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Original Research Article

Prospective, Randomized, Three-Arm, Open- Label Study to Compare the Efficacy and Tolerability of Oral Desloratadine, Rupatadine and Ketotifen in Seasonal Allergic Rhinitis

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Abstract

Aim: To compared efficacy and tolerability of desloratadine, rupatadine and ketotifen in SAR.

Patients and Methods: This was a prospective, randomized, three-arm, open- label comparative study of desloratadine, rupatadine and ketotifen in SAR. The study was conducted at Department of ENT, ANMMCH, Gaya, Bihar, India. The duration was one year. The severity of SAR symptoms was assessed by the Total Nasal Symptom Score (TNSS), which is a subjective graded scoring system based on the severity of nasal symptoms. Quality of life (QoL) was measured using a 12-item short form of the Medical Outcomes Study questionnaire (SF-12). SF-12 was administered at the start of the study and then at the end of the study.

Results: Total 180 patients were recruited for this study, divided into 3 groups. DES and RUP were equally effective but significantly better than KET in improving rhinorrhea, nasal congestion, TNSS and AEC. (p=0.05). All three study groups showed a gradual and progressive improvement in rhinorrhea. RUP was slightly faster than DES in improving rhinorrhea in the first 2 weeks (p>0.05).

Conclusion: DES and RUP are comparatively more effective and faster acting than KET. All the study medications were well tolerated with few mild, self-limiting, transient adverse events requiring no intervention.

Keywords: desloratadine, rupatadine, ketotifen, seasonal allergic rhinitis

Introduction

Allergic rhinitis (AR) is one of the most common diseases, representing approximately 20% of the general population. [1] 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 another40%of cases have a mixed cause. Allergic rhinitishasa relevant impact on society because of its high prevalence, association with an impaired quality of life, and the

presence of comorbidities such asatopy and asthma. [2] 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. [3]

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. [4] Symptoms such as sneezing, itching, watery eyes, and rhinorrhea are largely mediated through histamine H1 receptors. [5]

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.[6-8]

Around 09 – 42 % of the world's population are affected at least once with seasonal allergic rhinitis (SAR). [9] Around 20–30 % of the Indian population is estimated to suffer from SAR. [10] The burden of SAR in India is escalating. Patients are now presenting with more severity compared to a decade ago. [11]

Pharmacotherapy of SAR includes H1 antihistaminic given orally or topically, intranasal steroids, leukotriene receptor antagonists, mast cell stabilizers, anticholinergic agents and nasal decongestants. [12]

Among the anti-histamines desloratadine, rupatadine and ketotifen are commonly prescribed in our region. A comparative study needs to be done to evaluate the most suitable antihistamine for SAR. We could not find any relevant study comparing these drugs in India. Hence in this study, we aim to compare the efficacy and tolerability of desloratadine, rupatadine and ketotifen in SAR.

Materials & Methods:

This was a prospective, randomized, three-arm, open- label comparative study of desloratadine, rupatadine and ketotifen in SAR. The study was conducted at Department of ENT, ANMMCH, Gaya, Bihar, India for one year.

The duration was one year. Patients diagnosed with SAR, attending the department of ENT OPD were recruited for this study following our inclusion and exclusion criteria. This study was conducted according to the ICH-GCP guidelines and the revised Declaration of Helsinki. Written informed consent from all participants was obtained after fully explaining the study procedure in a language understood by them. For illiterate patients, informed consent document was read out by individuals not concerned with study or patient.

Inclusion criteria:

1. Subjects between 18 to 65 years of either gender with SAR
2. Total Nasal Symptom Score (TNSS of _ 6
3. Willing to give written informed consent and available for regular follow-up

Exclusion criteria:

1. Subjects suffering from non-SAR (i.e. perennial, vasomotor, infective, drug-induced rhinitis
2. Subjects who have received any of the drugs used in the management of SAR in the past 2 weeks.
3. Subjects receiving glucocorticoids and/or immunotherapy
4. Subjects with known hypersensitivity to any of the study drugs
5. Pregnant, lactating women and those planning to conceive

6. Chronic alcoholism and liver dysfunction

Each patient was asked about their present medical history, past history, drug history, special emphasis on allergy history was given, and its aggravating factors were recorded.

Personal history and family history too were noted. The severity of SAR symptoms were assessed by the Total Nasal Symptom Score (TNSS), which is a subjective graded scoring system based on the severity of nasal symptoms. Quality of life (QoL) was measured using a 12-item short form of the Medical Outcomes Study questionnaire (SF-12). SF-12 was administered at the start of the study and then at the end of the study. Vitals like pulse, BP, respiratory rate, etc. were assessed. Adverse effects were monitored during clinical examination at each visit.

