

Original article

Nasal allergies and beyond: a clinical review of the pharmacology, efficacy, and safety of mometasone furoate

Mometasone furoate nasal spray (MFNS; Nasonex[®], Schering-Plough Corporation, Kenilworth, NJ, USA) is an effective and well-tolerated intranasal corticosteroid approved for the prophylactic treatment of seasonal allergic rhinitis, and the treatment of perennial allergic rhinitis. MFNS is a potent molecule with a rapid onset of action and excellent safety and efficacy profiles. Having recently received approval for the treatment of nasal polyposis, data indicate that MFNS may also be effective in rhinosinusitis.

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Overview of allergic rhinitis

Prevalence

Allergic rhinitis is a chronic disorder that affects the upper respiratory airways and is characterized by inflammation of the mucous membranes (1). The pathophysiology of allergic rhinitis is a consequence of an immunoglobulin E-mediated reaction in the nasal mucosa to one or more otherwise innocuous environmental molecules or allergens (2, 3). Other forms of rhinitis include infectious rhinitis and non-infectious or non-allergic non-infectious rhinitis (arising from overactivity/underactivity of the autonomic nerve pathways) (4).

The prevalence of allergic rhinitis is increasing worldwide (5), and is ranked as the most common and troublesome allergic disorder in Westernized countries. Furthermore, it is one of the top 10 reasons for visits to primary care physicians in the USA (6). Interestingly, prevalence rates are higher in the Westernized population than in the rest of the global population (7). Between 20 and 40 million people in the USA are affected (8), and there is a similar overall prevalence (approximately 20%) of allergic rhinitis in the European adult population (7). Allergic rhinitis can affect patients at any stage of life. However, the peak incidence of allergic rhinitis appears to be in children and young adults, with a decrease in later

life (3, 8). In the USA, 10–30% of adults are affected with allergic rhinitis, while in children this figure is closer to 40% (9). Of interest, allergic rhinitis is seen more commonly in boys than in girls, although this sex difference lessens considerably following adolescence (2, 8).

Causes

Allergic rhinitis can be seasonal (SAR) or perennial (PAR), and in some patients both types are present. Studies suggest that in the USA, SAR affects approximately 10% of the general population, whereas PAR is found in 10–20% (8). Typical seasonal allergens include grass, tree, and weed pollen, and certain outdoor mold (fungal) spores (4). Common perennial allergens are house dust mites, animal dander, cockroaches, indoor mold, and occupational allergens (1, 3). In the case of SAR, symptoms are periodic and are profoundly increased during certain seasons correlating with the seasonal variation in aeroallergens. In PAR, patients experience symptoms that are continuous or intermittent over the course of the year (10). A real-life study conducted for 1 year in patients with PAR to house dust mites showed that their nasal symptoms were consistently high for 65% of the time (11). However, these data also

indicate that patients with PAR do experience variations in the intensity of their symptoms.

In 2003, the Allergic Rhinitis and its Impact on Asthma (ARIA) group suggested that the classification of seasonal and perennial should be disbanded (12, 13). This was owing to the fact that observation of symptom patterns related to a single allergen could not always be assigned to either seasonal or perennial. As a consequence, patients are sometimes incorrectly classified; patients enrolled for participation in a cross-sectional survey, classified as having SAR, were in fact found to have persistent rhinitis, and vice versa (12). Therefore, the ARIA expert panel proposed to define allergic rhinitis on the basis of the duration of the experienced symptoms (number of days per week or the number of consecutive weeks per year), in combination with the severity of these symptoms (mild, moderate-severe). The terminology, SAR/PAR and intermittent/persistent, are still used variably today.

Underlying inflammatory processes

Inflammation plays a major role in allergic rhinitis: in sensitized individuals, exposure of the nasal mucosa to an allergen stimulates an early-phase allergic response, followed by a late-phase response several hours after initial allergen exposure (Fig. 1). In the early-phase response, allergens cross-link immunoglobulin E (IgE) on the cell surface of resident mucosal cells, including mast cells and basophils. This causes them to release chemical mediators, such as histamine. The mediators then bind to their receptors in the nasal mucosa activating nerves, increasing vascular permeability, and stimulating mucous secretion. This early-phase response takes place within minutes of initial allergen exposure and occurs in over 90% of patients (14). Characteristically, symptoms of nasal congestion, rhinorrhea, sneezing, pruritis (itching), and post-nasal drip occur.

In the late-phase response, chemokines and cytokines released by the resident mucosal cells after the initial stimulus act to recruit inflammatory cells, such as basophils and eosinophils (14). These become activated and release additional amounts of mediators, including histamine and leukotrienes. The same symptoms seen in the early-phase response recrudesce 4–12 h after initial allergen exposure and can last up to 24 h (2). This late-phase response is reported to occur in only half of all patients with allergic rhinitis (15).

Symptoms

The cardinal symptoms of allergic rhinitis include nasal congestion, rhinorrhea, sneezing, pruritis, and post-nasal drip, as mentioned above (15). Frequently, these symptoms are accompanied by non-nasal symptoms of itching of the eyes, ears, and palate, and redness and watering of the eyes (2). The early- and late-phase symptom

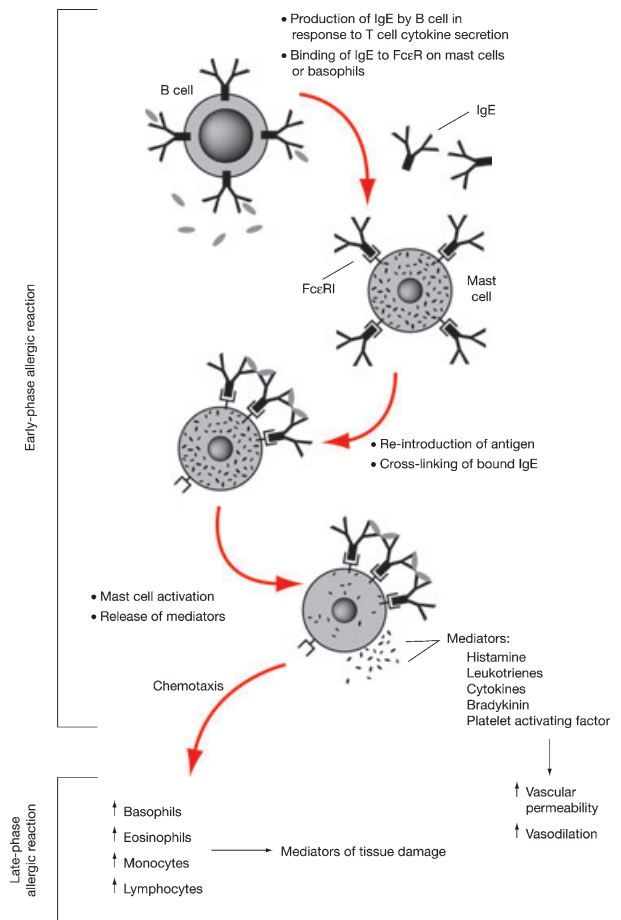


Figure 1. Mediators of nasal congestion in the early- and late-phase allergic response. Adapted from Ref. (10).

responses are generally indistinguishable. However, nasal congestion may dominate the late-phase response, with symptoms of rhinorrhea and sneezing occurring more often in the early-phase response (14). Furthermore, in the late-phase response, circulating inflammatory mediators can give rise to symptoms of fatigue and malaise (2).

