



A systematic review on the off-label use of montelukast in atopic dermatitis treatment

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Abstract

Background Atopic dermatitis (AD) is the most common form of eczema. As leukotriene mediators are involved in the inflammatory phase of atopic dermatitis, montelukast has been suggested as a possible therapy. **Aim of the review** To evaluate the safety and efficacy of montelukast off-label use for the treatment atopic dermatitis. **Method** A search was performed from database inception until March 2018 in six electronic databases for randomized-controlled-trials examining the use of montelukast for AD. **Results** Among 301 articles screened, 11 studies met the inclusion criteria and were included in the review. The study populations consist of paediatric and adult subjects with moderate-to-severe AD. Montelukast use was shown to improve symptoms such as pruritus in four studies. Another 2 studies reported that montelukast could improve symptoms similar to the standard regimen of topical steroid and oral antihistamine. However, five studies reported that montelukast had no effects in symptoms alleviation. The use of montelukast was associated with a similar safety profile to placebo and well-tolerated with minimal adverse effects. **Conclusion** There is limited evidence to suggest that the off-label use of montelukast is effective in treating moderate-to-severe AD. Further research with larger study populations employing standardized endpoint measuring instrument is warranted to further investigate the off-label use of montelukast in AD treatment. Until then, the use of conventional treatments including optimal daily skin hydration should remain the mainstay in the management of atopic dermatitis. In fact, for moderate-to-severe condition, steroid sparing immune-suppressants should still be used clinically until more effective and safer alternative is discovered.

Keywords Atopic dermatitis · Eczema · Leukotriene receptor antagonists · Montelukast · Off-label use · Systemic therapy

Abbreviations

AD	Atopic dermatitis
RCTs	Randomized controlled trials
LTRA	Cysteinyl-leukotriene-1 receptor antagonist
IgE	Immunoglobulin E
LTs	Leukotrienes
SCORAD	Severity Scoring of Atopic Dermatitis
SASSAD	Six Area, Six Sign Atopic Dermatitis
EASI	Eczema Area and Severity Index
ADASI	Atopic Dermatitis Area and Severity Index
IGA	Investigators' Global Assessment

LTE4	Leukotriene E4
EDN/EPX	Eosinophil-derived neurotoxin/eosinophilic protein X
ECP	Eosinophilic cationic protein
QoL	Quality of life
CDLQI	Children's Dermatology Life Quality Index
CBC	Complete blood count

Impacts on practice

- Montelukast should not be recommended for (off-label) use in moderate-to-severe atopic dermatitis treatment due to the limited evidence on efficacy.
- Until more convincing evidence is present, clinicians are recommended to focus on the present available systemic therapies of moderate-to-severe atopic dermatitis such as steroid sparing immune-suppressants.

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Introduction

Atopic dermatitis (AD), more commonly known as eczema, is a chronically relapsing inflammatory skin disorder that is characterized by pruritic rashes, and accompanied by cutaneous physiological dysfunction [1–4]. It is commonly associated with elevated level of immunoglobulin E (IgE) and a family history of atopic disorders which include bronchial asthma and allergic rhinitis [1, 2]. These three disorders have numerous common pathophysiological elements and are collectively referred to as the ‘atopic triad’ [2, 5]. AD affects approximately 20% of children, with majority of them in children less than the age of 5 years [6–8]. In adults, population studies report an overall prevalence of about 3% [8, 9]. AD patients often express embarrassment from the skin lesions, and the disease can adversely affect personal relationships and social interactions. The symptoms of AD, particularly pruritus, can be intractable and eventually lead to significant sleep deprivation and emotional distress [10].

At present, there are no effective therapeutic options that directed to the cure of this skin disorder, but various treatment options are available for symptomatic relief of the disease [11]. The use of emollients, avoidance of irritants, oral antihistamines and topical corticosteroids are the mainstay of the therapy for mild AD [11]. In moderate-to-severe conditions, the use of systemic oral glucocorticoids or other steroid-sparing immunosuppressive agents such as cyclosporine A, mycophenolate mofetil, azathioprine and methotrexate in addition to the treatment mentioned above are warranted [11]. Due to an overall unfavorable risk–benefit profile, these systemic agents are only recommended during the acute flare-up phase for a limited therapeutic period [11]. For the recent years, various case reports and clinical trials have also investigated the potential of biologic therapies such as dupilumab [12] and interferon gamma [13] in the treatment of severe AD. Of these biologics, dupilumab has received US FDA breakthrough therapy designation for adult AD [12]. However, considering the high cost of biologic therapy, this drug class may not be widely accessible to all the refractory moderate-to-severe AD patients. An overview of systemic therapies for AD [12, 14] is presented in Table 1.

Recent research suggests that leukotrienes (LTs) may play a role in the pathogenesis of AD [15–19]. Studies have shown that patients with severe eczema have activated circulating basophils *in vivo* and increased basophil releasability of LTs [20] and higher urinary LT levels compared to healthy volunteers [21], suggesting the potential use of leukotriene receptor antagonist in the treatment of AD.

