

The Effectiveness of Modern Antihistamines for Treatment of Allergic Rhinitis - An IPD Meta-Analysis of 140,853 Patients

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ABSTRACT

Background: Allergic rhinitis represents a worldwide health problem. The prevalence is increasing. The aim of this study was to analyse the correlation between the severity of allergic rhinitis and an adequate treatment dose of modern oral antihistamines.

Methods: From a comprehensive databank containing data from ten different open-label prospective observational studies including raw data of 140,853 patients with allergic rhinitis, symptomatology variables were analysed and scored to study the effects of treatment with four antihistamines (Desloratadine, Ebastine, Fexofenadine, Levocetirizine) alone or in combination with intranasal corticosteroids. The patient data were collected in 23,606 study centres from Germany, mostly medical specialist and some primary care physicians in private practice. The analyses were performed via individual patient data meta-analysis techniques.

Results: Finally 92,900 patient data from nine of ten studies could be analysed. One study with data of 47,953 patients was excluded due to incomplete treatment documentation. Both monotherapy analysis subgroups (Total Symptom Score and Total Nasal Symptom Score) were significantly better than those of their combinations with intranasal steroids. Monotherapy with levocetirizine was determined to be significantly more effective in lowering the Total Symptom Score ($p < 0.001$) and the Total Nasal Symptom Score ($p < 0.05$) than the other antihistamines. In the next stage, a greater positive effect of levocetirizine was demonstrated in relation to the severity of the clinical symptoms of allergic rhinitis (Total Nasal Symptom Score in cases with severe symptomatology [effect size = -0.09]).

Conclusions: Levocetirizine asserted itself as the only antihistamine compared with the others as significant in this analysis. The study authors recommend monotherapy with the new-generation antihistamine levocetirizine, especially in severe cases of allergic rhinitis.

KEY WORDS

allergic rhinitis, Desloratadine, Ebastine, Fexofenadine, Levocetirizine, treatment

ABBREVIATIONS

TNSS, Total Nasal Symptom Score; TOSS, Total Ocular Symptom Score; TSS, Total Symptom Score; IPD, Individual Patient Data.

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INTRODUCTION

Allergic rhinitis is considered the most significant atopic condition, affecting 65 million people in the United States alone.¹ Its estimated prevalence in central Europe shows that the disease affects 17 to 29% of the population, and is rising.² This rise needs to be observed and documented in the different regions of the world so that investigational results can be used to represent and indicate international rather than regional findings.²⁻⁸

Today's antiallergic therapy is based upon three measures: avoidance or elimination of the causative agent (allergen), anti-symptomatic pharmacotherapy, and specific immunotherapy. Along with intranasal corticosteroids, leukotriene receptor antagonists⁹ and mast cell stabilizers, modern, new-generation antihistamines are the pillars of the pharmaceutical component in the management of allergic rhinitis.

International guidelines recommend modern oral antihistamines for first-line treatment of allergic rhinitis and conjunctivitis in adults and children. The most effective treatment for allergic rhinitis are the intranasal corticosteroids; however, no sufficient data are available that supports the combined use of these two medications. Broadly speaking, each new patient should be considered and managed differently according to the duration and severity of the clinical picture, the patient's personal preferences, the accessibility and affordability of medications, and the success and effectiveness of a therapeutic option applied in the patient's particular case.¹⁰

Similar findings were presented by Benninger *et al.*,¹¹ who evaluated the impact of medications in the treatment of allergic rhinitis in the United States on nasal symptoms. An evidenced based review was conducted with finally 54 randomized, placebo controlled studies. The findings reveal that the treatment with intranasal steroids shows the greatest improvements for nasal symptoms. Regarding our analysis, the equal effectiveness for some patients treated with oral antihistamines is of special interest.

In this analysis, we have examined the effect of prescribing a less intricate, yet possibly more effective therapy for lowering the symptom score in allergic rhinitis: using modern antihistamines alone rather than the traditional combination of antihistamines and intranasal steroids. First tendencies and descriptions of this data pool on comparison between these two treatment options are already published by Mösges.¹²

METHODS

OBJECTIVES AND STUDY DESIGN

At the Institute of Medical Statistics, Informatics and Epidemiology (IMSIE), University of Cologne, Germany, we pooled and analysed already existing data from 140,853 patients with the clinical diagnosis of al-

lergic rhinitis that had been collected from ten open-label prospective observational studies conducted between 1998 and 2005 by pharmaceutical companies.

