

Leukotriene Receptor Antagonists in Allergic Eye Disease: A Systematic Review and Meta-analysis

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What is already known about this topic? Leukotriene receptor antagonists (LTRAs) are recommended for use in asthma and allergic rhinitis. No previous systematic review has specifically reviewed the available evidence to assess the effects of LTRAs on the symptoms of allergic ocular diseases.

What does this article add to our knowledge? In adults with seasonal allergic conjunctivitis, montelukast is more effective than placebo and less effective than oral antihistamines. High-quality clinical trials are needed to investigate the effect of LTRAs in other allergic ocular diseases.

How does this study impact current management guidelines? The systematic review highlights that LTRAs can be considered in the medical management of adult seasonal allergic conjunctivitis, either alone or in combination with oral antihistamines.

BACKGROUND: Allergic eye diseases are common and cause significant morbidity. Leukotrienes are implicated in the pathogenesis of seasonal and perennial allergic conjunctivitis (AC), commonly seen in conjunction with allergic rhinitis, and in vernal keratoconjunctivitis and atopic keratoconjunctivitis.

OBJECTIVES: To assess the available evidence for an effect of leukotriene receptor antagonists (LTRAs) on the ocular symptoms of allergic eye diseases.

METHODS: Selected studies, identified with systematic review search methods, were single/double-blind, randomized, controlled trials that compared LTRAs with other common treatments.

RESULTS: Eighteen trials, using the LTRA montelukast (in AC only), were identified. Six studies were suitable for meta-analysis, in patients with seasonal AC [treated over a 2-week period, symptoms scored 0 (mild) to 3 (severe)]. These trials were at low risk of bias without significant heterogeneity. Six

trials were analyzed and showed that montelukast improved patients' ocular symptoms to a greater extent than placebo, with a difference in mean change-from-baseline score of -0.10 (95% CI, -0.14 to -0.07 ; $P < .00001$). Three trials compared montelukast with oral antihistamine. The difference in mean change-from-baseline score was 0.08 (95% CI, 0.02 to 0.14 ; $P = .007$), in favor of antihistamines. Two trials compared montelukast and oral antihistamine with placebo. The difference in mean change-from-baseline score was -0.30 (95% CI, -0.38 to -0.21 ; $P < .00001$), in favor of combination treatment.

CONCLUSIONS: In seasonal AC LTRAs are more efficacious than placebo but less efficacious than oral antihistamines in adult patients. Clinical trials should be conducted to determine whether combination treatment with LTRA and oral antihistamine has a synergistic effect. Further research is required to clarify the role of LTRAs in other allergic eye diseases. © 2012 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1:65-74)

Key words: Leukotriene antagonists; Montelukast; Review; Meta-analysis; Allergic conjunctivitis; Allergic rhinitis; Eye diseases

Allergic eye diseases are common and cause significant morbidity.^{1,2} IgE-mediated allergic conjunctivitis (AC) accounts for most allergic eye disease and is generally seen in conjunction with allergic rhinitis (AR), to the extent that the combined condition is often referred to as allergic rhinoconjunctivitis (ARC). Other important (albeit less common) allergic ocular diseases are vernal keratoconjunctivitis (VKC)³ and atopic keratoconjunctivitis (AKC).⁴

The ocular symptoms of ARC, which are frequently under-reported,⁵ include itch, watering, discomfort, and redness of the conjunctivae.^{5,6} The ocular symptoms are experienced more frequently in seasonal disease than in perennial disease, although in a survey of Navy recruits with AR, nearly one-half of patients with perennial allergic rhinitis (PAR) also experienced ocular symptoms.⁷ Symptoms of ARC can lead to a significant impairment of social functioning and quality of life.⁸

VKC is a disease of childhood, usually presenting between the ages of 5 and 15 years. It affects boys more frequently (4:1) and is

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Abbreviations used

AC- Allergic conjunctivitis
 AKC- Allergic keratoconjunctivitis
 AR- Allergic rhinitis
 ARC- Allergic rhinoconjunctivitis
 ARIA- Allergic Rhinitis and its Impact on Asthma
 LTRA- Leukotriene receptor antagonist
 PAC- Perennial allergic conjunctivitis
 PAR- Perennial allergic rhinitis
 RQLQ- Rhinoconjunctivitis Quality of Life Questionnaire
 SAC- Seasonal allergic rhinitis
 SAR- Seasonal allergic conjunctivitis
 VKC- Vernal keratoconjunctivitis

more common in African and Asian countries. Patients may have a personal history of atopy.⁹ Clinical features include itchy, watery eyes with a stringy exudate and photophobia. Vision may be blurred, and sight can be threatened by epithelial erosion and plaque formation over the cornea (and later scarring). The disease may be asymmetrical in terms of severity and usually remits between 2 and 10 years from onset.^{1,3}

AKC in contrast is a disease of atopic adults. Patients experience persistent irritation of the eyes with mucoid discharge, photophobia, and blurring. Most patients have eyelid and periorbital eczema and/or asthma. Coexistent lid-margin infection is common, often as a result of staphylococcal infection.⁴ Vision may be threatened by corneal involvement and other complications such as retinal detachment.^{1,4}

The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines recommend the use of an oral or topical ocular antihistamine, an ocular mast cell stabilizer, or topical saline to manage AC.⁵ The ocular symptoms of VKC and AKC are treated in a similar way, although in most cases ocular corticosteroids, with their significant side effect profile, or immune modulators, may also be required to suppress inflammation and to prevent corneal involvement leading to visual impairment.^{3,4}

The cysteinyl leukotrienes are lipid mediators synthesized from arachidonic acid within a number of inflammatory cells, including mast cells, basophils, and eosinophils. The drugs montelukast, zafirlukast, and pranlukast block the leukotriene receptor cysteinyl leukotriene receptor 1.¹⁰ Mast cells, eosinophils, and leukotrienes themselves are implicated in the pathogenesis of AC, VKC, and AKC, as well as allergic rhinitis.^{3,11} In VKC and AKC T-helper cells are also likely to play a fundamental role.^{1,3,4,6,8} Leukotriene receptor antagonists (LTRAs) are included as a possible treatment for the nasal symptoms of ARC in the ARIA guidelines. To date they have not been used routinely in VKC or AKC.

