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Is Taking Montelukast as Monotherapy Effective in Relieving Daytime Nasal Symptoms in Individuals with Allergic Rhinitis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not montelukast as a monotherapy is effective in relieving daytime nasal symptoms in individuals diagnosed with allergic rhinitis.

STUDY DESIGN: A systemic review of three primary randomized controlled trials (RCTs) published in peer-review journals in 2018. All articles were published in the English language.

DATA SOURCES: One single-center, randomized, open-label study; one randomized, multicenter, double-blinded, phase III trial study; and one double-blinded, randomized, parallel-group, comparative study evaluating if montelukast taken as monotherapy can improve daytime nasal symptoms in individuals with allergic rhinitis. Sources were selected from Google Scholar and PubMed to answer the clinical question and all contained patient-oriented outcomes.

OUTCOMES MEASURED: The outcome measured was the relief of daytime nasal symptoms in individuals with allergic rhinitis using visual analog scales, self-reported diary entries, and patient questionnaire forms that were filled out at subsequent visits.

RESULTS: The study that was conducted by Bylappa and Delphine (*Int J Otorhinolaryngol.* 2018;4(2):467-472. Doi: 10.18203/issn.2454-5929.ijohns2018070) showed statistically significant daytime nasal symptom relief in montelukast therapy (p=0.005). The study conducted by Chen, Wang, Cao, et al. (*Int Forum Allergy Rhinol. 2018*;8(11). Doi:10.1002/alr.22197) showed statistically significant improvements in daytime nasal symptoms in at least 50% of patients after two weeks of montelukast therapy (p=0.001). The study of Park J, Park C, Cho, et al. (*Chest. 2018*;40(7). Doi: 10.1026/j.cest.2018.08.1013) showed statistically significant improvement of daytime nasal symptom relief with montelukast therapy as well (p=0.045).

CONCLUSION: The articles that were analyzed in this EBM review shows that montelukast as a monotherapy can improve daytime nasal symptoms in patients with allergic rhinitis. All three studies yielded statistically significant results. However, due to the limitations of all three studies such as small sample size, short trial period, open-label trial, and no intention to treat analysis, more research is needed in order to determine the validity of montelukast as a treatment of choice to relieve daytime nasal symptoms in patients with allergic rhinitis.

KEY WORDS: Montelukast, allergic rhinitis, randomized trial, monotherapy, nasal symptoms

INTRODUCTION

Allergic rhinitis is an inflammatory medical condition of the upper respiratory tract that is characterized by a syndrome of sneezing, rhinorrhea, nasal obstruction, and pruritis that is mainly caused by proinflammatory cells such as cytokines.[1] Common physical symptoms that patients often notice are itching of the nose, throat, ears, and eyes, as well as eye injection, swollen eyelids, and uncomfortable lacrimation of the eyes.[1] This problem is prevalent in the modern world, especially in the early spring and summer months due to pollen and dust. Not only is the condition of allergic rhinitis important in primary care settings, but often as well in ENT specialties. In the 21st century, it is estimated that the economic burden of treating allergic rhinitis alone in the United States exceeds $6 billion annually.[2] This systematic review will evaluate three articles that compare the efficacy of montelukast as a monotherapy in contrast to other common therapies in alleviating specifically the daytime nasal symptoms in patients with allergic rhinitis. This topic is important to the physician assistant (PA) profession because many PAs are involved in primary care, and allergic rhinitis is one of the most common complaints that patients often present with and seek treatment.