All studies on the four different antihistamines were funded and conducted by the companies themselves (Desloratadine/Essex Pharma GmbH, Ebastine/Almirall Hermal GmbH, Fexofenadine/Sanofi-Aventis Deutschland GmbH, Levocetirizine/UCB Pharma GmbH). In our analysis we focused on post-marketing studies, because of their practical design. The analysed antihistamines are from the modern generation and belong to well-established prescription medications at the time of examination. We received all observational studies on allergic rhinitis by the enterprises mentioned above. Besides, all investigations were released. The data were obtained via paper-based Case Report Forms, which were filled in by the investigators during the patients' visit at their practice. They were then transcribed into databases by the pharmaceutical companies.

We previously published observational studies conducted with azelastine for the treatment of allergic rhinitis.^{13,14} Those were not included as the route of application (nasal spray) differs from the other studies and this probably has a major impact on compliance and consequently effectiveness.

Our examination compares a single monotherapy with levocetirizine against its combination with intranasal corticosteroids and against the same specific effects of other new generation antihistamines.

An overview about the different study designs and the various investigation scores is given in Table 1. The nasal and eye symptoms which we included in the analysis were summarized to TNSS (including: nasal obstruction, secretion, sneezing and itching) and Total Ocular Symptom Score (TOSS) (including: tearing, itching/burning, redness), as far as possible, according to the availability of data about these variables. The baseline score (first screening) was assessed with patients who have not taken any study medication. The interval between baseline and end-point score amounts to four weeks in all studies.

The data collected were used to compare the effects of levocetirizine 5 mg tablets with those of either ebastine (2 × 10 mg, 1 × 20 mg), desloratadine (5 mg) or fexofenadine (120 mg) alone or in combination with intranasal corticosteroids. The effectiveness of administering the various antihistamines as monotherapy was then analysed further. This could be done by comparing each single nasal symptom score after their administration. In this stage, however, it was necessary to identify data from the 10 studies and extract a sufficient amount of relevant and valid information from them about the nasal symptoms which could then be used in the correlation process. The individual symptoms constituting the symptom scores, such as "sneezing and itching", "secretion" and "obstruction" were then grouped and classified