Study subjects were systemically randomized into three groups – desloratadine (DES), rupatadine (RUP) and ketotifen (KET), taking care to maintain similar demographics in all three groups. Based on the assigned group; desloratadine was given orally in a dose of 10mg OD, rupatadine was given orally in a dose of 10 mg OD and ketotifen was given in a dose of 1mg BD. All medications were given for 4 weeks. A wash-out period of 14 days was allowed for those patients previously receiving any prior medication for SAR.

Follow up was done for all patients every week during the treatment period of 4 weeks.

Results:

Total 180 patients were recruited for this study, which were divided into 3 groups having 60 patients in each group. The mean age was 27.91±6.02 for DES group, 31.73±11.72 for RUP group and 28.88±8.25 for KET group with no significant difference for age among the study groups demonstrating uniform distribution. Gender distribution among groups was uniform, there was no statistically significant difference among groups with regards to gender. [Table 1]

The majority of the subjects had early morning exacerbation of SAR symptoms (n=115, 63.8%) and 18.33% (n= 33) of the subjects had exacerbation of symptoms in the evening whereas 25.5% (n=46) of the subjects had no diurnal symptom exacerbations. The average duration of symptoms at presentation was about 5.0±1.88 days. The average history of SAR symptoms was about 4.12_1.59 years. The average number of symptoms at presentation were about 4.08±0.31. Average baseline nasal symptom scores and the TNSS score were consistent across the study groups with no statistically significant difference among groups with regards to symptomatology. The eosinophil count and AEC were increased above the normal range in some subjects (n=48, 26.6%). Hemoglobin levels were <10gm% in 3 subjects (n=3, 1.6%). [Table 1].

All three study groups showed a gradual and progressive improvement in rhinorrhea. RUP was slightly faster than DES in improving rhinorrhea in the first 2 weeks ($p>0.05$) but in the subsequent 2 weeks, both RUP and DES showed similar improvements. In comparison, KET showed a slower response than DES and RUP over the 4 week study period which was statistically significant ($p=0.05$). Overall DES and RUP were equally effective but significantly better than KET in improving rhinorrhea ($p=0.05$). [Table 2]

All three study medications were effective in improving sneezing over the 4 week study period. KET showed a slightly slower response in reducing sneezing than RUP and DES during the study period. At week 1, RUP was significantly better than KET in improving sneezing ($p=0.05$). But

at the end of the study, all the drugs were equally effective with no statistically significant intergroup difference in improving sneezing as compared to baseline (p=0.471). [Table 2]

All three study medications were equally effective in improving nasal itching with no statistical significance among the study groups (p value=1.00). [Table 2]

Mean TNSS improved gradually and progressively over the study period in all the three groups with DES and RUP being equally effective and faster than KET with a statistically significant difference (p > 0.05) [Table 2]

All three study groups demonstrated a gradual and progressive improvement in rhinorrhea. RUP was slightly faster than DES in improving rhinorrhea in the first 2 weeks (p>0.05) but in the subsequent 2 weeks, both RUP and DES showed similar improvements. In comparison, KET showed a slower response than DES and RUP over the 4 week study period which was statistically significant (p=0.05). Overall DES and RUP were equally effective but significantly better than KET in improving rhinorrhea (p=0.05). [Table 3].

All three study medications were effective in improving sneezing over the 4 week study period. KET showed a slightly slower response in reducing sneezing than RUP and DES during the study period. At week 1, RUP was significantly better than KET in improving sneezing (p=0.015). But at the end of the study (week 4), all the drugs were equally effective with no statistically significant intergroup difference in improving sneezing as compared to baseline (p=0.473). [Table 3]. All three study medications were equally effective in improving nasal itching with no statistical significance among the study groups. [Table3]. Improvement in nasal congestion was gradual and progressive over the study period in all the three groups with desloratadine and rupatadine being equally effective and faster than ketotifen in improving nasal congestion at all visits with a statistically significant difference (p= 0.0005). [Table 3]. Mean TNSS improved gradually and progressively over the study period in all the three groups with DES and RUP being equally effective and faster than KET with a statistically significant difference (p= 0.0005). [Table 3]

Compared to baseline absolute eosinophil counts (AEC), a decrease was observed and it was statistically significant for DES (p=0.036) and RUP (p=0.001) but it was not statistically significant for KET (p=0.055). RUP was significantly better than DES (p < 0.05). [Table 4].