The classic symptoms of allergic rhinitis are not only a consequence of a reaction of the nasal mucosa, but also of paranasal tissue. Sinus CT scans of patients (classified as having intermittent rhinitis) challenged to increasing concentrations of cypress pollen showed changes in the paranasal sinuses, thus reflecting the involvement of all upper airway tissues in allergic rhinitis (16).

Patients with SAR tend to present to the physician mainly with symptoms of watery rhinorrhea, repetitive sneezing, and also with nasal congestion, pruritis of the nose, ears, eyes, and palate, and watering eyes. Patients with PAR are more likely to complain of nasal congestion, which is often severe, along with post-nasal drip (3, 10). Regardless of type, patients often experience more than one symptom, and the severity of allergic rhinitis can range from mild to seriously debilitating. Although all these symptoms contribute to the discomfort of allergic

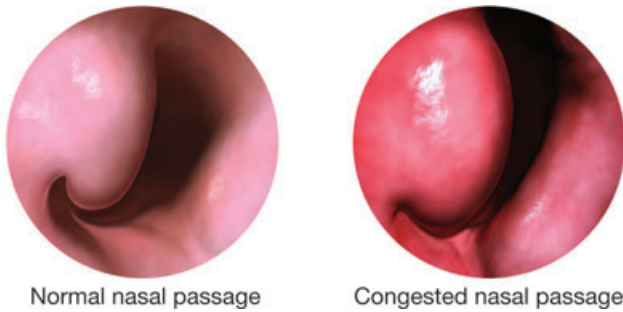


Figure 2. An illustrated example of congested and normal nasal passages.

rhinitis patients, nasal congestion is often perceived as the most bothersome of the complaints.

Nasal congestion, arising from vasodilation and increased permeability of the blood vessels with resultant edema of the cavernous venous sinusoids within the turbinates, is the usual predominating symptom of allergic rhinitis (13, 15). Edema of the nasal mucosa reduces nasal patency (17). It is this increased nasal resistance to airflow that gives rise to the troublesome symptom of nasal congestion (Fig. 2). Patients often describe their congestion as a 'blocked up' or 'stuffy' feeling, and it can be associated with a dry and irritated throat, and a decreased sense of smell and taste (18).

In a large internet survey of over 2000 patients with allergic rhinitis conducted by Roper Public Affairs Group of NOP World (19), all participants reported nasal congestion as an issue of their allergic rhinitis. Data showed that 40% of participants scored nasal congestion as severe (rated 9 or 10 on a 10-point scale) (Fig. 3), indicating that nasal congestion was the most bothersome complaint. Furthermore, 80% of participants responded that nasal congestion impacted their ability to sleep, while a third felt their nasal congestion interfered with their ability to perform normal daily activities: outdoor activities appeared worst affected (Table 1) (19). Therefore, it is not surprising that 63% of participants voted nasal congestion as the symptom they would most like to see prevented.

Quality of life

Allergic rhinitis can have detrimental effects on emotional and psychological well-being, and can impair learning or development in children, and performance at work or school (5, 19, 20). In addition, affected adults and children may suffer from shyness, depression, and anxiety (5).

As mentioned, impairment of nocturnal sleep is a major complication of allergic rhinitis, resulting in daytime somnolence and fatigue (19, 21, 22). Additionally, Young et al. (23) undertook a study in which they obtained data on the nasal congestion history and sleep problems of allergic rhinitis patients by means of a

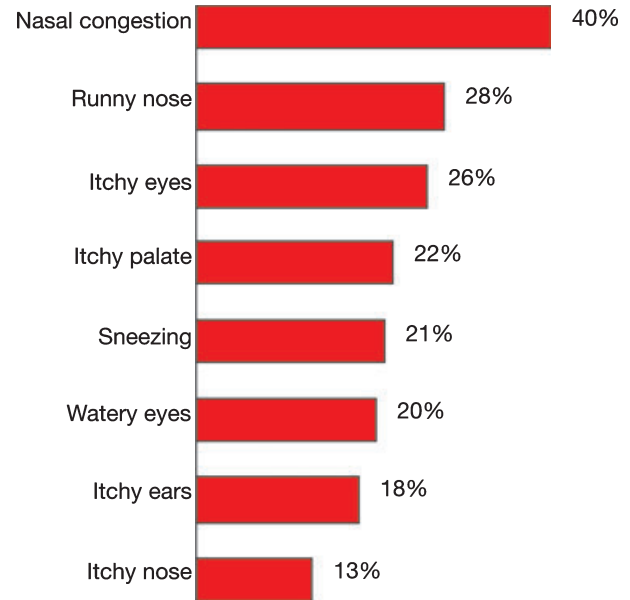


Figure 3. Forty percent of allergic rhinitis sufferers with nasal congestion rate their congestion as severe. Response was in answer to the following question: 'Of those symptoms you/your child experiences, please rate how severe each one is when it occurs, using a 10-point scale where 1 means not severe at all and 10 means extremely severe. The greater number you choose, the greater the severity'. 'Severe' was defined as a score of 9 or 10 on a 10-point scale. Percentages reflect the proportion of respondents who experienced a particular symptom (19).

questionnaire. Those participants with nasal congestion arising as a result of an allergy were 1.8 times more likely to suffer from sleep-disordered breathing than those without nasal congestion. Furthermore, those respondents with night-time symptoms of rhinitis were more likely to be habitual snorers. This survey suggests that nasal congestion is a predisposing factor for sleep-

Table 1. Nasal congestion has an impact on ability to perform daily activities in allergic rhinitis sufferers with congestion, regardless of congestion severity. Response was in answer to the following question: 'How often, if at all, does the nasal congestion from you/your child's allergy interfere with your/his/her ability to do the following activities when it is present? For each one, indicate whether it occurs frequently, occasionally, rarely or never' (19).

Among total respondents, % saying frequently	Severe (%) Moderate (%) Mild (%)		
Net: has frequent effect on daily activities	46*	32	22
Doing outdoor activities	28*	20	13
Spending time outdoors relaxing	27*	17	12
Exercising or participating in sports	19*	12	7
Doing chores around the home	18*	9	8
Overall daily routine	17*	10	6
Normal eating habits	13*	8	4
Participating in social activities	13*	7	4
Spending time indoors relaxing	10*	5	3

*Statistically significant difference compared with moderate and mild congestion.

disordered breathing with its associated daytime somnolence.

In a study conducted by Downie et al. (11) in patients with PAR to house dust mites, quality of life measurements were made every 3 months. The results indicated that non-specific measures of quality of life, such as reduced productivity and poor concentration, were significantly worse in the PAR group compared with control patients. Furthermore, this reduced quality of life was persistent all year round.

In another study, quality of life data were obtained from patients with PAR through the process of in-depth interviews (24). Patients reported that their disease had a serious emotional and social burden in terms of feelings of tiredness or depression, being unable to participate in normal activities, becoming easily irritated, and being unable to perform adequately at work. Interestingly, this study showed a stronger, subjective impact of rhinitis in women.

