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[Intervention Review]

Leukotriene receptor antagonists for eczema

Leila Ferguson¹, Masaki Futamura², Efstratios Vakirlis³, Reiji Kojima⁴, Hatoko Sasaki⁵, Amanda Roberts⁶, Rintaro Mori⁵

¹Department of Dermatology, St Helier Hospital, Surrey, UK. ²Department of Pediatrics, Nagoya Medical Center, Nagoya, Japan. ³A¹ Department of Dermatology, Aristotle University Medical School, Thessaloniki, Greece. ⁴Department of Health Sciences, School of Medicine, University of Yamanashi, Yamanashi, Japan. ⁵Department of Health Policy, National Center for Child Health and Development, Tokyo, Japan. ⁶Nottingham Support Group for Carers of Children with Eczema, Nottingham, UK

Contact address: Masaki Futamura, Department of Pediatrics, Nagoya Medical Center, 4-1-1 Sannomaru, Naka-ku, Nagoya, 460-0001, Japan. masakifutamura@gmail.com.

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ABSTRACT

Background

Eczema is a common, chronic, inflammatory skin condition that is frequently associated with atopic conditions, including asthma. Leukotriene receptor antagonists (LTRAs) have a corticosteroid-sparing role in asthma, but their role in eczema remains controversial. Currently available topical therapies for eczema are often poorly tolerated, and use of systemic agents is restricted by their adverse effect profile. A review of alternative treatments was therefore warranted.

Objectives

To assess the possible benefits and harms of leukotriene receptor antagonists for eczema.

Search methods

We searched the following databases to September 2017: the Cochrane Skin Specialised Register, CENTRAL, MEDLINE, Embase, and the GREAT database. We also searched five trial registries, and handsearched the bibliographies of all extracted studies for further relevant trials.

Selection criteria

Randomised controlled trials of LTRAs alone or in combination with other (topical or systemic) treatments compared with other treatments alone such as topical corticosteroids or placebo for eczema in the acute or chronic (maintenance) phase of eczema in adults and children.

Data collection and analysis

We used the standard methodological procedures expected by Cochrane. The primary outcome measures were change in disease severity, long-term symptom control, and adverse effects of treatment. Secondary outcomes were change in corticosteroid requirement, reduction of pruritis, quality of life, and emollient requirement. We used GRADE to assess the quality of the evidence for each outcome.

Main results

Only five studies (including a total of 202 participants) met the inclusion criteria, all of which assessed oral montelukast; hence, we found no studies assessing other LTRAs. Treatment ranged from four to eight weeks, and outcomes were assessed at the end of treatment; therefore, we could only report short-term measurements (defined as less than three months follow-up from baseline). Montelukast dosing was 10 mg for adults (age 14 years and above) and 5 mg for children (age 6 years to 14 years). One study included children (aged 6 years and above) among their participants, while the remaining studies only included adults (participant age ranged from 16 to 70 years). The participants

were diagnosed with moderate-to-severe eczema in four studies and moderate eczema in one study. The study setting was unclear in two studies, multicentre in two studies, and single centre in one study; the studies were conducted in Europe and Bangladesh. Two studies were industry funded. The comparator was placebo in three studies and conventional treatment in two studies. The conventional treatment comparator was a combination of antihistamines and topical corticosteroids (plus oral antibiotics in one study).

Four of the studies did not adequately describe their randomisation or allocation concealment method and were considered as at unclear risk of selection bias. Only one study was at low risk of performance and detection bias. However, we judged all studies to be at low risk of attrition and reporting bias.

We found no evidence of a difference in disease severity of moderate-to-severe eczema after short-term use of montelukast (10 mg) when compared with placebo. The outcome was assessed using the modified EASI (Eczema Area and Severity Index) score and SASSAD (Six Area, Six Sign Atopic Dermatitis) severity score (standardised mean difference 0.29, with a positive score showing montelukast is favoured, 95% confidence interval (CI) -0.23 to 0.81; 3 studies; n = 131; low-quality evidence).

When short-term montelukast (10 mg) treatment was compared with conventional treatment in one study, the mean improvement in severity of moderate-to-severe eczema was greater in the intervention group (measured using SCORAD (SCORing of Atopic Dermatitis) severity index) (mean difference 10.57, 95% CI 4.58 to 16.56; n = 31); however, another study of 32 participants found no significant difference between groups using the same measure (mean improvement was 25.2 points with montelukast versus 23.9 points with conventional treatment; no further numerical data provided). We judged the quality of the evidence as very low for this outcome, meaning the results are uncertain.

All studies reported their adverse event rate during treatment. Four studies (136 participants) reported no adverse events. In one study of 58 participants with moderate eczema who received montelukast 10 mg (compared with placebo), there was one case of septicaemia and one case of dizziness reported in the intervention group, both resulting in study withdrawal, although whether these effects were related to the medication is unclear. Mild side effects (e.g. headache and mild gastrointestinal disturbances) were also noted, but these were fairly evenly distributed between the montelukast and placebo groups. The quality of evidence for this outcome was low.

No studies specifically evaluated emollient requirement or quality of life. One study that administered treatment for eight weeks specifically evaluated pruritus improvement at the end treatment and topical corticosteroid use during treatment. We found no evidence of a difference between montelukast (10 mg) and placebo for both outcomes (low-quality evidence, n = 58). No other study assessed these outcomes.

Authors' conclusions

The findings of this review are limited to montelukast. There was a lack of evidence addressing the review question, and the quality of the available evidence for most of the measured outcomes was low. Some primary and secondary outcomes were not addressed at all, including long-term control.

We found no evidence of a difference between montelukast (10 mg) and placebo on disease severity, pruritus improvement, and topical corticosteroid use. Very low-quality evidence means we are uncertain of the effect of montelukast (10 mg) compared with conventional treatment on disease severity. Participants in only one study reported adverse events, which were mainly mild (low-quality evidence).

There is no evidence that LTRA is an effective treatment for eczema. Serious limitations were that all studies focused on montelukast and only included people with moderate-to-severe eczema, who were mainly adults; and that each outcome was evaluated with a small sample size, if at all.

Further large randomised controlled trials, with a longer treatment duration, of adults and children who have eczema of all severities may help to evaluate the effect of all types of LTRA, especially on eczema maintenance.

PLAIN LANGUAGE SUMMARY

Are non-steroidal anti-inflammatory medicines known as leukotriene receptor antagonists helpful and safe for eczema?

Review question

We wanted to see if anti-inflammatory leukotriene receptor antagonists (LTRAs) reduced symptoms or improved quality of life in adults and children with established eczema; if they are safe; and whether they could be recommended as an effective alternative eczema treatment. We included studies that compared LTRAs with other treatments alone, such as topical corticosteroids (anti-inflammatory steroid (synthetic hormone) medications), or with placebo (an identical but inactive treatment).

Background

Eczema, also called 'atopic eczema' and 'dermatitis', is a common dry skin condition. Eczema can be mild, moderate, or severe depending on how itchy or red the skin is, how much skin is affected, and its impact on daily life. Eczema is sometimes linked to a group of conditions, including asthma. Corticosteroids are a commonly used treatment, but long-term treatment can produce unwanted side effects, such as

skin thinning. LTRAs have been shown to improve asthma symptoms, and their use in eczema would reduce the amount of steroids used. LTRAs are not currently given for eczema, and whether they are effective for this condition is uncertain.

Study characteristics

This evidence is current to September 2017. We found five studies with a total of 202 participants (both genders). All included participants had moderate-to-severe eczema diagnosed by a specialist doctor. The studies lasted four to eight weeks. The study setting was unclear in two studies, multicentre in two studies, and single centre in one study; the studies were conducted in Europe and Bangladesh. All studies used the LTRA montelukast, at a dose of either 5 mg or 10 mg. Only one study included children (31 participants, age 6 years and older). The age range for the other four studies was 16 to 70 years. LTRA treatment was compared with placebo or conventional treatment, which includes currently used eczema treatments, such as steroid creams. Varied scoring systems were used to calculate the effect of the treatments on participants' eczema. Two included studies were funded by the company that produces montelukast.

Key results

Limited available data meant we were unable to draw firm conclusions on the effectiveness of LTRA in eczema. Like other reviews on this topic, this review is unlikely to change how eczema is treated because there is no convincing evidence that montelukast, the only LTRA that could be assessed, is helpful for eczema.

We found no evidence of a difference between montelukast and placebo in terms of improving eczema disease severity (low-quality evidence). When montelukast was compared with conventional treatment, participants using montelukast in one study saw an improvement in disease severity, but no difference was observed in another study. We are uncertain about these results because the quality of the evidence was very low.

None of the studies looked at long-term eczema control, moisturiser (emollients) use, or quality of life.

We found no evidence that montelukast lessened itching or reduced the need for steroid creams during treatment when compared to placebo (low-quality evidence). The studies comparing montelukast with conventional treatments did not assess these outcomes.

Participants in four studies did not experience side effects. In one study comparing montelukast with placebo, there were two reported incidents in the montelukast group that resulted in participant withdrawal: one episode of septicaemia (blood poisoning) and one episode of dizziness. However, it was not clear whether these were related to the montelukast treatment. Other mild side effects were reported (e.g. headache, stomach-related disturbances), but by participants in both groups. We therefore found no evidence of a difference between montelukast and placebo or conventional treatments, but this assessment is based on low-quality evidence.

Quality of the evidence

The quality of evidence was low for all but one key result, that is montelukast's effect on 'change (improvement) in disease severity' when compared with conventional treatment, the evidence for which was considered to be very low quality. Overall, very few studies addressed our review question.

Many outcomes were not assessed, including long-term control, and those that were assessed had relatively few participants, which were mainly adults. The studies focused solely on moderate-severe eczema, and there were concerns with the participants or investigators knowing which treatment was received.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Montelukast versus placebo for eczema

Montelukast compared with placebo for eczema

Patient or population: eczema

Setting: 2 studies were conducted in 2 centres each; setting of remaining study is unknown

Intervention: montelukast

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Montelukast				
Change (improvement) in disease severity (4 to 8 weeks) SMD (modified EASI score and SASSAD)	The mean improvement score ranged across placebo group from 0.68 to 1.9.	The mean improvement in the intervention group was 0.29 higher (0.23 lower to 0.81 higher).	-	131 (3 RCTs)	⊕⊕⊕⊖ LOW ¹	
Effect of long-term control (> 3 months)	See comment	See comment	-	-	-	Not measured, as longest follow-up was only 8 weeks
Adverse effects (4 to 8 weeks)	See comment	See comment	-	131 (3 RCTs)	⊕⊕⊕⊖ LOW ¹	2 adverse events were reported (1 episode of septicaemia and 1 dizzy spell in the montelukast group) out of 29 participants (Friedmann 2007). No adverse effects were observed in the other 2 studies (Nettis 2002; Veien 2005), but Nettis 2002 reported an equivalent dropout rate in both montelukast and placebo groups due to aggravation of eczema or loss to follow-up.

Requirement for corticosteroid (steroid-sparing effect)	See comment	See comment	-	58 (1 RCT)	⊕⊕⊕⊕ LOW ¹	The frequency of topical corticosteroids use was not significantly different between montelukast and placebo treatments using a 5-point scale (Friedmann 2007).
Reduction of pruritus (score range 0 to 10; higher score means better improvement)	The mean change in improvement of pruritus score from baseline was 0.8 in the placebo group.	The mean change in improvement of pruritus score from baseline was 0.7 lower in the montelukast group.	-	58 (1 RCT)	⊕⊕⊕⊕ LOW ¹	The study authors assessed this difference as non-significant (but no P value or standard deviations provided) (Friedmann 2007).
Improvement in quality of life	See comment	See comment	-	-	-	No studies evaluated quality of life.
Need for emollient use	See comment	See comment	-	-	-	No studies evaluated emollient requirement.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **EASI:** Eczema Area and Severity Index; **RCT:** randomised controlled trial; **SASSAD:** Six-Area, Six-Sign Atopic Dermatitis; **SMD:** standardised mean difference

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹We downgraded by two levels, one level due to imprecision because the total number of participants included in all studies was insufficient; and one level due to indirectness because the studies only included adults with moderate-to-severe eczema, with no evidence from those with mild eczema or paediatric patients.

