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Minimal persistent inflammation in allergic rhinitis: implications for current treatment strategies

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Summary

Patients with allergic rhinitis have traditionally been placed into 'seasonal' and 'perennial' categories, which do not account for the subclinical inflammatory state that exists in many patients. In subjects with seasonal and perennial allergic rhinitis, even subthreshold doses of allergen have been found to cause inflammatory cell infiltration in the nasal mucosa, including increases in expression of cellular adhesion molecules, nasal and conjunctival eosinophilia, and other markers of inflammation, which do not result in overt allergy symptoms. This state – which has been termed 'minimal persistent inflammation' – may contribute to hyperreactivity and increased susceptibility to development of clinical symptoms as well as common co-morbidities of allergic rhinitis, such as asthma. Treating overt allergy symptoms as well as this underlying inflammatory state requires agents that have well-established clinical efficacy, convenient administration, potent anti-inflammatory effects and proven long-term safety, so that long-term continuous administration is feasible. Of the three major classes of commonly used allergic rhinitis medications – intranasal corticosteroids, anti-histamines, and anti-leukotrienes – intranasal corticosteroids appear to represent the most reasonable therapeutic option in patients who would benefit from continuous inhibition of persistent inflammation.

Keywords: allergic rhinitis, intranasal corticosteroids, minimal persistent inflammation, nasal allergy inflammation

Introduction

Allergic rhinitis (AR) is an inflammatory condition of the nasal mucosa elicited by an interaction between environmental allergens and immunoglobulin (Ig)E in sensitized individuals. It is characterized by nasal symptoms including congestion, sneezing, itching and rhinorrhoea, as well as ocular effects such as eye itching, tearing and redness. The rate of self-reported AR across Europe is as high as 18·7% [1]. In the United States, AR affects approximately 10–30% of adults [2] and up to 40% of children, or an estimated 20–40 million patients [2], making it the sixth most common chronic illness [3]. Moreover, up to one-third of patients with allergies never visit a physician, suggesting that AR's true prevalence may be underestimated [4]. AR prevalence rates have increased in recent decades [5], most notably in low-prevalence countries [6] and among children [5,6]. Although long-term changes in pollen levels will probably vary by region, current climate models predict an earlier onset [7,8] and extended duration [9,10] of seasonal allergens. Warmer temperatures also increase pollen quantity [8,11–15]; thus, the prevalence and severity of allergic diseases is likely to increase over time.

Pollen allergens are seasonal while dust mites and animal dander are present year-round, and AR has been classified traditionally as seasonal (SAR) or perennial (PAR) [16]. However, individuals sensitized to seasonal allergens may experience symptoms throughout the year, and those sensitized to perennial allergens may experience intermittent symptoms. Because of these findings, the Allergic Rhinitis and its Impact on Asthma (ARIA) group has proposed the new classifications of intermittent AR, in which symptoms occur < 4 days per week or < 4 consecutive weeks per year, and persistent AR, in which symptoms are present > 4 days per week and > 4 consecutive weeks per year [6]. Many practitioners utilize the ARIA classification because it focuses on relevant characteristics of patients' symptoms [17].

Allergen exposure varies depending on the time of year and the success of allergen-avoidance measures. Patients may appear asymptomatic during periods of low allergen

exposure; however, chronic up-regulation of inflammatory cells and mediators has been observed in nasal passages of AR patients during symptom-free periods [6]. This 'minimal persistent inflammation' [6,18] primes the nasal mucosa, leading to increased sensitivity to allergens and non-specific irritants, and increased inflammatory response to a given level of allergen exposure [19–24].

While AR treatment is guided typically by the need to reduce symptoms, e.g. at the start of allergy season, symptom-based therapy does not address inflammation that is present during symptom-free periods [e.g. minimal persistent inflammation (MPI)]. A number of authors have suggested that treatment strategies that reduce inflammation during asymptomatic periods may have positive effects on the onset, progression and severity of AR [25–28]. This paper reviews the pathophysiological processes underlying MPI and discusses the potential impact of treatment strategies to address these processes.

Pathophysiology

AR is a prototypical immediate hypersensitivity reaction, wherein the binding of allergen to mast cell-bound IgE results in rapid mast cell degranulation, increased levels of inflammatory mediators, local infiltration of inflammatory cells and, in many cases, a recurrence of symptoms several hours after initial allergen exposure [29]. This response can be described as an initial allergen sensitization during which individuals with genetic and environmental risk factors develop hypersensitivity to specific allergen(s), followed by triggering of the acute response in which subsequent allergen exposure results in the rapid release of inflammatory mediators [18,30].