Montelukast, a cysteinyl-leukotriene-1 receptor antagonist (LTRA) is an oral medication approved by the FDA for prophylaxis and chronic treatment of asthma and allergic rhinitis [22–24]. Due to numerous common pathophysiological

elements of the ‘atopic triad’ including activated circulating basophils and leukotrienes [2, 5], therapies that can reduce *in vivo* synthesis of leukotrienes should ameliorate symptoms of atopic dermatitis [25–27]. The first study which showed montelukast may be useful in patients with AD came from an observational study by Biswas et al., which noted montelukast was able to improve the skin condition in patients with AD [28]. This had led to several recent studies which had examined the response of montelukast in AD patients [1, 29–31]. In a case series by Hon et al. [30], the author reported an improvement in total SCORAD score of their patients between 30–84% when treated with montelukast. In contrast, Silverberg et al. found no demonstrated benefit of montelukast in another study [31].

Aim of the review

To assess the possible role of montelukast in atopic dermatitis, we performed a systematic review of randomized controlled trials (RCTs) that evaluate the safety and efficacy of montelukast as a potential therapeutic option for atopic dermatitis.

Method

Data sources and searches

We performed a systematic search in five electronic databases: PubMed, Embase, CINAHL, AMED and Web of Science to identify for published studies investigating the efficacy and safety of montelukast off-label use in the treatment of skin allergy conditions. The search terms included “safety OR efficacy OR effectiveness”, “anti-leukotriene OR leukotriene receptor antagonist OR LTRA OR montelukast”, “skin allergy OR atopic dermatitis OR eczema”. All search were performed from database inception until March 2018. This search was supplemented with a search on ClinicalTrials.gov to identify for additional studies.

Study selection

Studies which met the following criteria were eligible for inclusion: (1) examined the use of montelukast for the treatment of atopic dermatitis; (2) reported the efficacy and/or adverse event profiles of montelukast; (3) randomized interventional trials and (4) available as full text. Studies were excluded if; (1) only abstract were available; (2) case series/case reports; (3) non-interventional studies or (4) articles published in foreign languages other than English medium. In accordance with the criteria, articles were screened independently based on the relevance of titles and abstracts by

Table 1 Overview of systemic therapies for moderate-to-severe AD patients

Drug	Dosage (adult)	Dosage (paediatric)	Dosage form and scheduling	Important adverse effects	Laboratory monitoring parameters
<i>Non-biologic drugs</i>					
Cyclosporine [14] (is the only approved non-biologic drug for systemic treatment of adult AD)	3–6 mg/kg/day standardly 150–300 mg/day	3–6 mg/kg per day	Oral cyclosporine should be administered in divided doses twice daily and taken at the same time every day for maximum benefit	Infection, nephrotoxicity, hypertension, tremor, hypertrichosis, headache, gingival hyperplasia, and increased risk of skin cancer and lymphoma	Blood count, creatinine, urea, cholesterol, triglycerides, electrolytes
Azathioprine [14]	1–3 mg/kg/day	1–4 mg/kg/day	Azathioprine is currently available in the US in tablet form only, although liquid formulations can be compounded. It may be given once daily	Nausea, vomiting, other gastrointestinal symptoms (bloating, anorexia, cramping), headache, hypersensitivity reactions, elevated liver enzymes, and leukopenia	Leucocyte count, liver enzymes
Methotrexate [14]	7.5–25 mg/week	0.2–0.7 mg/kg/week	Methotrexate is readily available in solution (for intramuscular or subcutaneous injection) and oral tablet form. Methotrexate is usually given as a single weekly dose	Elevated liver enzymes, cytopenias, Interstitial pneumonitis, pulmonary fibrosis, ulcerative stomatitis, nausea, vomiting, diarrhea, malaise, fatigue, Chills and fever, dizziness, risk of infection, GI ulceration and bleeding, photosensitivity, alopecia, risk of malignancies:	Blood count, liver enzymes
Mycophenolate mofetil [14]	1.0–1.5 g orally twice daily	1200 mg/m ² daily, which corresponds to 30–50 mg/kg daily	Mycophenolate mofetil is available in oral suspension, capsules, and tablets, and is given twice daily	Gastrointestinal disturbances, fatigue, hematological abnormalities flu-like syndrome, liver dysfunction	Blood count, liver enzymes
Systemic oral glucocorticoids [14]	0.5–1.0 mg/kg* *A taper is indicated to decrease the risk of adrenal suppression *Regardless of the taper schedule, flare of the dermatitis upon steroid discontinuation may be expected	Systemic steroids are not recommended for children with AD unless they are required to manage comorbid conditions (such as asthma exacerbations), or are given as part of a short-term transition protocol to non-steroidal systemic immunomodulatory agents	Prednisone and prednisolone are available as a tablet or oral solution for enteral administration, while triamcinolone acetonide is available as a suspension for intramuscular injection	hypertension, glucose intolerance, gastritis, weight gain, decreased bone density, adrenal suppression, and emotional lability, decreased linear growth (for paediatric patients)	Blood count, glycaemia
<i>Biologic drugs</i>					
Dupilumab (anti-Interleukine-4 receptor-α) [12]	600 mg (i.e., two 300-mg injections) subcutaneously (SC) once, and then 300 mg SC every other week	Safety and efficacy not established	Only available in 300 mg/2 mL single-dose prefilled syringe	Increased risk of infection, headache, gastrointestinal disturbances, injection site reactions	Blood count, liver enzymes

