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SAFETY AND EFFICACY OF COMBINATION OF MONTELUKAST AND LEVOCETRIZINE IN THE SYMPTOMATIC TREATMENT OF ALLERGIC RHINITIS AND ASTHMA: PHASE IV CLINICAL STUDY

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ABSTRACT

Introduction- Allergic rhinitis (AR) and allergic asthma are caused by an IgE-mediated inflammatory reaction and treatment of AR symptoms requires a stepwise approach depending on the severity and duration of symptoms. A combination of Levocetirizine which is selective, potent, oral histamine H (1) receptor antagonists and Montelukast which is a selective and orally active cysteinyl leukotriene-receptor antagonist (LTRA) is used for the treatment of Allergic rhinitis and Asthma. This Phase IV study trial evaluates the efficacy and safety of the combination of Levocetirizine and Montelukast for the treatment of Allergic Rhinitis or Allergic Asthma. **Methodology-** Total 270 patients were recruited for the study, of which 256 patients completed the study trial and 14 patients were lost to follow up. Assessment of the efficacy was made by the reduction in TSS and four point Likert-type scales. Safety assessment was done by analyzing the adverse events during the trial. **Results-** The reduction in TSS from 6.61 (baseline) to 2.94 (day 5) and 0.71 (day 10) was observed. 49 episodes of adverse events occurred and reported which were of mild intensity. **Conclusion-** A combination of Levocetirizine and Montelukast is safe and effective in the treatment of Allergic Rhinitis or Allergic Asthma.

KEYWORDS: Allergic rhinitis, Asthma, Levocetrizine, Montelukast.

INTRODUCTION

Allergic Rhinitis, a common and often debilitating condition[1] is a heterogeneous disorder that despite its high prevalence remains often undiagnosed.[2] Allergic Rhinitis involves the IgE-mediated hypersensitivity reactions against inhaled allergens, involves nasal mucosal inflammation driven by type 2 helper T (Th2) cells.[3] This is usually characterized by symptoms such as sneezing, nasal itching, nasal congestion and watery rhinorrhea.[2]

Allergic rhinitis constitutes about 55 % of all the allergies. In India, Allergic rhinitis ranges between 20% and 30%. According to the International study of Asthma and Allergies in childhood (ISSAC) phase 1 (1998), in India nasal symptoms alone were present in 12.5% children in 6-7 years age group and 18.6% in 13- 14 years age group, However in ISSAC phase 3 (2009) study, prevalence of nasal symptoms increased to 12.9% and 23.6% in 6-7 and 13-14 year age groups, respectively. The prevalence of AR is increasing all over the world. In the United States, AR is estimated to affect approximately 60 million peoples, and the prevalence is about 10-30% in adults and nearly 40% in children.[4]

Asthma is a chronic inflammatory pulmonary airways disorder, which is marked by the bronchial hyper-responsiveness with recurrent episodes of wheezing, coughing, tightness of the chest and shortness of breath that leads to the lower airway obstruction. Asthma affects approximately 300 million people around the world. In children, males have a higher asthma risk; in adults, females have a higher prevalence.[5]

Levocetirizine is the third generation antihistamine used for the treatment of both seasonal and perennial allergic Rhinitis.[6] Levocetrizine is a selective, potent, oral histamine H (1) receptor antagonists and a R-enantiomer of cetirizine dihydrochloride which has pharmacodynamically and pharmacokinetically favorable characteristics which includes rapid onset of action, high bioavailability, high affinity and occupancy for the H1-receptor, limited distribution, minimal hepatic metabolism together with minimal untoward effects.[6] The safety data obtained from the clinical trials on

administration over long periods in almost all the pediatric age groups suggest that levocetirizine use is considered to be safe and is not associated with relevant adverse effects on the central nervous system (CNS).[6]

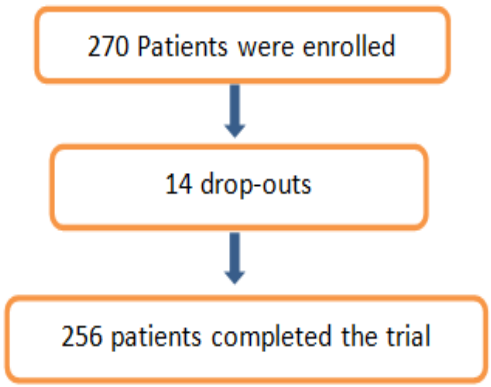
Montelukast is a selective and orally active cysteinyl leukotriene-receptor antagonist (LTRA) indicated for the maintenance treatment of asthma and to relieve symptoms of seasonal allergies in adults and children. Montelukast is an effective and well-tolerated agent with no difference in bioavailability in young and elderly patients.[7]

