A Randomized, Open Label, Prospective, Comparative, Multicentric Study to Evaluate the Efficacy and Safety of Montelukast and Fexofenadine Fixed-dose Combination vs Montelukast and Levocetirizine Fixed-dose Combination in Allergic Rhinitis

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ABSTRACT

Background: Allergic rhinitis (AR) has impact on the physical, psychological and social aspects of the patients' life and work. Therefore, it is imperative to identify the treatment options for AR. **Objective:** This randomized, open label, prospective, two arm, comparative, multicentric study evaluated the efficacy and safety of montelukast 10 mg + fexofenadine 120 mg (MF) fixed dose combination (FDC) versus montelukast 10 mg + levocetirizine 5 mg (ML) FDC in subjects with AR. **Materials and methods:** The adult subjects were randomized to either treatment: ML (n = 62), MF (n = 56), administered once-daily for 14 days. The primary endpoint was the change in total symptom score (TSS) (the sum of total nasal symptom score [TNSS]) and total ocular symptom score (TOSS]) at the end of study as compared to baseline. The secondary endpoints were TNSS and TOSS: At the end of study as compared to baseline, physician's and patient's global assessment for efficacy and tolerability and adverse events. **Results:** Both groups were comparable with respect to demographic characters and vital parameters. In MF group, the reduction in TSS at the end of study was 93.86% as compared to 87.71% in ML. The changes in TNSS and TOSS at the end of study were 92.52% and 95.34% in MF group as compared to 85.58% and 92.23% in ML group. Global impression by investigator showed 53.23% subjects rated excellent to very good with MF as compared to 36.36% subjects with ML. Global impression by subjects showed excellent to very good rating for 50% subjects with MF and for 34.54% subjects with ML. **Conclusions:** Montelukast + fexofenadine showed better improvement in symptoms of AR and a better global impression by both investigators and subjects compared to montelukast + levocetirizine.

Keywords: Allergic rhinitis, montelukast + fexofenadine, montelukast + levocetirizine

Rhinitis is inflammation of the mucous membrane of the nose and is usually caused by the common cold or an allergy. Allergic rhinitis (AR) is caused by a reaction of the body's immune system to an environmental trigger. It occurs when an allergen, such as pollen, dust or animal dander is inhaled by an individual with a sensitized immune system. This heterogeneous disorder is often undiagnosed despite its high prevalence. It is characterized by one or more symptoms including sneezing, itching, nasal congestion and rhinorrhea.[1] About 40 million people in the United States alone are affected by AR, and the incidence is increasing.[2] The pathophysiology of AR is complex. A strong genetic component to the allergic response is driven through mucosal infiltration and action on plasma cells, mast cells and eosinophils. The allergic responses are described as the 'early' and 'late' phase responses. Early phase response occurs within minutes of exposure to the allergen and may result in sneezing, itching and clear rhinorrhea while late-phase response that occurs 4-8 hours after allergen exposure tends to cause congestion, fatigue, malaise, irritability and possibly neurocognitive deficits.[1] In India, AR is not considered as a disease of significant importance,

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although 75% of children and 80% of asthmatic adults were observed to have symptoms of rhinitis.[3] Traditionally, AR has been categorized as seasonal or perennial, depending on whether an individual is sensitized to cyclic pollens or to year-round allergens.[4] The Allergic Rhinitis and its Impact on Asthma (ARIA) workshop report proposed that patients be categorized as 'intermittent' and 'persistent' while severity was classified as 'mild' and 'moderate-to severe'. The ARIA guidelines have another classification of the patients with AR depending on their predominant symptom, as 'sneezers-runners' and 'blockers'. The 'blockers' had significantly higher sinusitis and had higher sensitization to fungi.[3,4]

