

Original article

Treatment of nonallergic perennial rhinitis

Summary Nonallergic perennial rhinitis (also commonly referred to as vasomotor rhinitis) is a chronic non-IgE-mediated condition that is characterized by symptoms which are similar to those seen in allergic rhinitis, but which persist for over nine months each year. Although treatment of vasomotor rhinitis involves the use of either intranasal corticosteroids or antihistamines, the corticosteroids are generally not effective in treatment of all the symptoms of vasomotor rhinitis and have generally been shown to be effective in patients with eosinophilia. With the exception of azelastine, the only topical antihistamine to be approved by the FDA for the treatment of nonallergic rhinitis, the antihistamines have also produced inconsistent results. While clinical studies of azelastine have demonstrated that this drug is highly efficacious in the treatment of all the symptoms of vasomotor rhinitis, mechanistic studies have demonstrated that azelastine has potent anti-inflammatory effects (in particular attenuation of the expression and synthesis of pro-inflammatory cytokines, leukotrienes, and cell adhesion molecules), which are likely to contribute to its clinical efficacy. Furthermore, pharmacokinetic studies have suggested that since azelastine has a more rapid onset of action, compared to most other antihistamines and intranasal corticosteroids, then azelastine nasal spray may be considered as primary therapy for patients with symptoms of both allergic and/or vasomotor (nonallergic perennial) rhinitis.

G. Ciprandi

Allergy, San Martino Hospital, Genova, Italy

Key words: Nonallergic perennial rhinitis, vasomotor rhinitis, azelastine, antihistamines, anti-inflammatory, substance P, inflammatory cytokines, cell adhesion molecules.

G. Ciprandi
Allergy,
San Martino Hospital
Genova,
Italy
E-mail: gio.cip@libero.it

Introduction

Nonallergic perennial rhinitis, commonly referred to as vasomotor rhinitis in daily clinical practice, is a chronic form of noninfectious rhinitis that persists for over 9 months each year, and is characterized by signs and symptoms that are identical to those seen in patients with allergic rhinitis (i.e., rhinorrhoea, nasal obstruction, sneezing and postnasal drip). Unlike allergic rhinitis, the etiology of vasomotor rhinitis is unknown and not associated with IgE-mediated mechanisms, infection, structural lesions, systemic disease, drug abuse, or eosinophilia. However, the symptoms can be triggered by a variety of nonspecific stimuli such as changes in temperature and/or humidity, strong odors, respiratory irritants, spicy foods and alcoholic beverages (1, 2). Clinically, patients with vasomotor rhinitis may generally be subdivided as being “sneezers”, “runners” or “blockers”, depending on whether the predominant symptom is sneezing, rhinorrhoea or nasal congestion/blockage, respectively. Although there is overlap of these symptoms in some patients they cannot readily be assigned to any one of these groups.

Currently, there are no specific diagnostic tests for vasomotor rhinitis, and therefore this is essentially a diagnosis of exclusion. Diagnosis of vasomotor rhinitis is confirmed when a patient presenting with typical rhinitis symptoms triggered by “nonallergic” stimuli shows: (i)

negative skin tests for allergy; (ii) a lack of symptoms following allergen exposure; and (iii) other possible causes of nonallergic rhinitis, such as drug-induced rhinitis, food-induced rhinitis, occupational rhinitis, hormonal rhinitis, nonallergic rhinitis with eosinophilia syndrome (NARES), etc., are ruled out.

Treatment of vasomotor rhinitis

Treatment strategies of nonallergic rhinitis have traditionally involved avoidance of environmental factors or triggers that initiate rhinitis symptoms, pharmacotherapy, and less commonly surgery (3). Pharmacotherapy involves use of either decongestants in patients whose main symptom is nasal congestion, or intranasal anticholinergics in patients whose predominant symptom is rhinorrhoea. In contrast to these tailored treatments for specific symptoms, it is thought that nonspecific “broad-based” therapy with topical steroids and topical antihistamines, may be the more appropriate treatment option, since the symptoms of vasomotor rhinitis are often variable and alternate from obstructive/congestion to secretory/rhinorrhoea (2). Although fluticasone propionate, budesonide and beclomethasone, are the only topical steroids to have been approved by the FDA in the USA for treatment of nonallergic rhinitis, the efficacy of these

drugs has been inconsistent, and none have been shown to significantly improve all four major symptoms of nasal congestion, rhinorrhoea, sneezing, and postnasal drip in vasomotor rhinitis. Furthermore, the topical steroids have been useful mostly for treatment of more severe symptoms in patients in whom an inflammatory pathogenesis is a prominent feature of their disease. Evidence suggests that in patients who do not respond to treatment with nasal steroids, treatment with nonconventional therapies such as intranasal capsaicin, in particular, may be beneficial since this leads to a significant and long-term reduction in nasal hyperreactivity, nasal airway resistance and nasal symptom scores (4, 5). However, similar large-scale double-blind, placebo-controlled clinical trials of capsaicin in well-characterized patients with vasomotor rhinitis patients are presently lacking, and therefore these findings for capsaicin therapy await confirmation. Although antihistamines, which have normally been used for treatment of allergic rhinitis, have also been tried in the treatment of vasomotor rhinitis, these have also been shown to produce inconsistent effects. Furthermore, apart from topical azelastine, which is presently the only antihistamine preparation to be approved by the FDA, the majority of antihistamines are thought be of little or no benefit in the treatment of nonallergic rhinitis.