Three meta-analyses have assessed the effect of LTRAs in ARC.¹²⁻¹⁴ The review by Rodrigo and Yanez¹³ is the only one to have considered the effects of LTRAs specifically on ocular symptoms [in seasonal allergic rhinitis (SAR) only]. Since this most recent meta-analysis in 2006 there have been several other trials published that compared LTRAs with placebo or other treatments that have included ocular symptoms as an outcome.¹⁵⁻²² A clear need remains therefore to ascertain the degree of positive effect, if any, that LTRAs may have on the symptoms of allergic eye disease. This has been addressed in the present systematic review and meta-analysis.

METHODS**Study retrieval and selection**

The predefined criteria for selecting studies are shown in Table 1. The following databases were searched systematically: CENTRAL (Cochrane Central Register of Controlled Trials), Medline, PubMed, Embase, Google Scholar, Web of Science (citation index); Open SIGLE (citation index for grey literature), National Technical Information Service, International Standard Randomized Controlled Trial Number register scheme, ClinicalTrials.gov, and pharmaceutical trial registers (as available). Full details of all search strategies and search terms used are available from the authors on request.

Searches were conducted between December 12, 2010, and March 2, 2011, with no restriction of language or publication date. The bibliographies of retrieved review articles and selected studies were reviewed. Study authors/organizations were contacted by email for further details if necessary. Translation services were not available; therefore, foreign language studies were excluded if contacting authors was unsuccessful. In one instance an author provided a database of their raw data for an unpublished study (T. Guerrero, email communication, May and June 2011).²³ The *a priori* research protocol for this systematic review was unregistered.

Data extraction and risk of bias assessment

Searches, data collection, and data analysis were performed by one author (J.G.). Data from each article were extracted onto a prepiloted paper data collection form. Summary statistics were estimated from bar charts in 2 studies.^{24,25}

An assessment of the risk of bias within each study was made by assessing 8 prespecified domains, following the methodology of Cochrane Collaboration.²⁶ Risk-of-bias tables for each study were generated from these data and were used to make an overall assessment of the risk of bias specifically for ocular symptoms as an outcome, at both the individual study level and *across* studies (high, low, unclear risk). Information necessary to make these assessments was extracted from the study paper and by contacting the authors with individualized questionnaires that contained open-ended questions.

Data analysis

Data suitable for meta-analysis were entered into the software package, RevMan version 5.1 (Review Manager; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). The multicenter studies presented change-from-baseline symptom scores. Given the greater relative contribution of these studies, a decision was reached to exclude from the meta-analyses any studies that had *not* reported change-from-baseline scores, to allow use of a standardized mean difference. Those remaining studies suitable for meta-analysis had all in fact used the same scale for their symptom scoring, making it possible to use the mean difference in change-from-baseline scores rather than a standardized mean difference. The mean difference is preferable in that it can be related directly back to the symptom scale used when interpreting effect size.

Data measured at 2 weeks were used because this was the most common time point for outcome measurement in the studies suitable for meta-analysis. Sensitivity analyses were performed to incorporate different outcome timings and doses and were planned to be performed in the event of significant heterogeneity and for studies at high or unclear risk of bias. The

TABLE I. Criteria for selecting studies for inclusion in the systematic review

Disease and type of study	Participants	Exclusion criteria	Intervention	Outcome(s)
Allergic conjunctivitis (or allergic rhinoconjunctivitis): single/double-blind randomized controlled trials	Adults (≥ 16 y); children (< 16 y); community or hospital setting Symptoms of perennial or seasonal ARC or AC, as defined by the ARIA guidelines (or similar) and a positive skin prick test and/or specific IgE to a likely culprit allergen	Other ocular diseases that cause similar symptoms to AC, for example, AKC; VKC; nasal polyposis; chronic rhinosinusitis (nonallergic); drug-induced or occupational nasal or ocular disease	LTRA alone or in combination with other treatments for ARC/AC against placebo or other treatments Other treatments: intranasal/ocular/oral antihistamines; INS; topical ocular mast cell stabilizer; topical ocular saline	Change in ocular (conjunctival) symptoms after treatment, assessed by a symptom score (or assessed by the eye domain of the Juniper RQLQ)
Vernal keratoconjunctivitis: single/double-blind randomized controlled trials	Children (< 16 y); hospital or community setting; clinical diagnosis based on typical symptoms	Other causes of ocular disease causing similar symptoms, for example, AKC, AC, giant papillary conjunctivitis, infective (eg, trachoma)	LTRA alone or in combination with other treatments for VKC against placebo or other treatments Other treatments: topical ocular mast cell stabilizer; topical ocular or oral antihistamines; topical ocular NSAIDs; topical ocular corticosteroid; topical ocular cyclosporine	1. Change in ocular symptoms after treatment, assessed by a symptom score 2. Proportion of participants experiencing deterioration in vision in LTRA and comparison groups, assessed by clinician
Atopic keratoconjunctivitis: single/double-blind randomized controlled trials	Adults (> 16 y); hospital or community setting; diagnosis based on clinical symptoms, including a personal or family history of atopic dermatitis and/or asthma	Other causes of ocular disease causing similar symptoms, for example, VKC, AC, giant papillary conjunctivitis, Sjögren disease	LTRA alone or in combination with other treatments for the noninfective ocular symptoms of AKC against placebo or other treatments Other treatments: topical ocular mast cell stabilizer; topical ocular or oral antihistamines; topical ocular NSAID; topical ocular corticosteroid; topical ocular cyclosporine	1. Change in ocular and periorbital symptoms after treatment, assessed by a symptom score 2. Proportion of participants experiencing deterioration in vision in LTRA and comparison groups, assessed by clinician

INS, Intranasal corticosteroid; NSAID, nonsteroidal anti-inflammatory drug.

generic inverse method of meta-analysis available in RevMan 5.1 was used.

The presence of clinical and/or methodologic heterogeneity was assessed. The presence of statistical heterogeneity was assessed with the χ^2 test and the inconsistency statistic (the latter being useful if the χ^2 result is significant). In the absence of marked heterogeneity a fixed-effect meta-analysis model was used.

RESULTS

Figure 1 shows the outcome of the search process. Eighteen eligible randomized controlled trials were identified, from 17 articles published between 2000 and 2010 and 1 in the form of a conference poster title.^{18-20,23-25,27-38} Two articles published information about the same study.^{19,20} However, the study itself contained 2 trials, and these were considered separately.

All the studies related to trials of patients with ARC. No studies were found in which only the ocular symptoms of ARC were considered or in which an ocular symptom score was the primary

outcome. Randomized controlled trials of LTRA use in AKC or VKC were not identified. Twelve trials studied patients with SAR, 5 with PAR, and 1 with persistent AR. Randomized controlled trials that compared LTRA with topical antihistamines, topical mast cell stabilizers, or topical saline in ARC were not identified.

