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Efficacy and Safety of Fixed-Dose Combination of Montelukast-Desloratadine 10mg/5mg in Mexican Adults with Persistent Allergic Rhinitis: a Double Blind, Randomized, Controlled and Multicenter Study

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Summary

Persistent allergic rhinitis (RAP) manifests symptoms frequently and constantly. The current treatment of RAP with antihistamines and antileukotrienes is recommended as second-line treatment for the relief of the symptoms of the disease. Therefore, the objective of the present study was to compare the efficacy and safety of the combination of montelukast / desloratadine (MKDES) versus the combination of montelukast / loratadine (MKLOR) in adults with a diagnosis of RAP. The present was a multicenter, controlled, prospective, longitudinal, randomized, double-blind clinical study, with two parallel arms of active treatment (MKDES 10/5 mg vs MKLOR 10/10 mg) every 24 hours orally for 6 weeks. Efficacy was established by clinical evaluation through validated scales. Eighty-six patients were randomized, and of them, 74 were analyzed by protocol. The questionnaires on RAP symptoms and quality of life indicators with both treatments showed that more than 90% of the patients did not present symptoms or were only mild at the end of the study, so that both treatments significantly improved the symptoms of the disease. The adverse events presented in both arms were mild to moderate. Finally it could be shown that the efficacy of MKDES is not inferior to MKLOR. Therefore, both treatments are effective and safe as second-line treatment if monotherapy does not provide sufficient improvement.

Keywords: Montelukast; Desloratadine; Loratadine; Allergic rhinitis

Introduction

Allergic rhinitis (AR) is a pathology that affects around 40% of the world population, while in Mexico a total estimated prevalence of 15% is reported [1,2]. RA is considered a type 1 hypersensitivity reaction that occurs as a symptomatic disorder of the nose, produced by exposure to inhaled antigens that trigger an inflammatory response mediated by IgE in the nasal membranes, according to the definition of the Initiative of the Allergic Rhinitis and its Impact on Asthma (ARIA) [3].

The two most frequent symptoms that affect the quality of life of the patient are rhinorrhea and nasal congestion. Half of the patients with RA in Mexico suffer from persistent rhinitis and the congestive component is present in almost 90% of the patients [3].

RA can be classified as persistent when symptoms occur 4 or more days a week or for 4 or more weeks [4]. Regarding severity, mild symptoms do not affect sleep or daily activities, on the contrary, moderate to severe symptoms affect the performance of these activities and are associated with fatigue, changes in mood, cognitive disorders, depression and anxiety [5]; therefore it is important to assess the impact on the quality of life of the patient.

The treatment of RA requires avoiding contact with the allergen as much as possible, pharmacotherapy and in some cases immunotherapy [6]. The ARIA guidelines recommend the use of second-generation antihistamines, intranasal corticosteroids, antileukotrienes, and immunotherapy for the treatment of rhinitis [4].

Montelukast is an antileukotriene that binds with high affinity and selectivity to the cysteinyl-leukotriene receptor 1 (CysLTR-1), thus inhibiting the physiological actions of leukotrienes C4, D4 and E4, directly linked to the symptoms of RA. This drug is extensively metabolized by cytochrome P450 (CYP) 3A4, CYP2C8,

and CYP2C9; In studies with therapeutic doses, plasma concentrations of montelukast metabolites are undetectable at steady state in adult and pediatric patients. Montelukast is not associated with significant drug interactions when used at recommended doses, unlike other leukotriene inhibitors such as zafirlukast and zileuton that are more selective for CYP [7,8]. For its part, desloratadine is a second-generation antihistamine selective antagonist of histamine H1 receptors, it does not penetrate the central nervous system, it has a high affinity for said receptor compared to cetirizine, ebastine, loratadine and fexofenadine, in addition, desloratadine has a longer half-life (27 h), which produces a substantial benefit in nasal and ocular symptoms in patients with moderate AR compared to other second-generation antihistamines [9-11].

The bioavailability of montelukast is not altered by the co-administration of desloratadine, its combination seems safe and effective to subjectively and objectively reduce nasal obstruction and other symptoms of RAP, in addition, patients experience improvement in sleep quality, daytime activity and quality of life during combination therapy [12,13].

The combination of these two drugs represents a comprehensive treatment for the allergic process, since it is aimed at two of the mediators that play a relevant pathophysiological role; The therapeutic effects of desloratadine theoretically have advantages over loratadine present in another pharmaceutical combination currently prescribed in the Mexican population, whose characteristics are suitable as an active comparator in the present study. Therefore, the primary objective of our study was to compare the efficacy of the fixed-dose combination montelukast / desloratadine versus montelukast / loratadine when administered once daily.

