EFFICACY OF MONTELUKAST IN ALLERGIC RHINITIS TREATMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS

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To my dearest parents, Dr Girija Devi Krishnamoorthy and Mr Krishnamoorthy Pakirisamy, thank you for your unmatched sacrifices and giving me the gift of what I am today.

Lastly, all praise to God for blessing me with this opportunity. I am truly grateful.

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ABSTRAK

Pengenalan: Dalam rawatan alergik rhinitis (AR), ubat montelukast mempunyai potensi untuk digunakan sebagai alternatif atau sebagai tambahan kepada ubat oral antihistamine (OAH) atau ubat intranasal corticosteroid.

Objektif: Untuk menilai keberkesanan ubat montelukast dalam rawatan alergik rhinitis.

Kaedah: Kajian literatur elektronik dibuat dalam 'Cochrane Central Register of Controlled Trials CENTRAL' 'EMBASE' dan 'MEDLINE' dari 1966 sehingga 21^{hb} Januari 2019. Penyelidikan yang mematuhi syarat-syarat untuk layak dinilai, iaitu 'Randomized control trials(RCTs)' yang membandingkan Montelukast dengan 'placebo' ataupun rawatan standard. Penyelidikan utama yang dinilai ialah skor gejala hidung waktu siang (DNS) dan skor gejala hidung waktu malam (NNS). Penyelidikan lain-lain yang dinilai skor gejala komposit (CSS), skor gejala mata waktu siang (DES) dan kualiti hidup (RQLQ). Meta-analisa dilakukan menggunakan perisian Review Manager 5.3 (RevMan 2014) dan data dikumpulkan menggunakan model kesan rawak.

Keputusan: Lima belas penyelidikan melibatkan 10387 peserta mematuhi syarat-syarat layak dinilai. Montelukast lebih berkesan apabila dibandingkan dengan 'placebo' dalam membantu DNS (MD -0.12, 95% CI -0.15 to -0.08; P < 0.001), NNS (MD -0.09, 95% CI -0.13 to -0.05; P < 0.001), CSS (MD -0.08, 95% CI -0.11 to -0.06; P < 0.001), DES (MD -0.17, 95% CI -0.33 to -0.02; P < 0.030) and RQLQ (MD -0.34, 95% CI -0.49 to -0.20; P < 0.001). OAH lebih berkesan apabila dibandingkan dengan montelukast dalam membantu DNS (MD 0.08, 95% CI 0.03 to 0.13; P=0.002), CSS (MD 0.03, 95% CI -0.02 to 0.07; P=0.270), DES (MD 0.06, 95% CI 0 to 0.12; P=0.040) and RQLQ (MD 0.03, 95% CI -0.05

to 0.12; P=0.430). Montelukast lebih berkesan dari OAH dalam membantu NNS (MD -0.03, 95% CI -0.08 to 0.03; P=0.330). Semburan Intranasal fluticasone lebih berkesan berbanding montelukast dalam membantu DNS (MD 0.71, 95% CI 0.44 to 0.99; P < 0.001) dan NNS (MD 0.63, 95% CI 0.29 to 0.97; P < 0.001). Kombinasi montelukast dan OAH lebih berkesan berbanding OAH dalam membantu DNS (MD -0.15, 95% CI -0.27 to -0.03; P =0.010), NNS (MD -0.16, 95% CI -0.28 to -0.05; P =0.006), CSS (MD -0.12, 95% CI -0.25 to -0.01; P =0.070), DES (MD -0.12, 95% CI -0.30 to 0.06; P =0.180) and RQLQ (MD -0.10, 95% CI -0.28 to 0.08; P =0.290). Kombinasi montelukast dan OAH lebih berkesan berbanding montelukast dalam membantu DNS (MD 0.15, 95% CI 0.08 to 0.21; P<0.001), NNS (MD 0.05, 95% CI -0.09 to 0.19; P=0.510), CSS (MD 0.1, 95% CI 0.03 to 0.17; P=0.007), DES (MD 0.18, 95% CI 0 to 0.36; P=0.050) dan RQLQ (MD 0.07 95% CI -0.15 to 0.29; P=0.530). **Kesimpulan**: Montelukast berkesan dalam rawatan pesakit AR yang mempunyai gejala hidung waktu malam dan juga sebagai terapi kombinasi bersama-sama OAH dalam meningkatkan pengurusan rawatan AR.

