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Research Article

Clinical Effect of Montelukast in Asthmatic Patients with Allergic Rhinitis Treated with Intranasal Corticosteroids or Oral Antihistamines. A Real-Life Cohort Study

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Abstract

Introduction: Cysteinyl leukotrienes are responsible for common symptoms in patients with rhinitis and asthma, including edema of the airways, contraction of smooth muscle, the presence of inflammatory cells, increased blood flow, edema of the mucosa and increased mucus secretion. This situation requires a therapeutic approach that concomitantly acts on the mediators responsible for the common symptoms.

Objective: To compare the effectiveness of second-generation oral antihistamines (cetirizine-levocetirizine), nasal corticosteroids (mometasone furoate-ciclesonide), montelukast combined with a second-generation oral antihistamine and montelukast combined with nasal corticosteroids, in a cohort of patients with a history of asthma, who consulted for treatment of allergic rhinitis.

Patients and methods: A cohort study was conducted, including patients older than 18 years, with a history of controlled asthma, who consulted with allergic rhinitis. The outcome variable was the delta between the initial score and the final score of the Total Nasal Symptom Score (TNSS). The comparison groups were second-generation oral antihistamines, nasal corticosteroids, montelukast in combination with second-generation oral antihistamines, or montelukast in combination with nasal corticosteroids.

Results: A total of 350 patients enrolled in the cohort, 303 (87%) of whom attended the follow-up. Of these, 59.4% (180/303) received oral antihistamines; 12.2% (37/303) corticosteroids for intranasal application; 16.2% (49/303) montelukast 10 mg / day plus antihistamine; and montelukast 10 mg / day plus intranasal corticosteroid in 12.2% (37/303). The overall median difference in TNSS scores was 4, in the group of antihistamines it was 2; in intranasal corticosteroids it was 4; in montelukast plus antihistamines it was 5 and in montelukast plus intranasal corticosteroids it was 7 (p-value: 0.0001).

Conclusion: The alternative that showed the greatest reduction in symptoms was the combination of intranasal corticosteroids in combination with montelukast, followed by the combination of H1 antihistamines and montelukast.

Keywords: Allergic rhinitis; Asthma; Cetirizine; Ciclesonide; H1 histamine receptor antagonists; Levocetirizine; Mometasone furoate; Montelukast.

Introduction

Data on the prevalence of allergic rhinitis are heterogeneous, depending on the different populations [1] and to be as high as 25% in the pediatric population [2] and up to 40% in adults [3], while the prevalence of asthma symptoms in the adult population can range between 2 and 27%. As reported by the study of the burden of disease due to asthma, it is estimated that globally there may be more than 300 million people with this condition and that by 2025 there could be around 400 million affected [4].

Although these two diseases have been considered independent conditions, different studies have shown that allergic respiratory diseases are not limited to specific anatomical areas, such as the nasal cavity or the bronchi, but are present throughout the respiratory system, giving rise to a broad set of clinical disorders, including rhinitis and asthma, which are closely related clinically, pathophysiologically and epidemiologically [5-7]. Thus, it has been possible to establish a high frequency of combined symptoms of allergic rhinitis and asthma, finding for example that in the United States the prevalence of allergic rhinitis among the asthmatic population is greater than 50% and in some American and European population groups, this prevalence may reach 100% [8].

The presence of these two pathologies in the same individual may be a cause of high economic impact, as has been reported in different studies [8]. In the North American population, using the medical record data of 9,226 asthmatic patients with allergic rhinitis and 18,172 patients with asthma, it was documented that patients who present with both pathologies had a greater demand in the prescription of asthma medications (inhaled β agonists: 54% versus 48%; inhaled steroids 33% versus 22%) [9]. Additionally, in a series

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of 1,245 patients, a group of researchers was able to establish that the cost of annual treatment in patients with asthma and concomitant rhinitis was, on average, 46% higher than the cost of treatment of patients with an exclusive asthma diagnosis [10].

Given the current level of knowledge about the existence of different mediators, cytokines and growth factors that are involved in the chronic inflammation present in rhinitis and asthma, treatment guidelines recommend that physicians verify the presence of asthma in patients with allergic rhinitis and vice versa, seeking to offer an integrated therapeutic approach for both conditions [5].