Table 1 Overview: ten open-label prospective observational studies

	Desloratadine (Feb. 2001- Sep. 2001)	Desloratadine (Dec. 2001- Mar. 2002)	Desloratadine (Mar. 2001- May 2002)	Ebastine (Apr. 2002- Aug. 2004)	Ebastine (Mar. 2004- Sep. 2005)	Levocetirizine (Jan. 2001- Sep. 2001)	Fexofenadine (4 studies from Jan. 1998- Aug. 2001)
Study data:							
Patients	adults: ≥18 years	adults: ≥18 years children: ≥12 years	adults: ≥18 years children: ≥12 years	adults: ≥18 years children: ≥12 years	adults: ≥18 years children: ≥12 years	adults: ≥18 years children: ≥12 years	adults: ≥18 years children: ≥12 years
Duration / Dose	6 weeks, 2 visits / 5 mg daily	4 weeks, 2 visits / 5 mg daily	4 weeks, 2 visits / 5 mg daily	4 weeks, 2 visits / 20 mg daily (2 × 10 mg)	4 weeks, 2 visits / 20 mg daily (1 × 20 mg)	4 weeks, 3 visits / 5 mg daily	4 weeks, 4 visits / 120 mg
No. of patients/ Study centres	47,953/ 10,000	7,498/ 1,000	13,183/ 3,506	4,704/ 1,000	4,307/ 1,000	17,678/ 2,100	45,530/ 5,000
Medical scores							
nasal symptoms (sum score)		✓					
obstruction	✓	✓	✓	✓	✓	✓	✓
secretion	✓	✓	✓	✓	✓	✓	✓
sneezing	✓	✓	✓	✓	✓	✓	✓
itching	✓	✓	✓	✓	✓	✓	✓
ocular symptoms (sum score)				✓	✓	✓	✓
tearing	✓		✓				
itching/ burning	✓		✓				
redness	✓		✓				
Baseline characteristics							
Treatment regimen	AH AH + INS	AH AH + INS	AH AH + INS	AH AH + INS	AH AH + INS	AH AH + INS	AH AH + INS
No. of patients (with complete data)	-- --	676 526	1581 354	818 569	535 318	3307 169	9000 995
Age (±SD)	-- --	38.0 (±14.2) [†] 39.5 (±14.3)	40.3 (±14.7) 39.6 (±13.6)	37.5 (±14.8) 36.87 (±13.3)	39.0 (±15.1) 40.8 (±13.9)	35.4 (±13.9) 34.2 (±12.9)	35.9 (±13.2) [†] 36.8 (±14.2)
TNSS (±SD)	-- --	7.5 (±0.7) [†] 7.6 (±0.7)	7.8 (±0.8) [†] 7.9 (±0.8)	7.9 (±0.8) 7.7 (±0.8)	7.8 (±0.8) 7.9 (±0.8)	7.8 (±0.8) 7.8 (±0.8)	7.8 (±0.8) 7.8 (±0.8)
Nasal obstruc- tion (±SD)	-- --	2.5 (±0.6) [†] 2.8 (±0.5)	2.5 (±0.6) [†] 2.7 (±0.5)	2.5 (±0.6) [†] 2.7 (±0.5)	2.4 (±0.6) [†] 2.6 (±0.6)	2.4 (±0.7) [†] 2.6 (±0.6)	2.5 (±0.6) [†] 2.6 (±0.6)
Total symptom score (±SD)	-- --	2.5 (±0.5) [†] 2.6 (±0.5)	3.0 (±0.5) 3.0 (±0.5)	3.0 (±0.5) 3.0 (±0.5)	3.0 (±0.5) 3.0 (±0.5)	3.0 (±0.5) 3.0 (±0.5)	3.0 (±0.5) 3.0 (±0.5)
Intranasal steroids (Intake across all studies)	Mometason (Nasonex®) --> 60% Fluticason (Flutide nasal) --> 20% Triamcinolonacetonid - nasal spray (Nasacort®) --> 10% Beclometason - nasal spray (Beconase® plus generics) --> 5% Budesonid (Pulnicort nasal® plus generics) --> 5%						

[†] significant in comparison to AH + INS ($p < 0.05$).

into three categories of mild, moderate and severe symptoms.

DATA CLEARANCE AND PLAUSIBILITY CHECK

The data sets were examined for plausibility and errors. Whenever it was not possible to rectify the variables of a data set, missing values were assumed instead. After controlling for plausibility, patient data sets with less than 50% of all data necessary for calculation of analysis parameters were identified, in order to be excluded from the final analysis file.

PATIENTS

All patients were at least twelve years old. The average age of the patients in the different studies was 36.11 up to 39.9 years. The gender distribution showed a greater number of females (55.3%). In addition to the age and gender, the anamnesis of the patients was examined. All included patients declared at the beginning of treatment that they were already affected by allergic rhinitis for more than six years on average. 31.7% of all study participants indicated that they suffered for more than 10 years from this disease. There were no study differences in the median of the severity in ocular or nasal symptoms at baseline.

STATISTICS

The statistical calculations performed on the extracted data were conducted using the statistic software SPSS version 20 and the Cochrane Collaboration's Review Manager 5.1 software.

The individual results of these studies had not yet been published; thus, we speak here of a "pooled analysis" or an "individual patient data (IPD) meta analysis". The analysis was realized via two methodologies. On the one hand the effect estimates were calculated separately for each trial and then combined using the meta-analysis techniques by Review Manager. Therefore study-specific effects were calculated by weighted mean differences. The overall effect was estimated using the 'inverse variance' method. For homogeneous and heterogeneous study-specific effects, the 'fixed effects' and 'random effects' models were used. On the other hand all data from the studies were pooled to one "mega trial" to perform a single analysis with the statistic software SPSS. Both analyses showed nearly the same results, so that the random effect model was used to neutralize possible bias.^{15,16}

The data pool was examined and analyzed further in order to obtain data on the effectiveness of therapy for allergic rhinitis in these patients. Due to the diversity of the available data, the number of subjects was different for each sample taken from the various studies included in the evaluation process.