Co-morbidities of allergic rhinitis

Untreated allergic rhinitis can lead to impaired quality of life and the development of chronic inflammatory obstruction and infection. Worse still, patients can suffer from mucosal damage, and other diseases of the upper and lower respiratory airways. Epidemiological survey data suggest that allergic rhinitis is closely associated with, and is possibly a causative factor for, co-morbidities such as otitis media, rhinosinusitis, and asthma. The link between allergic rhinitis and other inflammatory diseases possibly exists because of the common airway passages affected by these disorders (25).

These co-morbidities of allergic rhinitis are discussed in more detail below.

Otitis media

Otitis media is defined as an infection of the middle ear with acute onset, presence of middle ear effusion (MEE), and signs of middle ear inflammation. Otitis media most commonly occurs in children. The co-existence of both allergic rhinitis and otitis media is common; in fact, it has been reported that 40–50% of children diagnosed with otitis media also have allergic rhinitis (25).

A hypothesis to describe how nasal inflammation in allergic rhinitis can lead to otitis media has been proposed: prolonged nasal inflammation can induce inflammation of the Eustachian tube, which subsequently imposes negative pressure on the middle ear. Owing to reduced ventilation resulting from the forced pressure exerted on the middle ear, the middle ear cavity can fill with nasopharyngeal secretions that contain bacteria, viruses, and/or allergens. The presence of these unwanted bacteria can give rise to acute bacterial otitis media (25). The link between otitis media and allergic rhinitis,

however, is weaker than that of otitis media and adenoid enlargement.

Rhinosinusitis

As discussed, allergic rhinitis frequently co-exists with, and is a high-risk factor predisposing patients to, other inflammatory conditions of the upper airway, including rhinosinusitis. Indeed, the two disorders appear to be linked such that rhinosinusitis is rarely seen in the absence of rhinitis (10). Given this link between the two disease modalities and the growing need for standardization in classification and treatment of rhinosinusitis, a task force of the European Academy of Allergology and Clinical Immunology (EAACI) has recently put forward its recommendations in the EP³OS document (26, 27).

Rhinosinusitis, also termed sinusitis, is a condition with increasing prevalence (28). It is defined as inflammation of the paranasal mucous membranes, which leads to nasal obstruction, poor drainage, and nasal infection. The acute form of rhinosinusitis is characterized as a viral infection. Bacterial infection can arise secondary to, and possibly as a consequence of, the primary viral form (28) and is presumed when symptoms persist for more than 7 days (29). Classic symptoms of acute rhinosinusitis include nasal congestion, purulent discharge, fever, headache, facial pain, and post-nasal drip (30). Levels of non-specific cytokines are increased in rhinosinusitis and it would appear that these mediators play an important role in the pathophysiology of this condition (31).

The co-existence of allergic rhinitis and rhinosinusitis probably arises because of the fact that both inflammatory disorders involve mucociliary dysfunction, tissue edema, and increased mucous production (5). A potential model has been proposed to explain the progression of allergic rhinitis to rhinosinusitis: nasal congestion arising from allergic rhinitis can obstruct the sinus passages making it difficult for nasal secretions to pass through. Accumulation of these secretions can lead to further obstruction and mucosal swelling, thereby creating the ideal environment for the growth of an infective agent that can lead to acute rhinosinusitis.

Asthma

Asthma is a chronic, debilitating disease characterized by life-threatening symptoms. Compelling evidence from a number of epidemiological surveys suggests that allergic rhinitis is an important risk factor in the development of asthma (5). Allergic rhinitis and asthma are often found to co-exist; indeed, 40% of allergic rhinitis patients also have lower airway disease (32). In a recent study in which the probable association of PAR (caused by house dust mites) with bronchial symptoms was assessed, it appeared that patients with

PAR were more at risk of developing bronchial symptoms than the control patients (healthy adults) (33). Another study showed that over 95% of patients with asthma also suffered from nasal allergies (34). Additionally, asthma symptoms are found to worsen in allergic rhinitis patients during the pollen season (10).

In a population-based study of patients with allergic rhinitis and patients with allergic asthma, re-evaluation at follow-up (median time = 7 years, 10 months) showed that all subjects with allergic asthma to pollen had allergic rhinitis to pollen as well (35). Similar results were seen in a 23-year follow-up study of college students in whom 85% of asthmatic patients had developed allergic rhinitis at follow-up (36). Therefore, it is thought that allergic rhinitis and asthma may be manifestations of the same disease (32, 37).

The association between allergic rhinitis and asthma could involve a number of mechanisms. Clearly, IgE is the common initiating step that gives rise to inflammation in both diseases with differences between the two conditions largely being due to the structural differences between the nose and the lungs (38). Another hypothesis is that dysfunction of the nose could negatively impact the lower airways; for example, allergen provocation in the nose of patients can lead to decreased pulmonary function (39). Furthermore, it has been proposed that interaction between the systemic pathway, including the bloodstream, between the upper and lower respiratory tracts can contribute to asthma signs and symptoms (32).

Recent ARIA guidelines characterize allergic rhinitis and asthma as manifestations arising from one syndrome and/or shared airway. Thus, it is felt that a combined strategy should be employed to treat both the upper and lower airways to combat the occurrence and symptoms of both disorders (13). Although guidelines help practitioners and patients make appropriate decisions, a study of the medications used in the treatment of allergic rhinitis and asthma suggested that guidelines should be simple, with methodologies being the main focus of concern (40).

Costs of allergic rhinitis and its co-morbidities

Although not classified as a life-threatening disease, allergic rhinitis has a considerable impact on public health and the economy. Costs can be divided into two categories: direct, which refers to the cost of physician visits, laboratory tests, and medication; and indirect, which refers to decreased productivity arising as a result of absenteeism (from both school and work) or impaired functioning (20). The direct costs for allergic rhinitis are staggering: in 1997, for the 40 million people estimated to have allergic rhinitis in the USA, \$4.5 billion was spent on direct medical costs and a further \$3.4 billion was lost to indirect costs (41). Costs incurred as a result of treating

associated inflammatory disorders, such as otitis media, rhinosinusitis, and asthma, further add to the overall costs for allergic rhinitis (20).

Treatment of nasal allergies

The need for effective pharmacotherapy to combat the significant healthcare costs, co-morbidity, and impaired functioning and productivity costs arising as a result of allergic rhinitis is of paramount importance. Unfortunately, data from the Roper Survey indicated that only 20% of respondents were satisfied with their present form of treatment (19). Furthermore, data suggest that many patients with allergic rhinitis will have had their symptoms for a number of years prior to seeking relief (42). Identifying the ideal form of therapy that will help treat symptoms effectively and safely over extended periods of use requires a thorough evaluation of each patient and their symptoms. Although allergen avoidance should always be considered and advocated, this treatment regime may only be effective in a limited number of special cases, such as pet dander allergy, and may warrant unwanted social consequences.

A number of pharmacological interventions exist for the treatment of allergic rhinitis. Optimal therapy aims to target the inflammatory cells and mediators to prevent and alleviate the inflammatory symptoms of allergic rhinitis, including nasal congestion. The range of allergic rhinitis symptoms effectively treated by each treatment option varies according to the mode of action of each form of therapy.

