Efficacy and Safety of Montelukast Plus Fexofenadine Fixed Dose Combination in Allergic Rhinitis: Results of Post-Marketing Study in India

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Abstract

Background: Allergic rhinitis is one of the most common conditions in clinical practice. Montelukast and second generation antihistamine fexofenadine are routinely used in the management of allergic rhinitis. Individually both drugs have been found to be effective in allergic rhinitis. Fixed dose combination of montelukast 10 mg plus fexofenadine 120 mg is available in India is also used in the treatment of allergic rhinitis. Objective: To evaluate the efficacy and safety of montelukast and fexofenadine fixed dose combination in the management of patients with allergic rhinitis. Material and methods: Post marketing observational study was conducted in 809 patients from all over India. All the patients were treated with montelukast 10 mg plus fexofenadine 120 mg fixed dose combination once daily for 14 days. The primary outcome criteria was the change in total symptom score (Sum of total nasal symptom score and total ocular symptom score) at the end of study compared to baseline. The secondary outcome criteria included change in total nasal symptom score (nasal congestion, rhinorhea, nasal itching, and sneezing) and total ocular symptom score (Itching/burning eyes, tearing/watering eyes and eye redness) at the end of study compared to baseline and physician's and patient's global assessment for efficacy and tolerability. The patients were evaluated at baseline, day 7 and day 14 for efficacy evaluation while the safety parameters were assessed at screening and day 14. Results: The fixed dose combination of fexofenadine plus montelukast was significantly effective in reducing total symptom score, total nasal symptom score and total ocular symptom score (p<0.0001 for all parameters). The global assessment of efficacy evaluation by both patient and investigators demonstrated “excellent to good” efficacy in >95% of patients. Most of the study population reported “good” tolerability with the fixed drug combination. No adverse events were reported in the study. Conclusion: The fixed dose combination of fexofenadine plus montelukast was found to be efficacious and well tolerated in allergic rhinitis in Indian adult patients.

Keywords
allergic rhinitis, montelukast, fexofenadine

Introduction

Rhinitis is defined as inflammation of the nasal mucosa. Allergic rhinitis is a symptomatic disorder of nose induced by allergen exposure. It is characterized by symptoms like sneezing, itching, rhinorhea and nasal obstruction. Allergic rhinitis is often associated with ocular symptoms1. Allergic rhinitis affects 10–30% of adults and up to 40% of children2. It is a global health problem causing major illness and disability. It has wide adverse impact on the patient in
different aspects like affecting social life, school, work and sleep.

Histamine is one of the key mediators released from mast cells and basophils which play a major role in the pathophysiology of rhinitis. H₁ antihistamines are the first-line medicines for the treatment of allergic rhinoconjunctivitis. When selecting an oral H₁ antihistamine, it is important to consider the clinical efficacy and balance it against the risk of adverse effects of an antihistamine. First-generation H₁-antihistamines have detrimental effects on sleep and learning. Allergic diseases are also known to impair the functions. The detrimental effects caused by first generation H₁ antihistamines may be exacerbated by the allergic diseases. Newer antihistamines provide similar efficacy as first-generation antihistamines but with less sedation. Montelukast, a leukotriene receptor antagonist, is effective in improving daytime and night-time symptoms of allergic rhinitis. A study by Cingi C et al. demonstrated both objective and subjective evidence with combination of montelukast plus fexofenadine combination therapy in allergic rhinitis. The combination of fexofenadine plus montelukast was more effective compared to fexofenadine alone in the control of allergic rhinitis symptoms. However, there are no published studies with fixed dose combination of montelukast plus fexofenadine in India.

Objective

The present study was conducted to evaluate the efficacy and safety of montelukast and fexofenadine fixed dose combination in the management of patients with allergic rhinitis in Indian adult patients.

Materials and methods

A post marketing observational study was carried out in 809 patients from 81 centres across India. Male and female patients > 18 years of age suffering with allergic rhinitis willing to sign written informed consent form and comply with study procedure were enrolled in the study. Patients having bronchial symptoms along with allergic rhinitis were also allowed to be part of the study. Children and adolescent (<18 years of age), pregnant, lactating women, patients with severe asthma requiring emergency room treatment within 1 month or hospitalization within 3 month before the trial, patients with upper respiratory tract infection or acute/chronic pulmonary disorder and patients with known hypersensitivity to montelukast or fexofenadine or other piperazine derivatives were excluded from the study. Patient requiring other anti-histamine, corticosteroids, cromolyn sodium, nedocromil and inhaled cholinergics, oral or long acting beta-agonist, theophylline and other leukotriene modifiers were not enrolled in the study. Decongestants, anti-inflammatory medicines and other rescue medicines for allergic rhinitis were not permitted during the study.

All the enrolled patients were treated with one tablet of montelukast 10 mg plus fexofenadine 120 mg fixed dose combination for 14 days.

Evaluation criteria

The primary outcome criteria was the change in Total Symptom Score [(TSS: sum of total nasal symptom score (TNSS) and total ocular symptom score (TOSS))] at the end of study compared to baseline.

The secondary outcome criteria included change total nasal symptom score (TNSS) (nasal congestion, rhinorrhea, nasal itching, and sneezing) and total ocular symptom score (TOSS) (itching/burning eyes, tearing/watering eyes and eye redness) at the end of study compared to baseline, physician’s and patient’s global assessment for efficacy and tolerability.

Total nasal symptom score (TNSS) and total ocular symptom score (TOSS) were graded on 4-point categoric scale (0 = none/ no symptoms, 1 = mild symptoms, not affecting any activities during the day/sleep at night; 2 = moderate symptoms affecting at least one activity or disturbing sleep; 3 = severe symptoms affecting >2 daily activities or disturbing sleep all night or most of the night)

Safety of the fixed dose combination was evaluated by analyzing the type, number, frequency and proportion of patients with adverse events during the study.