ETHICS

The data examined here were raised prospective within the scope of not randomized not controlled observation studies. In Germany no approval by an ethical commission is needed, because here exclusively the therapeutic care is documented. Information about these regulations are published by the Federal Institute for Drugs and Medical Devices in Germany. However, all patients had to sign a privacy policy and had agreed that their pseudonymized data can be used for analysis. All patients who took part in the observation studies had delivered their written informed consent, to the capture, storage and processing of their pseudonymized data.

RESULTS

One of the three studies with desloratadine (47,953 patients) had to be excluded from the analysis due to incomplete treatment documentation especially at the items describing treatment modalities and symptoms, which were essential to generate symptom scores. Furthermore patients of this study showed a high proportion of missing data and were excluded within the analysis step "data clearance".

The indirect statistical comparison of pooled data from the selected treatment groups yields effect sizes for each individual antihistamine when compared to its combination with intranasal corticosteroids (Fig. 1, 2). The results were split in two groups "Levocetirizine" and "Other antihistamines", because the investigations proved no significant results between the other subgroups tests. Levocetirizine asserted itself as the only antihistamine that compared significantly with the others as in this analysis. The negative sign indicates a significantly more positive effect of the respective monotherapy on patient symptom improvement relative to that of use in combination with an intranasal steroid.

Both monotherapy analysis subgroups were significantly better than those of their combinations with intranasal steroids. The largest effect size on both TSS (including TNSS and TOSS) and TNSS was identified for levocetirizine treatment. Despite the apparently wider 95% confidence intervals for both scores (TNSS = 0.27 and TSS = 0.1), levocetirizine proved to be significantly more effective especially in reducing the total symptom scores ($p < 0.001$) compared to the medications in the subgroup "other antihistamines". The confidence intervals for the subgroup "other antihistamines" were 0.06 for TNSS and 0.02 for TSS, demonstrating a relatively high precision of results. The numbers of subjects included in each of the analysis subgroups, however, at 48,265 in the TNSS and 49,512 in the TSS groups receiving "other antihistamines" and 9,796 for the TNSS and 10,863 for the TSS groups obtaining levocetirizine, were clearly higher for the former group, thus possibly having had an influence on the 95% confidence intervals and

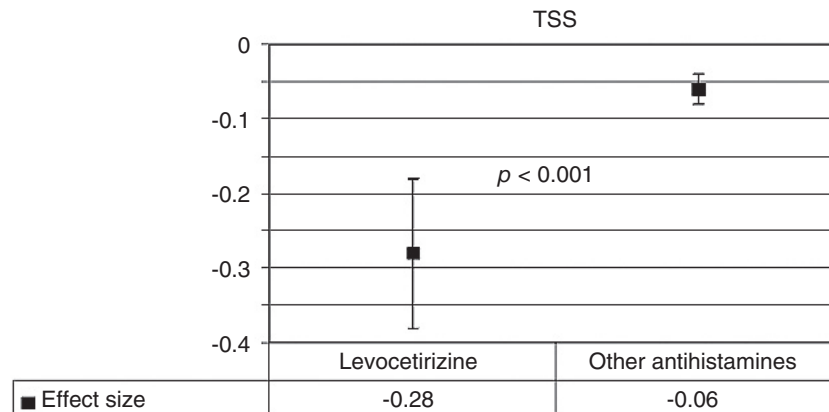


Fig. 1 TSS, monotherapy vs. combination therapy. Difference in effect size in total symptom score when comparing antihistamine monotherapy with the combination of the respective antihistamine (levocetirizine or any of the other antihistamines) plus application of an intranasal steroid. Significance level = test for subgroup differences (“Levocetirizine” versus “Other antihistamines”).

