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Review Article

Role of Nasal Corticosteroids in Allergic Rhinitis

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Abstract

Intranasal corticosteroids are acknowledged as a reliable first-line treatment for allergic rhinitis (AR). There are several intranasal corticosteroids in the market, namely, budesonide, flunisolide, fluticasone propionate, beclomethasone dipropionate, triamcinolone acetonide, and mometasone furoate. Each one is effective in preventing persistent AR and treating seasonal AR. In general, they provide relief from rhinorrhea, itching and the early and late stages of an allergic reaction which is marked by sneezing, with studies demonstrating practically total symptom avoidance in the late period. The justification for using topical intranasal corticosteroids to treat allergies is that it is possible to reach sufficient medication concentrations at receptor sites in cases of rhinitis within the nasal mucosa. This results in symptom management and lowers the danger of harmful systemic consequences. The negative effects are typically around the nasal area mucosa, including sneezing, burning, and stinging. Regardless of the formulation, 5–10% of people get headaches and epistaxis. The only differences between treatment agents are potency, patient preference, dosage plans, and the method and mode of distribution.

Key words: Allergic rhinitis, Corticosteroids, Nasal mucosa, Rhinorrhea

INTRODUCTION

Allergic rhinitis (AR) is a persistent inflammatory condition affecting 10–30% of Americans and more than 1 billion individuals globally, with a rising frequency. AR can significantly affect the standard of care for patients due to expensive healthcare. AR can also lead to significant problems and poses a threat to the emergence of asthma. AR is mediated by an antibody condition, where the nasal mucosa is inflamed due to the interplay between allergens and antibodies to immunoglobulin E. This complex attaches to the surface of mast cells, that when activated, produce a variety of inflammatory mediators, causing instantaneous allergy symptoms and an allergic reaction.[1] A common classification for AR is based on the frequency and duration of symptoms. It can be divided into intermittent AR (4 days/month) and persistent AR (PAR) (4 days per week and lasting 4 weeks). It can alter academic performance and may impact a child's ability to focus, in addition to generating stress, a lack of social integration, and a degree of familial dysfunction. Therefore, clinical investigations are crucial to discover a therapy that works well and is safe for use with young patients who have AR.[2]

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Intranasal corticosteroid spray (INCS) is one of the first-line therapies for treating AR since it is the most effective anti-inflammatory medication. Figure 1[3] systematically explains the sensitization process. INCS is beneficial for AR patients, particularly for those with nasal obstruction or moderate-to-severe AR. Proinflammatory gene transcription is inhibited and anti-inflammatory gene transcription is activated by INCS. It, then, prevents the release of cytokines and the invasion of inflammatory cells. According to a study that examined medication-taking behavior in a real-world scenario, although INCS has medical advantages, only 11.3% of patients reporting data from 7–100 days, strictly adhered to the medicine. Use of inhaled corticosteroids on an as-needed basis, in combination with long-acting β-agonists is recommended for treatment of step-two asthma.[4]

An INCS is generally advised for everyday use over an extended period of time, because its accumulating effects peak after at least 2 weeks of use. Clinical symptoms can lessen on the 1st day, and the initial application takes effect 6–24 h thereafter. As a result, even when the symptoms are under control, patients often do not adhere to the prescribed course of action or quit taking the prescription.[4]

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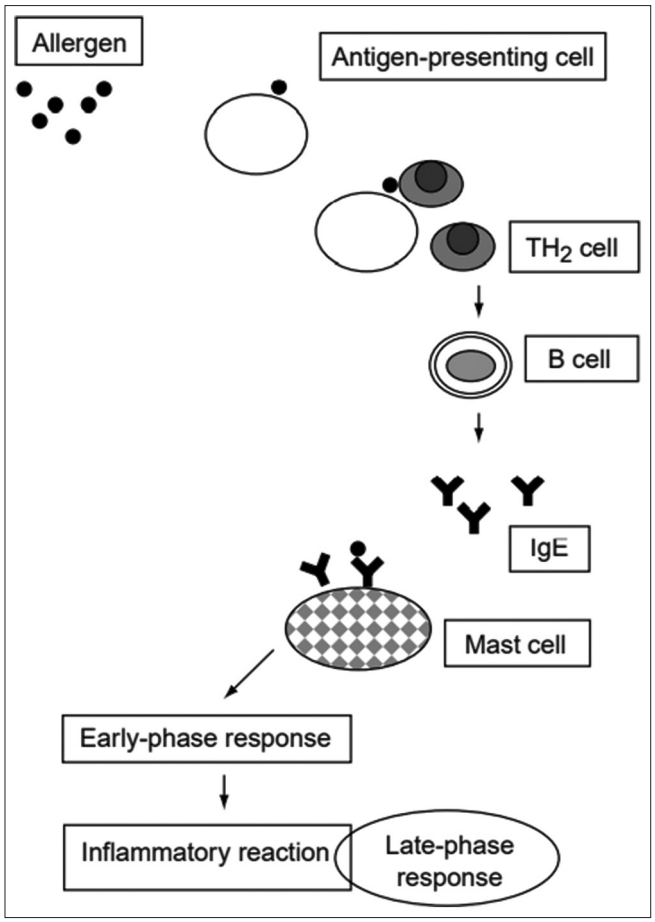

Figure 1: Schematic representation of the sensitization process adapted from Trangsrud *et al.*, the Journal of Human Pharmacology and Drug Therapy. 2002;22(11):1458-67.

