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Efficacy of Levocetirizine Compared with Montelukast for the Treatment of Allergic Rhinitis



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ABSTRACT

Allergic rhinitis (AR) is an IgE mediated type 1 reaction of the nasal mucosa to airborne allergens. Affects 10% to 30% of the adult population and the epidemiologic evidence suggest that the prevalence of AR has been rising. Levocetirizine dihydrochloride (LCTZ) is a potent H1-receptor antagonist, and Montelukast sodium (MLKT) is a selective leukotriene receptor antagonist, has been approved for the treatment of AR. The objective of the study was to compare the efficacy of LCTZ, 5 mg, and MLKT, 10 mg in reducing the symptoms of AR in a four-week treatment period. A prospective, randomized, parallel study was conducted in 67 patients of AR. The patients were assigned to three groups; 23 received LCTZ, 5 mg/day, 22 received MLKT, 10 mg/day and placebo in 22. An RQLQ were prepared and asked to patients in their first (baseline) visit and during their follow up periods. Out of 67 patients, the majority of patients were in the age group of 20-29yrs (44.19%). Female predominance was seen in the study. Compared with MLKT, LCTZ appeared to be more efficacious at week second and third. LCTZ improved most of the symptoms better than MLKT. Our data suggest that LCTZ is a viable treatment for AR and is well positioned as a leading antihistamine, has superior efficacy to MLKT and more cost-effective than MLKT. In conclusion, this study showed that LCTZ, 5 mg was more effective than MLKT, 10 mg in patients with AR.



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INTRODUCTION

Allergic Rhinitis (AR) is an Immunoglobulin E (IgE) mediated type 1 reaction of the nasal mucosa to airborne allergens, affecting between 10% to 30% of the adult population and epidemiologic evidence suggests that the prevalence of AR has been rising.^[1,2] The existence of hay fever in children is increasing globally. Around 40% of children affected by hay fever in some parts of France, The UK, Australia, India, South America, Hong Kong and Africa^[3].

AR and Asthma are well associated, and AR is a risk factor for asthma. There is the link between these two in epidemiologic, histologic and pathophysiologic features. These include the high numbers of inflammatory cells such as mast cells and eosinophils in the airway. On exposure to airborne allergens, they are activated and undergo degranulation and produce inflammatory substances, including cysteinyl leukotrienes (CysLT), histamine, prostaglandin D₂ and kinins.^[4, 5]

The symptoms of AR results from an IgE mediated process by the exposure of nasal mucosa to airborne allergens^[6]. The symptoms of AR include nasal congestion, rhinorrhea, sneezing, nasal itching, and itchy/watery eyes, and it affects individual's ability to function in daily life. The symptom also influences negatively on the quality of life (QOL) and has substantial economic and social impact.^[7]

Histamine and CysLT are important inflammatory mediators in AR. Their actions are executed through binding to specific receptors, thus therapeutic agents that block this binding have been important areas of clinical and pharmacological research.^[8]

Antihistamines are the first choice of treatment for AR. There are two generations of antihistamines first generation and second generation. Among these two, the second generation of antihistamines is more suitable because they are highly selective to H₁ and efficiently reduces the symptoms of AR with fewer side effects when compared with the first generation of antihistamines.^[9, 10]

Levocetirizine dihydrochloride (LCTZ) is a second-generation antihistamine. The high power and specificity of LCTZ as an inverse agonist for the H₁receptor have been demonstrated both at the level of endothelial cells and of smooth muscle fibro cells of blood microcirculation. On these sites, the antagonism of histamine is responsible for the inhibition of the increase in vascular permeability and vasodilation. Inhibition of edema formation and

mucus secretion represent the result of Levocetirizine effects on skin and respiratory mucosa, respectively. These pharmacological actions underlie the therapeutic effect of LCTZ in urticaria and rhinitis. ^[11]

Montelukast sodium (MLKT) is a selective leukotriene receptor antagonist (LTRA) and it inhibits the cysteinyl leukotriene (CysLT) receptor on target cells thereby reduces the symptoms of AR. It is used for the treatment of seasonal or perennial allergic rhinitis, and for prophylaxis and chronic treatment of asthma. Both LCTZ and MLKT are used for the treatment of AR but act by different pathways responsible for the allergic response that produce the symptoms of AR ^[2].