Cysteinyl leukotrienes are a group of mediators responsible for the presence of common symptoms in patients with rhinitis and asthma. In the latter, they cause edema of the airways, contraction of smooth muscle and the presence of inflammatory cells and in the case of patients with rhinitis, they induce an increase in blood flow, cause edema and produce an increase in mucus secretion, responsible for nasal obstruction [11].

Recommendations for the treatment of patients diagnosed with allergic rhinitis include the use of antihistamines-H1 and corticosteroids for intranasal application, given their potential effect on the symptoms of rhinorrhea, nasal congestion, itchy nose and lacrimation [5]. However, in patients who have both pathologies, the need arises for a treatment that concomitantly intervenes on the mediators responsible for the common symptoms (e.g.inflammatory infiltrate of the nasal and bronchial mucosa). Montelukast is an anti-leukotriene drug that has been shown to be effective in controlling asthma symptoms and improves lung function by inhibiting the cysteinyl leukotriene receptor [12] and in patients with allergic rhinitis, has also been shown to be effective in reducing daytime and nighttime nasal symptoms [13].

Currently, in the context of the clinical practice of primary care in Colombia, the number of consultations has increased, where it is necessary to provide treatment to patients with allergic rhinitis and coexistence of asthma. In the therapeutic arsenal for the management of rhinitis, there are antihistamines and intranasal corticosteroids. More recently, the combined use of these alternatives with montelukast has been increasing, under the theoretical assumption of improving the control of symptoms, by the intervention of early- and late- phase mediators of allergic rhinitis.

Based on the above approaches, the present real-life study was conducted, with the aim of comparing the effectiveness of second-generation oral antihistamines (cetirizine-levocetirizine), corticosteroids for nasal application (mometasone furoate-ciclesonide), montelukast combined with a second-generation oral antihistamine and montelukast combined with nasal corticosteroids, in a cohort of patients with a history of asthma, who consulted for treatment of allergic rhinitis.

Patients and Methods

Design

An analytical observational cohort study was carried out, within the framework of a surveillance registry of clinical outcomesand use profiles of a group of medications from the portfolio of the Abbott-Lafrancol laboratory (Biomedical Registry of follow-up to medical care and clinical outcomes in common pathologies: RBDC).

Inclusion and exclusion criteria

Through a sequential sampling strategy, the study included patients older than 18 years, with a history of controlled asthma, who consulted with allergic rhinitis according to the definition and classification criteria proposed in the Allergic Rhinitis and its Impact on Asthmastudy: ARIA study[3], as well as those who were candidates to be treated -at the discretion of the treating physician- with any of the following management schemes: second-generation oral antihistamines (cetirizine or levocetirizine), corticosteroids for nasal application (mometasone furoate or ciclesonide), combined montelukast with a second-generation oral antihistamine (cetirizine or levocetirizine), or montelukast combined with nasal corticosteroids (ciclesonide or mometasone furoate). The care of these patients was provided by a group of 21 primary care physicians, between July and December 2016, in 11 cities in Colombia (Bogotá, Medellin, Bucaramanga, Cali, Cartagena, Manizales, Barranquilla, Santa Marta, San Juan del Cesar, Florida Blanca and Palmira). Patients with a history of difficult-to-manage asthma or uncontrolled asthma at the time of study entry were excluded.

Enrollment and follow-up procedure

Each of the doctors in the program, in the context of their routine clinical practice, provided care to their patients and according to their criteria assigned the corresponding treatment. Each patient candidate to be enrolled in the registry was asked for their informed consent to analyze the data of their clinical evolution over a period of 12 weeks. In each case, the professional prescribed the treatment and allowed the research group to know the baseline and follow-up data. Clinical control appointments were defined by the treating physician, however, for the purposes of analysis, the last control available at week 12 of follow-up (± 2 weeks) was considered. Participating physicians were unaware of the study hypothesis (blind study).

