ORIGINAL ARTICLE

Clinical Use of Oral Antihistamines and Intranasal Corticosteroids in Patients With Allergic Rhinitis

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Abstract

Background: Second-generation oral antihistamines (AH) and intranasal corticosteroids (ICS) are the most widely used drugs for allergic rhinitis (AR).
Objective: To obtain information on the preferences for and applications of these drugs under conditions of routine clinical practice.
Methods: We performed a multicenter multidisciplinary observational study. Participating physicians completed a questionnaire with information on preferences for and application of drugs for AR, patient characteristics, and physician/patient satisfaction with the treatment provided (visual analog scale).
Results: A total of 1008 physicians participated in the study (primary care physicians, 53%; ear, nose, and throat specialists, 28%; allergologists, 19%). Treatment preferences in AR were AH combined with ICS (7.68), AH (7.25), and ICS (6.94). AH and ICS were used continuously by 58% and 71% of patients, respectively. Physicians reported having a good knowledge of the Allergic Rhinitis and its Impact on Asthma guidelines (93%), and 90% claimed to follow the guidelines.
A total of 4040 patients were recruited (52% females, mean [SD] age 34 [14] years). The findings for AR were as follows: mean (SD) duration, 9 (8) years; persistent AR, 52%; mild AR, 72%; moderate AR, 7%; and severe AR, 1%. Patients considered the disorder to be well controlled/almost controlled (79%). As for treatment, 77% followed the regimen recommended by the physician. Oral treatment (41%) and intranasal treatment (22%) were preferred, while 35% showed no preference for any given administration route. The treatments prescribed were AH combined with ICS (66%), AH (20%), ICS (11%), other antihistamines (4%), and other drugs (6%). Combination treatment was the preferred therapy, regardless of the type of rhinitis.
Conclusions: Physicians prefer and more often use combination treatment with oral AH and ICS, regardless of the frequency and intensity of AR.

Key words: Oral antihistamines. Intranasal corticosteroids. Allergic rhinitis. Treatment

Resumen

Antecedentes: Los antihistamínicos orales de segunda generación (AH) y los corticoides nasales (ICS) son los fármacos más empleados en el tratamiento de la rinitis alérgica (RA).
Objetivo: Obtener información sobre las preferencias y uso de estos fármacos en condiciones de práctica clínica habitual.
Método: Estudio observacional, multicéntrico y multidisciplinar. Los médicos participantes rellenaron un cuestionario donde se recogieron el uso y preferencias de los fármacos empleados en el tratamiento de la RA, las características de los pacientes tratados, y la satisfacción por parte del médico y del paciente con el tratamiento empleado (escala visual analógica).
Resultados: Participaron 1.008 médicos (53% Atención primaria, 28% ORL, 19% Alergología). Las preferencias en el tratamiento farmacológico de la RA fueron: AH combinados con ICS (7,68), AH (7,25), ICS (6,94). Utilizaban de forma continua los AH el 58% y los ICS en el 71%. Se reclutaron 4.040 pacientes (52% mujeres, edad media de 34±14 años). Datos de la RA: tiempo de evolución 9±8 años; persistente 52%, leve 72%, moderada 27% y 1% grave. El 79% de los pacientes tenían sensación de buen control o estar casi controlados de su enfermedad. El 77% seguía las pautas de tratamiento recomendadas por el médico. Preferían el tratamiento oral 41%, nasal 22%, y en el 35% la vía de administración era indiferente mientras fuera efectivo. El tratamiento prescrito a los pacientes fue: AH combinado con ICS 66%, AH 20%, ICS11%, otros antihistamínicos 4% y otros fármacos 6%. La asociación fue la terapia preferida, con independencia del tipo de rinitis.
Conclusiones: Los médicos prefieren y utilizan con mayor frecuencia el tratamiento combinado de AH orales y ICS en el tratamiento de la RA con independencia de la frecuencia e intensidad de la rinitis.

Palabras clave: Antihistamínicos orales. Corticoides intranasales. Rinitis alérgica. Tratamiento.

