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Original Research Article

Evaluation of efficacy of fixed dose combination of montelukast and levocetirizine compared to monotherapy of montelukast and levocetirizine in patients with seasonal allergic rhinitis

Kiran Bylappa[1]*, Wilma Delphine Silvia C. R.[2]

[1]Department of ENT, ESI Post Graduate Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India
[2]Department of Biochemistry, Akash Institute of Medical Sciences and Research Centre, Devanahalli, Bangalore, Karnataka, India

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***Correspondence:**
Dr. Kiran Bylappa,
E-mail: widel.2011@gmail.com

ABSTRACT

Background: Allergic rhinitis (AR) is a global health problem. Almost 10%–25% of population worldwide is affected by AR. Seasonal allergic rhinitis (SAR) is caused by an IgE-mediated reaction to seasonal aeroallergens and is fairly easy to identify because of the rapid and reproducible onset and offset of symptoms in association with pollen exposure. SAR can result in hyperresponsiveness to allergens. Treatment of allergic rhinitis is aimed to achieve optimal symptom control and reduce nasal congestion, sneezing and rhinorrhea over the course of the entire day and night.
Methods: Out of total 274 subjects, 92 subjects in the FDC of montelukast 10 mg and levocetrizine 5 mg group, 92 subjects in montelukast 10 mg group and 90 subjects in levocetrizine 5 mg group were enrolled in the study. The total study duration was 16 days. Criteria for evaluation of primary efficacy were mean change in day time nasal symptoms score from baseline to end of treatment. Mean change in night time symptoms score from baseline to end of treatment. Mean change in day time eye symptoms score from baseline to end of treatment. Patient's and physician's global evaluation of allergic rhinitis at the end of treatment. Mean change in rhinoconjunctivitis quality-of life score from baseline to end of treatment.
Results: Primary efficacy endpoint that fixed dose combination (FDC) of montelukast 10 mg and levocetirizine 5 mg was superior to montelukast 10 mg monotherapy or levocetirizine 5mg monotherapy in the treatment of patients with seasonal allergic rhinitis. Other secondary endpoints and global impression results are also supporting the therapeutic benefit of fixed dose combination over monotherapy.
Conclusions: FDC of montelukast 10 mg and levocetirizine 5 mg was superior to montelukast 10 mg monotherapy or levocetirizine 5 mg monotherapy in the treatment of patients with seasonal allergic rhinitis.

Keywords: Seasonal allergic rhinitis, Montelukast, Levocetirizine, Rhinorrhea, Nasal congestion

INTRODUCTION

Allergic rhinitis is a common inflammatory condition of the upper respiratory tract and is characterized by one or more symptoms including sneezing, itching, nasal congestion, and rhinorrhea. Frequently, there is associated palate, throat, ear, and eye itching as well as eye redness, puffiness, and watery discharge. The symptoms of allergic rhinitis result from a complex allergen-driven mucosal inflammation caused by interplay between resident and infiltrating inflammatory cells and a number of vasoactive and proinflammatory

mediators, including cytokines. Seasonal allergic rhinitis is one type of allergic rhinitis and is commonly referred to as hay fever. Seasonal allergic rhinitis (SAR) is caused by an IgE-mediated reaction to seasonal aeroallergens and is fairly easy to identify because of the rapid and reproducible onset and offset of symptoms in association with pollen exposure. SAR can result in hyperresponsiveness to allergens such as cigarette smoke, once pollen season is over. Allergic rhinitis affects between 10% and 30% of all adults and as many as 40% of children.[1] A survey carried out in India shows that 20–30% of the population suffer from allergic rhinitis.[2,3] In India, symptoms of rhinitis were reported in 75% of children and 80% of asthmatic adults.[4,5]

The symptoms of allergic rhinitis result from the action of several mediators, the best known of which is histamine, but which also include kinins, tryptase, prostaglandins (particularly PGD2) and leukotrienes (particularly the cysteinyl leukotrienes LTC4 and LTD4).[7]