ABSTRACT

Introduction: In treating allergic rhinitis (AR), montelukast has the potential to be used as an alternative or addition to oral antihistamine (OAH) or intranasal corticosteroid.

Objectives: To assess the effectiveness of montelukast in treating AR.

Methods: An electronic literature search was performed using Cochrane Central Register of Controlled Trials, EMBASE and MEDLINE from 1966 to 21st January 2019. The eligibility criteria were randomized control trials comparing montelukast with placebo or other standard treatments. The primary outcomes assessed were daytime nasal symptom score (DNS) and nighttime nasal symptom score (NNS). The secondary outcomes assessed were composite nasal symptom score (CSS), daytime eyes symptom score (DES) and rhinoconjunctivitis quality of life questionnaires (RQLQ). Meta-analysis was done using Review Manager 5.3 software based on the random-effects model.

Results: Fifteen studies of 10387 participants met the inclusion criteria. Montelukast was effective than placebo in improving DNS (MD -0.12, 95% CI -0.15 to -0.08; P < 0.001), NNS (MD -0.09, 95% CI -0.13 to -0.05; P < 0.001), CSS (MD -0.08, 95% CI -0.11 to -0.06; P < 0.001), DES (MD -0.17, 95% CI -0.33 to -0.02; P < 0.030) and RQLQ (MD -0.34, 95% CI -0.49 to -0.20; P < 0.001). OAH was superior than montelukast in improving DNS (MD 0.08, 95% CI 0.03 to 0.13; P=0.002), CSS (MD 0.03, 95% CI -0.02 to 0.07; P=0.270), DES (MD 0.06, 95% CI 0 to 0.12; P=0.040) and RQLQ (MD 0.03, 95% CI -0.05 to 0.12; P=0.430). Montelukast was superior than OAH in improving NNS (MD -0.03, 95% CI -0.08 to 0.03; P=0.330). Intranasal fluticasone spray was superior than montelukast in improving DNS (MD 0.71, 95% CI 0.44 to 0.99; P < 0.001) and NNS (MD 0.63, 95% CI 0.29 to 0.97; P < 0.001). A combined montelukast and OAH was superior than OAH in in improving DNS

(MD -0.15, 95% CI -0.27 to -0.03; P =0.010), NNS (MD -0.16, 95% CI -0.28 to -0.05; P =0.006), CSS (MD -0.12, 95% CI -0.25 to -0.01; P =0.070), DES (MD -0.12, 95% CI -0.30 to 0.06; P =0.180) and RQLQ (MD -0.10, 95% CI -0.28 to 0.08; P =0.290). A combined montelukast and OAH was superior than montelukast improving DNS (MD 0.15, 95% CI 0.08 to 0.21; P<0.001), NNS (MD 0.05, 95% CI -0.09 to 0.19; P=0.510), CSS (MD 0.1, 95% CI 0.03 to 0.17; P=0.007), DES (MD 0.18, 95% CI 0 to 0.36; P=0.050) and RQLQ (MD 0.07 95% CI -0.15 to 0.29; P=0.530).

Conclusion: Montelukast is effective in treating AR patients with nocturnal symptoms and as add on combination therapy with OAH in the stepping up management of AR.