Montelukast acts by blocking the action of leukotriene D4 (and secondary ligands, leukotrienes C4 and E4) on the cysteinyl leukotriene receptor CysLT1 in the lungs and bronchial tubes by binding to it. This prevents the bronchoconstriction otherwise caused by the leukotriene and results in reduced inflammation. By inhibiting the action of D4 (LTD4) at the CysLT1 receptor, Montelukast also prevents airway edema, smooth muscle contraction and enhanced secretion of thick, viscous mucous.[7] In the literature, there is increasing recognition of a link present between Asthma and AR.[8]

A combination of Montelukast and Levocetirizine tablets are easily available and studied for the treatment of Allergic Rhinitis with Asthma. However, due to the insufficient clinical data available for this combination, a phase 4 clinical study trial was conducted so as to assess the safety and the efficacy profile of the combination of Levocetrizine and Montelukast for the treatment of Allergic Rhinitis with Asthma.

MATERIALS AND METHODS

A Phase IV, non- randomized and non- Comparative clinical trial was conducted across 12 Investigational centers across India for a duration of 10 days. A total of 270 patients were screened for the study and 256 patients completed the study and 14 patients were lost to follow-up.



Inclusion criteria

The study included both male and female patients between 18-65 years of age. The enrolled patients were confirmed to be diagnosed with Allergic rhinitis. The patients that adhere to this protocol should be included for the study.

Exclusion criteria

This clinical study trial excluded patients that were thought to be hypersensitive to the study drugs. Pregnant and lactating mothers were barred from the study. Also patients diagnosed with mental and psychiatric illness and those who cannot give informed consent were excluded from the study trial.

Study intervention

A combination of Montelukast (10mg) and Levocetirizine (5mg) in the tablet form was provided free of cost to the patients by the sponsor. Study dosage and administration- Patients were advised to take 1 tablet for a day for a study period of 10 days.

Table no 1: Flow chart of the study.

Activity	Visit 1 Day 1	Visit 2 Day 5	Visit 3 Day 10
Physical Examination	Done	Done	Done
Drug dispensing	Done	Not Done	Not done
Safety Evaluation	Not Done	Done	Done
Efficacy evaluation	Not done	Done	Done

Study procedure

The clinical trial was conducted for a period of 10 days and all the eligible patients satisfying the inclusion and exclusion criteria were recruited for the study. A detailed medical history was taken by thorough clinical examination and physical examination that included the vital signs, systemic and general examination was conducted by the investigators. Patients would be informed about the nature of the study and an informed consent would be taken.

Patients will be given 10 MTnL tablets free physician samples and advised to take in the dose of 1 tablet for a day for a study period of 10 days. A diary of the daily symptoms has to be maintained by the patients. In case of any safety-related issues and adverse events, the investigator can withdraw the patient from the trial and treat according to the severity of the symptoms. Three visits were outlined for the patients recruited in this study- V0 (Baseline visit) day 1, V1 (reevaluation visit) day 5 and V2 (conclusion visit) day 10. Complete Medical history of the patient was recorded and physical examination along with the Total Symptom Score and adverse event occurring were esteemed during each visit. Investigators were asked to discontinue the study drug in case of serious adverse events and with discretion or clinical experience in case of mild to moderate adverse events.

Concomitant Therapy

No Pharmacological intervention and medication including topical decongestants (sprays, drops and aromatic oils), antibiotics, multi-vitamins and multiminerals were allowed during the study duration other than the study drug.

Non-pharmacological interventions like drinking warm/hot water at regular intervals and steam inhalation were allowed and encouraged during the study.

Efficacy Assessment

The primary assessment was done by analyzing the reduction in TSS (Total symptom score) which was a score of all the symptoms on a eleven-point scale (0 to 10) where 0 is no symptom and 10 means maximum tolerated symptoms. The TSS scale was further extrapolated to the Likert-type symptom severity scale with 4 grades- no symptoms (0 on TSS), mild (1-4 on TSS), Moderate (5-8) and Severe (9-10 on TSS).

