

EDITORIAL

Clinical & Experimental Allergy

Unsticking eosinophils

This editorial discusses the findings of the paper by Robinson et al. [4] pp. 1866–74.

R. W. Costello¹ and D. M. Murphy²

¹Department of Medicine, Beaumont Hospital, Dublin, Ireland and ²The Department of Respiratory Medicine, Cork University Hospital, Wilton, Cork, Ireland

As a class of pharmaceutical agents, the traditional indication for statin drugs has been for their lipid-lowering capabilities. This lipid-lowering action is mediated via targeting of the mevalonate pathway through inhibition of the enzyme, HMG CoA reductase causing decreased downstream cholesterol production. Inhibition of the mevalonate pathway also attenuates production of isoprenoids. These compounds facilitate activation of the small GTP-binding proteins, Rac, Ras, Rho and CDC42, which are critical to the functioning of diverse intracellular kinase pathways. By effecting this process, statins potentially modulate cellular production of pro-inflammatory compounds [1]. In addition, statins also induce compositional changes within the cell membrane via actions on lipid rafts causing subsequent interference with receptor-ligand binding at cell surfaces [2]. In *ex vivo* culture models statins have been shown to have multiple, diverse potential anti-inflammatory and anti-remodelling actions [1–3].

Eosinophils are important in the pathogenesis of allergic conditions including rhinitis and asthma. The mainstay of treatment of these conditions is through the use of corticosteroids, which function in part through the inhibition of eosinophil recruitment. There is considerable interest in finding safe, oral, non-steroid-based therapies that may inhibit the migration of these cells because in many patients inflammation is widely dispersed and so not appropriate for topical therapy. For example, patients with both asthma and rhinitis would benefit from an agent that targets both the upper and lower airways. The current study from Robinson et al. in this issue of *Clinical & Experimental Allergy* [4] adds to the growing wealth of experimental data in support of an anti-inflammatory role

for statins. In their study the effect of several types of statin on eosinophil adhesion to ICAM-1 and VCAM-1 under flow conditions was investigated. The principal finding of this study was that, and in keeping with the diverse pharmacological characteristics of the statins, two of the five statins tested displayed an ability to attenuate GM-CSF-stimulated adhesion of eosinophils to ICAM-1. None of the agents was effective in inhibiting eosinophil adhesion to VCAM-1. Intriguingly, the anti-adhesive action of only one of these two agents appeared to be dependent on HMG CoA reductase inhibition, suggesting additional pathway targeting by statins.

Eosinophils are difficult to study due to the small numbers of these cells among granulocytes. The typical isolation procedure of negative immune selection yields between 1 and 5×10^6 eosinophils. This means that using the standard techniques to study cell interactions under flow, where relatively large numbers of cells are required limits the number of experiments that can be performed. The study by Robinson reports the use of a novel micro-flow system (Cellix 8, Dublin, Ireland) that allows relatively small numbers of cells to be studied under the flow conditions as are present in post-capillary venules. In the study by Robinson the eosinophil interactions in these experiments were performed with recombinant adhesion molecule proteins. An extension of this work would be to examine, *ex vivo*, transendothelial migration through the use of cultured endothelial cells in this flow system.

So do the findings reported by Robinson and colleagues support the use of statins in asthma? In a murine model (ovalbumin [OVA]) of asthma, pre-treatment of mice with simvastatin was shown to decrease bronchoalveolar lavage (BAL) inflammatory cells including eosinophils, as well as BAL levels of the inflammatory cytokines, IL-4 and IL-5. Simvastatin also decreased IL-4, IL-5, IL-6 and INF- γ levels in thoracic lymph node cultures [5]. A further murine model (OVA) has demonstrated that lung lavage IL-4, IL-13, and TNF- α levels were all reduced by treatment with simvastatin. Furthermore, simvastatin treatment before methacholine bronchial challenge increased

Correspondence:

R. W. Costello, Department of Medicine, Beaumont Hospital, Beaumont, Dublin 9, Ireland.

E-mail: rcostello@rcsi.ie

Cite this as: R. W. Costello and D. M. Murphy, *Clinical & Experimental Allergy*, 2009 (39) 1778–1779.

lung compliance and reduced airway hyperreactivity [6]. These *ex vivo* and animal models certainly point to potential immunomodulatory clinical benefits for the statins in asthma.

The promising work in models has been followed up with human studies. Menzies *et al.* [7] performed a randomized, double-blind, crossover study of 16 subjects with mild-moderate asthma. Enrolled subjects were on regular inhaled steroid but all anti-inflammatory medications were stopped for 1 week before the study. Patients received 1 month treatment (or placebo) with 20 mg once daily simvastatin for 2 weeks, followed by 40 mg once daily for a further 2 weeks with subsequent cross-over. Despite measuring an array of airway physiological parameters and markers of inflammation in both blood and sputum, the only measurable effect was on cholesterol. A further study, examined the effect of atorvastatin in chronic, symptomatic, atopic asthmatics on < 1000 mcg beclomethasone equivalent and a short-acting β -agonist only [8]. This study was again cross-over in design. The authors reported no effect of treatment on lung function or quality-of-life scores. There was a reported decrease in sputum macrophage counts but with a reciprocal increase in the relative proportion of neutrophils. Of the multitude of sputum biomarkers measured, atorvastatin significantly reduced leukotriene B₄ only. There was also a reported decrease in cholesterol and a borderline decrease in C-reactive protein. Hence two well-designed clinical studies of stable asthma have yielded similar convincing negative results.

So do the findings reported by Robinson and colleagues that only eosinophil adhesion to recombinant ICAM-1 and not VCAM-1 was inhibited by fluvastatin and lovastatin explain these negative studies in asthma? Both of these studies were performed with different statins, and not all statins are the same. The studies were also performed over a relatively short time period and were essentially 'passive' observational studies of stable asthma. Much of the animal data has been gained from

challenge models, such as the OVA-challenged murine asthma model. It may now be time to explore the effect of various statins on inflammatory cell airway recruitment in response to an inhaled allergen, including studies in steroid naïve subjects. In addition, it may be informative to examine parameters such as airway remodelling over a longer time frame or in asthma phenotypes such as neutrophil dominant asthma in which ICAM-1 is possibly more important for cell recruitment. As with all good studies the paper by Robinson provides some clear answers and some difficult new questions.

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