Three trials studied pediatric patients. Eight adult category studies included patients between the ages of 15 and 18 years.^{25,28,30,31,33,35-37} These trials were kept within the subgroup of adult studies.

Six of the 18 studies were suitable for inclusion in meta-analyses. These were multicenter double-blind, controlled, parallel design studies in SAR sponsored by Merck Research Laboratories.

The adult trials studied 9017 patients in total, with an age range from 15 to 85 years. The mean age of participants in adult studies was between 25 and 35 years. The pediatric studies included 175 children aged from 2 to 14 years. One study was conducted in preschool children.²⁷ All studies used montelukast.

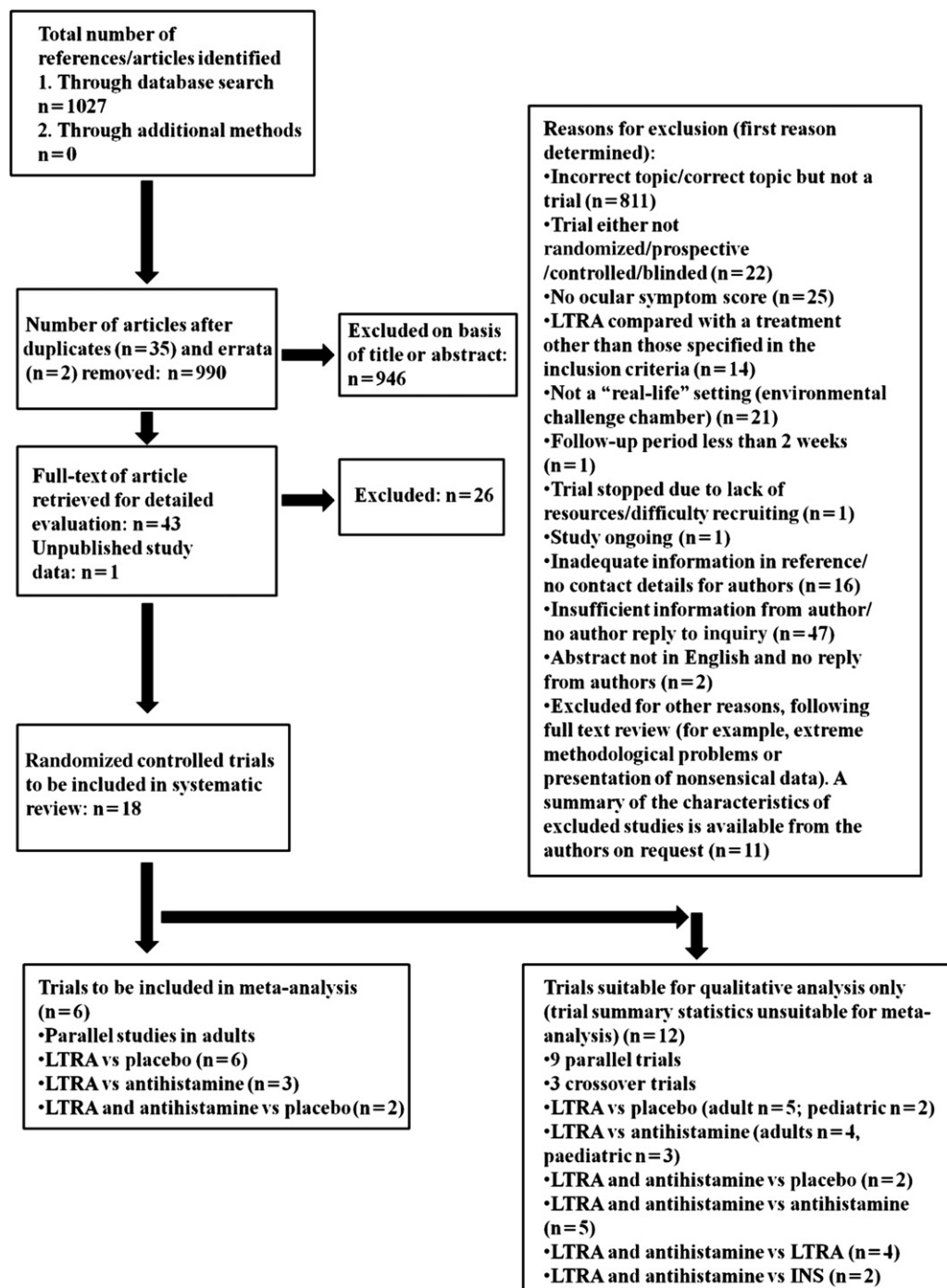


FIGURE 1. Flow chart shows the results of the search strategy.

The studies examined patients with a range of severities of ARC from mild to moderate/severe. Only 8 of the 18 studies specifically specified the severity of the patients' ocular symptoms.^{30-33,35-38} The severity of ocular symptoms in the patients in the 6 studies included in the meta-analyses was mild to moderate (in each study the mean symptom score in each treatment arm was between 1.4 and 1.6, of a total of 3).

Table II shows the important characteristics of the 6 studies included in the meta-analyses. Table E1 (in this article's Online Repository at www.jaci-inpractice.org) gives details of study

design and reasons for exclusion of the remaining 12 trials from meta-analysis. Table III shows the overall risk of bias for each of the 18 studies. Studies at unclear or high risk of bias were not included in sensitivity analyses because of a lack of trials with suitable summary statistics to permit this.

