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EDITORIAL

Combination therapy with anti-mediator drugs in allergic disease

Introduction

Inflammatory mediators are local hormones that act via specific cell-surface receptors in an autocrine or paracrine manner to modulate the behaviour of inflammatory leucocytes and structural cells in inflamed tissues. The classical inflammatory mediators are the autacoids such as histamine, cysteinyl-leukotrienes (cys-LT), LTB_4, prostanoids, bradykinin, and platelet-activating factor (PAF). Potent, selective, safe and long-acting compounds that inhibit the synthesis or block the receptors of individual autacoids have been developed over the last 20 years. The leukotriene (LT) modifiers (montelukast, pranlukast, zafirlukast, zileuton) have entered clinical practice for asthma, and the non-sedating H_1 histamine antagonists (cetirizine, loratadine, terfenadine) are front-line therapies for allergic rhinitis and allergic skin disease. Potent inhibitors of prostanoid synthesis (NSAIDs) have been available for 100 years, but the new cycloxygenase-2-selective inhibitors (celecoxib, rofecoxib) may combat inflammation without the gastric and other adverse effects associated with traditional NSAIDs. Experimental antagonists of LTB_4, PAF and the mast cell protease, tryptase, have also been investigated in clinical trials in asthma and other diseases, with mixed results.

LT modifiers and other anti-mediator therapies have been shown to provide excellent clinical benefit in significant subgroups of patients. Many have advantages with respect to patient compliance and favourable adverse effect profiles compared to anti-inflammatory corticosteroids. The perception emerging from clinical trials is that anti-mediator monotherapies may be less efficacious than corticosteroids against the broad spectrum of inflammatory processes in allergic disease, arousing growing interest in the concept of combination therapy with two or more anti-mediator drugs, not only in asthma but also in inflammatory diseases of the nasal airway and skin. The paper from Professor Lipworth's group at Dundee University published in this issue of *Clinical & Experimental Allergy* [1] provides important evidence that combination therapy with two anti-mediator drugs, specifically a LT modifier and an H_1 histamine antagonist, can provide additive and complementary anti-inflammatory outcomes that match those afforded by topical corticosteroids. This review will focus on clinical trials of anti-mediator cotherapy, particularly with combinations of LT modifiers and antihistamines, in the treatment of allergic asthma, exercise-induced bronchoconstriction, allergic skin disease (eczema, urticaria), and allergic rhinitis.

Allergic asthma

The effects of therapy with LT modifiers in asthma have been extensively reviewed [2,3], but there are relatively few studies investigating LT modifier therapy in combination with other anti-mediator drugs. Early data on the relative contributions of LT and other mediators to allergic bronchoconstriction in human lung came from *in vitro* studies. Bronchial tissue from 144 asthmatic and non-asthmatic subjects was stimulated to contract *in vitro* by treatment with anti-IgE or specific allergen; contractions were inhibited by up to 60% by first-generation LT modifier drugs (ICI-198615, MK-886), with the remainder of the contraction blocked by the H_1 antihistamines mepyramine and metiamide [4]. The cyclooxygenase (COX) inhibitor indomethacin and a PAF antagonist (WEB2086) had no effect. A synergistic effect in blocking mast cell-dependent contraction of human bronchus *in vitro* has been confirmed using the more potent cys-LT antagonist MK-571 and the antihistamine chlorpheniramine, with inhibition of 28%, 16% and 82%, respectively, for MK-571 alone, chlorpheniramine alone, and the combination of both drugs [5].

In vivo, involvement of mast cell mediators in the early airway response (EAR) to allergen is supported by measurements in bronchoalveolar lavage (BAL) fluid. Baseline levels of LTC_4 and tryptase in BAL fluid are higher in atopic asthmatics, and increase further within minutes of local allergen challenge, together with increases in histamine, prostaglandin (PG)D_2 and thromboxane (Tx)A_2 [6,7]. The cellular sources of LTC_4 and other mediators during the late airway response (LAR) are less clearly understood, with infiltrating eosinophils, basophils and monocytes being candidates. In 12 mild allergic asthmatics, the production of LTC_4, histamine and PGD_2 during the EAR and LAR was assessed indirectly by measuring their urinary metabolites LTE_4, Nτ-methyl-histamine and 9α,11β-PGF_2, respectively, at hourly intervals after challenge with inhaled allergen [8]. Compared to baseline, urinary levels of all three mediator metabolites increased by two–three-fold within the first hour after challenge, with slightly smaller but still significant rises in all three metabolites during the LAR. Urinary levels of EPX did not

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change during the EAR or the LAR, suggesting that eosinophils are not activated during either response. PGD_2 is not generated by basophils, so the rise in 9α,11β-PGF_2 together with histamine and LTC_4 during the LAR may indicate a second phase of mast cell activation.