The Chinese official followed AR and its Impact on Asthma, 2008, guidelines to advise a first dose of fluticasone furoate nasal spray (FFNS) for adults and adolescents of 110 μg once a day (≥12 years). However, the use of FFNS in Chinese clinical practice is not widespread due to a paucity of data on safety and effectiveness. The study examined the effectiveness and comparing the safety of FFNS with a placebo in a Chinese pediatric population with an age range of 2–12 years. The study reported that FFNS 55 μg or 110 μg has favorable efficacy and safety profiles in Chinese pediatric populations, supporting its usage in clinical treatment for AR children, particularly younger children aged 2–6 years.[2]

A by Hoang *et al.* reported that participants in the low-adherence group (28%) nonetheless experienced a considerable improvement in their overall nasal health when compared to the baseline symptoms. The effectiveness of as-needed INCS in comparison to routine INCS is still up for debate.[4] The current review focuses on the use of corticosteroids in treatment of AR.

OVERVIEW OF TREATMENT OF AR

Better health and the best results depend on individuals taking their medication as prescribed and patient adherence is crucial to the treatment of any disease. Adherence with INCS is essential to effectively control AR over the long term, and non-adherence can get in the way of treatment. Most AR patients should receive treatment before exposure to allergens to manage allergy symptoms. The patient education is necessary to boost compliance with INC therapy, because patients would not be aware of the necessity to take their medication frequently for maintenance rather than only when necessary to try to cure acute symptoms. As previously indicated, avoiding the trigger is the main non-pharmacologic treatment for AR.[1]

TREATMENT DIFFERENT FROM CORTICOSTEROIDS

Second-generation antihistamines are preferable since earlier first-generation antihistamines tend to cause drowsiness, thus restricting their use. Psychomotor-cognitive impairment, confusion, agitation, and anticholinergic symptoms are a few other side effects related to first-generation antihistamines. Clinical research indicates that co-administration of corticosteroids and antihistamines does not appear to confer any long-term advantages over corticosteroids alone, despite the apparent complementary mechanisms of action between the two drugs.[3]

Topical and oral decongestants are α-receptor agonists that cause vasoconstriction of vessels in the nasal mucosa, and thus provide relief of nasal congestion. However, they have no effect on other symptoms such as rhinorrhea, sneezing, or itching. Due to the potential for rebound congestion, or rhinitis medicamentosa, the use of topical decongestants should be restricted to no more than 5 days at a time. If a patient needs treatment over 5 days, oral decongestants should be taken. A benefit of decongestants over antihistamines is that they are effective when taken as needed and do not need to be administered before antigen exposure.[3]

Oral decongestants have several side effects that should be avoided in certain medical conditions, including uncontrolled hypertension, hyperthyroidism, diabetes mellitus, and benign prostatic hyperplasia. The side effects include central nervous system stimulation, cardiovascular stimulation, and urinary retention. The mast cell stabilizer, cromolyn sodium, prevents and treats all nasal symptoms of early-and late-phase responses. The best results come from using it as a preventive measure. It should

be administered daily for several weeks before allergen exposure for the best relief. The majority of people find it relatively safe, with the most common side effect of localized nasal mucosal irritation.[3]

Immunotherapy is a progressive, methodical method of injecting the problematic antigen subcutaneously in increasing doses in an effort to increase immunity toward the antigen. Typically, it is saved for patients with significant symptoms that interfere with daily living activities, whose effects are caused by a small number of recognizable allergens, and who do not benefit from conventional treatments.[3]

Immunotherapy is expensive and could be fatal if an anaphylactic reaction develops. The anti-IgE monoclonal antibody olizumab, indicated for subcutaneous therapy of seasonal AR (SAR) in adults and children, is awaiting approval from the Food and Drug Administration. Olizumab is a monoclonal antibody that is humanized and recombinant that targets circulating IgE. Clinical research suggests that it might help patients who do not respond to corticosteroids or antihistamines, or as an additional therapy.[3]