Table 1 (continued)

Drug	Dosage (adult)	Dosage (paediatric)	Dosage form and scheduling	Important adverse effects	Laboratory monitoring parameters
Interferon gamma (IFN- γ) [14]	There is no recommended optimal dose of IFN-G for the treatment of atopic dermatitis. Dosages for FDA-approved indications are based on body surface area of adult Body surface area > 0.5 m ² : 50 mcg/m ² SC 3 times/week Body surface area ≤ 0.5 m ² : 1.5 mcg/kg SC 3 times/week	There is no recommended optimal dose of IFN-G for the treatment of atopic dermatitis. Dosages for FDA-approved indications are based on body surface area of children Body surface area > 0.5 m ² : 50 mcg/m ² SC 3 times/week Body surface area < 0.5 m ² : 1.5 mcg/kg SC 3 times/week	IFN- γ is available solely in solution form for subcutaneous injection. Usually administered three times weekly	fatigue, fever, nausea, vomiting, myalgia	Blood count, liver enzymes, renal function tests and urinalysis

two authors (WKC and SWHL) and potentially relevant records were retrieved. Any disagreement was resolved through a discussion.

Data extraction and quality assessment

Data from eligible studies were extracted independently by two authors (WKC and SWHL) using a standardized extraction template developed for the study including the study designs, eligibility criteria, participants demographics, interventions, comparators, efficacy results, safety outcomes and other relevant notes from the authors. We subsequently assessed the study quality of RCTs using the Cochrane Risk of Bias Tool [32]. Any disagreement was resolved through discussion among the authors and an adjudicator if necessary.

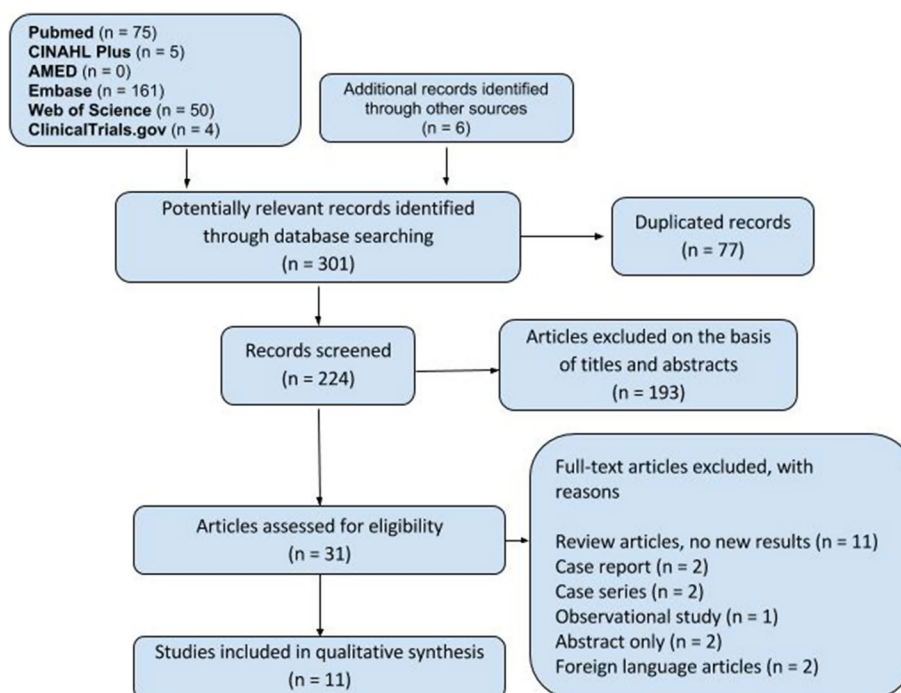
Results

Literature search and quality assessment

Of 301 articles identified, 31 were selected for full text review and 11 articles were included in the final qualitative analysis (Fig. 1). Four of the trials investigated the effects of montelukast in pediatrics with AD (aged 2–16 years) [33–36], four trials examined only adult participants [37–40] and the remainder three comprised of a mixture of children and adults [41–43] (Table 2). These studies included a total of 385 participants with sample size ranging from 8 [37] to 61 [38] patients. Most studies included both male and female participants except one study which recruited only male subjects [39]. The protocols duration ranged between 4 and 20 weeks, with dosages between 4 and 10 mg once daily. In general, montelukast 4 or 5 mg was used in pediatric subjects while 10 mg was used for adult population. Of the eleven RCTs, 9 were placebo-controlled [33–39, 41, 43] and two were using active comparators respectively [40, 42]. The RCTs were conducted in 9 different countries; Korea [33], Qatar [34], Hong Kong [35], United States (two studies) [36, 37], Finland [38], Italy (two studies) [39, 40], United Kingdom [41], Bangladesh [42] and Denmark [43].