INTRODUCTION

Description of the condition

Allergic rhinitis is a disease which imposes a universal burden [1]. It may occur simultaneously with other diseases such as asthma. In fact, the concept of ‘one airway one disease’ shows that both these pathologies frequently develop hand in hand [2, 3]. Worldwide, the prevalence of allergic rhinitis varies. The prevalence reported in Western Europe was 23%, and in the Asian population, they were as high as 40-46% [3]. Allergic rhinitis can be regarded as the most prevalent immune-mediated disease with an increasing presence [4]. The allergic reaction that occurs in the disease is now regarded as a dynamic process rather than a one-off event. Allergic rhinitis occurs after a sensitized individual is exposed to a specific trigger, for example, house dust mite, pollen or dander [5]. A cascade of events following the trigger occur at a molecular level that leads to classical symptoms of allergic rhinitis.

The classical symptoms, which occur in allergic rhinitis, are sneezing, rhinorrhea, nasal obstruction, and pruritis [6]. Hyposmia is also another symptom of allergic rhinitis. As much as 60% of allergic rhinitis patients have been shown to suffer from anomalies of smell [7]. Apart from these, excessive daytime somnolence and sleep disturbances are known symptoms, which occur due to nocturnal nasal blockage [8]. In extreme cases, there would be increased pressure within the paranasal sinuses. In other instances, patients may develop ear fullness or earache as a result of eustachian tube dysfunction [9]. Of all the symptoms identified, the most disturbing symptom and the most challenging to cure is nasal obstruction [10].

Based on the symptoms, allergic rhinitis can be divided into persistent or intermittent (temporal) and mild / moderate-severe (severity) using the 'Allergic Rhinitis and its Impact on Asthma Guide' [11] .There is another new classification by Okubo et al. that is the sneezing type or the obstruction type [12]. Based on Japanese guidelines, sneezing and rhinorrhea is caused by histamine and classified as one 'subtype' of allergic rhinitis. Obstruction subtype is due to leukotriene mediated symptoms of nasal blockage. Even though allergic rhinitis is never life-threatening, it's significance is always underplayed [1]. Allergic rhinitis not only affects the quality of life of the patient, but it also has a negative implication on society [6, 13]. School absenteeism and economic loss due to financing of medication are among its downside [5].

Description of the intervention

The basis of allergic rhinitis is a type I hypersensitivity response of the nasal mucosa due to a trigger (allergen), mediated by Immunoglobulin E [9, 1]. During this response, there is plenty of chemoattraction of cells and molecules [4]. A salient characteristic of allergic rhinitis is the aggregation of eosinophils [14]. Besides the presence of inflammatory cells (mast cells, eosinophils, neutrophils, and T cells), there is an increase in proinflammatory mediators like histamine and leukotrienes in the nasal secretions [15]. Although histamine was first described in 1910, leukotriene was relatively new and was only described in 1979 [16, 17]. It is now understood that leukotrienes like LTC4, LTD4 and LTE4 (all 3 are known as cysteinyl leukotrienes, CysLTs) are eosinophilic chemoattractants, (the key in allergic rhinitis). As such, montelukast blocks these leukotriene receptors and prevents its action. The

actions of CysLTs namely are :i) increase vascular permeability ii) mucous production iii) smooth muscles constriction iv) migration of eosinophils [1].

It has also been understood that histamine is crucial in the development of symptoms like sneezing and itching (due to nervous stimulation) as well as rhinorrhea (due to glandular secretions). As such, antihistamine medication is well for the above symptoms, but not effective against obstruction; in contrast to leukotriene, which primarily causes nasal block and increases nasal airway resistance [1, 15] .

How the intervention might work

Allergen avoidance and environmental control are crucial in the treatment of allergic rhinitis [18]. Nonetheless, montelukast is an effective drug for treatment. The principal treatment in allergic rhinitis is intranasal steroid [19, 20]. However, both antihistamine and antileukotriene have shown to be as effective in the treatment of allergic rhinitis [15]. The effect of histamine on the nasal block is short-lived and only noticeable at high concentrations. Leukotriene, however, mainly functions to increases nasal block. Antileukotriene treatment was found to be comparable to antihistamines and intranasal corticosteroid. Leukotriene levels are increased in allergic rhinitis patients following allergen exposure, which justifies the role of montelukast in allergic rhinitis treatment [18]. There has been a significant improvement in the quality of life after montelukast treatment when combined with intranasal steroid as compared to monotherapy.