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Introduction

Allergic rhinitis (AR) is a very common disorder that affects quality of life and generates important health care and social costs [1-3]. The Allergic Rhinitis and its Impact on Asthma Update (ARIA 2008) [3] assigns recommendation grade A to second-generation oral antihistamines (AH) and intranasal corticosteroids (ICS) in the treatment of AR. ICS are a treatment option in moderate-severe intermittent and mild persistent AR and constitute the treatment of choice in moderate-severe persistent AR. AH are recommended as a possible treatment option in mild or moderate-severe intermittent AR and in mild persistent AR. Combined therapy with AH and ICS is contemplated in the ARIA guidelines for moderate-severe persistent AR that does not progress favorably after 2-4 weeks of treatment with ICS, in the same way that other guidelines recommend adding AH in the case of persistent sneezing and nasal itching in patients taking ICS [4]. Despite the recommendations of the guidelines, randomized studies of seasonal AR in children and adults comparing both treatment options have demonstrated no increased benefit of adding AH to treatment with ICS [5-14].

ICS have been shown to be more effective than AH in the treatment of AR. In their meta-analysis, Weiner et al [15] demonstrated the superiority of ICS over AH in seasonal AR with respect to symptoms of rhinitis, whether evaluated overall or separately (level of evidence, Ia). This benefit was even obtained when administration was on demand [16] or when objective parameters such as peak nasal inspiratory flow were evaluated [17]. A recent review selected 38 studies of seasonal AR that confirmed the superiority of ICS over AH, together with 13 studies of perennial AR in which AH were found to be superior, although the latter data were considered to be of variable quality [18]. Despite these findings, AH are the most widely used drugs in the treatment of AR [19]. According to the *Alergológica 2005* study in Spain, patients visiting allergy clinics with suspected AR had undergone treatment with AH in 82% of cases, followed by ICS in 24% of cases. Following the visit, the allergologist prescribed an AH in 86% of cases and an ICS in 68% [20].

Considering the above data, we decided to carry out a study with the primary objective of evaluating the preferences for and applications of oral AH and ICS in the treatment of AR in the context of routine clinical practice. We also defined the following secondary objectives: *a)* to evaluate the characteristics of patients with AR seen in primary care, allergy clinics, and ear, nose and throat (ENT) clinics, as well as the treatment prescribed; *b)* to assess the degree of AR control according to the patient's criteria; *c)* to assess physician and patient satisfaction with AR treatment; and *d)* to evaluate adherence to therapy and patient preferences regarding the administration route.

Material and Methods

After obtaining approval from the Clinical Research Ethics Committee of Nuestra Señora de Valme Hospital in Seville, Spain, we performed a multicenter multidisciplinary observational study during the year 2008. We evaluated the size of the sample based on the results of previous studies on AH and ICS to set the total number of participating physicians (physicians from throughout Spain, with no special interest in rhinitis), distribution of specialty, and number of patients that each physician would select.

Physicians

The participating physicians had to complete a questionnaire specifying their specialty, place of work, knowledge and application of the ARIA guidelines, characteristics of patients with AR seen in their practice, and preferences regarding treatment (1, least often used option; 10, most often used option). In addition, they had to select 4 consecutive patients (after obtaining informed consent) who had been diagnosed with AR, were seeking help for their disease, and had already received treatment for AR in the past. Physicians also recorded demographic characteristics, etiology of AR, classification of the disease according to its duration and severity both in the absence of treatment (based on recall) and after treatment, drugs used until the visit, duration of treatment in the last year, physician satisfaction with the AR treatment used by the patient in the last year (visual analog scale [VAS]: 0, very dissatisfied; 10, very satisfied), and the drugs prescribed at the study visit.

AR was classified according to its duration (intermittent or persistent) based on the criteria of the ARIA guidelines as follows: intermittent (IAR), symptoms ≤4 days a week or ≤4 weeks; and persistent (PER), symptoms >4 days a week for >4 consecutive weeks. Severity was classed as mild, moderate, or severe based on the ARIA criteria modified by Valero et al [21] as follows: mild (normal sleep; normal daily life and sport and leisure activities; normal work productivity or school performance; no symptoms causing discomfort), moderate (alteration of 1, 2, or 3 of these items), and severe (alteration of all 4 items).

Patients

Each study patient completed a questionnaire exploring personal opinion about control of AR in the last year, adherence to treatment, satisfaction with AR treatment in the last year using a VAS similar to that used by the physician, whether information had been received regarding the use of devices for intranasal administration, and preference regarding administration route.

Statistical Analysis

The statistical analysis was carried out using SAS (Statistical Analysis System) version 9.1.3. All tables, figures, and plots were generated from the number of valid cases, which was the number considered for the calculation of percentages and other statistics. Continuous variables were reported as the number of valid cases, mean (SD), median, and range. Categorical variables were reported as the number of valid cases and the percentage of each category. Variables exhibiting asymmetrical frequency distributions were described with their median and interquartile ranges. Statistical significance was set at a P value of <.05.