Treatment of allergic rhinitis is aimed to achieve optimal symptom control and reduce nasal congestion, sneezing and rhinorrhea over the course of the entire day and night. Pharmacotherapy for allergic rhinitis includes oral and intranasal antihistamines, intranasal corticosteroids, oral and intranasal decongestants, intranasal anticholinergics, intranasal cromolyn and leukotriene receptor antagonists.[1,8] Antihistamines are effective in reducing pruritis, sneezing and watery rhinorrhea and are a mainstay therapy for allergic rhinitis. Most new second generation antihistamines have minimal or no sedating properties and less anticholinergic effects and are therefore preferable to first generation antihistamines in most cases.[9] Second generation antihistamines are in general recommended for mild to moderate disease as first line therapy.[8,10]

Levocetirizine is a third-generation antihistamine that has been approved for the relief of symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in adults and children aged >6 years. In studies reviewed, Levocetirizine 5 mg/day was effective in reducing symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis and improving quality of life, with an acceptable tolerability profile.[11] Montelukast provides significant relief from symptoms of seasonal allergic rhinitis.[12] It competitively and reversibly inhibits cysteinyl leukotrienes (CysLTs), specifically leukotrienes D4 (LTD4). A review of literature including a meta analysis supports the claim of montelukast as a viable alternative for the treatment of SAR. Its benefits are generally equivalent to antihistamines when used as monotherapy regarding efficacy and quality of life improvement.[8,10]

There are only limited studies available for the effect of combination therapy of montelukast and levocetirizine on the Indian population. Hence this present study was therefore designed to evaluate the efficacy of Montelukast 10mg and levocetirizine 5 mg tablet compared to montelukast 10mg monotherapy and levocetirizine 5 mg monotherapy in patients with seasonal allergic rhinitis.

METHODS

This was a double-blind, randomized, parallel-group, comparative study to evaluate the efficacy, of FDC of montelukast 10 mg and levocetirizine 5 mg tablet versus montelukast 10 mg tablet monotherapy and levocetirizine 5 mg tablet monotherapy in the treatment of patients with seasonal allergic rhinitis. Male or female patients ≥18 to <60 years at the time of informed consent, who were diagnosed as having a documented clinical history of seasonal allergic rhinitis (for at least 2 years) with exacerbations during the study season associated with regular day time nasal symptoms of at least mild-to-moderate severity for the symptoms of nasal congestion, nasal pruritus and rhinorrhea during the screening period and/or exhibiting a positive allergen test. The Patients willing to comply with the protocol requirements were included in the study. The excluded subjects were pregnant or lactating women/female patient of child bearing potential who did not agree to remain abstinent or use medically acceptable methods of contraception/ patient with known hypersensitivity to any of the components of the formulation/patient with a history of anaphylaxis and/or other severe local reaction(s) to skin testing/patient with a history of allergies to more than two classes of medications or allergy to or intolerance of antihistamines/patient with alcohol or drug dependence/ patient with perennial rhinitis with little or no seasonal exacerbations; non-allergic rhinitis or ocular infection within 3 weeks before the trial.

Out of total 274 subjects, 92 subjects in the FDC of montelukast 10mg and levocetrizine 5 mg group, 92 subjects in montelukast 10 mg group and 90 subjects in levocetrizine 5 mg group were enrolled in the study. The total study duration was 16 days. The study comprised of 5 study visits which included visit 1- screening, visit 2–randomization to double blind treatment on day 1, visit 3 on day 3, visit 4 on day 7 of study treatment and visit 5–end of treatment (after day 14). Patients who met the inclusion and exclusion criteria were enrolled at visit 2 and randomized in 1:1:1 ratio to receive either the FDC of montelukast 10 mg and levocetrizine 5 mg tablet or montelukast 10 mg tablet or levocetrizine 5mg tablet for 14 days treatment period.

Institutional ethics committee clearance was obtained. At the screening visit, a written informed consent was taken followed by allergen testing, vital signs, physical examination, hemogram, serum biochemistry, urine analysis, urine pregnancy test, chest X-ray and 12 lead ECG. At visit 2, visit 3 and visit 4; efficacy, physical examination and vital signs were measured. Thereafter at end of study visit 5; vital signs, physical examination,

hemogram, serum biochemistry, urine analysis, ECG, efficacy assessments were measured. Adverse events (AEs) that happened during the study period were followed either as a telephonic follow up or as an unscheduled visit and recorded in source documents and on the case record form (CRF) till 30 days post last dose of investigational product or till resolution of AE, whichever was earlier.