In contrast, a recent study showed that segmental allergen challenge led to high production of LTC_4 in nine out of 18 asthmatic patients, averaging a 234-fold increase over baseline, while the remaining nine showed no significant change [9]. The 'high LT producer' subgroup also showed significant eosinophil infiltration post-antigen, and higher production of LTB_4 and Th2-type cytokines including IL-4, IL-5, IL-6, and TNFα, compared to the low LT producer subgroup. That the excess LT production caused the eosinophil influx was demonstrated by significant blockade of BAL eosinophilia by oral treatment with the LT synthesis inhibitor zileuton in the high LT producer subgroup, and not in the low LT producer subgroup. The study suggests a leukotriene-dependent subphenotype of allergic asthma linked to eosinophilia that is predictive of good anti-inflammatory responses to LT modifier therapy.

Although LTC_4, LTB_4, PAF, histamine, PGD_2 and tryptase are generated during immediate allergic responses in the lung, some of these mediators may make relatively little individual contribution to bronchoconstriction. Compared to placebo, the LTB_4 receptor antagonist LY293111 (112 mg td) administered for 3 days to 12 atopic asthmatic subjects reduced BAL fluid neutrophil counts and myeloperoxidase levels 24 h after inhaled allergen challenge [10]. LY293111 had no effect on basal lung function, the EAR, LAR, bronchial responsiveness, or BAL fluid eosinophil counts. Potent and long-acting PAF antagonists including modipafant and SR27417A have also been extremely disappointing in the inhaled allergen challenge model [11]. The tryptase inhibitor APC366 had no effect on bronchial responsiveness or the EAR in 16 mild–moderate allergic asthmatics, and produced only minor inhibition of the LAR [12]. Whether these agents may provide additive, synergistic or complementary benefits if combined with other anti-mediator agents is unknown.

In contrast, a large number of studies of oral pre-treatment either with cys-LT receptor antagonists (LTRA) or LT synthesis inhibitors consistently show inhibition of the EAR to allergen challenge by 75–80% and the LAR by 40–60% [13–15].The remainder of each response may be attributable to other autacoids. In an early study in seven atopic non-asthmatic subjects, pre-treatment with the H_1 antihistamine terfenadine (180 mg) 3 hours before inhaled allergen challenge blocked the area under the FEV_1 curve (AUC) during the EAR by 50% compared to placebo, while the potent NSAID flurbiprofen (150 mg daily for 3 days) reduced the EAR by only 26%. However, the combination of terfenadine and flurbiprofen was no more effective in blocking the EAR than terfenadine alone [16], suggesting that the contribution of prostanoids is small.

Thus, from trials of anti-mediator monotherapies, it can be surmized that allergen-stimulated bronchoconstriction is dependent primarily on cys-LT and histamine, with PGD_2 perhaps making a minor contribution. To test this hypothesis directly requires randomized, placebo-controlled crossover trials of an LTRA and an antihistamine alone and in combination, with an adequate washout period between each arm of the trial. Such a study examined the effect of twice-daily oral therapy for 1 week with the LTRA zafirlukast (80 mg bd), the antihistamine loratadine (10 mg bd), and the combination of both drugs in 12 allergic asthmatics with proven early airway responses (EAR) and late airway responses (LAR) to inhaled allergen challenge [17].

As a percentage of placebo, zafirlukast alone reduced the mean values for FEV_1 area-under-the-curve (AUC) in the EAR by 62% and in the LAR by 55%, while loratadine alone inhibited the EAR by 25% and the LAR by 40%. The combination of zafirlukast and loratadine reduced the EAR by 75% and the LAR by 74%, both significantly greater than placebo, and significantly greater than either drug alone in the LAR. In the EAR, the effect of zafirlukast on the EAR was significantly greater than that of loratadine. Thus, cys-LTs play the predominant role in the EAR, while cys-LTs and histamine contribute more equally to the LAR, which is thought to mimic persistent airway inflammation in chronic asthma.