According to the studies conducted in India, AR has proven to often restrict the patient's quality-of-life (QoL). It has impact on the physical, psychological and social aspects of the patients' life and also on their work. Additionally, sleep-related QoL is also adversely affected by AR.[3] Meltzer et al[5] have reported a study to affirm that the patients with AR had added effects on various aspects of their daily life. The patients complained of disturbed sleep in the night and fatigue and distraction during the day due to their symptoms. In most cases, nasal problems such as nasal congestion and rhinorrhea caused disturbances in breathing and sleep. The ARIA guidelines also have included sleep disturbances as a key factor in their definition of severity based on the impact of rhinitis on health-related QoL (HRQoL).[5] The Nasal Allergy Survey Assessing Limitations (NASAL) measured the burden of disease of AR in the United States by comparing the health status of adults with current hay fever, AR or nasal allergies with a national sample of adults without nasal allergies. NASAL showed that the burden of disease of AR imposed a social and economic cost on the patient and on society through its impact on work performance. In addition to keeping them from working, their health limited them from doing well at work compared with other co-workers. Their estimated productivity reduced to 71% on days when their nasal symptoms were at their worst from an average of 89% on days when they did not have nasal symptoms.[5]

The studies have also identified a major effect on the QoL in Indian patients. However, AR is seldom given the importance it deserves.[3] We need to identify the treatment options for AR. This study was planned to evaluate efficacy and safety of fixed-dose combination (FDC) of montelukast and fexofenadine.

MATERIALS AND METHODS

This randomized, open label, prospective, two arm, comparative, multicentric, Phase IV trial was conducted with an objective to evaluate the efficacy and safety of montelukast and fexofenadine FDC versus montelukast and levocetirizine FDC in the management of subjects with AR. The total treatment period was 14 days. The study was conducted in keeping with the principles described in the Declaration of Helsinki and Indian GCP guidelines. The study protocol and the sites were approved by the Institutional and Independent Ethics Committee. The eligible subjects were randomized into 1:1 (MF: ML) using permuted block design. They were assigned to arm-1 or arm-2 as per predetermined randomization schedule as follows:

- **Arm-1 (MF):** FDC of montelukast 10 mg + fexofenadine 120 mg tablet - One tablet once-daily for 14 days.
- **Arm-2 (ML):** FDC of montelukast 10 mg + levocetirizine 5 mg tablet - One tablet once-daily for 14 days.

The study was conducted at four sites, i.e., Mumbai, Chennai, two sites at Bangalore. It was planned to screen 140 subjects to enrol 120 in order to get 100 completed subjects at the end of the study. The subjects of either gender between age groups of 18-75 were included after obtaining informed consent from them.

Subjects diagnosed with AR (a total nasal symptom score [TNSS]; the sum of all the 4 individual nasal symptoms [nasal congestion, rhinorrhea, nasal itching and sneezing] scores of 6 or greater and/or a total ocular symptom score [TOSS]; the sum of all the three individual ocular symptom [itching/burning eyes, tearing/watering eyes and eye redness] scores of 4 or greater) were enrolled. Subjects were scrutinized for inclusion criteria having bronchial symptoms along with AR, signs and symptoms and willingness to regular follow-up.

Subjects with severe asthma, upper respiratory tract infection or acute or chronic pulmonary disorder, were excluded from the study. Subjects with known hypersensitivity to montelukast or fexofenadine or other piperazine derivatives and pregnant or lactating women and females of child-bearing potential not practicing contraception were not enrolled in the study.

Subjects on antihistamines, corticosteroids (in any dosage form), cromolyn sodium, nedocromil, inhaled cholinergics, oral or long-acting beta-agonists, theophylline and leukotriene modifiers were excluded from the study. Also subjects on nasal decongestants, anti-inflammatory drugs and AR rescue medications were not permitted during the course of the trial.

Study Procedures

The subjects were enrolled in the study after ensuring the fulfilment of inclusion/exclusion criteria. They

were assigned to either of the two treatment arms as per predetermined randomization schedule. The enrolled subjects were followed-up for assessing signs and symptoms (efficacy parameters) of AR on Day 7 and Day 14. The safety parameters were assessed at screening, Day 7 and Day 14. Global assessment for efficacy and tolerability by investigator and subjects were assessed at Day 14.

Efficacy Endpoints

The primary endpoints of this study included:

- The change in total symptom score (TSS) (the sum of TNSS and TOSS) at the end of study as compared to baseline.