Sensitization

Atopy begins with the establishment of allergen sensitization. Initial sensitizing exposure may occur *in utero* [31], and sensitivity is often established very early in childhood [32]. Intensity and persistence of exposure during the first years of life appears to influence whether the initial sensitization will progress to frank allergic disease or regress to a non-atopic phenotype [33]. After sensitization has been established [30], interleukin (IL)-4 interacts with the antigen-major histocompatibility complex (MHC) on activated antigen-presenting cells (APC) to stimulate the differentiation of naive T cells [T helper type 0 (Th0)] into Th2 cells. Atopy-promoting Th2 cells release a number of proinflammatory cytokines (IL-2, IL-3, IL-4, IL-5, IL-9, IL-10, IL-13) and granulocyte–macrophage colony-stimulating factor (GM-CSF) [30,34], whose effects include differentiation and localization of immune cells to the site of exposure; IgE-type class switching of B cells; and increased synthesis of IgE, which binds to specific receptors on mast and other immune cells [30] (Fig. 1).

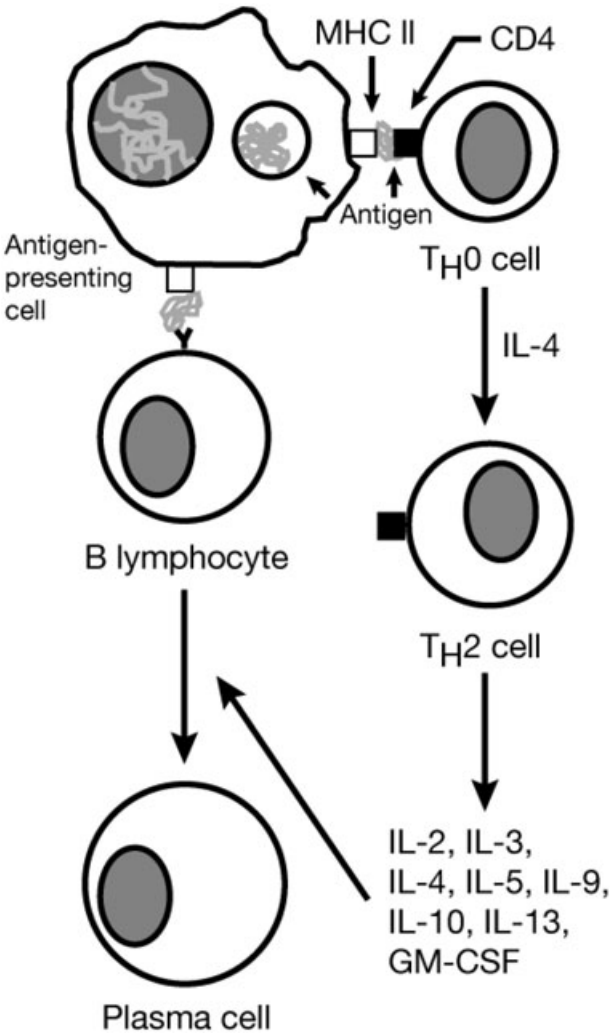

Fig. 1. Simplified schema of the differentiation of T helper type 2 (Th2) cells and activation of B lymphocytes in the establishment of sensitization to airway allergens. Reprinted from Journal of Allergy and Clinical Immunology, volume 104, number 4, part 1, DS Pearlman, Pathophysiology of the inflammatory response, pages S132–S137, copyright © 1999, with permission from Elsevier [30]. GM-CSF: granulocyte macrophage colony-stimulating factor; MHC II: major histocompatibility complex II.

Acute- and late-phase response

Asymptomatic up-regulation of inflammation occurring during the sensitization phase makes possible the symptomatic acute-phase response. Mast cell-derived mediators (histamine, leukotrienes, platelet-activating factor, bradykinin, etc.) cause the classic early-phase symptoms of AR (congestion, itching, sneezing and rhinorrhoea) [35]. While acute symptoms often disappear within 1 h [36], these early-phase mediators also initiate a complex network of inflammatory phenomena in the nasal mucosa – involving adhesion molecules, Th2 cells, cytokines and other inflammatory mediators [35] – that evolves over several hours following