The risk of bias for the ocular symptom score outcome across studies within each drug comparison is summarized as follows: quantitatively analyzed studies (ie, those included in the meta-analyses) were at low risk, and qualitatively analyzed studies were overall at high risk. Although there were insufficient numbers of

TABLE II. Characteristics of the 6 studies included in the meta-analyses

Study	Trial design	Protocol	Age, y	Relevant outcomes
Meltzer, 2000 ³⁰	Multicenter randomized, double-blind, placebo-controlled parallel group study (n = 460)	1-wk single-blind run-in period; 2 wk of treatment Montelukast 10 mg <i>nocte</i> vs montelukast 20 mg <i>nocte</i> vs montelukast 10 mg <i>nocte</i> and loratadine 10 mg <i>nocte</i> vs placebos	15-75 y Median ages within the 5 groups were between 33 and 37 y	Daytime ocular symptom score Juniper RQLQ
Nayak, 2002 ³¹	Multicenter randomized, double-blind, placebo-controlled parallel group study (n = 907)	7-d single-blind placebo run-in period; 2 wk of treatment Montelukast 10 mg <i>nocte</i> vs loratadine 10 mg <i>nocte</i> vs montelukast 10 mg <i>and</i> loratadine 10 mg <i>nocte</i> vs placebos	15-85 Mean $\pm$ SD: LTRA, 35.0 $\pm$ 11.0 Antihistamine, 37.0 $\pm$ 13.0 Combined group, 38.0 $\pm$ 13.0 Placebo, 37.0 $\pm$ 13.0	Daytime ocular symptom score Juniper RQLQ
Philip, 2002 ³²	Multicenter randomized, double-blind, placebo-controlled parallel group study (n = 1302)	3- to 5-d single-blind, placebo run-in period; 2 wk treatment. Montelukast 10 mg <i>nocte</i> vs Loratadine 10 mg <i>nocte</i> vs placebo	18-64 Mean $\pm$ SD: LTRA, 37.0 $\pm$ 13.0 Placebo, 36.0 $\pm$ 12.0 Antihistamine, 36.0 $\pm$ 13.0	Daytime ocular symptom score Juniper RQLQ
Philip, 2004 ³³	Multicenter randomized, double-blind, placebo-controlled parallel group study (n = 831)	3-5 day single-blind placebo run-in period; 2 weeks of treatment Montelukast 10 mg <i>nocte</i> vs placebo	15-80 Mean $\pm$ SD: LTRA, 33.0 $\pm$ 13.2 Placebo, 33.6 $\pm$ 13.7	Daytime ocular symptom score Juniper RQLQ
van Adelsberg, 2003 ³⁵	Multicenter randomized, double-blind, placebo-controlled parallel group study (n = 1214)	3- to 5-d single-blind placebo run-in period; 2 wk of treatment Montelukast 10 mg <i>nocte</i> vs loratadine 10 mg <i>nocte</i> vs placebo	15-82 Mean $\pm$ SD: LTRA, 36.0 $\pm$ 14.0 Antihistamine, 35.0 $\pm$ 13.0 Placebo, 36.0 $\pm$ 13.0	Daytime ocular symptom score Juniper RQLQ
van Adelsberg, 2003 ³⁶	Multicenter randomized, double-blind, placebo-controlled parallel group study (n = 1079)	3- to 5-d single-blind placebo run-in period; 4 wk of treatment Montelukast 10 mg OD vs loratadine 10 mg OD vs placebo	15-82 Mean $\pm$ SD: LTRA, 36.0 $\pm$ 13.0 Antihistamine, 39.0 $\pm$ 13.0 Placebo, 36.0 $\pm$ 12.0	Daytime ocular symptom score End of dosing ocular symptom score Juniper RQLQ

OD, Once daily; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.

studies to produce a funnel plot, we encountered difficulty in obtaining details of a number of industry-funded registered trials and conference abstract titles, suggesting possible publication bias.

Effect of interventions

All studies in the meta-analyses were at low risk of bias, with no evidence of significant clinical, methodologic, or statistical heterogeneity (the latter based on χ^2 results with associated *P* values of greater than .10).

LTRA versus placebo. Six double-blind, randomized, controlled trials that compared LTRA (n = 1969) with placebo (n = 1971) in SAR in participants aged 15 years or older were suitable for meta-analysis.^{30-33,35,36} LTRA improved patients' ocular symptoms from baseline at 2 weeks, with a difference in mean change-from-baseline of -0.10 , in favor of montelukast (95% CI, -0.14 to -0.07 ; *P* < .00001; Figure 2). The symptom scoring system used by the trials was out of a maximum of 3 (3 equalling severe). In sensitivity analyses, if the 4-week data from van Adelsberg et al³⁶ was used, the difference in mean change-from-baseline was -0.11 (95% CI, -0.14 to

-0.07 ; *P* < .00001). If data from the 20-mg daily montelukast group was used *or* the 10-mg and 20-mg group data were combined from the same study, then the mean change-from-baseline equalled 0.10 (95% CI, -0.13 to -0.07 ; *P* < .00001).

LTRA versus oral antihistamine. Three double-blind randomized, controlled trials that compared LTRA (n = 1055) with oral antihistamine (n = 436) in SAR in participants aged older than 15 years were suitable for meta-analysis.^{30,35,36} The difference in mean change-from-baseline ocular symptom scores at 2 weeks was 0.08 (95% CI, 0.02 to 0.14 ; *P* = .007) in favor of oral antihistamines (Figure 3). In sensitivity analyses, if the 4-week data from van Adelsberg et al³⁶ was used, the difference in mean change-from-baseline was 0.07 (95% CI, 0.01 to 0.13 ; *P* = .007). If data from the 20-mg daily montelukast group in van Adelsberg et al³⁶ was used, the difference in mean change-from-baseline scores at 2 weeks was 0.09 (95% CI, 0.04 to 0.15 ; *P* = .001), and, if the 10-mg and 20-mg group data from the same study was combined, the difference was 0.09 (95% CI, 0.03 to 0.15 ; *P* = .003).

TABLE III. Overall risk of bias of each study for the outcome of ocular symptoms: review authors' judgment