The enrolled patients were followed up for assessing signs and symptoms at baseline, day 7 and day 14 while the safety parameters were assessed at screening and day 14. Global assessment for efficacy and tolerability by investigator and patient was assessed at the end of study i.e. on day 14.

Statistical analysis

Data describing quantitative measures were expressed as mean (± SD) or the median with range while qualitative variables were presented as counts and percentage. For symptoms score, Friedman test was used for overall
comparison of baseline and follow up visits, followed by post-hoc Wilcoxon sign rank test for individual values at each follow up visit versus baseline values. All the statistical tests were interpreted at 5% level of significance and “p” value <0.5 was considered as significant.

Results

A total of 809 patients were enrolled from 81 centres across the country. The mean age of the patients (n=785) in the study was 35.87 (±12.05). Male to female ratio was 6.3: 3.7.

Treatment with fixed dose combination resulted in significant decrease in total symptom score compared to baseline (p<0.0001) (Fig. 1).

The total ocular symptom score also reduced significantly compared to baseline (p<0.0001) (Fig. 3). More than >95% of patients reported “excellent-good” efficacy as per the global assessment of efficacy evaluation by both patient and investigators (Fig. 4).

Montelukast plus fexofenadine fixed dose combination was effective in reducing all the individual nasal symptoms (nasal congestion, rhinorrhea, nasal itching and sneezing) (p<0.0001) as well as ocular symptoms. (burning/itching of eyes, tearing/watering of eyes and redness of eyes) (p<0.0001) (Tables 1 and 2).
Ninety three percentage patients reported “good” tolerability of the fixed dose combination of montelukast plus fexofenadine. The global assessment done by both investigators (n=809) and patients (n=808) reported “good to moderate” tolerability by >99% of the patients (Fig. 5).

Adverse event was not reported by any patient during the study.

Table 1
Reduction in individual nasal symptom score

<table>
<thead>
<tr>
<th></th>
<th>Nasal congestion</th>
<th>Rhinorrhea</th>
<th>Nasal itching</th>
<th>Sneezing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.25</td>
<td>2.23</td>
<td>1.87</td>
<td>2.15</td>
</tr>
<tr>
<td>Day 7</td>
<td>1.14</td>
<td>0.96</td>
<td>0.75</td>
<td>0.84</td>
</tr>
<tr>
<td>Day 14</td>
<td>0.23</td>
<td>0.16</td>
<td>0.13</td>
<td>0.19</td>
</tr>
</tbody>
</table>

(p<0.0001 for all symptoms)

Table 2
Reduction in individual ocular symptom score

<table>
<thead>
<tr>
<th></th>
<th>Burning/Itching of eyes</th>
<th>Tearing/Watering of eyes</th>
<th>Redness of eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.28</td>
<td>1.12</td>
<td>0.88</td>
</tr>
<tr>
<td>Day 7</td>
<td>0.55</td>
<td>0.42</td>
<td>0.28</td>
</tr>
<tr>
<td>Day 14</td>
<td>0.08</td>
<td>0.06</td>
<td>0.03</td>
</tr>
</tbody>
</table>

(p<0.0001 for all symptoms)

Fig. 5
Global assessment of safety

Safety analysis

Ninety three percentage patients reported “good” tolerability of the fixed dose combination of montelukast plus fexofenadine. The global assessment done by both investigators (n=809) and patients (n=808) reported “good to moderate” tolerability by >99% of the patients (Fig. 5).

Adverse event was not reported by any patient during the study.

Discussion

This study evaluated the efficacy and safety of fexofenadine plus montelukast fixed dose combination in Indian patients with allergic rhinitis. The results demonstrated that fixed dose combination is significantly effective in reducing all the symptoms of allergic rhinitis.

Fexofenadine is a selective, non-sedating H1 receptor antagonist having an additional impact on the inflammatory mediators, other than histamine. These anti-inflammatory effects may provide benefit to some of the responses of an acute allergic reaction. Montelukast is a highly selective cysteinyl leukotriene type-1 receptor antagonist of leukotreine D4. It is an alternative for the treatment of seasonal allergic rhinitis. The benefits of montelukast monotherapy in seasonal allergic rhinitis are equivalent to antihistamines. The literature review also establishes that the addition of an antihistamine to montelukast may have added benefits.

Second-generation antihistamines have little effect on congestion. Cingi C et al compared monotherapy of fexofenadine versus fexofenadine-montelukast combination and fexofenadine-placebo combination for 21 days in 275 patients. The authors showed effectiveness of combination treatment in terms of significantly better control of nasal congestion both subjectively i.e. using patient diary and
visual analog scale evaluations, as well as objectively by using rhinomanometry and physical examination compared to fexofenadine alone and fexofenadine-placebo combination. This study used montelukast and fexofenadine separately.

Our study demonstrated effectiveness of fixed dose combination of montelukast plus fexofenadine in reducing nasal congestion. The fixed dose combination has an advantage of reduced pill burden and in turn may improve patient compliance.

The second-generation H1 antihistamines cause much less sedation. They are essentially free of sedation at recommended therapeutic doses for the treatment of allergic disorders.

The results of this study demonstrate that fixed dose combination of montelukast plus fexofenadine is an significantly effective and well tolerated option for the treatment of allergic rhinitis.

Conclusion

The fixed dose combination of fexofenadine plus montelukast was found to be efficacious in reducing all nasal symptoms, ocular symptoms as well as total symptom score of allergic rhinitis. The fixed dose combination was well tolerated without any adverse event.

Acknowledgement

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References