Rupatadine and Levocetirizine for Seasonal Allergic Rhinitis

A Comparative Study of Efficacy and Safety

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Objective: To determine the better agent among rupatadine fumarate and levocetirizine dihydrochloride for seasonal allergic rhinitis. Although treating and ensuring a decent quality of life to patients is challenging, an increasing understanding of pathomechanisms has revealed the potentiality of new-generation antihistamines in the treatment of seasonal allergic rhinitis.

Design: A 2-week, single-center, randomized, open, parallel group comparative clinical study between rupatadine and levocetirizine in patients with seasonal allergic rhinitis.

Setting: A tertiary care center.

Patients: Following inclusion and exclusion criteria, 60 patients were assigned to either the rupatadine or levocetirizine group.

Interventions: Two-week treatment with rupatadine or levocetirizine.

Main Outcome Measures: After 2 weeks, all post-drug symptoms were listed, baseline laboratory investigations (total and differential leukocyte count and IgE level) were repeated, and clinical improvement was assessed in terms of change in Total Nasal Symptom Score, Rhinocconjunctivitis Quality of Life Questionnaire score, and laboratory parameters.

Results: Differential count ($P=0.01$) and absolute eosinophil count ($P=0.009$) was significantly lowered by both drugs, but rupatadine was found to be superior. In the rupatadine group there was a significantly higher reduction ($P=0.004$) in IgE level and Total Nasal Symptom Score ($P<.001$) compared with the levocetirizine group. There was a decrease of 18.08% ($P=0.02$) in Rhinocconjunctivitis Quality of Life Questionnaire score in the rupatadine group, which was significantly greater compared with the levocetirizine group. Incidence of adverse effects was less in the rupatadine group compared with the levocetirizine group.

Conclusion: Rupatadine is a better choice for seasonal allergic rhinitis compared with levocetirizine because of its better efficacy and safety profile.

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Allergic rhinitis (AR) is one of the most common diseases, representing approximately 20% of the general population. Allergic rhinitis is the general term that encompasses seasonal AR, perennial AR, and perennial AR with seasonal exacerbations. Seasonal AR accounts for 20% of cases and perennial AR for 40% of cases, and another 40% of cases have a mixed cause. Allergic rhinitis has a relevant impact on society because of its high prevalence, association with an impaired quality of life, and the presence of comorbidities such as atopy and asthma. Seasonal AR is normally triggered by various types of pollen from trees, grasses, and weeds, as well as outdoor mold spores. The major symptoms include sneezing, rhinorrhea, nasal obstruction, and nasal or pharyngeal pruritus. Quantitatively, histamine is the most abundant preformed mediator in the early-phase response, and its implication in many of the symptoms of the disease has been clearly demonstrated. Symptoms such as sneezing, itching, watery eyes, and rhinorrhea are largely mediated through histamine $H_1$ receptors. Current treatments for AR include antihistamines, decongestants, leukotriene modifiers, and intranasal corticosteroids. Oral antihistamines are an effective first-line pharmacologic treatment for the relief of itching, sneezing, and rhinorrhea associated with AR.

Rupatadine is a novel chemical entity that shows both antihistamine and anti–platelet-activating factor effects through its interaction with specific receptors and not through physiological antagonism. The efficacy of rupatadine as a treatment for
AR has been investigated in adults and adolescents in several international, randomized, double-blind, and multicenter trials. Dose-ranging, placebo-controlled studies to evaluate the efficacy and safety of several doses (10 and 20 mg) of rupatadine showed that all doses of rupatadine were more effective than placebo in alleviating the symptoms in a dose-dependent manner.\textsuperscript{12,13}

Levocetirizine—the R-enantiomer of cetirizine dihydrochloride with pharmacodynamically and pharmacokinetically favorable characteristics—has been proved to be safe and effective for the treatment of AR with a minimal number of adverse effects in many clinical trials.\textsuperscript{14-19}

The primary goal of treating patients with seasonal AR is to give symptomatic relief. At present, the market is flooded with “me-too” drugs, and physicians are inundated with promotional literature from pharmaceutical companies. Therefore, our present study is an effort to determine the better agent between rupatadine and levocetirizine for seasonal AR.