Sample size

To calculate the sample size the formula for comparing more than two treatments, applied by Day et al.[14] was employed. The assumptions for the calculation were obtained through a preliminary pilot study conducted with 30 patients, where an expected mean difference in the TNSS of 3 points was established for the antihistamine group and 6 for the montelukast treatment group, with an estimated standard deviation of 2.5 points, assuming an alpha value of 0.05 and a beta value of 0.2. Based on this calculation, it was determined that the minimum number of subjects per treatment group would be 37 patients and a total sample of 148 subjects. This sample size was taken as a reference value for each group; however, the final sample included all the enrolled patients in a period of six months.

Variables of interest

Variables of age, sex and current use of inhaled corticosteroids for asthma management were recorded. The outcome variable was defined as the Total Nasal Symptoms Score (TNSS) [15], which includes runny nose, itchy nose, sneezing and nasal obstruction. Each symptom was measured on a Likert scale (0: no symptoms; 1: mild symptoms; 2: moderate symptoms; 3: severe symptoms) [16]. The TNSS reports possible values between 0 and 12, where 0 is the absence of symptoms and 12 is the highest possible intensity of symptoms. The comparison groups defined for the analysis were

given by the prescribed treatment variable as follows: Second-generation oral antihistamines (cetirizine or levocetirizine), nasal corticosteroids (mometasone furoate or ciclesonide), montelukast plus second-generation oral antihistamine (cetirizine or levocetirizine), or montelukast plus nasal corticosteroids (ciclesonide or mometasone furoate).

Statistical Analysis

A general description of the variables was made, using frequency measures, central tendency statistics and dispersion according to the measurement scale. For the prescription type variable, absolute and relative frequencies were calculated by comparison group. Baseline characteristics by treatment group were described, including age, sex and use of inhaled corticosteroids. Regarding the clinical outcome of interest (TNSS), it was measured at the admission of the patient to the cohort and at the end of the follow-up (12 ± 2 weeks). Based on these two measurements, the difference was calculated, corresponding to the improvement gradient of each patient (initial TNSS-final TNSS = improvement Δ). Initial, final and gradient scores were described for each comparison group, reporting the median, 25th percentile, 75th percentile, mean and Standard Deviation (SD). For the hypothesis test, since the improvement gradient variable did not present normal distribution, the Kruskal-Wallis non-parametric test and the Dunn posthoc test were applied. A p-value of 0.05 was defined for the hypothesis test.

Ethical Aspects

This project complied with the national and international ethical guidelines for research and was approved by an independent Ethics Committee (Ethics Committee: Bogotá Surgery Society-San José Hospital. Bogota, Colombia). Patients agreed to their records being analyzed for medical and scientific purposes.

Results

The cohort was composed of 350 patients, of whom a total of 303 patients attended the follow-up at week 12 (± 2 weeks), for a level of adherence of 87%. The age of those included ranged from 18 to 86 years, with a median of 33 years; 62.4% of the sample were women (189/303) and 24% had a current prescription for inhaled corticosteroids to manage their history of asthma. The description of baseline characteristics can be found in table 1.

The prescription was distributed among oral antihistamines (levocetirizine: 5 mg orally once daily; cetirizine: 10 mg orally once daily) in 59.4% (180/303); intranasal corticosteroids (mometasone furoate: 50 mcg, 2 sprays each nostril once daily; ciclesonide: 50 mcg nasal spray: 2 sprays each nostril once daily) in 12.2% (37/303); montelukast 10 mg / day plus antihistamine in 16.2% (49/303) and montelukast 10 mg / day plus intranasal corticosteroid in 12.2% (37/303).The detail of the distribution by treatment group is presented in table 2.

Characteristic	H1-Anti (n = 180)		INC (n = 37)		H1-Anti + MLK (n = 49)		INC + MLK (n = 37)		Total (n = 303)	
	n	%	n	%	n	%	n	%	n	%
Women	115	62.8	22	62.9	29	59.2	23	63.9	189	62.4
INHC	43	23.8	8	21.6	12	24.4	10	27	73	24
	p50	p25-p75	p50	p25-p75	p50	p25-p75	p50	p25-p75	p50	p25-p75
Age	35	25-53	27	22-48	32	21-40	33	22-47	33	23-50
Basal TNSS	9	5-11.5	9	7-9	9	8-11	9	8-11	9	6-11

Table 1: Baseline characteristics of included patients.

