ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Combination of intranasal fluticasone and azelastine for difficult-to-control allergic rhinitis in adolescents

Combinação fluticasona e azelastina intranasal no tratamento de adolescentes com rinite alérgica de difícil controle

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ABSTRACT

Introduction: Allergic rhinitis has a high prevalence and is responsible for a significant impact on the quality of life of affected individuals, reflecting negatively on school performance, social life, and work. An association of fluticasone propionate and azelastine hydrochloride (FP+AZE) has been recommended for patients with difficult-to-control allergic rhinitis. **Objective:** To evaluate treatment response to FP+AZE in adolescents with difficult-to-control moderate/severe persistent allergic rhinitis (MSPAR). **Methods:** This was a prospective, open-label, uncontrolled clinical trial for a therapeutic intervention in adolescents with difficult-to-control MSPAR treated at a specialized outpatient clinic. **Results:** There was significant improvement in all studied variables, showing better MSPAR control with FP+AZE. Using the minimal clinically important difference as an evaluation parameter, 83% of the patients improved. There were no reports of serious adverse events; a bitter taste was reported by 38.5% of patients, and 2 discontinued use due to an adverse event. **Conclusion:** FP+AZE was a well-tolerated, safe, and effective treatment for MSPAR. The most commonly reported adverse events were local.

Keywords: Allergic rhinitis, steroids, nasal obstruction.

RESUMO

Introdução: A rinite alérgica (RA) tem prevalência elevada e é responsável por impacto significativo da qualidade de vida destes pacientes, refletindo-se negativamente no desempenho escolar, na vida social ou no trabalho. A associação de propionato de fluticasona e cloridrato de azelastina (PF-AZE) tem sido recomendada no tratamento de pacientes com rinite alérgica de difícil controle. **Objetivo:** Avaliar a resposta ao tratamento com PF+AZE administrado a crianças e adolescentes com RA persistente moderada-grave (RAPMG) de difícil controle. **Métodos:** Ensaio clínico aberto não controlado prospectivo com intervenção terapêutica em que participaram adolescentes (n = 65) com RAPMG de difícil controle acompanhados em ambulatório especializado. **Resultados:** Houve melhora estatisticamente significante de todas as variáveis estudadas, o que mostrou melhor controle da rinite com a combinação PF+AZE. Utilizando-se a diferença mínima clinicamente importante como parâmetro de avaliação, 83% dos pacientes tiveram melhora da doença. Não houve relato de evento adverso grave, gosto amargo foi relatado por 38,5% dos pacientes e dois interromperam o esquema por evento adverso. **Conclusão:** A combinação PF+AZE foi bem tolerada, segura e eficaz no tratamento de pacientes com RAPMG. Eventos adversos locais foram os mais comumente relatados.

Descritores: Rinite alérgica, corticosteroides, obstrução nasal.

Introduction

Allergic rhinitis (AR) is a frequent inflammatory disease of the mucosal lining of the nasal cavity whose clinical manifestations may have a great impact on the quality of life of affected patients, in addition to negatively impairing sleep, school or work performance, and social life, among others.[1] In Brazil,

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an epidemiological study identified a prevalence of AR ranging from 25% and 30% among children and adolescents.[2]

Pharmacological treatment of AR includes the following drugs: topical or oral H1-antihistamines, intranasal corticosteroids (INCS), leukotriene receptor antagonists, and, occasionally, oral corticosteroids.[1,3,4]

INCS are the most effective and safe drugs to control allergic inflammation and AR, when administered at recommended doses in adults and children for the treatment of persistent forms. However, patients with severe forms may remain symptomatic even with a treatment combining INCS and another control medication.[1,3,4]

Recently, the combination of an INCS (fluticasone propionate) and an antihistamine (azelastine hydrochloride) (FP+AZE) became available for topical intranasal use in patients with moderate/severe persistent AR (MSPAR)[5], which was subsequently extended to all forms of AR, regardless of its type and severity.[1,6,7]

The use of FP+AZE in patients with AR, compared to fluticasone alone, showed to be a clinically more effective combination in controlling symptoms since the first day of treatment, and remained effective during the 1-year follow-up.[8] In a previous study, 75% of patients treated with FP+AZE experienced symptom relief and a positive impact on quality of life and treatment adherence. Furthermore, good tolerance and low incidence of adverse events were observed, similar to what occurred with fluticasone alone.[8] Thus, FP+AZE began to be recommended to patients with MSPAR aged over six years and with uncontrolled disease.[1,9]

Therefore, the aim of this real-life study was to evaluate treatment response to intranasal FP+AZE for four weeks in adolescents with MSPAR that remained uncontrolled despite being effectively treated.