Below we review each form of therapy, highlighting its mode of action and its relative advantages and disadvantages in the treatment of allergic rhinitis.

Intranasal corticosteroids

Glucocorticoids, such as mometasone furoate (MF) and fluticasone propionate, are among the most potent and effective agents available for the treatment of allergic rhinitis. National and international guidelines, such as the ARIA document by a taskforce of the EAACI and those of the American Academy of Allergy, Asthma & Immunology (AAAAI), recommend intranasal corticosteroids as first-line therapy when nasal congestion is a major component of the patient's allergic rhinitis (10, 43). Indeed, it has been shown that patients with allergic rhinitis administered with the therapeutic scheme based on international guidelines, have a significant improvement in their symptoms compared with those patients receiving non-standardized treatment (44).

Initially available as systemic agents, the well-documented side effects and therefore restricted use of corticosteroids led to the development of intranasal formulations (6, 14). A further rationale for the

development of topical formulations was to achieve and maintain high drug concentrations at the receptor sites within the nasal mucosa, which would help improve efficacy, while minimizing the risk of systemic adverse effects (43, 45).

Intranasal corticosteroids have a rapid onset of action – normally within 4–12 h of the first dose – low systemic absorption, and an excellent efficacy and safety profile, even when administered over several days. Patients from the Roper Survey reported that relief from congestion was the greatest benefit achieved with the use of intranasal corticosteroids (19). Although the exact mode of action of these agents has not yet been fully elucidated, it is thought that they function by inhibiting onset of the inflammatory response, and reducing the number of inflammatory cells, including mast cells (42). Furthermore, reduced vascular permeability of the nasal mucosa to inflammatory cells and mediators leads to relief from inflammatory symptoms (42, 46).

As well as ameliorating the symptom of nasal congestion, other day- and night-time symptoms, including rhinorrhea, sneezing, and pruritis, are relieved by intranasal corticosteroids (21). They are also partially effective in treating ocular symptoms (43).

Antihistamines

Antihistamines (oral or intranasal) act by blocking the histamine (H₁) receptor, thus inhibiting the resultant inflammatory cascade. They act within 1–2 h of administration and remain effective for up to 12–24 h (21, 43). Unlike their first-generation counterparts, second-generation antihistamines do not impair performance, and offer an improved safety profile (1). However, while symptoms of rhinorrhea, sneezing, and pruritis are relieved (10), antihistamines only have a limited effect on preventing or alleviating nasal congestion (42, 43).

Decongestants

Oral decongestants are alpha-adrenergic-agonist drugs that function by constricting capacitance vessels in the turbinates. By reducing blood flow to the nasal mucosa, decongestants prevent nasal edema and congestion (10, 14). Antihistamines and decongestants are often used in combination to treat the entire portfolio of symptoms seen in allergic rhinitis, including ocular symptoms of itching (42). However, oral decongestants are associated with numerous side effects, including insomnia and irritability. Furthermore, the fact that oral decongestants exert non-selective vascular constriction means they have limited use in patients with hypertension and ischemic heart disease (1, 14).

The intranasal (topical) forms of decongestants have a more rapid onset of action compared with the oral formulations (10). However, they are often associated with rhinitis medicamentosa – a phenomenon whereby

the efficacy of the drug is progressively reduced with continued application (14). Ultimately, symptoms of nasal congestion are exacerbated. This indicates that intranasal decongestants are a poor choice of therapy in patients where nasal congestion is a predominant and long-lasting symptom (10).

Leukotriene receptor antagonists

Leukotriene receptor antagonists are currently indicated for the treatment of asthma (47). The idea that asthma evolves as a continuum of allergic rhinitis-mediated inflammation of the same airway suggests a potential for leukotriene receptor antagonists in the treatment of allergic rhinitis (13). It is hypothesized that leukotriene receptor antagonists function by inhibiting the binding of leukotrienes to the C₄ receptors (47).

Evaluation of data in a review paper by Meltzer (48) suggests a role for leukotriene receptor antagonists as either initial or adjuvant therapy (to antihistamines) for the treatment of allergic rhinitis. Furthermore, Storms (49) suggested that leukotriene receptor antagonists could be used as prophylactic treatment for the persistent minimal inflammatory symptoms of allergic rhinitis during asymptomatic periods. This could delay or prevent the onset of inflammatory symptoms during the allergy seasons. Leukotriene receptor antagonists, however, prove less effective than intranasal corticosteroids (47).

Mast cell stabilizers

Mast cell stabilizers may function by preventing dissolution of the mast cell wall and hence degranulation and subsequent induction of inflammatory mediators, although the mode of action is not proven (42). The most commonly used mast cell stabilizer is cromolyn sodium (14). It is recommended that cromolyn sodium be used four to six times daily and this dosing regimen could hinder compliance (1). Furthermore, efficacy is reduced if the drug dosing is not adhered to. Moreover, chromones have a very marginal effect, much less than that of antihistamines or intranasal corticosteroids, on nasal symptoms. The duration of their action is relatively short-lived (14, 42).

The role of mometasone furoate in the treatment of allergic rhinitis, rhinosinusitis, and nasal polyposis

Mometasone furoate is a glucocorticoid molecule, which was designed to improve upon existing intranasal corticosteroids in terms of efficacy and safety.

Pharmacological properties

Here we discuss the pharmacological properties of MF, highlighting the potential clinical relevance of each and

how these properties make MF a potent and efficacious, yet well tolerated, glucocorticoid for the treatment of symptoms associated with inflammatory disorders of the upper airways.

Effects of MF on the early- and late-phase inflammatory responses. It was formerly thought that intranasal corticosteroids inhibit the late-phase inflammatory response only, with little or no effect on the early-phase response (46). However, clinical study data indicate that MF exerts its action on both the early- and late-phase responses. A double-blind, crossover study in which 21 patients with ragweed-induced allergic rhinitis were randomized to receive either mometasone furoate nasal spray (MFNS) 200 mcg once daily (QD) or placebo for 2 weeks was conducted to determine whether pretreatment with MFNS impacts specific inflammatory markers of both the early- and late-phase inflammatory responses (50). Data from enzyme-linked immunosorbent assays indicated that histamine levels in the nasal lavages sampled during the early-phase response (30 min after allergen challenge) were significantly reduced in patients receiving MFNS compared with those receiving placebo. Furthermore, at the late-phase response (6 h after allergen challenge), levels of IL-6, IL-8, and eosinophils were also reduced in MFNS vs placebo recipients. Therefore, it is postulated that MFNS exerts its anti-inflammatory action through inhibition of such mediators. These data account for the fact that MFNS has proven efficacy in the relief of symptoms associated with both the early- and late-phase responses.

Onset of action. When first introduced, there was a perception that intranasal corticosteroids, despite demonstrating efficacy and safety in the treatment of allergic rhinitis, were slow acting. However, clinical study data indicate that MFNS exerts relief from allergic rhinitis symptoms within 5–7 h proceeding the first dose administration. Berkowitz et al. (51) conducted a study to evaluate the time to onset of action of MFNS. In this multi-center, double-blind study, 201 patients symptomatic for SAR were randomized to receive MFNS 200 mcg QD or placebo for 2 weeks during the spring allergy season. Onset of action of MFNS, defined as the time when patients experienced clinically significant symptom relief, was assessed through the use of patient diary cards for the first 3 days following treatment. After 12 h, 28% of MFNS recipients experienced clinically significant moderate symptom relief compared with 13% of patients receiving placebo ($P < 0.01$; Fig. 4). Furthermore, median time to moderate symptom relief was 35.9 h in patients who received MFNS compared with > 72 h for those receiving placebo.

