Allergic rhinitis: Continuous or on demand antihistamine therapy?

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Summary

Allergic rhinitis is an inflammatory disease of the nasal mucosa, caused by an IgE-mediated reaction after exposure to the allergen to which the patient is sensitized. Histamine is the most important preformed mediator released in the early stage of the allergic reaction, and also contributes to the late phase of the latter, exhibiting proinflammatory effects.

Minimal persistent inflammation is a physiopathological phenomenon induced by the presence of an inflammatory cell infiltrate, together with ICAM-1 expression in the epithelial cells of the mucosa exposed to the allergen to which they are sensitized, in the absence of clinical symptoms. This molecule is considered to be an allergic inflammatory marker.

The priming effect first described by Connell in 1968 consists of the reduction in the allergen concentration required to elicit a nasal hyper-response when performing a daily nasal exposure test. This implies that with natural exposure to inhaled allergens, small amounts of environmental allergen will maintain the patient symptoms, and thus of course minimal persistent inflammation.

Considering the above, it is questionable whether antihistamines should be administered on a continuous basis or upon demand.

The antihistamines, and fundamentally the second-generation drugs, have been shown to exert an antiinflammatory effect, and this effect is greater when the drug is administered continuously than when administered upon demand. Likewise, a reduction in treatment cost and an improvement in quality of life among patients treated on a continuous basis has been documented. However, no studies have been specifically designed to clarify the indication of treatment on a continuous basis or upon demand, as occurs in the GINA. As a result, the individualization of treatment according to the concrete characteristics of each patient seems to be the best approach, at least for the time being.

Key words: Allergic rhinitis. Antihistamines. Minimal persistent inflammation. Priming effect. Continuous Treatment. Treatment upon demand.

Resumen

La rinitis alérgica es una enfermedad inflamatoria de la mucosa nasal provocada por una reacción mediada por IgE tras la exposición a un alérgeno al que el paciente está sensibilizado. La histamina es el mediador preformado más importante liberado en la fase temprana de la reacción alérgica, y también contribuye a la fase tardía de la misma, presentando efectos proinflamatorios.

La inflamación mínima persistente es un fenómeno fisiopatológico provocado por la presencia de un infiltrado celular inflamatorio, junto a la expresión de ICAM-1 en las células epiteliales de las mucosas expuestas al alérgeno al que están sensibilizadas, en ausencia de sintomatología clínica. Se considera un marcador de inflamación alérgica.

El efecto *priming* descrito por Connell en 1968 consiste en la reducción de la concentración necesaria de alérgeno para obtener una hiperrespuesta nasal si se realiza una prueba de exposición nasal diaria. Esto implica que con una exposición natural a alérgenos inhalados, pequeñas cantidades de alérgeno ambiental mantendrán la sintomatología del paciente y, por supuesto, una inflamación mínima persistente.

Teniendo en cuenta todo lo anterior es discutible si los antihistamínicos deben ser administrados de forma continua o a demanda.

Los antihistamínicos, prinicipalmente los de segunda generación, han demostrado tener un efecto antiinflamatorio, y que este efecto es

mayor si la administración del fármaco se realiza de forma continua que si se realiza a demanda. Así mismo se ha objetivado una reducción de costes del tratamiento y una mejora de la calidad de vida de los pacientes que han recibido el tratamiento de forma continua. Pero no existen estudios específicamente diseñados para clarificar la indicación del tratamiento continuo o a demanda como ocurre con la GINA, por lo que individualizar el tratamiento de acuerdo con las características del paciente parece, por el momento, la mejor postura a seguir.

Palabras clave: Rinitis alérgica. Antihistamínicos. Inflamación mínima persistente. Efecto *priming*. Tratamiento continuo. Tratamiento a demanda.

Introduction

Allergic rhinitis is an inflammatory disease of the nasal mucosa induced by an IgE-mediated reaction, following exposure to an allergen to which the affected patient is sensitized. Clinically, the condition manifests as nasal itching (pruritus), sneezing, rhinorrhea (runny nose) and congestion. The condition is classified as intermittent or persistent, depending on the duration of the symptoms, and as mild or moderate-severe depending on their intensity [1]. The co-existence of conjunctival symptoms in the form of eye itching, conjunctival injection and lacrimation is common.

