Assessment of cost effectiveness of antihistaminics in allergic rhinitis patients in rural region by Nasal cytology: a simple and inexpensive tool

Ganesh S. Pentewar*, Ranjit J. Wagh, Aparna S. Chincholkar

INTRODUCTION

Allergic rhinitis (AR) is an IgE-mediated hypersensitivity reaction of nasal mucosa which is characterized by sneezing, itching, watery nasal discharge and a sensation of nasal obstruction. A characteristic feature of allergic inflammation is local accumulation of inflammatory cells including T lymphocytes, mast cells, eosinophils, basophils and neutrophils.1 Release of various mediators from these cells is responsible for the symptoms of allergic rhinitis. Accumulation of additional inflammatory cells such as eosinophils and T cells occurs in response to various chemokines. These inflammatory cells can be easily identified in nasal mucosa or secretions by performing nasal biopsies and then, preparing nasal smears to confirm the diagnosis of allergic rhinitis. Moreover, these methods are simple, reproducible, easy to perform and cost effective as compared to other diagnostic tests for allergic rhinitis.2,3

The present study was planned to evaluate the diagnostic value of nasal smear as a simple, non-invasive and inexpensive method for diagnosing allergic rhinitis and used as a simple tool for comparing cost effectiveness among commonly used oral antihistaminics. Antihistaminic are effective in patients with allergic rhinitis having eosinophilia. When antihistaminic are given continuously

ABSTRACT

Background: This study was to assess the usefulness of nasal smear as a quick, easy and inexpensive diagnostic method for allergic rhinitis and for assessment of the cost effectiveness of antihistaminics.

Methods: This study was conducted in rural setting of tertiary care hospital. Nasal smears were taken from 52 patients with a clinical history of nasal allergy having nasal congestion score of at least 3 or more. Nasal smears were stained with Hematoxylin-Eosin and examined by pathologists.

Results: A total of 52 patients 13 in each groups of the age group 18 to 65 years (Mean age, 33.73±10.23 years); 48.08% are Female and 51.92% are Male were randomized and received either Cetirizine, Levocetirizine, Loratadine, or Fexofenadine over a period of one week. The association of eosinophil before and after the treatment was obtained using logistic regression analysis for each treatment separately. Eosinophil is marginally associated with Cetirizine before and after treatment.

Conclusions: Evaluation of eosinophils in nasal smear is an insensitive but cheaper test for the diagnosis of allergic rhinitis and use as a simple tool for comparison of cost effectiveness among commonly used oral antihistaminics. Pharmacoeconomic analysis of present comparative clinical study shows that cetirizine is a better choice in comparison with levocetirizine, loratidine and fexofenadine due to its cost effectiveness.

Keywords: Allergic rhinitis, Antihistaminics, Cost effectiveness, Eosinophilia, Nasal cytology

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for seven days. Clinical improvement is accompanied by decreases in numbers of effector cells in target organs eosinophil. In this research we explore correlation of eosinophilia and antihistaminic therapy for allergic rhinitis. Our expectation is that a greater understanding of the underlying mechanisms of allergens will identify potential biomarkers that could predict or monitor the response to treatment. The nasal mucosa is the most accessible for the non-invasive study part of the respiratory system. The nasal cytology is a research method evaluating cells located within it, and it is mainly used as an additional test in allergic rhinitis. This method allows to assess the pathophysiologic changes occurring in the nasal mucosa and monitor response to applied treatment and thus has both diagnostic and therapeutic values. An extremely precious feature of this research is its non-invasiveness and painlessness as it does not require any anaesthesia, and it is cheap and simple to make.

The aim of this study was to evaluate the cytological picture of nasal mucosa in allergic rhinitis and their correlation with antihistaminic treatment. In addition, the objective was also to determine the suitability of the nasal mucosa for the diagnosis of allergic rhinitis and assessment of cost effectiveness of antihistaminic in allergic rhinitis patients.

METHODS

The study enrolled a total of 52 allergic rhinitis patients. All patients enrolled in the study were patients of the Department of otorhinolaryngology, MIMER medical college, Talegaon Dabhade. The study was approved by the Institutional Ethical Committee (IEC). In order to ensure better reliability of the results, only patients clinically diagnosed with allergic rhinitis were eligible on the basis of nasal congestion score. They are divided into four different groups as per antihistaminic treatment.

- Group I consisted of a total of 13 patients, including 6 male and 7 females who received Cetirizine.
- Group II consisted of a total of 13 patients, including 4 male and 9 females who received Levocetirizine.
- Group III consisted of a total of 13 patients, including 7 male and 6 females who received Loratidine.
- Group IV consisted of a total of 13 patients, including 10 male and 3 females who received fexofenadine.