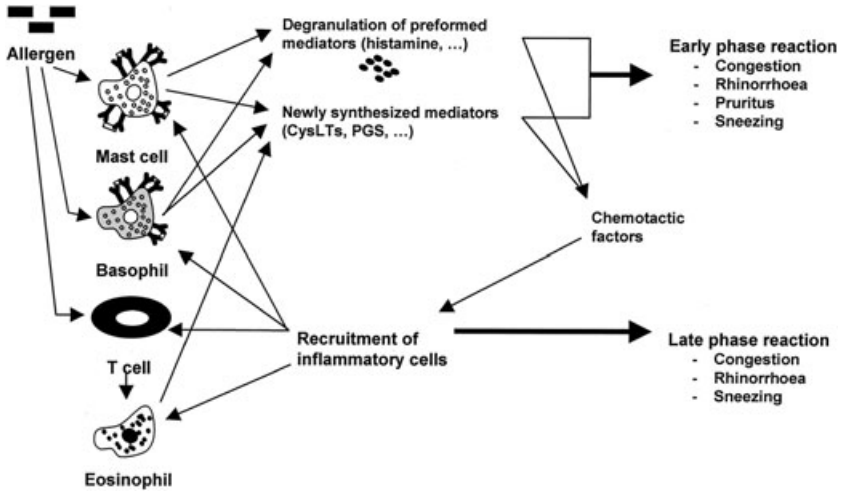

Fig. 2. Allergen-induced mast cell degranulation initiates the inflammatory cascade. Histamine and other mast cell-derived mediators (CysLTs, etc.) cause early phase symptoms within seconds. Local infiltration of inflammatory cells (eosinophils, basophils) occurs in response to up-regulation of chemokines [regulated upon activation normal T cell expressed and secreted (RANTES), eotaxin, etc.], adhesion molecules [intercellular adhesion molecule-1 (ICAM-1), etc.], and growth factors [interleukin (IL)-4, granulocyte–macrophage colony-stimulating factor (GM-CSF), etc.]. Infiltration leads to further release of inflammatory mediators and hypersensitivity of the nasal mucosa, which contribute to late phase symptoms and priming. Adapted with permission from Storms WW. Minimal persistent inflammation, an emerging concept in the nature and treatment of allergic rhinitis: the possible role of leukotrienes. Ann Allergy Asthma Immunol 2003; **91**:131–40. Copyright 2003 by American College of Allergy, Asthma and Immunology [27]. CysLT: cysteinyl leukotriene; PG: prostaglandin; VCAM: vascular cell adhesion molecule.

allergen provocation [30]. Components of this inflammatory cascade, including cytokines, chemokines and leukotrienes, stimulate proliferation and inhibit apoptosis of immune cells [37]. They also act as chemoattractants, promoting migration and infiltration of immune cells at the challenge site [37]. In addition, early-phase mediators increase expression of cell-surface adhesion molecules [intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1)] on endothelial and epithelial cells in the nasal mucosa [38,39], which promote migration of inflammatory cells (eosinophils, basophils and neutrophils) from the circulation and cell adhesion to the inflammation site [27,30,35] (Fig. 2).

Inflammatory cell infiltration and accumulation of activated eosinophil products is credited with inducing the late-phase response [30], characterized by a recurrence of symptoms 3–11 h following initial challenge, in up to 80% of patients with AR [40,41]. Subjects who develop late-phase symptoms have been found to have significantly higher numbers of eosinophils and neutrophils in nasal lavage samples [42–44]. Activated eosinophils secrete eosinophil cationic protein (ECP) and other mediators that stimulate eosinophil proliferation, migration and adhesion [30]; amplify production of Th2 cytokines [37,27]; and damage endothelial cells. ECP levels in nasal lavage samples have also been shown to correlate with symptoms 24 h later [45].

Repeated exposure to nasal allergens leads to long-term changes in local and systemic inflammation, including up-regulation of circulating eosinophils and allergen-specific IgE [46], increased levels of adhesion molecules in airway mucosa [18] and enhanced systemic response to allergen challenge [46]. Furthermore, in children with asthma, early sensitization and chronic exposure to perennial allergens may be significantly detrimental to long-term lung function [33].

Minimal persistent inflammation

In studies in the late 1960s, Connell identified and characterized 'priming', a local, reversible and non-specific up-regulation of sensitivity and responsiveness to allergen that follows repeated allergen exposure [47]. These experiments assessed changes in post-challenge nasal symptoms and allergen threshold dose, defined as a 33–50% reduction in nasal patency, in pollen-sensitive subjects who underwent repeated allergen challenge. Subjects with out-of-season AR were challenged on 4 consecutive days; with each successive daily challenge, post-challenge symptoms occurred earlier and were more severe, even as the allergen threshold dose decreased. Subjects were then challenged weekly throughout the pollen season. An inverse relationship between environmental allergen levels and allergen threshold dose was noted; allergen threshold dose decreased from preseason to midseason and increased from midseason to end of season.