Recently the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines changed the old classification of AR (Seasonal / perennial) and suggested 'seasonal' to 'intermittent', and from 'perennial' to 'persistent' AR. It is further divided into. (Mild, moderate-severe) depending on the severity of the symptoms and quality of life of the patient. ^[3,4]

The objective of this prospective, randomized, parallel, placebo-controlled study was to compare the efficacy of oral LCTZ, 5mg, and MLKT, 10mg in reducing the symptoms of AR.

MATERIALS AND METHODS

Study Design

This was a 4-week; parallel-randomized, placebo-controlled monocenter study comparing the efficacy of oral LCTZ-5mg, and MLKT-10mg in reducing symptoms of AR in patients came to the outpatient department with AR symptoms, conducted at the RMMC Hospital (Chidambaram, Tamil Nadu, India). During the period from September 2009 to March 2010. A comparative study design was chosen in which symptoms were assessed at precise intervals to allow for the determination of the intensity of the action of LCTZ compared with MLKT - as well as a relative assessment of treatment efficacy. Outcome measures were responses to the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), daily nasal symptom score. During the first visit, subjects completed the RQLQ. Then subjects were randomized and assigned to either LCTZ or MLKT group. They were given the medication and instructed its usage. The subjects returned in 4 weeks for their second and third visit and completed another RQLQ.

Subjects

We selected 108 allergic adult male and female subjects who were in the age group of 18 to 60 years. 32 subjects are failed in screening. The selected 76 subjects are divided and given LCTZ to one group of 25 subjects, and the other groups of 25 subjects were given MLKT and to the last, group of 26 subjects, placebo drug has been given. Out of the 76 patients, 67 completed the study. Main inclusion criteria included a clinical history of AR. In addition, the patients are in the age of 18- 60 years. The patients having associated illness like mild asthma and diabetes are also included in the study.

Exclusion criteria include patients with the nasal polyp, a significantly displaced septum; subjects with asthma requiring medication other than short-acting β_2 - agonist were excluded. Those subjects who had been treated with systemic steroids during the previous 30 days, intranasal steroids in the past 2 weeks or immunotherapy in the last 2 years. Oral antihistamines or decongestants in the past 7 days, or topical antihistamines or decongestants in the past 24 hours. Pregnant or lactating women were excluded from the study.

Study Drugs

LCTZ, 5mg, MLKT, 10mg and matching placebos were applied as tablets for oral administration.

Rhinoconjunctivitis quality of life

RQLQ was prepared and given to the patients. It was completed on their first visit (Baseline score) and during their visits in 4 weeks treatment period. The questionnaire includes the daytime nasal symptoms and nighttime symptoms. Each symptom scores on a scale from 0 to 3. (0, no symptoms; 1, mild symptoms; 2, moderate symptoms and 3, severe symptoms).

Safety Assessments

Safety and tolerability were assessed by adverse events monitoring, physical examination and laboratory examinations.

RESULTS

Patient Disposition and Baseline Characteristics

The 108 subjects who were screened for eligibility, 32 were ineligible for randomization; 76 were randomized, of whom 67 completed the study (Fig.1). 25 patients were assigned to the LCTZ group (5mg daily), 25 to the MLKT group (10mg daily) and 26 to the placebo group. 9 of the original patients in 76 were excluded from the study because they have not completed the study (2 in LCTZ group, 3 in MLKT group and 4 in the placebo group). The baseline characteristics are summarized in Table 1. Overall 50.74% of patients were women and in the age group of 20-48 years. There were no clinically meaningful differences among the treatment groups in any baseline character, including baseline symptom scores, secondary diagnosis, and concomitant drug therapies.

