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ORIGINAL ARTICLE

The Effectiveness of Levocetirizine in Comparison with Loratadine in Treatment of Allergic Rhinitis —A Meta-Analysis

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ABSTRACT

Background: Oral antihistamines are considered the gold standard therapy for allergic rhinitis to date. The goal of this investigation is to make an indirect comparison between loratadine, an oral antihistamine available over-the-counter (OTC) in the USA, and the more modern antihistamine levocetirizine. Only double-blind, placebo-controlled (DBPC) studies involving monotherapy with the active substances levocetirizine and loratadine were included in the meta-analysis.

Methods: The medical databases EMBASE and Medline were searched systematically for all relevant studies completed by the end of 2009. Only DBPC studies conducted in normal environmental settings were included. Furthermore, the Jadad scale was used to guarantee the quality of the studies involved. The "standardized mean difference" (SMD) method was applied for calculating the study-specific effects to neutralize the variability between studies.

Results: The results of a total of seven published DBPC studies met all criteria for inclusion in meta-analysis. The meta-analysis showed that levocetirizine was significantly more effective than loratadine in improving the total symptom score (TSS) ($p < 0.01$). The effect sizes were calculated as -0.59 (95% confidence interval -0.89, -0.29) for levocetirizine and -0.21 (95% confidence interval -0.31, -0.1) for loratadine when compared to placebo.

Conclusions: The results of this meta-analysis illustrate greater effectiveness for treatment with the active substance levocetirizine as monotherapy in reducing allergic symptoms when compared to treatment with loratadine.

KEY WORDS

allergic rhinitis, double-blinded placebo-controlled study, levocetirizine, loratadine, meta-analysis

ABBREVIATIONS

CI, Confidence interval; DBPC, Double-blind, placebo-controlled; OTC, Over-the-counter; PAR, Persistent allergic rhinitis; PER, Perennial allergic rhinitis; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SMD, Standard mean difference; SAR, Seasonal allergic rhinitis; TSS, Total symptom score.

INTRODUCTION

Antihistamines are considered a mainstay and standard of treatment for allergic rhinitis with many patients preferring oral medication to intranasal formulations.[1,2] Previous studies have produced evidence showing the effectiveness of oral H_1 blockers in reducing histamine-mediated symptoms such as rhinorrhea, eye symptoms, sneezing and nasal itching; however, a weaker effect on the relief of nasal congestion

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was noted.[3] Moreover, antihistaminic medications are not only capable of reducing the symptomatology of the affected patients, but also have a positive influence on the subjective effectiveness parameters such as quality of life.[4,5]

This meta-analysis was aimed at creating a comparison between the TSS of two medications that are used to treat allergic diseases, especially allergic rhinitis: loratadine, as an OTC drug available including the United States since 2002, and the modern prescription drug levocetirizine, which was approved at the end of 2001. No meta-analysis of comparing these both drugs currently exists.

The cost effectiveness yielded by levocetirizine in the treatment of persistent allergic rhinitis (PAR) has been demonstrated in a number of studies.[4,6]

A meta-analysis of levocetirizine with respect to the early and late effects on nasal obstruction is also available. A placebo-controlled and significant superiority could be demonstrated for levocetirizine after 2 hours and persisting over 6 weeks under both natural and artificial conditions.[7]

Improvement in health-related quality of life and the health status in patients with PAR could also be proven. This conclusion was drawn by the XPERT Study Group in the study conducted by Walter Canonica, *et al*.,[8] in which a total of 551 patients took a daily dose of 5 mg levocetirizine or placebo over 6 months and whose symptoms were evaluated based on the RQLQ (Rhinoconjunctivitis Quality of Life Questionnaire) and the SF-36. In particular, a positive correlation between symptom severity and long-term treatment effects of levocetirizine on the health status could be identified.

METHODS

The meta-analysis was conducted at the Institute of Medical Statistics, Informatics and Epidemiology (IMSIE), Cologne, Germany, for which data from seven double-blind, placebo-controlled (DBPC) studies of levocetirizine and loratadine completed by the end of 2009 were collected for subsequent comparison. In the studies included, the subjects were both patients with seasonal (intermittent) allergic rhinitis (SAR) and also those with a clinical picture of PAR or perennial allergic rhinitis (PER). In all studies to loratadine a dose of 10 mg was chosen. On the other hand a dose of 5 mg was used in the studies with levocetirizine. In all, 1,603 patients were included in the loratadine study group and 635 in the levocetirizine group. The quality of the selected studies was verified using the Jadad scale, with only those studies having ≥4 points included in the meta-analysis.[9] Counted among these points, for example, was a report about the statistical method, information about the drop outs, the enumeration of the in- and exclusion criteria or the description of study blinding. Furthermore, studies carried out in an environmental exposure unit were not included in the analysis.