The remaining 25% of each response may be due to PGD_2 release [8]. Inhibition of prostanoid synthesis with aspirin and other COX inhibitors can trigger acute hypersensitivity reaction in the lungs, nasal airways and skin of aspirin-sensitive patients, probably by removing the anti-inflammatory effects of COX-derived PGE_2 [18]. However, it is possible that combining an LTRA and an antihistamine with an antagonist at the thromboxane receptor (TP), which mediates the bronchoconstrictor activities of PGD_2 and TxA_2 [19], may provide 100% protection against the early and late responses to inhaled allergen challenge.

Data from inhaled allergen challenge models may not predict clinical results in persistent asthma. In a large, randomized, placebo-controlled crossover trial, the effects of oral therapy for 2 weeks with the LTRA montelukast (10 mg od) alone vs. cotherapy with loratadine (20 mg od) plus montelukast (10 mg od) were investigated in 136 chronic asthmatic adults with FEV_1 values of 50–80% of predicted and 15% reversibility with an inhaled $beta_2$-agonist [20]. The combination of montelukast and loratadine produced significantly greater increases in FEV_1 (13.8% vs. 9.7%, $P < 0.001$), and reductions in inhaled $\flat_2$-agonist use

(35% vs. 27%, $P < 0.05$) and daytime symptom scores (approximately 25% vs. 19%, $P < 0.001$), compared to montelukast alone. The study confirms the additive effects of LT and histamine blockade in clinical asthma, and supports the case for further clinical trials.

Exercise-induced bronchoconstriction

Mast cell involvement has also been implicated in exercise-induced bronchoconstriction (EIB). For example, urinary excretion of the mast cell marker 9α,11β-PGF_2 was found to increase following bronchoconstriction induced by exercise [21]. Several studies have shown that exercise challenge of susceptible patients is in fact followed by a rise in urinary LTE_4 levels, and that EIB is attenuated by LTRA therapy [22]. The oral 5-LO inhibitor ABT-761 (200 mg) given 5 hours before challenge inhibits both the exercise-induced rise in urinary LTE_4 and the fall in FEV_1 by about 50% [23]. In a 12-week placebo-controlled study of 110 patients with EIB (> 20% fall in FEV_1), oral montelukast (10 mg od) attenuated the area under the FEV_1 curve within 60 min of challenge by 47%, reduced the maximal decrease in FEV_1 by 32%, and shortened the recovery time by 27% [24].

To test the hypothesis that exercise-induced bronchoconstriction may depend on both cys-LT and histamine activity, 16 asthmatic subjects with proven EIB of at least 15% following exercise challenge received oral zafirlukast (80 mg bd), loratadine (10 mg bd), the combination of both drugs, or placebo, in a randomized double-blind crossover trial for 1 week before exercise challenge [25]. Expressed as a percentage inhibition of the area under the FEV_1 curve during the 60 min after challenge, treatment with zafirlukast alone significantly attenuated EIB by 57% compared to placebo, while treatment with loratadine alone had no significant effect (− 9%). The combination of zafirlukast and loratadine reduced EIB by 65%, not significantly better than zafirlukast alone. Taken together with the study on autacoid metabolites in urine [21], the data suggest that EIB is mediated predominantly by cys-LT and PGD_2, probably derived from mast cells, and that surprisingly, histamine plays no significant role in this response. The study confirms the usefulness of LTRA monotherapy in preventing EIB. Although the attenuation of EIB by LTRA with or without antihistamine cotherapy is modest set against the protection afforded within the first hour following inhalation of a short-acting β_2-agonist (80–90%), it is comparable to the protection afforded by long-acting β_2-agonists over a 12-h period (55–70%) [26].

Allergic skin disease

Cys-LTs and histamine increase blood flow and cause oedema when injected into human skin. Vascular responses to intradermal LTD_4 show wide intersubject variability, but are significantly blocked by oral zafirlukast [27]. Both LTC_4 and histamine are generated in skin following dermal allergen challenge of atopic subjects, with histamine appearing within the first hour after challenge and LTC_4 peaking at 4 h [28].

There are few published studies on therapy with LT modifier drugs in inflammatory skin disease, and no controlled clinical trials of antimediator cotherapy. However, in a case report of four patients with atopic dermatitis (eczema), marked symptomatic improvements were observed following treatment with oral zafirlukast, which reduced the percentage of affected body surface area affected and the use of steroids and antihistamines [29]. In an open trial of zafirlukast in 15 patients with urticaria, symptomatic improvements were seen in eight patients with chronic disease, irrespective of concurrent use of antihistamines, while zafirlukast was less effective in seven patients with acute allergic urticaria reactions [30]. This may reflect a greater importance of histamine in acute reactions. Two cases of chronic urticaria associated with aspirin sensitivity were also responsive to LT modifier therapy (zileuton or zafirlukast), allowing reductions in antihistamine rescue medication [31].

