

REVIEW

Topical corticosteroids in allergic rhinitis; effects on nasal inflammatory cells and nasal mucosa

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Introduction

Allergic rhinitis is a high-prevalence disease and is at best a nuisance and at worst incapacitating. Allergic rhinitis is characterized by nasal itching, sneezing, watery rhinorrhoea and nasal obstruction, and may be accompanied by itching in the throat, eyes and ears, epiphora and oedema around the eyes. The patient may complain of seasonal or perennial symptoms, although the latter may show seasonal exacerbations. The symptoms of perennial allergic rhinitis differ from those of seasonal allergic rhinitis; nasal blockage often dominates and eye itching is rarely a problem. Reasons for the difference in symptoms between seasonal and perennial allergic rhinitis are unknown. In recent years much knowledge has been gained in the understanding of the pathophysiologic mechanisms underlying allergic rhinitis. Various effects of treatment on symptoms and signs of allergic disease have extended our knowledge of the pathophysiology of allergic inflammation. In this review the effects of nasal corticosteroid treatment in perennial allergic rhinitis are discussed, with emphasis on mechanisms of allergic inflammation.

Mechanism of the inflammatory response in allergic rhinitis

In the initial phase, the allergen interacts with sensitized mast cells to release mediators, which induce the symptoms of rhinitis. IgE-dependent activation of mast cells results in release of preformed, granule-derived mediators (e.g. histamine and tryptase) and newly formed, membrane-derived mediators (e.g. leukotrienes D₄, C₄, and prostaglandin D₂). These mediators cause vasodilatation and an increase in vascular permeability, resulting in nasal blockage. Increased glandular secretion results in mucous

rhinorrhoea. Stimulation of afferent nerves may provoke itching and sneezing. The release of tumour necrosis factor- α (TNF- α) from mast cells, as has been demonstrated during the immediate allergic reaction in the nose, and IL-4 promote up-regulation of several adhesion molecules (including intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)). This results eventually in firmer leucocyte–endothelial adherence and allows leucocyte (including eosinophil) trans-endothelial migration under chemotactic stimuli. The co-release of IL-5 will promote eosinophil differentiation, production and chemotaxis and prolongation of its survival [1,2]. Uptake of the allergen by IgE-positive Langerhans cells in the nasal epithelium leads to allergen presentation to T lymphocytes with their consequent activation and elaboration of Th2-type cytokines [3,4]. In nasal mucosal biopsies taken from allergic patients 24 h after allergen challenge outside the pollen season, a marked increase in CD4⁺ T lymphocytes is seen [5]. Furthermore, T lymphocytes are the principal source of Th2-type cytokines [6,7]. Cytokine release from T lymphocytes thus contributes to the amplification and maintenance of airway inflammation, with mast cell mediator cytokine release initiating the process. The identification of mast cells, T lymphocytes and eosinophils as sources of cytokines may suggest an autoregulatory function of these cells through the generation and release of proinflammatory cytokines, resulting in the persistence of allergic inflammation. Apart from cytokines, which tend to have highly specific receptors, we now know there are several chemokines whose receptors show a considerable degree of cross-reactivity. Chemokines also contribute to neutrophil, T cell, mast cell and eosinophil chemotaxis and activation [8–12].

Treatment of allergic rhinitis

The management of allergic rhinitis can be divided into three therapy regimens: (i) allergen avoidance, (ii) pharmacotherapy, and (iii) immunotherapy. In most

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patients allergen avoidance will not result in complete relief of symptoms. There is a residue of symptoms requiring medical management. The use of various therapies is based on an understanding of the mechanisms of symptom development.

Nowadays, topical intranasal glucocorticosteroids have become the first-line therapy for the treatment of perennial allergic rhinitis. Steroids not only reduce nasal obstruction, but also nasal discharge and sneezing. In comparative studies they have proved more effective in symptomatic control of allergic rhinitis than sodium cromoglycate [13] and antihistamines [14]. In severe cases of allergic rhinitis short courses of systemic corticosteroids can be of use, but should only be used with caution and when there are no contraindications [15].