The study-specific effects identified were measured, and pooled values were then aggregated to a single common treatment group. Due to the different rating scales used in the various studies and based on the diverse parameters, the inverse variance method was applied in which the results were expressed as "standardized mean differences". The expected influence factors included differences in drug administration methods (dose, duration, etc.), the attributes of the patient populations, structuring of baseline factors, and the inclusion and exclusion criteria of each study. The statistical calculations performed on the extracted data were conducted using the Cochrane Collaboration's Review Manager 5.0 software.

RESULTS

Table 1 gives an overview of the studies of levocetirizine[4,10,11] and loratadine[12-15] that were included in the meta-analysis with the results of comparison with placebo treatment. The settings and detailed information for every study are listed in Table 2.

The heterogeneity of the results was examined using the chi^2 test. The results for levocetirizine and loratadine appeared homogeneous in the subgroups. To avoid possible bias, the random effects model was used to minimize the pooled risk arising from the individual variation within each study. The advantage of this method is the more conservative comparison of the results of the individual studies, since broader confidence intervals are specified. Smaller studies in particular thus receive more importance. The bias that could result from the weighting of different-sized study groups is thereby diminished.

Figure 1 illustrates the detailed data and the forest plot of the individual studies that were examined in this analysis. The left half of the forest plot represents the experimental group receiving antihistamine, and the right half shows the placebo control group. Figure 2 shows the effect sizes of both antihistamine drugs under study, taking placebo effects as a point of reference for comparison. In the pooled results of the meta-analysis, both antihistamines show a statistically significant, greater effect than placebo ($p < 0.01$).

The indirect comparison demonstrates that the pooled effect for levocetirizine is greater than that of loratadine. The 95% confidence intervals (CI) for the estimated mean effects of both drugs are 0.3 for levocetirizine and 0.1 for loratadine, indicating the high precision of the values for the loratadine study group and the two relatively small studies in the levocetirizine study group. Due to the homogeneity among the studies, the results demonstrate that levocetirizine is significantly more effective than loratadine as an antihistaminic therapy ($p < 0.01$). This superiority is also apparent in Figure 1, in which the ranges of the 95% CI of the three studies on levocetirizine have nearly

Table 1 Studies included in the meta-analysis

Medication	Number of patients	Number of studies	Statistical method	Effect size [95% CI] (*Antihistamine versus Placebo*)
Levocetirizine	320 (Placebo: 315)	3	Standard mean difference (random)	-0.59 [-0.89; -0.29] $p < 0.01$
Loratadine	756 (Placebo: 847)	4	Standard mean difference (random)	-0.21 [-0.31; -0.10] $p < 0.01$

Table 2 Characteristics of studies included in meta-analysis

Study reference	Study design	Patients	Indication	Drugs/Duration	Outcome score
Levocetirizine					
Bachert, C., *et al.* 2004	DBPC, randomized, multicenter, multinational 1-week run-in phase	≥18 years 547 patients completed	Persistent allergic rhinitis, skin prick test or specific IgE (for at least house dust mite or 1 pollen allergen)	Levocetirizine 5 mg, placebo 4 weeks, once daily	Total 5 Symptoms Score: rhinorrhea, sneezing, nasal congestion, nasal and ocular pruritus
Ciebiada, M., *et al.* 2006	DBPC, randomized 2-week run-in phase	18-65 years 40 patients completed	Persistent allergic rhinitis, at least 2-year history, skin prick test (house dust mite, cat and dog)	Levocetirizine 5 mg, placebo 6 weeks, once daily	Daytime Nasal Symptom Score: congestion, rhinorrhea, itching, sneezing Daytime Eye Symptom Score: itching, redness, tearing, puffy eyes
Lee, CF., *et al.* 2009	DBPC, randomized 1-week screening	6-12 years 48 patients completed	Perennial allergic rhinitis, at least 1-year history, skin prick test (house dust) and specific IgE (mite)	Levocetirizine 5 mg, placebo 12 weeks, once daily	Total Symptom Score: nasal: rhinorrhea, stuffiness/congestion, itching, sneezing, eye: itching/burning, tearing/watering, redness other: itching of ear/ or palate
Loratadine					
van Adelsberg, J., *et al.* 2003	DBPC, randomized, multicenter, parallel group 3-5 days placebo-controlled run-in phase	15-82 years 580 patients completed	SAR, at least 2-year history, skin test (fall allergens)	Loratadine 10 mg, placebo 4 weeks, once daily	Daytime Nasal Symptom Score: congestion, rhinorrhea, pruritus and sneezing Daytime Eye Symptom Score: tearing, pruritus, redness and puffiness
Anolik, R. 2008	DBPC, randomized, multicenter parallel group Run-in phase 3-7 days	≥12 years 330 patients completed	SAR, at least 2-year history, skin prick test	Loratadine 10 mg, placebo 15 days, once daily	Total Symptom Score: nasal: discharge, stuffiness, sneezing, itching eye: tearing, redness, itching other: ear/palate itching
Hampel, F., *et al.* 2004	DBPC, randomized, parallel group 4-day screening	12-70 years 324 patients completed	SAR, at least 2-year history, skin prick test (ragweed allergen)	Loratadine 10 mg, placebo 4 weeks, once daily	Total Symptom Score: nasal: discharge, congestion, sneezing, itching eye: itching, watering
Ratner, P., *et al.* 2004	DBPC, randomized, parallel group 4-day screening	12-70 years 369 patients completed	SAR, at least a 2-year history, skin prick test (ragweed or other fall allergens)	Loratadine 10 mg, placebo 2 + 2 weeks once daily	Total Symptom Score: nasal: discharge, congestion, sneezing, itching eye: itching, watering

