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Original Research Article

Pharmacoeconomic assessment and comparing efficacy between cetirizine, levocetirizine, loratadine and fexofenadine in allergic rhinitis patients

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ABSTRACT

Background: A successful treatment of allergic rhinitis is considered not only as relief from sneezing, itching, rhinorrhoea, congestion but also as the functional impact on the patient's daily life. The cost of treating allergic rhinitis and indirect costs related to loss of workplace productivity are substantial.
Methods: The present study was single centered, open label, randomized, four Arm, parallel-group, comparative clinical study between orally administered Cetirizine, Levocetirizine, Loratadine and Fexofenatidine in patients with allergic rhinitis conducted at MIMER Medical college and Dr. Bhausaheb Sardesai hospital in rural Maval Taluka in Pune district of Maharashtra State.
Results: Total Nasal Symptom Score differs significantly for all the treatment groups. Subsequent pairwise contrasts using a Bonferroni adjustment reveals maximum reduction of symptoms in Levocetirizine group. Cost effectiveness ratio was effective for Levocetirizine followed by Cetirizine, Loratadine, and Fexofenadine.
Conclusions: From the analysis of results, the study shows that both Levocetirizine and Cetirizine control the symptoms of allergic rhinitis better as compared to Loratadine and Fexofenadine but Levocetirizine was a better choice in comparison to others due to its cost effectiveness.

Keywords: Allergic rhinitis, Cetirizine, Fexofenadine, Loratadine, Levocetirizine, Pharmacoeconomic assessment, Total nasal symptom score

INTRODUCTION

Allergic rhinitis (AR) is an inflammatory disease of the nasal mucosa induced by an allergen. The disorder is clinically characterized by nasal itching, sneezing, nasal congestion or stuffiness and rhinorrhea or runny nose that are reversible either spontaneously or as a result of treatment. AR is a global health problem, with a prevalence of between 9-42% among the general population. In India allergic rhinitis is the commonest form of allergy and constitutes more than 50% of all allergies seen in clinical practice.[1-3] Medicines are the most common therapeutic intervention and form a small but significant proportion of total health care cost. Cost of medicines are growing constantly due to the availability of patented new drugs, preference of drug therapy over invasive therapy, discovering various off label uses of existing drugs and the irrational drug prescription.[4] The direct cost of treating allergic rhinitis and the indirect cost related to loss of workplace productivity resulting from the disease are substantial. Rhinitis is also a significant cause of lost school attendance. Patients are affected by the high pricing of drugs and though the symptoms improve, the poor patient's compliance sets in if the regimen is heavy on the pocket.[5,6] Knowledge of the concepts of pharmacoeconomics are therefore essential for physicians to prescribe individualized drug therapy based on essential drug concept i.e. STEP (suitability, tolerance, efficacy and

price of the drug) as well as rational utilization of the drug (RUD) criteria, with minimal costs to improve the cost-effectiveness of the drug therapy.[7] The present study is aimed to compare the efficacy and cost effectiveness between the four most common orally used second generation antihistaminics, viz. Cetirizine, Levocetirizine, Loratadine, Fexofenadine.[8]

METHODS

The present study was single centered, open label, Randomized, Four Arm, parallel-group, comparative clinical study between orally administered Cetirizine, Levocetirizine, Loratadine and Fexofenatidine in patients with Allergic Rhinitis (AR) conducted at MIMER Medical college and Dr. Bhausaheb Sardesai hospital in rural Maval Taluka in Pune district of Maharashtra State.

Enrollment

The study was approved by Institutional Ethical Committee. Patients diagnosed as AR were identified from the ear nose and throat out patient department (ENT OPD). Once identified, they were briefed about the study and activities.

If they were apparently willing to take part in the study, a copy of a patient information sheet and informed consent form was given to patient. A copy of the patient diary was issued to patient and asked them to record nasal symptoms as per instruction.

Inclusion criteria

Patients were ought to meet all of the inclusion criteria.