In 15 adult patients who required systemic corticosteroid therapy, treatment with oral H_1 and H_2 antihistamines alone did not provide effective control of chronic urticaria, as defined by withdrawal of systemic steroids [32]. However, the addition of zafirlukast (20 mg bd) to H_1 and H_2 antagonists achieved control in 9/15 patients (60%); in four of the six patients refractory to zafirlukast, control was achieved by the addition of cyclosporin. Overall, histamine H_1 and H_2 blockade combined with either an LTRA or cyclosporin allowed sustained withdrawal of systemic steroids in 13/15 patients (87%). In a recent study, seven patients with chronic idiopathic urticaria received either oral montelukast (10 mg qd) or zafirlukast (20 mg bd), in conjunction with an H_1 antihistamine in most cases; all patients' symptoms resolved within 4 weeks, and within 1 week for most patients [33]. The combination of montelukast and cetirizine has been reported to be effective in delayed pressure urticaria [34].

In patients with chronic atopic eczema, therapy with systemic corticosteroids will generally clear the skin briefly but cessation of the systemic therapy will invariably be accompanied by return, if not worsening of the atopic eczema. Chronic use of very high potency topical corticosteroids can lead to cutaneous atrophy and often loss of effectiveness. The studies discussed above, and the highly variable clinical responses seen to antihistamines

alone in eczema and urticaria, provide a rationale for further studies both of monotherapy with LTRA and of combination therapy with LTRA and antihistamines, especially as a treatment alternative in the patient with chronic atopic eczema.

Allergic rhinitis

In contrast to asthma, long-acting non-sedating H_1 antihistamines such as loratadine, cetirizine and terfenadine are front-line therapy for allergic rhinitis, but their effectiveness is often low. LT modifiers have not been licensed for allergic rhinitis, but early evidence of a role of LT in allergic rhinitis came from clinical trials of LT modifiers in allergic asthma patients, some of whom reported symptomatic improvements in their concomitant allergic rhinitis.

Topical instillation of cys-LT in the nasal airway is associated with long-lived nasal blockage (congestion) and increased nasal resistance (measured by rhinomanometry), while nasal administration of histamine additionally causes rhinorrhoea, nasal itch and sneezing, suggesting activity on neural reflexes as well as on the vasculature [35]. Cys-LT, histamine, tryptase and PGD_2 all appear in nasal lavage fluid of allergic subjects within an hour of allergen challenge, suggesting mast cell activation, while in the late response, increases in cys-LT and histamine, but not PGD_2 or tryptase, suggest activation of infiltrating basophils [36].

Treatment of allergic rhinitis patients with the LT synthesis inhibitor zileuton (800 mg) significantly reduced levels of LT in nasal lavage and inhibited congestion following intranasal allergen challenge [37]. In a double-blind placebo-controlled trial in 159 patients with allergic rhinitis, a single dose of the LTRA zafirlukast (20 or 40 mg) significantly inhibited nasal congestion within 2 hours of dosing, and also, surprisingly, reduced symptoms of sneezing and rhinorrhoea [38]. It is not clear why a larger dose of zafirlukast (100 mg) had no significant effect.

The largest study of anti-mediator cotherapy in seasonal allergic rhinitis is a double-blind, placebo-controlled, parallel-group trial of 2 weeks of oral treatment with montelukast alone (10 mg or 20 mg od), loratadine alone (10 mg od), montelukast plus loratadine (10 mg each), or placebo, in 460 adult patients from 12 centres [39]. The combination of montelukast and loratadine significantly improved the primary endpoint of daytime nasal symptom score (including nasal blockage, itch, sneezing and rhinorrhoea), compared both to placebo and to therapy with montelukast or loratadine alone. The improvement in daytime symptom scores with the combination therapy occurred within the first day of treatment. Compared to placebo, cotherapy with montelukast and loratadine also significantly improved secondary endpoints including night-time symptoms, eye symptoms, global evaluations by patient and physician, and rhinoconjunctivitis quality-of-life score.

Notable features of the study [39] were firstly that neither montelukast (10 mg or 20 mg) nor loratadine alone significantly improved the primary endpoint of daytime nasal symptoms compared to placebo, although both increased some secondary endpoints such as night-time symptoms and rhinoconjunctivitis QOL. Secondly, the overall effects of the combination therapy were relatively modest, amounting to reductions in nasal symptoms of around 25–40% from baseline. The study did not resolve the question of whether such improvements will be of real clinical value when compared to topical corticosteroids and when diluted by real-world adherence to drug regimens.