Summary of findings 2. Montelukast versus conventional treatment for eczema

Montelukast compared with conventional treatment for eczema

Patient or population: eczema

Setting: 1 study was conducted in a single centre; the setting of the other study is unknown

Intervention: montelukast

Comparison: conventional treatment (topical corticosteroid and oral antihistamine +/- oral antibiotics)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Conventional treatment	Montelukast				
Change (improvement) in disease severity (4 weeks) SCORAD score	The mean improvement in severity score was 4.73.	The mean improvement in severity score in the intervention group was 10.57 units greater (4.58 greater to 16.56 greater).	-	31 (1 RCT)	⊕⊕⊕⊕ VERY LOW ¹	Another study with 32 participants reported no significant difference in SCORAD between the montelukast (mean improvement = 25.2 points) and conventional treatment (mean improvement = 23.9) (6 weeks follow-up) groups (Capella 2001), but the authors did not provide the statistical values needed to calculate standard deviation, thus we could not pool these data.
Effect of long-term control (> 3 months)	See comment	See comment	-	-	-	Not measured, as longest follow-up was only 6 weeks
Adverse effects (4 to 6 weeks)	See comment	See comment	-	63 (2 RCTs)	⊕⊕⊕⊕ LOW ²	2 studies reported no adverse effects (Capella 2001; Rahman 2006).
Requirement for corticosteroid (steroid-sparing effect)	See comment	See comment	-	-	-	Not evaluated in either study
Reduction of pruritus	See comment	See comment	-	-	-	Not evaluated in either study
Improvement in quality of life	See comment	See comment	-	-	-	Not evaluated in either study
Need for emollient use	See comment	See comment	-	-	-	Not evaluated in either study

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **SCORAD:** SCORing of Atopic Dermatitis

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

¹We downgraded by three levels: one level due to imprecision because the total number of participants included in the study was insufficient; a second level due to indirectness because the study only included adults with moderate-to-severe eczema, with no evidence from those with mild eczema or paediatric patients; and a third level due to risk of bias because the outcome assessors were not blinded.

²We downgraded by two levels: one level due to imprecision because the total number of participants included in the studies was insufficient; and one level due to indirectness because the studies only included adults with moderate-to-severe eczema, with no evidence from those with mild eczema or paediatric patients.

BACKGROUND

Description of the condition

Eczema, also known as 'atopic eczema' or 'dermatitis', is a common, chronic, relapsing inflammatory skin condition (Johansson 2004). Eczema causes dry itchy skin, which tends to flare intermittently, due to various internal and external factors (Ring 2012).

Eczema often occurs in families with atopic diseases including asthma, allergic rhinitis/hay fever (and food allergy), and atopic eczema. These diseases share a common pathogenesis, and are frequently present together in the same individual and family. The word 'atopy' refers to the genetic tendency to produce immunoglobulin E (IgE) antibodies in response to small amounts of common environmental proteins such as pollen, house dust mite, and food allergens (Stone 2002; Thomsen 2015). Around 30% of people with eczema develop asthma, and 35% develop allergic rhinitis (Luoma 1983). However, it is known that atopy does not concurrently occur in all people with atopic eczema. In view of this, there have been proposals to use the term 'eczema' to define people both with and without atopy. In agreement with the 'revised nomenclature for allergy for global use' (Johansson 2004), and similar to other Cochrane Reviews evaluating eczema therapies (van Zuuren 2017), we have therefore used the term 'eczema' throughout the review.

Eczema presents early in life in most cases. Around 65% of children with eczema are affected by 18 months of age. Some of these cases resolve in early childhood, and by adulthood, 60% have resolved (Spergel 2010). Although the prevalence is lower in adults, for those who have the condition, it is often more severe and chronic in nature (Katsarou 2011). The most distressing symptom is itching, which causes skin damage and in turn more itching (i.e. the itch-scratch cycle), which leads to the visible signs of eczema (Yarbrough 2013). The impact on quality of life can be considerable, especially in severe cases. Eczema can reduce school or work attendance (Holm 2006), and can lead to disturbed sleep for the affected person and their family (Moore 2006; Reid 1995).

Eczema is a multifactorial disease, with genetic and environmental factors contributing to varying extents in different individuals and populations (Thomsen 2007). It is a chronic condition, so effective management involves recognising triggers, reducing allergens and irritants, and frequent emollient application (Akdis 2006). In addition, topical corticosteroids and calcineurin inhibitors are sometimes required (Eichenfield 2014).

Global prevalence studies suggest that eczema is widespread throughout the world, in low-, middle-, and high-income countries, and recent research shows that eczema prevalence is rising (Odhiambo 2009). Eczema affects daily activities and quality of life as well as consuming a significant portion of time and funding in both primary and secondary care (Gupta 2004). Parents of children who suffer from eczema, adults with eczema, and clinicians alike would welcome other topical therapies for the management of eczema during both the maintenance and exacerbation phases. Given the concern about local side effects with topical corticosteroid use, there is a particularly strong drive to find other treatments to treat exacerbations of eczema (Guttman-Yassky 2013).

Description of the intervention

During an exacerbation of eczema, the mainstay of treatment is the daily application of topical corticosteroids of varied strength depending on the severity of the flare and the site of involvement (Eichenfield 2014a; Ring 2012). Due to unwanted side effects such as skin thinning, clinicians usually prescribe topical corticosteroids at the lowest effective potency for short durations, typically no more than 14 days (NICE 2007). If topical corticosteroids alone are ineffective, clinicians sometimes have no alternative but to ascend the treatment ladder to oral corticosteroids during periods of severe flares (Ring 2012a).

Other topical treatments apart from corticosteroids exist, such as topical calcineurin inhibitors, pimecrolimus, and tacrolimus, but none have been found to be superior, and each treatment has its own side effect profile that restricts its use (Ashcroft 2007). Eczema sufferers and carers of children with eczema attempt to comply with complex schedules of topical treatment and emollient application, but often find these difficult to adhere to when combined with everyday demands (Bass 2015).

People with severe eczema who do not respond to topical therapy require systemic therapies, such as corticosteroids, antihistamines, antibiotics, ciclosporin, azathioprine, mycophenolate mofetil, methotrexate, and leflunomide; biologics; and phototherapy (Simon 2011).

Topical corticosteroids are the first-line treatment for eczema exacerbations (Eichenfield 2014a; Ring 2012). However, patients, their families, and healthcare professionals try to limit their use because of their potential unwanted side effects or the widespread fear of corticosteroids (corticophobia) (Artik 2003). In many cases, concerns about the potential for side effects often result in underuse of topical corticosteroids, leaving the eczema poorly controlled (Arkwright 2013). Topical corticosteroids are categorised by strength: mild, moderate, potent, or very potent (Ring 2012). The main side effect of skin thinning is typically observed after application of very potent preparations, especially in sensitive skin areas (e.g. facial or genital eczema), for prolonged periods, as is sometimes necessary in cases of severe eczema (Callen 2007). Systemic corticosteroids can be used for the treatment of severe cases of eczema and are often prescribed for a short course, since long-term use can have numerous side effects, including metabolic, central nervous system, musculoskeletal, cutaneous, and ophthalmic disorders, and suppression of the immune system (Sidbury 2014). Systemic administration of steroids improves the clinical appearance of the lesions and relieves symptoms, but the disease quickly relapses once the medication is discontinued (Sidbury 2014). Other treatments without such side effects would therefore be welcomed.

Leukotrienes are a class of inflammatory mediators derived from arachidonic acid through the 5-lipoxygenase pathway (Iversen 1994). The use of leukotriene receptor antagonists (LTRAs) as an anti-inflammatory medicine in successfully treating asthma has been widely confirmed in the literature (Bisgaard 2005; Robertson 2007). The two most widely prescribed LTRAs are montelukast (sold as Singulair) and zafirlukast (sold as Accolate) (Asthma Canada 2018). The US Food and Drug Administration and public health organisations in other countries have approved the prescription of the LTRA montelukast for long-term preventive therapy for young children with asthma (Papadopoulos 2012).

Normally prescribed in oral form, LTRAs are currently thought to be safe to use for both adults and children (Chauhan 2012). The global asthmatic guidelines recommend LTRAs for children aged five years and younger (GINA 2014). Although LTRAs are not superior to corticosteroids as monotherapy for asthma (Chauhan 2012), they have a role as a corticosteroid-sparing agent in chronic asthma (Joos 2008). In terms of acute asthma, there is no supporting evidence to use oral LTRAs in adults and children (Watts 2012). Topical corticosteroids are pivotal in the treatment of eczema, in the way that inhaled corticosteroids are for asthma (Darsow 2005). To our knowledge, LTRAs are not routinely prescribed for eczema. However, it is possible that LTRAs may have a role in the treatment of eczema as they have in asthma, particularly given their potential as a steroid-sparing agent.

Given their role in long-term prevention in asthma as well as their safety profile in asthma studies, it is possible that LTRAs may have a similar role in eczema. Many people with eczema find currently available topical treatments to be time-consuming to apply and inconvenient. Alternative oral agents available to people with eczema are either restricted to short-term use (prednisolone) or have significant safety concerns (e.g. ciclosporin, methotrexate, and other systemic agents). Leukotriene receptor antagonists, which can be administered orally and purport an acceptable safety profile, were therefore worth reviewing. The available research to date has shown conflicting results, and there exists some controversy as to the efficacy of LTRA in eczema. We decided to conduct this review to address this uncertainty.

How the intervention might work

One study, Adamek-Guzik 2002, noted that the level of urinary leukotriene increased during exacerbations of eczema in adults, and that there was no difference in levels of urinary leukotriene between non-eczematous healthy controls and eczema participants during remission phases. It would therefore be reasonable to suppose that leukotriene production may correlate with skin inflammation during flares of eczema. Additionally, one study, Oymar 2005, observed increased urinary leukotriene E4 in children with severe eczema. This suggests there may in fact be a relationship between the degree or severity of skin inflammation and leukotriene production. This evidence prompted the idea that the blockade of leukotriene production with LTRAs may help reduce skin inflammation, and therefore LTRAs may be effective in treating eczema. Leukotriene receptor antagonists might have a corticosteroid-sparing effect that would be beneficial in eczema (Sher 2012).

Why it is important to do this review

Eczema is a common worldwide skin disease treated by primary care physicians, dermatologists, and paediatricians. Patients and caregivers often have a strong desire to find alternatives to corticosteroids. If shown to be effective and safe, LTRAs are candidates for inclusion in eczema treatment procedures because they might reduce the use of topical corticosteroids. Previous studies of LTRAs for eczema have shown conflicting results. This systematic review aimed to provide evidence about the effectiveness of LTRAs in eczema and to review the safety profile of LTRAs in people with eczema.

The plans for this review were published as a protocol 'Leukotriene receptor antagonists for atopic eczema' (Futamura 2014).

OBJECTIVES

To assess the possible benefits and harms of leukotriene receptor antagonists for eczema.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials, both published and unpublished. We included trials reported only as abstracts if sufficient information was available to assess methodology and risk of bias.

We did not include cross-over trials or quasi-randomised trials.

Types of participants

We included adults and children with established eczema. A physician's diagnosis of eczema was compulsory. We included all trial settings, and we did not restrict for inclusion by age, ethnicity, or gender of participants, or severity of eczema.

Types of interventions

Interventions included treatment with systemic (oral or intravenous) LTRAs alone or in combination with other (topical or systemic) treatments in the acute or chronic (maintenance) phase of eczema compared with other treatments alone or placebo. Other treatments included all topical or systemic treatment, including corticosteroids, topical calcineurin inhibitors, immunomodulators, and alternative medicines.

We excluded trials comparing other interventions with the same dose of LTRA between groups, that is a trial assessing groups with LTRA and treatment A versus LTRA and treatment B. These trials do not test the effects of LTRAs, but instead the efficacy of other treatments.

Types of outcome measures

We reviewed the primary and secondary outcomes listed below. We divided results into effects in the short term, which we defined as less than three months, and long term, which we defined as three months or more.

Primary outcomes

1. Change in disease severity assessed by SCORAD (SCORing of Atopic Dermatitis) severity index, EASI (Eczema Area and Severity Index), SASSAD (Six Area, Six Sign Atopic Dermatitis) severity score, IGA (Investigator's Global Assessment), or any validated scoring system for eczema in the short and long term. A reduction in the score using these validated scoring systems equates to an improvement of the participant's eczema.
2. Effect of long-term control, such as time to relapse of 'flare' in the maintenance (flare-free) phase.
3. All adverse events, including allergic reactions and impact on quality of life and skin.

