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Original Research Article

Expert opinion on the prescription practice of antihistamines for the management of allergic rhinitis in Indian settings

S Manjula^{1*}, M Krishna Kumar¹¹Dept. of Medical Services, Micro Labs Limited, Bangalore, Karnataka, India

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ABSTRACT

Background: Several clinical studies corroborate the synergistic effects of montelukast in conjunction with antihistamine for reducing the symptoms and quality of life of AR patients. Some studies also highlighted a significant quantitative differences in the prescribing patterns of antihistamines across different countries. So, this study aimed to gather expert opinions on the management of allergic rhinitis (AR) using antihistamines alone or in various combinations in Indian settings.

Materials and Methods: The cross-sectional, multiple-response, 23-item survey was primarily focused on current practices, clinical observations, and experiences related to AR and the utilization of oral histamines for disease management. The study involved otorhinolaryngologist from diverse settings in India.

Results: Out of 435 participants, 29% reported sneezing as the common AR symptoms. The majority (84.83%) favoured antihistamine and leukotriene receptor antagonist combinations for AR treatment. Specifically, 52% preferred levocetirizine, while 43% favoured fexofenadine. About 63% opted for polytherapy with oral antihistamines and anti-leukotrienes for AR management. Of these, 48% chose levocetirizine and montelukast for various AR symptoms. According to 60% of participants, fexofenadine + montelukast effectively improved nasal and eye symptoms. Around 64% preferred levocetirizine + montelukast for nighttime nasal symptoms, while 55% chose fexofenadine + montelukast for daytime nasal symptoms. Around 64% of the respondents favoured levocetirizine + montelukast for improving all AR symptoms, and 69% favoured antihistamine + montelukast for its cost-effectiveness.

Conclusion: Experts recommend antihistamine and leukotriene receptor antagonist combinations for managing AR symptoms, with levocetirizine and fexofenadine being popular choices. Polytherapy with these combinations was favoured, especially for managing nighttime and daytime nasal symptoms.

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1. Introduction

Allergic rhinitis (AR) is a major public health concern, affecting 400 million subjects globally.¹ Approximately 55% of the allergies diagnosed in India are classified as AR, and the associated symptoms can interfere with cognitive and emotional functioning, significantly impacting the patient's quality of life.^{2,3} Decongestants, intranasal corticosteroids, leukotriene receptor antagonists, and

oral/intranasal H1-antihistamines were the cornerstones of AR therapy. The increasing popularity of second-generation antihistamines could be attributed to comparable efficacy and decreased incidence of side effects as compared to their first-generation counterparts.⁴ Levocetirizine, a potent second-generation H1 receptor antagonist, effectively treats persistent AR, improving the quality of life and reducing comorbidities and societal costs.⁵ Montelukast, an extremely selective leukotriene D4 type I receptor antagonist, combines bronchodilator and anti-inflammatory properties.⁶

* Corresponding author.

E-mail address: drmanjulas@gmail.com (S. Manjula).

Clinical studies corroborates the synergistic effects of montelukast in conjunction with antihistamine for reducing the symptoms of AR.^{7,8} Compared to levocetirizine monotherapy, concurrent treatment with montelukast improves both symptoms and the quality of life in individuals with AR.⁹ Additionally, the combination of fexofenadine and montelukast has been reported to have better efficacy than antihistamine drugs alone in controlling AR symptoms.¹⁰ Some studies also highlighted that there was a significant quantitative differences in the prescribing patterns of antihistamines across different countries.¹¹ The current survey aims to gather expert opinions on the use of antihistamines alone or in various combinations for the management of AR in Indian settings.

2. Materials and Methods

This was a clinician's perspectives based cross sectional study where we conducted a multiple-response questionnaire based survey among otorhinolaryngologists with experience in treating AR in the major Indian cities from June 2022 to December 2022.

2.1. Questionnaire

The questionnaire booklet named LAMINAR (Levocetirizine + Montelukast And Montelukast + Fexofenadine in the management of Allergic Rhinitis) study was sent to the otorhinolaryngologists who were interested to participate. The LAMINAR questionnaire booklet consisted of 23 questions, with the majority of them focused on the current practices, clinical observations, and experiences related to AR and the use of oral histamines for managing the disease. The study was conducted after receiving approval from Bangalore Ethics, an Independent Ethics Committee which was recognized by the Indian Regulatory Authority, Drug Controller General of India.