The secondary endpoints included:

- TNSS at the end of study as compared to baseline
- TOSS at the end of study as compared to baseline
- Individual parameters of TNSS at the end of the study as compared to baseline
- Investigator and subject's global assessment for efficacy and tolerability
- To evaluate the safety by assessing the type, number, frequency and proportion of subjects with adverse events (AEs) during the study.

The scores for TNSS and TOSS were graded on 4-point categoric scale:

0 = None/no symptoms

1 = Mild symptoms, but 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.

The safety parameters and AEs during the study were assessed by monitoring AEs, vital signs and physical examination and assessment of blood chemistry during each visit.

Statistical Methods

Analysis was done on intention-to-treat (ITT) population which included all subjects who had taken at least one dose of study medication and was used for the analysis of the primary efficacy endpoint and safety evaluation. Repeat measures analysis of variance (ANOVA) (parametric) and Friedman test (nonparametric repeat measures ANOVA) was applied for the change in efficacy variables from baseline over the course of study. The change in grade of global improvement or clinical success or response rate from baseline value till the end of study treatment (Day 10) was analyzed by using McNemer's Chi-square test. For all statistical tests, the significance level was taken as $p < 0.05$.

RESULTS

A total of 118 subjects were enrolled at four sites. Table 1 shows the demographic characters of the population. The number of male subjects (64.29%) was more than the number of female subjects (35.71%) in ML group. The subjects were evaluated for vital parameters like pulse rate and systolic and diastolic blood pressure. The baseline values were similar in the two treatment groups and there was no significant change in vital parameters throughout study. The other parameters like age, height and weight were comparable in both the groups. The symptoms of AR at the screening are presented in Table 2. In both the groups, most frequently reported symptoms were sneezing followed by running nose, watery eyes and red eyes.

The baseline values and the values of TNSS throughout the study period are represented in Table 3. The baseline mean TNSS score in MF group was 7.89%. There was reduction in the mean TNSS value from

Table 1. Demographic Characters

	MF (n = 62)		ML (n = 56)	
	N	%	N	%
Male	33	53.23	36	64.29
Female	29	46.77	20	35.71

Table 2. Present Symptoms Data of Patients Enrolled

	MF (n = 62)		ML (n = 56)	
	No	%	No	%
Sneezing	51	82.26	51	91.07
Running nose	25	40.32	29	51.79
Watery eyes	22	35.48	26	46.43
Redness of eye	22	35.48	22	39.29
Nasal congestion	17	27.42	16	28.57
Itching/burning eyes	13	20.97	11	19.64
Nasal blockade	4	6.45	5	8.93
Cough	3	4.84	0	0.00
Fatiguability	3	4.84	1	1.79
Nasal itching	2	3.23	1	1.79
Headache	1	1.61	1	1.79
Fever	1	1.61	1	1.79
Breathlessness	1	1.61	1	1.79

Table 3. Percentage Change in TNSS from Baseline

	MF (n = 62)		ML (n = 56)	
	Mean	**SD**	**Mean**	**SD**
Baseline	7.89	2.07	7.80	1.99
Day 7	3.16	2.08	3.25	2.30
Day 14	0.59	1.02	1.13	1.24
Change from baseline	**Mean ch.**	**% ch.**	**Mean ch.**	**% ch.**
Day 7	-4.72	-59.88	-4.55	-58.35
Day 14	-7.30	-92.52	-6.68	-85.58

Table 4. Scores for Individual TNSS

	MF (n = 62)		ML (n = 56)	
	Mean	**SD**	**Mean**	**SD**
Nasal congestion				
Baseline	2.18	0.74	2.16	0.63
Day 7	0.98	0.76	1.11	0.73
Day 14	0.21	0.45	0.38	0.52
Rhinorrhea				
Baseline	2.08	0.84	2.11	0.76
Day 7	0.79	0.70	0.86	0.70
Day 14	0.13	0.38	0.20	0.40
Nasal itching				
Baseline	1.52	0.86	1.43	0.87
Day 7	0.58	0.69	0.50	0.71
Day 14	0.06	0.31	0.13	0.33
Sneezing				
Baseline	2.11	0.75	2.11	0.82
Day 7	0.76	0.74	0.86	0.80
Day 14	0.22	0.42	0.43	0.57