Approximately 19.9 million adults aged 18 and older have been seen by a medical provider within the last 12 months, and 5.6 million children under the age of 18 have been evaluated by providers and diagnosed with allergic rhinitis within the last 12 months.[3] Even though the condition of allergic rhinitis is prevalent, it is still unknown about the exact "definitive treatment" for this condition because every patient reacts to various medications differently. Also, it is unknown if symptoms will spontaneously worsen or improve with age in certain individuals.[2] There are several known methods that are used to treat the condition of allergic rhinitis, such as antihistamines (azelastine, cetirizine, levocetirizine, loratadine, etc.),

nasal corticosteroids (beclomethasone dipropionate, budesonide), mast cell stabilizers (sodium cromoglycate), nasal saline wash, decongestants (pseudoephedrine, phenylephrine, oxymetazoline), and immunotherapy (allergy shots for desensitization).[4] Many of these therapies may be used in different combinations depending on what is effective for the individual. Antihistamines are normally classified as the gold standard of treatment for relieving daytime nasal symptoms in patients with allergic rhinitis and it is normally taken once a day as needed, although there has been more evidence supporting the use of nasal corticosteroids.[1] The main therapy that will be discussed in this review will be montelukast as a monotherapy in cases where traditional antihistamines or intranasal corticosteroids do not provide relief. Montelukast is normally a drug commonly used in patients with mild to moderate asthma but has been shown to be an effective agent in the management for the daytime nasal symptoms in patients with allergic rhinitis.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not montelukast as a monotherapy is effective in relieving daytime nasal symptoms in individuals diagnosed with allergic rhinitis.

METHODS

The three studies used in this systemic review include one single-center, randomized, open-label study; one randomized, multicenter, double-blinded, phase III trial study; and one double-blinded, randomized, parallel-group, comparative study. All three studies evaluate if montelukast used as monotherapy is effective in alleviating the severity of daytime nasal symptoms in patients with allergic rhinitis. The studies measure the outcomes using various

methods such as a visual analog scale, patient-reported diary entries, and questionnaires that determine if symptoms are actually improved during and after the treatment trials. Populations in each study include both males and females diagnosed with mild to severe allergic rhinitis.

Each primary study in this review included the key words: “montelukast”, “allergic rhinitis”, “randomized trial”, “monotherapy”, and “nasal symptoms”, which were found on Google Scholar and PubMed databases. Articles were chosen based on their importance and relevancy of relating to the clinical question and also had patient-oriented outcomes (POEMs) that would make an immediate difference in a patient’s quality of life. All three primary articles were published in the year 2018 in the English language in order to obtain the most updated information available. Table 1 shows the demographics of each primary study used. An inclusion criterion that was used to choose the articles include that these studies were not yet written about in any existing systematic reviews or meta-analyses. Exclusion criteria of articles included studies that were written or published more than 10 years ago, studies that did not use montelukast monotherapy as one of the therapeutic treatment groups, studies that were done before the most recent meta-analysis or systematic review were written, studies that were not relevant to the clinical question, and studies that failed to include any POEMs.

OUTCOMES MEASURED

The outcome that was measured in each study was the relief of daytime nasal symptoms in the individuals with the diagnosis of allergic rhinitis based on various methods. The outcome of each study that were used included visual analog scale, patient-recorded diary entries, or patient questionnaires to measure how efficacious the use of montelukast as a monotherapy was in the relief of the daytime nasal symptoms that patients were experiencing, such as rhinorrhea and daytime nasal congestion.

Table 1: Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Bylappa K, Delphine S.[1] (2018)	A double-blinded, randomized, parallel-group, comparative study.	274	18-60 years old.	Patients were at least 18 and had mild-moderate intensity of allergic rhinitis.	Lactating or pregnant Patients. Patients who did not want to use contraception . Patients who had ever had anaphylactic shock.	0	A fixed dose combination of montelukast/levo cetirizine (10 mg/ 5 mg) verses Montelukast 10 mg
Chen H, Wang Y, Cao F, Zhang L, Wang C.[5] (2018)	A single-center, randomized, open-label study.	100	18-60 years old.	Patients who were at least 18 and had moderate -severe allergic rhinitis	Patients who were pregnant, had another chronic disease or received antibiotics or other treatment in the past 7 days.	15	Monotherapy intranasal budesonide verses Montelukast 10 mg
Park J, Park C, Cho Y, Choi B.[6] (2018)	A randomized, multicenter, double-blinded, phase III trial.	228	>15 years old.	Patients were at least 16 and had mild-moderate intensity of allergic rhinitis.	Patients with nonallergic rhinitis, any lung diseases, or upper respiratory tract infection or has had nasal surgery.	19	A fixed dose combination of montelukast/levo cetirizine (10 mg/ 5 mg) verses Montelukast 10 mg.