Why it is important to do this review

Nasal congestion is one of many important symptoms of allergic rhinitis. Effectiveness of montelukast in curing symptoms is important to be assessed. Reviews on Montelukast have been performed in 2009 [21] and 2004 [22]. New trials regarding Montelukast for the treatment of allergic rhinitis have emerged. The current review serves as an update to whether the conclusion on the effectiveness of Montelukast would change in the presence of these new trials.

References

1. Van Hoecke H, Vandenbulcke L, Van Cauwenberge P. Histamine and leukotriene receptor antagonism in the treatment of allergic rhinitis: an update. Drugs. 2007;67(18):2717-26. doi:10.2165/00003495-200767180-00006.

2. Li L, Wang R, Cui L, Guan K. Efficacy of montelukast as prophylactic treatment for seasonal allergic rhinitis. Ear Nose Throat J. 2018;97(7):E12-e6.

3. Kim MK, Lee SY, Park HS, Yoon HJ, Kim SH, Cho YJ et al. A randomized, multicenter, double-blind, phase III study to evaluate the efficacy on allergic rhinitis and safety of a combination therapy of montelukast and levocetirizine in patients with asthma and allergic rhinitis. Clin Ther. 2018;40(7):1096-107.e1. doi:10.1016/j.clinthera.2018.04.021.

4. Braido F, Riccio AM, Rogkakou A, Massacane P, Guerra L, Fumagalli F et al. Montelukast effects on inflammation in allergic rhinitis: a double blind placebo controlled pilot study. Eur Ann Allergy Clin Immunol. 2012;44(2):48-53.

5. 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(2):140-5. doi:10.2500/aap.2008.29.3097.

6. Chen H, Lou H, Wang Y, Cao F, Zhang L, Wang C. Comparison of the efficacy and mechanisms of intranasal budesonide, montelukast, and their combination in treatment of patients with seasonal allergic rhinitis. Int Forum Allergy Rhinol. 2018;8(11):1242-52. doi:10.1002/alr.22197.

7. Dalgic A, Dinc ME, Ulusoy S, Dizdar D, Is A, Topak M. Comparison of the effects of nasal steroids and montelukast on olfactory functions in patients with allergic rhinitis. Eur

Ann Otorhinolaryngol Head Neck Dis. 2017;134(4):213-6. doi:10.1016/j.anorl.2016.05.012.

8. Santanello NC, DeMuro-Mercon C, Shah SR, Schenkel EJ, Ratner PH, Dass SB et al. Validation of the nighttime symptoms score as a clinically relevant measure of allergic rhinitis. Allergy Asthma Proc. 2006;27(3):231-9.

9. Erdoğan BA, Sanlı A, Paksoy M, Altın G, Aydın S. Quality of life in patients with persistent allergic rhinitis treated with desloratadine monotherapy or desloratadine plus montelucast combination. Kulak burun bogaz ihtisas dergisi : KBB [Journal of ear, nose, and throat]. 2014;24(4):217-24. doi:10.5606/kbbihtisas.2014.48108.

10. Ciebiada M, Gorska-Ciebiada M, Barylski M, Kmiecik T, Gorski P. Use of montelukast alone or in combination with desloratadine or levocetirizine in patients with persistent allergic rhinitis. Am J Rhinol Allergy. 2011;25(1):e1-6. doi:10.2500/ajra.2011.25.3540.

11. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens W, Togias A et al. Allergic rhinitis and its impact on asthma (ARIA) 2008. Allergy. 2008;63:8-160.