When allergen exposure ceased, subjects reverted to a non-hypersensitive, non-primed state, with recovery rates varying by intensity of the priming process. In controlled challenge experiments, allergen threshold dose decreased and recovery interval increased with successive weekly priming episodes. Following priming by environmental

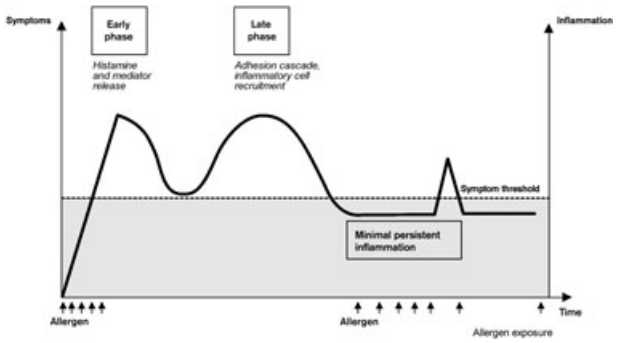

Fig. 3. The paradigm of minimal persistent inflammation. When subliminal exposure to an allergen occurs, the patient is symptom free but subclinical inflammation is present. Reprinted with permission from Passalacqua G, Ciprandi G, Canonica GW. The nose-lung interaction in allergic rhinitis and asthma: united airways disease. Curr Opin Allergy Clin Immunol 2001; **1**:7–13, copyright Lippincott Williams & Wilkins [48].

allergens during that allergy season, increased sensitivity could be demonstrated for up to 2 months after the end of pollen season. These experiments also showed that priming with one allergen results in hypersensitivity to other allergens and that priming is a local phenomenon; subjects who underwent unilateral nasal challenge demonstrated hypersensitivity only in the challenged nostril.

In the intervening 4 decades, our understanding of the biochemical and cellular mechanisms involved in priming has increased substantially. More recently, the term 'MPI' has been used to describe a phenomenon whereby repeated exposure to low levels of allergen produces no allergy symptoms but does elicit a state of heightened sensitivity to subsequent allergen exposure [18,48] (Fig. 3). In the nasal mucosa, MPI is characterized by the presence of inflammatory cells (eosinophils, neutrophils) and increased ICAM-1 expression on epithelial cells [49], which have been documented in patients with SAR and PAR during symptom-free periods [18,42,50]. Building on Connell's work [19,47], MPI offers a theoretical construct to explain the priming effect, and suggests that patients with MPI may be at increased risk for developing allergy symptoms and therefore may benefit from anti-inflammatory treatment during symptom-free periods.

Patients with PAR, typically sensitized to allergens that are present in the environment year-round (animal dander, household dust mites, etc.) are subject to persistent natural allergen exposure even when AR symptoms are not clinically evident [18]. Indeed, studies have repeatedly found evidence of significant nasal inflammation, including increased numbers of eosinophils and neutrophils, increased markers of inflammatory cell activation (tryptase, eosinophil protein X and myeloperoxidase) and increased ICAM-1 expression in samples obtained from nasal airways of asymptomatic subjects with PAR [18,42,44,51]. Data suggest that, although clinically silent, MPI reduces the dose of allergen required to provoke allergy symptoms. Allergen threshold dose was lower in mite-sensitive subjects compared with out-of-season pollen-sensitive subjects [42]. In symptom-free subjects with PAR, reduction in threshold dose was inversely correlated with prechallenge eosinophil levels [44], and occurrence of late-phase symptoms was also associated with higher numbers of prechallenge inflammatory cells in these subjects [42,44]. However, no correlation between prechallenge nasal ICAM-1 levels and occurrence of a late-phase response was noted [42].

Unlike mite- and dander-sensitive patients, individuals with SAR are typically sensitized to pollen and other allergens that are essentially absent outside of the allergy season. In studies performed during the winter months, no significant differences between pollen-sensitive subjects and non-allergic controls were noted regarding numbers of inflammatory cells (eosinophils, mast cells), markers of eosinophil activation or expression of ICAM-1 [42,44,52] in nasal lavage or brush samples. However, number of prechallenge mast cells correlated positively with severity of post-challenge sneezing and congestion, as well as with the number of late-phase eosinophils [52]. Subjects with out-of-season SAR also demonstrated increased levels of histamine and ECP in nasal lavage samples when challenged repeatedly with 1/100th of the allergen dose required to elicit symptoms [53].