- Patient with a clinical history of AR.
- Patients aged above 18 years inclusive of either sex.
- The combined score of Total nasal symptoms score (TNSS) (nasal congestion, rhinorrhea, nasal itching, sneezing) sum of morning and evening symptom score must be at least 8 and nasal congestion severity score (NCS) sum of morning and evening congestion score must be at least 3 at screening.[9]
- Patient with ability to understand and sign written informed consent form.
- Patients willing to comply with the protocol requirements.

Exclusion criteria

- Known hypersensitivity to antihistaminics.
- Alcohol or drug dependence.
- Concomitant medications that could affect the efficacy of study drugs.
- Clinically significant nasal disease (other than AR) or significant nasal structural abnormalities including nasal polyps; clinically relevant respiratory tract malformations; recent nasal biopsy (within 2 months); nasal trauma; nasal surgery; atrophic rhinitis.
- Asthma requiring chronic use of inhaled or systemic corticosteroids, routine use of beta-2 agonists.
- Respiratory tract infection or disorder within 2 weeks of the first visit or a respiratory tract infection during first visit;
- Antibiotics for acute conditions within 2 weeks of the first visit.
- Pregnant or lactating women.
- Psychiatric illness.
- Topical corticosteroids in concentrations in excess of 1% hydrocortisone for dermatological conditions within 1 month of study initiation.

Randomization

A total of 52 patients (13 per each group) were assigned sequentially to each of the 4 study groups.

All the study patients received their respective medication orally daily in the evening for 1 week period.

- Group A- Tab Cetirizine Hydrochloride 10mg
- Group B- Tab Levocetirizine Hydrochloride 5mg
- Group C- Tab Loratadine 10mg
- Group D- Tab Fexofenadine Hydrochloride 120mg

Visit 1: Baseline screening and randomization to study treatment group (day 1)

Following procedures were performed on the first day of the subject enrolment:

1. Medical history
2. Physical Examination and Vital signs
3. Patient recording in patient diary (Morning Nasal symptoms score at the time of visit and evening Nasal symptoms score just before administration of antihistaminics)
4. Issue of study medications for 1 week treatment.

Visit 2: End of study (day 8)

Following procedures were performed on the eighth day:

1. Physical Examination and Vital signs
2. Checking for Patient's recording in patient diary (Nasal symptoms score)

Efficacy assessment

Patients were provided with Patient's Diary. This was filled by patient in the morning at the time of screening and randomization visit and in the evening (immediately before study drug administration) to obtain the baseline and daily Total Nasal Symptom Score for next 7 days.

Nasal symptoms

- Nasal Congestion
- Rhinorrhea
- Nasal itching
- Sneezing

Each of the above symptoms was rated on a 4-point scale as follows:

Score grade description:

- 0 None (No sign /Symptom evident);
- 1 Mild (Sign/ Symptoms clearly present, but minimal awareness; easily tolerated);
- 2 Moderate (Definite awareness of sign / Symptoms that is bothersome but tolerable);
- 3 Severe (Sign / Symptoms that is hard to tolerate; causes interference with activities of daily living and / or sleeping).

Efficacy variable

1. Mean change in Total Nasal Symptom Score (sum of scores of Nasal Congestion, Rhinorrhea, Itching and Sneezing) from Baseline to End of treatment.
2. Mean change in Total Nasal symptom score = End of treatment score [(Morning TNSS average Day 2 (next morning after first dose) - Day 8) + (Evening TNSS average Day 2- Day 8)] - Baseline visit score [(Morning TNSS of Baseline visit) + (Evening TNSS of Baseline visit prior to first dose)]
3. Cost effectiveness analysis; e.g. drug A and drug B.[10,11]

Cost-effectiveness ratio (CER) = Cost $_A$ / Effect $_A$ (Net Cost/ Net Health Benefit)

Incremental cost-effectiveness ratio (ICER) = Cost $_A$ – Cost $_B$ / Effect $_A$ – Effect $_B$

Concomitant interventions

No treatment for allergic rhinitis other than study medication was allowed during course of treatment. If rescue medications were required during study, such patients have to be excluded from study.

Adherence assessment

Compliance to study medication and patient diary entries were strictly verified during follow-up visit. The patients received the drugs from our institutional medical store.