QoL based on the SF-12 questionnaire was done at the end of the study. Increments observed in the physical component scores (PCS) of the SF-12 questionnaire were statistically significant in all three study groups (p= 0.001). However, there was no statistically significant intergroup difference in the improvement observed in the physical QoL (p = 0. 782). [Table 5]

The majority of the subjects in all groups (n=104, 57.7%) reported no serious ADRs [Table 6]. RUP appeared to have better tolerability as the total number of adverse events were marginally less. The commonly reported ADRs were somnolence, headache, fatigue and dry mouth. The reported ADRs were probable in causality, mild in intensity, transient, self-limiting and resolved over time without any intervention/sequelae. [Table 6]

Table 1: Baseline demographics Desloaratdine (n=60)

Desloaratdine (n=60)		Rupatadine (n=60)	Ketotifen (n=60)
Mean age in years (%) No. of females	27.91±6.02 33 (55%)	31.73±11.72 28 (46.6%)	28.88±8.25 24 (40%)
Diurnal symptom variation*			
Early morning	36 (60%)	45 (75%)	34 (56.6%)
Afternoon	00	00	03 (05%)
Evening	17 (28.3%)	13 (21.6%)	03 (05%)
Night	02 (03.3%)	04 (06.6%)	00
Nil	14 (23.3%)	9 (15%)	23 (38.8%)
Duration Of Symptoms (Days)	5.2±1.95	5.12±2.34	5.44±1.93
No. Of Symptoms At Presentation	5.82±0.71	5.41±0.63	5.32±0.54
Severity of symptoms			
Rhinorrhea	1.93+0.40	1.98+0.53	1.91+0.32
Sneezing	1.91+0.52	1.88+0.69	1.82+0.50
Itching	1.38+0.69	1.20+0.43	1.21+0.44
Nasal congestion	1.85+0.52	1.97+0.60	1.93+0.43
TNSS H/o SAR (years) Eosinophil Count > 4%	7.75±0.82 4.67±1.61 21 (35%)	7.70±0.94 3.71±1.75 16 (26.6%)	7.89±0.77 4.22±1.89 11 (18.3%)
Absolute eosinophil count > 440 cells/mm3	17 (28.3%)	12 (20%)	11 (18.3%)
Hb (< 10 gm %)	03 (05%)	00	01 (1.6%)

*Some subjects had symptom exacerbation at multiple times of the day. 6 subjects in RUP group and 3 subjects in DES group and 1 subject in KET group had symptom exacerbation both in morning and evening. 2 subjects in RUP group and 1 in DES group had symptom exacerbation in morning and night.

Table 2: Change in nasal parameters and tnss from baseline

	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	P-value
Rhinorrhea						
Desloratadine Rupatadine Ketotifen	1.91±0.39 1.95±0.56 1.90±0.41	0.78±0.61 0.62±0.77 0.96±0.31	0.17±0.46 0.19±0.58 0.81±0.62	0.11±0.31 0.20±0.20 0.29±0.50	0.04±0.27 0.08±0.20 0.18±0.46	0.05*
Sneezing						
Desloratadine Rupatadine Ketotifen	1.7±0.48 1.81±0.66 1.79±0.51	0.23±0.51 0.12±0.47 0.39±0.53	0.17±0.20 0.06±0.3 0.19±0.31	0.08±0.28 0.03±0.17 0.1±0.41	0.04±0.13 0.03±0.19 0.06±0.16	0.471
Nasal Itching						

Desloratadine Rupatadine Ketotifen	1.33±0.48 1.18±0.31 1.18±0.45	0.19±0.27 0.2±0.39 0.15±0.26	0.10±0.20 0.04±0.2 0.07±0.13	0.0±0.0 0.0±0.0 0.06±0.17	0.0±0.0 0.0±0.0 0.0±0.0	1.00
Nasal Congestion						
Desloratadine Rupatadine Ketotifen	1.80±0.6 1.95±0.60 1.14±0.52	0.89±0.61 0.80±0.70 1.47±0.63	0.40±0.47 0.31±0.50 0.95±0.32	0.05±0.30 0.02±0.3 0.70±0.61	0.01±0.11 0.07±0.30 0.41±0.49	0.0005*
TNSS						
Desloratadine Rupatadine Ketotifen	6.80±0.76 6.6±0.98 6.70±0.62	1.97±1.22 1.60±1.61 2.71±0.92	0.70±0.94 0.66±1.27 1.0±0.97	0.10±0.30 0.11±0.9 0.80±0.89	0.11±0.20 0.1±0.38 0.56±0.45	0.0005*

Table 3: Summary of the Treatment outcome at the end of the study period

	Desloratadine		**Rupatadine**		**Ketotifen**		
Symptoms	Change in score from baseline Mean+SD	% change from Baseline	Change in score from baseline Mean+SD	% change from Baseline	Change in score from baseline Mean+SD	% change from Baseline	P value
Rhinorrhea	-1.92±0.38	98.01	-1.98±0.48	95.03	-1.80±0.32	90.02	0.05
Sneezing	-1.70±0.29	98.77	-1.79±0.59	97.82	-1.79±0.50	96.80	0.473
Itching	-1.35±0.50	100	-1.29±0.29	100	-1.20±0.44	100	1.000
Nasal congestion	-1.80±0.7	98.89	-1.90±0.59	95.90	-1.7±0.60	85.91	0.0005
TNSS	-7.02±0.89	98.80	-6.80±0.98	98.47	-6.20±0.97	91.01	0.0005