Exclusion criteria for patients in all groups, participating in the study were current respiratory tract infection, Patients with history of hypersensitivity to antihistaminics. Concomitant medication that could affect the efficacy of study drugs, chronic use of inhaled or systemic corticosteroids. Pregnant or lactating women, usage of nasal corticosteroids within 14 days, usage of antihistamines within 14 days preceding the survey. Each test was preceded by obtaining informed consent from the patient. In the case of the examination in the nasal cavity of the secretions, the sample was taken after purging the nose. In each patient, the material for cytological examination has been collected from the middle third of the inferior turbinate. The samples were taken from one nasal cavity with nasal scraping method (using a nasal curette) and then transferred to a microscopic slide. The samples were spread onto a slide glass, air-dried, fixed, and stained with Haematoxylin and Eosin stain (Merck Limited). The samples were then evaluated for the presence or absence of eosinophil by examining 45x magnification high power fields (HPFs) with Nikon Eclipse 50 I Pentahead microscope (Nikon Corporation, Japan).

The analysis was based on identifying in successive fields of the presence of particular cell types: ciliated and non-ciliated columnar cells, mucous (goblet) cells, basal, and squamous cells, neutrophils and eosinophils. No adverse effects were observed in any patient which could result from the research itself.

Efficacy variable

- Mean change in % of eosinophil in nasal smear from Baseline to End of treatment.
- Cost effectiveness analysis.

Statistical analysis was performed using the statistical software Microsoft SPSS 19.0. (SPSS Inc., Chicago, USA). Data was summarized using Mean, Median and Standard Deviation. Mean change in Nasal smear for eosinophil before and after treatment were done. Statistical differences were considered statistically significant for which the level of statistical significance fulfilled the condition of p < 0.05. Logistic regression analysis and odds ratio were used for analysis of qualitative data. The statistician was blinded to the groups during analysis.

RESULTS

A total of 52 patients 13 in each groups of the age group 18 to 65 years (Mean age, 33.73±10.23 years); 48.08% are Female and 51.92% are Male were randomized and received either Cetirizine, Levocetirizine, Loratadine, or Fexofenadine over a period of one week. Mean compliance with treatment was 100% for all four treatment groups. The baseline demographic data and clinical characteristics of all 52 patients participated in this study have been compared in the Table 1. The association of eosinophil before and after the treatment was obtained using logistic regression analysis for each treatment separately in the Table 2. Eosinophil is marginally associated with Cetirizine before and after treatment and has been have been compared in the Figure 1 and Figure 2.

Average cost-effectiveness calculations

The average cost effectiveness = Net Cost (Rupees ₹) / Net Health Benefit = ₹ / %. Mean change in nasal smear eosinophil

The average cost effectiveness of intervention for Cetirizine = Net Cost/ Net Health Benefit = ₹26.25 / 0.4= ₹ 65.625 per cure
Table 1: Comparison of demographic data and clinical characteristics of the patients participated in the study (n=52).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cetirizine (n=13)</th>
<th>Levocetirizine (n=13)</th>
<th>Loratadine (n=13)</th>
<th>F</th>
<th>p’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31.85±9.45</td>
<td>39.38±14.39</td>
<td>32±1.011</td>
<td>31.69±7.22</td>
<td>1.858</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>6 (46.16%)</td>
<td>4 (30.77%)</td>
<td>7 (53.84%)</td>
<td>10 (76.92%)</td>
<td>3 (23.08%)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>7 (53.84%)</td>
<td>9 (69.23%)</td>
<td>6 (46.16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCS</td>
<td>4.46 ± 0.66</td>
<td>3.87 ± 0.68</td>
<td>4 ± 0.82</td>
<td>4.15 ± 0.55</td>
<td>1.905</td>
</tr>
</tbody>
</table>

The values are expressed as mean±SD, NCS = Nasal congestion score, *one way ANOVA

Table 2: Comparison of Eosinophil in Nasal secretion smear baseline and at the end of each treatment.

<table>
<thead>
<tr>
<th>Groups(n=13)</th>
<th>Baseline</th>
<th>End of treatment</th>
<th>Total</th>
<th>Odds</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetirizine</td>
<td>Absent</td>
<td>7</td>
<td>2</td>
<td>9</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>8</td>
<td>5</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>Absent</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>8</td>
<td>5</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Loratadine</td>
<td>Absent</td>
<td>5</td>
<td>3</td>
<td>8</td>
<td>6.67</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>6</td>
<td>7</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>Absent</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>5.79</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>4</td>
<td>9</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

n=13 patient

The association of eosinophil before and after the treatment was obtained using logistic regression analysis for each treatment separately. Eosinophil is marginally associated with Cetirizine before and after treatment.

Table 3: Pharmacoeconomic assessments (cost effectiveness analysis).