Secondary outcomes

1. Requirement for any topical or systemic corticosteroids, i.e. LTRA permits the lowering or minimising of the dose of corticosteroids

needed, thus sparing some of the undesirable side effects of corticosteroids.

2. Reduction of pruritus.
3. Improvement in quality of life with any validated scoring system.
4. Need for emollient use.

'Summary of findings' table

We included two 'Summary of findings' tables in which we summarised the findings for both our primary and secondary outcomes for the most important comparisons. We used the GRADE definitions to assess the quality of the evidence in the included studies for each outcome, which we summarised in the 'Summary of findings' tables. The GRADE assessments were based on five domains: study limitations (risk of bias), inconsistency of results, indirectness of evidence, imprecision, and publication bias. Evidence could be downgraded for these domains from high to moderate, low, or very low (Schünemann 2013).

Search methods for identification of studies

We aimed to identify all relevant randomised controlled trials regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

The Cochrane Skin Information Specialist searched the following databases up to 7 September 2017 using strategies based on the draft strategy for MEDLINE in our published protocol (Futamura 2014):

- the Cochrane Skin Specialised Register using the strategy in [Appendix 1](#);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (2017, Issue 8), in the Cochrane Library using the strategy in [Appendix 2](#);
- MEDLINE via Ovid (from 1946) using the strategy in [Appendix 3](#);
- Embase via Ovid (from 1974) using the strategy in [Appendix 4](#); and
- the Global Resource for Eczema Trials (GREAT) (Centre of Evidence Based Dermatology (www.greatdatabase.org.uk)) using the strategy in [Appendix 5](#).

We (the review author team) searched the following database up to 7 September 2017:

- ISI Web of Science (from 1945) using the strategy in [Appendix 6](#).

Trial registries

We (the review author team) searched the following trial registries to 7 September 2017 using the terms 'atopic eczema (dermatitis)', 'leukotriene', 'montelukast', 'zafirlukast', 'zileuton', and 'pranlukast':

- the ISRCTN registry (www.isrctn.com);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au);
- the World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch); and
- the EU Clinical Trials Register (www.clinicaltrialsregister.eu/).

Searching other resources

References from included studies

We checked the bibliographies of the included studies for further references to relevant trials.

Adverse effects

Although we did not perform an adverse events search, we assessed all effects of LTRA reported in the treatment trials identified by our search, including any reported adverse effects or events. We acknowledge that these studies were not specifically designed to identify adverse effects, but we felt it would be useful to include these data as it is highly relevant to clinical decision-making.

Data collection and analysis

Some parts of the Methods section of this review use text that was originally published in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), or have been taken from a standard template used by the Cochrane Pregnancy and Childbirth Review Group.

Selection of studies

Two review authors (MF and LF) independently selected the trials according to the inclusion criteria. Any differences of opinion were resolved through discussion by consulting a third review author (RM) if required.

Data extraction and management

We designed a data extraction form. Two review authors (MF and LF) independently extracted the data from eligible studies using the agreed-upon form. We sought to record the study design, characteristics of participants, and types of interventions and doses of treatment used in each study. We also recorded the demographics of participants, results according to our outcome measures, and adverse effects. We further recorded methods of randomisation, treatment concealment, etc. to enable a 'Risk of bias' assessment for each study. Any discrepancies were resolved through discussion or by consulting a third review author (RM) if required. We entered data into Review Manager 5 and checked the data entry for accuracy. When any information was unclear, we attempted to contact the authors of the original reports to ask them to provide further details. Data expressed in figures without actual numbers were extracted using WebPlotDigitizer software (WebPlotDigitizer).

Assessment of risk of bias in included studies

Two review authors (MF and RK) independently assessed the risk of bias for eligible studies, which we summarised in the 'Risk of bias' table for each included study in [Characteristics of included studies](#). Assessment of the risk of bias included evaluation of the following components for each included trial, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to resolve any disagreements by discussion or by involving a third review author.

1. Random sequence generation (checking for possible selection bias)

- For each included study, we described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

- We assessed the methods as low risk of bias (e.g. referring to a random number table or computer random number generator); high risk of bias (e.g. sequence generated by date of birth or admission); or unclear risk of bias.
- We only included randomised controlled trials.

2. Allocation concealment (checking for possible selection bias)

- For each included study, we described the method used to conceal allocation to intervention prior to assignment and assessed whether intervention allocation could have been foreseen in advance of or during recruitment or changed after assignment.
- We assessed the methods as low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); high risk of bias (e.g. open random allocation; unsealed or non-opaque envelopes); or unclear risk of bias.

3. Blinding of participants, personnel (checking for possible performance bias), and outcome assessment (checking for possible detection bias)

- For each included study, we described the methods used, if any, to blind study participants, personnel, and outcome assessors from knowledge of which intervention a participant had received. We considered studies to be at low risk of bias if they were blinded or if we judged that the lack of blinding would be unlikely to affect results. We considered studies to be at high risk of bias if they were not blinded or if we judged that the lack of blinding would be likely to affect results.
- We assessed the methods as low risk of bias (e.g. both participants and outcome assessors were blinded); high risk of bias (e.g. neither were blinded); or unclear risk of bias for participants, personnel, and assessors.

4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data)

- For each included study, we described the completeness of data, including attrition and exclusions from the analysis. We assessed risk of bias of incomplete outcome data with the overall level of missing data. We stated whether the study reported attrition and exclusions, the numbers included in the analysis at each stage (compared with the total number of randomised participants), and the reasons for attrition or exclusion where disclosed, as well as whether missing data were balanced across groups. Where studies reported sufficient information or the trial authors could supply it, we included missing data in our analyses.
- We assessed methods as low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups); high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation); or unclear risk of bias.

5. Selective reporting (checking for reporting bias)

- For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found.

- We assessed the methods as low risk of bias (where it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review had been reported); high risk of bias (where not all of the study's prespecified outcomes were reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported); or unclear risk of bias.

6. Other bias (checking for bias due to problems not covered by items one to five above)

- For each included study, we described any important concerns we had about other possible sources of bias.
- We assessed whether each study was free of other problems that could put it at risk of bias, classifying each study as at low, high, or unclear risk of other bias.

7. Overall risk of bias

- We made explicit judgements as to whether studies were at high risk of bias, according to the criteria provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the overall risk of bias as low when all domains were classified as low risk; unclear when at least one domain was classified as unclear risk; and high when at least one domain was judged as high risk. With reference to items one to six above, we assessed the likely magnitude and direction of the bias and whether we considered that it was likely to impact on the findings. We planned to explore the impact of the level of bias by undertaking sensitivity analyses (see [Sensitivity analysis](#)).
- We considered trials that were classified as being at low risk of bias in all of the above domains as trials at low risk of bias. We considered trials to be at unclear risk of bias when at least one of the domains was at unclear risk of bias and none of the domains was at high risk of bias, and trials to be at high risk of bias when at least one of the domains was at high risk of bias.

Measures of treatment effect

For dichotomous data, we planned to calculate and present results as summary risk ratios (RR) with 95% confidence intervals (CI).

For continuous data, we calculated mean differences (MD) except where continuous outcomes were reported in different units, in which case we calculated a standardised mean difference (SMD). Where studies measured continuous outcomes with different scales and provided commonly used measures of effect, such as standard deviation or standard error, we calculated SMDs with 95% CIs from individual studies.

Unit of analysis issues

We included both individual- and cluster-randomised controlled trials. In the event that we included trials with multiple arms, we included the comparisons considered relevant to the review as two-arm comparisons, with adjustment to avoid double-counting where appropriate. We analysed the data of the cluster-randomised trial using the methods described in Section 16.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* if we found such data at the selection stage.

Dealing with missing data

For included studies, we noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data on the overall assessment of treatment effect by undertaking sensitivity analysis.

For all outcomes, we carried out analyses on an intention-to-treat basis to the greatest degree possible, that is we attempted to include all participants randomised to each group in the analyses, and we analysed all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention.

For dichotomous data, we assumed the missing values to have a poor outcome. For continuous data, we considered imputing the mean change from baseline and corresponding standard deviation or, where applicable, the after-value scores.

We contacted the original authors of all studies to enquire if they had any missing data that they did not report in the trial ([Table 1](#)). In cases where outcome data were not available, we carried out an available-case analysis.

Assessment of heterogeneity

We evaluated the clinical implications of treatment effects differing between trials. We assessed statistical heterogeneity using the I^2 statistic. When the I^2 statistic for each primary outcome was greater than 80%, we did not undertake meta-analysis, but applied a narrative approach instead. When the I^2 statistic for each primary outcome was between 50% and 80%, then significant heterogeneity was present, which we planned to explore by looking for differences in participants and treatment factors.

Assessment of reporting biases

We planned to assess reporting bias if more than 10 studies were suitable for inclusion in the meta-analysis, and draw funnel plots for the primary outcomes using the log of effect measure and standard errors for individual studies. Additionally, for continuous outcomes, we planned to use the original linear regression test proposed by Egger ([Egger 1997](#)). We planned to perform a linear regression of the intervention effect estimates on their standard errors, weighting by $1/(\text{variance of the intervention effect estimate})$. For dichotomous outcomes, we planned to use the modified regression test proposed by Harbord ([Harbord 2006](#)). If asymmetry was detected in any of these tests or was suggested by a visual assessment, we planned to perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using Review Manager 5 software. We used random-effects meta-analysis to produce an overall summary. We planned to treat the random-effects summary as the

average range of possible treatment effects, and we discussed the clinical implications of treatment effects differing between trials.

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity, we planned to investigate it using subgroup analyses and sensitivity analyses. We planned to consider whether an overall summary was meaningful, and if it was, we would use random-effects analysis to produce it.

We planned to carry out the following subgroup analyses:

- age of participants: children (16 years old or under) versus adults; and
- drug preparation, route of administration, dose, duration, frequency, who delivers it to participants, and whether deliverers need to be trained.

We planned to use the following outcomes in subgroup analysis:

- change in disease severity;
- effect of long-term control; and
- adverse events.

We were unable to carry out the planned subgroup analysis to evaluate differences in participants and treatment factors due to insufficient data.

Sensitivity analysis

We were unable to perform a sensitivity analysis due to insufficient data. In future updates we may be able to conduct sensitivity analysis to assess the effect of studies at high risk of bias on the results

RESULTS

Description of studies

We have included all of the primary and secondary outcomes in [Summary of findings for the main comparison](#) and [Summary of findings 2](#).

Results of the search

The searches of the six databases (see [Electronic searches](#)) retrieved 158 records after removal of duplicates. Our searches of the trial registries did not produce any further results. We reviewed the references of the included studies but did not identify any additional suitable studies. Of the 158 records, we excluded 137 after analysing their titles and abstracts. We obtained the full text of the remaining 21 records. We excluded 14 studies that did not meet the inclusion criteria after full-text screening (see [Characteristics of excluded studies](#)). We included five studies in the review (see [Characteristics of included studies](#)), and assessed two studies as awaiting classification (see [Characteristics of studies awaiting classification](#)). The screening process is further described in the study flow diagram ([Figure 1](#)).

Figure 1. Study flow diagram.

Included studies

Five studies (involving a total of 202 participants) met the inclusion criteria of this review and are summarised in the [Characteristics of included studies](#) tables.

Design

Three studies were double-blind trials ([Friedmann 2007](#); [Nettis 2002](#); [Veien 2005](#)); one was single-blind ([Capella 2001](#)); and one was an open-label trial ([Rahman 2006](#)). All five trials included individually randomised participants.

Sample sizes

The sample sizes for the five studies ranged from 20 to 60 participants.

Setting

Two studies were two-centre trials ([Friedmann 2007](#); [Veien 2005](#)), and one study was conducted in a single centre ([Rahman 2006](#)). The other two studies did not report information about setting. Studies were conducted in Italy (two studies), the United Kingdom, Bangladesh, and Denmark.

Participants

Participants of one study included children aged six years and above ([Rahman 2006](#)). The remaining studies did not include children; the age range in these studies was from 16 to 70 years. One study included only men ([Nettis 2002](#)), with the remaining studies including both genders. Study participants were diagnosed with moderate-to-severe eczema in four studies ([Capella 2001](#); [Nettis 2002](#); [Rahman 2006](#); [Veien 2005](#)), and only moderate eczema in

one study ([Friedmann 2007](#)). With regard to coexisting asthma, one study reported that 15 of 32 participants had allergic asthma ([Capella 2001](#)).