INCS

Nasal symptoms connected to both early-and late-phase allergic reactions can be efficiently prevented and treated with intranasal corticosteroids. They generally reduce rhinorrhea, sneezing, nasal congestion, and itching. In certain studies, they have been demonstrated to almost entirely eliminate late-phase symptoms. A complete response to the medications could take up to several weeks, even though some relief might start to show in a few days.[3]

Intranasal corticosteroids have a complicated and unclear mechanism of action. Whether the chemicals enter the nasal mucosa or affect the target cells is unknown. Corticosteroids have distinct effects on mediators and inflammatory cells involved in allergic reactions. Leukotrienes, mast cells, and prostaglandins seem to be involved as mediators. The medications also work by preventing the generation of cytokines, activation of eosinophils, and T lymphocytes, particularly TH2 cells. Topical corticosteroids allow sufficient medication concentrations at receptor sites in the nasal mucosa. This helps to regulate symptoms and lowers the possibility of systemic adverse events (AEs). Even though all intranasal corticosteroids currently available are safe and effective for managing AR, it is essential to consider variations in efficacy, side effects, and clinical characteristics. In most cases, the degree of cutaneous vasoconstrictive action from a skin model determines the topical potency of corticosteroids. According to this model, mometasone furoate and fluticasone propionate are two medications that are more effective than other intranasal corticosteroids. Although there is no direct relationship between the degree of vasoconstriction and anti-inflammatory potency, it does describe some of the clinical effectiveness of the medications in AR.[3]

The ability to bind to glucocorticoid receptors is another indicator of potency. According to one study, the order of lowest to highest receptor-binding affinities includes dexamethasone, triamcinolone acetonide, budesonide, fluticasone propionate, and mometasone furoate. In a related investigation, fluticasone's affinity was greater than that of the beclomethasone, dexamethasone, and budesonide active metabolites.[3]

INCs have limited systemic bioavailability and very low rates of systemic AEs, such as growth suppression or the suppression of the hypothalamic-pituitary-adrenal axis, which are occasionally reported with oral steroids.[1]

The most recent practice parameter was created by the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma, and Immunology, with suggestions for clinicians, depending on the quality of the evidence on making treatment decisions for their patients with AR. These guidelines state that INCs are the most efficient single therapy for easing and reducing the symptoms of SAR and persistent AR (PAR) symptoms, including nasal congestion.[1]

Recently, the efficacy of INCS has been evaluated in the treatment of AR. Pediatric AR patients between the ages of 2 and 12 were randomly assigned to receive either FFNS 55 or 110 mg or a placebo in a phase 4, randomized, double-blind, and placebo-controlled trial. Electronic diary cards were filled out to document the symptoms, usage of rescue medications, and treatment compliance. Anterior rhinoscopy and total therapeutic response were assessed and documented.[2]

In this trial, once daily FFNS 55 μg and 110 μg were compared to a vehicle placebo nasal spray to determine their effectiveness and safety in treating juvenile AR patients. Before randomization, there was a treatment-free run-in period (4–14 days), followed by 4 weeks of double-blind therapy and then a 3-7-day treatment-free follow-up period. Figure 2 displays the fluticasone furoate nasal spray FFNS randomization.[2]

In total, 92% of patients finished the study, and 12% of patients in the placebo group discontinued treatment early, compared to 7% in the once daily FFNS 55 μg and once