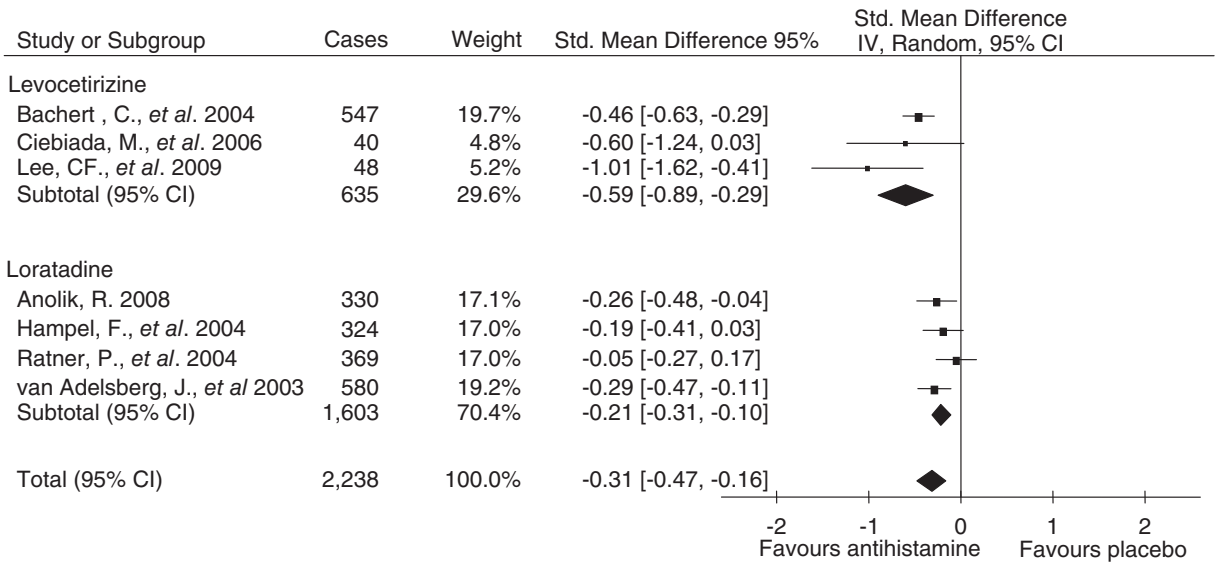

Fig. 1 Forest plot of the meta-analysis.