A different picture emerges when subjects with SAR are examined proximal to the onset of seasonal allergen exposure. Significant nasal inflammation has been demonstrated in asymptomatic subjects with SAR who were assessed during the first week of the season and after the end of seasonal allergy symptoms [50,54]. Ricca *et al.* demonstrated that inflammation is present prior to the initial onset of allergy symptoms, during symptom-free periods and for at least 4 weeks after pollen counts and symptoms had returned to baseline levels (Figs 4 and 5) [50]. Increases in

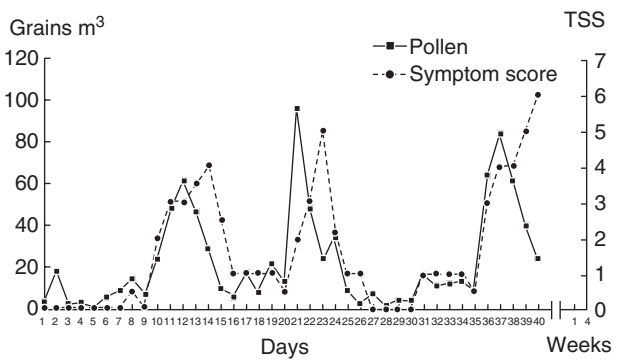

Fig. 4. Mode of daily total symptom scores and pollen counts in subjects with seasonal allergic rhinitis. Reprinted from Ricca V, Landi M, Ferrero P *et al.* Minimal persistent inflammation is also present in patients with seasonal allergic rhinitis. J Allergy Clin Immunol 2000; **105**:54–7, with permission from Elsevier [50]. TSS: total symptom score.

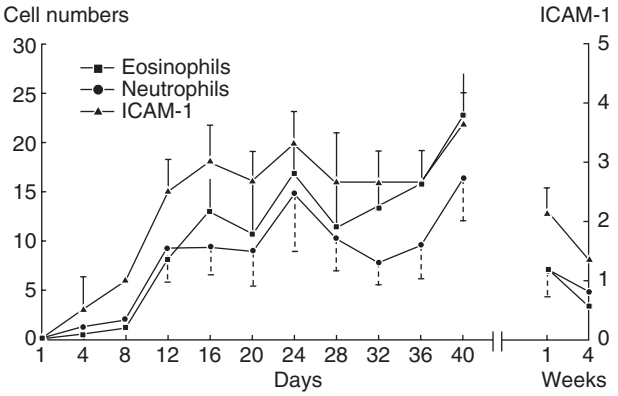

Fig. 5. Eosinophil and neutrophil counts in nasal scrapings and intercellular adhesion molecule-1 (ICAM-1) positivity on nasal epithelial cells (± standard deviation) in subjects with seasonal allergic rhinitis. Reprinted from Ricca V, Landi M, Ferrero P *et al.* Minimal persistent inflammation is also present in patients with seasonal allergic rhinitis. J Allergy Clin Immunol 2000; **105**:54–7, with permission from Elsevier [50].

eosinophils, neutrophils and ICAM-1 expression preceded the onset of allergy symptoms, which were clinically evident only after pollen counts increased dramatically from day 10 onward. Similarly, Bachert *et al.* found that IL-1, leukotrienes, ECP and histamine levels in nasal secretions remained elevated significantly 6 weeks after pollen levels and symptom scores had returned to preseason levels [44,54].

ICAM-1 and asthma in MPI

By stimulating migration and adherence of inflammatory cells, ICAM-1 mediates local infiltration at the site of allergen challenge; increased expression following allergen challenge is essential to the enduring up-regulation of inflammatory cells in AR [35,55]. Patients with AR show an increased risk of developing asthma and vice versa [56–59], and it has been suggested that up-regulation of ICAM-1 may be an important mechanistic linkage between these two diseases [60,61]. Functionally, subjects with AR, with or without co-morbid asthma, demonstrate increased lower airway constriction, increased sensitivity to bronchoconstricting agents and increased inflammatory cells in sputum samples following nasal allergen challenge [62,63]. Severity of allergen-induced nasal inflammation appears to correlate with the resulting pulmonary response, in that there is an inverse correlation between nasal lavage ICAM-1 and IL-6 levels and pulmonary function [62]. In addition, subjects with active AR symptoms demonstrated increased lower airway eosinophils [60,61], whereas subjects with out-of-season SAR did not [63]. Sputum samples from the latter group did show increased early markers of inflammation, including ICAM-1 and ECP [63], suggesting that MPI may be present throughout the upper and lower airways during symptom-free periods.

In addition to being a receptor for T cell-specific ligands [64], ICAM-1 is also the major receptor for human rhinoviruses [65], a frequent cause of upper respiratory infections in children. Up-regulation of ICAM-1 is associated with increased susceptibility to infections [35], which are an important trigger of asthma exacerbations. Some authors have suggested that chronic up-regulation of ICAM-1 may increase susceptibility to asthma exacerbation [66–68].