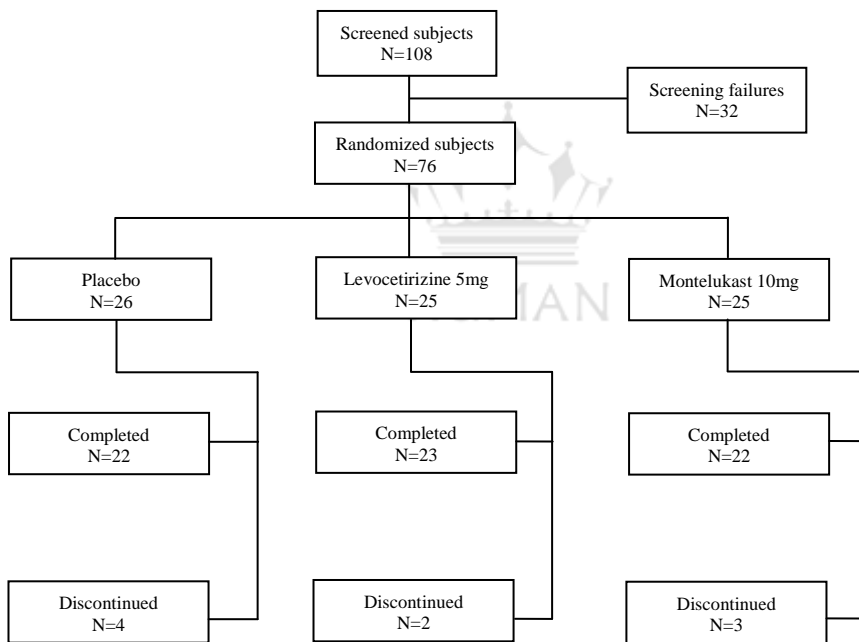


Figure: 1. Disposition of subjects

Table no. 1: Patient Baseline Characteristics

| Patient Characteristics | Treatment Groups | | |
|--|------------------|------------------------|---------------------|
| | Placebo N=22 | Levocetirizine N=23 | Montelukast N=22 |
| Demographics | | | |
| 1. Age (years) [Range] | 31.5 (20– 58) | 32.57 (22 – 58) | 31.9 (20 – 48) |
| 2. Sex, n (%) | | | |
| Male | 13 (59) | 8 (34.78) | 12 (55) |
| Female | 9 (40.9) | 15 (65.2) | 10 (45) |
| 3. Weight (kg) | 61.8 | 59.42 | 66.65 |
| 4. Height (cm) | 167.4 | 165.95 | 168.8 |
| 5. Allergic History | | | |
| Duration of allergic rhinitis (years) | 3.0 | 6.66 | 2.45 |
| History of allergic conjunctivitis, n(%) | 13 (59) | 18 (78.26) | 15 (65) |
| History of asthma, n(%) | 1 (4.76) | 1 (4.76) | 2 (10) |
| 6. Baseline efficacy measures | | | |
| Rhinoconjunctivitis quality- of - life score | 2.1 | 1.93 | 2.1 |

Medication Efficacy

Both LCTZ and MLKT have significantly reduced symptoms when compared with placebo group. LCTZ was appeared to be more efficacious than MLKT at week 2, 3 and week 4 when compared with MLKT while comparing both, LCTZ improved most symptoms better than MLKT. For nasal congestion, LCTZ and MLKT were better than placebo during all periods (except for MLKT during the last week of treatment) but there was no difference between the two active treatment groups. For cough symptom, both LCTZ and MLKT have not shown any significant benefit over placebo. For other symptoms like sneezing, rhinorrhea and nasal itching LCTZ was superior to MLKT and placebo. There was no serious adverse event noted in all the three groups.