Studies of azelastine in treatment of vasomotor rhinitis

The efficacy of intranasal azelastine in the treatment of seasonal and perennial allergic rhinitis has been well documented and shown to be on par with other commonly used antihistamines, in terms of symptom relief, nasal patency, tolerability, and improvements in

patients' quality of life measures (6–8). Additionally, it has been demonstrated that topical azelastine, together with topical levocabastine, has the fastest onset of effect of within 15–30 min of application, compared with the other antihistamine preparations in current use (6).

More recently, two studies have demonstrated that intranasal azelastine is also highly efficacious in the treatment of nonallergic rhinitis, in particular vasomotor rhinitis, because it treats the total symptom complex (i.e. rhinorrhea, nasal congestion, sneezing and postnasal drip) in this condition, without discriminating between any of the predominant symptoms. In the first study, two multicenter, randomized, double-blind, parallel-group trials were performed to investigate the effect of azelastine nasal spray on nasal symptoms in well characterized patients who had a diagnosis of vasomotor rhinitis for at least 1 year, coupled with negative skin tests to a mixed panel of seasonal and perennial allergens, and negative nasal eosinophil cytology (9). After a 1-week lead-in period, a total of 426 patients were treated for 3 weeks with either azelastine nasal spray or placebo (two sprays per nostril twice daily), during which period they recorded their symptoms scores twice-daily (morning and evening) using diary cards. The primary outcome measure was the overall reduction from baseline in the total vasomotor rhinitis symptom score (TVRSS) for rhinorrhea, sneezes, nasal congestion and postnasal drip, over the 21-day treatment period. The study demonstrated that, in both trials, azelastine spray significantly improved both the TVRSS and individual symptom scores from baseline when compared with placebo.

In another multicenter, randomized, double-blind, parallel-group study, Gehanno and colleagues (10) treated 89 well-characterized vasomotor rhinitis patients, with

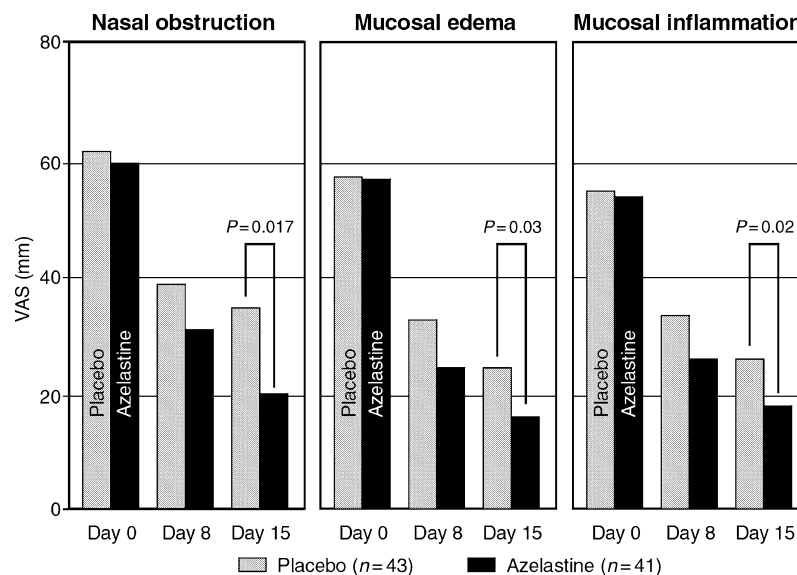


Figure 1. Effect of azelastine nasal spray or placebo on nasal obstruction, mucosal edema and nasal mucosal inflammation in patients with vasomotor rhinitis. (Modified from Gehanno et al. 2001 (10) and reprinted with kind permission.)

either azelastine or matched placebo nasal spray (one spray three times daily) for 15 days. The primary outcome measure was the reduction of nasal symptoms, including nasal obstruction, rhinorrhea, sneezing, anosmia, and olfactometry. This study demonstrated that by the end of the treatment period azelastine significantly improved nasal obstruction and rhinorrhea, compared with placebo, and additionally significantly decreased edema and inflammation of the nasal mucosa, as indicated by a reduction in the VAS score (Fig. 1). Furthermore, global evaluation by both the physician and the patient demonstrated that azelastine was a well tolerated and significantly better overall treatment for vasomotor rhinitis.

Putative mechanisms underlying the effects of azelastine in vasomotor rhinitis

Both preclinical and clinical studies have suggested that the effect of azelastine in vasomotor rhinitis may involve antiallergic/anti-inflammatory effects, in particular attenuation of the effects of neurokinins such as substance P, inhibition of mast cell degranulation, and inhibition of synthesis and/or release of pro-inflammatory cytokines and adhesion molecules, which influence migration and activation of inflammatory cells.