Efficacy of corticosteroid therapy in perennial allergic rhinitis

It is generally appreciated that the treatment of perennial allergic rhinitis is more difficult compared with seasonal rhinitis. Reasons for this difference in efficacy may be the chronic low-grade exposure to allergens in perennial allergic rhinitis compared with the high exposure to allergens in patients with seasonal rhinitis. In addition, the more pronounced nasal obstruction in perennial allergic rhinitis results in diminished access of the topical corticosteroid therapy to the site of inflammation [16]. Not all nasal symptoms experienced by patients with perennial allergic rhinitis can be attributed to allergy. In perennial allergic rhinitis with continuous exposure to allergens, sensitivity not only to allergens, but also to non-specific irritants such as perfumes and tobacco smoke is increased. Consequently, part of the symptoms may be due to non-specific hyperreactivity [17]. This non-specific hyperreactivity may continue to cause complaints and should be addressed by the physician as part of the treatment.

Fluticasone propionate has been proved effective in previous studies concerning seasonal and perennial allergic rhinitis [18–20]. A number of studies have now shown that reasonable efficacy of intranasal steroids is reached as soon as 1–3 days [21,22]. In perennial allergic rhinitis it was assumed to take 2–4 weeks of topical corticosteroid treatment to obtain maximal symptom relief [16]. However, in a long-term 1-year study with fluticasone propionate and patients with perennial allergic rhinitis, it was found that, after an initial reduction in 1 month, a further reduction of symptoms was obtained until 10 months after the start of the treatment [23]. This phenomenon was also observed in childhood asthma with Budesonide treatment, where symptoms improved during 18 months of treatment and the PD₂₀ response to histamine stabilized after 22 months'

treatment [24]. The same has been shown for antihistamines, where prolonged treatment continued to enhance quality of life [25].

It is generally advised to start local corticosteroid treatment before the start of symptomatology [26]. However, there are different opinions concerning the moment to start with corticosteroid treatment in seasonal rhinitis. Bousquet *et al.* advise starting therapy before the onset of the season [27]. However, Andersson *et al.* showed that only 1 day of pretreatment with corticosteroids abolished the allergen-induced increase in nasal hyperresponsiveness [28]. Others have found in nasal allergen provocation studies that a pretreatment period of 1 or 2 weeks with a topical corticosteroid reduced nasal symptoms significantly compared with a placebo [29–31]. In an allergen challenge study performed outside the season it was investigated whether a 6-week pretreatment period with fluticasone propionate would give complete relief of nasal symptoms [32]. Symptoms were well controlled after allergen provocation of patients who had used active pretreatment, but were not totally abolished. Comparing these results with the results of others using a shorter pretreatment period, no beneficial effect of a 6-week period could be observed. In order to find the optimal pretreatment period, further studies are necessary.

Safety and side-effects of topical corticosteroid therapy

Many patients with perennial allergic rhinitis use intranasal steroids continuously over several months and sometimes years to reduce their symptoms. Intranasal corticosteroids are considered safe regarding their effect on nasal mucosa after long-term use. Earlier studies investigating the safety of intranasal steroid sprays like Beclomethasone Dipropionate and Budesonide showed no evidence of mucosal damage or systemic side-effects [33–35].

One year of local corticosteroid treatment in perennial allergic disease showed no systemic side-effects and no evidence of mucosal damage and even showed improvement of the nasal mucosa in nasal mucosal biopsies [23,36]. Long-term use was found to be associated with a few adverse events such as headache, crusts and upper and lower respiratory tract infections comparable to placebo [23]. Interestingly, epistaxis was only reported in the fluticasone propionate group and not the placebo group, and must be considered to be caused by the corticosteroid. However, biopsy study of the nasal mucosa showed no signs of histological damage or atrophy. Epistaxis was never a reason to stop fluticasone propionate treatment. No signs of mucosal candidiasis in the nose or throat were found after long-term fluticasone propionate treatment.

Long-term intranasal treatment of adults with 200–400 µg/day of Beclomethasone Dipropionate, Budesonide

and Flunisolide has shown that the risk of systemic adverse events is very small [37]. In studies in which either long-term or high-dose treatments of fluticasone propionate were used, no evidence of systemic side-effects was found [18–20,23]. Recent data indicate that children receiving an adult dose of intranasal Budesonide (200 µg twice daily for 6 weeks) show short-term growth inhibition as measured by lower leg length (knemometry) [38], whereas this did not occur when 200 or even 400 µg were given once daily [39]. Long-term studies in children have shown no effect on growth after 1 year's use of normal dosages of mometasone but a significant growth reduction after 1 year's use of BDP in normal dosages [40,41]. Very recently, Richards & Scadding reported no effect on children's growth of intranasal and inhaled fluticasone propionate [42].