Methods

This open-label, uncontrolled study included adolescents (12 to 20 years) with uncontrolled MSPAR for at least six months followed at a specialized outpatient clinic. The diagnosis of MSPAR was made by an allergist physician[1], and allergic sensitization to at least one aeroallergen (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blomia tropicalis*, *Blatella germanica*, *Periplaneta americana*, cat dander, dog epithelium, pollen mixture, fungal mixture) was confirmed by positive specific serum IgE and/or prick test (diameter of wheal at least 3 mm greater than the negative control).[10]

All adolescents had uncontrolled MSPAR (medical opinion), because they remained symptomatic despite treatment with INCS and/or oral antihistamine.

Patients diagnosed with uncontrolled asthma, upper airway anatomical malformation, systemic diseases, cognitive deficit, active or recent (within the last three weeks) respiratory infection, as well as those using systemic corticosteroid in the last 30 days and/or allergen-specific immunotherapy, or receiving immunosuppressant therapy, were not included in the study.

Once patients were admitted, their current drug regimen was interrupted, and they started a new drug regimen with a combination of a fixed dose of intranasal FP (50 µg/ spray) and AZE (137 µg/spray) (1 spray/nostril twice a day) for 30 (± 5) days.

The following variables were measured at the beginning and at the end of the study: nasal symptom score (NSS), extra-nasal symptom score (ENSS), a questionnaire named RCAT (Rhinitis Control Assessment Test), a visual analogue scale (VAS) on nasal allergic rhinitis control, and peak nasal inspiratory flow (PNIF).

The NSS was calculated from the sum of the scores given by adolescents for: nasal obstruction, nasal itching, runny nose, sneezing, and post-nasal drip, whose intensity in the previous week was quantified with scores ranging from 0 (absent) to 3 (intense).[11] Therefore, NSS ranged from 0 to 15 points, and rhinitis was classified into mild (0 to 4 points), moderate (5 to 10 points), or severe (11 to 15 points).[11] The ENSS (0 to 12 points) was calculated similarly for the following symptoms: ocular itching, eye tearing, ocular hyperemia, and pharyngeal itching.[11]

The RCAT, a self-administered instrument translated and validated to Brazilian Portuguese[12], consists of six questions related to symptoms experienced in the previous week, and each question received scores, according to frequency of reporting, ranging from: 5 for never, 4 for rarely, 3 for sometimes, 2 for often, and 1 for very often. The sum of all questions gives the final score, and adolescents with a total score ≤ 22 were classified as having uncontrolled rhinitis.[12]

Control of nasal symptoms in the previous week was also assessed by the VAS (0 mm = no discomfort to 100 mm = maximum discomfort).[13] An objective

assessment of nasal function was performed by measuring PNIF in liters per minute (L/min), using a peak nasal inspiratory flow meter (Clement Clark®, UK), and the best of three measurements was considered, with a variation of less than 10%.[14]

Medical opinion about AR control (controlled, partially controlled, or uncontrolled) was recorded at the beginning and at the end of the study. The presence of adverse events was investigated in the final assessment of the study.

Individual clinical response for each outcome was defined according to the minimal clinically important difference (MCID), which was established as 23 mm for the VAS[13]; 3.0 points for RCAT[5]; 4.5 points for the NSS[15]; 3.6 points for the ENSS[13]; and 20 L/min for PNIF.[16]

Mean difference in the values obtained at the beginning and at the end of the study was compared using the Student's *t* test for paired samples. A level of significance of 5% was established to reject the null hypothesis.