RESULTS

This review assesses whether or not taking montelukast as monotherapy can assist in improving and relieving daytime nasal symptoms in patients with allergic rhinitis. All three studies measured the alleviation of the some of the most common symptoms that the majority of patients tend to present with. Data from all three individual studies complement one another.

The purpose of the study that was conducted by Bylappa and Delphine[1] was to examine the efficacy of montelukast monotherapy (10 mg) in comparison to either a fixed dose combination of montelukast/levocetirizine (10 mg/5mg) or levocetirizine monotherapy (5 mg) in relieving daytime nasal symptoms. This was a pilot study that recruited 274 patients who were diagnosed with seasonal allergic rhinitis. Demographics used in this study were males and females between the ages of 18-69 years old who were diagnosed with seasonal allergic rhinitis for at least 2 years of mild to moderate severity.[1] Patients were excluded if they were pregnant, lactating, or had allergic reactions to the treatments.[1]

Each patient underwent one of the three possible therapies which concluded a total of 5 study visits over a period of 14 days.[1] Some of the most important outcomes that were measured in this study were the patient's physical examination throughout the visits and their response to 28 questions on a self-reported questionnaire that included their change in daytime nasal symptoms.[1] The criteria to evaluate the study's efficacy were the average mean change in daytime nasal symptoms score (i.e. nasal congestion, rhinorrhea, itching, and sneezing) from the baseline of the study until the end of the study.[1] There were no patient compliance issues that were noted in this particular study and no patients voluntarily or were forced to withdraw. Overall, the therapies were favorable with each subject group reporting statistically significant data showing that each therapy worked in relieving their daytime nasal symptoms.[1] This study

included an intention-to-treat analysis and showed that the mean change in the daytime nasal symptoms of montelukast monotherapy was -0.93 (p=0.005, 95% CI -0.295 to -0.052) and levocetirizine monotherapy was -0.98 (p=0.0425, 95% CI -0.250 to -0.004).[1] This study showed that montelukast when used as monotherapy did alleviate daytime nasal symptoms in patients with allergic rhinitis and showed that patients can improve their quality of life (QOL) with this method of therapy. Of the 92 patients that were only taking montelukast as monotherapy, 86.5% reported that they had positive global impression (score of "better" to "very much better" in their symptom questionnaire) compared to 88% of the 90 patients that were only taking levocetirizine.[1] This study overall reported that dual therapy of montelukast/levocetirizine worked the best in alleviating the daytime nasal symptoms in patients after a 14 day period than the monotherapies but that all 3 therapies still work regardless.[1] It is interesting to note that in this study, combination therapy of montelukast with levocetirizine performed better than either monotherapies with mean change from baseline of -1.10 (p=0.0159).[1]

The study conducted by Chen et al.[5] evaluated the relief in daytime nasal symptoms in patients either taking intranasal budesonide or montelukast 10 mg over a period of 2 weeks.[5] The study required each patient not to have had any kind of treatment for at least 1 week prior to the start of the study.[5] A total of 67 patients between the ages of 18 to 60 with a diagnosis of moderate to severe seasonal allergic rhinitis were assigned randomly to either one of the two groups. 33 patients were started on intranasal budesonide consisting of 4 sprays daily per nostril and 34 patients were started on daily montelukast for a duration of 14 days.[5] Five patients from the intranasal budesonide group and 8 patients from the montelukast group failed to adhere to the treatment regimen and were withdrawn from the study in the end results.[5] A visual analog scale (VAS) was a questionnaire that patients had to fill out in regard to their symptoms (i.e.

congestion, rhinorrhea, itching, sneezing, and eye symptoms). This scale was used to determine the efficacy and change in the daytime nasal symptoms of the patients at baseline and after the 14 days of treatment. The scale ranged from 0-10 (0 meaning having no symptoms and 10 meaning having the most severe and bothersome symptoms).[5] Exclusion criteria for this study is shown in Table 1.