Interventions

All studies used montelukast 10 mg for adults (age 14 years and above) or 5 mg for children (age 6 years to 14 years) in tablet form taken orally as the LTRA intervention; three studies compared this with placebo ([Friedmann 2007](#); [Nettis 2002](#); [Veien 2005](#)), and two studies compared this with conventional treatment ([Capella 2001](#); [Rahman 2006](#)). Conventional treatment included oral antihistamine and topical corticosteroid in both [Capella 2001](#) and [Rahman 2006](#), but [Capella 2001](#) also included oral antibiotics (clarithromycin) in the conventional treatment arm. Two of the three studies using a placebo tablet did not allow participants in either arm to use topical corticosteroids.

The intervention periods varied: 4 weeks in 2 studies ([Rahman 2006](#); [Veien 2005](#)), 6 weeks in 2 studies ([Capella 2001](#); [Nettis 2002](#)), and 8 weeks in 1 study ([Friedmann 2007](#)).

Outcomes

All studies assessed disease severity using validated scores such as SCORAD, EASI, or SASSAD. The outcomes and type of data collected in the included studies are provided in [Table 2](#).

The outcome measures varied: for example, different scoring systems were used, and these were analysed using varied measures of effect, which effectively precluded their quantitative comparison. We sought further details of the five included studies from the study contact authors (see [Table 1](#)), but unfortunately we were unable to obtain additional data beyond those reported in

the published papers either because the author(s) did not reply or because they did not possess additional data. We extracted data from the figure in [Nettis 2002](#) using WebPlotDigitizer software ([WebPlotDigitizer](#)). We performed analyses using available data from the included studies and estimated values using data from relevant studies where possible.

Excluded studies

We excluded 14 studies from our search that did not meet our inclusion criteria (see [Characteristics of excluded studies](#)). Three of these were reviews, and we checked their references for reports of any other relevant studies. One was not a comparative study, and one was not a randomised controlled trial. One study included

participants with other atopic diseases, and as we were unable to separate out the specific effects of LTRA on eczema, we excluded the study. Seven studies were cross-over trials, and a further reference was related to one of the cross-over trials.

Studies awaiting classification

Two studies were published as conference abstracts ([Craig 2002](#); [Melamed 2010](#)). We attempted to contact the authors, but to date we have not received any reply (see details in [Characteristics of studies awaiting classification](#)).

Risk of bias in included studies

The 'Risk of bias' assessment is summarised in [Figure 2](#).

Figure 2. Risk of bias summary: review authors' judgements regarding the level of risk of bias for each type of bias for all included studies.

	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 2001	?	?	+	-	+	+	+
Friedmann 2007	+	+	+	+	+	+	?
Nettis 2002	?	?	?	?	+	+	+
Rahman 2006	?	?	-	-	+	+	+
Veien 2005	?	?	?	?	+	+	?

All but one study, [Nettis 2002](#), were published as full papers after the CONSORT statement became well recognised ([CONSORT 2010](#)). However, most studies did not adequately elaborate on their methodology ([Characteristics of included studies](#)).

Allocation

Random sequence generation

We assessed four studies that inadequately described their method of randomisation as at unclear risk of bias ([Capella 2001](#); [Nettis 2002](#); [Rahman 2006](#); [Veien 2005](#)). [Friedmann 2007](#) used computer-

generated randomised sequence; we judged this study to be at low risk of bias for this domain.

Allocation concealment

We considered [Capella 2001](#), [Nettis 2002](#), [Rahman 2006](#), and [Veien 2005](#) to be at unclear risk of bias as they did not describe their method of allocation concealment. [Friedmann 2007](#) used containers labelled with sequential participant numbers; we judged this study to be at low risk of bias for allocation concealment.

Blinding

Overall, the included studies made efforts to blind participants. We acknowledge that the risk of performance bias is potentially higher in studies comparing LTRA to conventional therapies without placebo, due to the drug delivery mode (e.g. topical versus oral). We have explored how authors attempted to overcome this. [Capella 2001](#) tried to minimise outwardly appreciable differences between treatments: the treatment group received oral montelukast, a placebo tablet, and a topical placebo gel, while the control group received an oral antibiotic, oral antihistamine, and topical corticosteroid ointment. However, as this was a single-blind randomised controlled trial where outcome assessors were not blinded, we therefore considered the study to be at high risk of bias. [Friedmann 2007](#) supplied montelukast and placebo tablets in containers labelled with sequential participant numbers. They blinded treatment allocation to participants and investigators throughout the trial, which we judged to be at low risk of bias for this domain. In the [Veien 2005](#) study, placebo tablets were also used, and the code was not broken until all statistical calculations had been performed, but the method of blinding were not described. We therefore judged this study to be at unclear risk of bias.

[Nettis 2002](#) was a double-blind study, but the method of blinding was not described, and therefore the risk of bias was unclear. [Rahman 2006](#) was an open-label study, which we judged as at high risk of bias.

Incomplete outcome data

In three studies, all participants completed the trial ([Capella 2001](#); [Nettis 2002](#); [Rahman 2006](#)). The remaining two studies performed intention-to-treat analysis. Two participants in [Friedmann 2007](#) and six in [Veien 2005](#) dropped out after randomisation. We therefore judged all studies as at low risk of bias for this domain.

Selective reporting

We judged all trials to be at low risk of bias, as the authors reported on all their planned outcomes.

Other potential sources of bias

We considered [Friedmann 2007](#) and [Veien 2005](#) as at unclear risk of bias because they were funded or supported by the company that sells montelukast.

We did not draw funnel plots to assess reporting bias because the review included only five studies.

Overall risk of bias

We judged three studies as at unclear risk of bias ([Friedmann 2007](#); [Nettis 2002](#); [Veien 2005](#)), and two studies as at high risk of bias ([Capella 2001](#); [Rahman 2006](#)).

Effects of interventions

See: [Summary of findings for the main comparison Montelukast versus placebo for eczema](#); [Summary of findings 2 Montelukast versus conventional treatment for eczema](#)

Three studies compared montelukast with placebo ([Friedmann 2007](#); [Nettis 2002](#); [Veien 2005](#)), and two compared montelukast

with conventional treatments ([Capella 2001](#); [Rahman 2006](#)). We have therefore divided the effects, data and analyses into 'versus placebo' ([Analysis 1.1](#), [Analysis 1.2](#); [Analysis 1.3](#), [Summary of findings for the main comparison](#)) and 'versus conventional treatment' ([Analysis 2.1](#), [Analysis 2.3](#), [Summary of findings 2](#)) for each outcome, where available.

1. Montelukast versus placebo

i) Primary outcome 1: change in disease severity in the short term and long term

All three studies for the comparison montelukast versus placebo assessed this outcome, for 4 weeks in [Veien 2005](#), 6 weeks in [Nettis 2002](#), and 8 weeks in [Friedmann 2007](#).

[Veien 2005](#) reported using the modified EASI (Eczema Area and Severity Index) score, which they calculated as the sum of the pruritus scores (0 to 3) and the EASI score. The modified EASI decreased from 8.9 to 6.8 in the montelukast group (n = 25) and from 9.5 to 7.6 in the placebo group (n = 28) (no standard deviations (SDs) provided). The difference between the groups was not significant (P = 0.46, confidence interval not stated) ([Analysis 1.1](#)).

[Nettis 2002](#) showed a 20% reduction of SCORAD (SCORing of Atopic Dermatitis) scores after six weeks of treatment with montelukast (n = 10), which was a significant decrease compared with placebo (n = 10) (P = 0.021, confidence interval not stated). No raw data were provided ([Analysis 1.1](#)). We extracted data from the figure provided in the text using WebPlotDigitizer software ([WebPlotDigitizer](#)), which showed that mean scores changed from 56.07 to 45.81 in the montelukast group and 60.85 to 60.17 in the placebo group after six weeks.

[Friedmann 2007](#) evaluated the effect of montelukast on disease severity with SASSAD (Six Area, Six Sign Atopic Dermatitis) and IGA (Investigator's Global Assessment). They found no significant difference between mean SASSAD score changes in the montelukast group (mean ± SD; 1.41 ± 12.2, n = 29) and the placebo group (1.76 ± 12.2, n = 29) (mean difference 0.35, 95% confidence interval (CI) -5.93 to 6.63) ([Analysis 1.1](#)).

Although these studies met our inclusion criteria, they only addressed a restricted version of our review questions in terms of the population, outcomes, and comparators used. We therefore downgraded this evidence due to indirectness as participants all had moderate-to-severe eczema with no mild cases or paediatric participants. We also downgraded evidence due to imprecision related to the small sample size: the three relevant studies only included a total of 139 participants.

We were able to pool data from the three included studies, involving 131 participants. Participants were treated with either montelukast or placebo ([Analysis 1.2](#), [Figure 3](#)). There was no significant difference in improvement in disease severity for montelukast versus placebo (standardised mean difference 0.29, 95% CI -0.23 to 0.81). The I² statistic was 51%, which corresponds to a moderate amount of heterogeneity ([Figure 3](#)). Even if we had based our conclusions on data from two studies, [Friedmann 2007](#); [Veien 2005](#), without using the extracted data from the figure ([Nettis 2002](#)), the overall result would not have substantially changed.

Figure 3. Forest plot of comparison: 1 Montelukast versus placebo, outcome: 1.2 Improvement in disease severity. **ii) Primary outcome 2: effect of long-term control**

We defined three months or more as long term. We found no data evaluating this outcome, as the longest included study was of only eight weeks' duration.

iii) Primary outcome 3: adverse events

All three studies reported on this outcome (total of 131 followed participants). We judged the quality of evidence for the outcome adverse events as low, downgrading due to imprecision (small sample size and low event rate) and indirectness because only participants with moderate-to-severe eczema were included. Additionally, these were treatment studies, and as such not specifically designed to detect this outcome.

[Friedmann 2007](#) reported one serious adverse event of septicaemia and one dizzy spell in 29 participants in the montelukast group, both of which resulted in withdrawal from the study ([Analysis 1.3](#)). Although the authors did not comment on whether these effects were thought to be related to the treatment, it seems unlikely that septicaemia was treatment-related. The authors reported that one participant withdrew due to worsening of eczema in the placebo group. Other adverse events of a fairly mild nature like respiratory tract infections, headache, flares of eczema, and mild gastrointestinal disturbances were observed and according to the authors were "fairly evenly distributed between montelukast and placebo groups".

No adverse effects were observed in the 35 participants who received montelukast and the 38 who received placebo in the other two studies ([Nettis 2002](#); [Veien 2005](#)). [Veien 2005](#) reported a dropout rate of six participants: four in the montelukast group and two in the placebo group. This was due to aggravation of eczema or loss to follow-up. The authors reported that there was no significant difference between groups in terms of dropout rate (χ^2 test for contingency tables, $P = 0.62$). All participants in the [Nettis 2002](#) study completed the study.

iv) Secondary outcome 1: requirement for any topical or systemic corticosteroids

None of the three studies permitted use of systemic corticosteroids during their trials.

Among these studies where topical corticosteroids were not part of the control arm (i.e. where montelukast was compared to placebo), [Friedmann 2007](#) only permitted the use of topical corticosteroids as needed. [Friedmann 2007](#) evaluated the frequency of topical corticosteroid use with a 5-point scale ("twice daily", "once daily", "alternative days", "occasionally", and "none"), but did not evaluate the amount of steroid used. The frequency of topical corticosteroid usage did not reveal any steroid-sparing effect ($n = 58$) ([Table 3](#)).

The other two studies ([Nettis 2002](#) and [Veien 2005](#) involving 79 randomised participants) did not permit the use of topical corticosteroids; therefore, neither study was designed to detect steroid-sparing capacity.

We judged the quality of evidence as low, downgrading due to imprecision and indirectness because the outcome was assessed in only one study ([Friedmann 2007](#)), which included only 58 evaluable participants who were all adults with moderate-to-severe eczema.

v) Secondary outcome 2: reduction of pruritus and undesirable skin conditions

Only one study involving 58 participants evaluated pruritus score separately to disease severity ([Friedmann 2007](#)). The other studies used SCORAD or EASI, which included pruritus scores as one of their outcomes; however, no other study reported a pruritus score independently in their results.

In [Friedmann 2007](#), mean pruritus score at baseline (using a visual analogue scale, range 0 to 10) was 5.8 in the montelukast group ($n = 29$) and 5.7 in the placebo group ($n = 29$). The response to treatment was reported as mean improvement in pruritus score, and an improvement of 0.1 was seen in the treatment group and 0.8 in the placebo group. The mean difference was 0.7 (placebo superior to montelukast) on the visual analogue scale. The authors assessed this difference as non-significant (but provided no P value or SDs).