Criteria for evaluation of primary efficacy were mean change in day time nasal symptoms score (average of scores of nasal congestion, rhinorrhea, itching and sneezing) from baseline to end of treatment. Mean change in night time symptoms score (average of scores of difficulty going to sleep, night time awakening and nasal congestion on awakening) from baseline to end of treatment. Mean change in daytime eye symptoms score (average of scores of tearing, pruritus, redness and puffiness) from baseline to end of treatment. Patient's and physician's global evaluation of allergic rhinitis at the end of treatment. Mean change in rhino conjunctivitis quality-of life score {questionnaire containing 28 items in seven domains (activities, sleep, nasal symptoms, eye symptoms, non-hay fever symptoms, practical problems and emotional functions)} from baseline to end of treatment.

Statistical analysis

Different scores were summarized and compared between treatment groups using analysis of covariance (ANCOVA) and by considering the baseline score as covariate. The 95% confidence intervals for the difference in mean change in symptoms score or RQOL score was constructed for the treatment groups. In case a significant p-value ($p \leq 0.05$) was found, it was concluded that there was a statistical significant difference between treatment groups in change from baseline to end of the treatment for symptom scores or RQOL score.

RESULTS

The least square mean change in the day time nasal symptoms score from baseline to end of treatment were 1.10, -0.93 and -0.98 for the FDC of montelukast 10 mg and levocetrizine 5 mg group, montelukast 10 mg group and levocetrizine 5 mg group, respectively, demonstrating significant improvements compared to the baseline ($p<0.0001$) for all three groups. Difference in the mean change for day time nasal symptoms score between the three treatment groups was by ANCOVA, considering the day 1 score as covariate and was statistically significant (p=0.0159) (Table 1).

Table 1: Mean change in day time nasal symptoms score.

Visit	Statistics	Montelukast 10 mg + Levocetirizine 5 mg	Montelukast 10 mg	Levocetirizine 5 mg	P value[1]
		(N=92)	(N=92)	(N=90)	
	LSM (SE)	-1.10 (0.056)	-0.93 (0.053)	-0.98 (0.057)	0.0159
Mean change from baseline (95% CI)			[-0.295 - -0.052]	[-0.250 - -0.004]	
(Day 1 to Day 14)	**P value[2]**		0.0054	0.0425	
	P value[3]	0.0000	0.0000	0.0000	

[1]p-value is calculated for the comparison of treatment groups using ANCOVA with baseline RQOL Score as covariate.; [2]p-value is calculated for the comparison between treatment groups by using ANCOVA with Estimate Statement; [3]P-value is calculated for the comparison of mean change within each treatment arm by using paired t-test.

Table 2: Mean change in nighttime symptoms score.

Visit	Statistics	Montelukast 10 mg + Levocetirizine 5 mg	Montelukast 10 mg	Levocetirizine 5 mg	P value[1]
		(N=92)	(N=92)	(N=90)	
	LSM (SE)	-0.71 (0.049)	-0.60 (0.048)	-0.68 (0.051)	0.1229
Mean Change from baseline 95% CI			[-0.218 - -0.001]	[-0.140 - 0.078]	
(Day 1 to Day 14)	**P value[2]**		0.0474	0.5767	
	P value[3]	0.0000	0.0000	0.0000	

[1]p-value is calculated for the comparison of treatment groups using ANCOVA with baseline RQOL Score as covariate; [2]p-value is calculated for the comparison between treatment groups by using ANCOVA with Estimate Statement; [3]P-value is calculated for the comparison of mean change within each treatment arm by using paired t-test.

After performing ANCOVA between FDC and each monotherapy group, statistically significant differences favoring FDC of montelukast 10 mg and levocetrizine 5 mg over montelukast 10 mg (p=0.0054) or levocetrizine 5 mg (p=0.0425) were observed for the mean change in day time nasal symptom scores from baseline to end of treatment.