12. Okubo K, Kurono Y, Fujieda S, Ogino S, Uchio E, Odajima H et al. Japanese guideline for allergic rhinitis 2014. Allergol Int. 2014;63(3):357-75.

13. Hashiguchi K, Okubo K, Inoue Y, Numaguchi H, Tanaka K, Oshima N et al. Evaluation of Montelukast for the Treatment of Children With Japanese Cedar Pollinosis Using an Artificial Exposure Chamber (OHIO Chamber). Allergy Rhinol (Providence). 2018;9:2152656718783599. doi:10.1177/2152656718783599.

14. Ciebiada M, Barylski M, Gorska Ciebiada M. Nasal eosinophilia and serum soluble intercellular adhesion molecule 1 in patients with allergic rhinitis treated with montelukast alone or in combination with desloratadine or levocetirizine. Am J Rhinol Allergy. 2013;27(2):e58-62. doi:10.2500/ajra.2013.27.3881.

15. 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(3):280-8. doi:10.1046/j.1398-9995.2003.00416.x.

16. Murphy RC, Hammarström S, Samuelsson B. Leukotriene C: a slow-reacting substance from murine mastocytoma cells. Proceedings of the National Academy of Sciences. 1979;76(9):4275-9.

17. Dale HH, Laidlaw PP. The physiological action of β-iminazolylethylamine. The Journal of physiology. 1910;41(5):318-44.

18. Shen C, Chen F, Wang H, Zhang X, Li G, Wen Z. Individualized treatment for allergic rhinitis based on key nasal clinical manifestations combined with histamine and leukotriene D4 levels. Braz J Otorhinolaryngol. 2018. doi:10.1016/j.bjorl.2018.09.007.

19. Pinar E, Eryigit O, Oncel S, Calli C, Yilmaz O, Yuksel H. Efficacy of nasal corticosteroids alone or combined with antihistamines or montelukast in treatment of allergic rhinitis. Auris Nasus Larynx. 2008;35(1):61-6. doi:10.1016/j.anl.2007.06.004.

20. 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(5):557-62. doi:10.1001/archotol.129.5.557.

21. Wei C. The efficacy and safety of H1-antihistamine versus montelukast for allergic rhinitis: a systematic review and meta-analysis. Biomed Pharmacother. 2016;83:989-97. doi:10.1016/j.biopha.2016.08.003.

22. Xiao J, Wu WX, Ye YY, Lin WJ, Wang L. A network meta-analysis of randomized controlled trials focusing on different allergic rhinitis medications. Am J Ther. 2016;23(6):e1568-e78. doi:10.1097/mjt.0000000000000242.

OBJECTIVES

The objective of this systematic review and meta-analysis was to determine the effectiveness of montelukast in allergic rhinitis

Primary outcomes

1. Daytime nasal symptom score
2. Nighttime nasal symptom score

Secondary outcomes

1. Composite symptom score
2. Daytime eye score
3. Rhino conjunctivitis quality of life
4. Blood eosinophil level

MANUSCRIPT

Title page

Systematic Review

Efficacy of montelukast in allergic rhinitis treatment: a systematic review and meta-analysis

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Abstract

Introduction In treating allergic rhinitis (AR), montelukast has the potential to be used as an alternative or addition to oral antihistamine (OAH) or intranasal corticosteroid.

Objective To assess the effectiveness of montelukast in treating AR.

Methods An electronic literature search was performed using Cochrane Central Register of Controlled Trials, EMBASE and MEDLINE from 1966 to 21st January 2019. The eligibility criteria were randomized control trials comparing montelukast with placebo or other standard treatments. The primary outcomes assessed were daytime nasal symptom score (DNS) and nighttime nasal symptom score (NNS). The secondary outcomes assessed were composite nasal symptom score (CSS), daytime eyes symptom score (DES) and rhinoconjunctivitis quality of life questionnaires (RQLQ). Meta-analysis was done using Review Manager 5.3 software based on the random-effects model.