Among the different disorders that may be associated to allergic rhinitis, mention must be made of bronchial asthma (rhinitis being an important risk factor for the development of asthma), sinusitis, otitis media, nasosinusal polyposis, respiratory infections and alterations in dental occlusion.

The prevalence of allergic rhinitis in the world population is high, varying from 10-40% according to the geographical setting considered [2]. The disease has a negative impact upon quality of life (performance at work and in school, social activities) and generates important direct as well as indirect economical costs. Allergic rhinitis is an important public health problem. However, despite the above considerations, and because of the apparently mild nature of the disorder, it usually does not receive the deserved attention by physicians, and in most cases is not treated as required.

The H1 histamine receptor belongs to the family of receptors coupled to protein G, and it is characterized by an equilibrium between its active and inactive conformations [3]. Binding of the histamine molecule to the H1 receptor stabilizes the latter in its active conformation. The H1 antihistamines (anti-H1 drugs) combine with and stabilize the inactive form of the H1 receptor; this mechanism is known as inverse agonism. The antihistamines have been divided into first and second generation drugs, according to their pharmacokinetic properties, structural characteristics and adverse effects.

Histamine from the mast cells and basophils is the most important preformed mediator released in the early phase of the allergic reaction. Histamine stimulates smooth muscle and exerts a vasodepressive effect. Such actions have been known for almost a century, though in recent years histamine also has been reported to modulate inflammatory responses. It also contributes to the late phase of the allergic reaction, as will be seen later on. The use of H1 antihistamines in allergic disease was initially designed only to block histamine action, without taking into account other parallel actions. It is now known that the H1 antihistamines exert effects different from those that can be explained on the grounds of H1 block alone. A number of second-generation H1 antihistamines have been shown to reduce mediator release, inflammatory cell infiltration, and the expression of adhesion molecules by epithelial cells. To summarize, anti-H1 drugs have been shown to exert an antiinflammatory effect [4].

Attitude towards oral H1 antihistamine use in allergic rhinitis, on the part of the international consensus guides

Both in the ARIA document [1] and in a recent update to the latter [5] on the use of oral antihistamines for the treatment of intermittent and persistent allergic rhinitis in both adults and children, level A evidence was attributed to such prescription (recommendation based on randomized, controlled clinical trials or metaanalyses). Thus, the indication of such drugs for the treatment of allergic rhinitis is not questionable.

Oral anti-H1 drugs are effective for treating all the symptoms of allergic rhinitis, though their efficacy falls short of that of the topical nasal corticoids in providing relief from nasal congestion.

Allergic rhinitis and histamine

As has been commented above, allergic rhinitis is an inflammatory disorder of the nasal mucosa in which histamine plays a key role. Taking into account the inflammatory nature of the disease, and focusing on histamine - particularly as regards its activity upon the late phase of the allergic reaction - the following effects have been documented [6]:

- Increased secretion of proinflammatory cytokines and adhesion molecules.
- Increased allergen-induced eosinophil chemotaxis.
- Increased mast cell chemotaxis.
- Inhibition of neutrophil activation and degranulation.
- Increased angiogenesis within the inflamed tissues, this being required for perfusion of the latter and for favoring cell arrival within the inflammatory site, via induction of vascular endothelial growth factor (VEGF) [7].

On the basis of the above, it can be affirmed that histamine exerts much more complex functions than initially believed, and moreover exerts proinflammatory action.

Minimal persistent inflammation and the *priming* effect: two phenomena to be taken into account

a) Minimal persistent inflammation (MPI)

Minimal persistent inflammation is a physiopathological phenomenon referring to the presence of an inflammatory cell infiltrate (eosinophils, neutrophils) associated with the expression of intercellular adhesion molecule-1 (ICAM-1 / CD-54) in the epithelial cells of the mucosa exposed to the allergen, in the absence of clinical symptoms.

