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Editorial

Combined mediator antagonism for allergic rhinitis

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The drug treatment for allergic rhinitis comprises the use of intranasal corticosteroids, as well as histamine and cysteinyl leukotriene antagonists. Current guidelines advocate the use of histamine receptor antagonists for the treatment of intermittent or persistent allergic rhinitis, particularly due to seasonal pollen exposure, as these drugs have a fast onset of action (1). These drugs tend to be more effective for histamine mediated type symptoms such as sneezing, itching and rhinorrhoea, rather than on nasal blockage, which tends to be better controlled on intranasal corticosteroid therapy (2, 3). The cysteinyl leukotrienes are considered to be more responsible for symptoms of nasal congestion in allergic rhinitis, although their current role remains to be clearly defined in the light of emerging data (1, 4).

Given the potential role for using combined mediator blockade with both histamine and leukotriene antagonists in allergic rhinitis, this has resulted in a number of clinical studies looking at a variety of outcome measures. Moreover, as there is a recognized link between allergic inflammation in the upper and lower airways, the use of combined mediator antagonism offers the potential for treating the unified airways in patients who have concomitant allergic rhinitis and asthma, as an alternative to using topical intranasal plus inhaled corticosteroids (5).

The relative roles of histamine and cysteinyl leukotrienes have been studied using various challenge models in the upper and lower airways. An *in vitro* study in sensitized human bronchus showed that blockade of mast cell-mediated contraction occurred to a greater degree with a combination of a histamine antagonist (chloropheniramine), and a leukotriene antagonist (MK-571) when compared with either drug alone (6). *In vivo* allergen broncho provocation testing in asthmatics found zafirlukast to reduce the early asthmatic response to a greater degree than loratadine, while each drug conferred a similar degree of protection against the late response (7). However the combination of both drugs was significantly more effective than either drug alone, suggesting additive antagonism. Interestingly in the skin, two separate studies have shown that fexofenadine but not montelukast attenuates the cutaneous allergen response, with there being no additivity when both drugs are given together (8, 9).

Nasal challenge studies have also been performed which are pertinent to allergic rhinitis. The response to nasal mannitol challenge, an indirect acting pro-inflammatory osmotic stimulus, in patients with persistent allergic rhinitis, was attenuated to a significant degree by single doses of either desloratadine 5 mg or montelukast 10 mg when compared with placebo (10). In a nasal challenge study using another indirect stimulus, adenosine monophosphate, which acts via priming and degranulation of airway mucosal mast cells, also in persistent allergic rhinitis, a significant degree of attenuation of response was seen with either fexofenadine 180 mg or montelukast 10 mg given for 1 week compared with placebo, although there was no additive effect when both drugs were given in combination (11). In the same study, total nasal symptom scores were also significantly improved by either drug given alone compared with placebo, but again no additivity of response was seen with the combination.

In this issue of 'Allergy', Kurowski et al. (12) report on a parallel group trial evaluating the effects of prophylactic treatment with either montelukast 10 mg or cetirizine 10 mg alone or in combination, given for 6 weeks prior to the grass pollen season and for a further 6 weeks during the season to patients with seasonal allergic rhinitis. In a fourth comparator group patients were pretreated for

6 weeks with placebo and then switched for the subsequent 6 weeks to receive montelukast and cetirizine together. A variety of outcome measures were evaluated including nasal symptom scores as well as nasal lavage fluid analysis. Pointedly no mention was made as to the primary outcome measure to power the study, which makes it somewhat difficult to interpret the various data presented, particularly for any negative findings. In this respect, the sample size for this type of parallel group study was rather small, while fewer patients completed the in-season period in the group who had placebo followed by combination therapy ($n = 9$), as compared with those receiving combination therapy throughout ($n = 16$). Another potential confounding factor was the somewhat variable pollen count, which appears not to have been factored into the analysis as a covariate. This is particularly important given the apparent inter-patient variability in response to treatment. It is also rather difficult to assess the true impact of treatments on symptoms in this study because there was no placebo comparator group during the pollen season, but only prior to the season. For example, during the pollen season in the group who were pretreated with placebo followed by combination therapy, the mean symptom score was between 1 and 2 (on a 6-point scale), suggesting that they were not severely affected.