Effects on Substance P

Substance P is a member of the tachykinin family of neuropeptides localized to sensory nerve endings throughout the body, but is especially important in the areas of immunologic importance, such as the respiratory tract, eye skin, and gastrointestinal tract (11). In the airways, Substance P is localized predominantly to capsaicin sensitive unmyelinated nerves, and following release leads to different effects, including: (i) increased airway responsiveness to methacholine; (ii) increased mucus secretion from submucosal glands; (iii) vasodilation; (iv) vascular permeability; (v) angiogenesis; and (vi) activation and/or chemotaxis of mast cells, eosinophils, macrophages and fibroblasts (12). Topical application of Substance P to the human nasal mucosa has also been shown to increase the expression of several cytokines, suggesting that this neuropeptide may have important chronic immune effects in nasal disease (13).

Some studies have suggested that the clinical efficacy of azelastine in vasomotor rhinitis may be a consequence of its effects on Substance P. Shinoda and colleagues (14) investigated the effect of treatment with azelastine 1 mg twice daily for 4 weeks, on concentrations of Substance P and vasoactive intestinal protein (VIP) in nasal secretions of 20 patients with nasal allergy to house dust mite and 40 healthy subjects without any allergies. These authors demonstrated that the level of Substance P, but not VIP, in nasal secretion was significantly higher in the individuals with nasal allergy, compared with controls and that

treatment with azelastine significantly decreased the level of Substance P, but not VIP. Importantly, the degree of azelastine-induced reduction in Substance P was directly linked with the degree of clinical improvement in all the symptoms of rhinitis (Fig. 2), suggesting that the level of

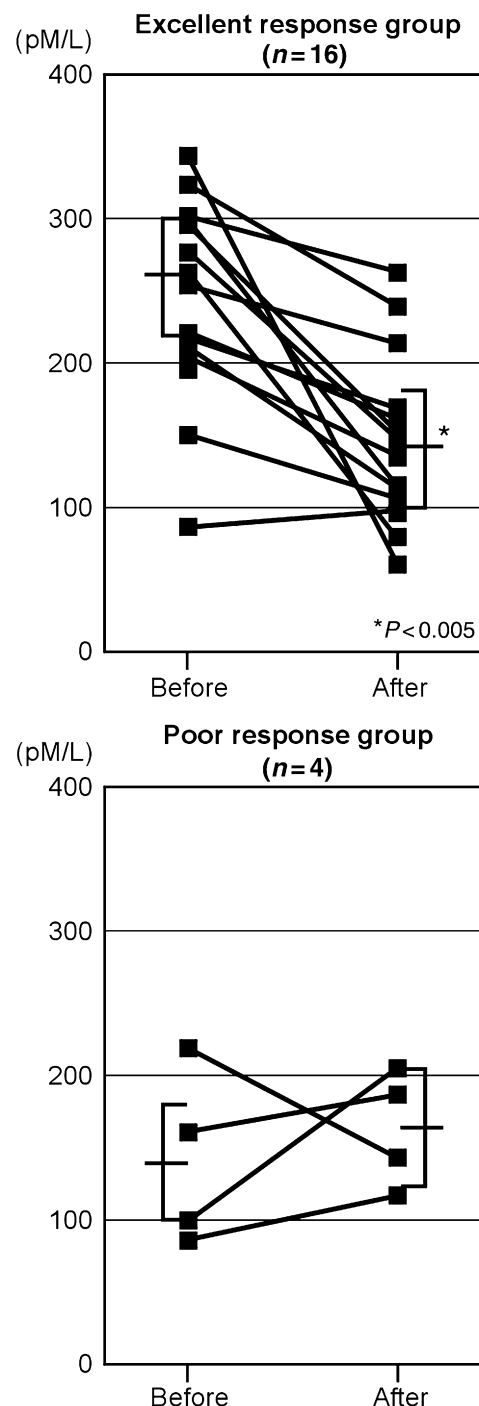


Figure 2. Substance P levels before and after treatment in patients demonstrating either an excellent or poor clinical response to treatment with azelastine. (*P < 0.005) (Modified from Shinoda et al. 1997 (14) and reprinted with kind permission.)

Substance P in nasal secretions may reflect the clinical state of nasal symptoms and therefore be useful as an objective parameter for evaluating the anti-inflammatory effects of antihistamines.

In another study, Nieber and colleagues (15) investigated the effect of azelastine, 4 mg b.i.d. for 3 weeks, on allergen-induced release of Substance P in bronchoalveolar (BAL) and nasal (NAL) lavage collected from grass pollen asthmatics and healthy subjects. This study also demonstrated that baseline levels of Substance P in the asthmatics were significantly greater than in healthy subjects and that pretreatment with azelastine protected significantly against allergen-induced release of Substance P in BAL and NAL in the asthmatic patients. In contrast, azelastine pretreatment did not show any significant effect on allergen-induced release of Substance P in the healthy subjects.