Methods

A controlled, randomized, double-blind, confirmatory therapeutic, prospective, longitudinal, parallel-group clinical study with two active treatment arms, and multicenter was carried out in which Mexican adult patients with a diagnosis of RAP of at least one year were enrolled evolution, without asthma diagnosis, to evaluate the efficacy of the combination montelukast / desloratadine 10/5 mg capsules from Laboratorios Liomont SA de C.V. compared to montelukast / loratadine 10/10 mg tablets (Montaclar®) given every 24 hours (taken in the evening) by mouth for 6 weeks. The patients were enrolled after obtaining informed consent. The study and all the documents delivered or applied to the patients were authorized by the Research and Research Ethics Committees in compliance with local regulations. All procedures were carried out in compliance with the Declaration of Helsinki, Good Clinical Practices and current regulations in Mexico.

Efficacy was determined through the global score of the SNOT-20 questionnaire (Sino-Nasal Outcome Test) [14], in addition, the information collected through medical history, physical examination with anterior rhinoscopy, the score of the T5SS questionnaire (Total 5-Symptom Score) [15], and the Treatment Satisfaction Questionnaire for Medication (TSQM) [16]. Assessments were carried out during the baseline assessment (day -7), at the start of treatment (day 1), at day 21 (follow-up), and at the end of treatment (day 42).

The primary efficacy endpoint was established as the difference between the baseline global score and the global score obtained at the last visit to the sixth week of the SNOT-20 questionnaire. If the subtraction from the baseline score minus the score from the last visit has a value greater than zero (positive), it is interpreted as a favorable result, while the value less than zero is interpreted as an unfavorable result. We consider that a change greater than 3 points in the global SNOT-20 score is a cutoff that indicates a general improvement in the symptoms and conditions of the disease evaluated by the questionnaire.

The secondary efficacy variables correspond to the SNOT-20 area under the curve (AUC) of each visit, the SNOT-20 indicators by treatment and by visit, the severity classification of the SNOT-20 scores, the T5SS questionnaire in its baseline score difference minus score at day 42 (method similar to the primary variable), T5SS indicators by treatment and by visit (21 days and 42 days), severity classification of T5SS scores, rescue drug use (Inhaled mometasone, prohibited in the first 10 days and use allowed up to 2 weeks), as well as the TSQM questionnaire scores.

Statistical analysis used the Student's t test and the Mann-Whitney U test for comparison of means, and in the non-inferiority test. A linear regression method was used to evaluate the potential impact of the demographic and baseline variables on the analysis of the primary efficacy variable (change in SNOT-20). For the analysis of the secondary efficacy variables on a categorical scale (nominal or ordinal), Fisher's exact test was used. The demographic and baseline characteristics are presented with descriptive statistics. Statistical analysis was performed using Stata® version 15 (StataCorp, Texas, United States) and NCSS® 11 (NCSS, LLC. Kaysville, Utah, United States) and East® version 6 (Cytel Inc, United States) programs. . The level of significance was set at 5% (Type I error, $\alpha = 0.05$), except for the non-inferiority test, which, because it was one-sided, was set at 2.5% (Type I error, $\alpha = 0.025$).

Results

Forty-four patients in the montelukast / loratadine (MKLOR) control group and 42 patients in the montelukast / desloratadine (MKDES) test group were studied for a total of 86 patients randomized to the intention-to-treat population. During the database review, under double-blind conditions, subjects with baseline SNOT-20 scores <3 (visits on day -7 and day 1) were discarded according to the eligibility criteria, leaving 37 patients in each group for a total of 74 individuals in the population per protocol (Figure 1).

The population per protocol (n = 74) allowed evaluating the efficacy variables (primary and secondary); while in the intention-to-treat population (n = 86), demographic variables, secondary clinical variables, TSQM, safety and as confirmatory analysis of the primary efficacy variable were evaluated.

Of the 86 patients, 62.8% (n = 54) were women, however, both the gender proportion and the rest of the demographic variables and vital signs did not show clinically relevant differences between the treatment groups (Table 1).