Study	Assessment of the risk of bias
Chen, 2006 ²⁷	Unclear risk
Comment	Lack of information about domains such as masking and allocation concealment.
Chervinsky, 2004 ²⁸	High risk
Comment	Insufficient information was provided on baseline patient characteristics. Ocular symptom scores were not published.
Ciebiada, 2006 ¹⁹ and 2008 ²⁰	High risk
Comment	Results section subject to selective reporting. It is unclear how the baseline ocular symptom result was calculated, against which effectiveness was measured.
Cingi, 2010 ¹⁸	High risk
Comment	Lack of an ITT analysis carries a significant risk of bias.
Guerrera, 2006 ²³	Low risk
Comment	Although potentially the investigators could have known which treatment the participants were taking during the trial (sealed envelopes available to them), the masking of participants themselves was adequate, and the authors stated in communication that no envelopes were opened before the end of the study.
Hsieh, 2004 ²⁹	High risk
Comment	Inadequate information in article to make judgment about many domains. Results section subject to selective reporting.
Kurowski, 2004 ²⁴	Unclear risk
Comment	Insufficient information available to categorize as either high or low risk.
Meltzer, 2000 ³⁰	Low risk
Comment	All domains were low risk.
Nayak, 2002 ³¹	Low risk
Comment	Exact numbers analyzed in each group were not outlined in the article. However, authors stated that they used a mITT analysis. Other domains were low risk.
Patel, 2005 ²⁵	Low risk
Comment	Although the authors did not specify the exact numbers analyzed in each group, they did outline that a mITT analysis was used. Other domains were low risk.
Philip, 2002 ³²	Low risk
Comment	Although the exact numbers analyzed in each group were not outlined in the article, the authors stated that they used a mITT analysis. Majority of domains were low risk.
Philip, 2004 ³³	Low risk
Comment	Although the authors did not mention whether an ITT analysis was used, all other multicenter Merck studies have done so, and, in addition, the percentages of patients dropping out because of lack of efficacy was the same in both intervention groups (0.7%). All other domains were low risk.
Saengpanich, 2003 ³⁴	High risk
Comment	Lack of an ITT analysis leads to a significant risk of bias in outcome reporting.
van Adelsberg, 2003 ³⁵	Low risk
Comment	All domains were low risk.
van Adelsberg, 2003 ³⁶	Low risk
Comment	Although the actual numbers analyzed in each group were not specified in the article, there was explanation of the mITT analysis used. Other domains were at low risk.
Wilson, 2000 ³⁷	High risk
Comment	Excluding patients on the basis of compliance (if this actually occurred) with small numbers in each intervention group carries a significant risk of bias. Presented final scores despite baseline ocular symptom scores differing between groups.
Wilson, 2001 ³⁸	High risk
Comment	This was a single-blind study. Stated in methods that noncompliant patients and dropouts were excluded from the analysis. Statistical comparisons made between the active treatment periods and the placebo washout periods were at high risk of bias because the participants were aware when they were taking placebo.

ITT, Intention to treat; mITT, modified intention to treat.

LTRA and oral antihistamine versus placebo (in adults). Two double-blind, randomized controlled trials compared LTRA and oral antihistamine ($n = 377$) with placebo ($n = 233$)^{30,31} (Figure 4). The difference in combined mean change-from-baseline scores at 2 weeks for ocular symptoms was -0.30 (95% CI, -0.38 to -0.21 ; $P < .00001$) in favor of the combination of LTRA and oral antihistamine.

Qualitatively analyzed studies. Twelve other studies were identified which compared montelukast alone or in combination with a variety of other categories of medications.^{18-20,23-25,27-29,34,37,38} A summary of the different drug comparisons is outlined in Table IV. These trials were unsuitable for inclusion in the meta-analyses for a number of reasons, including insufficient data or presentation of summary statistics

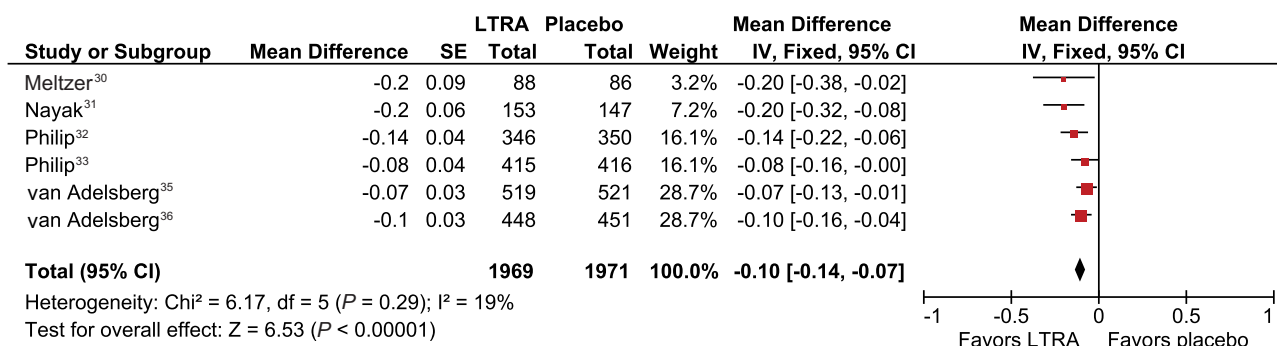


FIGURE 2. Forest plot shows the difference in pooled mean change-from-baseline ocular symptom scores between patients receiving LTRA (montelukast) and those receiving placebo.

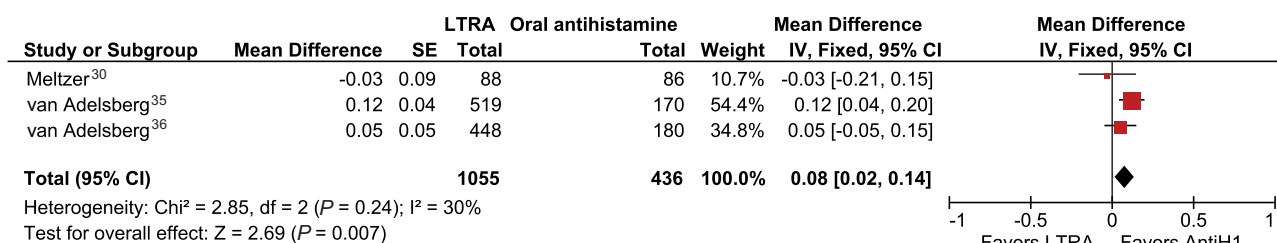


FIGURE 3. Forest plot showing difference in pooled mean change-from-baseline ocular symptom scores between patients receiving LTRA and those receiving oral antihistamine (Antih1).

that made entry into the meta-analysis with other study data impossible. Most of the qualitatively analyzed studies were categorized as being at unclear or high risk of bias; therefore, they would only have been included in meta-analyses as part of a sensitivity analysis even if inclusion had been possible. Two of the 12 studies were identified as being at low risk of bias. The first of these, conducted by Patel et al.,²⁵ was a double-blind, randomized placebo-controlled trial of montelukast versus placebo for 6 weeks in 1992 in patients aged older than 15 years with PAR. The difference between groups in least squares mean change-from-baseline for the eye domain of the Juniper Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), although statistically significant in favor of montelukast, was not a clinically relevant difference (difference of <0.5).³⁹ The severity of ocular symptoms in each group was unclear from the article. One unpublished pediatric double-blind, randomized controlled trial compared montelukast with levocetirizine in 50 children aged 6 to 14 years with SAR and mild ocular symptoms over 2 weeks.²³ The difference in average change-from-baseline scores between groups was not statistically significant when we applied a Mann-Whitney test to the raw data ($P = .29$).