H1-Anti: H1 Antihistamines. INC: Intranasal Corticosteroids. INHC: Inhaled Corticosteroids. MLK: Montelukast. n: Number of subjects. %: percentage. p: Percentile. TNSS: Total Nasal Symptom Score.

Characteristic	H1-Anti (n = 180)		INC (n = 37)		H1-Anti + MLK (n = 49)		INC + MLK (n = 37)		Total (n = 303)	
	n	%	n	%	n	%	n	%	n	%
Cetirizine	79	43.9							79	26.1
Levocetirizine	101	56.1							101	33.3
Total Antihistamines	180	100							180	59.4
Ciclesonide			7	18.9					7	2.3
Mometasone furoate			30	81.1					30	9.9
Total intranasal corticosteroids			37	100					37	12.2
Cetirizine + Montelukast					24	49.0			24	7.9
Levocetirizine + Montelukast					25	51.0			25	8.3
Total Antihistamines + Montelukast					49	100			49	16.2
Ciclesonide + Montelukast							9	24.3	9	3.0
Mometasone Furoate + Montelukast							28	75.7	28	9.2
Total intranasal corticosteroids + Montelukast							37	100	37	12.2
Total	180	100	37	100	49	100	37	100	303	100

Table 2: Distribution by treatment groups.

H1-Anti: H1 Antihistamines. INC: Intranasal Corticosteroids. MLK: Montelukast. n: Number of subjects. %: percentage.

Clinical Performance

Baseline TNSS scores ranged from 5 to 12 points, with a median of 9 and an average of 8.6. There were no statistically significant differences between the distributions of these baseline scores by treatment group (p-value: 0.092).

After 12 weeks of follow-up, the global median was 5 points, the average was 4.7 and 50% of the subjects achieved values between 3 and 6 points. The lowest final median was for the group treated with montelukast plus intranasal corticosteroid (median: 3). We found a significant difference between the combination of montelukast plus intranasal corticosteroid and the other alternatives evaluated (p-value: 0.0001).

The final effect obtained in each patient was obtained by calculating the delta between the severity of the initial symptoms and the severity reached at the end of the treatment (Δ = baseline TNSS-final TNSS). The global median of this difference was 4 points and the average was 3.9 points. The greatest difference was found in the group treated with montelukast plus intranasal corticosteroid, with a median of 7 points of difference. The smallest difference was found in the group of antihistamines, with a median of 2 points of difference (p-value: 0.0001). Table 3 presents the descriptive statistics for each group and table 4 presents the performance of each treatment using a matrix of comparisons with p-values for the specific comparison between groups.

Discussion

The primary objective of this study was to evaluate the effectiveness of montelukast combined with H1 antihistamines, or intranasal corticosteroids, compared to the usual treatments with second-generation oral antihistamines or intranasal corticosteroids, in patients with allergic rhinitis and a history of asthma. The combination of montelukast plus corticosteroid for intranasal application showed the highest level of effectiveness compared to the other alternatives, given a greater decrease in the difference in baseline and final TNSS scores. It is worth noting that the combination of montelukast with H1 antihistamines showed superior performance to the use of intranasal corticosteroids and that of H1 antihistamines, but inferior to the effect achieved by the combination of montelukast and intranasal corticosteroids. Additionally, the comparison allowed us to corroborate the superiority of intranasal corticosteroids compared to second-generation H1 antihistamines, as has been demonstrated in previous studies [17].

After an extensive search of the literature, it was not possible to identify studies that had evaluated the role of anti-leukotriene drugs combined with intranasal corticosteroids or with second-generation oral anti-H1 antihistamines, in conditions similar to those of real life, in patients with a history of asthma and symptoms of allergic rhinitis. In this process, various comparisons between intranasal corticosteroids and antihistamines were documented[17]: Montelukast compared to intranasal corticosteroids [18], or compared to antihistamines [19] and some studies with close comparisons to those proposed in the present investigation as montelukast combined with fluticasone [20], or combined with an antihistamine [21], or comparisons between corticosteroid plus antihistamine versus corticosteroid plus montelukast [22].