The least square mean change in the night time symptoms score from baseline to end of treatment were -0.71, -0.60 and -0.68 in the ITT population and -0.71, -0.61 and -

0.68 in the PP population for the FDC of montelukast 10 mg and levocetrizine 5 mg group, montelukast 10mg group and levocetrizine 5 mg group. This mean change in night time symptoms score (i.e. improvement in symptoms) between the groups was not statistically significant but numerically greater in FDC as compared to monotherapy (Table 2).

Table 3: Mean change in day time eye symptoms score.

Visit	Statistics	Montelukast 10 mg + Levocetirizine 5 mg	Montelukast 10 mg	Levocetirizine 5 mg	P value[1]
		(N=92)	(N=92)	(N=90)	
	LSM (SE)	-0.59 (0.041)	-0.55 (0.039)	-0.55 (0.043)	0.6083
Mean change from baseline 95% CI			[-0.131 - 0.048]	[-0.127 - 0.054]	
(Day 1 to Day 14)	**P value[2]**		0.3618	0.4232	
	P value[3]	0.0000	0.0000	0.0000	

[1]p-value is calculated for the comparison of treatment groups using ANCOVA with baseline RQOL Score as covariate; [2]p-value is calculated for the comparison between treatment groups by using ANCOVA with Estimate Statement; [3]P-value is calculated for the comparison of mean change within each treatment arm by using paired t-test.

Table 4: Mean change in rhinoconjunctivitis quality-of-life score.

Visit	Statistics	Montelukast 10mg + Levocetirizine 5mg (N=92)	Montelukast 10mg (N=92)	Levocetirizine 5mg (N=90)	P value[1]
	LSM (SE)	-1.34 (0.065)	-1.13 (0.065)	-1.28 (0.065)	0.0582
Mean change from baseline 95%CI			[-0.396 - -0.032]	[-0.242 - 0.121]	
(Day 1 to Day 14)	**P value[2]**		0.0211	0.5130	
	P value[3]	0.0000	0.0000	0.0000	

[1]p-value is calculated for the comparison of treatment groups using ANCOVA with baseline RQOL Score as covariate; [2]p-value is calculated for the comparison between treatment groups by using ANCOVA with Estimate Statement; [3]P-value is calculated for the comparison of mean change within each treatment arm by using paired t-test.

Table 5: Summary of patient's global evaluation of allergic rhinitis.

Global impression	Montelukast 10 mg + Levocetirizine 5 mg	Montelukast 10 mg	Levocetirizine 5 mg
	(N=92); n (%)	(N=92); n (%)	(N=90); n (%)
Very much better	23 (28.0)	12 (14.6)	23 (27.4)
Much better	19 (23.2)	26 (31.7)	22 (26.2)
Better	36 (43.9)	33 (40.2)	29 (34.5)
Unchanged	3 (3.7)	6 (7.3)	9 (10.7)
Worse	1 (1.2)	4 (4.9)	1 (1.2)
Much worse	0 (0.0)	1 (1.2)	0 (0.0)
Very much worse	0 (0.0)	0 (0.0)	0 (0.0)

The least square mean change in the day time eye symptoms score from baseline to end of treatment were -0.59, -0.55 and -0.55 in the ITT population and -0.61, -0.59 and -0.61 in the PP population for the FDC of montelukast 10 mg and levocetrizine 5 mg group, montelukast 10 mg group and levocetrizine 5 mg group, respectively. This mean change in day time eye symptoms score (i.e. improvement in symptoms) between the groups was not statistically significant but numerically greater in FDC as compared to monotherapy (Table 3).

The least square mean change in the rhinoconjunctivitis quality-of- life score from baseline to end of treatment were -1.34, -1.13 and -1.28 in the ITT population and -1.34, -1.17 and -1.28 in the PP population for the FDC of montelukast 10 mg and levocetrizine 5 mg group, montelukast 10 mg group and levocetrizine 5 mg group, respectively. This mean change in the rhinoconjunctivitis quality-of- life score (i.e. improvement in quality of life) between the groups was not statistically significant but numerically greater in fixed dose combination as compared to monotherapy (Table 4).