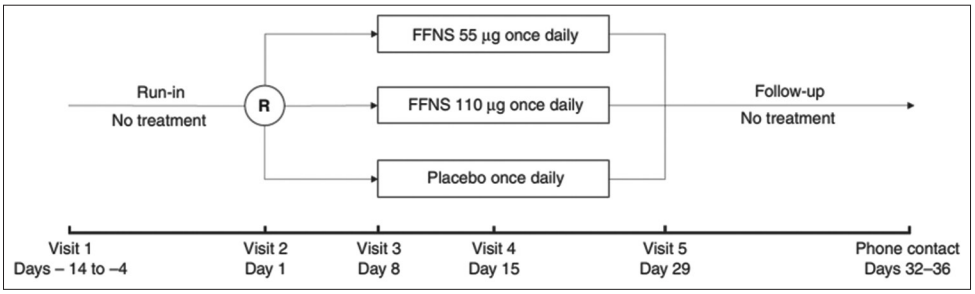

Figure 2: Fluticasone furoate nasal spray randomization

daily FFNS 110 μg groups. Reaching the stopping criterion specified in the protocol was the main cause of the early withdrawal. Overall, data from the intent-to-treat (ITT) sample showed that FFNS 55, 110, and pooled FFNS 55/110 μg had numerically greater LS mean changes from baseline in reflective total nasal symptom score (rTNSS) than placebo. Over the first 2 and 4 weeks, the LS mean difference was statistically significant ($P < 0.001$). There was no statistically significant difference between therapy with FFNS 55 μg and FFNS 110 μg in any age group, according to *post hoc* analyses. The ITT group versus placebo demonstrated the same statistically significant LS mean changes as from baseline in rTNSS in children with moderate and severe baseline nose symptoms ($P < 0.001$). In patients with substantial baseline ocular symptoms, *post hoc* analyses showed that the LS mean changes from baseline in rTOSS were statistically significant between the FFNS 55 μg group and the FFNS 110 μg group throughout the first 4 weeks (−0.06 versus −0.58, $P = 0.046$). A total of 33% of patients treated with FFNS 55 μg and 43% treated with FFNS 110 μg regarded their overall response to therapy as "significantly improved" after the first 2 weeks of treatment.[2]

As opposed to the placebo group, in the subgroup of patients aged 2–6 years, a similar pattern was seen. Substantially, more patients treated with FFNS 55 μg ($P = 0.005$) and FFNS 110 μg ($P < 0.001$) had their overall response to treatment judged by their caregivers as "significantly better" compared to those treated with placebo. After receiving treatment for 4 weeks, this pattern was still present.[2]

Four placebo-controlled studies found that FFNS significantly reduced AR symptoms and had an acceptable safety profile.[1] Fluticasone propionate nasal spray (FPNS) and FFNS were compared, and it was discovered that FFNS was favored over FPNS in terms of aroma, aftertaste and leakage down the throat/nose. According to the findings of two trials, FFNS was generally preferred over mometasone furoate nasal spray.[1]

Since INCs are so effective at preventing and treating the symptoms of both early-and late-phase reactions, they are preferred for PAR, which is defined as occurring more than 4 days per week or 4 weeks per year. The effectiveness of FFNS 110 μg once daily for 2 weeks in adult and adolescent patients with SAR was assessed by a combined analysis of 5 randomized placebo-controlled trials. Compared to the placebo group, there were notable improvements in each patient's specific nasal and ocular symptoms in the FFNS group. These improvements were consistent irrespective of the patient's ethnicity, pollen allergy season or location.[1]

Unpleasant side effects are another major cause for not taking nasal allergy medicine as prescribed. These INC negative effects are primarily sensory in nature and are highly dependent on the characteristics of the device and spray. INCs have a number of sensory qualities that help patients accept the drug and be inclined to adhere to their treatment. These qualities are traits of the drug, including the device and spray itself (such as flavor, aroma, irritability, or leaking).[1]

To compare the effects of as-needed INCS against regular INCS, as-needed antihistamine, or placebo, systematic searches for randomized controlled trials were conducted. TNSS and disease-specific quality of life were the primary objectives (DSQoL). Analysis of subgroups by AR subtype (perennial vs. seasonal), age (adults vs. children), dosage (high vs. low), and INCS systemic bioavailability (old- vs. new-generation formulation) was primary outcomes. INCS with <1% systemic bioavailability was considered new-generation INCS, which included mometasone furoate, fluticasone furoate, fluticasone propionate, and ciclesonide.[4]

In general, the risk of bias in missing outcome data was modest across all eight RCTs. In 75%, 50% and 63% of the included RCTs, respectively, some issues with the randomization process, deviation from intended interventions, and selection of the reported results were discovered. A substantial risk of measurement bias was present in 63% of the evaluated studies.[4]

This comprehensive review and meta-analysis showed that regular INCS use was superior to INCS used only, when necessary, in terms of enhancing TNSS, DSQoL, and nasal patency. These results support the conventional wisdom that the maximum benefits of INCS for clinical improvement can be realized after up to 2 weeks of continuous use. The study showed that the daily reflective TNSS of the subjects who got 110 μg of FFNS considerably increased.[4]

The goal of consistent INCS use is to reduce ongoing inflammation and maintain a long-term control of clinical symptoms. Both patients with SAR and those with persistent AR have been found to have minimal chronic inflammation.[1]

New-generation INCS used on an as-needed basis may benefit from decreased corticosteroid exposure and fewer side effects, especially in the case of pediatric and adolescent populations. The as-needed INCS revealed some advantages that outweighed the disadvantages. Since INCS shows an effect between 6 and 24 h after being administered, the majority of nasal symptoms can be resolved in a single day. A 15-min quick onset was observed when INCS and an intranasal antihistamine were combined, pointing to an alternate on-demand application. These results may help to explain why the majority of patients preferred the as-needed INCS, which is consistent with the low adherence to INCS in real-world settings.[4]

CONCLUSION

When comparing INCs for prevention and treatment of AR symptoms, sensory properties have been demonstrated to affect patient preference. Health-care professionals can help patients understand the value of sensory qualities by giving them advice. In addition, proper use of these medications depends on the patient understanding of how they operate, which should result in more effective pharmacotherapy.

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