Because of variations in methodology and within-study statistical and reporting differences, it was difficult to reach any definite conclusions about the effect of pollen counts on efficacy in seasonal allergic conjunctivitis (SAC).

Assessment of the quality of the body of evidence with the approach of Grading of Recommendations Assessment, Development, and Evaluation

Table IV outlines the level of quality of evidence assigned to each comparison, graded from very low to high.⁴⁰ Evidence from

high-quality randomized controlled trials is initially assigned the grade "high" but can be downgraded to moderate, low, or very low in the presence of a number of factors. If present, these factors are outlined in Table IV. For comparisons in which a meta-analysis was performed, only those studies included in the analysis were considered when assigning an appropriate level of evidence.

DISCUSSION

The quality of available evidence was such that it was only appropriate to draw conclusions for the following comparisons about the effect of LTRAs on conjunctival symptoms of seasonal ARC: LTRA versus placebo, LTRA versus oral antihistamine, and LTRA and oral antihistamine versus placebo (all in patients aged 15 or older and all using montelukast). The evidence for these comparisons was graded as moderate.

The systematic review and meta-analysis determined that LTRAs are more efficacious than placebo but less efficacious than oral antihistamines in improving seasonal AC symptoms.

The studies included in the 3 meta-analyses all used the same scale to assess the severity of eye symptoms (0 = none to 3 = severe). There was no published minimal clinically significant change value for this scale. Although montelukast reduced ocular symptoms to a greater extent than placebo, the magnitude of the effect was small. Antihistamines had a greater effect than montelukast on symptoms. The magnitude of this difference was again small.

The combination of montelukast and oral antihistamines together led to a greater reduction compared with placebo than montelukast alone compared with placebo. This is not surprising given that the second meta-analysis showed antihistamines to have a small but greater benefit than montelukast. The

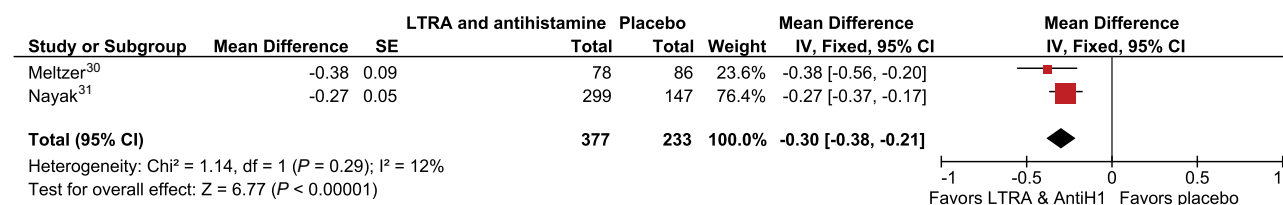


FIGURE 4. Forest plot showing difference in pooled mean change-from-baseline ocular symptom scores between patients receiving LTRA and oral antihistamine (AntiH1) and those receiving placebo.

TABLE IV. GRADE⁴⁰ levels of evidence assigned for each comparison (with respect to ocular symptoms)

Comparison	Level of evidence	No. of studies	Reason(s) for downgrading
LTRA vs placebo in SAR (adults)	Moderate	6 ^{30-33,35,36}	Possible publication bias
LTRA vs oral antihistamine in SAR (adults)	Moderate	3 ^{30,35,36}	Possible publication bias
LTRA and oral antihistamine vs placebo in SAR (adults)	Moderate	2 ^{30,31}	Possible publication bias
LTRA vs placebo in PAR/persistent AR (adults), qualitative analysis only	Low	4 ^{18-20,25}	Most studies at high risk of bias. Ciebiada ^{19,20} was subject to selective reporting and design limitation. Cingi ¹⁸ did not use an ITT analysis. Unexplained heterogeneity of results also occurred in Ciebiada. ^{19,20}
LTRA vs placebo in PAR (pediatric), qualitative analysis only	Low	2 ^{27,29}	Chen ²⁷ at unclear risk of bias. Hsieh ²⁹ was at high risk with imprecision in results (did not report any results numerically).
LTRA vs oral antihistamine in PAR (adults), qualitative analysis only	Low	2 ^{19,20}	Ciebiada ^{19,20} at high risk of bias because of selective reporting and design limitation. Unexplained heterogeneity of results also occurred in these studies.
LTRA vs oral antihistamine in SAR (pediatrics)			No assessment made because there was only one (unpublished) study in this category. ²³
LTRA vs oral antihistamine in PAR (pediatrics), qualitative analysis only	Low	2 ^{27,29}	Chen ²⁷ at unclear risk of bias. Hsieh ²⁹ was at high risk with imprecision in results (did not report any results numerically).
LTRA and oral antihistamine vs placebo in PAR (adults), qualitative analysis only	Low	2 ^{19,20}	Ciebiada ^{19,20} at high risk of bias because of selective reporting and design limitation. Unexplained heterogeneity of results also occurred in these studies.
LTRA and oral antihistamine vs oral antihistamine or LTRA alone in SAR (adults), qualitative analysis only	Low	3 ^{24,30,37}	Meltzer ³⁰ at low risk of bias. Kurowski ²⁴ at unclear risk, and Wilson ³⁷ at high risk of bias. Differences in methodology between studies.
LTRA and oral antihistamine vs oral antihistamine or LTRA alone in PAR (adults), qualitative analysis only	Low	2 ^{19,20}	Ciebiada ^{19,20} at high risk of bias because of selective reporting and design limitation. Unexplained heterogeneity of results also occurred in these studies.
LTRA and oral antihistamine vs INS in SAR (adults), qualitative analysis only	Low	2 ^{34,38}	Saengpanich ³⁴ and Wilson ³⁸ at high risk of bias. Design limitation in the study of Wilson ³⁸ (crossover trial not the optimal study design in SAR).

GRADE, Grading of Recommendations Assessment, Development, and Evaluation; INS, intranasal corticosteroid; ITT, intention to treat.

magnitude of the improvement seen with dual therapy was greater than one might expect from a purely additive effect (based on the first 2 meta-analyses), suggesting the existence of a potential synergistic effect from combined treatment. However, it must be borne in mind that this was not a direct head-to-head comparison of combination therapy versus LTRA or antihistamine alone. Trials that are adequately powered to detect differences in ocular symptoms should be conducted to investigate whether combined treatment has a synergistic effect.