Statistical analysis

Statistical analysis was performed by using Statistical Package for the Social Sciences SPSS 19.0. (SPSS Inc. Chicago, USA).

Data was summarized using Mean, Median and Standard Deviation.

'Paired t' test was used to compare Mean changes in patients before and after treatment.

Probability <0.05 was considered statistically significant.

Analysis of variance was used to compare treatment groups for the quantitative primary and secondary outcomes.

In case of significant results, subsequent pairwise contrasts using a Bonferroni adjustment were made between the treatment groups. 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% Females and 51.92% Males 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).

Average cost-effectiveness calculations

Noncompeting choice

Noncompeting choice cost effectiveness has been done because in this study many possible options to choose from that are not mutually exclusive. Noncompeting choice cost effectiveness uses the average cost effectiveness by dividing the cost of the intervention by the benefit of the intervention.

The average cost effectiveness = Net Cost (Rupees ₹) / Net Health Benefit = ₹ / Mean change in TNSS (%)

The average cost effectiveness of intervention for Cetirizine = Net Cost / Net Health Benefit = ₹26.25 / 0.5075= 51.73 / % effect

Using this same means of calculation, the average cost effectiveness for intervention of Levocetirizine was ₹ 47/ % effect, Loratadine was ₹ 69.40/ % effect and for Fexofenadine was ₹ 144.57/ % effect (Table 2, Table 3 and Table 4).

DISCUSSION

The demographic characteristics of the study participants and the baseline symptom scores viz. Total Nasal Symptom Score (TNSS), Nasal Congestion Score prior to dosing were comparable among the four treatment groups (Table 1).

Table 1: Comparison of demographic data and clinical characteristics of the patients participated in the study (n=52).

Parameters		Cetirizine n=13	Levocetirizine n=13	Loratadine n=13	Fexofenadine n=13	F	p*
Age (years)		31.85±9.45	39.38±14.39	32±1.011	31.69±7.22	1.858	0.149
Sex	Male (%)	6 (46.16%)	4 (30.77%)	7 (53.84%)	10 (76.92%)		
	Female (%)	7 (53.84%)	9 (69.23%)	6 (46.16%)	3 (23.08%)		
TNSS		12±1.22	10.77±1.48	10.92±1.44	10.69±1.25	0.461	0.635
NCS		4.46±0.66	3.87±0.68	4±0.82	4.15±0.55	1.905	0.141

Table 2: Comparison of Total Nasal Symptom Score (TNSS) before and after treatment.

Groups (n=13)	Total nasal symptom score				
	Baseline score	End of treatment score	Mean change in score	t	p
Cetirizine	12±1.22	5.90±0.62	6.09±0.60	27.18	<0.001**
Levocetirizine	10.77±1.48	4.02±0.43	6.75±-1.04	20.23	<0.001**
Loratadine	10.92±1.44	4.64±0.60	6.27±0.83	22.87	<0.001**
Fexofenadine	10.69±1.25	5.09±0.43	5.59±0.81	20.21	<0.001**
F	0.461	28.678			
p	0.635	<0.0001***			

The values are expressed as mean ± SD, n=13 patient. ** represents statistical significant of p<0.001 when compared before and after treatment (Paired 't' test), *** significant at p<0.0001 when compared between treatment groups using one-way analysis of variance (ANOVA) with post-hoc Bonferroni's test.

ANOVA comparison between groups (<0.0001) i.e. TNSS differs significantly for all the treatment groups. Subsequent pairwise contrasts using a Bonferroni adjustment reveales maximum reduction in Levocetirizine group.

Table 3: Pharmacoeconomic assessments (cost effectiveness analysis) summary of Cost Effectiveness Ratio (CER).