2.2. Participants

An invitation was sent to leading otorhinolaryngologists in managing AR in the month of March 2022 for participation in this Indian survey. About 435 allergy experts from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. Otorhinolaryngologists were requested to complete the questionnaire without discussing with peers. A written informed consent was obtained from each allergists prior initiation of the study.

2.3. Statistical analysis

Descriptive statistics were used to analyze the data, with percentages representing categorical variables. The distribution of each variable was illustrated using both frequency and percentage distributions. Furthermore,

bar charts were generated using Excel 2013 (version 16.0.13901.20400) to visually represent the data findings.

3. Results

Of 435 participants, 29% reported sneezing as the common symptom observed in AR, followed by congestion and running nose by 26%, and 23% of the respondents respectively (Figure 1).

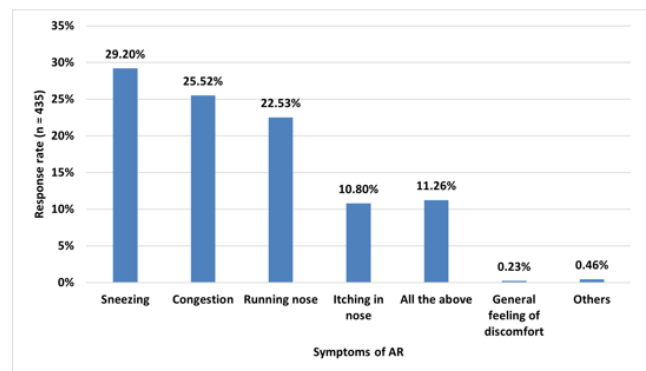


Figure 1: Response to the common symptoms observed in AR in routine practice

The majority of the participants (84.83%) preferred combinations of antihistamines and leukotriene receptor antagonists for the treatment of AR (Table 1). Specifically, 52% of the respondents favoured levocetirizine for AR management, while 43% preferred fexofenadine (Table 2). Approximately 63% of the respondents opted for polytherapy involving the combination of oral antihistamines and anti-leukotrienes for the management of AR. As per the survey, the most preferred antihistamine combination for AR management was levocetirizine + montelukast (46%), followed by fexofenadine + montelukast (22%).

Table 1: Response on the preferred choice of treatment for the management of AR in routine practice

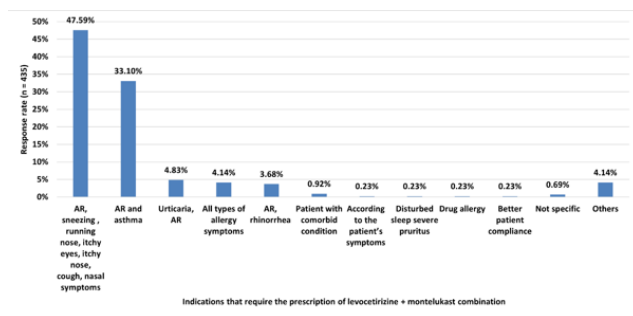
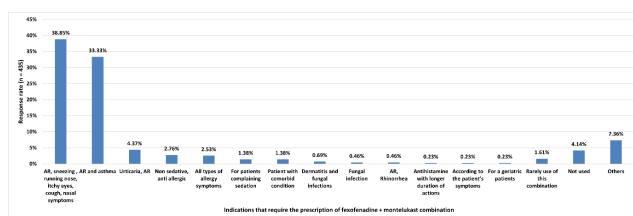
| Preferred choice of treatment for the management of AR | Response rate (n = 435) |
|---|-------------------------|
| Only antihistamine | 9 (2.07%) |
| Leukotriene receptor antagonists | 52 (11.95%) |
| Combination of antihistamine and leukotriene receptor antagonists | 369 (84.83%) |
| Intranasal corticosteroid sprays | 1 (0.23%) |
| Nasal spray with antihistamines | 2 (0.46%) |
| Others | 2 (0.46%) |

Approximately 48% of the participants preferred the combination of levocetirizine and montelukast for treating symptoms such as AR sneezing, runny nose, itchy eyes and nose, cough, and nasal symptoms. However, 33% of the participants favoured this combination for managing