**METHODS**

**PATIENTS**

The study was conducted on 60 patients with seasonal AR attending the Ear, Nose, and Throat Department, Prathima Institute of Medical Sciences, Karimnagar, India. The study population included male and female patients 12 years or older with a history of seasonal AR of 6 months or longer and requiring treatment and a documented positive allergy skin test result during the previous year. Patients were excluded for the following reasons: use of concomitant medication(s) that could affect the efficacy of candidate drugs; any existing medical or surgical condition that could affect the metabolism of drugs under study; clinically significant nasal disease (other than seasonal AR) or significant nasal structural abnormalities including nasal polyps and clinically relevant respiratory tract malformations; recent nasal biopsy (within 2 months); nasal trauma; nasal surgery; atrophic rhinitis; rhinitis medicamentosa (within 2 months); active asthma requiring treatment with inhaled or systemic corticosteroids, routine use of β-agonists, or both; known hypersensitivity to antihistamines; history of respiratory tract infection or disorder within 2 weeks of the first visit or a respiratory tract infection during the first visit; antibiotic use for acute conditions within 2 weeks of the first visit; treatment with systemic corticosteroids within 2 months of study initiation; and treatment with topical corticosteroids in concentrations in excess of 1% hydrocortisone for dermatologic conditions within 1 month of study initiation. Pregnant and breastfeeding women were also excluded.

**STUDY DESIGN**

The present study is a 2-week, randomized, open-label (non-blinded), parallel group comparative clinical study between rupatadine and levocetirizine in patients with seasonal AR conducted in a single center. The study was approved by the institutional ethical committee, and procedures followed in this study were in accordance with the ethical standard established by the Ethical Guidelines for Biomedical Research on Human Subjects (Indian Council of Medical Research, 2006). Written informed consent was obtained from all the patients who participated in the study after explaining the patient’s diagnosis, the nature and purpose of a proposed treatment, the risks and benefits of a proposed treatment (rupatadine or levocetirizine), and the risks and benefits of the alternative treatment. After randomization, the patients were divided into 2 treatment groups: 30 patients were allocated to the levocetirizine group, who received levocetirizine dihydrochloride, 10 mg once daily, and another 30 patients were allocated to the rupatadine group, who received rupatadine fumarate, 10 mg once daily, for 2 weeks. The patients received the drugs free of cost from our institute pharmacy. At the first visit, after detailed history was taken on baseline symptomatology, clinical evaluation (including Total Nasal Symptom Score [TNSS], Rhinconjunctivitis Quality of Life Questionnaire [RQLQ] scoring, and laboratory investigations [total count/total leukocyte count, differential count, absolute eosinophil count, and IgE level]) were performed. After 2 weeks, all post–drug therapy symptoms were noted, baseline laboratory investigations were repeated, and clinical improvement was assessed in terms of change in TNSS, RQLQ score, and laboratory parameters.

**EFFICACY AND SAFETY VARIABLES**

The efficacy variables were change from baseline to day 14 in the severity of rhinitis symptoms based on TNSS, in quality-of-life parameters for patients 18 years or older measured using the RQLQ,\textsuperscript{20} in serum IgE level, and in total and differential leukocyte counts.

The study began with a 1-week, single-blind lead-in period, and patients received placebo capsules. Patients qualified for entry into the lead-in period if they had a TNSS of 8 or greater and a nasal congestion score of 2 or greater or a severity of rhinorrhea of 3 or greater and a nasal congestion score of 2 or greater over the previous 12 hours (12-hour reflective TNSS). Symptom severity was determined by the TNSS, which consisted of runny nose, sneezing, nasal itching, and nasal congestion, scored on a severity scale from 0 to 3 (0=none, 1=mild, 2=moderate, and 3=severe), such that the maximum possible TNSS is 24. To be eligible for entry into the treatment period, patients must have recorded a morning or evening TNSS of 8 or greater on at least 3 days during the lead-in period and a morning or evening nasal congestion score of 3 or at least 3 days.

The RQLQ is a disease-specific, validated quality-of-life questionnaire developed for the measurement of physical, emotional, and social problems common to adults and adolescents with allergies. The version of the RQLQ administered depended on patient age, with patients aged 12 to 17 years assessed with the adolescent RQLQ and patients 18 years and older assessed with the adult RQLQ. Patients rated experiences over the past week for questions related to activities, sleep (adults only), nonhay fever symptoms (adolescents only), practical problems, nasal symptoms, eye symptoms, emotions, and nonhay fever symptoms (adolescents only).

Total leukocyte count and differential count was performed with a hemocytometer, and IgE level was estimated by a chemiluminescent immunoassay.