Methods	Cetirizine	Levocetirizine	Loratidine	Fexofenadine
Method 1 Cost consequence Analysis (CCA)	Net Cost (at the end of 1 week treatment)			
	₹ 26.25	₹ 29.46	₹ 39.84	₹ 75.58
	Net health benefit (% mean change in TNSS)			
	50.75	62.67	57.41	52.29
Method 2 Average Cost Effectiveness Ratios (net cost/ net health benefit)	₹ 26.25 / 0.5075 = ₹ 51.73 per cure	₹29.46 / 0.6267 = ₹ 47 per cure	₹39.84 / 0.5741 = ₹ 69.40 per cure	₹75.58 / 0. 5229 = ₹ 144.54 per cure

Table 4: Average cost effectiveness ratio.

Intervention	Net health benefit mean change in TNSS (%)	Net cost cost / 7 Tab (Rupees)	Average cost effectiveness ratio (₹ / % effect)
Levocetirizine	62.67	₹29.46	₹47 / % effect
Cetirizine	50.75	₹26.25	₹ 51.73 / % effect
Loratadine	57.41	₹39.84	₹69.40/ % effect
Fexofenadine	52.29	₹75.58	₹144.57/ % effect

The mean TNSS was significantly reduced in all 4 study groups, Overall TNSS was reduced to 50.75%, 57.41% and 52.29% respectively in Cetirizine, Loratadine and Fexofenadine groups, where as it was reduced maximally in Levocetirizine group, i.e. 62.67% (Table 2).

Cost effectiveness analysis

Noncompeting choice

Levocetirizine should be preferred because it has the lowest cost-effectiveness ratio compared to the other interventions (i.e. ₹ 47/ % effect vs ₹ 51.73/% effect or ₹ 69.40/ % effect or ₹144.57/ % 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 and Table 4).

Competing choice

In competing choice method of cost-effectiveness analysis, the incremental cost-effectiveness ratio (NOT average cost effectiveness) 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 Cetirizine, Loratadine and Fexofenadine vs Levocetirizine. so incremental cost-effectiveness ratio has not been done.

The results of this study corroborate with those of a previous study done by Ralph Mosges et al, in which monotherapy with Levocetirizine was found to be significantly more effective in lowering the Total Nasal Symptom Score than the Desloratadine and Fexofenadine alone or in combination with intranasal corticosteroids. A meta-analysis has illustrated greater effectiveness for treatment with the active substance levocetirizine as monotherapy in reducing allergic symptoms when compared to treatment with Loratadine.[12] Ciprandi G et al, in a pilot study demonstrated the effectiveness of levocetirizine in: (i) relieving nasal symptoms, (ii) improving nasal airflow, (iii) reducing leucocyte infiltration, and (iv) diminishing cytokine levels.[13] Friedrich Horak et al, evaluated Levocetirizine was more effective than fexofenadine at and later than 22 hours after drug intake, an indication of the longer-duration of action of levocetirizine.[14] Stubner P et al, study also concluded that Levocetirizine was superior to loratadine in improving symptoms in seasonal AR and that there was a similar trend in perineal AR.[15]

The findings were consistent across the literature, suggesting Levocetirizine improved outcomes, leading to incremental cost savings and cost-effectiveness.[16] Anthi Rogkakou et al, concluded that Levocetirizine was well-tolerated, safe, and suitable for continuous and long-lasting treatment. Furthermore, a long-term treatment with Levocetirizine reduces overall costs (direct and indirect costs) for both persistent allergic rhinitis and associated comorbidities, with a consequently important impact on socioeconomic aspects.[17-19]

CONCLUSION

The present study was carried out in the patients of Allergic Rhinitis, visiting the ENT OPD at a tertiary care hospital in the rural areas of Maval Taluka of Pune District, Maharashtra. Nasal symptoms were assessed by Total Nasal Symptom Score and pharmacoeconomic assessment by cost effectiveness analysis. Cetirizine did not prove any superior to other antihistaminics in clinical efficacy but it was equally effective in controlling the nasal congestion. Levocetirizine appears to be statistically significantly effective and offers relief from almost all of the individual nasal symptoms viz. nasal congestion, rhinorrhea, itching, and sneezing within a week and TNSS. Levocetirizine was a rapidly and sustainably effective antihistaminic for the treatment of AR and most cost effective when evaluated with pharmacoeconomic criteria such as cost effectiveness analysis.

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