We are not aware of any data on nasal fluticasone propionate and growth inhibition in children, but in asthmatic children using inhaled fluticasone in 200 and 400 µg daily, no short-term growth inhibition was seen [43]. In the treatment of perennial allergic rhinitis in children 4–11 years old, 100 and 200 µg fluticasone propionate once daily for a period of 12 weeks has been proved safe, with no evidence of systemic corticosteroid effect [44]. It is too early to judge the clinical significance of these results for long-term treatment, especially when different treatments for asthma, eczema and rhinitis are combined [26,45].

Effect of topical corticosteroid treatment on inflammatory cells and cytokines in nasal mucosa

The symptomatology of allergic rhinitis is considered to be the result of the accumulation and activation of infiltrating inflammatory cells, releasing mediators and cytokines. Corticosteroids can suppress many stages of the allergic inflammatory process. This may explain their potent effect on allergic symptomatology. Allergic inflammation and the effects of treatment can be studied in many forms, including single provocation with a large dose of allergens (punch on the nose), usually performed in patients with a pollen allergy; repeated daily allergen provocations to simulate a more naturally proceeding disease; naturally occurring seasonal allergic disease; and, finally, naturally occurring perennial allergic disease [46–49]. Of course, studying differences and therapeutic effects using the single provocation method is considerably easier than studying naturally occurring perennial disease. However, although exaggerated provocation is a useful study tool, the findings need to be confirmed in naturally occurring disease in order to be completely reliable.

In this overview, we will concentrate on the effect of local corticosteroid treatment on migratory cells and

cytokines that invade the nasal mucosa during allergic inflammation in perennial allergic rhinitis.

Mast cells

Data on the effects of allergen provocation on mast cell numbers in the nasal mucosa are contradictory, and comparison of results from different authors is restricted by different immunohistochemical techniques [50]. The knowledge of mast cell dynamics has increased enormously over the last 10 years owing to the use of monoclonal antibodies directed against neutral proteases, such as tryptase and chymase, and IgE for the staining of mast cells in the airway mucosa. These new monoclonals have shown that mast cells in nasal biopsy sections cannot be stained with metachromatic stains, such as toluidine blue and alcian blue, when they are degranulated [51].

There are few studies investigating the effect of local corticosteroid treatment on mast cells in allergic rhinitis using monoclonal antibodies against IgE, tryptase and chymase. The data available seem to point to different reactions due to the forcefulness of the allergen stimulus and the intensity of the therapy applied. Bradding found a reduced influx of tryptase-positive cells in the epithelium, and no change in the lamina propria using fluticasone propionate 200 µg once daily in seasonal allergic rhinitis compared with placebo [52]. Juliusson described the same using Budesonide 400 µg [30]. In our Department, fluticasone propionate 200 µg daily was compared with placebo in a 2-week daily threshold allergen provocation study in patients with an isolated grass pollen allergy. A reduction in tryptase-positive cells was found in the epithelium, but not in the lamina propria [53]. When using fluticasone propionate 400 µg, both in epithelium and lamina propria a significant inhibition in mast cell influx compared with placebo was seen after allergen provocation [54]. Rak *et al.* found a reduction in mast cells in the lamina propria using fluticasone propionate 200 µg, but this was found in an allergen provocation study with a large single-allergen dose [48]. In perennial allergic rhinitis, using fluticasone propionate 200 µg, a significant reduction in epithelial mast cells, but not in the lamina propria, was found [55]. Godthelp *et al.* described, in a perennial allergic rhinitis study comparing fluticasone propionate 400 µg, fluticasone propionate 200 µg and placebo, a significant reduction in tryptase and chymase-positive cells in the epithelium for both therapies compared with placebo [56]. In the lamina propria a significant reduction was found after treatment with fluticasone propionate 400 µg, but not after treatment with fluticasone propionate 200 µg. These data lead us to conclude that epithelial mast cells are reduced by local corticosteroid treatment. Reduction of the numbers of mast cells in the lamina propria can only be

demonstrated under extreme conditions, either by using a large allergen stimulus or high-dose treatment.