Table 5. Percentage Change in TOSS from Baseline

	MF (n = 62)		ML (n = 56)	
	Mean	**SD**	**Mean**	SD
Baseline	3.87	2.57	3.68	2.28
Day 7	1.43	1.42	1.50	1.69
Day 14	0.18	0.47	0.29	0.56
Change from baseline	**Mean ch.**	**% ch.**	**Mean ch.**	**% ch.**
Day 7	-2.44	-63.16	-2.18	-59.22
Day 14	-3.69	-95.34	-3.39	-92.23

Table 6. Percentage Change in TSS from Baseline

	MF (n = 62)		ML (n = 56)	
	Mean	**SD**	**Mean**	**SD**
Baseline	11.60	3.83	11.48	3.35
Day 7	4.64	3.34	4.75	3.69
Day 14	0.77	1.43	1.41	1.66
Change from baseline	**Mean ch.**	**% ch.**	**Mean ch.**	**% ch.**
Day 7	-6.96	-59.99	-6.73	-58.63
Day 14	-10.83	-93.36	-10.07	-87.71

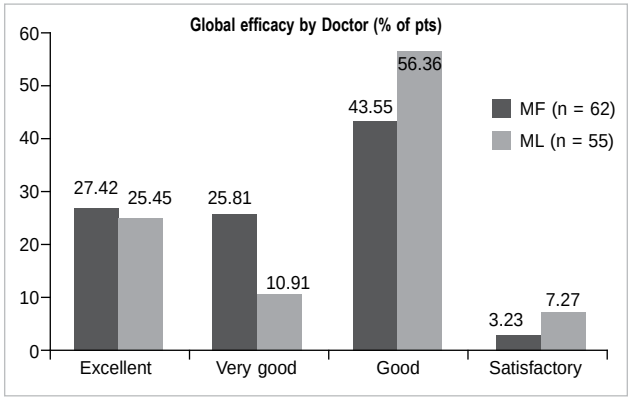
baseline by –4.72 (59.88%) on Day 7, by –7.30 (92.52%) on Day 14. Similarly, the baseline mean TNSS value in ML group was 7.8%. The reduction in the mean TNSS values from baseline was –4.55 (58.35%) on Day 7 and –6.68 (85.58%) on Day 14.

The individual nasal scores for each parameter are presented in Table 4. At the end of study, the MF group showed better reduction from baseline in the mean scores for individual parameters as compared to ML group. Nasal congestion showed reduction of -1.97 (90.37%) for MF group and -1.79 (82.64%) for ML group. For rhinorrhea, the reduction was - 1.95 (93.8%) for MF group and -1.91 (90.68%) for ML group. Nasal itching showed reduction of -1.45 (95.74%) for MF group and -1.30 (91.25%) for ML group. For sneezing, the reduction was -1.90 (89.75%) and -1.68 (79.66%) for MF and ML groups, respectively.

Table 5 depicts the baseline values and the values of TOSS at different visits. The mean TOSS at baseline in MF group was 3.87%. There was reduction in the mean TOSS value from baseline by -2.44 (63.16%) on Day 7, by -3.69 (95.34%) on Day 14. Similarly, the baseline mean TOSS value in ML group was 3.68%. There was reduction in the mean TOSS values from baseline by -2.18 (59.22%) on Day 7, by -3.39 (92.23%) on Day 14.

The baseline values and the values of TSS at different visit periods are presented in Table 6. The mean baseline score of TSS in MF group was 11.60%. There was reduction in the mean TSS value from baseline by -6.96 (59.99%) on Day 7, by -10.83 (93.36%) on Day 14. The baseline mean TSS value in ML group was 11.48%. There was reduction in the mean TSS values from baseline by -6.73 (58.63%) on Day 7, by -10.07 (87.71%) on Day 14.