The second study showed a reduction in the daytime nasal symptoms in all therapeutic groups with similar efficacy in both groups.[5] All symptoms of allergic rhinitis were alleviated using either one of the treatments.[5] There were no recorded adverse or negative side effects attributed to either of the regimen for patients after the 2-week therapy.[5] Based on the results of this study, 13 patients still had uncontrolled nasal symptoms in the montelukast therapy group and 13 patients reported relief of their symptoms.[5] As for the intranasal budesonide therapy group, 4 patients still had uncontrolled nasal symptoms and 24 patients reported relief of symptoms after the trial.[5] Persistence of symptoms such as sneezing (montelukast n = 11, budesonide n = 1l; $p<0.05$) and nasal blockage (montelukast n=8, budesonide n=2; p=0.255) were significant to favor intranasal corticosteroid therapy, however, because this study was not sufficiently powered, the overall treatment effect was small. Other symptoms such as rhinorrhea or nasal itching did not reach statistical significance.[5] The end results of this study show that even though more patients reported daytime nasal relief symptoms with intranasal budesonide therapy after 2 weeks than the montelukast group, a number of patients still did report nasal symptom relief with montelukast. [5]

The study conducted by Park et al.[6] evaluated the safety and efficacy of either using a fixed dose combination of montelukast/levocetirizine (10mg/5mg) in contrast with montelukast (10mg) to assess relief of daytime nasal symptoms in patients diagnosed with mild to moderate

severity allergic rhinitis who were older than 15 years of age (average age of patients was 43.32).[6] All patients had at least two symptoms of rhinorrhea, sneezing, pruritis, a positive skin prick allergy test to at least 1 out of 10 common environmental allergens, or nasal obstruction.[6] Exclusion criteria for this study are shown in Table 1. A total of 333 patients were screened to be in the study and 228 patients were chosen to partake in the study with 210 patients completing the study.[6] There were 116 patients in the fixed-dose combination group and 112 patients in the montelukast group.[6] 10 patients withdrew from the dual-combination therapy group, while 9 patients withdrew from the monotherapy group.[6] Both males and females were chosen for the study, with 66.67% females.[6] The study was done in a total of 5 weeks (1 week of placebo therapy and 4 weeks of the actual intervention therapy).[6] Blinding was able to be achieved in this study as patients did not know which oral medication they were receiving.[6]

Data was collected from patients using a diary self-entry cards to document their symptoms (rhinorrhea, sneezing, pruritis, and nasal obstruction) on a 4-point scale (0 = none, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms).[6] During the placebo week, the average of all the patient's total daytime nasal symptoms had a score of 6 or greater out of 12.[6] Efficacy end points that were measured in the study used the intention-to-treat approach.[6] Based on the information that was presented in the study, there is a change from the baseline with decreased daytime nasal symptoms for the combination fixed dose group of -0.98 and -0.81 for the montelukast group ($p=0.045$), which met statistical significance. However, since the study was not a powered study, the treatment effect overall was not large. Significance can also be seen with change in baseline with sneezing in combination therapy vs monotherapy (-1.08 vs -0.81, $p=0.005$). There were no differences with other symptoms including rhinorrhea, nasal obstruction, or pruritis. The results of the study show that even though monotherapy with

montelukast is not as effective as dual-combination of montelukast/levocetirizine, it can still be used to provide relief of symptoms in patients with allergic rhinitis.