In a second study, Berkowitz et al. (52) assessed the time to onset of symptom relief with MFNS in an outdoor park setting. In this single-center, double-blind, parallel-group study, 239 patients symptomatic for SAR were randomized to receive a single dose of MFNS

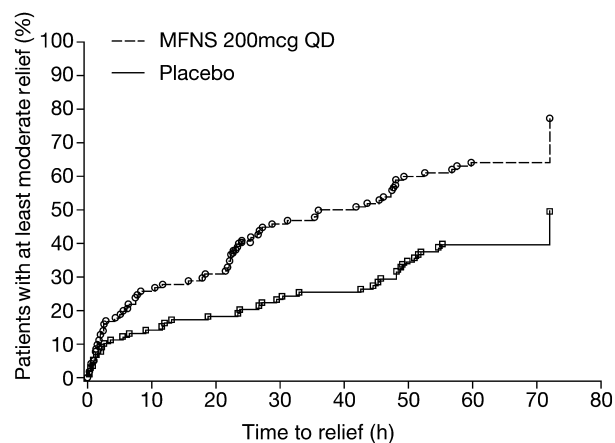


Figure 4. Cumulative percentage of patients achieving at least moderate relief from their symptoms of allergic rhinitis. Source: Berkowitz et al. (51). Permission received from Blackwell Publishing.

200 mcg or placebo following maximized seasonal allergen exposure in an outdoor park setting. After treatment administration, patients remained in the park for 12 h and recorded their symptoms on an hourly basis using a patient diary card. Improvements in total non-nasal and total nasal symptoms, in terms of mean decrease from baseline, were significantly greater in MFNS vs placebo recipients at 5 h following treatment. Similarly, improvements in total nasal symptoms at 7 h after dosing were significantly greater in patients who received MFNS compared with placebo recipients.

Data from the above studies indicate that MFNS does indeed provide relief from symptoms of SAR within 5–7 h of active treatment initiation.

Potency. Comparative *in vitro* glucocorticoid receptor-binding assays conducted in whole cell extracts provide an indication of the relative affinity of an intranasal glucocorticoid for its recombinant human glucocorticoid receptor and are indicative of *in vivo* potency. Data from such assays showed that MFNS bound more avidly to its receptor compared with other glucocorticoids, such as fluticasone propionate and budesonide (binding affinity 1235 vs 813 and 258, respectively (53)). However, the exact relevance of this higher binding affinity, in terms of its effect in the human patient, is still unclear.

On formation, the glucocorticoid–receptor complex migrates to the nucleus and binds to specific DNA sequences termed glucocorticoid response elements. This complex activates expression of anti-inflammatory proteins, which act to alleviate the inflammatory symptoms associated with allergic rhinitis. Studies in cultured cell lines indicate that MF was potent in this respect (54). Furthermore, results from an *in vitro* assay conducted in a murine cell line showed that MF was also able to inhibit the synthesis of various cytokines (54).

The above are preclinical data and the exact mode of action of MF *in vivo* is still to be fully understood. However, data from these *in vitro* experiments highlight the fact that MFNS has greater levels of potency compared with other intranasal glucocorticoid molecules.

Efficacy

The efficacy and safety of MF have been demonstrated in a robust program of clinical trials and through extensive clinical use. Below we review the clinical data that support the use of MFNS in the prevention and treatment of allergic diseases of the upper respiratory tract.

In allergic rhinitis. Clinical data show that MFNS is not only effective in treating the symptoms of moderate-to-severe SAR (55, 56), but that it is also effective in preventing the onset of symptoms in such patients (57). Furthermore, MFNS has proven efficacy for the sustained treatment of PAR (58).

Symptoms

MFNS has proven efficacy in treating the nasal and non-nasal, as well as the day- and night-time symptoms of SAR. A study conducted by Meltzer et al. (55) in which patients with SAR were randomized to treatment with MFNS 200 mcg QD ($n = 80$) or placebo ($n = 41$) for 2 weeks, showed that the total SAR symptoms score, which consisted of both nasal (nasal congestion, sneezing, rhinorrhea, and itching) and non-nasal (itching or burning eyes, tearing eyes, eye redness, and itching of ear/palate) symptoms, was statistically significantly reduced *vs* placebo (-47% *vs* -30% , $P = 0.049$). Individual assessment of scores for each nasal symptom scores also showed consistently greater improvement in the MFNS group *vs* placebo. Furthermore, the mean total morning scores, assessed following the morning dose, were significantly reduced in the MFNS treatment group *vs* placebo group (week 1: -26% *vs* -11% , $P = 0.02$; week 2: -39% *vs* -24% , $P = 0.029$).

Similarly, a double-blind, double-dummy, parallel-group study of 497 adult patients with moderate-to-severe SAR compared the efficacy of once-daily doses of MFNS (100 or 200 mcg) with that of placebo and budesonide dipropionate administered as 200 mcg twice daily (BID) (56). Data analysis indicated that MFNS 200 mcg was significantly superior to placebo in reducing the total symptoms score ($P < 0.05$; composed of the four individual nasal (as above) and four individual non-nasal (as above) scores over the treatment period. A similar pattern was seen for the total nasal symptoms scores, whereby severity of individual symptoms was improved, and MFNS 200 mcg was significantly superior to placebo ($P < 0.001$). Indeed, at the end of the 4-week treatment period, 75% of patients dosed with MFNS experienced relief from their total nasal symptoms compared with 60% of placebo recipients (Fig. 5).

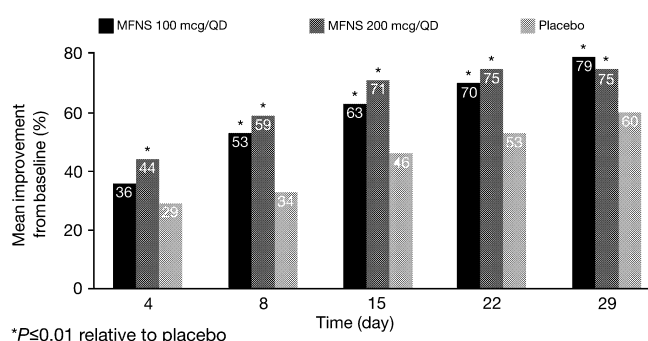


Figure 5. Physician-evaluated improvements in total nasal symptoms scores of patients with moderate-to-severe SAR treated with MFNS. Adapted from Hebert et al. (56).

Interestingly, one study suggests that MFNS is also effective in treating the symptom of cough, which is commonly reported in allergic rhinitis and is thought to arise as a result of post-nasal drip (59). In this double-blind, multi-center study, 245 patients with at least a 1-year medical history of moderate SAR were randomized to receive MFNS 200 mcg QD or placebo. Patients treated with MFNS showed significant improvement in the severity of their daytime cough compared with those treated with placebo ($P = 0.049$).