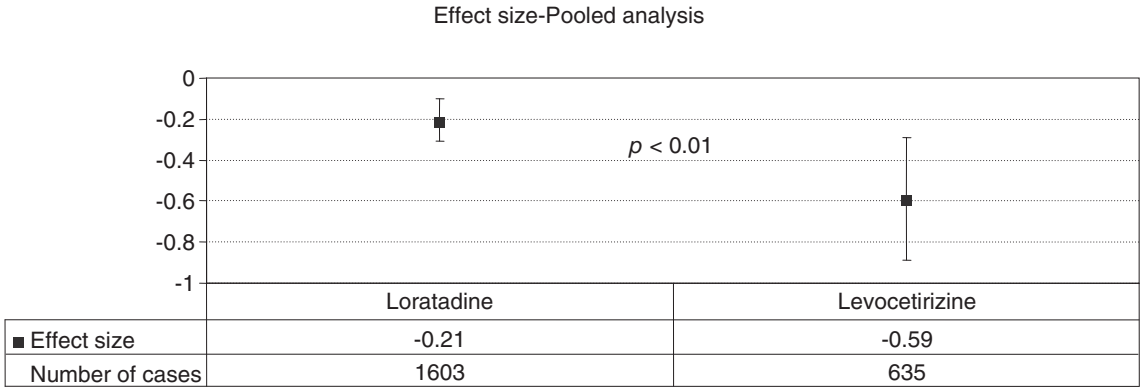

Fig. 2 Results of the meta-analysis.

all a negative sign in opposite to the loratadine group. Due to its low patient numbers and the large CI associated with them, only the study by Ciebiada M, *et al*.[10] has a positive sign, although just 0.03.

DISCUSSION

Besides examining monotherapy using one of the antihistamines focussed upon here, various studies have also investigated other medications as monotherapy or combination therapy. Such trials, however, are not addressed here based on the sole consideration of levocetirizine and loratadine as monotherapy. The only study that tested just one AH (levocetirizine) versus placebo for its effectiveness was the trial conducted by Bachert C, *et al*..[4] This study included patients who displayed allergic reactions to both grass pollen and house dust mites. Even though the indications of the studies differ from one another in both subgroups in terms of the types of allergic diseases (SAR, PAR, PER), the study features are comparable. Besides the identical study design, the outcome scores in the various study groups were also observed to be homogeneous. Due to the specific type of allergy, the duration of administration differed in the levocetirizine group only in two studies with somewhat lower patient numbers.[10,11] Compared to the average study duration of four weeks, the durations in these two studies were 6 weeks[10] and 12 weeks,[11] respectively. As for the loratadine study group, only the study conducted by Anolik[12] deviated from the average with a study length of 15 days. The type of dosis and its frequency were identical in all studies. All patients took the study medication daily.

The uniform assessment of the disease symptom severity in the patients who were included in the studies is certainly more difficult based on the individual study parameters. Elementary consistencies, however, could be observed. This applies first of all to the medical history of the subjects with AR, which for patients across all studies was required to have been

present for at least 1-2 years. Furthermore, the patients in all studies were examined for symptom severity in a run-in phase or screening phase prior to the baseline visit. The study by van Adelsberg, *et al*.[15] observed the patients for symptoms of AR by means of a 3- to 5-day placebo-controlled run-in phase. In the study by Lee, *et al*.,[11] patients who showed symptoms of moderate to severe AR (according to ARIA[1]) were admitted after a one-week screening phase. This is the only study that examined patients aged up to 12 years. Besides TSS, changes in quality of life were also observed in children for 12 weeks (Pediatric Rhinoconjunctivitis Quality of Life Questionnaire). Significant superiority of levocetirizine over placebo could be demonstrated hereby at the same time. The study design by Ciebiada, *et al*.[10] provided for a two-week run-in phase. In the process, the patients had to exhibit a nasal congestion score of at least 2 on a 4-point scale. Likewise, patients in the study by Hampel, *et al*.[13] and Ratner, *et al*.[14] had to show moderate to severe symptoms after a four-day screening phase. Patients in the study by Bachert, *et al*.[4] were examined with respect to their symptoms. Patients were only then included who reported a total symptom score >6 of 15 for at least 4 days during the run-in phase. Participants of the study by Anolik[12] had to keep a diary for 3-7 days in which they assessed their symptoms. As inclusion criteria, values were considered to be >=2 for moderate nasal congestion, at least 6 for TNSS, and at least 11 (4-point scale 0-3) for TSS at screening and baseline visits.

Conclusions regarding the relative effectiveness of the two medications should be drawn carefully. Despite the significant effects, the strength of this value cannot be interpreted without considering the confidence interval in which it lies. Direct assumptions about the superiority of one of the substances over the other cannot be made. Furthermore, attention should be paid to the large number of studies which need to be finally analyzed and summarized into a meaningful effect size. Such indirect comparisons only create a trend of assumptions that, given a stable basis, need to be confirmed via direct comparisons made in further studies. Besides, the problem of publication bias is one of the main issues encountered in the dispatch of meta-analyses and systematic reviews.

After final consideration during and following the review process, certain factors were recognized that could have had an influence on the results of the meta-analysis. These factors included the variation in types of AR, the spectrum of severity of the patient conditions, the differences in the evaluation scales used in each study, the recording of the symptomatology from different viewpoints (patient vs. doctor), and the variation in intake of medications in terms of dose schedules in the subgroups.