Table 2: Response on the preferred antihistamine for the management of AR in routine practice

| Preference of antihistamine for the management of AR | Response rate (n = 435) |
|--|-------------------------|
| Fexofenadine | 187 (42.99%) |
| Levocetirizine | 227 (52.18%) |
| Bilastine | 11 (2.53%) |
| Ebastine | 4 (0.92%) |
| Others | 6 (1.38%) |

AR and asthma (Figure 2). On the other hand, 39% of the respondents opted for the fexofenadine and montelukast combination to address symptoms of AR, sneezing, runny nose, itchy eyes, itchy nose, cough, and nasal symptoms. Similarly, 33% of the respondents preferred this combination for managing AR and asthma (Figure 3). It was worth noting that 51% of the respondents preferred using levocetirizine and montelukast for 1-4 weeks, while 40% of them favoured the fexofenadine and montelukast combination for the same time frame.

**Figure 2:** Response to the indications that require the prescription of levocetirizine + montelukast combination in routine practice**Figure 3:** Response to the indications that require the prescription of fexofenadine + montelukast combination in routine practice

Among the respondents, 52% preferred the levocetirizine + montelukast combination, while 39% suggested the fexofenadine + montelukast combination for alleviating nasal congestion (Table 2). According to 60% of the participants, the use of fexofenadine + montelukast combination was effective in improving the daytime and nighttime nasal symptoms as well as daytime eye symptoms.

Table 3: Response on the medications used alone or in combination for the improvement in nasal congestion in routine practice

| Medications | Response rate (n = 435) |
|---------------------------------|-------------------------|
| Levocetirizine + montelukast | 227 (52.18%) |
| Fexofenadine + montelukast | 168 (38.62%) |
| Bilastine + montelukast | 31 (7.13%) |
| All the above | 3 (0.69%) |
| Deflazacort | 1 (0.23%) |
| Intranasal corticosteroid spray | 3 (0.69%) |
| Others | 2 (0.46%) |

Approximately, 64% of the participants preferred the levocetirizine + montelukast combination for the management of nighttime nasal symptoms whereas, fexofenadine + montelukast combination was preferred by 55% of the respondents for the management of daytime nasal symptoms (Table 3). Around 64% of the respondents considered the effectiveness of levocetirizine + montelukast in treating all AR symptoms as the key advantage when prescribing the drug, and 69% opted for the antihistamine + montelukast combination due to its cost-effectiveness. Furthermore, around 56% of the respondents preferred the 10-tablet package for the antihistamine + montelukast combination when prescribing to AR patients, while 30% of the respondents favoured the 15-tablet package.(Table 4)

Table 4: Response to the recommended medications for improving day and nighttime symptoms in clinical practice

| Medications for improving day and night time symptoms | Response rate (n = 435) | |
|---|-------------------------|--------------------------|
| | Daytime nasal symptoms | Nighttime nasal symptoms |
| Levocetirizine + montelukast | 159 (36.55%) | 278 (63.91%) |
| Fexofenadine + montelukast | 240 (55.17%) | 121 (27.82%) |
| Bilastine + montelukast | 29 (6.67%) | 25 (5.75%) |
| All the above | 1 (0.23%) | 4 (0.92%) |
| Nasal corticosteroid | 2 (0.46%) | 0 |
| Cetirizine + phenylephrine | 0 | 1 (0.23%) |
| Not tried in children | 0 | 1 (0.23%) |
| Not attempted | 4 (0.92%) | 5 (1.15%) |

4. Discussion

The current survey highlights the preference and effectiveness of leukotriene receptor antagonists and antihistamine combinations for managing AR in routine clinical practice. As per the current survey, levocetirizine + montelukast was highly preferred for nighttime symptoms, possibly due to its effectiveness in promoting better sleep

quality. While fexofenadine + montelukast was favoured for managing daytime symptoms, indicating its effectiveness in providing relief for daily activities. This indicated that the side effect of sedation with first generation antihistamines which perfectly suited for nighttime symptoms whereas the newer generation antihistamines taken irrespective of time because of minimal effects on sedation.¹² A study conducted by Xu et al. supported these findings, suggested that selective H1-antihistamines and leukotriene receptor antagonists were both safe and effective for treating systemic AR. However, selective H1-antihistamines were better suited for managing daytime nasal symptoms, including congestion, rhinorrhea, pruritus, and sneezing. In contrast, leukotriene receptor antagonists were more effective for addressing nighttime symptoms like difficulty falling asleep, nocturnal awakenings, and nasal congestion upon awakening.¹³ Additionally, Liu et al. found that leukotriene receptor antagonists combined with H1-antihistamines can enhance the effectiveness of treatment against daytime nasal symptoms such as sneezing, itching, and rhinorrhea. However, this combination may not be as effective for managing nighttime nasal symptoms or ocular symptoms. These findings suggested that a combined therapy approach may be more beneficial for individuals with persistent AR.¹⁴