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Results

Questionnaire Completed By the Physician

Participating physicians: A total of 1008 physicians (mean age, 45 [8.6] years; 65% males) participated in the study. The physicians worked predominantly in urban areas (73%) and had a mean of 20 (9) years of experience. Fifty-three percent were primary care physicians, 28% ENT specialists, and 19% allergologists. Fifty-one percent worked in the hospital setting, 43% in an outpatient clinic, and 6% in both; 55% worked in public health centers.

Patient classification according to the ARIA guidelines: Physicians considered that the patients seen in their practice presented IAR in 47% of cases and PER in 53%. As regards disease severity, 72% of the cases were mild, 27% moderate, and 1% severe, with no differences between the different medical specialties (Table 1). Ninety-three percent of the physicians reported a good knowledge of the ARIA guidelines and 90% said they followed its recommendations.

Physician preferences in the treatment of AR: The preferred treatment option was the combination of AH and ICS (7.68 [2.13]), followed by AH (7.25 [2.00]) and ICS (6.94 [1.96]). The preferences by medical specialty are shown in Table 2. In the case of AH (topical or systemic), 58% of physicians preferred to provide such treatment on a continuous basis, while allergologists preferred to administer the treatment on the basis of patient demand (57%). Eighty-five percent prescribed AH at the doses recommended in the Summary of Product Characteristics. As for ICS, 71% of the physicians preferred to prescribe these on a continuous basis. Physician satisfaction with the treatment used for AR in the last year scored 6.85 (2.13).

Table 1. Percentages of Patients With Allergic Rhinitis According to Medical Specialty[a]

	PC	ENT	ALL	Total
Duration, %				
Intermittent	48	46	47	47
Persistent	52	54	53	53
Severity, %				
Mild	73	71	72	72
Moderate	25	28	27	27
Severe	2	1	1	1

Abbreviations: ALL, allergology; ENT, ear, nose, and throat; PC, primary care.
[a]According to the modified severity classification of the Allergic Rhinitis and its Impact on Asthma guidelines modified by Valero et al [21].

Table 2. Drug Treatment Preferences in Allergic Rhinitis According to Medical Specialty[a]

	PC	ENT	ALL	Total
AH + ICS	7.52 (1.99)	8.05 (1.90)	7.64 (2.66)	7.68 (2.13)
AH	7.53 (1.95)	6.85 (1.79)	6.98 (2.31)	7.25 (2.00)
ICS	7.00 (1.82)	7.20 (1.99)	6.33 (2.13)	6.94 (1.96)

Abbreviations: AH, oral second-generation antihistamine; ALL, allergology; ENT, ear, nose, and throat; ICS, intranasal corticosteroid; PC, primary care.
[a]Visual analog scale, 0 to 10 cm.

Patient Characteristics

A total of 4040 patients were recruited (52% females), with a mean age of 34 (14) years. The duration of AR was 9 (8) years. The causes of AR were pollen 68%, dust mite 52%, animal epithelia 21%, and fungi 9%.

Classification of AR: When the patients were receiving no treatment for the disease, AR was classified as PER in 52% of cases, mild in 72%, moderate in 27%, and severe in 1%. Moderate AR was characterized by the alteration of a mean of 1.88 items (median, 2), with significant differences between patients with moderate IAR (1.71) and PER (1.98) ($P<.0001$). In descending order of frequency, the items affected were symptoms causing discomfort (68%), alteration of daily life and sport and leisure activities (52%), sleep disturbances (46%), and altered work productivity or school performance (23%).

When the patients were receiving treatment for the disease, AR was classified as IAR in 71% of cases ($P<.0001$) and mild in 89% ($P<.0001$) (Figure 1). In this case, the number of altered items in AR patients with moderate severity decreased significantly to 1.64 (median, 1) ($P<.0001$).