MPI was initially described for bronchial asthma [8], though posteriorly it was also described in relation to allergic rhinitis secondary to hypersensitivity to dust mites [9], where patients without symptoms but permanently exposed to the acarids (mites) presented nasal mucosal inflammation. It was considered a marker of allergic inflammation [10], since ICAM-1 is only expressed in the mucosal epithelial cells of allergic patients when they are in contact with the allergen - but not in non-allergic patients, or allergic patients when not exposed to the allergen [11,12]. ICAM-1 belongs to the immunoglobulin superfamily, and is constitutively expressed by T and B lymphocytes, monocytes and fibroblasts. A very important characteristic of ICAM-1 is that it is the epithelial cell receptor for over 90% of all rhinoviruses, which bind to the receptor in order to penetrate and infect the cell. Once within the cell, the rhinoviruses increase ICAM-1 expression at the epithelial cell surface, thereby favoring the penetration of more rhinoviruses [13].

b) The *priming* effect

The term "priming effect" was introduced by Conell in 1968. While conducting nasal exposure tests with *Ambrosia* pollen, he found that with daily provocation, less pollen was needed (between 10 and 100 times lesser amounts of allergen) to elicit the same response, i.e., hyper-responsiveness developed. Approximately one week without provocation was required in order for this effect to disappear. This means that if an allergic patient is permanently exposed to the allergen to which he or she is sensitized, then the presence of the allergen even at low concentrations will suffice to induce a persistent nasal inflammatory phenomenon that will exacerbate with only minimal increments in the usual exposure to the causal allergen.

c) Why are both these phenomena important?

On one hand, permanent exposure to small amounts of an allergen to which the patient is sensitized increases nasal hyper-responsiveness, i.e., in practical terms the persistent inhalation of a small amount of allergen induces evident symptoms. Under natural conditions, exposure to inhaled allergens - particularly those that are perennial and with the greatest seasonal variability according to the geographical setting involved - shows a similar tendency. This means that although the patient may attempt to minimize exposure, he or she always will be exposed to small amounts of allergen that maintain the symptoms. No massive exposure is required for this to occur (though massive exposure may occasionally take place).

On the other hand, the persistence of allergen exposure favors the presence of MPI - which in turn also favors nasal hyper-responsiveness, with the consequences stated above. Patients sensitized to pollen have been reported to show nasal hyper-responsiveness to methacholine outside the pollination season [14]. Furthermore, however, the presence of ICAM-1 expression increases the co-morbidity of rhinitis, as has been described in a number of articles, favoring the presence of upper airways infections and the subsequent deterioration of the quality of life of these individuals [15].

The antiinflammatory effect of antihistamines

As has been commented above, histamine exerts potent proinflammatory action, and antihistamines could possess different effects within the complex network of inflammatory reactions of an allergic nature.

Inverse agonism *per se* does not explain anti-H1 drug action upon the adhesion molecules, upon cell migration towards the site of inflammation, or upon the inhibition of proinflammatory cytokine production. In fact, these antiinflammatory effects are inherent to the second-generation H1 antihistamines, and are not seen in the case of the first-generation drugs [4,16] - though both generations interact equally with the H1 receptor. Nevertheless, a recent study has reported inhibition of inflammatory mediator expression with chlorpheniramine [17].

Histamine, though a series of biochemical steps, activates protein kinase C (PKC). PKC in turn activates both ERK (a subfamily of mitogen-activated protein kinases, or MAPKs) and nuclear factor κB (NF-κB).

ERK is associated with the production of anti-apoptotic, differentiation and genic expression phenomena (e.g., cytokine expression), and with cell growth and proliferation regulatory processes (e.g., inflammatory cells) [18].

NF-κB is a cytoplasmic transcription factor which after activation penetrates the cell nucleus and binds to promoter regions of genes that regulate the synthesis of adhesion molecules, chemokines, proinflammatory cytokines, cyclooxygenase-2 (Cox-2) inducible nitric oxide synthase (iNOS). NF-κB is activated in those locations where inflammation is found in different disease processes (rheumatoid arthritis, multiple sclerosis, chronic demyelinating inflammatory polyneuropathy, allergic rhinitis and asthma, inflammatory bowel disease, arteriosclerosis, gastritis associated to *H. pylori*, and systemic inflammatory response syndrome, or SIRS) [19].