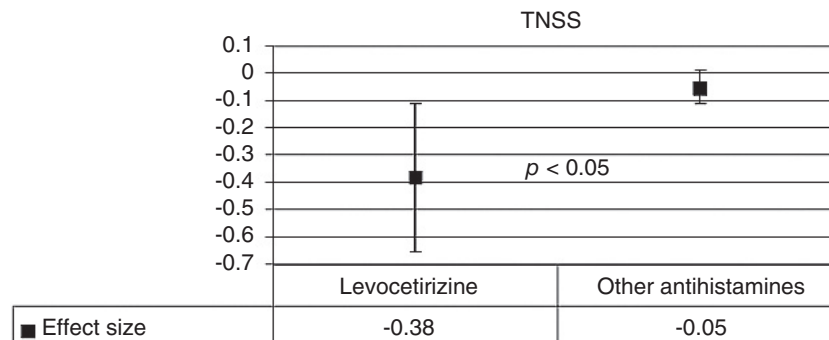


Fig. 2 TNSS, monotherapy vs. combination therapy. Difference in effect size in total nasal symptom score in favours of monotherapy when comparing antihistamine monotherapy with the combination of the respective antihistamine (levocetirizine or any of the other antihistamines) plus application of an intranasal steroid. Significance level = test for subgroup differences (“Levocetirizine” versus “Other antihistamines”).

accounting for the broad levocetirizine confidence interval.

Accordingly, TNSS could then be determined for each subject, placing them in either the “mild/moderate” or “severe” TNSS subgroups, whether the classification of allergic rhinitis according to ARIA is “mild” and “moderate/severe”.¹⁰ The individual definition of this scoring system is¹⁷:

Mild = sign/symptom clearly present, but minimal awareness; easily tolerated.

Moderate = definite awareness of sign/symptom that is bothersome but tolerable.

Severe = sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping.

Figure 3 illustrates a trend towards effect because of the greater numerical effectiveness of levocetiriz-

ine monotherapy in reducing the symptoms “moderate obstruction” (mean effect = -0.04) and “severe obstruction” (mean effect = -0.07) compared to the group of other antihistamines. The positive effect from levocetirizine on the nasal symptom “obstruction” was already demonstrated in a meta-analysis.¹⁸ In addition, our results show the differentiation in severity.

The effect for “other antihistamines” was taken as a reference point (zero line) for comparison with the results for levocetirizine effectivity. The number of cases represents the total number of patients for both groups. The negative sign of the effect size means that levocetirizine has the greater positive effect which, although possible to demonstrate here, was not found to be statistically significant in any individual symptom subgroup. Further analysis of the data

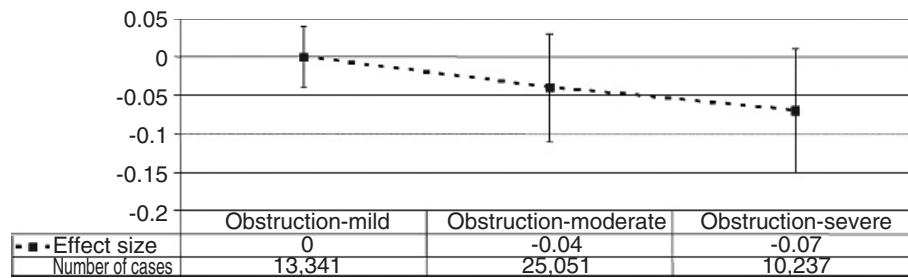


Fig. 3 Nasal symptom “obstruction”-levocetirizine vs. other antihistamines. Difference in effect size in nasal symptom score “obstruction” when comparing levocetirizine with any of the other antihistamines as monotherapy. Number of cases = Number of included patients from all studies.

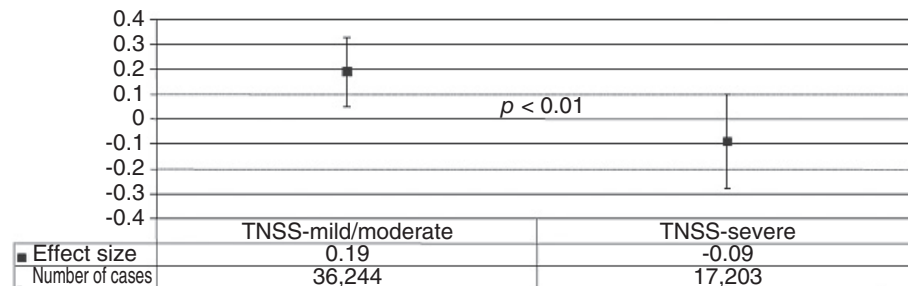


Fig. 4 TNSS-levocetirizine vs. other antihistamines. Difference in effect size in total nasal symptom score when comparing levocetirizine with any of the other antihistamines as monotherapy. Significance level = test for subgroup differences (“TNSS-mild/moderate” versus “TNSS-severe”).

pool for the individual symptom scores revealed that the effect size increases proportionally with the increase in severity of the scored symptoms. For these results, the curve for the mean effect size on the individual symptom scores is positively skewed to the right. Upon overall examination of the total score for severe nasal symptoms, levocetirizine was found to have a numerically higher treatment success (effect size -0.09), shown in Figure 4.