Contrasting the findings reported in this study with some of the identified works, it was possible to establish consistency with the results of the Pinar et al clinical trial, who compared the effectiveness of four treatment groups: Intranasal corticosteroid (mometasone furoate), corticosteroid intranasal plus desloratadine, intranasal corticosteroid plus montelukast and the fourth group of intranasal saline. After one month of follow-up, these investigators documented a greater reduction in nasal symptom score in the group of patients treated with montelukast and intranasal corticosteroid.

Type of treatment	TNSS	p25	p50	p75	Mean	SD
H1-Anti (n = 180)	Baseline	5	9	11.5	8.3	2.8
	Final (12 weeks)	4	5	7	5.3	2.8
	Δ (Baseline-Final)*	0	2	4	3	2.9
INC (n = 37)	Baseline	7	9	9	8.3	1.8
	Final (12 weeks)	3	4	5	4.4	1.2
	Δ (Baseline-Final)*	3	4	5	3.9	1.7
MLK + H1-Anti (n = 49)	Baseline	8	9	11	9.2	2.1
	Final (12 weeks)	4	5	5	4	1.6
	Δ (Baseline-Final)*	4	5	7	5.2	2.9
MLK + INC (n = 37)	Baseline	8	9	11	9.2	1.9
	Final (12 weeks)	2	3	4	2.9	1.5
	Δ (Baseline-Final)*	5	7	8	6.3	2.2
Total (n = 303)	Baseline	6	9	11	8.6	2.6
	Final (12 weeks)	3	5	6	4.7	2.5
	Δ (Baseline-Final)*	1	4	6	3.9	2.9

Table 3: Descriptive statistics by treatment group.

H1-Anti: H1 Antihistamines. INC: Intranasal Corticosteroids. MLK: Montelukast. n: Number of subjects. p: Percentile. TNSS: Total Nasal Symptom Score. SD: Standard Deviation. Δ (Baseline-Final) *: delta calculation is obtained from the difference of the baseline score minus the final score in each patient. From this resulting variable, the p50 or median, p25, p75, mean and SD are presented. This calculation does not necessarily coincide with the subtraction of the global estimator obtained from the baseline median minus the final one.

Comparison	Baseline				Final (12 weeks follow-up)				Δ (Baseline-Final)			
	Median (p25-p75)	H1-Anti	INC	MLK + H1-Anti	Median (p25-p75)	H1-Anti	INC	MLK + H1-Anti	Median (p25-p75)	H1-Anti	INC	MLK + H1-Anti
		9 (5-11.5)	9 (7-9)	9 (8-11)		5 (4-7)	4 (3-5)	5 (4-5)		2 (0-4)	4 (3-5)	5 (4-7)
INC	**9 (7-9)**	0.42			**4 (3-5)**	0,013			**4 (3-5)**	0,018		
MLK + H1-Anti	**9 (8-11)**	0,079	0,098		**5 (4-5)**	0,001	0,335		**5 (4-7)**	0,000	0,037	
MLK + INC	**9 (8-11)**	0,085	0.10	0.48	**3 (2-4)**	0,000	0,004	0,008	**7 (5-8)**	0,000	0,000	0,030

Table 4: Comparative matrix of p-values between distributions of TNSS scores by treatment group (Dunn test for comparisons between groups).

TNSS: Total Nasal Symptom Score. H1-Anti: H1 Antihistamines. INC: Intranasal Corticosteroids. MLK: Montelukast. p: Percentile. Δ (Baseline-Final): difference between baseline and final score. The value in the cell corresponds to the p-value of the comparison between treatments (Dunn's test). Values less than 0.05 were considered significant.

Based on this evidence, the authors concluded that although intranasal corticosteroids have been shown to be effective, the addition of montelukast has a superior effect on nasal symptoms and quality of life, so this combination should be considered for this type of patient [22].