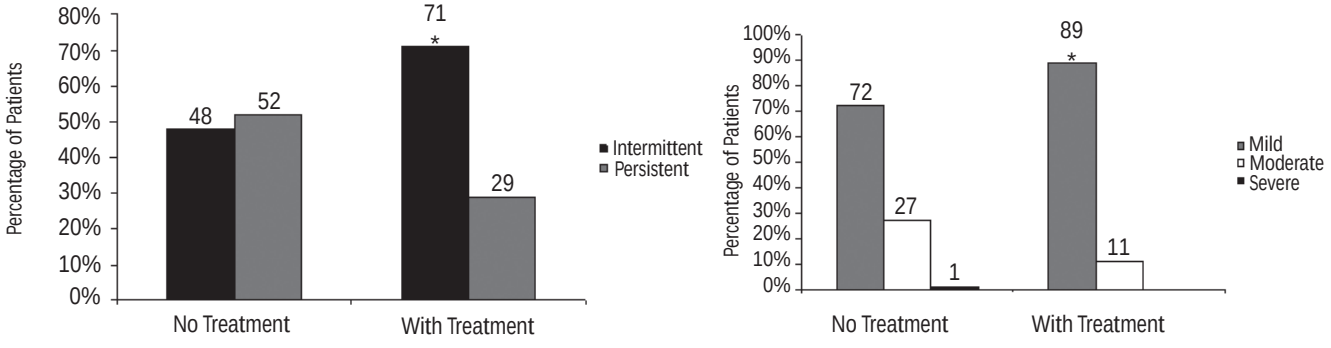

Figure 1. Allergic Rhinitis and its Impact on Asthma (modified by Valero et al [21]) classification of allergic rhinitis patients according to whether the patient is receiving treatment.

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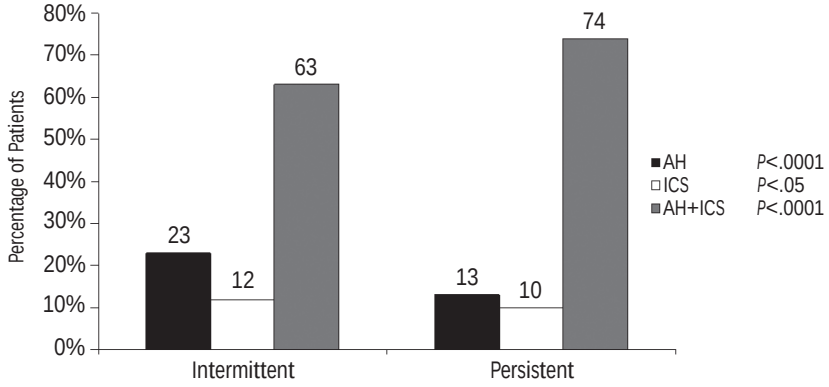

Figure 2. Current medication prescribed according to duration of AR symptoms (Allergic Rhinitis and its Impact on Asthma criteria: intermittent or persistent). AH indicates antihistamine; ICS, inhaled corticosteroid.

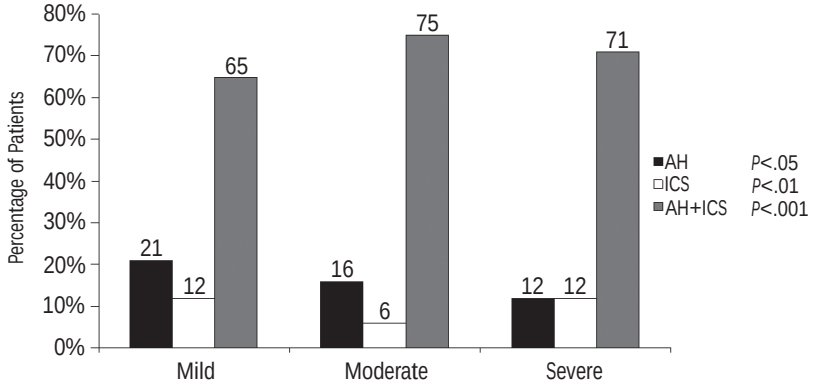

Figure 3. Current medication prescribed according to the severity criteria of the Allergic Rhinitis and its Impact on Asthma (mild, moderate, or severe), as modified by Valero et al [21]. AH indicates antihistamine; ICS, inhaled corticosteroid.

The most recent treatment consisted of AH (38%), ICS (10%), and the combination of AH and ICS (33%). Mean duration of drug treatment in the last year was 1-3 months (61% of the patients), 3-6 months (25%), and 6-12 months (14%).

Treatment prescribed at the visit: The treatment prescribed was AH combined with ICS in 66% of cases, AH in 20%, ICS in 11%, other antihistamines in 4%, and other drugs in 6%. In all 3 medical specialties, the combination of AH and ICS was the preferred treatment option, regardless of the duration and severity of AR (Figures 2 and 3).