Patients with PAR have a more pronounced and sustained inflammation of nasal mucosa, which may explain the higher risk of asthma in patients with AR sensitive to perennial compared with seasonal allergens [69]. Studies have also shown the clinical relevance of upper airway inflammation in lower airway disease. Patients with co-morbid AR and asthma who received treatment for their AR symptoms had lower utilization of healthcare resources compared with those who did not receive AR-specific therapy [70].

Clinical implications

These data suggest that MPI may have a priming effect, resulting in a hyperreactive state in which the threshold dose of allergen is reduced and the severity and duration of allergic response is increased [27,47]. When exposure to allergen is too low to provoke symptoms, a weak inflammatory infiltration occurs in the nasal mucosa [71]. Some authors have suggested that clinically apparent symptoms represent only the 'tip of the iceberg' of the allergic reaction, although the consequences of occult inflammation and hyperreactivity may be substantial [50]. From a clinical perspective, while allergen avoidance is an essential part of disease management, avoidance measures alone are generally ineffective at improving symptoms [6]. This suggests that therapeutic strategies for AR should be revised and aimed at reducing inflammatory phenomena as well as symptoms, i.e. continuous treatment throughout the entire period of allergen exposure rather than on a symptomatic, as-needed basis [50]. Currently, three major options that may have effects on MPI – the anti-histamines, the anti-leukotrienes and intranasal corticosteroids (INS) – are available for treating AR.

Anti-histamines

Anti-histamines improve early-phase H_1-receptor-mediated symptoms such as sneezing, itching, rhinorrhoea and, to a lesser degree, nasal congestion [72]. In *in vitro* studies, loratadine and desloratadine inhibited significantly histamine-induced expression of ICAM-1, P-selectin, IL-6 and IL-8 [73,74], with desloratadine demonstrating more potent cytokine inhibition than loratadine [74]. Desloratadine has also been shown to inhibit phorbol 12-myristate 13-acetate-induced expression of IL-4 [75] and decrease eosinophil viability [76]. Jiinquan *et al.* assessed *ex vivo* leucocyte migration and ECP production in subjects who received high-dose cetirizine (10–20 mg/day) [77]. Although cetirizine inhibited

migration significantly, there was no effect on ECP levels. In clinical trials of patients with symptomatic AR, significantly decreased levels of nasal mucosal inflammatory cells and mediators have been observed after treatment with two different second-generation anti-histamines [1,78,79].

Although anti-histamines are used commonly on demand, some authors have suggested that continuous use of anti-histamines may reduce MPI by reducing the infiltration of inflammatory cells [49,80]. The effects of continuous anti-histamine therapy on allergen sensitivity or responsiveness in symptom-free patients with AR have not been evaluated, but studies have compared inflammatory markers in patients receiving continuous *versus* on-demand therapy. In pollen-allergic subjects, cetirizine [81] and azelastine [82] administered continuously for 4 and 12 weeks, respectively, were significantly more effective than on-demand treatment in reducing nasal eosinophils and neutrophils; azelastine also inhibited ICAM-1 expression [82]. Greater reductions in adhesion molecules and eosinophils were also observed with daily *versus* on-demand treatment with loratadine or cetirizine in patients sensitized to perennial allergens [83,84]. No difference in nasal lavage ECP levels was observed after 1 month of continuous compared with on-demand desloratadine in pollen-sensitive children [85]. Similarly, no significant difference in nasal eosinophils or ICAM-1 levels was observed after 6 months of continuous or on-demand levocetirizine in patients with persistent AR [86]. Twelve months of continuous terfenadine was compared with placebo in mite-allergic children with AR and/or asthma (on-demand therapy was not assessed) [87]. Nasal eosinophils, neutrophils and ICAM-1 were reduced with terfenadine *versus* placebo at some but not all monthly assessments.

Second-generation anti-histamines effectively reduce early-phase symptoms, but their effects on inflammation are less consistent [27]. In addition, greater improvement in nasal symptoms with continuous *versus* on-demand anti-histamine treatment has not been demonstrated consistently [81,82,85,86]. Decreased bronchial hyperreactivity was also observed in two studies [81,85]. These data suggest that continuous therapy results in better clinical outcomes compared with on-demand therapy. However, because allergy symptoms were present when treatment was initiated in the studies cited [81,82,85,86], these data reflect the impact of continuous treatment on clinically apparent inflammation rather than on changes in subclinical MPI levels.

