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EDITORIAL

Is there a place for anti-remodelling drugs in asthma which may not display immediate clinical efficacy?

M. Inman

Airway remodelling in asthma, like vascular remodelling in atherosclerotic disease, is thought to occur in response to repeated inflammatory insults, and ultimately contributes to the pathophysiology of the disease. In asthma, these structural changes are many, and include thickening of the airway wall, associated with loss of epithelial organisation, goblet cell hyperplasia, subepithelial fibrosis, increased vascularisation, fibroblast and myofibroblast proliferation, and smooth muscle hyperplasia and/or hypertrophy. Several of these structural changes are increasingly thought to play a role in airway dysfunction in asthma [1].

While the concept that most, if not all, components of airway wall remodelling develop as a result of ongoing inflammatory events seems entirely plausible, direct support for this is relatively sparse in asthma literature. Moreover, this is not an easy issue to address experimentally, as by the time patients present to their physician and are diagnosed with asthma, they usually display markers of airway remodelling processes similar to those in patients with long-standing asthma [2]. Thus, several researchers have turned to animal models, where specific aspects of airway remodelling have been induced during periods of prolonged airway allergen challenge. One such model is presented in this issue of the *European Respiratory Journal* by CHRISTIE *et al.* [3]. This model is similar to several others, in that mice are sensitised to ovalbumin (OVA) and then intermittently challenged with OVA over a period of several weeks. Outcomes in this and other similar models are that each allergen challenge is associated with inflammatory events similar to those seen in the asthmatic airway, particularly those occurring during exacerbations of the disease. Consistent with the concept that repeated inflammatory insults underlie specific remodelling events, CHRISTIE *et al.* [3] have confirmed pervious observations from their own and other labs that repeated allergen challenge results in structural changes in the airway wall as well as airway hyperresponsiveness.

The specific issue addressed by CHRISTIE *et al.* [3] is whether remodelling and functional changes observed in mice subjected to chronic allergen challenge can be prevented by concomitant treatment with the corticosteroid fluticasone. They observed that treatment initiated at the onset of allergen challenge was effective at preventing increases in airway wall laminin, but interestingly was not effective at preventing airway hyperresponsiveness. This observation that concomitant treatment with corticosteroids was able to markedly reduce an aspect of airway wall remodelling is consistent with previous observations in a rat model of chronic allergen challenge [4]. Interestingly, in that study, treatment was also effective at preventing airway hyperresponsiveness. Why this was not the case in the CHRISTIE *et al.* [3] study is not clear, although as assessment of airway function was within 24 h of the most recent allergen challenge, it is not possible to say whether the observed dysfunction was secondary to the presence of inflammatory mediators or to structural abnormalities, or even an unrelated factor.

The results of the studies of CHRISTIE *et al.* [3] and that of VANACKER *et al.* [4], as well as previous observations that anti-leukotriene agents are capable of preventing allergen-induced airway wall structural changes [5], point to a potential new approach to asthma management. If, in fact, some aspects of airway wall remodelling are functionally important, then should treatment strategies be devised to prevent this development? This would be quite different than the current approach that treatment in asthma be aimed at symptomatic control and possibly also the control of eosinophilic airway inflammation [6]. For one thing, this approach would require a screening process, where indices of airway remodelling are identified prior to the clinical manifestations of the disease. The reason for this is that, to date, available treatment strategies have minor effects on aspects of remodelling once established either in patients or animal models.

Thus, we are in a position where it appears that some aspects of remodelling may be functionally important, and the development of these could be prevented with early introduction of appropriate treatment, probably at a time when there is no clinical evidence of the disease. Again in analogy to cardiovascular disease, this would be similar to the control of asymptomatic hypertension in an attempt to prevent vascular wall remodelling and risk of ischemic disease. However, vast amounts of research are required before we can get to this stage. For example, it is not known which remodelling events require targeting; whether this remodelling occurs at a time when targeting is feasible; how to identify those individuals who will progress toward functionally important remodelling (*i.e.* we need a marker like hypertension, which may turn out to be genetic); and whether such intervention would have a clinically relevant outcome. This is not meant as a negative comment, rather a reflection that there is an increasing amount of information, such as that from the CHRISTIE *et al.* [3] manuscript, that will have potentially major implications on how we view and manage asthma.

Correspondence: M. Inman, St Joseph's Hospital - Firestone Institute, 50 Charlton Ave, Hamilton, Ontario L8N 3Z5, Canada. Fax: 1 9055216125. E-mail: inmanma@mcmaster.ca

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