SAFETY AND TOLERABILITY

As mentioned in the results section, monotherapy with montelukast was reported by patients as being well tolerated in all three primary studies. The Park et al.[6] study suggests cholelithiasis as a serious adverse effect, and 1 patient in the study group of 110 patients developed this condition. Some adverse effects that patients should be mindful of before taking montelukast include neuropsychiatric effects (i.e. suicidal thoughts or depression), minor headaches, otitis, coughing, conjunctivitis, dermatologic effects, myalgias, and abdominal pain.[7,9] Nonetheless, montelukast is a drug that is safe to use in pregnant patients, does not contain any known carcinogen, and also does not require to be renally adjusted in patients with kidney failure.[7] In cases of acute overdose, only benign findings were documented such as polydipsia, hyperactivity or somnolence, GI upset, and headaches.[7] No known antidote exists currently for cases of acute montelukast overdose.[7] Montelukast is contraindicated in patients who cannot tolerate it due to hypersensitivity reactions, as well as patients with phenylketonuria.[7] Phenylalanine is an amino acid that can be used to create certain proteins in the human body.[8] Patients with phenylketonuria cannot break down or metabolize phenylalanine.[8] When phenylalanine continues to build up in the body, problems can arise such as neurological deficits, seizures, and other brain damage.[8] Montelukast is safe and effective in relieving daytime nasal symptoms in patients who did not show improvement with antihistamines. There are currently no black box warnings for the usage of montelukast in patients of any age.[9] All in all, there were no major adverse events or injuries that can be solely

attributed to the usage of montelukast in alleviating daytime nasal symptoms in patients with allergic rhinitis.

DISCUSSION

The objective of this EBM systematic review is to determine whether or not using montelukast as monotherapy can relieve daytime nasal symptoms in individuals with allergic rhinitis. Each study evaluated the efficacy and safety using different scales and methods to determine the end result of the therapy. All three studies showed that monotherapy with montelukast provided at least some nasal symptom relief in patients. Although other methods were shown to have improved symptoms better (i.e. intranasal budesonide or a fixed-dose combination of montelukast/levocetirizine), using montelukast as monotherapy is still a plausible treatment regimen in patients who tolerate the medication well.

The results of all three studies combined showed that using montelukast as monotherapy do improve daytime nasal symptoms in patients with allergic rhinitis, no matter how large or small of an impact. However, due to the limitations of all three studies, further research is needed in order to provide additional information about the efficacy of montelukast and current results are inconclusive, especially long-term effects. Some flaws in each of the 3 primary studies would be that the trials were done in a short period of time with limited patient population. It is important to note that future studies should try to incorporate equal amounts of both male and female genders in their studies, and use patients ranging from mild to moderate to severe allergic rhinitis including tables to separate the different demographics.

LIMITATIONS

The study conducted by Bylappa and Delphine [1] had the limitations of having a short trial period (16 days), no table showing the demographic of their patient population, and a small

population patient size (274 total patients). The study conducted by Chen et al.[5] had the limitations of not being able to achieve treatment blinding, not having an intention-to-treat analysis, having a small sample size (100 total patients), and having a short trial period (14 days). The study conducted by Park et al.[6] had the limitations of having a small sample size (228 total patients) and having a short trial period (5 weeks). Since all three studies used small sample sizes and have short trial periods, it is difficult to draw long-term conclusions based on just these studies to make the assumptions. Gender and ethnicity could also be limitations in these studies because they did not specify the race of the patients.

CONCLUSIONS

With the rising population of patients being diagnosed with allergic rhinitis, it is important for medical providers to know multiple ways to approach this condition. Even with minor relief, patients will still see the immediate effects of montelukast if traditional usage of antihistamine monotherapy is ineffective for them. Every year comes with different allergens from many places around the world, so one should consider using montelukast as monotherapy and see if it works if it is an affordable option, since the price of Montelukast is comparable with antihistamines and intranasal corticosteroids. Medical providers should continue to look for new interventions and improve on the treatment of allergic rhinitis and to tailor treatment regimens to each individual patient.

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