Assuming that the results for effect sizes and mean differences for the whole study data arose merely because of random variation, it can be said that the effectiveness of levocetirizine treatment is better in the case of severe nasal symptoms than in mild to moderate ones ($p < 0.01$) although the confidence limit bars slightly overlap (0.05).

DISCUSSION

The effectiveness of using newer antihistamines in urticaria for severe allergic symptoms has been previously studied by Staevska, M. *et al.*¹⁹ In this study, the doses of levocetirizine and desloratadine were raised stepwise at certain intervals. Levocetirizine’s ability to act as a “strong” modern antihistamine was further underlined in these results.

In various investigations and studies the superior-

ity of new generation antihistamines compared with placebo was proven. These findings were summarized and discussed by creating systematic reviews and meta-analysis for all antihistamines analysed here.²⁰⁻²⁴ In the meta-analysis by Ratner, *et al.*²³ ebastine was compared to loratadine, also an antihistamine from the second generation for the systemic use of allergic diseases. Here ebastine could show a greater decrease in mean rhinitis score from baseline over two and four weeks compared to loratadine and placebo. In the publication by Holgate, *et al.*²⁵ four different published studies on levocetirizine were analysed for meaningful outcome measures. The authors support, that levocetirizine should be used for short-term and long-term treatment of allergic rhinitis. In particular the improvement in quality of life regarding long-term treatment is mentioned. Furthermore levocetirizine improves the symptom score after 24 hours compared to fexofenadine and desloratadine. Similar findings for the effectiveness of levocetirizine are shown in the meta-analysis by Khiany and Weinstein.²² Their data prove that levocetirizine is highly effective in reducing the total symptom score and the Rhinoconjunctivitis Quality of Life Questionnaire score.

Our pooled-analysis illustrates that levocetirizine is

significantly more effective than other antihistamines in symptom alleviation. As presented in the results of this publication, the statistically proven overall advantage of levocetirizine over the other antihistamines could not be verified further in the subanalysis of its effect on the various specific nasal symptom scores. However, a clear tendency in the correlation between symptom severity and levocetirizine drug effectivity could be observed. This can clearly be demonstrated for the symptom of nasal blockage, a major weakness of the second generation antihistamines. The more pronounced these symptoms are, the clearer the superiority of levocetirizine shows up. One may argue, that the effect size of 0.07 is "less than small" according to Cohen's definition.²⁶ However the contrast that we observe in this investigation is not between placebo and an active drug as it is normally the case in such meta-analyses but between well established modern antihistamines of the latest generation. The effect we find here is about half of the size reported for the difference between a nasal steroid and second generation antihistamine.²⁷ Surprisingly, the effect of levocetirizine alone in lowering nasal symptoms is stronger than that of its combination with nasal steroids. Similar findings have been described before.¹² This effect has been attributed to reduced compliances with a treatment scheme that includes two different routes of application, oral and local. For the alleviation of nasal blockage regular intake of medication is essential since other mediators than Histamine are involved. Their down regulation requires continuous intake as has been shown by Canonica, *et al.*²⁸ In this analysis we can demonstrate that the superiority of antihistamine monotherapy is more pronounced when the "strong" antihistamine levocetirizine is used than when other modern antihistamines are prescribed alone or in combination with intranasal corticosteroids.

Possible confounders that may have had an effect on the reliability of this investigation's results may include: variations in the number and age distribution of subjects in the study subgroups, subjects' concomitant illnesses, patients' compliance, degree of symptom severity determined for initiating treatment, and finally, study duration.

Since the study data lack homogeneity, we were not able to demonstrate with statistical significance a positive correlation between the alleviation of nasal symptom severity and effective treatment with the active substance levocetirizine. However a tendency could be shown from the extracted data. Therefore, as a consequence of this analysis of a database containing the data from 92,900 patients with allergic rhinitis, the administration of levocetirizine as monotherapy should be considered a primary treatment choice for patients with moderate to severe allergic rhinitis symptoms.

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