Global impression for efficacy by investigator showed 53.23% subjects were rated excellent to very good with MF, whereas with ML it was only 36.36%. Similarly,



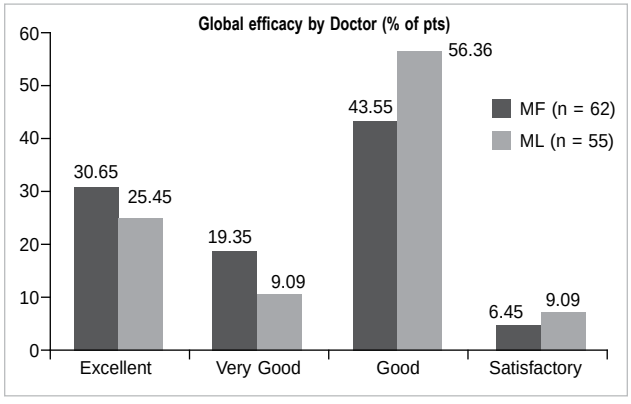
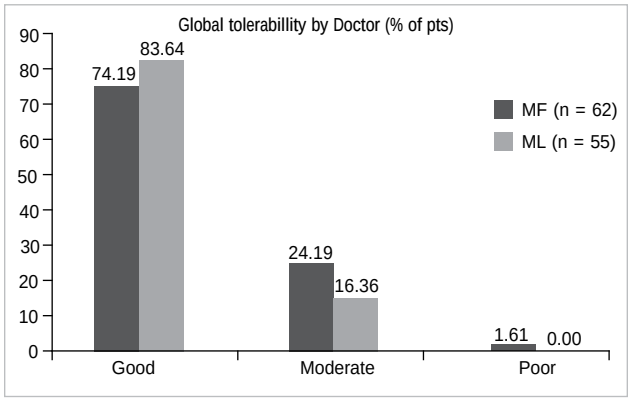


Figure 1. Global efficacy assessment.



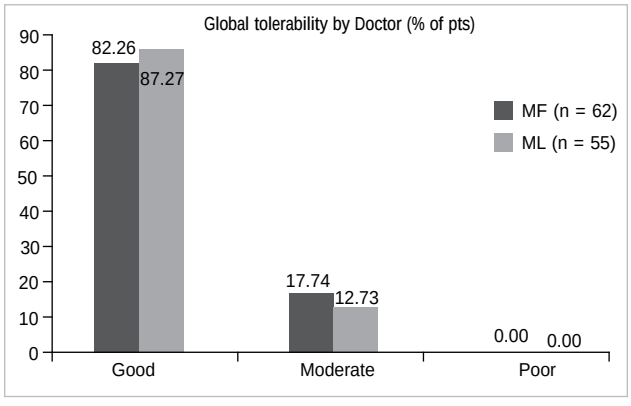


Figure 2. Global tolerability assessment.

global impression for efficacy by subjects showed that 50.00% had excellent to very good rating with MF compared to 34.54% in ML (Figs. 1 and 2).

Figure 2 depicts the global assessment for tolerability by investigators and subjects in both groups. In global assessment for tolerability by investigators on Day 14 showed that 74.19% subjects in MF group had good response to therapy, whereas 83.64% subjects had good response to therapy in ML group. The global assessment for tolerability by subjects on Day 14 showed that 82.26% subjects in MF group had good response to therapy and 87.27% subjects in ML group had good response to therapy. In safety assessment, 98.39% subjects showed good to excellent safety with MF, while 96.37% subjects showed good to excellent safety with ML. There were no clinically significant changes observed in the vital parameters of pulse rate and blood pressure, and laboratory parameters. No serious AE occurred in any of the patient enrolled. There were total three mild-to-moderate AEs, which were reported. Thus, MF administered for 14 days was safe for use and did not cause any AEs. The subjects were also observed for sedation. Though, the differences were not statistically significant, it was observed that sedation was more common in ML (23.21%) group compared to MF (9.68%) group. The two treatments were compared at baseline with respect to the demography and baseline scores to test randomization success. Data of age, symptom scores and laboratory parameters were compared between the two treatment arms using one way ANOVA. Change from baseline in the symptom scores were calculated and were compared between the two treatments using one way ANOVA. Ordinal data of overall assessment (outcome) were compared between the two groups using Mann-Whitney 'U' test. Discrete data was compared between the two treatments using Chi-square test. All testing was done using 2-sided tests at 95% confidence intervals.