*DES and RUP were better in improving rhinorrhea then KET as compared to baseline (p=0. 05)

Table 4: Effect of study drugs on absolute eosinophil Count

Study Drugs	Baseline (Mean± SD)	Visit 4(Mean± SD)	p-value
Desloratadine* Rupatadine Ketotifen	572.3 ±331 361.6 ±269 480.7±378	529.70±280 365.21±252 401.0±301	0.036 0.001 0.05

Table 5: Quality of life (qol) assessment by standard form 12(SF-12) physical component scores

Physical component Scores(PCS)	Treatment Groups Baseline Mean + SD	Visit 4 Mean+ SD	95%CI Lower bound Upper Bound	P Value (t-test)

Desloratadine	50.22+3.81	60.3-0.89	-19.167	-12.691	0.001
Rupatadine	42.7+3.24	61.2+0.83	-19.572	-14.571	0.001
Ketotifen	46.10+1.62	57.9+1.77	-19.408	-11.614	0.001

Table 6: Adverse events

ADR	Desloratadine	(%)	Rupatadine	(%)	Ketotifen	(%)
No Adverse Effects	38	63.3	39	65	27	45
Somnolence	11	18.3	10	16.7	11	18.3
Headache	7	11.7	5	8.33	4	6.67
Fatigue	6	10	4	6.67	7	11.7
Dry mouth	4	6.67	-	-	7	11.7
Nausea	-	-	1	1.67	-	-
Dizziness	-	-	-		1	1.67

Discussion:

Recent studies have proved that platelet-activating factor is an important mediator of AR. Platelet-activating factor causes vasodilatation and an increase in vascular permeability that may contribute to the appearance of rhinorrhea and nasal congestion. [13, 14] Platelet-activating factor and histamine are known to complement each other in vivo; histamine is a mediator of early response, being released from preformed reservoirs in mast cells, whereas platelet activating factor is mainly synthesized de novo. [2] 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 close similarity between rupatadine and desloratadine had been expected in relation to the findings in the previous studies reported with SAR patients.[14]The findings of this study are in accordance with previous meta-analysis with desloratadine in comparison with placebo, involving several controlled clinical trials with higher degrees of variability.[16]Nevertheless, direct comparisons involving large samples are relatively infrequent in the literature,[15] and overall, there were no results significantly favoring levocetirizine or fex-ofenadine over desloratadine in terms of their effects on AR symptoms.

Despite the actual preference of Allergic Rhinitis and its Impact on Asthma classification, no previous studies with desloratadine or rupatadine were released before 2006 in patients with intermittent or persistent AR that could determine the efficacy based on the duration of the severity of symptoms and their impact on quality of life.[17-19]When this study was designed, the AR patients were involved accordingly with the traditional classification of SAR given that the sample size being estimated was only being based on previous studies with SAR patients reported with desloratadine and rupatadine.[20-23] Nevertheless, desloratadine, rupatadine, and levocetirizine are the only anti-H1 compounds that have been shown to be effective and safe under this Allergic Rhinitis and its Impact on Asthma classification.[24]

Previous studies of Meta-analysis on DES and RUP demonstrated significant efficacy of DES and RUP over placebo.[25] A direct comparative study between RUP 10mg and DES 5mg by Lukat et al. demonstrated no significant difference

between DES and RUP in nasal symptom improvement in SAR and our study also showed similar results where we found no statistically significant difference between DES and RUP.[26] A meta-analysis of DES showed that DES was as equally effective as the newer 2nd generation antihistamines like levocetirizine and fexofenadine in AR/SAR and this can be correlated to the observation of our study where DES and RUP were equally effective [27]. A meta-analysis of RUP demonstrated a significant efficacy over ebastine, cetirizine and levocetirizine [25].

Previous studies have assessed the effect of RUP and DES on AEC reduction and have shown statistically significant reduction in AEC by RUP and also showed that RUP was better than DES. Similar results were observed in our study [28].

Previous studies have demonstrated a significant improvement in QoL for DES and RUP. However, no comparative data is available to demonstrate a significant change in QoL for antihistamines like DES or RUP. [29-32]

Conclusion:

DES and RUP are comparatively more effective and faster acting than KET. All the study medications were well tolerated with few mild, self-limiting, transient adverse events requiring no intervention.

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