[Veien 2005](#) included a modified EASI, which was calculated by adding the traditional EASI score to a pruritus score, measured using a 10-centimetre 0-to-3 visual analogue scale. The primary endpoint was the modified EASI, and the secondary endpoint was the "pruritus score during the trial as a percentage of the baseline value". However, the authors did not provide data from the pruritus score independent of the EASI; therefore, we could not pool these data with those of [Friedmann 2007](#).

[Nettis 2002](#) reported a combined score of daytime pruritus and sleep loss, which was not statistically significant between the two treatments (F -test = 0.08, $P = 0.92$), nor was it significant for either group before and after treatment (F -test = 1.95, $P = 0.18$). The authors describe recording these "subjective criteria" separate to the SCORAD but do not elucidate on the scoring system. As no actual data (other than graphical representation), mean values, or SDs were provided, we could not further analyse this finding.

We judged the quality of this evidence as low, downgrading due to imprecision and indirectness because [Friedmann 2007](#) included only 58 evaluable participants, who were all adults with moderate-to-severe eczema.

vi) Secondary outcome 3: improvement in quality of life

No studies specifically used this outcome measure.

A global assessment scale provided by participants provides some information related to quality of life. One study (involving 58 evaluable participants) reported a participant-assessed measure of treatment success (Friedmann 2007), which was defined as "better" or "markedly improved" on a seven-point scale. Out of 29 participants in the montelukast group, six reported success; in the placebo group 10 out of 29 participants reported success. There was no significant difference between groups. Mean sleep disturbance scores are also relevant to this outcome: the mean improvement using a visual analogue scale (range 0 to 10) was 1.0 in the treatment group and 1.6 in the placebo group. Again, there was no significant difference between groups.

Nettis 2002 reported a combined score of daytime pruritis and sleep loss, but the difference between the two treatments was not statistically significant (F-test = 0.08, P = 0.92), nor was it significant for either group before and after treatment (F-test = 1.95, P = 0.18). The authors describe recording these "subjective criteria" separate to the SCORAD but do not elucidate on the scoring system. As no actual data (other than graphical representation), mean values, or SDs were provided, we could not further analyse this finding.

vii) Secondary outcome 4: need for emollient use

Liberal emollient use was permitted in both treatment arms in all three studies (Friedmann 2007; Nettis 2002; Veien 2005, involving 139 randomised participants). None of the studies evaluated the amount or frequency of emollient use.

2. Montelukast versus conventional treatment

i) Primary outcome 1: change in disease severity in the short term and long term

Two of the five included studies used this comparison (involving 63 participants). Treatment with montelukast was compared with conventional treatment for four weeks in the Rahman 2006 study and six weeks in the Capella 2001 study (Analysis 2.1).

Rahman 2006 showed that the SCORAD score (mean $\pm$ SD) decreased for the montelukast group from 52.70 ± 15.95 to 37.41 ± 6.04 at 4 weeks (P = 0.003), but the score only changed from 53.31 ± 15.17 to 48.58 ± 14.37 (P = 0.088) in the conventional treatment group. The mean difference in improvement in disease severity between groups was 10.57 (95% CI 4.58 to 16.56, P < 0.001, n = 31), in favour of the montelukast group (Analysis 2.2, Figure 4).

Figure 4. Forest plot of comparison: 2 Montelukast versus conventional treatment, outcome: 2.2 Improvement in disease severity.

Capella 2001 reported a significant improvement of disease severity measured using SCORAD (i.e. a decrease in score) in both the montelukast group (the mean reduced from 49.1 at baseline to 23.9 after 6 weeks) and the conventional treatment group (from 48.2 at baseline to 24.3 at 6 weeks). However, there was no significant difference in medians of SCORAD variations between the montelukast and conventional treatment groups (Mann-Whitney, P < 0.05). No standard deviation was provided; therefore, we were unable to pool the data from this study with that of Rahman 2006 without having to make serious assumptions about the exact P value and true standard deviation.

We judged the quality of evidence for this outcome as very low, downgrading due to risk of bias, indirectness, and imprecision because outcome assessors were not blinded, and the sample size of each study was small. In addition, participants in these studies only had moderate-to-severe eczema; mild cases were not included.

ii) Primary outcome 2: effect of long-term control

We defined three months or more as long term. We found no data evaluating this outcome, as the longest included study was of only six weeks' duration.

iii) Primary outcome 3: adverse events

Both studies reported on this outcome. We judged the quality of evidence on adverse events as low, downgrading due to imprecision and indirectness because only 63 participants were evaluated, and only participants with moderate-to-severe eczema were included. Additionally, these were treatment studies, and as such not specifically designed to detect this outcome.

Neither of the studies reported any adverse effects in the montelukast group (32 participants) (Capella 2001; Rahman 2006) (Analysis 2.3). Capella 2001 commented that no side effects were reported by participants or observed by the authors in the montelukast or control group. Rahman 2006 only commented about the montelukast group, reporting that montelukast was "excellently tolerated".

iv) Secondary outcome 1: requirement for any topical or systemic corticosteroids

Neither study permitted use of systemic corticosteroids during their trials.

Both studies compared montelukast with conventional treatments that included topical corticosteroids (Capella 2001 and Rahman 2006, a total of 63 out of 202 participants). These studies were therefore not designed to detect steroid-sparing capacity.

v) Secondary outcome 2: reduction of pruritus and undesirable skin conditions

No studies evaluated the effect of montelukast on reduction of pruritus or on undesirable skin conditions compared with conventional treatment.

Although they reported no specific data, [Capella 2001](#) did mention that "according to patients' impressions, pruritus was the most influenced SCORAD item by both montelukast and conventional groups, immediately followed by sleep loss and inflammatory signs". This study found no significant difference in SCORAD scores before and after treatment between treatment groups, but as the authors did not provide further data on this specific measure, we were unable to use this information in our analyses.

Interestingly, [Rahman 2006](#) also reported that "according to patients' impressions, pruritus was the most influenced SCORAD item... followed by sleep loss and inflammatory signs", but did not provide any specific data to support this or enable further analysis. The authors of this study reported that the overall SCORAD was significantly improved after four weeks in the montelukast group but not in the group received conventional treatment, and there was a significant difference between montelukast and control groups at four weeks ($P = 0.001$).

vi) Secondary outcome 3: improvement in quality of life

No studies specifically used this outcome measure.

However, sleep disturbance is one of the most important parameters when assessing quality of life. Although they reported no specific data, [Capella 2001](#) did mention that "according to patients' impressions, pruritus was the most influenced SCORAD item by both M (montelukast) and C (conventional) groups, immediately followed by sleep loss...". This study found no significant difference in SCORAD scores before and after treatment between treatment groups, but did not provide further data on this specific measure.

[Rahman 2006](#) also reported that "according to patients' impression pruritus was the most influenced SCORAD item followed by sleep loss and inflammatory signs", but did not provide any specific data to support this or enable further analysis. The authors of this study reported that the overall SCORAD was significantly improved after four weeks in the montelukast group but not in the group received conventional treatment, and there was a significant difference between montelukast and control groups at four weeks ($P = 0.001$).

vii) Secondary outcome 4: need for emollient use

In one study, emollient use was included in the conventional treatment arm, which was compared with montelukast ([Capella 2001](#)). [Rahman 2006](#) did not provide details of emollient use. Neither study evaluated the amount or frequency of emollient use.

DISCUSSION

Summary of main results

Based on evidence from five studies involving a total of 202 participants contributing data to the objectives of our review, we found that the impact of LTRAs on eczema is uncertain. These findings are demonstrated quantitatively in our 'Summary of

findings' tables ([Summary of findings for the main comparison; Summary of findings 2](#)).

All trials were short term in duration (four to eight weeks) and assessed moderate-to-severe eczema, so the effects of LTRA in milder cases of eczema remain uncertain. Reported outcomes were measured at the end of treatment. None of our included studies evaluated the need for emollient use or improvement in quality of life. All five studies used montelukast; therefore, we could draw no conclusions about other LTRAs. Two of the five included studies had funding links to the drug manufacturer. We excluded a number of studies looking at the effect of montelukast because they had a cross-over design, which was an exclusion criterion of this review.

Alternative oral agents used in eczema have significant safety profiles, and topical agents are often poorly tolerated resulting in poor compliance, so a review of the adverse effects of montelukast was particularly relevant. As per our objectives, we reviewed the number of reported adverse effects in the five included studies. All studies explicitly reported on adverse effects (giving a total of 101 participants taking montelukast).

Montelukast versus placebo

(See [Summary of findings for the main comparison.](#))

With regard to change in disease severity, we found no evidence of a difference between montelukast (10 mg) and placebo in terms of mean improvement (3 studies, $n = 131$), reduction of pruritus (1 study, $n = 58$), or topical corticosteroid use (1 study, $n = 58$). We assessed the quality of this evidence as low.

In all three studies (131 participants) in this comparison, there were only two reported adverse effects (septicaemia and dizziness) that resulted in withdrawal (both occurred in the same study). The most serious of these adverse effects, a "brief septicaemic episode", is not a recognised side effect of montelukast, and it seems unlikely that it would have been related to the treatment. Mild adverse effects such as respiratory tract infections, headache, and mild gastrointestinal disturbances were reported fairly evenly in both intervention groups. We therefore found no evidence that montelukast treatment results in more adverse events than placebo. However, restrictions such as number of participants and characteristics of participants resulted in the downgrading of the evidence on adverse effects to low quality, meaning we have only limited confidence in this conclusion.

Montelukast versus conventional treatment

(See [Summary of findings 2](#).)

Both of the studies in this comparison reported that none of the participants experienced adverse effects; these studies did not report on reduction of pruritus or topical corticosteroid use.

Although montelukast improved disease severity compared with conventional treatment in one study ($n = 31$), another study showed no clear difference ($n = 32$); however, we are uncertain about these results because the quality of the evidence was very low.

Overall, there was a lack of studies that sought to answer our review questions, and therefore the participant numbers included in this review were relatively low. There were no studies that explored the longer-term impact of montelukast, and therefore we were

unable to draw any conclusions about the role of montelukast in maintenance therapy for eczema.

We hoped to be able to perform subgroup analysis of effects of LTRA in children versus adults, but only one out of the five included studies recruited both adults and children as participants ([Rahman 2006](#)). Consequently, it is difficult to comment on the role of LTRA in the paediatric population. More evidence on the paediatric population would be helpful because this group is likely to benefit most from steroid-sparing agents, as children have more eczema and may potentially be on steroids longer and thus have more lifetime side effects from steroids.

Overall, insufficient studies met our inclusion criteria to enable us to provide a sound meta-analysis or robust conclusions. The included studies mostly failed to adequately report on methods of allocation and blinding, thus preventing appropriate bias categorisation. As with other research on treatments in eczema, the study period was unanimously short term, which prevents us from commenting on the role of LTRA in long-term maintenance (a facet of eczema that is very important to many eczema sufferers).

Overall completeness and applicability of evidence

Overall, the objectives of this review were not fully addressed, hence external validity is weak. There was an overall lack of evidence that met our inclusion criteria; we needed more randomised controlled trials to evaluate whether LTRAs are as good as conventional therapies, or at least significantly better than placebo. However, all studies did report specifically on the adverse effects of LTRA.

Studies used varied outcome measures and did not always provide commonly used measures of effect, such as standard deviation or standard error, and therefore we were unable to combine results to the degree we would have liked, in order to provide a risk ratio. We contacted authors of some included and excluded studies to request more information, but unfortunately did not receive positive replies to help our cause. There was also a lack of explicit evidence to enable a thorough analysis of our secondary outcomes (corticosteroid-sparing ability, quality of life, and emollient use). Furthermore, most study participants were adults, and one study only included men aged 18 to 28, making the results potentially less generalisable to all individuals with eczema.

We did not find any studies that evaluated the effect on long-term control. The treatment periods for all five studies were relatively short (four to eight weeks) given that eczema is a chronic condition. Studies with a longer treatment and follow-up duration were not identified in this review.

The pathophysiology of eczema is complex: genetic and environmental factors contribute to different extents in different populations. With this in mind, LTRA may in fact be beneficial only in a subgroup of eczema sufferers, where their underlying pathogenic process is different to the majority. Equally, LTRA may be completely ineffective in eczema overall. The subgroup of those with eczema and asthma would be worth evaluation, because this phenotype might theoretically have a better response to montelukast than those with eczema only. Only one of our included studies included participants with both eczema and asthma ([Capella 2001](#)), but we were unable to conduct any sensitivity analyses on this subgroup.