Patient Opinion

Control of AR symptoms: Patients considered that their usual treatment afforded total symptom control in 19% of cases, almost complete control in 60%, little control in 16%, and no control in 3%. No treatment was administered in 2% of cases.

Adherence to prescribed treatment: Most patients (77%) reported having taken the recommended doses for all or most of the indicated period of time, while 20% reported adherence for only a short period of time, or only when the symptoms manifested or were intense. One percent increased the dosage because the prescribed dose was considered to be insufficient, 1% never took the prescribed medication, and 1% had no indicated treatment.

Information on intranasal administration: Most patients (65%) reported having been instructed on how to use the device for intranasal administration.

Preferences in relation to the route of administration of treatment for AR: Oral treatment was preferred by 41% of patients, intranasal treatment by 22%, and injection by 2%, while 35% showed no preference for any given administration route, provided it was effective. Patient satisfaction with the treatment used for AR in the last year received a score of 7.24 (2.02).

Discussion

The main results of this study are as follows: *a)* Physicians predominantly (66%) prefer and use combinations of AH with ICS for the treatment of AR in their routine clinical practice; *b)* AH are used slightly more frequently on a sustained basis (58%) than on demand (42%); *c)* ICS are mainly used on a sustained basis (71%); *d)* Most physicians (85%) prescribe AH at the doses recommended in the Summary of Product Characteristics; *e)* While not strictly adhering to the recommendations of the ARIA guidelines in the treatment of AR, most of the participating physicians (about 90%) report good knowledge of and adherence to its recommendations; *f)* Most patients (79%) claim to have the disease under complete or near complete control; and *g)* The disease control reported by patients is reflected by a lesser duration and severity of AR.

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The combination of AH and ICS was the preferred and most widely used option (66%) for the treatment of AR in routine clinical practice, irrespective of the type of symptom duration (intermittent/persistent) or severity (mild/moderate/severe) for all 3 types of specialists (primary care, ENT, allergologists). Combined therapy with AH and ICS is contemplated in the ARIA guidelines for moderate-severe persistent AR that is not controlled with ICS [3]. Curiously, no analysis has been made of the level of recommendation of this therapeutic option in the new ARIA revision, in which the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was applied [22]. Although combination with an AH does not appear to increase the benefit obtained with an ICS alone in seasonal AR [5-14], it would be advisable to conduct further studies to assess aspects such as the intensity and frequency of the symptoms of AR or the usefulness of the combination in PER [18]. From a theoretical perspective, combination treatment can be justified by the different mechanisms of action of the drugs involved, with a faster effect in the case of AH, which acts upon the symptoms of the immediate phase (sneezing, itching, aqueous rhinorrhea), and with a more relevant role for ICS in the late phase, characterized by predominance of inflammation and nasal congestion [23]. Under conditions of routine clinical practice, stepwise therapy is advised, considering the results of clinical trials, patient preferences, and the true conditions of tolerance [24]. Accordingly, AH are regarded as first-line treatment for AR, while ICS may be more appropriate as add-on therapy in patients whose symptoms are not controlled. However, if, as has been reported by studies on seasonal AR [5-14], the combination of an AH with ICS does not improve the efficacy of the latter, then we may be facing an unjustified increase in the cost of drug treatment for AR, when such combination therapy is used with the frequency recorded in our study. One pharmacoeconomics study estimated the total cost per person and year (medical and pharmaceutical cost) to be US$777 for the combination of AH and ICS, US$409 for AH, and US$401 for ICS [19].

Far behind the combination of AH and ICS, administration of AH in monotherapy was the second treatment choice, and ICS in monotherapy the third preferred option for all types of rhinitis. In a study of prescription practice according to whether a symptom intensity algorithm is used or treatment is based on free choice of prescription, greater effectiveness was recorded with the former option. These data probably reflect the use of ICS in 84% of the cases in the algorithm-based prescription group, compared with only 32% of cases in the control group [25].

According to the recent revision of the ARIA guidelines [22], ICS are strongly recommended as treatment for AR (high-quality published evidence) and in preference to AH in both seasonal and persistent AR. Despite the benefit of ICS with AH for all symptoms of AR [15], we found AH to be the preferred monotherapy option by our physicians for any form of rhinitis (except the severe presentations, where the percentage was similar to the moderate forms of the disease). In contrast, other studies have reported an increase in ICS use when AR is of greater intensity [26]. Considering that ICS could inhibit the naso-ocular reflex and prove effective for the treatment of the accompanying ocular symptoms without having to add other drugs to ensure control, prescription would reduce the cost of treatment [27], an important consideration in a disease with such a high prevalence in our setting [28].