Inhibition of mast cell degranulation

The role of mast cells and the mechanisms underlying the release of their mediators in allergic airway disease have been well documented. However, some studies have demonstrated that nonspecific stimuli such as cold dry air, which leads to hypertonicity of the nasal lining fluid, can also lead to activation of nasal mast cells (16). Proud and colleagues (17) have demonstrated that provocation of susceptible individuals with cold, dry air leads to increased

recoveries of both histamine and tryptase, confirming that mast cell degranulation occurs during this reaction. Similarly, Togias and colleagues (18, 19) have shown that cold dry air challenge also leads to release of other mast cell markers, including prostaglandin D₂, and immuno-reactive sulfidopeptide leukotrienes in nasal lavage of allergic rhinitis and subjects with a history of nasal symptoms of rhinorrhea and congestion upon a cold or dry environmental exposure. Additionally, these authors have demonstrated that nasal provocation with hot, dry air also leads to release of histamine, although other mast cell mediators were not examined (20).

In this regard several animal and human studies have demonstrated that activation of mast cells can be attenuated by azelastine, thereby possibly explaining an important mechanism underlying the efficacy of this drug in vasomotor rhinitis. Studies with rodent peritoneal or cultured mast cells demonstrated that azelastine inhibited both allergen and nonallergen-induced release of histamine, sulfidopeptide leukotrienes and cytokines (particularly TNF α) *in vitro*, and that some of these effects were seen at concentrations as low as 10⁻⁸–10⁻⁶M (21–24). Detailed mechanistic studies have suggested that azelastine-mediated inhibition of mast cell degranulation may be a consequence of interference with protein kinase C activity (7).

Similarly, studies with human mast cells have also demonstrated that azelastine inhibited the release of

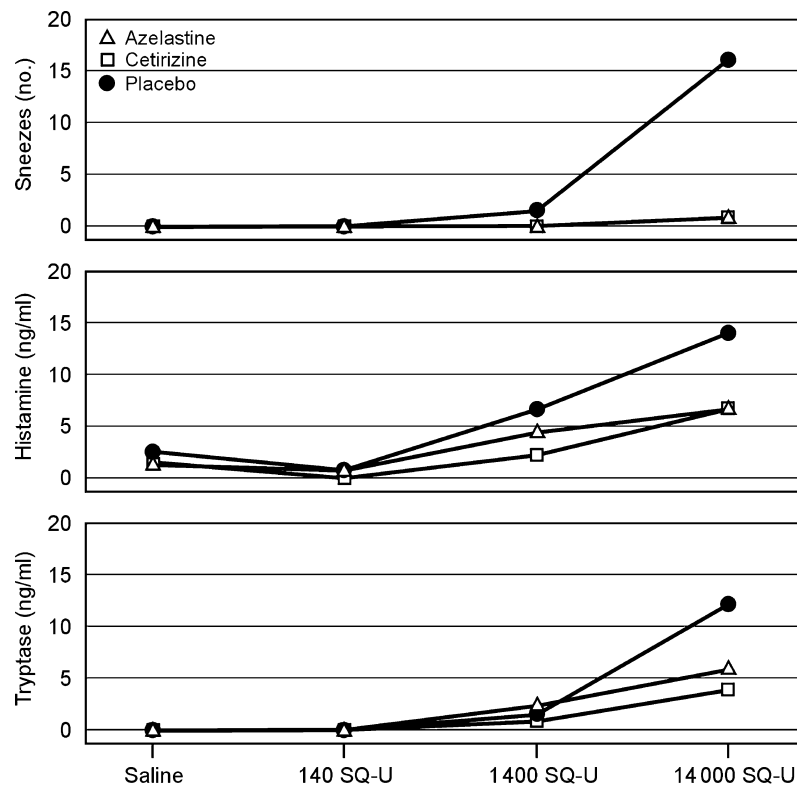


Figure 3. Effect of azelastine and cetirizine on allergen-challenge-induced sneezes, and histamine and tryptase release in nasal mucosa of allergic rhinitis patients. (Modified from Jacobi et al. 1999 (27) and reprinted with kind permission.)

histamine, prostaglandin D₂, tryptase, leukotrienes, and cytokines (IL-3, IL-6, IL-8, TNF α) (25, 26). A recent study has investigated the effect of azelastine nasal spray (0.14 mg per nostril twice daily), oral cetirizine 10 mg every day, or placebo for 1 week, on allergen-induced release of mast-cell mediators from the nasal mucosa of allergic rhinitics outside the pollen season, using a randomized, double-blind, double-dummy, three-way crossover design (27). This study demonstrated that allergen challenge led to a significant increase in the levels of histamine and tryptase in nasal lavage of these patients and that these markers of mast cell activation were significantly reduced by both azelastine and cetirizine, compared with placebo (Fig. 3). However, despite this evidence for the inhibitory effects of azelastine on mast cell activation and function, this hypothesis awaits confirmation by well-controlled clinical trials in this group of patients.