Quality assessment

Only four studies (~36%) described the random sequence generation and allocation concealment of the studies adequately (Fig. 2) [33–35, 41]. Two included studies (~18%) had a high risk of participant and personnel blinding as these were open label or single-blind studies (Fig. 3) [40, 42]. Seven studies (~64%) [33–36, 38, 39, 43] did not specify

Fig. 1 Flow chart of the study selection process

how blinding of outcomes was implemented whereas two studies (~18%) clearly specify the protocol in their methodology [37, 40]. Only two studies (~18%) described the use of intention-to-treat analysis when evaluating the outcomes [41, 43]. One study (~9%) had been rated high risk of attrition and selective in reporting as the authors did not report the number of patients completed the study and all the pre-specified endpoints measurement respectively [36]. Four studies (~36%) received funding from the manufacturers of montelukast (Fig. 2) [34, 36, 38, 41].

Clinical severity and extent of atopic dermatitis

Of the eleven RCTs included in the review, ten of the studies utilized scoring system tools to assess the drug response in terms of improvement in severity and extent of AD disease (Table 3) [33, 35–43]. One study conducted by Ehlayel et al. [34] assessed the clinical outcome using a surrogate endpoint of number of rescue medication required during intervention period instead of any clinical scoring tools. The scoring systems used by the investigators varied, with Severity Scoring of Atopic Dermatitis (SCORAD) being the most commonly utilized instrument by the investigators (four studies) [33, 39, 40, 42]. The other studies used Six Area, Six Sign Atopic Dermatitis (SASSAD) [41], Eczema Area and Severity Index (EASI) [43], Investigators' Global Assessment (IGA) rating [36] and Atopic Dermatitis Area and Severity Index (ADASI) [37] scores respectively. Pei et al. assessed the severity of her study subjects by quantifying the six signs of AD; erythema, edema/population,

oozing/crusting, excoriation, lichenification and dryness. The extent of disease score was evaluated by estimating the percentage of body surface area affected by the atopic disease [35]. Another study carried out by Lehtimäki et al. [38] used patient self-reported questionnaires to assess the primary study outcome.

Montelukast versus placebo

Among the nine placebo-controlled studies, four trials [35–37, 39] demonstrated superiority of montelukast compared to placebo in the improvement of at least one clinical AD presentation. However, no significant differences were noted in the remaining studies. (Table 3) [33, 34, 38, 41, 43] In the study by Melamed et al. [36], the author demonstrated that montelukast was effective in alleviating the pruritus symptom as compared to the other clinical presentations of AD. This was similarly noted in two other studies which showed montelukast improved the overall clinical signs and symptoms of AD when 10 mg was used in adults [37, 39]. On the contrary, Pei et al. [35] also demonstrated the efficacy of montelukast in the improvement of disease severity such as erythema and papulation but not the extent of disease (i.e. percentage of body affected by AD).

Montelukast versus active treatment

In the two active-controlled trials [40, 42] both studies utilized topical steroid and oral antihistamines as the active comparators. The single blind, parallel study by Capella