95.1% patient had positive global impression (better to very much better) for the treatment given in FDC of montelukast 10mg and levocetrizine 5 mg group, compared to 86.5% patient in the montelukast 10 mg group and 88% patient in the levocetrizine 5 mg group in the PP population.

Physicians had positive global impression (better to very much better) for the treatment given in 95.1% of patients in the FDC of montelukast 10 mg and levocetrizine 5 mg group, compared to 86.5% in the montelukast 10 mg group and 84.5% in the levocetrizine 5 mg group in the PP population.

Overall, results of this study provided evidence for the primary efficacy endpoint that FDC of montelukast 10 mg and levocetirizine 5 mg was superior to montelukast 10 mg monotherapy or levocetirizine 5 mg monotherapy in the treatment of patients with seasonal allergic rhinitis. Other secondary endpoints and global impression results are also supporting the therapeutic benefit of fixed dose combination over monotherapy (Table 5).

DISCUSSION

In 1990, first human trial of 5– lipoxygenase inhibitor effect on nasal congestion showing reduced leukotriene synthesis with reduced nasal congestion.[13] Comparison of 10mg loratadine with the leukotriene receptor antagonist, pranlukast.[14] There are studies where concomitant therapy of levocetirizine with montelukast showed statistically significant improvement in nasal symptoms as compared to monotherapy.[15,16]

In the present study, a significant improvement as compared to baseline occurred for all the efficacy measures in the three treatment groups. Analysis of the primary efficacy endpoint– the day time nasal symptoms score provided evidence that FDC of montelukast 10mg and levocetirizine 5 mg was superior to montelukast 10mg monotherapy or levocetirizine 5 mg monotherapy in the treatment of patients with seasonal allergic rhinitis. At the end of treatment there was statistically significant evidence from the per protocol analysis that patients on FDC of montelukast 10mg and levocetrizine 5mg had a greater improvement in change from baseline in day time nasal symptoms score than patients who received montelukast 10mg (p=0.0266) or levocetrizine 5 mg (p=0.0409). These results were consistent with the Intent to treat analysis. In the ITT population statistically significant differences for the mean change in day time nasal symptom scores were also observed for the FDC of montelukast 10 mg and levocetrizine 5 mg compared to montelukast 10 mg monotherapy (p=0.0054) and levocetrizine 5 mg (p=0.0425).

Analysis of the secondary efficacy endpoints (night time symptoms score, day time eye symptoms score, and rhinoconjunctivitis quality-of-life score) provided numerically greater improvement in the night time symptoms score, day time eye symptoms score, and rhinoconjunctivitis quality-of-life scores in the FDC of montelukast 10 mg and levocetirizine 5 mg group as compared to the montelukast 10 mg monotherapy group or levocetirizine 5 mg monotherapy group. It was also noted that a greater number of patients in the FDC of montelukast 10 mg and levocetrizine 5 mg group demonstrated improvement in symptoms of allergic rhinitis as compared to patients in the montelukast 10 mg group and levocetrizine 5 mg group for the physician's and patient's global evaluation of allergic rhinitis at end of study. Results of our study is in agreement with the studies which have shown that levocetirizine alone and montelukast alone were effective on nasal symptoms and inflammatory markers, but the combined treatment offered an even better symptom control.[17]

CONCLUSION

It is concluded that the results of this study provided evidence for the primary efficacy endpoint– the day time nasal symptoms score that FDC of montelukast 10 mg and levocetirizine 5 mg was superior to Montelukast 10 mg monotherapy or levocetirizine 5 mg monotherapy in the treatment of patients with seasonal allergic rhinitis. The secondary efficacy variables provided evidence of a numerically greater reduction in these scores which were observed for the fixed dose combination. Assessment of the Physician's and Patient's Global Evaluation of Allergic Rhinitis indicated that a greater number of patients in the FDC of montelukast 10 mg and levocetrizine 5 mg group demonstrated improvement in symptoms of allergic rhinitis as compared to patients in the montelukast 10 mg group and levocetrizine 5 mg group. Large population study is required to substantiate the results of this study.

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