The discrepancy between the high efficacy of the ICS observed in clinical trials and prescription in actual clinical practice can be explained in part by failure of the ICS to reach their optimum effect, as a result of deficient administration, preference for the oral route, or poor tolerability of the intranasal route [29]. It is sometimes necessary to take into account the different organoleptic characteristics of each ICS in order to ensure good tolerance and adherence [30]. Likewise, in the absence of adequate information, the patient assumes that intranasal medication is reserved for periods of intense nasal symptoms as treatment on demand. In the present study, 65% of patients reported having received instructions on the use of intranasal medication.

Despite the lack of strict adherence to the ARIA guidelines for the treatment of AR, most of the participating physicians (about 90%) reported having a good knowledge of the guidelines and following their indications. In fact, the use of second-generation antihistamines compared with first-generation antihistamines for the treatment of AR, or the use of ICS in preference to other drugs, reflects this adherence to the guidelines. However, the observed preferential prescription of the combination of AH and ICS does not indicate adherence to the ARIA guidelines. In this sense, routine clinical application is not rigorous, or, at least, interpretation of the indications is not particularly strict. Few studies have evaluated the relationship between the ARIA severity classification and drug treatment. Of note, one study (1610 patients with AR) showed that the severity of rhinitis was seen to exert a greater influence than duration of the disease on choosing the corresponding drug treatment [31]. Another study found that the number of drugs used increased with the severity of the disease and impairment of quality of life [32].

AH were used almost indistinctly on a continuous basis (58%) or on demand (42%), and in most cases (85%) the doses recommended in the Summary of Product Characteristics were prescribed. This can undoubtedly help to minimize the onset of undesired effects. However, ICS were mostly administered on a sustained basis (71%), which seems reasonable considering their mechanism of action: optimum effects were reached after several days of administration. Comparison of the effect of administration on demand of ICS with that of AH revealed, once again, that the best results corresponded to ICS [16].

With the treatment used, most patients (79%) reported having achieved complete or almost complete control of their disease, with a reduction in the duration and severity of AR. Patient-rated and physician-rated satisfaction with the drug treatment received in the last year yielded scores of 7.24 and 6.85, respectively. A high percentage of patients (77%) claimed to have followed the recommended dosing instructions all or most of the indicated time; this undoubtedly contributed to the high percentage of symptom control and satisfaction with treatment expressed by both physicians and patients. In fact, when patients adhered to therapy, a significant increase was observed in the percentage of intermittent (71% vs 48%, $P<.0001$) and mild rhinitis (89% vs 72%; $P<.0001$), and the

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number of altered ARIA items of the patients with moderate disease decreased significantly (1.88 vs 1.64; $P<.0001$). Consistent with other studies, the aspect most often mentioned by patients was symptoms causing discomfort [26].

Oral administration was preferred by twice as many patients as for intranasal administration, while one-third showed no preference for any given route, provided it was effective. The new revised version of the ARIA guidelines, in which the GRADE methodology was applied, favors the preferential use of ICS over AH in both seasonal and persistent AR, although in patients with a strong preference for the oral route, AH may be a reasonable choice [22]. In a study in children, Wong et al [33] found 73% of patients to prefer oral medication, while only 11% showed a preference for the intranasal route. In turn, adherence to therapy was adversely affected in up to one-quarter of the children who disliked the intranasal route. Before prescribing these drugs, it is therefore important to ask patients about their preferences [24], since this facilitates success of treatment [34]. In some cases, adherence to treatment may even improve if the monotherapy option is chosen [35].

To summarize, although the medical literature offers sufficient evidence of the superior efficacy of ICS over AH in the treatment of AR, AH are the most commonly prescribed option in routine clinical practice, where patients show a preference for the oral route.

The literature shows no clear benefit of the combination of AH and ICS in seasonal AR. In fact, the recommendations of the ARIA guidelines are restricted to poorly controlled moderate-severe persistent AR. However, we found that the combination of AH and ICS was the first choice in all types of AR, in terms of both symptom duration (intermittent or persistent) and severity (mild, moderate, or severe).

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