Antigen-presenting cells and macrophages

Studies performed in perennial allergic rhinitis and in provocation studies showed that even low dosages of local steroids result in total disappearance of Langerhans cells during disease and a virtually complete inhibition of the influx of Langerhans cells during allergen provocation in the epithelium [47,53,55,56]. Also, a significant reduction in the number of Langerhans cells and HLA-DR⁺ cells during disease and a significant inhibition of the influx are seen in the lamina propria of the nasal mucosa [47]. No changes in macrophage cell numbers were seen after corticosteroid treatment of patients with perennial allergic rhinitis [55]. This is in accordance with Juliusson [57] and with studies in the lung [58].

T cells

The effect of local corticosteroid therapy on T cell numbers depends on the intensity of the allergen stimulus and the dose and duration of the therapy.

Rak *et al.* performed a provocation study in grass pollen-allergic patients. Nasal biopsies were performed before treatment and 24 h after an allergen provocation and were subsequently processed for immunohistology. Local corticosteroid treatment (high dose) resulted in a marked reduction in T lymphocytes and CD25⁺ (IL-2 receptor-bearing) cells in both the epithelium and submucosa [48]. In a similar study by our group a reduction was found in T cell numbers (CD3⁺, CD4⁺), but not in activated T cells (CD25⁺) in the epithelium and lamina propria after a single allergen provocation in the high-dose fluticasone propionate group [54].

Using low-dose fluticasone propionate treatment in perennial allergic rhinitis, no significant differences were found in the numbers of CD3⁺, CD4⁺, CD8⁺ and CD25⁺ cells in epithelium and lamina propria after 3 months of therapy [47]. However, after 1 year a significant decrease was found in CD3⁺, CD4⁺ and CD8⁺ cells in the epithelium. No significant changes were found in the CD25⁺ cells and no significant changes were found in the lamina propria [55]. In a double-blind comparison of two different doses of fluticasone propionate in the treatment of patients with perennial allergic rhinitis, a significant reduction was found in CD3⁺ and CD4⁺ cells in the epithelium and the lamina propria when fluticasone propionate 400 µg was compared with a placebo [56]. A distinction in the effect of fluticasone propionate on nasal mucosal lymphocytes between perennial and seasonal allergic rhinitis can be observed. In perennial allergic

rhinitis no change in the number of T cells is seen in the lamina propria after fluticasone propionate treatment [47,55]. However, after a strong allergen provocation outside the season in patients with seasonal allergic rhinitis, fluticasone propionate significantly reduced the number of T cells in the epithelium and lamina propria.

Conceptually, the antigen challenge in a perennial population is ongoing but less vigorous, therefore leading to a less prominent inflammatory infiltrate, which, theoretically, would be easier to inhibit using intranasal steroids. Despite that, the number of lymphocytes in the lamina propria was not inhibited by steroid treatment in the perennial patient group. Perhaps the number of lymphocytes devoted to allergen constitutes only a small proportion of total lymphocytes, hence the lack of inhibition by corticosteroids. Further studies are necessary to explain these differences in reactivity of T lymphocytes after corticosteroid treatment between perennial and seasonal allergic rhinitis.

Eosinophils

Studies performed in our group and by others such as Orgel *et al.*, Rak *et al.* and Bradding *et al.* showed that a considerable reduction in eosinophils, activated eosinophils and eosinophilic products occurs after local corticosteroid treatment [36,48,52,59–61]. Even when the allergen stimulus is large, as in allergen provocation studies, or when the local corticosteroid dose is relatively low, the decrease in cells is substantial. However, in an allergen challenge study, despite prolonged treatment with fluticasone propionate 400 µg, eosinophils were found to have increased significantly in nasal mucosa in the 24 h following a large allergen stimulus [32]. Surprisingly, in this study a significant increase of eosinophils in the placebo-treated group was seen in unchallenged nasal mucosa. This phenomenon has not occurred before in other studies, but it may be speculated that it is the unexplainable result of placebo treatment itself.