In the current survey, most of the respondents favoured polytherapy using the combination of oral antihistamine and oral antileukotriene for the treatment of AR, especially levocetirizine and montelukast. This preference was supported by the findings of Adsule and Misra, who reported the superiority of the levocetirizine and montelukast combination in the treatment of persistent AR compared to montelukast monotherapy alone.⁵ Furthermore, studies corroborated the efficacy of this combination for treating nasal symptoms of patients suffering from AR.^{15,16} Importantly, the international consensus statement on allergy and rhinology also pointed out that the combination of oral antihistamine with LTRA was superior in symptom reduction and quality of life (QOL) improvement compared to placebo and to either agent as monotherapy.¹⁷ Notably, a significant proportion of current survey respondents favoured the combination of fexofenadine and montelukast for relieving daytime nasal symptoms. In contrast, the combination of levocetirizine and montelukast was favoured for the treatment of nighttime nasal symptoms. In relation to the Allergic rhinitis and its impact on asthma (ARIA) guidelines, Almousa H et al. highlighted 82% of the clinicians preferred second generation oral antihistamines were considered safe which further supported the benefits of newer generation oral antihistamines.¹⁸

Current survey findings confirmed the benefits of combining an antihistamine with montelukast. This combined therapy effectively reduced symptoms and

offers complementary and enhancing effects. Adsule and Misra demonstrated that when levocetirizine and montelukast were used together, they produce more favourable effects on AR symptoms and quality of life compared to using levocetirizine alone.⁵ Cingi et al. also indicated that for treating AR symptoms, the combination of fexofenadine and montelukast was more beneficial than using antihistamines alone.¹⁹ Literature review showed that there was a scarcity of studies comparing the montelukast-levocetirizine combination with the montelukast-fexofenadine combination in AR patients. In a randomised controlled trial conducted by Mahatme et al., it was found that although the decrease in Total Nasal Symptom Score was higher in the montelukast-fexofenadine group, the montelukast-levocetirizine combination was found to be more cost-effective. The current survey findings further validated these findings with the help of clinicians.²⁰

These findings not only supported but also expanded upon previous research, demonstrating the safety and effectiveness of the leukotriene receptor antagonists and antihistamine combinations in the treatment of AR among Indian patients. The survey emphasized the clinical utility of such combinations in enhancing AR symptoms and the overall quality of life. The primary strengths of the study include a larger sample size of 435 specialists, the incorporation of expert opinions from knowledgeable allergy practitioners, and a comprehensive evaluation of the efficacy of different antihistamine combinations. Moreover, the survey recognized the importance of tailoring therapeutic choices to individual patient characteristics to achieve the best possible treatment outcomes. It was also important to acknowledge the limitations of the survey. The utilization of self-reported data could have introduced response bias and recollection bias, potentially impacting the representativeness of the sample. Furthermore, the non-randomized design of the study limited the ability to establish causality. To gain a more comprehensive perspective, it was paramount to consider these findings in light of these associated limitations.

5. Conclusion

Experts recommended the combinations of levocetirizine + montelukast and fexofenadine + montelukast to manage AR patients experiencing symptoms such as a runny nose, itchy eyes, coughing, and nasal congestion. Levocetirizine and montelukast were preferred for treating nighttime nasal symptoms, while fexofenadine and montelukast were recommended for daytime nasal symptoms. Clinicians also endorsed the combination of levocetirizine and montelukast for relieving nasal congestion.

6. Source of funding

None.

7. Conflict of Interest

None.

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Author biography

S Manjula, Senior Vice President  <https://orcid.org/0000-0001-9402-7244>

M Krishna Kumar, Senior General Manager  <https://orcid.org/0000-0002-8004-5297>

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