Inhibition of synthesis and/or release of pro-inflammatory cytokines and adhesion molecules

There is now considerable evidence that several antihistamines possess anti-allergic/anti-inflammatory activity, in addition to their normal antihistaminic activity, that is not related to their ability to antagonize the effects of histamine at the H₁ receptor. Indeed, it has been suggested that, many of these antihistamines could readily associate with and perturb the function of other non-H₁ histamine receptor cell membrane complexes and/or enzymes due to their cationic amphiphilic nature, thereby attenuating pathways which play a role in signaling and initiation of the inflammatory processes (28). These anti-inflammatory effects of the antihistamines have been extensively reviewed and shown to include decreased release of both preformed and newly generated pro-inflammatory mediators (cytokines, eicosanoids, adhesion molecules, etc.) from inflammatory cells, decreased cell migration, accumulation and activation of inflammatory cells (eosinophils, neutrophils), decreased expression of cell adhesion proteins on epithelial cells, decreased superoxide radical generation and up-regulation of the number and function of β_2 -adrenoreceptors (28, 29). A major criticism of the *in vitro* studies has been that significant anti-inflammatory activity was observed only at relatively high concentrations that were unlikely to occur in clinical practice. However, more recent studies have demonstrated that many significant inhibitory effects on inflammatory cell function occurred at drug concentrations equal to or lower than the therapeutic plasma concentration of the antihistamine under investigation (29).

Studies of the mechanisms underlying these anti-inflammatory effects of antihistamines have suggested that these may be either receptor-independent or receptor-dependent, of which the former may mediate the reduction in the release of preformed mediators, eicosanoids and oxygen free radical generation, at high

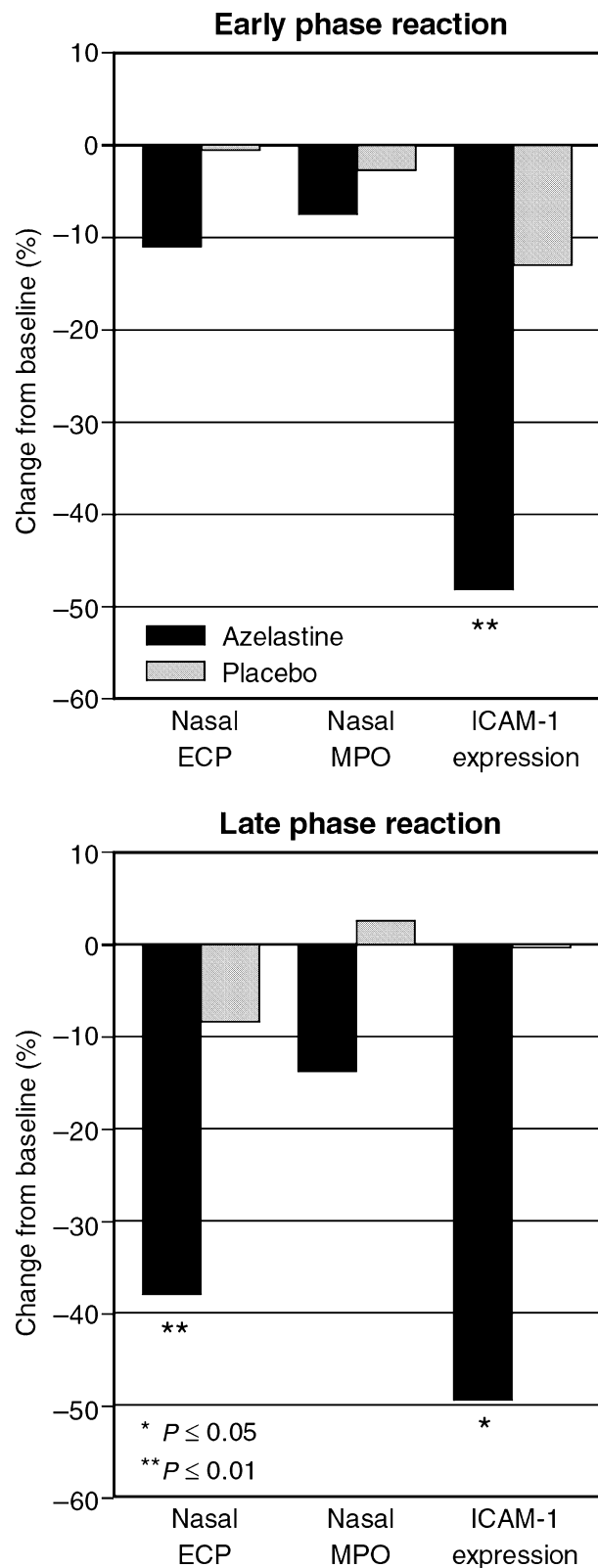


Figure 4. Effect of azelastine on allergen-induced changes in nasal ECP, MPO and ICAM-1 expression on epithelial cells. (Modified from Ciprandi et al. 1996 (36) and reprinted with kind permission.)

concentrations of antihistamines. Indeed, some *in vitro* studies have demonstrated that azelastine reduces the generation and release of leukotrienes B₄, C₄, and D₄, and oxygen radicals from activated human and animal polymorphonuclear leukocytes (29–31).

