weeks of treatment was superior (RD 36%, 95% CI 28–44). Treatment with dupilumab 300 mg Q2W and 300 mg QW after 16 weeks of treatment presented comparable results (300 mg Q2W: RD 31%, 95% CI 23–38) (300 mg QW: RD 30%, 95% CI 24–36) (Fig. S6.) For more information on secondary outcomes in this study, see Table SII. No studies investigated upadacitinib in combination with TCS with respect to EASI-90.

DISCUSSION

This review and meta-analysis are based on 19 RCTs, including 10 studies, in which concomitant use of TCS was allowed. The work was supported by a high degree of standardization brought about by the adoption of a Core Outcome Set and ensuring agreement on outcome measures (34). The results of the current analysis highlight the major potential of JAK inhibitors and dupilumab as effective treatments in moderate-to-severe AD after only 16 weeks of treatment, both alone and in combination with TCS. To date, only a single HTH study has compared JAK inhibitors (upadacitinib) with dupilumab directly, suggesting that upadacitinib 30 mg once daily as monotherapy demonstrated superior efficacy vs dupilumab 300 mg Q2W regarding EASI-70 and EASI-90 (31). This is similar to the broad conclusions of the current study, demonstrating that upadacitinib is associated with better improvement in EASI score than dupilumab as monotherapy.

Previous review studies have investigated the efficacy of systemic therapies in atopic dermatitis (35–38). A network meta-analysis, which included only RCTs published before October 2019, concluded in agreement with the current findings that upadacitinib 30 mg once daily had the numerically highest improvement in EASI-50, EASI-75 and EASI-90 in monotherapy RCTs, and abro-

citinib 200 mg once daily had the highest improvement in EASI-75 and EASI-90 in combination therapy RCTs (35). However, in the same study abrocitinib 200 mg once daily was also responsible for the highest improvement in EASI-50, as opposed to the current study, in which dupilumab 300 mg Q2W demonstrated superior efficacy than abrocitinib regarding improvement in EASI-50. A possible explanation for this difference could be that the network study investigated efficacy among both adolescents and adults, as opposed to the current study, in which only adults were included, and a larger number of RCTs investigating treatment with dupilumab was included, which may eventually impact the findings. A more recent network meta-analysis investigating systemic treatment for patients with moderate-to-severe AD concluded that treatment with abrocitinib 200 mg and upadacitinib 30 mg both daily were associated with slightly better scores of change in EASI score than dupilumab 300 mg Q2W (36). However, there are some important differences between this study (36) and the current study, including that, in this study, both children and adults with moderate-to-severe AD were included and the primary outcome was change in EASI score in general, and not specifically improvement in EASI-50, EASI-75 and EASI-90. At the same time, subgroup analysis in this network meta-analysis study limited to trials with and without concomitant use of TCS, respectively, did not substantially alter effect estimates or conclusions (36). This is, however, not in agreement with the findings of the current study or another previous network meta-analysis (35). Allowing patients to use concomitant topical corticosteroid (TCS) is an important factor in the design of randomised control studies (RCSs), which can be explained by the fact that TCS may increase treatment response in the intervention and control groups. This may be the reason why not concluding any difference in treatment responses among patients regarding the allowance of concomitant TCS was considered a limitation by authors of the network meta-analysis (36).

Another meta-analysis investigating the treatment of both adolescents and adults with moderate-to-severe AD based on improvement in EASI-75 concluded that the highest numerical achievement was seen in upadacitinib 30 mg once daily as monotherapy, and in abrocitinib 200 mg once daily as combination therapy, similar to the findings of the current study (37). However, the same study reported that the efficacy gap between abrocitinib and dupilumab was reduced with the consistent use of TCS, suggesting that concomitant use of TCS may partially compensate for the lower efficacy of dupilumab treatment (37). No data regarding improvement in EASI-50 and EASI-90 was reported in the meta-analysis study (37). The last similar review study investigating systemic treatment of AD was closely studied in order to discuss the results of the current study (38). However, this was not possible, due to the differences in these studies, including that the review study reported only the outcomes of included studies without investigating any direct comparison of the treatment drugs (38). At the same time, in the review article, systematic treatment of AD was investigated based on different studies, including RCTs, observational and meta-analysis among both paediatric and adult patients (38). The current study results for treatment with tralokinumab were consistent with previous network meta-analysis and review studies, suggesting that treatment with abrocitinib, upadacitinib and dupilumab were most effective compared with tralokinumab (35–37).