Safety Assessment

Patients were questioned for any adverse event. All the serious and non-serious adverse events were fully documented using clinical charts, original documents and case report form. The adverse events were categorized into non-serious adverse events and serious adverse events. Naranjo's scale of probability was used to classify the adverse event as non –drug related or drug related. Adverse events were followed up by the investigators till the symptoms subside.

Regulatory and Ethical Matters

The said combination is available in India and is classified as the schedule H drug which means it should be sold only in presence of prescription of a registered medical practitioner. All the patients participating in the study have read and signed the ICF.

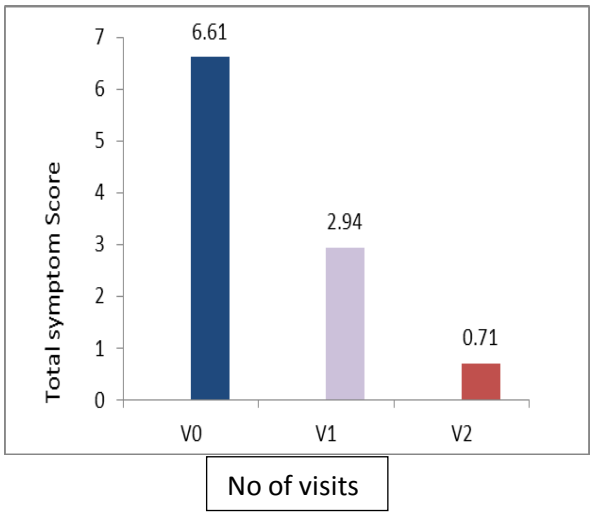
RESULTS

A Total of 270 patients were recruited at 12 centers across India. Out of which 256 patients completed the study and were analyzed.

Efficacy Analysis

Mean of the total symptom score (TSS) was recorded at all the visits (V0, V1 and V2) and thus the reduction on TSS was calculated. The mean TSS at V0 or the baseline visit at day 1 was 6.61 which was reduced to 2.94 at V1 or day 5 and further reduced to 0.71 on V2 or day 10.

The reduction in TSS corresponded with the improvement in general and physical examination of the patients.



X axis- No of visits, Y axis- Total symptom Score

Figure 1: Reduction in TSS at each visit.

Extrapolating the data to Likert-type symptom scale, at V0 or baseline the mean TSS corresponds to Moderate symptoms which was reduced to Mild in V2 or Day 5.

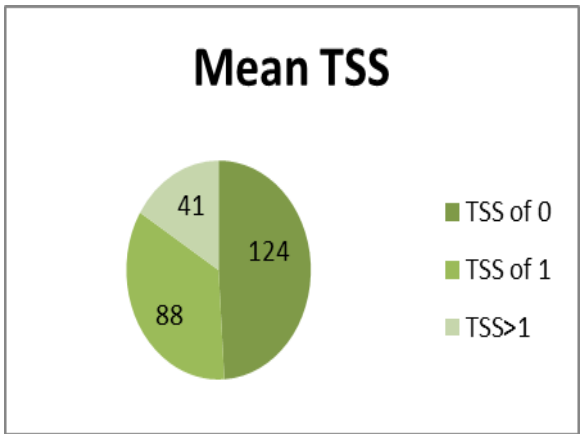


Figure 2: No of patients with TSS Score of 0, 1 and >1.

Out of the 256 patients, 41 patients had a TSS of 0 i.e no of symptoms on likert type symptom scale and another 88 had the TSS of 1 (Figure 2).

Safety analysis

The overall incidence of reported study drug related adverse events were **49 seen in 28 patients.** The list of adverse events with the number of episodes is mentioned in **Table 2.**

Adverse Events	No. of events	No. of patients	% of patients
Sedation and drowsiness	12	9	3.33 %
Hyperacidity	6	3	1.11 %
Dryness of mouth	9	6	2.22 %
Dizziness	22	10	3.70 %
Total	49	28	10.36 %

DISCUSSION

Allergic rhinitis and Asthma are common health problems that cause major illness and disability worldwide.[9] There indicates a close relationship between the upper and lower airways in allergic rhinitis with asthma, as Rhinitis is present in the majority of Asthmatic patients and only a significant minority of patients with Rhinitis have concomitant asthma.[10]