In contrast the receptor-dependent mechanisms are likely to be more predominant and important, because they primarily involve perturbation of signal transduction cascade/s at different levels, including inhibition of G-protein, protein kinase C and phospholipase C, inhibition of mobilization and utilization of intracellular Ca²⁺, and modulation of cAMP and cGMP levels (32). These have an overall inhibitory effect on the expression and synthesis of a large variety of pro-inflammatory cytokines, adhesion molecules and enzymes (e.g., iNOS and COX-2). Furthermore, since expression and synthesis of many of these mediators and enzymes has been shown to be under the control of nuclear factor- κ B (NF- κ B) responsive genes (33), it has been suggested that the antihistamines probably elicit their anti-inflammatory activity via inhibition of NF- κ B activity. Indeed, azelastine-mediated inhibition of cytokine (IL-1 α , IL-6, GM-CSF and TNF α) and nitric oxide generation in human peripheral blood lymphocytes, monocytes, gingival fibroblasts and mouse peritoneal macrophages has been shown to occur through inhibition of NF- κ B (23,34). Similarly, interference with Ca²⁺ signaling and protein kinase C activation has been shown to be the underlying mechanism of azelastine-mediated inhibition of TNF α transcription and synthesis in rat mast cells (23,35). More importantly, *in vivo* studies have demonstrated that treatment with intranasal azelastine significantly decreased nasal allergen challenge-induced eosinophil and neutrophil infiltration, eosinophil activation, and epithelial cell expression of ICAM-1 in the nasal mucosa of pollen-sensitive rhinitis patients, outside the pollen season (36). Furthermore these effects were observed during both the early and late phase reactions (Fig. 4). These findings are confirmed by another randomized, double-blind, placebo-controlled, parallel group study in 30 patients with seasonal allergic rhinitis, which demonstrated that treatment with azelastine (one puff

per nostril twice daily for three months during the pollen season), significantly decreased eosinophil and neutrophil infiltration and ICAM-1 expression in the nasal mucosa of these patients, compared with patients treated with placebo (37). Importantly, this study suggests that azelastine-mediated decrease in nasal inflammation is not a transient or short-term effect and that there is no tachyphylaxis.

Conclusion

Although several treatment strategies are available for vasomotor rhinitis, to date no single therapy has been shown to be significantly superior to the others. Whilst intranasal corticosteroids and antihistamines are the two main classes of drugs employed, the former have generally been shown to be effective in patients with eosinophilia and are generally not efficacious in treatment of all the symptoms of vasomotor rhinitis. The antihistamines, with the exception of azelastine, have also produced inconsistent results, and are generally not approved by the FDA for treatment of this condition. Both clinical and mechanistic studies of azelastine, however, have indicated that this drug is highly efficacious in the treatment of all the symptoms of vasomotor rhinitis, likely as a consequence of potent anti-inflammatory effects, in addition to its antihistaminic effects. Attenuation of the expression and synthesis of pro-inflammatory mediators (cytokines and leukotrienes) and cell adhesion molecules (ICAM-1), which play a pivotal role in the maturation, migration and activation of inflammatory cells such as eosinophils and mast cells, is thought to be of particular importance, since there is an association between the degree of nasal inflammation and nasal hyperreactivity and symptoms. Furthermore, since azelastine has a more rapid onset of action, as compared with most other antihistamines and intranasal corticosteroids, then it has been suggested that azelastine nasal spray should be considered as primary therapy for patients who have symptoms of both allergic and/or vasomotor (perennial nonallergic) rhinitis (9).

References

1. DRUCE HM. Allergic and nonallergic rhinitis. In: Allergy Principles, Practice. 5th edn, (Ed by MIDDLETON E JR, REED CE, ELLIS EF, et al.). St. Louis: Mosby-Year Book Inc, 1999, 1005–1016.
2. SETTIPANE RA, LIEBERMAN P. Update on nonallergic rhinitis. *Ann Allergy Asthma Immunol* 2001;**86**:494–507.
3. LIEBERMAN P. Treatment update: non-allergic rhinitis. *Allergy Asthma Proc* 2001;**22**:199–202.
4. FILIACI F, ZAMBETTI G, CIOFALO A, LUCE M, MASIERI S, LOVECCHIO A. Local treatment of aspecific nasal hyperreactivity with capsaicin. *Allergol Immunopathol* 1994;**22**:264–268.
5. BLOM HM, VAN RIJSWIJK JB, GARRELDIS IM, MULDER PGH, TIMMERMANS T, GERTH VAN WIJK R. Intranasal capsaicin is efficacious in non-allergic, non-infectious perennial rhinitis. A placebo-controlled study. *Clin Exp Allergy* 1997;**27**:796–801.
6. SCADDING GK. Clinical assessment of antihistamines in rhinitis. *Clin Exp Allergy* 1999;**29**:77–81.
7. MCNEELY W, WISEMAN LR. Intranasal azelastine: a review of its efficacy in the management of allergic rhinitis. *Drugs* 1998;**56**:91–114.