<table>
<thead>
<tr>
<th>Methods</th>
<th>Cetirizine</th>
<th>Levocetirizine</th>
<th>Loratadine</th>
<th>Fexofenadine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method 1</td>
<td>Net Cost (at the end of 1 week treatment)</td>
<td>₹ 26.25</td>
<td>₹ 29.46</td>
<td>₹ 39.84</td>
</tr>
<tr>
<td>Cost consequence Analysis (CCA)</td>
<td>Net health benefit (% Mean change in nasal smear eosinophil)</td>
<td>40</td>
<td>40</td>
<td>42.85</td>
</tr>
<tr>
<td>Method 2</td>
<td>Average Cost Effectiveness Ratios (net cost/ net health benefit)</td>
<td>₹ 26.25 / 0.4</td>
<td>₹ 29.46 / 0.4</td>
<td>₹ 39.84 / 0.4285</td>
</tr>
<tr>
<td></td>
<td>= ₹ 65.625 per cure</td>
<td>= ₹ 73.65 per cure</td>
<td>= ₹ 92.97 per cure</td>
<td>= ₹ 170.03 per cure</td>
</tr>
</tbody>
</table>

Using this same means of calculation, the average cost effectiveness for intervention has been done for other treatment groups. The average cost effectiveness of intervention for Levocetirizine was ₹ 73.65 per cure, Loratadine was ₹ 92.97 per cure and for Fexofenadine was ₹ 170.03 per cure (Table 3).

Cost effectiveness analysis

In Noncompeting choice, Cetirizine should be covered first because it has the best (lowest) cost-effectiveness ratio compared to the other interventions (i.e. ₹ 65.625 / % effect vs ₹ 73.65 / % effect or ₹ 92.97 / % effect or ₹ 170.03 / % effect). This would be a more efficient way of spending money rather than starting with one of the other interventions that has a higher average cost-effectiveness ratio without any additional benefit (Table 3).

In competing choice method of cost-effectiveness analysis the incremental cost-effectiveness ratio has been done. This would allow to determine the marginal or incremental cost for an additional unit of health benefit when choosing between different interventions. But in this study there were no any additional health benefit by choosing other
antihistaminics vs cetirizine so incremental cost-effectiveness ratio has not been done. Infiltration of inflammatory cells to the nasal mucosa. Inflammation of nasal mucosal epithelial cells by antihistaminics and/or nasal antihistaminics has been studied for specific allergic rhinitis, but not for general rhinitis. The present study has determined the correlation of allergic rhinitis with the degree of eosinophilia. As a positive test, 

**Figure 1: Microphotograph of nasal smear at baseline of an AR patient (ABT13, FL308/13) receiving Cetirizine, showing clumps of mucosal epithelial cells along with eosinophils (H and E 40X).**

**Figure 2: Microphotograph of nasal smear at the end of treatment of an AR patient (AAT13, FL326/13) receiving Cetirizine, showing clumps of mucosal epithelial cells, no eosinophil seen (H and E 10X).**

**DISCUSSION**

The demographic characteristics of the study participants and the baseline symptom scores i.e. Nasal Congestion Score prior to dosing were comparable among the four treatment groups (Table 1). Rhinitis is a heterogeneous disorder characterized by one or more of the following nasal symptoms: sneezing, itching, rhinorrea, and/or nasal congestion. Studies reflect a more accurate prevalence of rhinitis but are likely to continue to underreport this disease. Approximately 50% of all cases of rhinitis are caused by an IgE mediated reaction to allergens. In this case symptoms arise as a result of local inflammation induced by aeroallergens such as pollens, molds, animal dander and house dust mites. The immune response involves the release of inflammatory mediators and the activation and recruitment of different inflammatory cells to the nasal mucosa. Inflammation of nasal mucosal epithelial cells by antihistaminics has been studied for specific allergic rhinitis, but not for general rhinitis. The present study has determined the correlation of allergic rhinitis with the degree of eosinophilia. As a positive test,
A smear was considered positive for eosinophilia with at least more than five eosinophils in each high power field of microscopic slide. By analyzing individual studies evaluating the problem of eosinophilia in the cytological picture, one can see the differences in the very definition of the term “significant eosinophilia.” This range is wide and it is ranging from 4% of all cells in Miller et al, Vaidya et al, found eosinophilia in at least 5% of these cells in the cytogram.24,25

A similar analysis was made by Miller et al, however assuming 4% as a criterion for eosinophilia. In their work, the sensitivity of the study in allergic rhinitis was 70%, with a specificity of 94%.24 In the Bakhshaei et al, study, eosinophilia diagnosis was assessed as a highly specific (88.5%) but less sensitive (51.3%) in the cytological examination of the nasal mucosa in patients with AR, with eosinophil counts of at least 10% number of cells in the smear.2

CONCLUSION

Based on the results of the study, the presence of eosinophil in nasal cytology is a good indicator of the likelihood of allergic rhinitis and in combination with other diagnostic tests leading to proper diagnosis. Nasal cytology with eosinophilia assessment can be a useful tool for early diagnosis of allergic rhinitis patients. Nasal cytology with allergic rhinitis is a helpful diagnostic test, usefulness of nasal cytology is limited due to the low sensitivity of the method and this inexpensive tool can be used for cost effective analysis of different drugs used commonly for the treatment of allergic rhinitis. It is worth emphasizing that until now, there have not been established any standards for testing and analysis of samples and that there is no consensus defining the value of “significant eosinophilia” in the nasal cytology.

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