It is worth noting that the evidence is not entirely consistent, given that there are studies such as the one published by Esteitie et al., who carried out a clinical trial of reduced sample size, in which they were unable to establish differences between the addition of montelukast to intranasal treatment with fluticasone [20]. The difference between the findings described and those of this study may lie in a low statistical power to establish the superiority of any of the groups (montelukast plus fluticasone: 28 patients vs. fluticasone plus placebo: 26 patients).

Regarding the evidence that has evaluated the effect of adding montelukast to treatment with H1 antihistamines, it is worth highlighting the findings of Kim et al., who found that montelukast plus levocetirizine showed a greater reduction in the nasal symptoms score than in the group treated exclusively with montelukast (p-value: 0.045) [23]. The results of our research did not include a group treated in monotherapy with montelukast, but they did document the superiority of the combination of montelukast plus second-generation H1 antihistamines compared to intranasal corticosteroids or second-generation monotherapy antihistamines.

Analyzing the documented effectiveness for H1 antihistamine therapy compared to intranasal corticosteroids, the results corroborate the existing evidence, in which the superiority of the latter has been documented [17,24]. A similar result had already been obtained in a previous study by our research group, but only in patients with allergic rhinitis without a history of asthma [24].

The results of our research also reveal the distribution of prescriptions in these patients, finding a very high percentage of H1 antihistamine use (59.4%), while intranasal corticosteroids that have been shown to be superior in different studies only reach one prescription percentage of 12.2% [17,21,24]. This description profile had already been documented by our research group in a previous study [24], in which only patients with allergic rhinitis had been included, without additional comorbidities. In this study, a low percentage of combinations of antihistamines and intranasal corticosteroids with montelukast can be seen (16 and 12.2% respectively). This behavior may be due to the fact that the potential to treat patients with a history of asthma, who present with allergic rhinitis symptoms, with two mechanisms of action that may be complementary and that in regards to effectiveness results, according to the findings described here are superior. Another factor that may influence the low level of combined use of these combination therapies may be due to the low cost of anti-H1 antihistamines in Colombia and their easy access, which would explain their high level of prescription.

As previously discussed, direct head-to-head comparisons between direct competing medications are not common and evidence to allow comparison of different therapeutic regimens is less common. Additionally, it is a common weakness in clinical trials that the patient populations included, consistently differ from patients treated by physicians in the usual routine [25]. Based on the above, we propose that the main strength of the present study is the contribution of real-life evidence, in which it was possible to compare four different treatment schemes, for patients with allergic rhinitis, who additionally had a history of controlled asthma.

It is inevitable mentioning that observational studies have limitations related to the presence of selection biases, which affect the magnitude of the estimates. However, the physicians who participated in this study were unaware of the hypotheses of the study and evaluated each case within the framework of their normal clinical work routine activities. The registry databases were consulted by an independent technical team that subsequently transferred the information to the analysis group. Despite the potential limitations, the findings are consistent with most of the available evidence and the strengths mentioned make this research an important input for clinical decision-making in the management of patients with allergic rhinitis and a history of asthma.

In conclusion, we must emphasize that it has been possible to document with evidence from the usual practice of a group of primary care physicians, that in patients with symptoms of allergic rhinitis and a history of asthma, a combination of intranasal corticosteroid combined with montelukast produces an effect superior in terms of reduction of nasal symptoms after 12 weeks of follow-up, compared to other alternatives such as montelukast combined with H1 antihistamines, intranasal corticosteroids or H1 antihistamines.

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References

1. Mims JW (2014) Epidemiology of allergic rhinitis. Int Forum Allergy Rhinol 4: 18-20.

2. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, et al. (2006) Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. Lancet 368: 733-743.

3. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, et al. (2008) Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 86: 8-160.

4. Masoli M, Fabian D, Holt S, Beasley R (2004) The global burden of asthma: Executive summary of the GINA Dissemination Committee report. Allergy 59: 469-478.

5. Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, et al. (2017) Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol 140: 950-958.

6. Bousquet J, Vignola AM, Demoly P (2003) Links between rhinitis and asthma. Allergy58: 691-706.

7. Braunstahl GJ, Prins JB, KleinJan A, Overbeek SE, Hoogsteden HC, et al. (2003) Nose and lung cross-talk in allergic airways disease. Clinical &Experimental Allergy Reviews 3: 38-42.