Regarding the safety of JAK inhibitors among patients with AD, few data are available. However, the safety of JAK inhibitors seems not to be very different in the studies, when used as monotherapy (26, 28, 39). Common adverse events associated with JAK inhibitor treatment regarding AD include eczema, headache and abdominal pain (26, 28, 39). In general, common adverse events linked to JAK inhibitors include infections of the upper respiratory tract, headache or diarrhoea (40–42). Blood count alterations seem to be reversible and normalize after withdrawal (43, 44). However, an increased risk of bacterial and viral infection, such as reactivation of herpes zoster infection, has been described to be more frequent than treatment with dupilumab (45–48). Although the overall incidence of serious adverse events associated with the use of JAK inhibitors for AD is low, data regarding the use of JAK inhibitors in other skin diseases suggest a potentially slightly increased risk of more serious adverse events, such as thromboembolic, cardiovascular and haematological events (49, 50). However, patients with AD are often younger and a relatively healthier patient population, and less susceptible to severe adverse events, compared with elderly individuals. This may be the reason why severe adverse events are less common or even unobserved in AD trials (51).

Study limitations

This study has some limitations. Only those studies investigating patients with moderate-to-severe AD were included. However, the studies used different definitions of severity. This could potentially have impact the conclusions.

The current study did not include the percentage change in EASI from baseline in the meta-analysis, since few studies provided the necessary data. This may also have had an impact on the conclusions.

There may be a risk of uneven distribution regarding studies investigating EASI-50, EASI-75 and EASI-90 as monotherapy and combination therapy. Unfortunately, upadacitinib was only presented as monotherapy and not as combination therapy, making comparison with the other drugs impossible when it comes to combination therapy. This may play a major role for the conclusion

of this study. However, the EASI responses appear to be higher for upadacitinib and dupilumab and, compared with other agents, significant conclusions cannot be drawn due to differences in study design and dose of medication.

The efficacy and safety of the drugs included in this review were investigated in weeks 12 or 16. However, further studies are needed to determine the long-term efficacy and safety of monoclonal antibodies and JAK inhibitors. In addition, abrocitinib, upadacitinib and baricitinib have only been studied among adults and adolescents (aged 12–17 years), which limits their use among lower age groups.

Conclusion

This review suggests that patients who have moderate-to-severe AD unresponsive to topical therapies may benefit from treatment with JAK inhibitors, such as upadacitinib, abrocitinib, and baricitinib. In this updated systemic review and meta-analysis, treatment with upadacitinib 30 mg once daily as monotherapy had the numerically highest efficacy regarding EASI-50, EASI-75 and EASI-90. In combination therapy studies with TCS, dupilumab 300 mg Q2W had the highest efficacy regarding EASI-50, and abrocitinib 200 mg once daily had the highest score regarding EASI-75 and EASI-90. The current findings suggest that treatment with JAK inhibitors may be associated with comparable results, both as monotherapy, but also in combination therapy with TCS. However, treatment with dupilumab seems to be most effective, when in combination therapy with TCS. Treatment with abrocitinib, upadacitinib and dupilumab seems to be more effective than tralokinumab. HTH studies are required in order to place new treatments in the correct order in AD guidelines.

Conflicts of interest: MASH reported receiving grants from Leo Foundation. GBEJ reported receiving grants from AbbVie, LEO Foundation, Afyx, InflaRx, Janssen-Cilag, Novartis, UCB, CSL Behring, Regeneron, Sanofi, Boehringer Ingelheim, Union Therapeutics, and Toosonix and personal fees from Coloplast, Chemocentryx, LEO Pharma, Incyte, Kymera, and VielaBio. KSI has been part of advisory boards and received personal fees from Astra Zeneca, Leo Pharma; Sanofi Genzymes and Eli Lilly. MASH, GBEJ and KSI declare that none of the conflicts of interest mentioned had any influence on the content of this manuscript.

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