Anti-leukotrienes

Cysteinyl leukotrienes are important mediators of nasal allergy symptoms, particularly nasal congestion [88] and leukotriene receptor antagonists are recommended for treatment of moderate-to-severe AR and asthma/AR co-morbidity [89]. These agents have been shown to reduce levels of IL-4 and IL-13 and to increase interferon-γ, a Th1 cytokine, thereby shifting an atopic Th2 cytokine pattern towards a non-atopic Th1 pattern [90]. Leukotriene receptor antagonists also reduce peripheral eosinophilia in patients with AR [91]; because local infiltration is dependent upon circulating eosinophils, it has been suggested that this confers a beneficial effect on MPI [27]. However, studies assessing the effects of leukotriene receptor antagonists on nasal infiltration are, as yet, unpublished.

Intranasal corticosteroids

Perhaps the strongest evidence exists for treating MPI with INS. These agents are the most potent medications available for management of AR, particularly in patients with moderate-to-severe disease [2,6,16,89]. Intranasal corticosteroids are highly effective in reducing early- and late-phase nasal congestion, rhinorrhoea, sneezing and nasal itching in SAR and PAR, without the side effects associated with systemic glucocorticosteroids [92]. Two large meta-analyses found superior efficacy for INS compared with oral or topical anti-histamines in reducing nasal symptoms and at least equal efficacy at relieving ocular symptoms [93,94].

The mechanisms by which glucocorticoids inhibit allergic inflammation are complex and not understood completely; however, efficacy is thought to owe to their effects on regulating expression of proteins associated with inflammation [95]. In the cytoplasm, glucocorticoids bind to and activate glucocorticoid receptors. This glucocorticoid receptor complex regulates DNA transcription by binding to positive and negative glucocorticoid response elements in promoter-activator regions of target genes [95]. Inhibition of gene expression also occurs via interactions between the glucocorticoid receptor complex and cytoplasmic transcription factors such as nuclear factor (NF)-κB and activator protein-1 (AP-1) [95–97].

Although the exact target genes are unknown [97], the downstream effect of INS appears to be down-regulation of the expression of a number of cytokines (IL-1, IL-3, IL-4, IL-5, IL-6, Il-10, IL-13, TNF-α, GM-CSF) and chemokines [IL-8, regulated upon activation normal T cell expressed and secreted (RANTES), eotaxin] that promote the proliferation, infiltration and activation of inflammatory cells [95,98–101]. Pretreatment with fluticasone propionate (FP) has also been shown to inhibit post-challenge cytokine mRNA levels in nasal biopsy samples from subjects with AR [102]. Differences in cytokine inhibition have been demonstrated among INS agents, with greater potency *in vitro* against atopy-promoting Th2 cytokines (IL-4, IL-5) observed with mometasone furoate (MF) and FP compared with older agents such as beclomethasone dipropionate (BDP), budesonide (BUD) and triamcinolone [98]. In addition, pretreatment with INS may shift post-challenge cytokine expression from a Th2 pattern towards a non-atopic Th1 pattern [103,104].

The impact of INS on inflammatory mediators and cells that are the basis for nasal priming and hyperresponsiveness has been well described. In clinical trials of subjects with AR,

INS inhibited allergen-induced expression of ICAM-1 on nasal epithelial cells [100,105]. Nasal airway infiltration, activation and survival of inflammatory cells such as eosinophils, basophils and mast cells were also reduced with INS treatment [104,106–110]. Although INS such as MF, FP and fluticasone furoate have exceedingly low systemic absorption [111,112], INS also inhibit systemic up-regulation of the inflammatory markers, including post-challenge circulating allergen-specific IgE antibodies [113] and eosinophil-progenitor cells [114,115].

INS also decrease specific and non-specific sensitivity in atopic nasal tissue, suggesting inhibition of the underlying inflammation. Although not classed as mast cell stabilizers, INS inhibit the allergen-induced release of histamine [99] and other mast cell-derived mediators in patients with AR [37,99,116–120]. In addition, INS increase the threshold dose of allergen [116] and histamine [117,121] required to elicit allergy symptoms. INS dramatically reduce or eliminate antigen-presenting Langerhans cells in the nasal epithelia [106,122–124] which may, in part, explain the effect of INS to eliminate the increased sensitivity seen in untreated, allergen-primed subjects with AR [116]. Furthermore, treatment with INS has been shown to reduce the number of emergency room visits in patients with both AR and asthma [70,125].