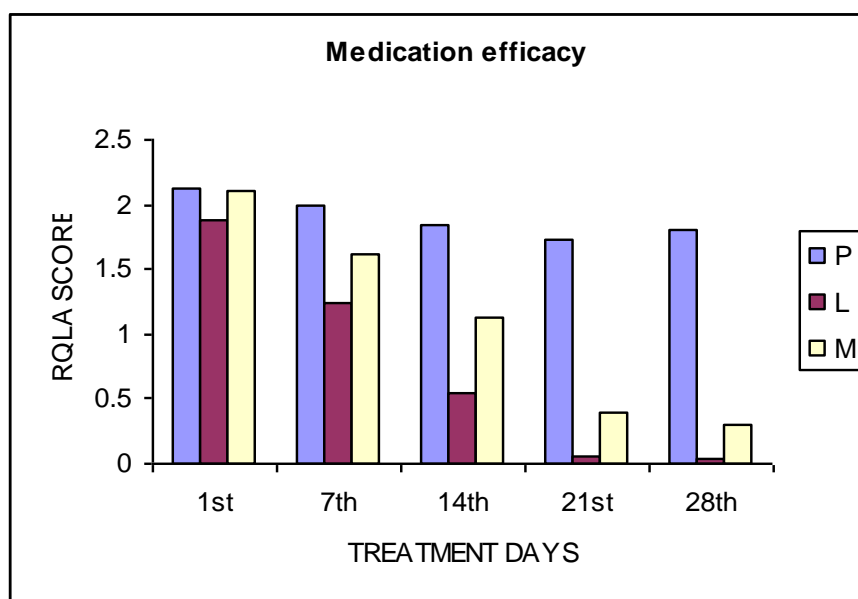


Fig no: 2 Medication efficacy

DISCUSSION

Oral antihistamines are the first line agents for the treatment of allergies in adults and children. First - generation antihistamines are associated with side effects such as sedation, dry mouth, and impaired psychomotor activity. Newer, Second-generation antihistamines, such as cetirizine, loratadine, fexofenadine, and Levocetirizine, act quickly and shows less sedative and anticholinergic effects ^[10].

The leukotriene receptor antagonist (Montelukast) is using for the treatment of allergic rhinitis. It selectively blocks the cysteinyl leukotriene receptors and effectively reduces the inflammatory response and peripheral blood eosinophil counts. Studies of leukotriene receptor antagonists also support the role of these agents in the treatment of AR ^[13]. The pharmacokinetics of MLKT is similar whether it is administered in the morning or in the evening; efficacy in seasonal allergic rhinitis was anticipated to be independent of the time dosing ^[5].

In our study of comparison of an H₁- antihistamine (LCTZ) and a leukotriene receptor antagonist (MLKT) for subjects with AR, LCTZ provided superior symptom control than MLKT. In all study periods, the symptom reduction achieved with LCTZ was higher than MLKT. Both the drugs were more efficacious than placebo and the safety of both compounds was very good.

Our study observations on efficacy and tolerability was supported by a recently published, 6-week study for the treatment of PAR comparing MLKT and LCTZ as monotherapy or in combination ^[14], study showed that for total daytime nasal symptoms LCTZ was significantly superior to MLKT monotherapy and, the combination of LCTZ and MLKT was better than MLKT or LCTZ monotherapy.

In another study to determine the effect of concomitant therapy with LCTZ and MLKT in SAR, a 4-week study, also proved that the combined treatment of LCTZ – MLKT significantly improved the day and night time nasal symptom score and daytime eye symptom score when compared to placebo or either treatment alone. All treatments were well-tolerated ^[15].

The distinct role of histamine and leukotrienes in the allergic inflammatory response are well known, where histamine is believed to be mainly responsible for the early phase symptoms of allergic rhinitis, and leukotrienes in nasal congestion and the maintenance of symptoms It was showed that LCTZ would be highly effective in controlling the histamine-mediated early phase response of allergic rhinitis.

CONCLUSION

Our data suggest that LCTZ is a viable treatment for SAR and is well positioned as a leading antihistamine, offering superior efficacy to MLKT and may be more cost-effective because MLKT is a more expensive option.

In conclusion, this study showed that LCTZ, 5mg was more effective than MLKT, 10mg in patients with allergic rhinitis.

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