Patients frequently report impaired olfactory function as a symptom of SAR. In a double-blind, placebo-controlled study, patients with a clinical history of allergic rhinitis were randomized to receive MFNS ($n = 13$) or placebo ($n = 11$) (60). A trend (approaching significance) in terms of improved olfactory function was seen between the MFNS and placebo treatment groups. Patients receiving MFNS became more sensitive to butanol, and overall odor threshold was significantly improved in this group after 2 weeks of treatment. Therefore, MFNS not only improves the classical inflammatory symptoms of SAR, but the olfactory function of the affected patient as well.

In summary, MFNS is effective in relieving morning and evening nasal symptoms of moderate-to-severe SAR, as well as SAR-associated cough and olfactory symptoms.

Once-daily dosing

MFNS is effective as a once-daily dosing regimen in the treatment of allergic rhinitis. A dose-ranging study was conducted by Bronsky et al. (61) to compare the clinical efficacy and tolerance of four doses of MFNS QD, and to determine the optimal therapeutic dose in adults with SAR. In this multi-center, double-blind study, 479 adult patients with moderate SAR were randomized to receive MFNS 50, 100, 200, or 800 mcg QD, or placebo for a treatment period of 28 days. While all four doses of active treatment reduced the total symptoms and total nasal symptoms scores, the 200 mcg dose was consistently more effective throughout the treatment period compared with placebo ($P < 0.05$). The 50 and 100 mcg doses of MFNS

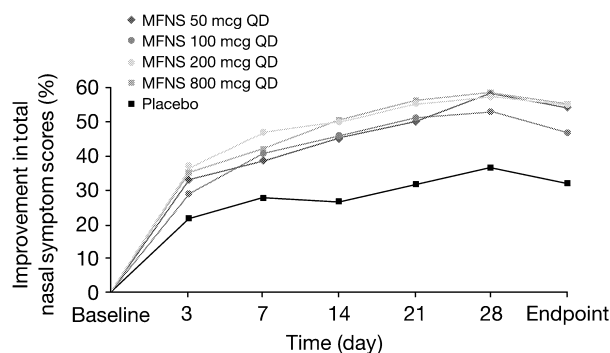


Figure 6. Mean percentage improvement from baseline in total nasal symptom scores. Adapted from Bronsky et al. (61).

demonstrated numerically significant efficacy during the first week of treatment compared with the 200 mcg dose, while the 800 mcg dose appeared to have efficacy comparable with the 200 mcg dose (Fig. 6).

Further clinical evidence is available to support a once-daily dosing regimen of MFNS in patients with PAR. In a double-blind, double-dummy, parallel-group, multi-center trial conducted in 550 patients with medically confirmed PAR, patients were randomized to receive either MFNS 200 mcg QD, fluticasone propionate 200 mcg QD, or placebo for a treatment period of 12 weeks (58). Data analysis showed that MFNS was significantly more effective, in terms of change from baseline in the morning and evening nasal symptom scores, vs placebo ($P < 0.01$). Improvements in individual symptom scores were also significantly improved compared with placebo ($P < 0.01$).

In another double-blind, double-dummy, parallel-group, multi-center study in which 427 patients with a confirmed medical history of PAR were randomized to receive either MFNS 200 mcg QD, beclomethasone dipropionate 200 mcg BID, or placebo for 15 days, MFNS proved to be more effective, in terms of change from baseline in the morning and evening nasal symptom scores, compared with placebo ($P \leq 0.01$). Efficacy of MFNS was indistinguishable from beclomethasone dipropionate (62). These data suggest that MFNS administered once daily is as effective as beclomethasone dipropionate.

Therefore, MFNS 200 mcg QD is established as the optimal dose for the effective control of symptoms associated with moderate allergic rhinitis, indicating that dosing every 24 h is possible with MFNS and this once-daily dose is at least as effective as other intranasal corticosteroids administered at the same dosing interval or as a twice-daily dose. Therefore, MFNS offers the advantage of once-daily treatment, which could allow for reduced treatment costs and improved compliance with treatment.

Prophylactic use

MFNS is the only intranasal corticosteroid in the USA that has been clinically proven and FDA-approved as an

effective prophylactic treatment to prevent the onset of the nasal symptoms associated with SAR, when therapy is initiated 2–4 weeks prior to the estimated start of the pollen season. In a double-blind, multi-center study, 349 patients with SAR to ragweed pollen were randomized to receive either MFNS 200 mcg QD, beclomethasone dipropionate 168 mcg BID, or placebo 4 weeks before the anticipated start of the ragweed season for a total treatment period of 8 weeks (57). The number of minimal symptom days was significantly greater in the MFNS recipients compared with the placebo group (83% vs 64%, respectively; $P < 0.01$). Patient-assessed nasal symptom scores (nasal congestion, sneezing, rhinorrhea, and nasal itching) were significantly reduced from the start of the ragweed season compared with placebo ($P < 0.01$), and were consistently reduced at each study visit for the duration of the treatment. Furthermore, analysis of the nasal symptom scores indicated that patients administered with MFNS experienced a significantly greater number of ‘minimal symptom’ days compared with placebo (mean = 27 vs 11 days, $P < 0.01$).

These data indicate that MFNS is an effective prophylactic therapy that prevents or delays the onset of symptoms if initiated prior to an allergy season.

In rhinosinusitis. Treatment of the viral form of rhinosinusitis should be directed toward relieving symptoms. However, antibiotics are often also prescribed. A meta-analysis of clinical data indicated that the degree of benefit afforded by antibiotics in this form of rhinosinusitis is small (63). Furthermore, because 85 to 95% of rhinosinusitis cases tend to resolve without antibiotic therapy and excessive antibiotic use is the principal factor in the emergence of antibiotic-resistant bacteria (64), it is recommended that antibiotic therapy be reserved for patients with severe rhinosinusitis and for patients whose symptoms persist for more than 7 days (64, 65). An overview of all treatment options, their relevance, and their level of evidence has recently been published by the EP³OS task force of the EAACI (26, 27).

Being an inflammatory disease, an anti-inflammatory treatment option appears to be a rational approach to relieving nasal and possibly sinus ostial obstruction in rhinosinusitis (25). Study data indicate that concomitant administration of intranasal corticosteroids is more effective, in terms of symptom relief, than antibiotic therapy alone (28). A controlled clinical trial looking at the value of intranasal corticosteroids in acute rhinosinusitis was a double-blind, multi-center trial of 407 patients with a history of recurrent acute sinusitis (66). Patients were randomized to receive amoxicillin clavulanate for 21 days and concurrent MFNS 400 mcg BID ($n = 200$) or placebo spray ($n = 207$) as adjuvant therapy. Patients recorded their symptoms scores twice daily for nasal congestion, rhinorrhea, headache, facial pain, post-nasal drip, and cough. Mean total symptoms scores were significantly reduced in patients receiving adjuvant

MFNS therapy compared with placebo (5.87 vs 5.05, $P = 0.01$), highlighting the anti-inflammatory benefits of MFNS.