DISCUSSION

Due to the impact of AR on HRQoL and QoL of patients, it becomes imperative to treat AR. Treatments available for AR include oral or topical antihistamines, oral leukotriene receptor antagonists, topical cortico-steroids, mast cell stabilizers, decongestants and anticholinergic agents. Among immunomodulatory

treatments, immunotherapy is gaining widespread use, while antibody treatment is restricted mainly to resistant cases, nasal irrigation, saline sprays, nasal glucocorticoids, antihistamines and immunotherapy.[6] Antihistamines like terfenadine and astemizole were being used since long time and had potential side effects. The newer antihistamines developed to replace these are loratadine, cetirizine and fexofenadine. Intranasal steroid sprays are more effective in patients with nasal stuffiness. The leukotriene receptor antagonists including zafirlukast and montelukast, when taken orally avoid the discomfort of nasal sprays and seem to have few side effects.[7]

Montelukast, an oral leukotriene receptor antagonist, is used for the treatment of asthma and AR. Fexofenadine is an antihistamine drug used in allergic symptoms. Antihistamine-decongestant combinations are used routinely for the treatment of seasonal AR. Recently, the combination of an antihistamine and a leukotriene receptor antagonist has been shown to be efficacious.

This study evaluated efficacy and safety of FDC of montelukast and fexofenadine. The two treatment groups were similar with respect to the demographic characters, personal history, baseline data and all other relevant characteristics, implying success of randomization. The mean baseline TNSS in MF group was 7.89%. There was reduction in the mean TNSS value from baseline by -4.72 (59.88%) on Day 7, by -7.30 (92.52%) on Day 14. Similarly, the baseline mean TNSS value in ML group was 7.8%. There was reduction in the mean TNSS values from baseline by -4.55 (-58.35%) on Day 7, by -6.68 (-85.58%) on Day 14. Although, the change in mean TNSS was not significant in both groups, the subjects treated with MF showed better symptomatic improvement compared to subjects treated with ML. The individual nasal scores for each parameter (nasal congestion, sneezing, nasal itching and rhinorrhea) were also assessed. The MF group showed better reduction from baseline in the mean scores for individual parameters as compared to ML group. The percentage reduction in the mean TOSS value from baseline was -2.44 (63.16%) on Day 7 and -3.69 (95.34%) on Day 14 in the MF group; whereas the percentage reduction for ML group for the mean TOSS values from baseline was -2.18 (59.22%) on Day 7 and -3.39 (92.23%) on Day 14. Although, the percentage change in mean TOSS was not significant in both groups, the subjects treated with MF had a greater improvement in symptoms of AR compared to subjects treated with ML.

TSS was sum of TNSS and TOSS. The reduction in the mean TSS values on Day 14 from baseline was 10.83 (93.36%) in MF group compared to 10.07 (87.71%) in ML group. Although, the change in mean TSS was not significant in both groups, the subjects in MF group had better symptomatic improvement compared to subjects treated with ML. It was observed at Day 14 that sedation was more commonly seen in ML (23.21%) group compared to MF (9.68%) group though the differences were not statistically significant. It is often seen that drowsiness or sedation affects QoL of AR patients.[8] This may or may not be related to the medication. However, it is an important factor to be considered while treating AR.

CONCLUSION

In this study, montelukast + fexofenadine showed better improvement in symptoms of AR and less incidence of sedation as compared to montelukast + levocetirizine.

Acknowledgments

Authors would like to thank Abbott Healthcare Pvt Ltd for funding and providing the study medications.

We would also like to thank the medical affairs team (Dr Qayum Mukaddam, Dr Prashant Khandeparkar and Dr Ashwini Nayak) and clinical research team (Dr Manoj Naik and Mr Tushar Fegade) of Abbott Healthcare Pvt Ltd, Mumbai for successful management of the study.

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