These results, and others not summarized here, show that the accumulation of activated eosinophils after allergen provocation is decreased by nasal steroid use. This reduction in eosinophil numbers tends to be more pronounced in the epithelium than in the lamina propria. The magnitude of this difference seems to be related to the intensity of the allergen challenge.

Cytokines

Bradding *et al.* showed a suppression of the number of IL-4 protein-positive cells in the lamina propria in a study in patients with seasonal allergic rhinitis receiving topical fluticasone nasal spray (200 µg daily) or a matching

placebo during the pollen season. Fluticasone treatment, however, failed to influence the number of IL-5 and IL-6 protein-positive cells [52]. In addition, Godthelp also found a significant reduction of IL-4 protein-positive cells in the epithelium and lamina propria after treatment with 400 µg fluticasone propionate in the double-blind comparison mentioned above of two different doses of fluticasone propionate in patients with perennial allergic rhinitis [56]. Using *in situ* hybridization, Masuyama *et al.* showed a decrease in the cells expressing RNA for IL-4, but not for IL-5, after treatment with fluticasone aqueous nasal spray [61]. In another study by the same authors, fluticasone inhibited IL-5 secretion by grass pollen-stimulated peripheral blood T cells in patients with seasonal rhinitis [62]. In our group, inhibition of mRNA for IL-4 and IL-5 was found in a threshold provocation model using polymerase chain reaction (PCR) techniques [60]. Using *in situ* hybridization, we found that fluticasone propionate treatment of patients with seasonal rhinitis reduced the numbers of IL-5 and IL-6 mRNA-positive cells in unchallenged nasal mucosa. After allergen provocation fluticasone propionate treatment inhibited the increase of IL-3, IL-5, IL-13, interferon-gamma (IFN-γ), and RANTES mRNA-positive cells. No effect on IL-4 was found in this study [54]. Recently, Wright *et al.* investigated the effect of corticosteroid treatment on Th2-type cytokine receptors after nasal allergen challenge [63]. Pretreatment with topical corticosteroids resulted in a decreased expression of IL-4 receptor and IL-5 receptor and increased expression of IFN-γ receptor in nasal mucosa, shedding further light on the effects of corticosteroids in reducing allergic mucosal inflammation.

Discussion

In the nasal mucosa of patients with seasonal and perennial allergic rhinitis, the number of inflammatory cells is increased compared with controls. Intranasal corticosteroid treatment was demonstrated to reduce these numbers. The reduction in cell numbers and probably also cytokines by local corticosteroid therapy differs from cell to cell. Some cells, such as antigen-presenting (Langerhans) cells and eosinophils, are highly sensitive to corticosteroid treatment. Others, such as T cells, are only significantly reduced in exaggerated situations, for instance after provocation with a high allergen dose or after treatment with a high dose of corticosteroids. Some cells, such as macrophages, are not influenced at all.

However, the significance of the reduction in numbers of inflammatory cells for understanding the efficacy of corticosteroids is uncertain. In symptomatic allergic patients, changes in nasal complaints are associated with corresponding changes in numbers of inflammatory cells.

Although several investigators found a statistical correlation between inflammatory cell numbers and nasal symptoms, others, including our group, could not demonstrate a statistically significant correlation between changes in cell numbers and changes in nasal symptoms. The latter is probably a better reflection of a causal relationship between cell numbers and nasal symptoms. We found that in non-symptomatic hay fever, patients' out of season fluticasone propionate treatment reduced the non-elevated number of mucosal Langerhans cells, T cells, eosinophils, mast cells and macrophages without any change in symptoms. Blom *et al.* showed a significant reduction in numbers of immunocompetent cells in patients with non-allergic, non-infectious perennial rhinitis (NANIPER) after treatment with fluticasone propionate, also without a change in nasal complaints [64]. It seems that nasal corticosteroids reduce inflammatory cells in nasal mucosa irrespective of the underlying nasal disease or condition (allergic or non-allergic rhinitis, challenged or non-challenged). From the above it is clear that it is very difficult to rate the changes in nasal mucosa cell numbers that occur after treatment in relation to the efficacy of the corticosteroid treatment at its true value. The corticosteroid-induced decrease in cell numbers probably contributes to the efficacy of the treatment, as fewer cells produce fewer mediators. Other factors such as cell activation and cell-derived proinflammatory mediators also have to be considered and may be more important.

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