Table 2 Patient demographic and study characteristics of RCTs

Author, country, year [reference]	Study design	Initial sample size	Drop out rate (%)	Male to female ratio (M/F)	Age range (year)	Study duration (weeks)	Study subjects
<i>Pediatrics</i>							
Jeon et al., Korea, 2016 [33]	Randomized, double-blind, placebo-controlled crossover study	54	20.4	21/22*	2–6	20	Moderate to severe atopic dermatitis diagnosed according to Hanifin and Rajka's criteria and with SCORAD > 15
Ehlayel et al., Qatar, 2016 [34]	Randomized, double-blind, placebo-controlled, crossover study	25	0	13/12	2–16	12	Moderate to severe AD
Pei et al., Hong Kong, 2001 [35]	Randomized, double-blind, placebo-controlled, crossover study	15	26.7	4/7*	6–16	12	atopic dermatitis diagnosed according to Hanifin and Rajka's criteria and resistant to conventional treatment (moderately potent topical steroid, soap substitutes, and emollients)
Melamed I et al., United States, 2017 [36]	Randomized, double-blind, placebo-controlled, parallel study	20	Not stated	11/9	1–8	9	Positive reactivity to food (indicated by skin or RAST test) and 10–25% body area affected with atopic dermatitis;
<i>Adults</i>							
Yanase et al., United States, 2001 [37]	Randomized double-blind placebo-controlled crossover study	8	0	M/F (not stated)	≥ 18	5	With at least 1 year of intermittent or persistent symptoms of atopic dermatitis
Lehtimäki et al., Finland, 2009 [38]	Randomized, double-blind, placebo-controlled, crossover study	61	26.2	12/33 ^a	18–40	6	Pollen-sensitized subjects who had allergic symptoms from both the upper and lower airways and allergic symptoms outside the airways (conjunctivitis, oral symptoms, eczema and/or urticaria)
Eustachio et al., Italy, 2003 [39]	Randomized, double-blind, placebo-controlled, parallel study	20	0	20/0	18–28	10	Severe AD with mean SCORAD index objective score > 40
Capella et al., Italy, 2001 [40]	Randomized, single-blind, active-controlled parallel study	32	0	18/14	18–56	6	Moderate to severe AD defined characterized by SCORAD ≥ 30
<i>Adults + children</i>							
Friedmann et al., United Kingdom, 2007 [42]	Randomized, double-blind, placebo-controlled parallel study	60	10	20/40	16–60	10	Moderate severity, defined by a six-area, six-sign atopic dermatitis (SASSAD) score in the range 12–50

Table 2 (continued)

Author, country, year [reference]	Study design	Initial sample size	Drop out rate (%)	Male to female ratio (M/F)	Age range (year)	Study duration (weeks)	Study subjects
Rahman et al., Bangladesh, 2006 [42]	Randomized, open label trial	31	0	17/14	≥ 6	4	Atopic dermatitis diagnosed according to Hanifin Rajka criteria, at least 1 year of intermittent or persistent symptoms of AD and SCORAD ≥ 30
Veien et al., Denmark, 2005 [43]	Randomized, double-blind, placebo-controlled parallel study	59	20.3	16/43	16–70	6	Moderate to severe atopic dermatitis diagnosed according to Hanifin and Rajka's criteria and with involvement of 5–35% of the body surface and a minimum score of 4.5 based on Rajka and Langeland's grading system

*Based on final sample size

et al. [40] also examined the use of oral antibiotic (clarithromycin) and hydrating creams, forming a quadruple combined regimen as the active comparator to montelukast group. In this study, montelukast is shown to be comparable to the quadruple regimen in term of efficacy. Similarly, the other open label study by Rahman et al. [42] demonstrated that montelukast is superior to the standard regimen of topical steroid and oral antihistamine.

Surrogate biological markers for severity of AD

Several studies also measured the levels of biological markers as the secondary outcomes, since they may be useful for identifying eosinophil activities in allergic diseases [11, 25–27, 33]. There were 3 different markers measured; namely the levels of urinary LTE4, eosinophil-derived neurotoxin/eosinophilic protein X (EDN/EPX) and eosinophilic cationic protein (ECP). Jeon et al. [33] reported that montelukast at 4–5 mg did not significantly improve the urinary markers of LTE4 and eosinophil protein X/eosinophil derived neurotoxin (EPX/EDN) in children with atopic dermatitis. Melamed et al. [36] reported a similar result in which montelukast has no significant effect on urinary LTE4. In contrast, Capella et al. [40] showed that montelukast 10 mg once daily significantly reduced the surrogate markers of serum ECP and EDN/EPX in adult subjects.

Quality of life (QoL)

Pei et al. [35] assessed the effects of montelukast in regards to improvement of QoL using the Children's Dermatology Life Quality Index (CDLQI). In this pilot trial of 15 participants, the subjective patient scores for the effect of AD on daily living during the interventional phase showed no significant differences between both treatment and placebo groups throughout the study.

Amount of rescue medication used during montelukast treatment period

Four studies [34, 36, 38, 41] reported the amounts of rescue medications (topical steroids, oral antihistamines and oral antibiotics) required during the treatment periods (Table 3). In all the studies, no significant differences in regards to amounts of rescue medications used during interventional periods were observed in between montelukast treatment groups and placebo groups [34, 36, 38, 41].

Safety outcomes of montelukast intervention

Eight studies [33, 35, 36, 39–43] reported the safety outcome for montelukast (Table 3). Five of the studies [36, 39, 40, 42, 43] reported no adverse effects related to montelukast.