The evidence that compared LTRA with placebo in perennial allergic conjunctivitis (PAC) was graded as low quality, but did include one large trial at low risk of bias.²⁵ From this one trial that measured the start and end-of-study eye domain of the Juniper RQLQ, there was no evidence to support the hypothesis

that LTRA is more effective in reducing ocular symptoms in PAR/PAC than placebo. Although no randomized controlled trials of LTRAs in VKC or AKC were identified during the study searches, one small open study of 12 pediatric and adult patients with VKC and asthma which used montelukast was found.⁴¹ Overall, both total symptom and total sign scores were significantly reduced after 15 days of montelukast treatment. Although promising, no conclusions can be drawn about the effectiveness of LTRAs in VKC because the study design is subject to significant risk of bias.

One previous systematic review has considered the effects of LTRAs on the ocular symptoms of SAR.¹³ Direct comparison with the results from our review is difficult, mainly because of differences in methodology, for example, missing studies from

some meta-analyses, differences in study inclusion criteria, and the use of standardized mean differences rather than mean differences in the review of Rodrigo and Yanez.¹³ In one comparison the summary statistic is in the opposite direction to the result from our review, despite the same trials being included in the meta-analysis. It is unclear from the researchers' methodology how this result was reached.

The updated 2010 ARIA guidelines suggest that montelukast can be used in adults and children with SAR and in preschool children with persistent AR.⁵ It is also suggested that oral antihistamines be used in preference to LTRAs in the same groups. The evidence obtained from this review can add an additional dimension to these *conditional* recommendations, supporting the consideration of use of montelukast in patients older than 15 years with SAC, either alone in patients who do not tolerate oral antihistamines or in combination with oral antihistamines.

In some of the areas that the review covered, further research is clearly required. Ideally, all future AR trials should include ocular symptoms as an outcome. Adequately designed large controlled trials are needed in both SAC and PAC in children and PAC in adults comparing LTRAs with placebo, antihistamines, and intranasal corticosteroid. Studies powered to detect differences in ocular symptoms should be conducted to assess whether dual therapy with LTRA and oral antihistamine has an additive or synergistic effect. Randomized controlled trials that compare LTRAs with placebo in VKC and AKC should be considered.

A number of strengths and limitations of this review are worth noting. The studies included in the meta-analyses were large, industry-sponsored multicenter trials, assessed to be at low risk of bias and without significant heterogeneity. The latter is reassuring when pooling results within a meta-analysis. It is desirable to include smaller or non-industry-funded studies in a meta-analysis. In this case this was not possible because of the type of statistics presented in these studies. Most of these trials were at high or unclear risk of bias; therefore, they could only have been included in sensitivity analyses.

Although ocular symptoms are clearly a patient-relevant outcome, the subjective nature of symptom reporting did in part lead to an observed placebo effect in many of the studies. Including those patients without ocular symptoms in the individual study analyses (which occurred in all but one of the studies³⁰) may serve to underplay the true difference in change-from-baseline scores between LTRA and placebo. It must be borne in mind however that excluding patients from analyses is a *post hoc* practice with limitations in its own right. Frequency of conjunctivitis symptoms was similar in intervention arms when stated in individual papers. Unfortunately, no studies were identified in which ocular symptoms of ARC were the primary outcome. Ideally, studies in which AC is considered as a separate entity from AR would allow patients to be selected and randomized on the basis of the severity of their eye disease. It is unsurprising however that we found this to be the case because AC, in general, is considered in conjunction with AR and is often regarded as less important than the nasal symptoms.⁵

At the review level a rigorous search of multiple databases was conducted. Several attempts were made to contact researchers at each stage of the review. Ideally, study identification and assessment should be done in parallel by 2 reviewers to reduce any potential chance of bias being introduced into the selection and assessment process.²⁶ This was not possible in this review because the work was conducted by one author (J.G.) as part of

a higher-degree thesis. Results from some studies could not be included because of the method of presentation of the data,^{28,31} for example, Nayak et al,³¹ which presented results as least squares mean difference *from* placebo in change-from-baseline scores. This precluded the inclusion of data in the combination LTRA and antihistamine group in a meta-analysis that compared dual therapy with either treatment alone.

In conclusion, this systematic review highlights that in SAC, LTRAs (evidence for montelukast only) are more efficacious than placebo but less efficacious than oral antihistamines, when treating patients aged 15 years or older.

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REFERENCES

1. Buckley RJ. Allergic eye disease—a clinical challenge. *Clin Exp Allergy* 1998; 28(Suppl 6):39-43.
2. Bielory L. Allergic conjunctivitis and the impact of allergic rhinitis. *Curr Allergy Asthma Rep* 2010;10:122-34.
3. Kumar S. Vernal keratoconjunctivitis: a major review. *Acta Ophthalmol* 2009; 87:133-47.
4. Guglielmetti S, Dart JKG, Calder V. Atopic keratoconjunctivitis and atopic dermatitis. *Curr Opin Allergy Clin Immunol* 2010;10:478-85.
5. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010;126:466-76.
6. Stahl JL, Cook EB, Barney NP, Graziano FM. Pathophysiology of ocular allergy: the roles of conjunctival mast cells and epithelial cells. *Curr Allergy Asthma Rep* 2002;2:332-9.
7. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca M, Passalacqua G, Pallesstrini E, et al. Seasonal and perennial allergic rhinitis: is this classification adherent to real life? *Allergy* 2005;60:882-7.
8. Scadding GK, Durham SR, Mirakian R, Jones NS, Leech SC, Farooque S, et al. BSACI guidelines for the management of allergic and non-allergic rhinitis. *Clin Exp Allergy* 2007;38:19-42.
9. Baryshak YR, Zavaro A, Monselise M, Samra Z, Sompolsky D. Vernal keratoconjunctivitis in an Israeli group of patients and its treatment with sodium cromoglycate. *Br J Ophthalmol* 1982;66:118-22.
10. Peters-Golden M, Gleason MM, Togias A. Cysteinyl leukotrienes: multifunctional mediators in allergic rhinitis. *Clin Exp Allergy* 2006;36:689-703.
11. Bisgaard H, Ford-Hutchinson AW, Charleson S, Taudorf E. Production of leukotrienes in human skin and conjunctival mucosa after specific allergen challenge. *Allergy* 1985;40:417-23.
12. Grainger J, Drake-Lee A. Montelukast in allergic rhinitis: a systematic review and meta-analysis. *Clin Otolaryngol* 2006;31:360-7.
13. Rodrigo GJ, Yanez A. The role of antileukotriene therapy in seasonal allergic rhinitis: a systematic review of randomized trials. *Ann Allergy Asthma Immunol* 2006;96:779-86.
14. Wilson A, O'Byrne P, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* 2004;116: 338-44.
15. Lombardo G, Quattrocchi P, Lombardo G, Galati P, Giannetto L, Barresi L. Concomitant levocetirizine and montelukast in the treatment of seasonal allergic rhinitis: influence on clinical symptoms. *Italian J Allergy Clin Immunol* 2006;16:63-8 (in Italian).
16. Santos CB, Hanks C, McCann J, Lehman EB, Pratt E, Craig TJ. The role of montelukast on perennial allergic rhinitis and associated sleep disturbances and daytime somnolence. *Allergy Asthma Proc* 2008;29:140-5.
17. Lu S, Malice MP, Dass SB, Reiss TF. Clinical studies of combination montelukast and loratadine in patients with seasonal allergic rhinitis. *J Asthma* 2009; 46:878-83.
18. Cingi C, Ozlugedik S. Effects of montelukast on quality of life in patients with persistent allergic rhinitis. *Otolaryngol Head Neck Surg* 2010;142: 654-8.