The study was approved by the Research Ethics Committee of Universidade Federal de São Paulo, and all patients signed an Informed Consent Form.

Results

Seventy-one adolescents were included in the study, of which six did not return to the final visit, and two withdrew treatment due to adverse events. Mean age of the 63 adolescents (55.6% female) who completed the study was 14 ± 2 years, ranging from 12 to 20 years. With regard to the presence of other allergic manifestations, 81% had asthma, 57% had atopic dermatitis, and 46% had allergic conjunctivitis. All participants had been treated with INCS, and 25% received oral systemic antihistamine without achieving AR control. Eighty-five percent of patients reported to be adherent to this treatment.

During initial assessment using the NSS, 21 (33.4%) adolescents were classified as having severe AR; 38 (60.3%), moderate AR; and 4 (6.3%) mild AR. According to RCAT scores, 48 (76.2%) patients had a score equal to or lower than 22 (uncontrolled AR); according to the VAS, 52 (82,5%) patients were graves/uncontrolled (VAS ≥ 50 mm); and finally, according to medical opinion, 71% had uncontrolled AR, and 29% had partially controlled AR. The average interval between assessments was 33 days.

Table 1 presents the values obtained by the different instruments used, at the two time points of the study. There was a significant reduction in NSS, ENSS, and VAS scores, as well as in increase in PNIF and RCAT.

The separate analysis of nasal and extra-nasal symptoms at the two study time points revealed a significant reduction in all of them at the end of the study (Figure 1). Figure 2 presents the individual variations in VAS, RCAT, and NSS scores.

Table 1
Clinical and functional outcomes assessed at the beginning and at the end of treatment with a combination of fluticasone and azelastine (n = 63)

Variable	Initial	Final	Mean difference	95%CI	p
RCAT	19.4	24.2	4.8	3.6 – 6.1	< 0.001
NSS	9.0	4.1	4.9	4.0 – 5.7	< 0.001
ENSS	5.1	2.4	2.7	1.8 – 3.5	< 0.001
VAS (mm)	58	29	29	23 – 35	< 0.001
PNIF (L/min)	88	106	18	8 – 29	0.01

RCAT = rhinitis control assessment test, NSS = nasal symptom score, ENSS = extra-nasal symptom score, VAS = visual analogue scale, PNIF = peak nasal inspiratory flow, 95%CI = 95% confidence interval.

Table 2 describes the percentages of patients who showed improvement (values higher than MCID) or worsening (values lower than MCID) in the different parameters, according to the MCID for each of them.

Similarly, it was found that, after treatment with FP+AZE was initiated, there was an increase in the number of patients classified by the physician as having controlled AR (0 *vs.* 71%), as well as a decrease in the number of those with uncontrolled AR (71% *vs.* 11%) (Figure 3).

Adverse events were reported by 56% of adolescents, with a predominance of bitter taste in the mouth (38%), and there were no serious events (Table 3). Six patients did not return to the final visit, and two discontinued therapy due to an adverse event (3.1%).

Discussion

In our real-life study, we confirmed the results observed by other investigators showing that intranasal FP+AZE is effective in controlling uncontrolled MSPAR among adolescents, despite treatment with INCS and/or oral H1 antihistamine H1.[11,17-28]

Regardless of the instrument used to assess efficacy of treatment with FP+AZE (VAS, NSS, RCAT, PNIF), a high rate of AR control was observed in our patients, considering the MCID, i.e., 87% experienced improvement in at least one instrument.

In a recent review on the treatment of moderate/severe AR with FP+AZE, this combination achieved a 44% and 64% greater nasal symptom improvement, respectively, compared to its components administered alone.[29] Although the patients treated in our study had not satisfactorily responded to treatment with INCS