Table 1: Baseline evaluation characteristics

Variable	MKLOR	MKDES
Gender (n = male / female)	15/29	17/25
Age (years)	35.5 (14.0)	32.2 (12.9)
Weight (kg)	73.3 (11.7)	69.3 (10.9)
IMC (kg/m²)	26.2 (3.9)	24.7 (4.1)
Body temperature (° C)	36.1 (0.2)	36.2 (0.3)
Heart rate (bpm)	73.4 (8.3)	71.3 (7.4)
Respiratory rate (bpm)	18.6 (2.3)	18.5 (1.9)
Systolic blood pressure (mmHg)	114.8 (12.2)	110.8 (14.3)
Diastolic blood pressure (mmHg)	74.7 (9.5)	72.5 (8.3)

BMI = body mass index, bpm = beats per minute, bpm = breaths per minute. Data of quantitative variables of day -7 expressed as mean (standard deviation).

The primary efficacy analysis reported that the change in the global score of the SNOT-20 questionnaire was greater than 3 points in both groups of the population per protocol, with a value of 3.54 points in those treated with MKLOR (-0.78 to 4.80) and for MKDES of 3.27 points (0.03 to 4.35), the difference of means (test-reference) was -0.26 points, whose lower limit of the 97.5% CI was -0.76 points, which does not exceed the margin of inferiority of -0.8 clinically relevant [17] (p = 0.0170), therefore the treatment with MKDES is not inferior to MKLOR. This was verified in the ITT population (p = 0.0056) with a mean difference of -0.22 points and a lower limit of the 97.5% CI of -0.67 points (Table 2).

Table 2: Primary efficacy analysis

Variable	n	MKLOR	MKDES	Non-inferiority		
		Media (DE)	Media (DE)	Δ	IC	p
SNOT-20	74	3.535 (1.012)	3.271 (1.117)	-0.264	-0.758	0.0170
	86	3.394 (0.983)	3.173 (1.082)	-0.221	-0.665	0.0056

Δ = difference of means, SD = standard deviation, CI = confidence interval

The mean and standard deviation of the change in the questionnaire score in the per-protocol population (n = 74) and in the intention-to-treat population (n = 86) are shown. The CI corresponds only to the lower limit of the 97.5% CI.

The potential impact of the demographic variables was evaluated by linear regression, considering the change in the global SNOT-20 score as the dependent variable and the treatment, research site, age, gender, and body mass index as independent variables. Only the research site had a significant effect on the primary efficacy variable (p <0.0001). Individuals from one center had a smaller change in score compared to the other centers. As this occurred in only 10 patients, it was not considered to have a significant impact on the conclusion of the non-inferiority test.

In the secondary efficacy analysis, the global scores from the baseline measurement to the last week showed a mean difference of -0.393 units of area under the curve, with no significant difference between both groups (p = 0.6667). No significant difference was found for the global change of the T5SS (p = 0.3902), which is consistent with the conclusion of non-inferiority of the primary efficacy variable. The global TSQM score was greater than 80% in both groups, as were the dimensions of effectiveness and convenience of use; the adverse events dimension suggested a high degree of tolerability (Table 3).

Table 3: Secondary variables efficacy analysis

Variable	n	MKLOR	MKDES	Δ [IC 95%]	p
SNOT-20 ABC	37/37	11.1 (4.0)	10.8 (3.8)	-0.39 [-2.2,1.4]	0.6667
T5SS	37/36	2.39 (0.73)	2.22 (0.88)	-0.16 [-0.54,0.21]	0.3902
TSQM	44/41				
Effectiveness		84.0 (16.6)	85.5 (19.8)	-	-
Adverse events		100 (0.0)	100 (0.0)	-	-
Convenience of use		88.3 (12.1)	89.4 (13.4)	-	-
Global		86.4 (13.8)	88.7 (13.5)	-	-

Δ = difference of means, CI = confidence interval, AUC = area under the curve

The mean and standard deviation of the evaluations in the per-protocol population (n 74, eg 37/37) and in the intention-to-treat population (n ≈ 86, eg 44/42) are shown.

The indicators of the SNOT-20 questionnaire were evaluated by group and by week, both treatments reduced the scores of the indicators without differences between the indicators of symptoms, nor in those of quality of life (Table 4).

Table 4: SNOT-20 questionnaire indicators

Symptoms	MKLOR / MKDES				
	Basal	Sem 2	Sem 3	Sem 4	Sem 6
Need to blow your nose	4.8/4.7	3.3/3.3	2.4/2.3	1.6/1.9	1.1/1.1
Sneezing	4.8/4.7	3.3/3.1	2.2/2.2	1.2/1.5	0.8/0.8