Results Fifteen studies of 10387 participants met the inclusion criteria. Montelukast was effective than placebo in improving DNS (MD -0.12, 95% CI -0.15 to -0.08; P < 0.001), NNS (MD -0.09, 95% CI -0.13 to -0.05; P < 0.001), CSS (MD -0.08, 95% CI -0.11 to -0.06; P < 0.001), DES (MD -0.17, 95% CI -0.33 to -0.02; P < 0.030) and RQLQ (MD -0.34, 95% CI -0.49 to -0.20; P < 0.001). OAH was superior than montelukast in improving DNS (MD 0.08, 95% CI 0.03 to 0.13; P=0.002), CSS (MD 0.03, 95% CI -0.02 to 0.07; P=0.270), DES (MD 0.06, 95% CI 0 to 0.12; P=0.040) and RQLQ (MD 0.03, 95% CI -0.05 to 0.12; P=0.430). Montelukast was superior than OAH in improving NNS (MD -0.03, 95% CI -0.08 to 0.03; P=0.330). Intranasal fluticasone spray was superior than montelukast in improving DNS (MD 0.71, 95% CI 0.44 to 0.99; P < 0.001) and NNS (MD 0.63, 95% CI 0.29 to 0.97; P < 0.001). A combined montelukast and OAH was superior than OAH in in improving DNS (MD -0.15, 95% CI -0.27 to -0.03; P =0.010), NNS (MD -0.16, 95% CI -0.28 to -0.05; P

=0.006), CSS (MD -0.12, 95% CI -0.25 to -0.01; P =0.070), DES (MD -0.12, 95% CI -0.30 to 0.06; P =0.180) and RQLQ (MD -0.10, 95% CI -0.28 to 0.08; P =0.290). A combined montelukast and OAH was superior than montelukast improving DNS (MD 0.15, 95% CI 0.08 to 0.21; P<0.001), NNS (MD 0.05, 95% CI -0.09 to 0.19; P=0.510), CSS (MD 0.1, 95% CI 0.03 to 0.17; P=0.007), DES (MD 0.18, 95% CI 0 to 0.36; P=0.050) and RQLQ (MD 0.07 95% CI -0.15 to 0.29; P=0.530).

Conclusion Montelukast is effective in treating AR patients with nocturnal symptoms and as add on combination therapy with OAH in the stepping up management of AR.

Key Points:

1. Montelukast is effective in treating the overall symptoms of allergic rhinitis when compared against placebo.
2. Montelukast is effective in treating the nighttime symptoms of allergic rhinitis when compared against oral antihistamine.
3. Combination therapy of montelukast with oral antihistamine is superior to oral antihistamine monotherapy or montelukast monotherapy in treating allergic rhinitis.

1 Introduction

Allergic rhinitis (AR) is regarded as the most prevalent challenging immune-mediated disease to treat [1]. Allergic rhinitis occurs after a sensitized individual is exposed to a specific trigger, such as house dust mite, pollen or dander [2]. After exposure to the triggering factor, a cascade of events at a molecular level follows that leads to classical symptoms of AR. The classical symptoms in AR are sneezing, rhinorrhea, nasal obstruction, itchiness and occasionally hyposmia [3, 4].

Sneezing, itchiness and rhinorrhea are caused by histamine while obstruction is due to leukotriene mediated effect [5]. Nasal blockage can lead to excessive daytime somnolence and sleep disturbances. Excessive daytime somnolence and sleep disturbances are known symptoms, which occur due to nocturnal nasal block [6]. Of these, the most disturbing symptom and the most difficult to treat is nasal obstruction [7]. Montelukast acts by blocking the leukotriene receptors, thus preventing its action and may improve AR symptoms, notably nasal block.

