

EDITORIAL

Clinical and Experimental Allergy

A need for circulating biomarkers of severe persistent asthma and its treatment

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The concept that asthma is an inflammatory disease of the airways provides the basis for the use of anti-inflammatory drugs such as corticosteroids and leukotriene modifiers in management guidelines to achieve disease control. Corticosteroids are especially effective in suppressing T-type helper (Th2)-type inflammation by action on a wide range of cell types that contribute to the inflammatory cascade. However, in about 10% of patients, these interventions fail to control symptoms and restore lung function. This more severe end of the asthma spectrum accounts for up to 50% of the health costs of this disease [1]. In severe allergic asthma, blockade of IgE using the humanized monoclonal antibody omalizumab is efficacious, but its use is limited by the level of total IgE and body weight [2]. Moreover, while one-third of such patients achieve substantial benefits and one-third some benefit with this therapy, in a further one third there is no clinical response. Despite extensive analysis of the clinical trial database and some analysis of genetic variations in the IgE pathway, there is currently no way of identifying 'responders' from 'non-responders' other than conducting a 16-week trial of treatment followed by a physicians global assessment of response using a wide range of end points [3].

When asthma adopts a severe phenotype the inflammatory profile may change. Thus, in non-controlled severe asthma receiving high doses of corticosteroids, increased neutrophils are frequently observed in sputum [4], lavage [5] and bronchial biopsies [6]. One explanation for this is that high dose inhaled corticosteroids enhance the survival of neutrophils by inhibiting apoptosis whereas the opposite is the case for eosinophils [7].

However, an alternative explanation for the neutrophilia associated with severe asthma is a change in inflammatory mechanisms with greater involvement of

Th1-type cytokines such as TNF- α , IFN- γ and IL-8. Th-1 type inflammation dominates in such chronic diseases as rheumatoid arthritis, inflammatory bowel disease and sarcoidosis. Among the cytokines known to contribute to these disorders is TNF- α , blockade of which by specific monoclonal antibodies or soluble p75 TNF receptor fusion protein (etanercept) results in disease remission [8]. In severe asthma a recent biopsy study [9] has also shown that TNF- α is over expressed with gene transcription being up to 30-fold higher than in well-controlled asthma and is paralleled by increased levels of TNF- α protein in bronchoalveolar lavage fluid and mucosal biopsies. Elevated TNF- α has also been found in the airways of those in status asthmaticus [5] or who have died from asthma [10]. In severe asthma TNF- α is mostly localized to mast cells, but increased membrane associated TNF, TNF converting enzyme (TACE, ADAM17) and the high (p75) and low (p55) affinity TNF receptors are over expressed on circulating mononuclear cells suggesting wider up regulation of TNF pathways in severe disease [11, 12]. Based on these observations and the clear unmet clinical need in corticosteroid refractory asthma, two recent small clinical trials have reported the efficacy of anti-TNF therapy in the form of etanercept administered subcutaneously twice weekly for 10–12 weeks [9, 12]. Most recently Erin et al. [13] in a placebo-controlled trial has reported the efficacy of infliximab in patients with moderate asthma with decreases in diurnal variation in peak expiratory flow rate, asthma exacerbations and asthma-free days along with significant reduction in sputum levels of TNF- α , IL-12, IL-6, IP10 and IL-8. These proof of concept studies have led to large clinical trials using both etanercept and blocking anti-TNF monoclonal antibodies. Clearly, it would be of great value if a biomarker(s) could be found that could predict the therapeutic response to TNF blockade.

In this issue of Clinical and Experimental Allergy, Silvestri et al. [14] have examined the levels of four cytokines TNF- α , IL-8, IL-16 and IL-13 in the circulation of severe, mild-moderate asthmatics and normal controls.

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They report that TNF- α and IL-8 levels are higher in those with severe asthma. They further report positive correlations found between serum TNF- α levels and exhaled nitric oxide (eNO) and circulatory neutrophil counts. Across all three groups both TNF- α and IL-8 levels correlated inversely with baseline forced expiratory volume. Despite IL-16 and IL-13 also being associated with severe asthma in genetic studies and in sputum [15, 16], circulating levels of these two cytokines were no different between the three subject groups. The authors conclude that circulating levels of TNF- α and IL-8 may serve as biomarkers to identify those severe asthmatic patients in whom anti-TNF therapy maybe efficacious. In a randomized controlled cross-over trial of etanercept in 10 patients with severe asthma Berry *et al.* [11] have shown that membrane-associated TNF (but not TACE, p55 or p75) on circulating mononuclear cells is a predictor of the therapeutic response to etanercept. Serum TNF and IL-8 of the promise of being additional useful markers of anti-TNF responsiveness. TNF- α is a potent inducer of IL-8 production by a wide variety of cells in the asthmatic airway including epithelial cells, endothelial cells, T cells, monocytes and fibroblasts [17]. Thus increased TNF production in severe asthma could through the induction of IL-8 could be responsible for the neutrophil influx characteristic of disease.

These findings add to the concept that the inflammation in severe asthma may alter in the direction of a more destructive Th-1/neutrophil-mediated response driven by TNF- α and possibly other Th-1 type cytokines including IFN- γ . The advent of targeted biological therapies in the treatment of chronic inflammatory diseases that now includes asthma mandates the need for biomarkers that are able to identify those patients who are most likely to respond to these potentially expressive therapies. In the case of anti-TNF treatment, increased levels of TNF in blood or on circulating cells may prove to be a good example although further studies are required to confirm this. The possibility that separate subpopulations of asthmatic patients are responsive to biologic therapies emphasizes the importance of heterogeneity of this disease and the importance of tailoring novel therapies to individual patients. This mandates the need for appropriate biomarkers that can be used to predict therapeutic responses to biologics.

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