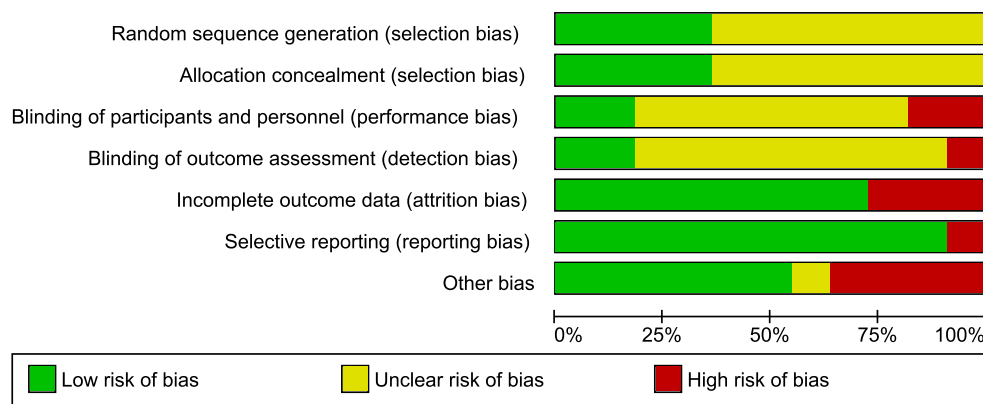


Fig. 2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Two studies shown that the drug was well-tolerated by the patients throughout the trials [33, 34]. In the remaining one study by Friedmann et al. [41], the author reported that there was an event of septicaemia which occurred in one of the montelukast treated patients at the end of the intervention period, but the patient had a rapid recovery. In the same study, another montelukast treated subject suffered from dizzy spells, and subsequently withdrew from the trial. Adverse events were otherwise of a fairly mild and included headaches, respiratory tract infections and mild gastrointestinal disturbances. Investigators of three other trials [33, 36, 40] also measured the complete blood count (CBC) of the study subjects and found no significant differences in between treatment and active/placebo groups, suggesting that montelukast did not cause any blood chemistry alteration.

Discussions

In this review, we found a total of 11 RCTs which examined the effects of montelukast in patients with AD. Overall, we noted conflicting results with six studies supporting the use of montelukast in AD [35–37, 39, 40, 42] and another five trials reporting otherwise [33, 34, 38, 41, 43]. In most of the RCTs, montelukast was able to significantly reduce the symptoms of pruritus in the patients examined. However, no significant differences in other outcomes were noted, suggesting the limited efficacy of montelukast in the overall amelioration of AD symptoms. Several reasons could have contributed to this observation. Firstly, to date, there is currently no single gold standard for assessing the disease severity of AD. In trials investigating control of atopic dermatitis, four main domains should be measured by the primary outcomes which include patient-reported symptoms, clinical signs, long-term control and health-related quality of life [44]. Without a standardized endpoint measuring

instrument, interpretation and comparison of outcomes between studies had become extremely difficult, precluding a meta-analysis. For example, we found that a few studies had the SCORAD index as a primary outcome assessment [33, 39, 40, 42] while others had used ADASI, SASSAD and EASI scoring tools [37, 41, 43]. There is now a recognition of the lack of uniformity in disease severity scale and efforts are currently underway to standardize these measurement [44].

Secondly, most of the studies had a relatively small sample size with the largest trial of only 61 subjects [38]. Most of the studies that demonstrated a positive dose response have relatively smaller sample size compared to studies with negative results, suggesting the possibility of type II errors due to the limited sample size and power. Furthermore, efficacy of montelukast was demonstrated only for a specific symptom rather than the whole disease spectrum. For instance, in the pilot study by Pei et al. [35] which examined 15 pediatric subjects, the authors found that despite an improvement in severity score, there were no significant differences in extent of disease and quality of life between the treatment and placebo groups. Similarly, Melamed et al. [36], Capella et al. [40] and Rahman et al. [42] only demonstrated that montelukast was able to help in alleviating the pruritus symptom but was totally devoid of activity on xerosis.

The inconsistent findings may also be due to the different degrees of disease severity examined. This may have led to studies that investigated more severe AD patients to be less likely to obtain favorable findings as compared to trials involving only mild to moderate AD subjects. Several studies had also allowed the use of concomitant medications such as antihistamines, antibiotics and topical steroids which could have resulted in more favorable results for the montelukast group [35–37, 40].

In order to evaluate the potential of montelukast as a steroid sparing agent or adjunct therapy, several studies also

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Capella, G. L. 2001	?	?	-	+	+	+	+
Ehlayel, M. S. 2008	+	+	?	?	+	+	-
Eustachio, N. 2002	?	?	?	?	+	+	?
Friedmann, P. S. 2007	+	+	+	?	+	+	-
Jeon, Y. H. 2016	+	+	?	?	+	+	+
Lehtimäki, L. 2009	?	?	?	?	-	+	-
Melamed, I. 2017	?	?	?	?	-	-	-
Pei, A. Y. S. 2001	+	+	?	?	-	+	+
Rahman, M. L. 2006	?	?	-	-	+	+	+
Veien, N. K. 2005	?	?	?	?	+	+	+
Yanase, D. J. 2001	?	?	+	+	+	+	+

Fig. 3 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

assessed the number of rescue medications used by participants during intervention periods [34, 36, 38, 41]. The most common rescue medications used were oral antihistamine, systemic antibiotics and topical corticosteroid creams, but none of the studies reported any significant reduction in the use of concomitant rescue medications. Analysis of outcomes from studies which reported safety data showed that montelukast was well tolerated, [33, 35] with some RCTs even reported that no adverse drug effects were observed in the study subjects [36, 39, 40]. Similarly, no clinically relevant differences in laboratory adverse events, including transaminase elevations were reported [33, 36, 40] and this

concur with a recent review by Storm et al. [45]. Taken together, these results provide very little evidence that montelukast is useful as either a mono-therapy or as an adjunct to AD treatment.