In this context, the well-designed and independently funded study reported in the current issue of *Clinical & Experimental Allergy* by Dr Wilson and colleagues is particularly important [1]. Although relatively small ($n = 22$), the single-blind double-dummy crossover trial compared the effects of 2 weeks of cotherapy with oral montelukast (10 mg od) plus cetirizine (10 mg od) with the effects of monotherapy with an intranasal corticosteroid, mometasone furoate (200 μg), in patients with seasonal allergic rhinitis (SAR) during the pollen season, following a 1-week placebo run-in period. The study endpoints combined objective measures, including domiciliary nasal peak inspiratory flow and laboratory measures of exhaled nitric oxide, nasal resistance by rhinomanometry, and nasal volumes by acoustic rhinometry, with subjective measures including rhinorrhoea, nasal blockage, nasal itch, sneezing, eye symptoms, and interference with daily activities, as recorded by daily diary cards. Both the cotherapy with montelukast plus cetirizine and the monotherapy with mometasone significantly improved domiciliary measures of peak nasal inspiratory flow and all nasal and eye symptom scores compared to pooled placebo, and there were no significant differences between the active treatment regimens. The falls in symptom scores and in scores of interference with daily activity were of the order of 50% with both treatment regimens. The laboratory measures (exhaled NO, acoustic rhinometry, rhinomanometry) showed no significant improvement with either active treatment compared to placebo.

The study is important for a number of reasons. Firstly, the marked effectiveness of montelukast plus cetirizine cotherapy on symptom scores for nasal blockage in this study, compared to the lack of effect of antihistamines on congestion in previous studies [40], confirms a

particular involvement of LTs in inducing nasal blockage in SAR, as well as contributing to other endpoints. This suggests a complementarity of anti-LT and antihistamine cotherapy that supplements their additive effects on other measures.

Secondly, the study indicates that routine domiciliary measures of disease activity are more sensitive to treatment effects than intermittent laboratory measures, and it confirms the value of domiciliary nasal peak inspiratory flow as an objective physiological measure that correlates well with subjective measures of disease severity and drug activity, as previously reported by the Dundee group [41]. Continuous domiciliary measures are more likely to reflect 'real-world' treatment effects than intermittent laboratory investigations.

Most importantly, previous studies have shown that treatment with an LTRA or an antihistamine alone are inferior to intranasal corticosteroids in allergic rhinitis [42,43]. By showing that across a range of objective and subjective measures of disease activity, oral cotherapy with montelukast plus cetirizine is equieffective with intranasal mometasone, the study suggests that oral combination therapy with an LTRA and an antihistamine represents a realistic alternative to topical corticosteroids as first-line anti-inflammatory therapy for SAR. The study provides a model for larger-scale and longer-term studies of combination therapy in SAR.

Conclusions

Allergic inflammatory processes depend on complex contributions from a network of inflammatory mediators, but the contributions of cysteinyl-leukotrienes and histamine may be quantitatively the most important in the final common pathways producing bronchoconstriction, vasodilation and leucocyte recruitment. The relative importance of these and other mediators varies between individual patients with specific allergic diseases, and between allergic diseases of the lung, nasal airway and skin. LT modifiers are increasingly used as additive therapy in mild–moderate asthmatics insufficiently controlled on β_2 agonists and corticosteroids. Combination therapy with LT modifiers and antihistamines may provide additive benefits in blocking pathophysiological endpoints to which both mediators contribute, and also complement each other by blocking a broader spectrum of inflammatory processes than either drug alone. The clinical benefits of combination therapy may match those of corticosteroids without the potential adverse effects of steroids and the consequent poor therapeutic compliance in many patients. The safety of LT modifiers and non-sedating antihistamines allows oral treatment that can provide synchronous therapy of asthma, allergic rhinitis and eczema in individual patients.

Further controlled studies with LTRAs, antihistamines, and other mediator antagonists, both as monotherapies and as combination therapy, will help to disentangle the relative contributions of LTs, histamine and other mediators to the diverse pathophysiological features of allergic diseases of the lung, nasal airway and skin. In the future, the development of drugs that block mediators such as interleukin-5, IL-4, TNFα, and eotaxin are likely to provide a wider range of therapeutic options and allow better targeting of specific combinations of anti-mediator drugs to those patients most likely to benefit.

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