19. Ciebiada M, Gorska-Ciebiada M, DuBuske LA, Gorski P. Montelukast with desloratadine or levocetirizine for the treatment of persistent allergic rhinitis. *Ann Allergy Asthma Immunol* 2006;97:664-71.
20. Ciebiada M, Ciebiada MG, Kmiecik T, DuBuske LM, Gorski P. Quality of life in patients with persistent allergic rhinitis treated with montelukast alone or in combination with levocetirizine or desloratadine. *J Investig Allergol Clin Immunol* 2008;18:343-9.
21. Razi C, Bakirtas A, Harmanci K, Turktas I, Erbas D. Effect of montelukast on symptoms and exhaled nitric oxide levels in 7- to 14-year-old children with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2006;97:767-74.
22. Sardana N, Santos C, Lehman E, Craig T. A comparison of intranasal corticosteroid, leukotriene receptor antagonist, and topical antihistamine in reducing symptoms of perennial allergic rhinitis as assessed through the Rhinitis Severity Score. *Allergy Asthma Proc* 2010;31:5-9.
23. Guerrero T, Cuomo B, Cossetti M, Fasoli L, Saretta F, Morittu A, et al. Is montelukast effective in allergic rhinitis in children? Presented at the 2006 European Respiratory Society Congress, Munich, Germany. Abstract 1527. Available from: <http://www.ers-education.org/pages/default.aspx?id=1219&idBrowse=6577&det=1>. Accessed April 15, 2011.
24. Kurowski M, Kuna P, Gorski P. Montelukast plus cetirizine in the prophylactic treatment of seasonal allergic rhinitis: influence on clinical symptoms and nasal allergic inflammation. *Allergy* 2004;59:280-8.
25. Patel P, Philip G, Yang W, Call R, Horak F, LaForce C, et al. Randomized, double-blind, placebo-controlled study of montelukast for treating perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2005;95:551-7.
26. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. (Updated March 2011) The Cochrane Collaboration, 2011. Available from: www.cochrane-handbook.org. Accessed July 14, 2011.
27. Chen ST, Lu KH, Sun HL, Chang WT, Lue KH, Chou MC. Randomized placebo-controlled trial comparing montelukast and cetirizine for treating perennial allergic rhinitis in children aged 2-6 years. *Pediatr Allergy Immunol* 2006;17:49-54.
28. Chervinsky P, Philip G, Malice MP, Bardelas J, Nayak A, Marchal JL, et al. Montelukast for treating fall allergic rhinitis: effect of pollen exposure in 3 studies. *Ann Allergy Asthma Immunol* 2004;92:367-73.
29. Hsieh JC, Lue KH, Lai DS, Sun HL, Lin YH. A Comparison of cetirizine and montelukast for treating childhood perennial allergic rhinitis. *Pediatr Allergy Immunol* 2004;17:59-69.
30. Meltzer EO, Malmstrom K, Lu S, Prenner BM, Wei LX, Weinstein SF, et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. *J Allergy Clin Immunol* 2000;105:917-22.
31. Nayak A, Philip G, Lu S, Malice M, Reiss T. Montelukast Fall Rhinitis Investigator Group. Efficacy and tolerability of montelukast alone or in combination with loratadine in seasonal allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial performed in the fall. *Ann Allergy Asthma Immunol* 2002;88:592-600.
32. Philip G, Malmstrom K, Hampel FC, Weinstein SF, LaForce CF, Ratner PH, et al. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. *Clin Exp Allergy* 2002;32:1020-8.
33. Philip G, Nayak A, Berger W, Leynadier F, Vrijens F, Dass S, et al. The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. *Curr Med Res Opin* 2004;20:1549-58.
34. Saengpanich S, deTineo M, Naclerio RM, Baroody FM. Fluticasone nasal spray and the combination of loratadine and montelukast in seasonal allergic rhinitis. *Arch Otolaryngol Head Neck Surg* 2003;129:557-62.
35. van Adelsberg J, Philip G, LaForce CF, Weinstein SF, Menten J, Malice MP, et al. Randomized controlled trial evaluating the clinical benefit of montelukast for treating spring seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2003;90:214-22.
36. van Adelsberg J, Philip G, Pedinoff A, Meltzer E, Ratner P, Reiss T. Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period. *Allergy* 2003;58:1268-76.
37. Wilson A, Dempsey O, Sims E, Coutie W, Paterson M, Lipworth B. Evaluation of treatment response in patients with seasonal allergic rhinitis using domiciliary nasal peak inspiratory flow. *Clin Exp Allergy* 2000;30:833-8.
38. Wilson A, Orr L, Sims E, Lipworth B. Effects of monotherapy with intra-nasal corticosteroid or combined oral histamine and leukotriene receptor antagonists in seasonal allergic rhinitis. *Clin Exp Allergy* 2001;31:61-8.
39. Juniper EF. Measuring health-related quality of life in rhinitis. *J Allergy Clin Immunol* 1997;99:S742-9.
40. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6.
41. Lambiase A, Bonini S, Rasi G, Coassin M, Bruscolini A. Montelukast, a leukotriene receptor antagonist, in vernal keratoconjunctivitis associated with asthma. *Arch Ophthalmol* 2003;121:615-20.