Results of this study suggest that at the moment, there is very little evidence to support the use of montelukast in AD. In fact, to date, only cyclosporine and dupilumab are approved for short-term treatment of severe refractory AD in United States and many European countries, with the other steroid sparing immunosuppressive agents being used off-label. In 2014, Garritzen et al. [46] published a medical chart review evaluating the effectiveness and safety of various immunosuppressive agents during 10-year treatment in a total of 334 AD adult patients and found that cyclosporine represented the first choice of systemic therapy; however, severe adverse events were often reasons for its discontinuation as well. Dupilumab was a recent licensed and approved biologic to be used for moderate-to-severe AD patients. However, due to the high cost of biologic therapy, dupilumab is not widely accessible to patients. As such, pharmacists as the drug experts can act as gatekeepers to ensure the judicious use of drugs. They can also act as a focal point of information to allay patients' fear concerning the safety of many pharmacotherapies used to treat AD.

Pharmacist, as primary care providers are an ideal position to help support patients with AD and their family members as they are often the first point of care to seek for medical help [46]. Having often cultivated a good rapport with their patients, they can assess their patients' understanding towards their disease and reinforce non-pharmacological treatments and eventually, ensure patient compliance. Some of the key topics could include highlighting educating on the goals of therapy and understanding triggers and when to avoid. In addition, they could also reinforce the importance of basic skin care practices such regular use of moisturisers as well as safety of topical corticosteroids when used appropriately.

This study has several limitations. Firstly, as with most systematic reviews, there are possibilities that some published or unpublished studies were not identified. To minimize this, we also searched for grey literature and checked the reference list of articles found. Most of the trials had only a very small sample size, and were of low quality, which had limited our ability to draw firm conclusions. As such, further randomized-placebo-controlled studies with larger populations, longer study duration and consideration of other confounding factors including concomitant use of traditional and complementary medicines are warranted to further investigate the efficacy of montelukast in the treatment of atopic dermatitis.

Table 3 Relevant findings of the RCTs

Author, country, year [reference]	Intervention	Concomitant therapy	Outcomes assessed	Relevant finding (s)
<i>Pediatrics</i>				
Jeon et al., Korea, 2016 [33]	Montelukast 4 mg OD (for < 6 years old) Montelukast 5 mg OD (for ≥ 6 years old)	Nil	1. SCORAD (objective + subjective assessment of severity of AD) 2. Urinary LTE4 3. Eosinophil-derived neurotoxin (EDN)	1. No statistically significant difference between montelukast and placebo groups in terms of i. SCORAD index ($P=0.43$) ii. Urinary LTE4 ($P=0.26$) iii. Urinary EDN ($P=0.10$) 2. No abnormal findings of CBC or blood chemistry (AST/ALT, BUN/creatinine, and protein/albumin) either before or after treatment 3. No patient was withdrawn due to an adverse event with respect to montelukast
Ehlayel et al., Qatar, 2016 [34]	Montelukast 5 mg OD (for < 12 years old) Montelukast 10 mg OD (for older children)	1. Nasal medications for allergic rhinitis 2. Inhaled asthma medications	Amount of 1. Oral antihistamine 2. Topical steroid 3. Oral antibiotics consumed during treatment period	During montelukast use, the amounts of oral histamines ($P=0.313$), or topical steroids ($P=0.300$), or oral antibiotic courses ($P=0.183$) were NOT significantly different from their counterparts during placebo use
Pei et al., Hong Kong, 2001 [35]	Montelukast 5 mg OD	1. Soap substitute (light liquid paraffin) 2. Emollient (aqueous cream) 3. Topical steroid (clobetasone butyrate cream bd)	1. Six signs of AD (objective) *Erythema *Edema/papulation *Oozing/crusting *Excoriation *Lichenification *Dryness 2. Extent of disease score 3. Children's Dermatology Life Quality Index (CDLQI) (subjective)	1. Statistically significant improvement in severity of AD in patients on active treatment compared with placebo ($p<0.05$) 2. The change in the median extent-of-disease score was not statistically significant for either group 3. The subjective patient score for the effect of AD on daily living remained similar throughout the study, both within and between different groups 4. All patients tolerated the drug and placebo well during the period of this study

Table 3 (continued)