We had to exclude some studies as they included participants with "atopic conditions" rather than specifying which results related to those with eczema versus asthma. We excluded cross-over trials because we could not exclude hangover effect of LTRAs after the washout period; given the natural variability of eczema severity, we felt this study design was less reliable than randomised controlled trials.

There are also concerns about the choice of comparator in the studies using "conventional treatment" ([Capella 2001](#); [Rahman 2006](#)). In one study oral antibiotics were used ([Capella 2001](#)), which is not standard treatment of eczema unless acutely infected. The other study used a very mild topical corticosteroid, which may have been inadequate for the severity of eczema in the group ([Rahman 2006](#)).

In the absence of further research, the findings of this review are unlikely to change current clinical practice; current international guidelines do not advocate LTRA at present for eczema due to insufficient evidence (see [Agreements and disagreements with other studies or reviews](#)).

Quality of the evidence

We included only five studies with a total of 202 participants in this review, and most studies lacked sufficiently detailed information to enable a meta-analysis. Hence, the body of evidence does not permit a robust conclusion regarding the effect of LTRAs in eczema and their adverse effects in this patient group.

Serious limitations were that all studies only included people with moderate-to-severe eczema and that each outcome was evaluated with a small sample size, if at all. Hence, we downgraded all outcomes for imprecision and indirectness, and considered the quality of evidence as low for all outcomes in the comparison of montelukast versus placebo. For the comparison of montelukast versus conventional treatment, we also considered the evidence for adverse effects as low quality for the reasons given above, but graded our primary outcome of change in disease severity as very low quality because the outcome assessors were not blinded, causing us to further downgrade for study limitations (see [Summary of findings for the main comparison](#); [Summary of findings 2](#)).

Even though we only downgraded one outcome for study limitations, there were further methodological uncertainties with regard to allocation and blinding. There was uncertainty in how participants were allocated to their groups in four of the five studies, rendering comments on overall bias challenging. Only three studies were double-blind; hence, we agree with the comment in [Friedmann 2007](#) stating that "Given the natural variability of eczema over time and the subjective nature of the condition, uncontrolled, unblinded studies should be interpreted with caution", and think this is very relevant to our review. In addition, some study reports had missing numerical data, which made the pooling of studies challenging.

Potential biases in the review process

We searched and re-searched the literature several times to avoid missing studies. Two review authors filtered studies to avoid any bias. We asked a third party to translate any studies published in languages not spoken by the review authors. We were unable to include two studies published as conference abstracts due to lack of

information on methods, despite contacting the authors to request more information. This was a restriction outside of our control. We attempted to conduct a comprehensive search for studies, but the fact that two studies, [Craig 2002](#); [Melamed 2010](#), have not yet been incorporated is a potential source of bias. We attempted to contact the authors of all included studies for further information, but none was provided ([Table 1](#)). The way we corresponded with study authors was limited to email in all cases. As we were unable to perform a full statistical meta-analysis (due to a lack of comparable outcome measures and varied participant groups), any conclusions drawn are based on the review authors' interpretation of the studies. However, given that results were conflicting and the evidence of low quality, there were no robust conclusions, so this limitation of the review process is unlikely to have introduced significant bias. We also had to rely on WebPlotDigitizer software to extract data that had not been provided in a usable format in one study ([Nettis 2002](#); [WebPlotDigitizer](#)).

Agreements and disagreements with other studies or reviews

Our included studies appear to fit with other recent systematic reviews and guidelines in the literature. In the UK, LTRAs are not part of the stepped approach to management of eczema in children up to the age of 12 ([NICE 2007](#)). The European Dermatology Forum, whose systematic review informed the guidelines for treatment of eczema ([Ring 2012](#)), stated that "at the moment there is not enough RCT [randomised controlled trial] evidence to support the safe use of leukotriene receptor antagonists in the treatment of AE [atopic eczema] itch". Similarly, recent American systematic review guidelines on eczema management state that "leukotriene inhibitors have limited data. Thus, it is difficult to determine the relative efficacy of available options" ([Sidbury 2014](#)). In Japan, systematic review guidelines include no data for LTRA ([Katayama 2014](#)). Another systematic review found, like our review, that the "results of these trials are inconsistent" ([Roekevisch 2014](#)).

Amongst recent publications not based on systematic review methodology, the conclusions have been more positive in favour of LTRA. For example, a journal club search based on a paediatric subset concluded that "montelukast can significantly reduce the severity of atopic dermatitis, albeit with less effect on disease extent" ([Holme 2013](#)). The authors commented that there may be "subgroups within the population that respond better to montelukast treatment", and therefore a "month long trial is reasonable". More trial data covering the paediatric population are needed in order to endorse these claims.

Potential adverse effects of LTRA detailed by the manufacturers and in other extensive literature on asthma include gastrointestinal disturbances, headache, hypersensitivity reactions, drowsiness, and neuropsychiatric effects including the potential for mood changes and suicidal ideation. In line with other literature, this review found that the rate of adverse effects reported with montelukast may be low (2 adverse incidents from 101 participants, which resulted in study withdrawal).

AUTHORS' CONCLUSIONS

Implications for practice

The overall objectives of this review were not well met by the evidence found: our findings are limited to montelukast, as this

was the only leukotriene receptor antagonist (LTRA) used in all five studies. It is possible that the two studies assessing montelukast versus placebo in [Characteristics of studies awaiting classification](#) might have altered the conclusions of the review had more data been available from them.

The majority of the participants in the included studies were adults, and all had either moderate or severe eczema. Furthermore, the trials were short term and did not measure some of our chosen outcomes. We were thus unable to draw conclusions on the effect of LTRA on children or those with mild or chronic eczema, as well as the following outcomes: need for emollient use, effect on long-term control, or improvement in quality of life.

We found no evidence of a difference between montelukast (10 mg) and placebo on disease severity, reduction of pruritus, or topical corticosteroid use (low-quality evidence).

Very-low quality evidence means we are uncertain of the effect of montelukast (10 mg) compared with conventional treatment on disease severity.

Participants in only one study reported adverse events, which were mainly mild (low-quality evidence).

Based on the evidence in this review, montelukast may add no benefit to current conventional eczema treatments more than placebo.

Implications for research

Given that the studies included in this review provided inconsistent results, we were unable to draw robust conclusions about the use of LTRA in eczema in the short term. Since most of the included studies focused on adults and lasted three months or less, further longer-term research focusing on children may be worthwhile, as may further studies in adults. Future trials might include people with eczema of varying severity (including mild eczema). Encouragingly, a study awaiting classification that we identified is looking solely at the effect of LTRA in the paediatric population ([Melamed 2010](#)).

Future randomised controlled trials should be rigorously designed and conducted, including undertaking a sample size calculation and ensuring blinding. Furthermore, they should follow the CONSORT statement to ensure that they adequately report on methodological aspects as well as complete and transparent reporting ([CONSORT 2010](#)). This will improve critical appraisal and interpretation as well as assessment of the validity of the results.

Eczema should not be grouped together with other atopic conditions, such as asthma; otherwise, conclusions that are separate to the effects in asthma cannot be extracted. However, the subgroup of those with eczema and asthma would be worth evaluation, because this phenotype might represent a more responsive group than those with eczema only. One included study involved participants with both eczema and asthma ([Capella 2001](#)), but we could not conduct any sensitivity analyses. All the included studies used montelukast as the LTRA for intervention. The current evidence on adverse effects means that this continues to be the LTRA of choice, for the time being. Any future studies should specially report on adverse effects.

Since the evidence does not currently support LTRA as an effective treatment for eczema, further studies comparing LTRA to

placebo may be warranted. Longer-term randomised controlled trials comparing montelukast with conventional treatment (topical steroids and emollients) versus conventional treatment alone that look at the effectiveness of LTRA as a maintenance therapy would only be worthwhile if positive effects were seen in trials of LTRA versus placebo. All studies included in this review had a treatment duration of eight weeks or less. A longer study period would enable evaluation of alternative outcome measures, such as flare-free remission periods. Future studies might also assess other available LTRAs such as zafirlukast (sold as Accolate).

Outcome measures currently in use include validated severity scores, and these are appropriate. Additional measures that would be beneficial include explicit recording of topical corticosteroid use to enable precise comparisons between groups, quality of life measures, emollient use, specific analysis of measures such as pruritus and sleep, as well as maintenance outcomes such as flare-free periods. All measures reported should include measures of effect, such as standard deviation, to enable review authors to conduct meta-analyses.

Many cross-over studies are being conducted in this area, due to the capacity of individuals to act as their own control. However, particularly with short study durations, this style of study is more challenging to analyse, as the effect of an intervention may hangover into the washout period and beyond. Additionally, eczema is a very variable condition, and this study design is

more suited to constant chronic conditions rather than relapsing remitting types. Any future trials should report adequately on methods of allocation and potential sources of bias, as many studies analysed here did not.

Conventional therapies in eczema involve laborious application of topical therapies and are often aimed at short-term acute flare resolution. A longer-term maintenance therapy that is more acceptable to patients is still needed. These recommendations for future research are valid to September 2017, the date of our last search.

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Spergel JM. Epidemiology of atopic dermatitis and atopic march in children. *Immunology & Allergy Clinics of North America* 2010;**30**(3):269-80. [PUBMED: 20670812]

Stone 2002

Stone KD. Atopic diseases of childhood. *Current Opinion in Pediatrics* 2002;**14**(5):634-46. [PUBMED: 12352260]

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Capella 2001

Methods	Randomised, single-blind, parallel-group, placebo-controlled trial
Participants	Setting: Department of Dermatology, University of Milan
	Country: Italy
	Inclusion criteria: 32 participants (18 males and 14 females) aged 18 years and above, who suffered from moderate-to-severe eczema with SCORAD $\geq$ 30
	Exclusion criteria were not described.

Thomsen 2007

Thomsen SF, Ulrik CS, Kyvik KO, Hjelmberg Jv, Skadhaug LR, Steffensen I, et al. Importance of genetic factors in the etiology of atopic dermatitis: a twin study. *Allergy and Asthma Proceedings* 2007;**28**(5):535-9. [PUBMED: 18034971]

Thomsen 2015

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Watts 2012

Watts K, Chavasse RJ. Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children. *Cochrane Database of Systematic Reviews* 2012, Issue 5. [DOI: [10.1002/14651858.CD006100.pub2](https://doi.org/10.1002/14651858.CD006100.pub2); PUBMED: 22592708]

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Capella 2001 (Continued)

Interventions	<p>Following a washout period of 10 days, participants received treatment of the M group or the C group for 6 weeks.</p> <p>M group: oral montelukast 10 mg once daily, oral placebo tablet thrice daily, and topical placebo gel twice daily</p> <p>C group: oral cetirizine 10 mg twice daily, oral clarithromycin 250 mg twice daily (for 10 days), and topical corticosteroid creams once daily</p>
Outcomes	<p>Outcomes included in this review:</p> <ul style="list-style-type: none"> • SCORAD index at baseline and after 6 weeks <p>Outcomes not included in this review:</p> <ul style="list-style-type: none"> • Serum ECP (eosinophilic cationic protein), EXR (eosinophilic protein X), eosinophils count at baseline (day 0) and after 6 weeks (day 42)
Notes	<p>Treatment costs of 2 groups was evaluated.</p> <p>No details of funding or declaration of conflicting interests</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "...were randomized to..."</p> <p>Comment: No details provided.</p>
Allocation concealment (selection bias)	Unclear risk	No information provided on concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "minimize outward appreciable differences", "...no means of communicating each other."</p> <p>Comment: Efforts were made to minimise differences between treatments.</p>
Blinding of outcome assessment (detection bias) All outcomes	High risk	<p>Quote: "...a single-blind"</p> <p>Comment: A single-blind trial (only participant was blinded)</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the trial.
Selective reporting (reporting bias)	Low risk	All outcomes were equivocal and all were reported.
Other bias	Low risk	Nothing particular

Friedmann 2007

Methods	Randomised, double-blind, parallel-group, placebo-controlled trial conducted in 2 centres
Participants	Setting: Department of Dermatology, Southampton General Hospital, Southampton, Hampshire, and Department of Dermatology, George Eliot Hospital, Nuneaton Warwickshire

Leukotriene receptor antagonists for eczema (Review)

Friedmann 2007 (Continued)

Country: UK

Inclusion criteria: 60 participants (20 men and 40 women) aged 16 to 60 years, who suffered from eczema for at least 1 year

Eczema was defined according to the criteria of Hanifin and Rajka.