Despite these potential problems with the study design, some interesting observations came out to light which are worthy of discussion. Prior treatment with combination therapy for 6 weeks followed by subsequent 6 weeks treatment with combination therapy was significantly superior to prior treatment with placebo followed by the same combination therapy. Indeed pretreatment with combination therapy produced a delay in the appearance of symptoms which occurred on subsequent pollen exposure. This was supported by evidence from nasal lavage fluid, where comparing preseason with in-season values, there was a significant increase in the percentage of eosinophils and concentration of eosinophilic cationic protein in the group who were pretreated with placebo followed by subsequent combination therapy, whereas in the group who received combination therapy throughout the 12 weeks, there was no such increase. Furthermore there was also a significant difference between the same two groups when comparing in-season values for both of these outcome measures from nasal lavage fluid. When comparing in-season symptom scores, values for rhinorrhoea, nasal itching and eye itching were significantly lower in patients who received combination therapy throughout as compared with those who received cetirizine alone throughout, although the magnitude of difference was rather small. Nasal lavage fluid in the group who received cetirizine throughout showed only small increases in eosinophils and eosinophilic cationic protein comparing preseason and in-season values, with there being no difference in comparison to values seen with combination therapy throughout. The results with montelukast alone throughout were disappointing in that the in-season symptom scores showed only a significant reduction for nasal itching, although the increase in eosinophils and eosinophilic cationic protein from nasal lavage fluid, while significant, appeared to be attenuated as compared with the group who received placebo followed by combination therapy.

The clinical implications of the findings of Kurowski et al. suggest that patients taking histamine and/or leukotriene receptor antagonists should start their treatment well in advance of the pollen season in order to achieve maximal effects, as per current guidelines. Although there were some observed trends to suggest additivity of response with montelukast and cetirizine, the small sample size and inter-patient variability in response precludes making any firm conclusions regarding combination therapy. No scatter plot of data for any of the outcome measures was presented which makes it difficult to evaluate the dispersion of individual responses to each treatment modality. This is particularly important because in real life clinical practice, one treats an individual patient rather than an average patient. Nonetheless, the most impressive finding here was of the difference in response during the pollen season between the two groups of patients who took the same combination therapy, depending on the preseason treatment modality.

It is also important to place the results of Kurowksi et al. in perspective of other published trials which have looked at combination therapy with histamine and leukotriene receptor antagonists in allergic rhinitis. Results of large multi-centre clinical trials in seasonal allergic rhinitis have revealed conflicting results, presumably associated with differences in sample size and pollen exposure patterns. In a study of 1302 patients (13), significant improvements in daytime nasal symptoms (the primary outcome) occurred with either loratadine or montelukast given alone, while in another study of 460 patients (14), neither loratadine nor montelukast as monotherapy conferred any significant benefits on daytime nasal symptoms (the primary outcome), while the latter was improved by the combination. In a study of 970 patients (15), loratadine and montelukast significantly improved daytime nasal symptoms, but the combination was no better than either drug alone.

In two other smaller single centre parallel group studies of seasonal allergic rhinitis, the combination of montelukast 10 mg and cetirizine 10 mg was no better than cetirizine alone on nasal symptoms or domiciliary nasal peak flow in 38 patients (16), while the combination of loratadine 10 mg and montelukast 10 mg was no more effective than montelukast alone on daytime and nighttime symptoms in 62 patients (17). In the latter study epithelial eosinophils from nasal biopsy were lower with montelukast alone than with the combination, which is rather difficult to explain.

Single centre studies which have compared combined histamine and leukotriene receptor antagonists *vs*

intranasal corticosteroids, have shown equivalent responses in two studies (18, 19) and inferiority in another (17), for effects on either nasal symptoms and domiciliary nasal peak flow. However only one of these studies which looked at prophylactic pretreatment for 2–3 weeks prior to the onset of the pollen season, showed superiority with intranasal corticosteroid *vs* combined antagonists (17). For patients who have concomitant asthma and allergic rhinitis, combination histamine and leukotriene antagonist therapy has been shown to be equally effective compared with combined inhaled and intranasal corticosteroids in one small single centre study (20).

In summary, there appears to be contradictory evidence from clinical trials regarding the potential for additivity of response in seasonal allergic rhinitis when using combined histamine and leukotriene receptor antagonists. In real life clinical practice there is likely to be a considerable inter-patient variability in response and the available data would suggest that a large proportion of patients with mild to moderate disease activity may be adequately controlled on antihistamine alone. For patients who are not controlled on antihistamine alone, adding in either a leukotriene receptor antagonist or an intranasal corticosteroid may be effective and our own anecdotal clinical experience from primary and secondary care is that some patients may benefit from using triple therapy, particularly for patients with severe persistent allergic rhinitis due to indoor or outdoor allergens. The use of combined oral antagonists may be an alternative option to combined topical corticosteroids for patients who have concomitant allergic rhinitis and asthma. In the situation of managed care or in the National Health Service where direct drug costs are important, effective monotherapy will be the aim for the majority of patients initially presenting to primary care. In this respect intranasal corticosteroids would seem to have the edge over antihistamines as monotherapy for allergic rhinitis. For patients with allergic rhinitis due to pollen exposure, the results of Kurowksi et al. reinforce the importance of always starting early before the onset of season in order to achieve the best results.

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