Tolerability was assessed in terms of reported adverse experiences and vital signs that included body temperature, systolic and diastolic blood pressure, and heart and respiration rates, which were measured at baseline and at the end of the study. All reported adverse drug reactions were graded according to the National Cancer Institute Common Toxicity Criteria and compared between the groups.

**STATISTICAL ANALYSIS**

The statistical calculation for the paired $t$ test, unpaired $t$ test, and Fisher test were performed with Instat $+$ version 3.036 statistical software (Statistical Services Centre, University of Reading, Reading, England). $P<.05$ was considered statistically significant.
RESULTS

PATIENT DISPOSITION AND BASELINE DEMOGRAPHICS

A total of 60 patients were randomized to 2 groups to receive either rupatadine (n = 30) or levocetirizine (n = 30). Postbaseline values were missing in 9 patients (4 in rupatadine group and 5 in levocetirizine group) because they were lost to follow-up because of noncompliance (n = 7) or adverse effects (n = 2). The treatment groups were comparable in demographic features and baseline clinical characteristics (Table 1). The patients ranged in age from 12 to 50 years (mean age, 29.6 years), and 45% were female and 55% male. The mean duration of seasonal AR was 22.2 months in the rupatadine group and 18.2 months in the levocetirizine group.

Efficacy Analysis

Change in Total and Differential Counts

The results in Table 2 reveal that there was an 11.02% decrease (P < .001) in total leukocyte count in the rupatadine group compared with 5.88% (P = .06) in the levocetirizine group. When the mean differences in the 2 groups were compared with the t test, the change was not statistically significant (P = .10). The change in neutrophil count in the levocetirizine group was not statistically significant (P = .052), but there was a significant decrease (P = .007) in the rupatadine group. There was a 32.95% decrease in eosinophil count in the rupatadine group compared with 22.59% in the levocetirizine group. The changes in both rupatadine and levocetirizine groups were statistically significant, and when the mean differ-

Table 1. Baseline Demographic Data and Clinical Characteristics of 60 Patients With Seasonal Allergic Rhinitis at the First Visit

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rupatadine Group</th>
<th>Levocetirizine Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients recruited, No.</td>
<td>30</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Patients at follow-up, No.</td>
<td>26</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Female sex, %</td>
<td>43</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>31.6 (10.9)</td>
<td>27.5 (10.7)</td>
<td>.10</td>
</tr>
<tr>
<td>Duration of allergic rhinitis, mean (SD), mo</td>
<td>22.2 (13.1)</td>
<td>18.2 (11.4)</td>
<td>.27</td>
</tr>
<tr>
<td>TLC, mean (SD), µL</td>
<td>9457.69 (1696.15)</td>
<td>9044.00 (2043.50)</td>
<td>.44</td>
</tr>
<tr>
<td>Differential neutrophil count, mean (SD), %</td>
<td>62.46 (5.57)</td>
<td>63.36 (5.03)</td>
<td>.55</td>
</tr>
<tr>
<td>Differential eosinophil count, mean (SD), %</td>
<td>6.89 (1.86)</td>
<td>7.08 (2.16)</td>
<td>.89</td>
</tr>
<tr>
<td>Absolute eosinophil count, mean (SD), µL</td>
<td>649.19 (205.66)</td>
<td>647.32 (279.13)</td>
<td>.73</td>
</tr>
<tr>
<td>IgE, mean (SD), IU/mL</td>
<td>339.46 (74.35)</td>
<td>319.12 (85.64)</td>
<td>.37</td>
</tr>
<tr>
<td>TNSS, mean (SD)</td>
<td>15.0 (3.4)</td>
<td>13.8 (2.8)</td>
<td>.14</td>
</tr>
<tr>
<td>RQLQ score, mean (SD)</td>
<td>3.65 (1.25)</td>
<td>3.12 (0.89)</td>
<td>.11</td>
</tr>
</tbody>
</table>

Abbreviations: RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; TLC, total leukocyte count; TNSS, Total Nasal Symptom Score.