Disease severity was required to be moderate, defined as an SASSAD score between 12 and 50 at visits 1 and 2.

Exclusion criteria included pregnancy and lactation, known sensitivity or contraindication to montelukast and any coexisting skin disease, illness, or other condition likely to require admission to hospital or impair assessments or influence treatment response.

Interventions	Following a screening visit, participants received placebo treatment for 2 weeks in a single-blind phase, followed by an 8-week period of treatment with montelukast 10 mg daily or placebo.
Outcomes	<p>Outcomes included in this review:</p> <ul style="list-style-type: none"> Investigator global assessment after 8 weeks of treatment Patient global assessment after 8 weeks of treatment SASSAD after 8 weeks of treatment Visual analogue scales to record the severity of pruritus after 8 weeks of treatment Visual analogue scales to record sleep disturbance after 8 weeks of treatment Topical corticosteroid usage after 8 weeks of treatment Adverse events <p>Outcomes not included in this review:</p> <ul style="list-style-type: none"> Skin affected (%) after 8 weeks of treatment
Notes	<p>Financial disclosure: This study was supported by Merck Sharp & Dohme.</p> <p>Institutions: Department of Dermatology, Southampton General Hospital, Southampton, Hampshire, UK and Department of Dermatology, George Eliot Hospital, Nuneaton, Warwickshire, UK</p> <p>No other declaration of conflicting interests</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "in computer-generated randomized sequence"</p> <p>Comment: Participants were randomly allocated.</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "...supplied by the sponsor in containers labelled with sequential subject numbers"</p> <p>Comment: Participant allocation was concealed.</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "Investigators and subjects were blinded to the treatment allocation throughout the study."</p> <p>Comment: Participants were blinded to treatment allocation throughout the study.</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote: "Investigators and subjects were blinded to the treatment allocation throughout the study."</p>

Friedmann 2007 (Continued)

		Comment: Investigators were blinded to treatment allocation throughout the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One patient in each treatment group was lost to follow-up after baseline. An evaluable 'intention to treat population' of 29 subjects therefore remained in each group." Comment: Intention-to-treat analysis was carried out.
Selective reporting (reporting bias)	Low risk	All outcomes were described.
Other bias	Unclear risk	This study was supported by the company selling montelukast.

Nettis 2002

Methods	Randomised, double-blind, parallel-group, placebo-controlled trial
Participants	Setting: Department of Allergy and Clinical Immunology, Padiglione Chini Country: Italy Inclusion criteria: 20 participants (all male) aged 18 to 28 years, who suffered from severe eczema with mean objective score > 40 Exclusion criteria included pregnancy, pregnancy potential, and lactation; a history of liver disease; allergy to montelukast or cross-reacting medication; use of phenobarbital, phenytoin, or rifampicin.
Interventions	Participants received 10 mg montelukast or placebo orally for 6 weeks.
Outcomes	Outcomes included in this review: <ul style="list-style-type: none"> • SCORAD index at baseline, and after 3 and 6 weeks • Subjective symptoms (daytime pruritus and sleep loss) at baseline, and after 3 and 6 weeks Outcomes not included in this review: <ul style="list-style-type: none"> • Total blood cell count at baseline, and after 3 and 6 weeks • Blood chemistry (aspartate transaminase, total bilirubin, creatinine and urea) at baseline, and after 3 and 6 weeks
Notes	Very limited data available for extraction, as only a letter to the editor No details of funding or declaration of conflicting interests

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomized into..." Comment: No details provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.

Nettis 2002 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	A double-blind trial, but not described in detail
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	A double-blind trial, but not described in detail
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants dropped out.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	Low risk	Nothing particular

Rahman 2006

Methods	Open randomised, parallel-group, controlled study in a single centre
Participants	<p>Setting: Department of Dermatology & Venereology, BSMMU, Dhaka</p> <p>Country: Bangladesh</p> <p>Inclusion criteria: 31 participants (17 males and 14 females) aged 6 years and above, who suffered from eczema diagnosed with criteria of Hanifin and Rajka, at least year of intermittent or persistent symptoms of eczema and SCORAD ≥ 30</p> <p>Exclusion criteria included pregnant and nursing mothers; allergic to montelukast; acute and chronic liver disease.</p>
Interventions	Participants received 10 mg (5 mg for those aged 6 to 14) montelukast tablet orally, or conventional antihistamine and 1% topical hydrocortisone for 4 weeks.
Outcomes	<p>Outcomes included in this review:</p> <ul style="list-style-type: none"> • SCORAD score after 4 weeks of treatment • Adverse effects
Notes	No details of funding or declaration of conflicting interests

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "a open randomized control study"</p> <p>Comment: No information provided.</p>
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias)	High risk	<p>Quote: "a open randomized control study"</p> <p>Comment: Open RCT</p>

Leukotriene receptor antagonists for eczema (Review)

Rahman 2006 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "a open randomized control study" Comment: Open RCT
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants dropped out of the study.
Selective reporting (reporting bias)	Low risk	Quote: " ...in a pre-designed data sheet" Comment: All data were recorded and reported.
Other bias	Low risk	Nothing particular

Veien 2005

Methods	Randomised, double-blind, parallel-group, placebo-controlled trial conducted in 2 centres
Participants	Setting: Dermatology Clinic, Department of Dermatology, Aarhus University Hospital Country: Denmark Inclusion criteria: 59 participants (16 males and 43 females) aged 16 to 70 years, who suffered from eczema diagnosed with criteria of Hanifin and Rajka Disease severity was required to be moderate to severe, defined as the involvement of 5% to 35% of the body surface and a minimum score of 4.5 based on Rajka and Langeland's grading system. Exclusion criteria included infected eczema; a history of eczema herpeticum; pregnant and breastfeeding women; HIV positive
Interventions	Following a washout period of 2 weeks, participants received a 10 mg montelukast tablet or a placebo tablet once daily for 4 weeks.
Outcomes	Outcomes included in this review: <ul style="list-style-type: none"> EASI score at baseline, after washout, and after 1, 2, and 4 weeks Pruritus (visual analogue scale with score of 0 to 3) at baseline, after washout, and after 1, 2, and 4 weeks Adverse effects
Notes	The study was supported by Merck Sharp & Dohme, which produces montelukast. The first and third author are not paid by the company and have no financial interest in the manufacturers, but the second author is affiliated with Merck Research Laboratory.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.

Veien 2005 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind", "placebo tablet", "The code was not broken until completion of the trial and after all the statistical calculations had been carried out." Comment: No details provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind", "placebo tablet", "The code was not broken until completion of the trial and after all the statistical calculations had been carried out." Comment: No details provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "the intention-to-treat analysis" Comment: Intention-to-treat analysis was done.
Selective reporting (reporting bias)	Low risk	All outcomes were reported.
Other bias	Unclear risk	This study was supported by the company that sells montelukast.

EASI: Eczema Area and Severity Index

RCT: randomised controlled trial

SASSAD: Six-Area, Six-Sign Atopic Dermatitis

SCORAD: SCORing of Atopic Dermatitis

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Boguniewicz 2003	This is a narrative review.
Concha 2003	This is not a comparative study.
Ehlayel 2007	This is a cross-over trial with a 2-week washout.
Ehlayel 2008	This is the same trial as Ehlayel 2007 , mentioned with other outcomes.
Goh 2016	This is a cross-over trial.
Holme 2013	This is a systematic review. We checked all trials that had been referenced.
Jackson 2004	This is a cross-over trial with a 1-week washout and participants with other atopic diseases.
Jeon 2016	This is a cross-over trial with a 2-week washout.
Lehtimäki 2009	The participants had atopic rhinitis and asthma, with other allergic diseases including eczema.
NCT00903357	This is a cross-over trial with a 2-week washout.
Pei 2001	This is a cross-over trial with a 2-week washout.
Woodmansee 1999	This is not a randomised trial.
Yanase 2001	This is a cross-over trial with a 2-day washout.

Study	Reason for exclusion
Zouboulis 2003	This is a narrative review.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Craig 2002

Methods	Double-blinded, placebo-controlled, parallel study
Participants	Inclusion criteria: 60 participants with moderate-to-severe eczema
Interventions	Participants received 10 mg montelukast or placebo each day for 8 weeks
Outcomes	<ul style="list-style-type: none"> • SCORAD (SCORing of Atopic Dermatitis) score • Global assessment • Daily diary • Rash severity scoring
Temporary results	There was no significantly different effect between interventions. However, there was a positive trend suggesting benefit of montelukast in the paediatric subset.
Notes	American Academy of Allergy, Asthma & Immunology 2002 Annual Meeting abstract

Melamed 2010

Methods	Double-blinded, placebo-controlled, parallel study
Participants	Inclusion criteria: 20 participants aged 1 to 8, positive reactivity to food; 10% to 25% body area affected with eczema; and gastrointestinal symptoms
Interventions	Participants received montelukast or placebo for 9 weeks.
Outcomes	<ul style="list-style-type: none"> • Pruritus and atopic dermatitis flare-up scores • Nerve growth factor (NGF)
Temporary results	<p>The treatment with montelukast resulted in a:</p> <ul style="list-style-type: none"> • significant reduction in the pruritus score; • significant reduction in the use of rescue medication; • reduction in the level of NGF.
Notes	American Academy of Allergy, Asthma & Immunology 2010 Annual Meeting abstract

DATA AND ANALYSES

Comparison 1. Montelukast versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in disease severity (narrative table)			Other data	No numeric data
2 Improvement in disease severity	3	131	Std. Mean Difference (Random, 95% CI)	0.29 [-0.23, 0.81]
3 Adverse effects (narrative table)			Other data	No numeric data

Analysis 1.1. Comparison 1 Montelukast versus placebo, Outcome 1 Improvement in disease severity (narrative table).

Improvement in disease severity (narrative table)	
Study	
Friedmann 2007	The montelukast effect on disease severity with SASSAD and IGA. They found no significant difference between mean score changes in the montelukast group (mean $\pm$ SD; 1.41 ± 12.2) and the placebo group (1.76 ± 12.2)
Nettis 2002	A 20% reduction of SCORAD scores after 6 weeks of treatment with montelukast, and this was a significant decrease compared with placebo ($P = 0.021$)
Veien 2005	The modified EASI score, the sum of EASI score and the pruritus scores (0 - 3), decreased from 8.9 to 6.8 in the montelukast group and from 9.5 to 7.6 in the placebo group. The difference between the groups was not significant ($P = 0.46$)

Analysis 1.2. Comparison 1 Montelukast versus placebo, Outcome 2 Improvement in disease severity.

Study or subgroup	Mon- telukast N	Placebo N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
Friedmann 2007	29	29	-0 (0.263)		40.44%	-0.03[-0.54,0.49]
Nettis 2002	10	10	1.1 (0.487)		20.71%	1.09[0.13,2.04]
Veien 2005	25	28	0.2 (0.276)		38.86%	0.2[-0.34,0.74]
Total (95% CI)					100%	0.29[-0.23,0.81]
Heterogeneity: $\tau^2=0.11$; $\chi^2=4.07$, $df=2$ ($P=0.13$); $I^2=50.8\%$						
Test for overall effect: $Z=1.09$ ($P=0.28$)						
				Favours placebo		Favours montelukast

Analysis 1.3. Comparison 1 Montelukast versus placebo, Outcome 3 Adverse effects (narrative table).

Adverse effects (narrative table)	
Study	
Friedmann 2007	1 serious adverse event of septicaemia and 1 dizzy spell in 29 participants of the montelukast group. 1 worsening of eczema causing withdrawal of the trial in the placebo group. Other adverse events of a fairly mild nature like respiratory tract infections, headache, flares of eczema and mild gastrointestinal disturbances were observed and they were "fairly evenly distributed between montelukast and placebo groups" according to the authors.

Adverse effects (narrative table)

Study	
Nettis 2002	No adverse effects were observed.
Veien 2005	No adverse effects were observed.

Comparison 2. Montelukast versus conventional treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in disease severity (narrative table)			Other data	No numeric data
2 Improvement in disease severity	1	31	Mean Difference (IV, Random, 95% CI)	10.57 [4.58, 16.56]
3 Adverse effects (narrative table)			Other data	No numeric data

Analysis 2.1. Comparison 2 Montelukast versus conventional treatment, Outcome 1 Improvement in disease severity (narrative table).