Because subjects with MPI display increased sensitivity to allergen challenge [20], delay in onset of seasonal symptoms may be a clinical end-point for MPI inhibition. Prophylactic administration of INS has been shown to delay onset and reduce symptom severity in adults with SAR [25,26,28,126,127]. Randomized, placebo-controlled trials have compared once-daily MF with once-daily BUD or twice-daily BDP, initiated 4 weeks prior to the start of allergy season and continuing for 4 weeks into the season [25,26]. In both studies, prophylaxis with MF, BUD or BDP delayed significantly the onset of non-minimal symptoms (MF 27 days, BDP 27 days [25]; MF 26 days, BUD 34 days [26]) and resulted in a significantly higher proportion of days with no or minimal symptoms after the start of allergy season (MF 83%, BDP 77% [25]; MF 81%, BUD 82% [26]) *versus* placebo (64% [25]; 63% [26]). While no significant differences between active groups were observed for the above outcomes in either study, one study found that preseason nasal symptoms were significantly lower with MF *versus* BDP, as well as a trend towards longer delay to moderate-to-severe symptoms ($P = 0{\cdot}08$) [25].

In a dose-ranging trial of BUD in SAR prophylaxis, 364 subjects were randomized to begin BUD therapy (200 μg or 400 μg) or placebo 4 weeks prior to the pollen season, and then continued on one of the above doses of BUD after the start of the pollen season for 6 more weeks [127]. Subjects who received BUD prophylaxis had significantly lower symptom scores during only the first week of the pollen season compared with those who received preseason placebo. However, compared with subjects who received low-dose pre- and in-season treatment, subjects who received high-dose (400 μg) followed by low-dose (200 μg) treatment had numerically lower total and individual nasal symptoms for an additional 2–5 weeks. These results suggest that more potent suppression of inflammation in MPI can have lasting effects on symptoms during the pollen season [127].

Studies have also compared the efficacy of INS *versus* other AR treatment options for prophylaxis of SAR. Pullertis *et al.* compared FP, montelukast, montelukast with loratadine and placebo, each administered once daily, in 62 subjects with SAR. Treatment was initiated 2–3 weeks prior to the anticipated start of allergy season and continued throughout the season [128]. Daytime and night-time symptom scores were consistently lower with FP compared with the two other active treatment arms throughout the study [128], and these differences were increasingly evident as the pollen season progressed. In addition, treatment with FP abolished completely the pollen-induced increases in nasal eosinophils that were observed in the active- and placebo-treated arms [128]. Two studies have compared INS and mast cell stabilizers, which are indicated outside the United States for prophylaxis of SAR [129]. In a study by Bousquet *et al.*, subjects received disodium cromoglycate four times daily or FP once daily for 6 weeks, starting at least 1 week prior to the allergy season [126]. Subjects receiving FP reported significantly higher percentages of days without nasal symptoms, while reduction in ocular symptoms favoured disodium cromoglycate. However, approximately one-quarter of subjects were excluded from analysis, primarily for non-adherence, due probably to the required four-times-daily administration in both groups [126]. In addition, treatment was initiated after the start of pollen season in 18·3% of subjects included in the analysis; therefore, these results are not from a rigorously defined prophylactic regimen. In a recent study by Pitsios *et al.*, treatment was initiated 2–4 weeks before allergy season with once-daily MF or thrice-daily nedocromil and continued for up to 4 months [28]. Subjects receiving MF reported significantly more minimal-symptom days (77·6% *versus* 57·3%, $P < 0{\cdot}01$) and lower mean nasal symptom scores (1·46 *versus* 3·02). In contrast to the study by Bousquet *et al.*, all subjects completed the study; furthermore, all subjects were asymptomatic when treatment was initiated. MF was approved for prophylactic use in adults with allergen-identified SAR [130] and it is the only INS with this indication [131].

Conclusion

Allergen provocation in AR results in an acute- and late-phase inflammatory response characterized by up-regulation of inflammatory mediators and inflammatory cell infiltration of the nasal mucosa. A subclinical inflammatory state has also been described in symptom-free patients allergic to house dust mites or pollens, in which subthresh-

old doses of allergen stimulate small but significant increases in expression of cellular adhesion molecules, nasal and conjunctival eosinophilia and other inflammatory markers. This MPI appears to be present year-round in PAR and periseasonally in SAR, and may have a priming effect by increasing allergen sensitivity as well as an inflammatory response to allergen provocation. Therefore, treatment options that target underlying inflammation along with symptom relief should be considered. Further research is needed regarding the clinical relevance of MPI, and the timing and duration of treatment of subclinical inflammation. In light of the clear relationship between the upper and the lower airways [6], the relevance of nasal MPI to the lower airway inflammation has to be considered. Concerns have been raised regarding patient compliance in the absence of symptoms, but patients who are prone to more frequent exacerbations would be more likely to adhere to continuous therapy [27].

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Disclosure

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