[Indian J Chest Dis Allied Sci 2011;53:79-80]

Editorial

Statins and the Lung: Hope or Hype?

Statins (hydroxyl methyl CoA reductase inhibitors) exert their lipid lowering action by inhibition of the rate limiting step in cholesterol synthesis. These also have what are known as pleiotropic effects, independent of this lipid-lowering potential. These include improved endothelial function, reduced platelet aggregation, inhibition of matrix metalloproteinase release from the endothelium, coronary plaque stabilisation and, mainly their anti-inflammatory effects. Hence, their use in a wide variety of conditions other than hyper-cholesterolaemia is being explored.[1,2] This include chronic obstructive pulmonary disease (COPD).[2]

The role of systemic inflammation in COPD is increasingly gaining recognition.[3] Persistent airway inflammation leads to increased levels of circulating cytokines and inflammatory markers, like interleukin (IL)-7, IL-6, C-reactive protein (CRP), fibrinogen and tumour necrosis factor (TNF).[4] This spill-over of inflammation from the lungs has been implicated in the causation of the co-morbidities of COPD, namely, atherosclerosis, ischaemic heart disease (IHD), stroke, osteoporosis and cachaexia. Exacerbations of COPD are associated, not only with a decline in forced expiratory volume in the first second (FEV_1), but also with worsening of the systemic inflammation. Additionally, these patients also have increased circulating levels of prothrombotic factors, such as thrombin, tissue plasminogen activator and plasminogen activator inhibitor that account for increased cardiovascular risks in these patients. Concurrent COPD is also associated with an increased risk of cancer mortality.[3]

Statins have been found to influence cellular inflammatory processes in the lung. Studies have shown that they suppress serum CRP levels,[3] Th1 cell activation and also interferon-gamma production.[3,5] These have also been shown to suppress IL-8 production by human macrophages, and reduce macrophage recruitment into the lung by reducing the adhesion of monocytes to pulmonary vascular endothelium.[3]

Several studies have suggested a positive impact of statins on mortality and morbidity in COPD. Frost *et al*,[6] in two separate case control studies, showed that moderate-dose statin treatment dramatically reduced COPD mortality. Mortensen *et al*[7] found that the use of statins in COPD, prior to admissions for exacerbations, was associated with a reduced 90 day mortality. Blamoun *et al*[8] observed that statin use in COPD was associated with a significant reduction in exacerbations of COPD.

The rate of decline of FEV_1 is an important predictor of mortality and even cardiac death in patients with COPD. Non-randomised trials have suggested that statins may retard the rate of decline of FEV_1, but more studies are needed to confirm these findings.[9] Keddissi *et al*[10] studied the effect of statins on spirometric parameters of patients with both obstructive and restrictive lung diseases. They found a reduction in the annual decline of both FEV_1 and forced vital capacity (FVC) in patients on statins as compared to those with no history of statin use. These benefits were said to be independent of the smoking status or of the nature of the lung disease (restrictive or obstructive).

A reduction in endothelin-1 production with statin use was associated with improved exercise tolerance in patients with concomitant COPD and pulmonary hypertension.

Thus, there is an emerging body of data demonstrating the positive effects of statins on the course of COPD. However, Janda *et al*[2] have pointed out several methodological weaknesses in the current studies looking at the use of statins in COPD, and have stressed on the need for interventional studies to confirm these findings.

Most of the data on the beneficial effect of statins is circumstantial or retrospective with a dearth of randomised controlled studies. The effect of statins is confounded by the intricate relationship of COPD with cardiovascular disease (CVD). Both COPD and CVD share smoking as an important risk factor. However, IHD is an important cause of mortality in COPD. In fact, Huiart *et al*[11] found heart failure to be the most common cause of hospitalisation in COPD. They also found that IHD was a more common cause of death in COPD, than were the exacerbations of COPD themselves. This was the case even in life-long non-smokers with COPD. The systemic inflammation in COPD also contributes to the atherogenic mileu in COPD.[2,11]

It is not surprising that statins, with their known reduction in cardiovascular mortality, should have a similar impact on mortality in COPD. It is known that treatment of cardiovascular co-morbidity with statins among other standard drugs can improve outcomes in COPD.[16] Thus, the role of statins as an important disease-modifying group of drugs for COPD needs to be studied independent of their cardiovascular effects.

There are also some studies exploring the potential of statins in other lung diseases. In asthma, role for statins as a modifier of allergic airway inflammation and pulmonary antigen presentation has been suggested.[13] The use of statins in acute lung injury and community acquired pneumonia[14,15] and in transplant related bronchiolitis obliterans[16] is also under investigation. There have been encouraging

reports on the use of statins in pulmonary hypertension in a murine model, in *in vitro* studies and in improving of exercise capacity in COPD-related pulmonary hypertension.

The role of statins in interstitial lung disease (ILD), however, remains controversial; indeed while a study[20] looks at the use of statins as therapy for bleomycin induced lung fibrosis, a review of 14 cases by Thompson *et al*[21] implicates statins as a potential cause of ILD. Statins have also been implicated in the causation of respiratory muscle myopathy.[22]

Currently, several clinical trials[23] have been registered in the United States, to prospectively study the role of statins in respiratory diseases. Their results should help clarify the tantalising link between statins and the lung.

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