Down-regulation of NF- κB is the most likely mechanism by which anti-H1 drugs develop their antiinflammatory effects. In parallel, such down-regulation reduces the expression of proinflammatory cytokines. Nevertheless, the antihistamines also have been reported to exert other effects that can be classified as antiinflammatory, such as the inhibition of free oxygen radical production by alveolar macrophages via interaction with PKC [20]; the inhibition of NADPH oxidase [21]; the inhibition of angiogenesis via VEGF reduction [22]; or the reduction of granulocyte-macrophage colony stimulating factor (GM-CSF) release by the epithelial cells of the nasal mucosa, associated to secondary reduction in the number of eosinophils and their survival [23].

Reductions in ICAM-1 levels have been reported with oxatomide [24], cetirizine [25], terfenadine [26], azelastine [27], loratadine [28], desloratadine [29] and mizolastine [30]. Likewise, reductions in VCAM (vascular cellular adhesion molecule) have been observed with levocetirizine [31], as well as decreased platelet activating factor (PAF) with rupatadine [32], and lowered inflammatory cell counts (neutrophils, eosinophils) among allergic patients after receiving different anti-H1 treatments. Furthermore, such reductions are seen to be greater in patients receiving continuous treatment than in those using the medication upon demand [8-11, 33-36]. Dizdar et al. [37] found that total IgE and bronchial hyper-responsiveness did not increase during the pollination period in patients with allergy to grass pollen treated with desloratadine on a continuous basis - though both parameters increased significantly among those subjects receiving treatment upon demand.

In sum, it can be affirmed that the antihistamines exert an antiinflammatory effect, and that this effect is greater when the medication is administered continuously.

The effect of antihistamines upon symptoms control and quality of life

The symptoms of allergic rhinitis reduce patient quality of life (both children and adults), as a result of the physical and emotional disturbances, diminished performance at work and/or school, and sleep disturbances. Patients with persistent rhinitis suffer more symptoms, and these are moreover more severe, and require more symptomatic treatment than patients with intermittent rhinitis [38].

Different questionnaires have been used to assess quality of life among patients with allergic rhinitis, including the RQLQ (Rhinoconjunctivitis Quality of Life Questionnaire), the SF-36 (Short-form 36 Health Status Questionnaire) [39,40], Rhinasthma (a specific questionnaire for patients with rhinitis and/or asthma) [41], and the SPRINT (recently used and validated in the Spanish population). The TSS (Total Symptom Score) is used in most studies to record the sum of the intensity of symptoms (nose and eye itching, sneezing, runny nose, nose congestion or stuffiness), on a scale from 0-3. Of the typical symptoms of rhinoconjunctivitis, the most bothersome for the patient and the most resistant to anti-H1 treatment is nasal congestion. In this context, a criterion of optimum efficacy for the new antihistamines is their efficacy also against congestion [5].

The XPERT study [42] evaluated not only quality of life and the reduction in patient symptoms score, but also the reduction in direct and indirect costs associated with treatment, in patients with persistent rhinitis continuously treated with 5 mg a day of levocetirizine. Quality of life and the TSS both showed significant improvement after the first week of therapy, nose congestion decreased significantly after five weeks of treatment [43], and both the disorders associated to rhinitis and the global (direct and indirect) costs decreased. The study mentions that the MPI found in patients with persistent rhinitis can reduce their quality of life and social productivity - continuous treatment with levocetirizine being indicated in such situations.

Likewise, Ciprandi et al. [44] in children showed continuous cetirizine during 6 months to significantly reduce the symptoms of asthma and rhinitis, the need for additional medication, and the global cost of therapy.

The effect of the different second-generation antihistamines in terms of symptoms reduction in both perennial and seasonal rhinitis has been demonstrated by a series of studies [45-49].

Particular situations in which MPI theoretically should be present

a) Polysensitized patients

Polysensitized patients are commonly seen in allergy clinics (31.2%) [50]. They are naturally exposed to a larger number of aeroallergens during long periods of the year, or even all year long, depending on the geographical setting involved.

If such patients present persistent symptoms, and fundamentally in the case of those with sensitization to both types of allergen (perennial and seasonal), then the need for continuous treatment in order to improve symptoms and quality of life becomes evident.