Author, country, year [reference]	Intervention	Concomitant therapy	Outcomes assessed	Relevant finding (s)
Melamed I et al., United States, 2017 [36]	Montelukast 4 mg OD (for 2–5 years old) Montelukast 5 mg OD (for 6–8 years old)	1. 1% hydrocortisone cream when necessary 2. Antihistamine (cetirizine) when necessary	1. Investigators' Global Assessment (IGA) rating 2. Puritus score 3. Use of rescue medication 4. Urinary LTE4	1. No significant difference in IGA rating in between both active and placebo groups 2. Significant reduction in puritus score ($p=0.002$) 3. Non-significant reduction in the use of rescue medication (hydrocortisone cream: $p=0.056$, cetirizine: $p=0.056$) 4. Non-significant difference in urinary LTE4 in between both active and placebo groups 5. No safety concern regarding the blood chemistry result in both groups and all parameters are in normal limit range
<i>Adults</i>				
Yanase et al., United States, 2001 [37]	Montelukast 10 mg OD	1. Emollients 2. Antihistamine 3. Weak topical steroids when necessary	1. ADASI score *Erythema *Induration *Excoriation *Lichenification *Scaling *Erosion	Significant difference in atopic dermatitis scores between placebo and active agent ($p=0.014$) Improvement in • Scaling/dryness ($p=0.003$) • Lichenification ($p=0.009$) • Induration ($p=0.016$) • Erythema ($p=0.024$) • Erosions ($p=0.027$)
Lehtimäki et al., Finland, 2009 [38]	Montelukast 10 mg OD	1. Antihistamine 2. Inhaled asthma medications	1. Allergic symptoms assessed by questionnaire 2. The need for rescue medication i.e. oral antihistamines	1. Montelukast was not effective in treating allergic symptoms outside the airways in subjects suffering from different manifestations of the atopic syndrome 2. No differences between montelukast and placebo treatments in the need for oral antihistamines
Eustachio et al., Italy, 2003 [39]	Montelukast 10 mg OD	No other treatments for AD were allowed	1. SCORAD (objective + subjective assessment of severity of AD)	1. Significant reduction in disease activity (measured by SCORAD index) in the montelukast group compared with placebo Group. ($p<0.02$) 2. No adverse effects were observed by the investigators or reported by patients

Table 3 (continued)

Author, country, year [reference]	Intervention	Concomitant therapy	Outcomes assessed	Relevant finding (s)
Capella et al., Italy, 2001 [40]	Montelukast 10 mg OD + one placebo tab thrice a day + pharmacological inert, non-moisturizing, non greasy gel twice daily versus combined regimen (oral cetirizine + oral clarithromycin + topical corticosteroids + hydrating preparations)	1. Inhaled or intranasal drugs or eye drops in the event of co-existing allergic asthma, rhinitis or keratoconjunctivitis	1. SCORAD (objective + subjective assessment of severity of AD) 2. Eosinophilic cationic protein (ECP) 3. Eosinophilic protein X (EPX)	1. Similar SCORAD reductions in both groups 2. ECP, EPX levels significantly reduced within each group 3. Montelukast completely devoid of activity in skin dryness 4. No adverse effect of Montelukast was observed
<i>Adults + children</i>				
Friedmann et al., United Kingdom, 2007 [41]	Montelukast 10 mg OD	1. Emollients 2. Antihistamines 3. Topical steroids provided that the use of these had been stable over the preceding month	1. SASSAD score (objective) 2. Usage of topical steroids during treatment period	1. No significant differences between the treatment groups in any of the parameters used to assess treatment response 2. Adverse events were generally of a mild nature except for a brief septicaemic illness in one subject receiving montelukast
Rahman et al., Bangladesh, 2006 [42]	Montelukast 5 mg OD (age 6–14 years old) Montelukast 10 mg OD (> 14 years above) versus conventional antihistamines + topical hydrocortisone 1%	Nil	1. SCORAD (objective + subjective assessment of severity of AD)	1. Statistically significant SCORAD improvement ($P = 0.003$) was observed in montelukast group 2. Pruritus was the most Influenced SCORAD item by montelukast group immediately followed by sleep loss and inflammatory signs 3. Montelukast completely devoid of activity in skin dryness 4. No adverse effect of Montelukast was observed
Veien et al., Denmark, 2005 [43]	Montelukast 10 mg OD	1. No other active topical or systemic treatment was permitted during the trial 2. Ample supply of emollient was provided to be used freely	1. Eczema area and severity index (EASI) score 2. Pruritus score	1. No difference in efficacy was seen among patients who received montelukast and the group given placebo 2. No side effects were seen in either of the active or placebo group

Conclusion

Results of this study suggest that despite a favorable safety profile, there is limited efficacy evidence to suggest the off-label use of montelukast in treating atopic dermatitis, regardless of its severity. Longer duration studies involving larger groups of patients with well-defined study designs are warranted to obtain a more valid and reliable measurement of intervention effects. Until then, the more conventional treatments of optimal skin hydration and infection control remain the mainstay of AD management regardless of its severity.

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