8. Gaugris S, Sazonov-Kocevar V, Thomas M (2003) Burden of concomitant allergic rhinitis in adults with asthma. J Asthma 43: 1-7.

9. Halpern MT, Schmier JK, Richner R, Guo C, Togias A (2004) Allergic rhinitis: A potential cause of increased asthma medication use, costs, and morbidity. J Asthma 41: 117-126.

10. Yawn BP, Yunginger JW, Wollan PC, Reed CE, Silverstein MD, et al. (1999) Allergic rhinitis in Rochester, Minnesota residents with asthma: Frequency and impact on health care charges. J Allergy Clin Immunol 103: 54-59.

11. Dahlén SE (2003) Cysteinyl leukotrienes as common mediators of asthma and allergic disease. Clinical& Experimental Allergy Reviews 3: 69-73.

12. Reiss TF, Chervinsky P, Dockhorn RJ, Shingo S, Seidenberg B, et al. (1998) Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: A multicenter, randomized, double-blind trial. Montelukast Clinical Research Study Group. Arch Intern Med 158: 1213-1220.

13. Nayak A (2004) A review of montelukast in the treatment of asthma and allergic rhinitis. Expert opinion on pharmacotherapy 5: 679-686.

14. Day SJ, Graham DF (1989) Sample size and power for comparing two or more treatment groups in clinical trials. Bmj 299: 663-665.

15. Downie SR, Andersson M, Rimmer J, Leuppi JD, Xuan W, et al. (2004) Symptoms of persistent allergic rhinitis during a full calendar year in house dust mite-sensitive subjects. Allergy 59: 406-414.

16. Joshi A, Kale S, Chandel S, Pal DK (2015) Likert scale: Explored and explained. Current Journal of Applied Science and Technology 7: 396-403.

17. Price D, Kemp L, Sims E, von Ziegenweidt J, Navaratnam P, et al. (2010) Observational study comparing intranasal mometasone furoate with oral antihistamines for rhinitis and asthma. Prim Care Respir J 19: 266-273.

18. Martin BG,Andrews CP, van Bavel JH, Hampel FC, Klein KC, et al. (2006) Comparison of fluticasone propionate aqueous nasal spray and oral montelukast for the treatment of seasonal allergic rhinitis symptoms. Ann Allergy Asthma Immunol 96: 851-857.

19. Lu S, Malice MP, Dass SB, Reiss TF (2009) Clinical studies of combination montelukast and loratadine in patients with seasonal allergic rhinitis. J Asthma 46: 878-883.

20. Esteitie R, deTineo M, Naclerio RM, Baroody FM (2010) Effect of the addition of montelukast to fluticasone propionate for the treatment of perennial allergic rhinitis. Ann Allergy Asthma Immunol 105: 155-161.

21. Kim CH, Kim JK, Kim HJ, Cho JH, Kim JS, et al. (2015) Comparison of intranasal ciclesonide, oral levocetirizine, and combination treatment for allergic rhinitis. Allergy Asthma Immunol Res 7: 158-166.

22. Pinar E, Eryigit O, Oncel S, Calli C, Yilmaz O, et al. (2008) Efficacy of nasal corticosteroids alone or combined with antihistamines or montelukast in treatment of allergic rhinitis. Auris Nasus Larynx 35:61-66.

23. Kim MK, Lee SY, Park HS, Yoon HJ, Kim SH, et al. (2018) A randomized, multicenter, double-blind, Phase III study to evaluate the efficacy on allergic rhinitis and safety of a combination therapy of montelukast and levocetirizine in patients with asthma and allergic rhinitis. Clin Ther 40: 1096-1107.

24. Sanchez G, Castro C (2019) Prescription profile and clinical outcomes in patients with allergic rhinitis treated with oral antihistamines or nasal corticosteroids. Int Arch Otorhinolaryngol 23: 325-330.

25. Choudhry NK (2017) Randomized, Controlled Trials in Health Insurance Systems. New England Journal of Medicine 377: 957-964.

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