One of the strongest arm of this clinical study is that the Total Symptom Score is used as a criterion for efficacy assessment and that this data of TSS is extrapolated to Likert-type symptom scale which is the internationally acknowledged scale for assessment of the symptoms. One of the most impressionable thing of the TSS scale lies in the fact that it has 11 grades for the symptom assessment compared to the Likert-type symptom scale which has 4 grades thus increasing the sensitivity of the study. A reduction in Total Symptom score (TSS) in all the patients was observed in the phase IV post marketing surveillance study. The **TSS reduced** from **6.61 to 2.94** which is reduction of **44.47 %** and from **2.94 to 0.71** which is reduction of **24.14%.** The Total mean symptom score (TSS) was found to reduce at the conclusion visit i.e. at Visit 3.

In all the patients there was a reduction in the TSS scale. Majority of patients had no (TSS score of 0) to very less (TSS score of 1) at the end of 5 study days. Nearly all the patient's had 50% reduction in symptoms at every visit. A total of 49 adverse events were related to the study drug, of which dizziness was the most documented adverse event affecting 3.70 % the study population.

Ciebiada Metal., et al conducted a 32-week randomized, double-blind, placebo-controlled, crossover, double-armed study in 40 adult patients with history of persistent AR, clinical allergy to house-dust mites, and a total nasal symptom score of at least 5 (congestion of at least 2). There were four 6-week treatment periods separated by 2-week washout periods. Twenty patients received either montelukast or antihistamine, a combination of montelukast and antihistamine, or placebo. The sequence of treatment was randomly assigned. Nasal symptoms were assessed using a 4-point scale at baseline, daily during the 1st week and on days 14, 21, 28, 35, and 42 of treatment. Montelukast alone, levocetirizine alone, desloratadine alone, and the montelukast/antihistamine combinations significantly improved nasal symptoms during the first 24 hours. Improvement gradually increased during the 6 weeks of treatment, especially in patients receiving montelukast alone or in combination therapy with the antihistamine in both arms. Improvement at 42 days of treatment was significantly greater than that achieved on the 1st day of therapy in patients treated with the combination of montelukast and levocetirizine.[11] Thus, Montelukast alone or in combination with antihistamines gave a gradual increase in nasal symptom improvement within 6 weeks of treatment in patients with persistent Allergic Rhinitis (AR).

According to a study published by **Górska- Ciebiada M et al.,** A randomized, double-blind, placebo-controlled crossover study was performed to evaluate the effects of 6 weeks of treatment of persistent AR with levocetirizine, or montelukast alone or in combination. Patients were assigned to 2 arms: 20 received montelukast, and 20 received montelukast, levocetirizine, or both, 5 mg/d, or placebo. The treatment periods were separated by 2-week washout periods. Symptom scoring, skin prick tests, spirometry, rhinometry, and nasal lavage were performed the day before and the last days of the treatment periods. Eosinophil cationic protein levels were evaluated by means of nasal lavage. The mean +/- SD baseline nasal symptom score was 7.95 +/- 0.68 before treatment, 3.02 +/- 0.64 after levocetirizine use, 3.44 +/- 0.55 after montelukast use, and 2.14 +/- 0.39 after montelukast-levocetirizine use. The greatest improvement in nasal symptoms occurred after combination treatment. Decreases in the level of eosinophil cationic protein were greater after the combined use of montelukast and antihistamine (Levocetirizine) than after each agent given alone. Thus, for persistent AR, the combination of montelukast and levocetirizine is more effective than monotherapy with these agents.[12]

Mahatme MS[1] et al., compared the cost-effectiveness of montelukast-levocetirizine in patients of allergic rhinitis in a randomized, double-blind clinical trial. Seventy patients with AR participated in a prospective, randomized, double-blind, parallel, active-controlled, comparative 4-week trial. The patients between the age group of 18-65 years of either gender having moderate-severe intermittent or mild persistent AR were included in the study. The study inclusion criteria required the patients with total nasal symptom score (TNSS) of 5 or higher. The trial concluded that cost-effectiveness is more with montelukast-levocetirizine combination.

CONCLUSION

A combination of Montelukast (10mg) and Levocetirizine (5mg) is considered to be safe and provides symptomatic relief for the treatment of Allergic Rhinitis and Asthma.

Disclosure : This study was conducted as a part of Pharmacovigilance activity for MTNL Tablets marketed by Centaur Pharmaceuticals Pvt Ltd.

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