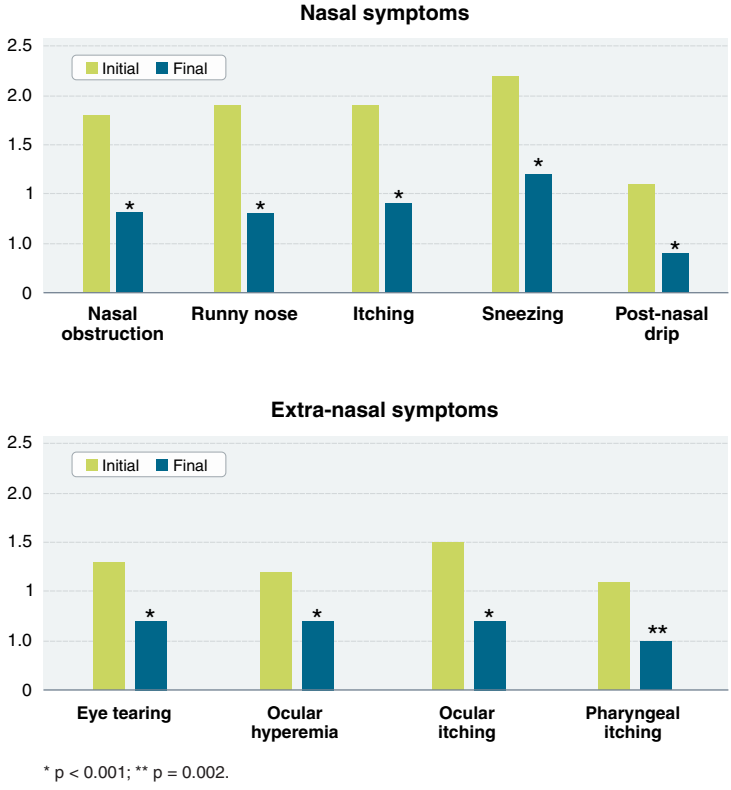

Figure 1
Mean individual scores for nasal and extra-nasal symptoms (ranging 0 to 3 points) at the beginning and at the end of the treatment with a combination of fluticasone and azelastine (n = 63)

alone or associated with systemic anti-H1, it is not possible to infer that combination was better than INCS alone, since patients had been using different products. However, when assessing patients *per se*, there was a significant reduction in the intensity of nasal and extra-nasal, consistent with findings reported by other authors.[11,17-28] (Figure 2).

Nasal obstruction, one of the most frequent symptoms of AR, is certainly one of the most bothersome for patients.[30] An assessment of PNIF, an objective measure of nasal patency, it was found that the group as a whole showed a significant improvement in PNIF after treatment with the combination and that 50% experienced an increase greater than 20 L/min, the MCID defined for this instrument.[16]

Another interesting data observed among our patients was the decrease in ENSS. Considering the MCID as the evaluation parameter, it was found that

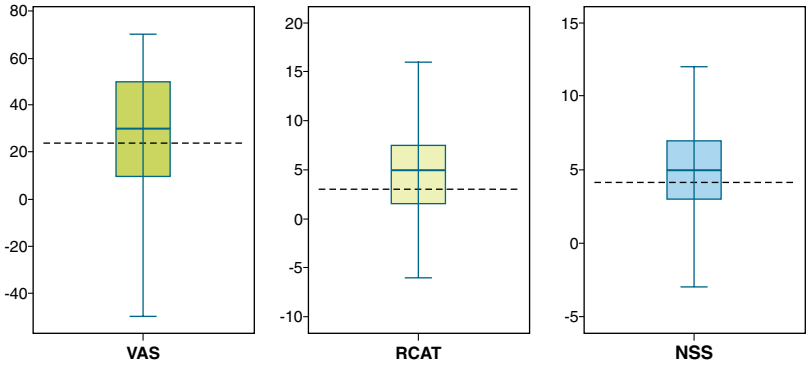

Figure 2
Individual variation of visual analogue scale (VAS), Rhinitis Control Assessment Test (RCAT), and nasal symptom score (NSS) at the end of treatment with a combination of fluticasone and azelastine compared to baseline (n = 63). Minimal clinically important difference for each outcome is shown by the dashed line

Table 2
Percentage of adolescents with clinical improvement and worsening after treatment with a combination of fluticasone and azelastine according to the MCID (n = 63)

Variable	MCID	Improvement		Worsening	
		n	(%)	n	(%)
RCAT	3.0	32	(50.8)	4	(6.3)
NSS	4.5	32	(50.8)	0	
ENSS	3.6	26	(41.3)	3	(4.8)
VAS (mm)	23	38	(60.3)	4	(6.3)
PNIF (L/min)	20	33	(52.4)	3	(4.8)

RCAT = rhinitis control assessment test, NSS = nasal symptom score, ENSS = extra-nasal symptom score, VAS = visual analogue scale, PNIF = peak nasal inspiratory flow, MCID = minimal clinically important difference.