In a second double-blind, multi-center study, 967 patients with confirmed moderate-to-severe acute rhinosinusitis were randomized to receive amoxicillin clavulanate 875 mcg BID for 21 days with either MFNS 200 mcg, MFNS 400 mcg, or placebo adjuvant therapy (67). Patients were requested to record their scores for six rhinosinusitis symptoms twice daily. Both MFNS 200 and 400 mcg resulted in significantly greater improvements in symptoms scores compared with placebo (50 and 51%, respectively, vs 44%, $P \leq 0.017$). This effect was maintained throughout the treatment period.

Both studies highlight the fact that MFNS as an adjuvant therapy to antibiotics, at a dose of either 200 or 400 mcg QD, is significantly more effective in the treatment of acute rhinosinusitis compared with antibiotics alone.

Emerging data suggest that MFNS may also be effective as monotherapy in the treatment of acute rhinosinusitis and such monotherapy could help decrease costs related with rhinosinusitis therapy. As most cases of acute rhinosinusitis appear to be due to viral as opposed to bacterial inflammation, the use of antibiotics is not pertinent. The aim of the following study was to test the efficacy of the anti-inflammatory action of MFNS in the treatment of acute rhinosinusitis compared with amoxicillin and placebo. In this double-blind, multi-center study, patients ($n = 981$) symptomatic for community-acquired acute rhinosinusitis (CAARS) for at least 7 days were randomized to receive MFNS 200 mcg QD, MFNS 200 mcg BID, amoxicillin 500 mcg three times daily (TID), or placebo (68). Patients with symptoms strongly suggestive of severe or complicated bacterial infection were excluded. MFNS 200 mcg BID was more effective at improving the major symptoms scores compared with amoxicillin and placebo ($P = 0.002$ and 0.001 , respectively). The superior efficacy of MFNS 200 mcg BID was apparent from day 2 of treatment compared with placebo ($P = 0.001$), and from day 4 compared with amoxicillin ($P \leq 0.012$).

In nasal polyposis. The EAACI position paper on rhinosinusitis and nasal polyps highlights the close link between the two disease modalities (26, 27). Although nasal polyps are not directly linked to allergic rhinitis, MFNS can also be successfully used in the treatment of this condition. Nasal polyposis arises following eosinophil-induced inflammation, and is a disease of the nasal and paranasal mucous membranes. It is characterized by the localized formation of nasal polyps (69), which are edematous, semi-translucent masses arising from the mucosal lining of the middle nasal meatus (70). Nasal polyposis presents the patient with symptoms of nasal congestion, difficulties in breathing, post-nasal drip, and loss of sense of smell (71). The condition appears to be

associated with increased levels of interleukin (IL)-5 (72). Indeed, one study reported significantly higher concentrations of the soluble IL-5 receptor subunit (SOL IL-5R α) in the serum nasal secretions and nasal tissues samples of patients with nasal polyposis (73).

There are few data on prevalence of nasal polyposis; however, in a study conducted in France, the prevalence of nasal polyposis in the general population was 2–11% (74), and while there appeared to be no gender differences, the occurrence of nasal polyposis was found to increase with age (74). Moreover, although prevalence in the general population is low (70), nasal polyposis has a severe impact on the quality of life of the affected patient (75).

Traditionally, surgical removal of the polyps from patients with nasal polyposis was the usual method to relieve symptoms. However, intranasal corticosteroids are now emerging as an alternative effective treatment option, with surgery being reserved for severe and non-responding nasal polyposis patients. In this disease setting, it is thought that intranasal corticosteroids function by down-regulating the production of cytokines, such as IL-5, thereby reducing eosinophil-mediated inflammation (28, 76). This therapy results in reduced symptoms of rhinitis, improved nasal breathing and reduced size and number of polyps, although intranasal corticosteroids appear to have less effect on improving sense of smell (77). Data also suggest that intranasal corticosteroids are most effective when the size of the polyp is small or medium (78). Furthermore, long-term use of intranasal corticosteroids appears to help prevent recurrence/relapse of nasal polyps, and can reduce the requirement for repetitive nasal surgery (78).

In two recently conducted, double-blind, parallel-group, multi-center, 4-month trials, patients (study 1, $n = 354$; study 2, $n = 310$) with bilateral polyposis and morning symptoms of nasal congestion were randomized to receive MFNS 200 mcg QD or BID, or placebo (79). In the first study, MFNS 200 mcg QD and BID reduced polyp size significantly compared with placebo (27%, $P = 0.011$; 33%, $P < 0.001$, vs 17%, respectively). Symptoms of nasal congestion, rhinorrhea, post-nasal drip and objective measures of peak nasal inspiratory flow were significantly improved over the treatment period. Mometasone furoate also improved sense of smell. The results of study 2 were similar and in both studies MFNS 200 mcg QD and MFNS 200 mcg BID both appeared to be effective in reducing nasal congestion.

These studies report that MFNS is an effective therapeutic option for the treatment of nasal polyposis and even improves the sense of smell, a major symptom complaint in patients. As a result, the need for surgery should be considerably reduced in many patients. MFNS has recently been approved in the USA and Europe for the treatment of nasal polyposis in adults; indeed, it is the only intranasal corticosteroid approved in the US.

Safety

Nasal histological studies. Long-term administration of intranasal corticosteroids led to concerns that chronic use of these agents could lead to histopathological changes, including atrophy of the nasal mucosa (80). Consequently, a study was conducted to assess tissue changes in the nasal mucosa of patients with PAR treated long term with MFNS. In this multi-center, open-label study, 69 patients were treated with MFNS 200 mcg QD for 12 months. Of the 52 patients who completed the study, nasal biopsy samples taken from 46 patients before and after treatment were assessed. Nasal biopsy data indicated that there was a significant reduction in the number of eosinophils and mast cells following MFNS treatment, which confirms that MFNS acts on the late-phase inflammatory response by reducing the number of eosinophils, and returns the nasal mucosa to its normal state (Fig. 7). Furthermore, MFNS did not cause atrophy of the nasal epithelium; in fact, in all patients assessed, no change in the thickness of the epithelium was observed. Furthermore, the number of intact ciliated epithelium was seen to increase from 59 to 71%.

In another study in which SAR patients were randomized to receive either MFNS 200 mcg QD ($n = 80$) or placebo ($n = 41$) for 2 weeks, patients' nasal mucosa was sampled before and after treatment (55). Nasal cytology results showed significantly reduced eosinophil and basophil counts following MFNS treatment vs placebo. These data correlate with those seen in the study described above. Albumin levels were also decreased

and correlated with the reduction in the number of inflammatory cells.

These study evidence suggest that long-term use of MFNS does not have an adverse effect on the nasal mucosa. MFNS appears to return the nasal mucosa to a normal state and preserves its integrity with no development of atrophic changes.

Systemic bioavailability. MFNS has an excellent systemic safety profile. Owing to complete first-pass metabolism, plasma concentrations of MFNS are below quantifiable levels, and consequently oral bioavailability of MF is low at $<0.1\%$ in adults (54, 81). Consistent with this, systemic absorption of MF is negligible: even at 20 times (4000 mcg) the recommended daily allergic rhinitis dose (200 mcg/day), MFNS has no adverse effect on urinary-free cortisol and plasma cortisol levels, or on suppression of the hypothalamic pituitary-adrenal (HPA) axis (82).