Ciprandi et al. [51] showed that continuous long-term treatment (3 years) with 10 mg of cetirizine a day in children monosensitized to dust mites and with manifestations of persistent rhinitis and/or intermittent mild asthma reduced the incidence of new sensitizations to aeroallergens, with respect to those receiving cetirizine upon demand.

b) Occupational / personal exposure to the allergen

Patients with occupational respiratory allergic disease are exposed to allergen action in their working environment, and for the full duration of the work shift. The measures adopted to avoid exposure are often insufficient in themselves, either because they are bothersome (e.g., the wearing of face masks) and are therefore not used, or because they are not effective and exposure - while lessened to some extent - is thus still sufficient to perpetuate the symptoms.

Another situation is represented by patients exposed to the allergen daily in their normal life (e.g., people with domestic pets who suffer allergy to animal epithelia). Continuous exposure generates persistent symptoms.

c) Perennial allergens

Exposure to perennial allergens is variable in terms of duration and allergenic range, depending on the geographical setting. In the case of dust mites (the most common perennial allergen source), certain temperature and humidity conditions are required (about 23ºC and 75% relative humidity) for allergen number (and thus also exposure) to increase.

However, and despite the term “perennial”, in many areas such allergens actually show seasonal variations (spring and autumn), fundamentally in areas of the Spanish Mediterranean coast, and of greater intensity if the patients are also sensitized to pollen [52]. For this reason, patients sensitized to perennial allergens can manifest intermittent symptoms [53].

d) Exposure to pollen with prolonged pollination periods

There is great variability in the pollinic range in Spain, depending on the geographical setting. Such variability does not refer only to the different majority pollens found in each

zone, or to the total pollen grains per cubic meter reached in each area, but also to the duration of the pollination periods - these moreover experiencing changes with the climatic conditions.

Thus, in areas with very mild spring and autumn seasons, as on the Spanish Mediterranean coast, species such as *Parietaria* extend their pollination period from February to June, with an additional peak from August to October - thus ensuring the maintenance of symptoms for almost the entire year.

e) Environmental pollution

As has been extensively commented in other articles of this same number, environmental pollution with diesel exhaust particles acts upon the healthy individual, increasing the presence of inflammatory cells in the airways, and the levels of histamine, cytokines (IL-6, IL-8), adhesion molecules (ICAM-1 and VCAM-1), neutrophils and platelets in the bloodstream. Such situations can lead to a type Th1- or Th2-mediated inflammatory response [54]. Ozone in turn exerts an oxidizing effect and irritates the airways. Exposure to nitrogen oxide (NO_2) can induce an airways inflammatory response and may favor sensitization to aeroallergens [55]. Environmental pollution also increases pollen allergenicity [56] and favors pollen presence, vehiculized by means of minute particles, during periods of the year that do not correspond to the natural pollination period [57]. Exposure to environmental pollution thus becomes another condition to be taken into account in patients with allergy to perennial and/or seasonal allergens, as a factor causing or favoring the persistence of symptoms.

Conclusions

Although many studies can be found in the literature on antihistamine use, symptoms control in patients with allergic rhinitis, and treatment cost, there is currently no evidence to indicate whether anti-H1 drug use on a continuous basis is better than treatment on demand.

Although the ARIA study [1] and the opinions of experts advise continuous treatment to control MPI and prevent the appearance of symptoms [58], other sources question the studies made in relation to the antiinflammatory effect of H1 antihistamines, citing the lack of uniformity in the models used, and placing in doubt the *in vivo* relevance of the results obtained *in vitro* [59,60]. In any case, the results of the XPERT [41] and ETAC studies (prevention of asthma in children sensitized to dust mites or grass, with atopic dermatitis treated on a daily basis with cetirizine during 18 months) [61] are favorable to the continuous use of anti-H1 medication. On the other hand, it is clear that the second-generation H1 antihistamines offer a good clinical and safety profile [62-66]; daily dosing, if required, is therefore not unreasonable.

The most reasonable approach thus appears to be the individualization of treatment according to the characteristics of each patient, and administration of the medication on a continuous basis or upon demand - taking into account the specific conditions involved (type of sensitization, continuous or discontinuous exposure, and geographical setting). Undoubtedly, further studies are needed, specifically designed to answer this question and to establish a management protocol similar to that of the GINA, which points to the convenience of treating not only what we see (symptoms) but also what we do not see but know to be there (MPI).

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