A review by Wei [8] showed montelukast is not as effective as an oral antihistamine (OAH) in improving the quality of life in AR patients. Another review by Xiao et al [9] found OAH more efficacious than montelukast in relieving AR symptoms. Both reviews, however, recommended further investigation into the role of montelukast in the treatment of AR [8, 9]. Hence, the role of montelukast in AR management remains unclear, and its potential benefit in the management algorithm of AR is not fully understood. To determine the role of montelukast in AR management, we conducted a meta-analysis assessing its efficacy in treating AR.

2 Methods

Our systematic review was done according to a protocol published in PROSPERO with identification serial number as CRD 42019133172. The methods and reporting were based on the Cochrane Collaboration [10] and the preferred reporting items for systematic reviews and meta-analyses statement [11]. The evaluation was done according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guideline [12].

2.1 Eligibility criteria

Randomized control trials (RCTs) comparing montelukast with placebo, combination therapy or other standard treatments, were included. Cross-over studies were excluded due to the carry-over effect. The eligibility criteria were all age groups diagnosed with AR (with allergic conjunctivitis or urticaria or asthma) of either gender or ethnicity. Allergic rhinitis must be diagnosed by clinicians. Studies in which diagnosis of AR was based on the participant or caregiver report alone were excluded. The follow-up period for outcomes was a minimum of 2 weeks.

2.2 Search strategy

An electronic literature search was performed using Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and MEDLINE from 1966 to January 2019. The search was performed using the keywords ‘allergic rhinitis’ and ‘montelukast’. We checked the reference list of identified RCTs and review articles to find unpublished trials or trials not identified by electronic searches. We searched for ongoing trials through the World Health Organization International Clinical Trials Registry Platform http://www.who.int/ictrp/en/ and www.clinicaltrials.gov. The search was restricted to English language only.

2.3 Study selection

Review authors (MK, NMN) scanned the titles and abstracts from the searches and obtained full-text articles when they appeared to meet the eligibility criteria, or when there was insufficient information to assess the eligibility. Eligibility of the studies was assessed independently, and the reasons for exclusion were documented. Any disagreements between the review authors were resolved by the third author (BA). We contacted the authors if clarification was needed.

2.4 Data extraction

Data were extracted using data collection forms. The reviewers (MK, NMN) independently extracted the trial characteristics (single or multicenter, country), baseline characteristics of the patients (age, sex, disease status), inclusion and exclusion criteria, the description of the intervention (thresholds, duration) and outcomes. If information was unclear or missing, the corresponding authors of the relevant trials were contacted. The primary outcomes were daytime nasal symptom score (DNS) and nighttime nasal symptom score (NNS). The secondary outcomes were composite nasal symptom score (CSS), daytime eyes symptom score (DES) and rhinoconjunctivitis quality of life questionnaires (RQLQ).

2.5 Risk of bias assessment

Risk of bias was done on all studies based on the Cochrane Handbook [10]. The risk of bias for the trials was classified into low risk, unclear risk or high risk. We assessed the risk of bias based on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, completeness of outcome data, the selectivity of outcome reporting and other bias. We resolved any disagreements by discussion.

2.6 Grading quality of evidence

We assessed the quality of evidence for primary and secondary outcomes according to GRADE methodology [12], classified as very low, low, moderate, or high, based on the risk of bias, inconsistency, indirectness, imprecision and publication bias.

2.7 Statistical analysis

We undertook meta-analyses using Review Manager 5.3 software (RevMan 2014) and used the random-effects model to pool data. We assessed the presence of heterogeneity in two steps. First, we assessed obvious heterogeneity at face value by comparing populations, settings, interventions and outcomes. Second, we assessed statistical heterogeneity by means of the I^2 statistic. Heterogeneity was interpreted as follows: 0 % to 40 % might not be important; 30 % to 60 % may represent moderate heterogeneity; 50 % to 90 % may represent substantial heterogeneity, and 75 % to 100 % would be considerable heterogeneity [10].