Table 2. Change in Different Parameters Over 2 Weeks in Study Groupsa

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rupatadine Fumarate Group</th>
<th>Levocetirizine Dihydrochloride Group</th>
<th>Difference Between the Groups</th>
<th>P Valueb</th>
<th>95% CI</th>
<th>P Valuec</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Visit</td>
<td>Second Visit</td>
<td>Mean Difference of Rupatadine</td>
<td>Mean Difference of Levocetirizine</td>
<td>P Valueb</td>
<td>95% CI</td>
<td>P Valuec</td>
</tr>
<tr>
<td>TLC</td>
<td>9457.69 (1696.15)</td>
<td>8415.39 (810.28)</td>
<td>−1042.30</td>
<td>&lt; .001</td>
<td>−1232.50 to 211.89</td>
<td>.10</td>
</tr>
<tr>
<td>Differential neutrophil count</td>
<td>62.46 (5.57)</td>
<td>59.50 (2.18)</td>
<td>−2.96</td>
<td>.007</td>
<td>−3.88 to 1.48</td>
<td>.37</td>
</tr>
<tr>
<td>Differential eosinophil count</td>
<td>6.89 (1.86)</td>
<td>4.62 (1.17)</td>
<td>−2.50</td>
<td>&lt; .001</td>
<td>−1.70 to −0.26</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Absolute eosinophil count</td>
<td>649.19 (205.66)</td>
<td>387.73 (104.97)</td>
<td>−301.90</td>
<td>&lt; .001</td>
<td>−232.10 to −37.90</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Serum IgE, IU/mL</td>
<td>339.46 (74.35)</td>
<td>286.19 (61.97)</td>
<td>−53.27</td>
<td>&lt; .001</td>
<td>−48.80 to −9.98</td>
<td>.004</td>
</tr>
<tr>
<td>TNSS</td>
<td>15.00 (3.35)</td>
<td>9.50 (2.37)</td>
<td>−5.27</td>
<td>&lt; .001</td>
<td>−2.24 to −0.81</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>RQLQ score</td>
<td>3.65 (1.25)</td>
<td>2.99 (0.92)</td>
<td>−0.66</td>
<td>&lt; .001</td>
<td>−0.64 to −0.06</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; TLC, total leukocyte count; TNSS, Total Nasal Symptom Score.
a Data are given as mean (SD) unless otherwise specified. Values in bold are statistically significant.
b Paired t test.
c Unpaired t test.
ences in 2 groups were compared, the change in the rupatadine group was statistically significant (P < .001). The decrease in absolute eosinophil count in both rupatadine and levocetirizine groups was statistically significant, and when the mean differences in the 2 groups were compared, the change in the rupatadine group was statistically significant (P < .001).

**Change in Serum IgE Level**

Serum IgE levels were measured at both visits, and the results are given in Table 2. In the rupatadine group, there was a reduction of 15.69% in IgE level compared with 7.55% in the levocetirizine group. The changes in both the groups were statistically significant. The comparative analysis of the mean differences in individual group were also statistically significant (P = .004).

**Change in TNSS**

The TNSSs were calculated at both visits. The results given in Table 2 reveal that there was a 36.67% decrease in TNSS in the rupatadine group compared with 18.02% in the levocetirizine group, and these changes in individual groups were statistically significant. A comparison of the mean differences was also statistically significant (P < .001). By considering a 25% decrease in TNSS as clinically significant, we found that 21 patients in the rupatadine group and 12 patients in the levocetirizine group showed clinically significant improvement. These findings were put in a 2 × 2 contingency table and tested by the Fischer test and were statistically significant (P = .02).

**Change in RQLQ Score**

The changes in the RQLQ score are given in Table 2, which shows that there was a decrease of 18.08% in the rupatadine group compared with 9.94% in the levocetirizine group. Both these changes were statistically significant. When the mean differences in the 2 groups were compared with the t test, the change in the rupatadine group was found to be statistically significant (P = .02). By considering a 25% decrease in RQLQ as clinically significant, we found that 17 patients in the rupatadine group and 8 patients in the levocetirizine group showed clinically significant improvement. These findings were put in a 2 × 2 contingency table and tested by the Fisher test and were statistically significant (P = .03).

**SAFETY ANALYSIS**

Both the drugs were well tolerated without any alarming adverse effects. In the levocetirizine group, 3 patients complained of drowsiness. One patient in each group complained of headache and fatigue. One patient in the rupatadine group and 2 patients in the levocetirizine group complained of dryness of mouth. Overall incidence of adverse effects was 11.5% in the rupatadine group, whereas it was 23.3% in the levocetirizine group.