Pediatric patients. MFNS is effective and well tolerated in children of all ages with allergic rhinitis. An evaluator-masked, multiple-dose, parallel-group study was conducted in two phases to assess the safety and tolerability of MFNS in 96 children aged between 3 and 12 years (83). In phase 1, older children aged between 6 and 12 years were randomized to receive MFNS 50, 100, or 200 mcg QD, or placebo for a treatment period of 7 days. Data indicated that plasma cortisol and 24-h urinary-free cortisol concentrations were not significantly changed from baseline compared with placebo. As a result, a second more rigorous assessment was conducted in younger patients aged between 3 and 5 years who were randomized to receive MFNS 50, 100, or 200 mcg QD, or placebo for a longer treatment period of 14 days. The results showed that MFNS had no effect on the HPA axis, and the most frequently reported treatment-related adverse event was headache.

The fact that intranasal corticosteroids have the potential of inducing a number of adverse effects is of concern to physicians and pediatric patients with allergic rhinitis. It has been reported that intranasal corticosteroids can inhibit secretion of growth hormone, and hence cause growth retardation/suppression in children (84). However, clinical study data indicate that MFNS does not induce growth retardation/suppression in children, even over long-term periods of use. A double-blind, multi-center trial was conducted in 98 patients aged between 3 and 9 years with a history of PAR to assess the effect of MFNS on growth. Patients were randomized to receive either MFNS 100 mcg QD or placebo for a treatment period of 1 year, over which time height was measured on a regular basis. No effects were seen regarding growth suppression in patients treated with MFNS at any time point, such that the mean standing heights were similar in both active treatment and placebo groups.

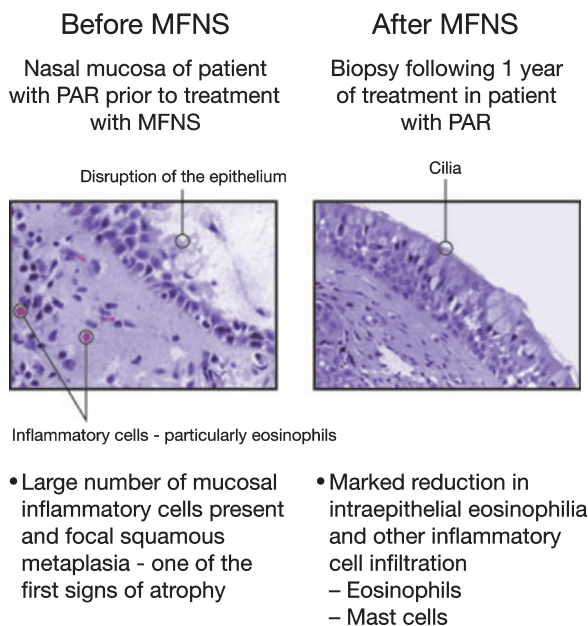


Figure 7. Reduction in inflammatory cells following 1 year of treatment with Nasonex® in a patient with PAR. Adapted from Minshall et al. (80).

The established safety profile of MFNS, combined with the absence of systemic adverse events and growth suppression, signifies that MFNS is an appropriate therapy for children with allergic rhinitis. Indeed, MFNS is the only intranasal corticosteroid that is approved for the treatment of allergic rhinitis in children as young as 2 years of age in the USA. In Europe, MFNS is approved for use in children aged 3 years and older in some countries, and 6 years or older in others.

Treatment-related adverse events. Clinical trials conducted to date in patients with allergic rhinitis have appropriately included evaluations of the safety of MFNS and possible related adverse events. Data resulting from trials using the recommended clinical dose of MFNS (200 mcg QD) demonstrate the safety of MFNS in adult, adolescent, and pediatric patients. The incidence of reported adverse events in patients treated with MFNS is similar to those receiving placebo or other intranasal corticosteroids (54). The most frequently reported adverse events are headache, epistaxis, viral infection, pharyngitis, and cough. Epistaxis was defined to include a wide range of bleeding episodes, from frank bleeding to bloody nasal discharge to flecks of blood in mucus. Cases of nasal irritation and nasal burning are infrequent and, when reported, mild in severity. Furthermore, the incidences and types of adverse events reported in patients of nasal polyposis treated with MFNS reflect those described above for allergic rhinitis patients (79).

Moreover, no significant adverse events or systemic effects have been reported in pediatric patients treated with MFNS for a year. Similarly, a 3-month study in which adult patients with PAR were treated with MFNS 200 mcg QD showed that the active treatment was well tolerated (58).

In summary, clinical data highlight the excellent safety profile of MFNS, indicating that it is well tolerated by patients in any age group, even over extended periods of treatment.

Discussion and conclusions

Allergic rhinitis, an inflammatory disorder that arises as a result of an underlying IgE-mediated response following allergen exposure, is a chronic disorder and its prevalence is increasing. Characterized by a number of symptoms, the severity of allergic rhinitis can range from mild to severe such that the quality of life of the patient can be greatly impaired. Despite this, and the fact that it can affect patients from an early age, allergic rhinitis still remains under diagnosed, uncontrolled and inadequately treated in a substantial proportion of patients.

Ineffective treatment of allergic rhinitis can not only impair quality of life, but can also lead to problems such

as sleep-disordered breathing, daytime fatigue, and inability to perform well normal day-to-day tasks. In addition, substandard management can lead to the development of complications such as otitis media, rhinosinusitis, and asthma. Furthermore, such co-morbidities and consequences can have a negative impact on the economy in terms of healthcare costs, reduced productivity, and absenteeism. Thus, it is important to highlight the need for improved and effective pharmacotherapy to reduce the suffering from allergic rhinitis and the associated disorders of the upper and lower respiratory tract.

While a range of treatment options exist for allergic rhinitis, national and international guidelines recommend intranasal corticosteroids as first-line therapy when nasal congestion is a major complication of a patients' disease. Mometasone furoate is one such intranasal corticosteroid and it has an excellent efficacy and safety profile. It appears to be a potent intranasal corticosteroid, with a high binding affinity for its glucocorticoid receptor. The rapid onset of action of MFNS provides patients with fast, effective, and sustained relief from their symptoms, including nasal congestion.

MFNS is effective in treating both nasal and non-nasal symptoms, and its effect is apparent on morning and evening symptoms. MFNS has proven efficacy in treating symptoms of SAR and PAR, and can also be used prophylactically to prevent or delay the onset of SAR symptoms if initiated prior to onset of the allergy pollen season.

MFNS displays an excellent safety profile and is well tolerated. Owing to its negligible bioavailability, it has no associated systemic effects, nor does it suppress the HPA axis. The absence of growth suppression in children has permitted approval for use in patients as young as 2 years in the USA and as young as 3 years in some European countries.

Additionally, MFNS has recently gained approval in the USA and Europe for the treatment of nasal polyposis and should help reduce the requirement for surgery in those patients. Currently being used as a successful adjuvant therapy to antibiotics in the treatment of acute rhinosinusitis, new emerging clinical data suggest that MFNS may also be effective as a monotherapy in the treatment of acute rhinosinusitis. Considering the body of evidence, MFNS is a valuable, effective, and well-tolerated first-line therapeutic option for the treatment of allergic rhinitis and associated inflammatory disorders of the upper airways.

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