Continuous nasal discharge	4.7/4.7	3.1/3.1	1.9/2.0	1.2/1.5	0.5/0.7
Cough	4.3/4.1	2.7/2.4	1.5/1.2	0.8/0.9	0.2/0.4
Discharge down the throat	4.3/4.2	2.8/2.4	1.6/1.5	1.0/1.1	0.6/0.6
Thick nasal discharge	4.1/4.0	2.7/2.3	1.4/1.4	1.0/0.9	0.5/0.5
Feeling of blocked ears	3.9/3.9	2.5/1.8	1.3/1.2	0.9/0.8	0.4/0.5
Dizziness	3.1/3.2	1.9/1.6	0.7/0.9	1.1/1.1	0.2/0.3
Earache	3.4/3.3	2.1/1.5	1.1/1.0	0.6/0.6	0.3/0.3
Pain and pressure in the face	4.2/3.7	2.6/2.0	1.5/1.1	0.8/1.1	0.5/0.5
Quality of life					
Difficulty falling asleep	4.4/4.2	3.0/2.7	1.7/1.8	1.3/1.3	0.4/0.7
Wake up during the night	4.3/4.4	3.0/2.9	1.8/1.7	1.3/1.1	0.4/0.5
Feeling that you slept badly	4.5/4.5	3.1/2.8	1.8/2.0	1.2/1.3	0.5/0.6
Wake up tired	4.5/4.4	2.8/3.0	1.9/1.9	1.2/1.4	0.4/0.8
Fatigue or tiredness	4.4/4.4	2.8/2.8	1.6/1.8	1.1/1.3	0.5/0.8
Lower productivity	4.2/4.2	2.6/2.4	1.6/1.5	0.9/1.1	0.4/0.8
Lower concentration	4.2/4.1	2.4/2.3	1.4/1.3	0.7/0.9	0.4/0.6
Frustrated, restless, or irritable	3.4/3.3	1.9/1.5	0.8/1.1	0.4/0.7	0.3/0.4
Sad	2.1/2.0	1.2/0.7	0.5/0.5	0.4/0.4	0.1/0.3
Embarrassed	2.1/2.1	1.3/0.7	0.6/0.4	0.3/0.2	0.2/0.2

The mean of the scores for each indicator per treatment and per week (Sem) is shown.

Meanwhile, the T5SS indicators evaluated by group and by week showed that both treatments reduced the score, with no differences between groups (Table 5).

Table 5: T5SS questionnaire indicators

Symptoms	MKLOR / MKDES		
	Basal	Sem 3	Sem 6
Nasal congestion	2.8/2.8	1.1/1.3	0.4/0.5
Sneezing	2.8/2.7	1.2/1.3	0.4/0.6
Rhinorrhea / runny nose	2.7/2.7	1.0/1.2	0.4/0.4
Nasal itching	2.6/2.6	0.8/1.0	0.2/0.4
Eye itching	2.5/2.5	0.8/1.0	0.1/0.3

The mean of the scores for each indicator per treatment and per week (Sem) is shown.

The severity levels of the SNOT-20 indicators in baseline conditions classified about 75% of the patients in the levels of “4 severe” or “5 cannot be worse” for both treatments. At the sixth week of treatment, more than 90% (91.9% MKLOR and 91.7% MKDES) of the patients were classified as “1 very mild” or “0 no problem”. The severity levels of the T5SS indicators in baseline conditions classified more than 70% of the patients in the maximum level "3 severe" for both treatments. In the sixth week, more than 90% (91.9% MKLOR and 91.7% MKDES) of the patients were classified as “1 mild” or “0 none”, which indicates that both treatments globally improved the five symptoms evaluated.

The use of rescue medication occurred in 5 of the 86 intention-to-treat patients. Four patients were recruited from the same center, four patients were from the MKDES group, two patients used rescue medication in the third week, three patients during the sixth week; and the duration ranged from 1 day to 18 days. The small number of patients who used rescue medication does not allow us to infer whether its use and duration were related to the assigned treatment.

Adverse events occurred in 4 of the 86 patients. A total of 12 adverse events (AE) were reported. Three patients from the MKLOR group reported 8 AE and one MKDES patient reported 4 AE. One case presented elevated aminotransferases (> 2 times the reference value), without concomitant medication and attributed by the investigator to the drug MKLOR. The event was closed after the subject showed improvement after stopping treatment.

Discussion

For some time, leukotriene receptor antagonists (LRAs) were considered secondary treatment for RAP in patients with asthma. The information available for RAP without asthma in the 2010 ARIA review showed ARLs with a small benefit in preschool children, limited efficacy in adults, and a high cost, therefore the recommendations pointed to oral antihistamines with a higher clinical value than the ARL [18]. A large number of patients with RA do not go to the medical consultation because they believe that their symptoms are "normal", others use over-the-counter medications, while only a small part go to consultation where they are diagnosed with moderate or severe RAP [19] . In the present study, the profile of selected patients

had a minimum of 3 in the SNOT-20 score, which could benefit from a combination with adequate potency and sustained action.

