

EDITORIAL

Does leukotriene modulation of eosinophil function explain the therapeutic effectiveness of receptor antagonists in some patients with asthma?

In this issue of *Clinical & Experimental Allergy*, Virchow *et al.* [1] present their observations that the leukotriene receptor antagonist, montelukast, inhibits eosinophil transmigration across vascular endothelial cells. This observation suggests a potentially relevant explanation for the therapeutic benefit of montelukast in the treatment of asthma in some patients. Moreover, the findings of Virchow *et al.* [1] may also explain the effects that leukotriene receptor antagonists have on the eosinophil-associated inflammatory responses in clinical asthma and models of asthma.

The role and contribution of leukotrienes to eosinophil recruitment to the airways is still under investigation. Nearly 10 years ago, Laitinen *et al.* [2] showed that inhaled leukotriene E₄ was associated with eosinophil recruitment to the airway in asthmatic subjects; the number of subjects studied was small, and neutrophils, as well as eosinophils, appeared in the airway. At about the same time, Sedgwick *et al.* used bronchoscopy to deliver antigen to airway segments; lavage was performed immediately and 48 h post-antigen challenge [3]. Forty-eight hours after antigen challenge, there was a large influx of eosinophils into the airway lumen and a marked increase in leukotriene (LT)C₄. There was also a significant correlation between airway eosinophilia and the LTC₄ concentrations ($r = 0.92$, $P < 0.0001$). These findings indicate that eosinophils are recruited to the airway following antigen challenge; IL-5 is associated with the recruitment process; activation of eosinophils in the airway generates large amounts of LTC₄ which can then contract airway smooth muscle; and this process can be further amplified through the chemotactic actions of the newly generated leukotrienes. Similar observations of eosinophil migration to the airway following antigen challenge have been observed by others [4].

To extend such observations to a clinical level, a number of investigators have evaluated the effects of leukotriene receptor antagonists on eosinophil recruitment to the airway. As noted by the authors, both montelukast and pranlukast reduce sputum and mucosal eosinophils [5,6]. In addition, Wenzel *et al.* [7] found the 5-lipoxygenase inhibitor; zileuton, reduced lavage fluid LTB₄, urinary LTE₄, and the percentage of airway eosinophils at 4 a.m. in nocturnal asthma. Finally, a number of clinical trials have shown montelukast to reduce circulating eosinophils during

treatment of asthma [8]. Thus, from a number of evaluations, there appears to be a link between leukotrienes and the appearance of eosinophils in asthma, and a reduction in these cells with the administration of leukotriene antagonists. Given the potential contribution of eosinophils to allergic inflammation, these observations assume clinical relevance.

To put the observations of Virchow *et al.* [1] in perspective, it is helpful to briefly review the factors that regulate eosinophil recruitment to the airway. Tissue eosinophilia is dependent upon a number of factors and processes including the differentiation and proliferation of bone marrow progenitor cells, adhesion to and migration through endothelial cells, chemoattraction, and retention and activation [9]. The initial step in this process is influenced by IL-5, which, along with GM-CSF and IL-3, is important in the terminal differentiation of the eosinophil [10]. IL-5 can also influence the contribution of leukotrienes to eosinophilic inflammation. Cowburn *et al.* [11] showed that IL-5 can increase the expression of the 5-lipoxygenase-activating protein (FLAP) in eosinophils and, through this mechanism, enhance production of cysteinyl leukotrienes. Furthermore, using a guinea pig model, Underwood *et al.* [12] found pretreatment of these animals with pranlukast inhibited both the bronchocontraction and eosinophilia to an inhalation of LTD₄. Moreover, administration of anti-IL-5 also blocked the eosinophilia to inhaled LTD₄ suggesting the response to LTD₄ included IL-5 generation. The specific steps in this response were not established but they further support a link between cysteinyl leukotriene generation, a cysteinyl-leukotriene-1-response, and eosinophilia.

Another step in eosinophil movement to the airway includes cell adhesion to endothelial tissue and their eventual transmigration. These processes are also complex and involve an ever-increasing array of cytokines and chemokines [13, 14, 15]. It is also known that the adhesive properties of the eosinophil are influenced by the inflammatory environment; to control for this possible influence, Virchow *et al.* [1] evaluated the effects of GM-CSF and IL-13 on the transmigration responses of the eosinophil. However, it would have been of interest had they evaluated the effects of cysteinyl-leukotriene-1 receptor antagonism in the presence of relevant chemokines, RANTES or eotaxin, rather than platelet-activating factor (PAF) at high concentrations (such as 10^{-5} M).

Finally, adhesion and eosinophil transmigration can affect cell function, including survival. Using pulmonary microvascular endothelial cells (HPMEC), Yamamoto *et al.* [16] found eosinophil adhesion and migration to be differentially regulated by VCAM-1 and ICAM-1. VCAM-1 appeared to be more important for eosinophil adhesion, whereas ICAM-1 had a greater influence on migration. There are no data given by Virchow *et al.* [1] to tell us which adhesion molecules are involved in his studies. This readout is not critical but is of interest in view of the use of human umbilical vein endothelial cells rather than pulmonary vascular tissue. In additional studies, Yamamoto *et al.* [17] found eosinophil transmigration across the HPMEC is associated with cell activation; increased expression of CD69 and enhanced survival, the latter related to increased expression and, possibly, generation of GM-CSF. The cysteinyl leukotriene pathway can also be involved in the promotion of eosinophil survival. Lee *et al.* [18] evaluated the effect of LTD₄, GM-CSF, and fibronectin on eosinophil survival. LTD₄ (10⁻⁶ M) was as effective in promoting eosinophil survival as GM-CSF (5 ng/mL). Blocking of the leukotriene receptor, lipoxygenase pathway, and FLAP all inhibited the eosinophil-survival-enhancing activity of LTD₄. Thus, the authors concluded that there is an autocrine cysteinyl leukotriene pathway which promotes eosinophil survival, and, hence, its likelihood to cause allergic inflammation.

Collectively, there is emerging evidence that the cysteinyl leukotrienes influence a number of key eosinophilic functions that may contribute to airway inflammation, including production, migration, and survival. The work by Virchow *et al.* [1] adds to this growing list of leukotriene-related activity on eosinophil function. Although most of their findings are based upon an *in vitro* model, they provide new information and possible mechanisms by which this new class of asthma therapeutics may influence a feature of asthma-eosinophilic inflammation.

References

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