According to Common Toxicity Criteria grading of adverse drug reactions, all the reported adverse effects were of grade 1 (mild) except in 2 patients. One patient in the rupatadine group complained of moderate headache, and 1 patient in the levocetirizine group complained of moderate dryness of mouth. Both the patients discontinued the treatment and were excluded from the study.

In this study, we found that differential and absolute eosinophil counts were significantly lowered by both drugs, but rupatadine was superior. In the rupatadine group there was a significantly higher reduction in IgE level than that in the levocetirizine group. There was a clinically and statistically significant decrease in TNSS and RQLQ score with rupatadine compared with levocetirizine. The incidence of adverse effects was lower in the rupatadine group than in the levocetirizine group.

This outdoor-based study was conducted at the Prathima Institute of Medical Sciences, Naganur, Karimnagar, Andhrapradesh, India, which is a tertiary care center. Most of the patients were from the district of Karimnagar, and a few were from Warangal and Adilabad, making the study population homogenous with minimum ethnic variation. In our study groups, most of the patients had history of the disease for at least 2 consecutive seasons when rhinitis is aggravated, which is why we have chosen the winter months (November-January) for conducting this study. The baseline data show that there is no statistically significant difference between the study groups with respect to demographic and clinical parameters.

Any allergic condition usually affects the percentage of eosinophils and its absolute count, which is probably why the effects of the drugs have not been directly reflected on total leukocyte count and neutrophil count. From the comparative changes in differential eosinophil count, we can conclude that there was better control of this hematological marker of AR with rupatadine compared with levocetirizine. In AR, absolute eosinophil count is performed routinely because it is a better parameter than differential eosinophil count. Because eosinophil is a major blood cell participating in any allergic reaction, a strict control of it is one of the important therapeutic modalities. In our study, rupatadine was superior in this aspect.

A diagnosis of allergy can be established in more than 90% of cases by estimating serum IgE level. Because AR is an IgE-mediated immunological response, treatment strategies depend on modulation of the immune response to interfere with the function of IgE antibodies. Rupatadine also proved to be better than levocetirizine in reducing IgE level.

The TNSS is a tool that reflects the severity of the symptoms in AR. Because our basic goal of treating AR is symptomatic relief, a significant decrease in TNSS has prognostic importance, and rupatadine was found to have an edge over levocetirizine.

The RQLQ was developed to measure the problems (physical, emotional, and social) of the patients with rhinoconjunctivitis experienced in day-to-day life. To ensure a decent quality of life, a reduction of RQLQ score is mandatory. In this study, rupatadine has been proved
models. Rupatadine, in addition, has anti-inflammatory (ie, mast cell degranulation inhibition, eosinophil chemotaxis) and in vivo in several type I hypersensitivity (H1 receptor and platelet-activating factor) antagonist and showed potent antiallergic activity in vitro and in vivo in several type I hypersensitivity models. Rupatadine is a mediator of early response, being released from preformed reservoirs in mast cells, whereas platelet-activating factor is mainly synthesized de novo. Furthermore, each of these mediators is able to promote the release of the other in some tissues and numerous target cells. So dual blockade of these mediators is likely to be a more effective treatment strategy for AR.

The superiority of rupatadine in this study may be attributed to its varied pharmacodynamic effects other than antihistaminic property. It is a platelet-activating factor antagonist and showed potent antiallergic activity in vitro (ie, mast cell degranulation inhibition, eosinophil chemotaxis) and in vivo in several type I hypersensitivity models. Rupatadine, in addition, has anti-inflammatory effects that act directly on the H1 receptor. Rupatadine has a high H1 receptor–binding affinity, which allows the molecule to inhibit the histamine-induced interleukin 6 and interleukin 8 production using concentrations that are below the plasma levels reached at the therapeutic dose.

In conclusion, from the results of the present comparative clinical analysis of rupatadine and levocetirizine, we conclude that rupatadine is a better choice in seasonal AR compared with levocetirizine owing to its better efficacy and safety profile. Because nonblinding was a limitation, the findings of this exploratory study should be confirmed by multicentric, randomized, double-blind, large population studies.

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Author Contributions: Dr Maiti had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Maiti, Jaida, and Palani. Acquisition of data: Rahman and Allala. Analysis and interpretation of data: Maiti. Drafting of the manuscript: Maiti and Allala. Critical revision of the manuscript for important intellectual content: Maiti, Rahman, Jaida, and Palani. Statistical analysis: Maiti. Administrative, technical, and material support: Allala. Study supervision: Rahman, Jaida, and Palani.

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