The effectiveness of modern antihistamines has been previously shown and published in international guidelines.[2] Preferred in today's clinical practice, both levocetirizine and loratadine clearly have fewer side effects and exhibit fewer sedating properties than their predecessors.[2,16,17] In this meta-analysis, however, the indirect comparison showed levocetirizine to be significantly more effective than loratadine in the treatment of allergic rhinitis ($p < 0.01$). This result should be investigated further in a direct comparative study.

In view of the effective symptomatic relief and the excellent side effect profile, both of which have a considerable effect on the quality of life of patients with allergic disease, more modern and effective preparations, such as levocetirizine, should be a primary treatment choice for allergic rhinitis.

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CONFLICT OF INTEREST

The authors Volker König and Juliane Köberlein have declared that no competing interests exist. The author Ralph Mösges has following relevant conflicts concerning this article: UCB Pharma (Consultant, Grant/Research Support, Speaker's Bureau), Schering-Plough Kenilworth, NJ (Consultant, Grant/Research Support, Speaker's Bureau) and Stada Arzneimittel AG (Consultant, Speaker's Bureau).

REFERENCES

1. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108**:147-334.
2. Bousquet J, Khaltaev N, Cruz AA *et al*. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;**63** (Suppl 86):8-160.
3. Simons FE. Advances in H1-antihistamines. *N Engl J Med* 2004;**351**:2203-17.
4. Bachert C, Bousquet J, Canonica GW *et al*. Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. *J Allergy Clin Immunol* 2004;**114**:838-44.
5. Guadano EM, Serra-Batlles J, Meseguer J *et al*. Rupatadine 10 mg and ebastine 10 mg in seasonal allergic rhinitis: a comparison study. *Allergy* 2004;**59**:766-71.
6. Bousquet J, Demarteau N, Mullol J *et al*. Costs associated with persistent allergic rhinitis are reduced by levocetirizine. *Allergy* 2005;**60**:788-94.
7. Patou J, De Smedt H, van Cauwenberge P, Bachert C. Pathophysiology of nasal obstruction and meta-analysis of early and late effects of levocetirizine. *Clin Exp Allergy* 2006;**36**:972-81.
8. Walter Canonica G, Bousquet J, Van Hammee G *et al*. Levocetirizine improves health-related quality of life and health status in persistent allergic rhinitis. *Respir Med* 2006;**100**:1706-15.
9. Jadad AR, Moore RA, Carroll D *et al*. Assessing the quality of reports of randomized clinical trials: is blinding nec-

essary? *Control Clin Trials* 1996;**17**:1-12.
10. Ciebiada M, Gorska-Ciebiada M, DuBuske LM, Gorski P. Montelukast with desloratadine or levocetirizine for the treatment of persistent allergic rhinitis. *Ann Allergy Asthma Immunol* 2006;**97**:664-71.
11. Lee CF, Sun HL, Lu KH, Ku MS, Lue KH. The comparison of cetirizine, levocetirizine and placebo for the treatment of childhood perennial allergic rhinitis. *Pediatr Allergy Immunol* 2009;**20**:493-9.
12. Anolik R. Clinical benefits of combination treatment with mometasone furoate nasal spray and loratadine vs monotherapy with mometasone furoate in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2008; **100**:264-71.
13. Hampel F Jr, Howland W 3rd, Van Bavel J, Ratner P. A randomized, double-blind, placebo-controlled study comparing the efficacy and safety of ebastine (20 mg and 10 mg) to loratadine 10 mg once daily in the treatment of seasonal allergic rhinitis. *J Investig Allergol Clin Immunol* 2004;**14**:56-63.
14. Ratner P, Hampel F Jr, Van Bavel J, Howland W 3rd. Efficacy and safety of ebastine 20 mg compared to loratadine 10 mg once daily in the treatment of seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled study. *Int Arch Allergy Immunol* 2004;**133**:371-9.
15. van Adelsberg J, Philip G, Pedinoff AJ *et al*. Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period. *Allergy* 2003;**58**:1268-76.
16. Verster JC, Volkerts ER. Antihistamines and driving ability: evidence from on-the-road driving studies during normal traffic. *Ann Allergy Asthma Immunol* 2004;**92**:294-303; quiz -5, 55.
17. Phan H, Moeller ML, Nahata MC. Treatment of allergic rhinitis in infants and children: efficacy and safety of second-generation antihistamines and the leukotriene receptor antagonist montelukast. *Drugs* 2009;**69**:2541-76.