The combined use of antihistamines and antileukotrienes has been reported to have efficacy advantages over monotherapy in patients with RAP. For example, the combination of montelukast with desloratadine or levocetirizine decreased nasal symptoms and eosinophilic cationic protein levels above that observed for the drugs alone [20]. The advantage of the therapeutic combination in the health-related quality of life and the nocturnal symptoms scale, obtained from the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), has also been verified, in addition, the presence of Adverse events were similar for placebo, montelukast, levocetirizine, or the combination of montelukast and antihistamine [21].

In the present study, treatment with montelukast plus loratadine or desloratadine achieved a difference greater than 3 global points on the SNOT-20 questionnaire in patients with RAP at week six; this change is clinically relevant and demonstrates the therapeutic utility of the combination. According to Piccirillo et al. the delta of 0.8 in the SNOT-20 score is considered clinically significant [14,17], so the difference in means reported here with a confidence interval within a lower margin than that cutoff allows us to affirm that the MKDES test treatment is not inferior to the MKLOR active comparator. The follow-up time used in this study was comparable to previous studies that evaluated the clinical effects of treatment with montelukast and antihistamines [20], although shorter than others [21]. However, the design of the present study and the SNOT-20 instruments and T5SS have demonstrated clinically relevant changes with adequate coverage of the proposed objective, both in the protocol population and in the intention-to-treat population. The evaluation time of six weeks of treatment and total evaluation is justified according to the criteria of other authors [22]; furthermore, the evaluation period is appropriate for the SNOT-20 primary efficacy instrument according to the validation history [14,17], as well as for the TSQM questionnaire. Reported TSQM scores of 84% to 100% are indicative of high patient satisfaction and excellent tolerability to the combined treatment.

A limitation of this study is that the evaluation window does not allow to check how symptoms behave with long-term treatment, for example, the XPERT study for RAP treated with levocetirizine evaluated nasal and ocular symptoms with T5SS from 4 weeks to the 6 months of treatment to report from when the symptoms improved and which remained stable throughout the treatment. In this study, levocetirizine significantly improved nasal congestion after the first month of treatment and continued for more than 6 months [16]. The evaluation window here was sufficient to verify that the symptoms improved from week 3 with indicators in the mean score of “1 mild”, and in week 6 with the mean score close to “0 none”. The evaluation of Ciebiada et al. for 32 weeks demonstrated the long-term effect of the combined treatment of montelukast and desloratadine or levocetirizine. However, their evaluation used a different instrument focused on nocturnal symptoms [21]. Future studies could evaluate the long-term effect of combined antileukotriene and antihistamine treatment on RAP in the Mexican population.

The severity levels of the indicators in the SNOT-20 and T5SS questionnaires showed that the conditions of quality of life and symptoms had very high scores in the baseline evaluation, 7 to 8 out of 10 patients were in the highest levels of severity, and at six weeks of the study the scores decreased to a minimum in 9 out of 10 patients, improvement achieved in both treatment groups.

The AEs expected and observed in the patients with the treatments under study were headache, dyspepsia and gastrointestinal discomfort, related to the use of montelukast or desloratadine [21,22], loratadine does not seem to be related to these symptoms, however, we observed these AEs in both treatment groups with clinical characteristics that did not leave a clear causal relationship. One patient from the MKDES group presented AE described as “gastritis”, “colitis” and “diarrhea”, while a patient from the MKLOR group presented “acute gastritis”, in both cases the causality was reported as “unclassifiable”. Headache occurred in a patient in the MKLOR group, with causality reported as "conditional" due to concomitant alcohol consumption, although it was prohibited. In most, concomitant medications were used to resolve the manifestations. As reported in the literature, the combination of the drugs under evaluation was safe considering that no serious AE was reported during the study, all the AE reported were mild or moderate, only one of them was from the MKDES group, while one AE Medication-related in the MKLOR group was self-limiting at the end of treatment. That said, it is possible to conclude that the test drug montelukast / desloratadine had adequate tolerability.

Conclusions

The combination of desloratadine with montelukast significantly improves the symptoms produced by RAP. Treatment evaluation demonstrated clinically relevant efficacy and safety, not inferior to the combination of montelukast with loratadine. These results suggest the MKDES combination as a treatment option when the patient requires the addition of a drug with mechanisms of action other than the antihistamine. In addition, the administration schedule can promote adherence and tolerability to treatment.

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