8. ZANDER KJ. Zur Lebensqualität Allergischer Rhinitiker – Ein Vergleich Topischer und Systemischer Therapie. In: Topische Therapie der allergischen Rhinitis. (Ed by Mösges R, et al.) Zülrich: Biermann, 1993, 130–137.
9. BANOV CH, LIEBERMAN P, FOR THE VASOMOTOR RHINITIS STUDY GROUPS. Efficacy of azelastine nasal spray in the treatment of vasomotor (perennial non-allergic) rhinitis. *Ann Allergy Asthma Immunol* 2001;**86**:28–35.
10. GEHANNO P, DESCHAMPS E, GARAY E, BAEHRE M, GARAY RP. Vasomotor rhinitis: clinical efficacy of azelastine nasal spray in comparison with placebo. *ORL* 2001;**63**:76–81.
11. PERNOW B. Substance P. *Pharmacol Rev* 1983;**35**:85–141.
12. BARNES PJ. Airway neuropeptides. In: *Asthma and Rhinitis*. 2nd edn, (Ed by WW BUSSE, ST HOLGATE). Oxford: Blackwell Science Ltd, 2000, 891–908.
13. OKAMOTO Y, SHIOTORI K, KODO K et al. Cytokine expression after topical administration of Substance P to human nasal mucosa. *J Immunol* 1995;**151**:4391–4398.
14. SHINODA M, WATANABE N, SUKO T, MOGI G, TAKEYAMA M. Effects of anti-allergic drugs on Substance P (SP) and vasoactive intestinal protein (VIP) in nasal secretions. *Am J Rhinol* 1997;**11**:237–241.
15. NIEBER K, BAUMGARTEN C, RATHSACK R, et al. Effect of azelastine on Substance P content in bronchoalveolar and nasal lavage fluids of patients with allergic asthma. *Clin Exp Allergy* 1993;**23**:69–71.
16. TOGIAS AG, PROUD D, LICHTENSTEIN LM, et al. The osmolality of nasal secretions increases when inflammatory mediators are released in response to inhalation of cold, dry air. *Am Rev Respir Dis* 1988;**137**:625–629.
17. PROUD D, BAILEY GS, NACLERIO RM, et al. Tryptase and histamine as markers to evaluate mast cell activation during the responses to nasal challenge with allergen, cold, dry air, and hyperosmolar solutions. *J Allergy Clin Immunol* 1992;**89**:1098–1110.
18. TOGIAS AG, NACLERIO RM, PROUD D, et al. Mediator release during nasal provocation. A model to investigate the pathophysiology of rhinitis. *Am J Med* 1985;**79**:26–33.
19. TOGIAS AG, NACLERIO RM, PROUD D et al. Nasal challenge with cold, dry air results in release of inflammatory mediators. Possible mast cell involvement. *J Clin Invest* 1985;**76**:1375–1381.
20. TOGIAS AG, PROUD D, LICHTENSTEIN LM, NACLERIO RM. Hot, dry air (HAD) is a more potent stimulus than cold, dry air (CDA) for causing rhinitis and for increasing the osmolality of nasal secretions. *Allergy Clin Immunol News Supplement* 1991;**1**:114.
21. CHAND N, PILLAR J, NOLAN K. et al. Inhibition of allergic and non-allergic leukotriene C₄ formation and histamine secretion by azelastine: Implication for its mechanism of action. *Int Arch Allergy Appl Immunol* 1989;**90**:67–70.
22. CHAND N. Effect of newer azelastine backups on allergic histamine secretion from peritoneal rat mast cells. Carter Wallace Study Report, PH-90–19, Asta Medica AG Report A-05610/6309, 1990.
23. HIDE I, TORIU N, NUIBE T, et al. Suppression of TNF-alpha secretion by azelastine in a rat mast (RBL-2H3) cell line: evidence for differential regulation of TNF-alpha release, transcription, and degranulation. *J Immunol* 1997;**159**:2932–2940.
24. MATSUO S, TAKAYAMA S. Influence of the anti-allergic agent, azelastine, on tumor necrosis factor-alpha (TNF-alpha) secretion from cultured mouse mast cells. *In Vivo* 1998;**12**:481–484.
25. SHICHIJO M, INAGAKI N, NAKAI N, et al. The effects of anti-asthma drugs on mediator release from cultured human mast cells. *Clin Exp Allergy* 1998;**28**:1228–1236.
26. LIPPERT U, MOLLER A, WELKER P, ARTUC M, HENZ BM. Inhibition of cytokine secretion from human leukemic mast cells and basophils by H₁- and H₂-receptor antagonists. *Exp Dermatol* 2000;**9**:118–124.
27. JACOBI HH, SKOV PS, POULSEN LK, MALLING HJ, MYGIND N. Histamine and tryptase in nasal lavage fluid after allergen challenge. effect of 1 week of pre-treatment with intranasal azelastine or systemic cetirizine. *J Allergy Clin Immunol* 1999;**103**:768–772.
28. CHURCH MK. Non H₁-receptor effects of antihistamines. *Clin Exp Allergy* 1999;**29**:39–48.
29. WALSH GM, ANNUNZIATO L, FROSSARD N, et al. New insights into the second generation antihistamines. *Drugs* 2001;**61**:207–236.
30. KATAYAMA S, TSUNODA H, SAKUM Y, KAI H, KATAYAMA TK. Effect of azelastine on the release and action of leukotrienes C₄ and D₄. *Int Arch Allergy Appl Immunol* 1987;**83**:284–289.
31. ACTERRACTH-TUCKERMANN U, SIMMET T, LUCK W, SZELENYI I, PESKAR BA. Inhibition of cysteinyl-leukotriene production by azelastine and its biological relevance. *Agents Actions* 1988;**24**:217–223.
32. SMIT MJ, HOFFMANN M, TIMMERMAN H, LEURS R. Molecular properties and signalling pathways of the histamine H₁-receptor. *Clin Exp Allergy* 1999;**29**:19–28.
33. YAMAMOTO Y, GAYNOR RB. Therapeutic potential of inhibition of the NF-κB pathway in the treatment of inflammation and cancer. *J Clin Invest* 2001;**107**:135–142.
34. YONEDA K, YAMAMOTO T, UETA E, OSAKI T. Suppression by azelastine hydrochloride of NFκB activation involved in generation of cytokines and nitric oxide. *Jpn J Pharmacol* 1997;**73**:145–153.
35. NAKATA Y, HIDE I. Calcium signalling and protein kinase C for TNF-alpha secretion in a rat mast cell line. *Life Sci* 1998;**62**:1653–1657.
36. CIPRANDI G, PRONZATO C, PASSALACQUA G, et al. Topical azelastine reduces eosinophil activation and intercellular adhesion molecule-1 expression on nasal epithelial cells: an antiallergic activity. *J Allergy Clin Immunol* 1996;**98**:1088–1096.
37. CIPRANDI G, RICCA V, PASSALACQUA G, et al. Seasonal rhinitis and azelastine: long- or short-term treatment? *J Allergy Clin Immunol* 1997;**99**:301–307.