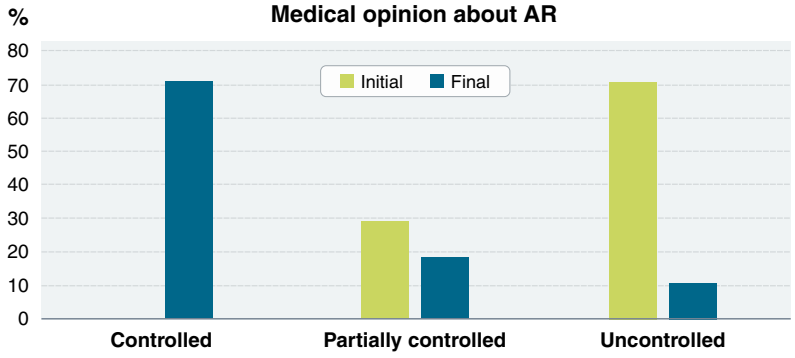

Figure 3
Percentage of adolescents classified as having controlled, partially controlled, and uncontrolled allergic rhinitis (AR) by the physician at the beginning and at the end of treatment with a combination of fluticasone and azelastine (n = 63)

more than 40% of patients experienced a decrease in ENSS, especially ocular itching. INCSs are believed to reduce ocular symptoms due to a class effect, because, when these drugs bind to glucocorticoid receptors, they promote increased expression of anti-inflammatory molecules and of beta-adrenergic receptors, in addition to decreased expression of pro-inflammatory cells and molecules, which increases the benefits of adding antihistamines.[31]

Table 3
Adverse events reported during treatment with a combination of fluticasone and azelastine (n = 65)

Adverse event	N	%
Bitter taste in the mouth	25	38.5
Pharyngeal discomfort	12	18.4
Nasal burning	8	12.3
Bad smell sensation	8	12.3
Headache	3	4.6
Epistaxis	1	1.5

Adverse events resulting from use of FP+AZE have been little frequent, with no reports of serious adverse events.[25] The most frequent adverse events have been: dysgeusia, nausea, sneezing, nasal discomfort, and epistaxis, all of them having low or very frequencies.[25] Although adverse events, mostly local reactions, were reported by a significant portion of our patients, only two discontinued the therapeutic regimen and withdrew the study.

Except for PNIF, all outcomes assessed here have a subjective component, because they depend on information provided by patients themselves. Therefore, the MCID was adopted in this study to assess results that are meaningful to patients and may be either self-reported or measured objectively. The MCID corresponds to the smallest change in outcome score that represents a significant change to patients.[32,33] Several methods are available to measure the MCID, but principal is that the change should be greater than the measuring error of the instrument that is being used to assess the outcome, and should be great enough for patients to perceive a clinical change.[32,33] Therefore, in the assessment of our outcomes, although few of those we used were validated to our population, we adopted cutoffs established by other authors.[5,13,15,16]

It is importantly to highlight that the percentage of patients with clinically important improvements

in the NSS and in the ENSS was much probably underestimated in our study. Due to the lack of specifically defined criteria for these scores, we decided to define more conservative values of 30% of the total for each score.[16]

The present study has some limitations. Since it was a real-life study, there was no comparison with a placebo group. Furthermore, there were no study arms assessing use of the drugs (fluticasone and azelastine) alone, thus hampering of these with FP+AZE.

In conclusion, INCS+AZE showed to be a well-tolerated, safe, and effective treatment for uncontrolled moderate/severe AR, which was revealed by a significant improvement not only of nasal symptoms but also of ocular symptoms.

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