We measured the treatment for continuous outcomes using mean differences (MDs) or standard mean difference (SMD) and relative risk (RR) with 95% confidence intervals (CIs) depending on data availability. We conducted subgroup analyses on the duration of treatment. Included trials were checked for the unit of analysis errors.

3. Results and analysis

3.1 Study selection

There were 578 records identified by database searching. There was one additional record identified using other sources. After removing the duplicates, there were 461 records. The records were screened, and 447 of them were excluded. Fourteen of the full-text articles comprising of 15 studies (1 article described 2 studies) were assessed for eligibility and included in the qualitative and quantitative synthesis (Figure 1).

3.2 Participants

Fifteen studies of 1038*7* participants met the inclusion criteria [13-26]. The characteristics of the included studies are shown in Table 1. Four of the studies were single-centre studies [13, 14, 18, 24], and the remaining 11 were multicenter studies [15-17, 19-23, 25, 26]. One study reported the mean age for the treatment and control groups, which was 33.6 years and 34.15 years, respectively [24]. Four studies reported the overall mean age of 30.75, ranging from 13 to 81 years [13, 17, 18, 26]. The remaining 10 studies reported age range from 15 to 81 years old [14-16, 19-23, 25]. All patients were required to demonstrate a positive AR history of at least 2 years in 11 studies [15-20, 23-26], a positive allergic reaction for 2 seasons in 2 studies [21, 22], clinical history of AR of 1 year in 1 study [14] and clinical history of AR irrespective of duration in 1 study [13]. All except 1 study [14] required patients to demonstrate a positive skin prick test.

3.3 Intervention

Participants in the studies were randomized into either two, three, four or five treatment groups. There were 6 studies with 2 treatment groups [13, 14, 17, 22, 24, 26]. Of these, 3 studies compared montelukast against placebo [17, 24, 26] and the remaining 3 compared i)

montelukast and fluticasone against placebo and fluticasone [13], ii) montelukast and levocetirizine against levocetirizine [14], and iii) montelukast against fluticasone [22].

There were 3 studies with 3 arms evaluating i) montelukast ii) loratadine and iii) placebo [15, 16, 25]. There were 4 studies with 4 arms; in which 2 studies evaluated i) montelukast, ii) placebo, iii) loratadine and iv) montelukast and loratadine [20, 23]; 1 study evaluated i) formoterol inhaler and fluticasone nasal spray, ii) formoterol inhaler and montelukast, iii) formoterol inhaler alone and iv) montelukast alone [21], and the remaining 1 study evaluated, i) fluticasone nasal spray, ii) montelukast, iii) montelukast and loratadine and iv) placebo [18]. There were 2 studies with 5 arms evaluating i) montelukast, ii) montelukast and loratadine, iii) loratadine alone and iv) a higher dose of montelukast [19] or beclomethasone nasal spray [20] and v) placebo.

Montelukast was given as an oral form in all 15 studies [13-26]. It was given in the evening or at bedtime in 8 studies [13, 14, 16, 17, 19, 23, 25, 26] and in the morning in 2 studies [15, 18]. In 5 studies, the time of day at which montelukast was administered was not stated [20-22, 24]. In 14 studies, irrespective of the treatment group, the dose of montelukast prescribed was 10 mg either as monotherapy or combined treatment [13-18, 20-26]. Only in 1 study, montelukast was given at a higher dose of 20 mg in the treatment group [19]. A period of 2 weeks of treatment was reported in 8 studies [16, 19, 20, 22, 23, 25, 26] while 7 studies reported treatment period of two to eight weeks [13-15, 17, 18, 21, 24].

3.4 Outcomes

The primary outcomes were reported in 14 studies [13-23, 25, 26] while the secondary outcomes were reported in 12 studies [13-17, 19, 20, 23-26]. The tool for assessing the RCQOL was a questionnaire developed by Juniper and Guyatt [27], which was used in 7