General discussion

Delegate: We treat allergic rhinitis very effectively with corticosteroids and antihistamines, so why do we need to keep differentiating between allergic and nonallergic

rhinitis and not just treat all rhinitis patients in the same way with these drugs?

Ciprandi: I think that is because different mechanisms operate in these conditions. We know that allergic rhinitis is characterized by an inflammatory response and therefore we tend to see not only inflammation but also exacerbation. In the case of vasomotor rhinitis, this is a complex of different conditions in which inflammation may be important in some patients, but not all. We also know that an antihistamine may reduce symptoms, via several mechanisms, namely antihistaminic and anti-inflammatory. For example, in some patients they may alter nasal activation of events, which are involved in nonallergic reactions.

Bachert: You are right in a way that the patient comes in with nasal symptoms and may be one does a nasal allergy test, except that many patients are not assessed in that way. In allergic rhinitis, of course you have the possibility of immunotherapy and also there are other more conventional treatments. I would say that we need to treat such patients symptomatically, as if they are nonallergic rhinitis patients. The point is that some studies have clearly shown that you can define those patients who have no inflammation, but do have symptoms and corticosteroids are not useful in these patients, and therefore in such patients one has to start with antihistamines. At least we know that in nonallergic rhinitis most of the antihistamines have not been shown to be effective, and therefore this is a major stage for the oral antihistamines. I think we should try to treat the disease according to what we know and avoid using antihistamines other than azelastine in higher doses, which may have cardiac effects that we do not know about yet.

Garay: Nobody has mentioned surgery, in particular vidian nerve excision, as a treatment option for nonallergic rhinitis. What are your views on this?

Bachert: This type of surgery is carried out in some countries, and in others it has been abandoned because any beneficial effects seem to be only temporary. Also, in the literature there is very little information on surgery as a therapeutic option for nonallergic rhinitis.

Garay: I agree with you that there is indeed very little information on this subject, but I feel that we should nevertheless look at this option in some detail because the intranasal corticosteroids are not very consistent in all patients.

Delegate: What are your thoughts about therapy in children and also what do you think about the use of antileukotrienes as add-on therapy in treatment of vasomotor rhinitis, since leukotrienes have been shown to be released in rhinitis?

Ciprandi: I certainly do not recommend the use of antileukotrienes for congestion and rhinorrhea when an allergic etiology has not been established. Anti-leukotrienes are more effective in bronchial asthma, and if you consider that there may be comorbidity of asthma and rhinitis, then these drugs may show some beneficial effects. However, although the antileukotrienes have been shown to reduce leukotriene synthesis, I do not know exactly what is the clinical importance of this in vasomotor rhinitis because these have certainly not been shown to treat all the symptoms of rhinitis. In this regard azelastine is currently the best therapy because it can reduce cytokines and adhesion molecules, which probably play the most important role in the pathophysiology of rhinitis. However as Professor Bachert has pointed out, I agree that one of the most important issues in the therapy of vasomotor rhinitis is that once diagnosis is confirmed, we should then start therapy in a logical manner on the basis of what we know about the symptoms and assess whether or not there is a real need for any specific therapy.