Improvement in disease severity (narrative table)

Study	
Capella 2001	A significant improvement of SCORAD score both in the montelukast group (mean: from 49.1 to 23.9) and the conventional treatment group (from 48.2 to 24.3). There was no significant difference between the groups.
Rahman 2006	Montelukast significantly improved the SCORAD score compared with conventional treatment ($P = 0.001$). In the montelukast group, the score (mean $\pm$ SD) decreased from 52.70 ± 15.95 to 37.41 ± 6.04 ($P = 0.003$); otherwise the score changed from 53.31 ± 15.17 to 48.58 ± 14.37 ($P = 0.088$) in the conventional group.

Analysis 2.2. Comparison 2 Montelukast versus conventional treatment, Outcome 2 Improvement in disease severity.

Study or subgroup	Montelukast		Conventional treatment		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Rahman 2006	16	15.3 (8.5)	15	4.7 (8.5)		100%	10.57[4.58,16.56]
Total ***	16		15			100%	10.57[4.58,16.56]
Heterogeneity: Not applicable							
Test for overall effect: $Z = 3.46$ ($P = 0$)							

Analysis 2.3. Comparison 2 Montelukast versus conventional treatment, Outcome 3 Adverse effects (narrative table).

Adverse effects (narrative table)

Study	
Capella 2001	No adverse effects were observed.

Adverse effects (narrative table)

Study	
Rahman 2006	No adverse effects were observed.

ADDITIONAL TABLES

Table 1. Contact history for data collection

Study	Author contacted	Question posed	Reply	Date contact letter was sent	Date reply was received
Craig 2002	Craig TJ	We asked whether the conference abstract had subsequently been published as a full article. Additionally, we requested missing data to complete our extraction form.	The author did not have any data and proposed that we seek the data on the clinical trials website. We could not find any additional data.	9 July 2015	26 October 2015
Melamed 2010	Melamed IR and Heffron MG	We asked whether the conference abstract had subsequently been published as a full article. Additionally, we requested missing data to complete our extraction form.	No reply	9 July 2015	-
Capella 2001	Capella GL	We requested additional analytical data for each group and full data on the eczema severity scores to provide missing outcome measures for the meta-analysis.	The author could not add anything to the data in the article.	27 October 2015	29 October 2015
Nettis 2002	Nettis E	We requested additional analytical data for each group and full data on the eczema severity scores to provide missing outcome measures for the meta-analysis.	The author no longer had the original data from the trial. No one in the Danish branch of MSD could provide further information about the trial.	27 October 2015	28 October 2015; 24 November 2015
Friedmann 2007	Friedmann P and Berth-Jones J	We requested additional analytical data for each group and full data on the eczema severity scores to provide missing outcome measures for the meta-analysis.	No reply	27 October 2015	-
Rahman 2006	Rahman ML	We requested additional analytical data for each group and full data on the eczema severity scores to provide missing outcome measures for the meta-analysis.	Invalid email address	27 October 2015	-
Veien 2005	Veien NK	We requested additional analytical data for each group and full data on the	No reply	27 October 2015	-

Table 1. Contact history for data collection *(Continued)*
eczema severity scores to provide missing outcome measures for the meta-analysis.

Table 2. Summary of study design and outcomes provided for included studies

Study	Comparison	Observation	Scale	Data
Capella 2001	Conventional treatment	6 weeks	SCORAD	n, median, mean, range
Nettis 2002	Placebo	6 weeks	SCORAD	n, F value, P value
Friedmann 2007	Placebo	8 weeks	SASSAD	n, Δmean, ΔSD, 95% CI, P value
Rahman 2006	Conventional treatment	4 weeks	SCORAD	n, mean, SD, P value
Veien 2005	Placebo	4 weeks	modified EASI	n, mean, P value

CI: confidence interval; EASI: Eczema Area and Severity Index; SASSAD: Six-Area, Six-Sign Atopic Dermatitis; SCORAD: SCORing of Atopic Dermatitis; SD: standard deviation

Table 3. Topical corticosteroid usage in Friedmann 2007

	-2 weeks	0 week	4 weeks	8 weeks
Montelukast				
Twice daily	8	6	9	7
Once daily	11	10	7	5
Alternative day	5	7	6	9
Occasional	4	6	6	3
None	2	1	1	2
Placebo				
Twice daily	8	8	5	4
Once daily	9	10	11	9
Alternative day	6	8	7	5
Occasional	4	4	6	7
None	3	0	0	1

The number of participants using topical corticosteroid according to frequency of use at each assessment point of the study. The data were extracted from Figure 2 of the publication, using WebPlotDigitizer software ([WebPlotDigitizer](#)).

APPENDICES

Appendix 1. Cochrane Skin Specialised Register/CRS-W search strategy

(leukotriene or montelukast or zafirlukast or pranlukast or zileuton or LTRA*) and (eczema or dermatitis or neurodermatitis)

Appendix 2. CENTRAL (Cochrane Library) search strategy

#1 MeSH descriptor: [Leukotriene Antagonists] explode all trees
#2 (leukotriene or montelukast or zafirlukast or pranlukast or zileuton):ti,ab,kw
#3 LTRA*:ti,ab,kw
#4 {or #1-#3}
#5 MeSH descriptor: [Eczema] explode all trees
#6 MeSH descriptor: [Dermatitis, Atopic] explode all trees
#7 MeSH descriptor: [Neurodermatitis] explode all trees
#8 MeSH descriptor: [Dermatitis] explode all trees
#9 eczema or dermatitis or neurodermatitis:ti,ab,kw
#10 #5 or #6 or #7 or #8 or #9
#11 #4 and #10

Appendix 3. MEDLINE (Ovid) search strategy

1. exp Leukotriene Antagonists/
2. leukotriene.mp.
3. montelukast.mp.
4. zafirlukast.mp.
5. pranlukast.mp.
6. zileuton.mp.
7. LTRA\$1.ti,ab.
8. or/1-7
9. exp Eczema/ or eczema.mp.
10. exp Dermatitis, Atopic/
11. exp Dermatitis/ or dermatitis.mp.
12. 9 or 10 or 11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized.ab.
16. placebo.ab.
17. clinical trials as topic.sh.
18. randomly.ab.
19. trial.ti.
20. 13 or 14 or 15 or 16 or 17 or 18 or 19
21. exp animals/ not humans.sh.
22. 20 not 21
23. 8 and 12 and 22

[Lines 13-22: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)]

Appendix 4. Embase (Ovid) search strategy

1. leukotriene.mp.
2. montelukast.mp.
3. zafirlukast.mp.
4. pranlukast.mp.
5. zileuton.mp.
6. LTRA\$1.ti,ab.
7. exp leukotriene receptor blocking agent/
8. exp leukotriene/
9. exp montelukast/
10. exp zafirlukast/
11. exp pranlukast/
12. exp zileuton/
13. or/1-12

14. eczema.mp. or exp ECZEMA/
15. exp DERMATITIS/ or dermatitis.mp.
16. exp atopic dermatitis/
17. neurodermatitis.mp. or exp NEURODERMATITIS/
18. or/14-17
19. crossover procedure.sh.
20. double-blind procedure.sh.
21. single-blind procedure.sh.
22. (crossover\$ or cross over\$).tw.
23. placebo\$.tw.
24. (doubl\$ adj blind\$).tw.
25. allocat\$.tw.
26. trial.ti.
27. randomized controlled trial.sh.
28. random\$.tw.
29. or/19-28
30. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
31. human/ or normal human/
32. 30 and 31
33. 30 not 32
34. 29 not 33
35. 13 and 18 and 34

Appendix 5. GREAT search strategy

leukotriene or montelukast or zafirlukast or pranlukast or zileuton

Appendix 6. ISI Web of Science search strategy

(leukotriene or montelukast or zafirlukast or pranlukast or zileuton or LTRA*) and (eczema or dermatitis or neurodermatitis) and random*

CONTRIBUTIONS OF AUTHORS

MF was the contact person with the editorial base.

All authors co-ordinated contributions from the coauthors and wrote the final draft of the review.

MF and LF screened papers against eligibility criteria.

MF, RK, and LF appraised the quality of papers.

MF, LF, EV, and RK extracted data for the review and sought additional information about papers.

MF and LF entered data into Review Manager 5.

MF and LF analysed and interpreted data.

MF, LF, RM, and HS worked on the Methods sections.

LF wrote the Discussion with contributions from EV.

EV and RK obtained data on ongoing and unpublished studies.

MF, LF, EV, and RK drafted the clinical sections of the Background and responded to the clinical comments of the referees.

RM and HS responded to the methodology and statistics comments of the referees.

AR was the consumer coauthor and checked the review for readability and clarity, as well as ensuring that outcomes are relevant to consumers.

AR and LF wrote the Plain language summary.

Disclaimer

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DECLARATIONS OF INTEREST

Masaki Futamura: "I have received lecture honoraria for speaking about atopic eczema from Maruho Co., Ltd. and TAIHO Pharmaceutical Co., Ltd. and for speaking about treatment of asthma from MSD KK and KYORIN Pharmaceutical Co., Ltd. MSD K.K. is a subsidiary of Merck & Co., Inc. and MSD K.K. and KYORIN Pharmaceutical Co., Ltd. sell a leukotriene receptor antagonist, Singlair or Kipres."

Leila Ferguson: Nothing to declare.

Efstathios Vakirlis: "I have received lecture honoraria from Meda Pharmaceuticals, LEO Pharma, Pierre Fabre, and La Roche Posay as an invited speaker for atopic dermatitis. I have received lecture honoraria from Novartis, Janssen, and Genesis as an invited speaker for psoriasis."

Reiji Kojima: Nothing to declare.

Hatoko Sasaki: Nothing to declare.

Amanda Roberts: Nothing to declare.

Rintaro Mori: Nothing to declare.

Antonia Lloyd-Lavery (clinical referee): "I have acted as co-investigator for three phase 3 clinical trials investigating different treatments for moderate-severe atopic eczema in adults (Atopix – OC459; Treble – Lebrikizumab; Café – Dupilumab)."

Masaki Futamura, lead author on the protocol of this Cochrane Review, became conflicted in terms of Cochrane's commercial sponsorship policy and has been replaced by Leila Ferguson, as lead author. Leila Ferguson has no relevant financial conflict of interest, and in the judgement of Cochrane Skin's editorial team, she has made a contribution equal to Masaki Futamura, which justifies her position as first author. This change has been discussed with and approved by the Funding Arbiters.

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- National Center for Child Health and Development, Japan.

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- The National Institute for Health Research (NIHR), UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This Cochrane Review uses the term 'eczema' in place of 'atopic eczema', which was used in the protocol. We made this change in order to align the terminology used for eczema across Cochrane Skin Reviews, and in keeping with World Allergy Organization guidance ([Johansson 2004](#)).

Types of outcomes: we removed the secondary outcome 'prevention of flares' due to overlap with primary outcome number two, 'effect of long-term control, such as time to relapse of "flare" in the maintenance ("flare"-free) phase'.

Types of interventions: in this section, we clarified that we would also be comparing against placebo.

Dealing with missing data: in our protocol we did not fully explain how we would handle missing data for dichotomous and continuous outcomes, therefore in the review we have clarified how we would handle missing data: "For dichotomous data, we assumed the missing values to have a poor outcome. For continuous data, we considered imputing the mean change from baseline and corresponding standard deviation or, where applicable, the after-value scores."

Assessment of reporting biases: we did not undertake any of the actions planned in the protocol with regard to this section because we included fewer than 10 studies.

Data synthesis: we planned to use fixed-effect models for all analyses. However, we chose the random-effects model for all analyses because we expected there would be some clinical and methodological heterogeneity between studies.

Subgroup analysis and investigation of heterogeneity/sensitivity analysis: if we identified substantial heterogeneity, we planned to investigate it using subgroup analyses and sensitivity analyses. However, we were not able to investigate heterogeneity or conduct any of our other planned subgroup or sensitivity analyses because we could only conduct one meta-analysis with only three studies included.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetates [administration & dosage] [adverse effects] [*therapeutic use]; Administration, Oral; Eczema [*drug therapy]; Leukotriene Antagonists [administration & dosage] [adverse effects] [*therapeutic use]; Quinolines [administration & dosage] [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans