enhancing the ability of the immune system to detect and remove malignant cells.

We therefore feel that caution is warranted when treating patients with asthma with statins; in some cases these drugs can represent more a poison than a snake oil.

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Competing interests: None.

Accepted 18 January 2009

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Authors' reply

Mascitelli and colleagues propose caution in the use of statins for asthma because they might provoke the development of cancer.

At present the relationship between statins and cancer is controversial. In some clinical studies statins might have been responsible for an increased rate of breast cancer[1] or prostate cancer.[2] On the other hand, statins are considered as anticancer drugs.[3] In a large-scale study, patients treated with statins were found to have a lower risk of cancer development.[3] The relationship between Tregs and cancer is also unclear. We agree that Tregs may suppress antitumour immunity. However, deficiency of Treg function might also result in oncogenesis. Furthermore, the immunosuppressive effect of statins is not only exhibited by increasing the number and function of Tregs, although there is a reciprocal developmental pathway for Th17 and Tregs. We did not examine the effect of pravastatin on the induction of Tregs in our experimental model of allergic airway inflammation, so it is not clear whether suppression of interleukin 17 (IL17) by pravastatin results in the development of Tregs.

Taken together, although we admit that careful observation is necessary, we do not think that the treatment of asthma with statins is contraindicated because of a possible risk of cancer.

In the accompanying editorial Rubin insists that statins are not necessary for the treatment of asthma because extremely effective medications are available for asthma and the safety of statins has not been fully confirmed.[4] However, there are still some patients with asthma who are resistant to current medications including systemic corticosteroids. For these patients, novel therapies are still awaited. One of the characteristic features of these patients—particularly those with more severe disease—during exacerbations and with cigarette smoking is a neutrophilic inflammation in the airway.[5] It is well established that IL17 plays an important role in the recruitment of neutrophils into the lung, and treatment with pravastatin decreased IL17 production in our study.[6] Statins might therefore be effective in some types of asthma with neutrophilic inflammation.

In summary, we consider that (1) to confirm the long-term safety of statins, further clinical studies with asthma or other disorders should be conducted; and (2) when the safety is definitely confirmed, statins could be a therapeutic candidate for some patients with severe steroid-resistant asthma.

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Competing interests: None.

Accepted 16 February 2009

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Effects of methacholine challenge on alveolar nitric oxide

Exhaled nitric oxide (FE_{NO}) is established as a surrogate of airway inflammation.[1] Based on the two-compartment model of nitric oxide production in the lungs, the contribution of the alveolar compartment to exhaled nitric oxide (CA_{NO}) can be calculated.[2] CA_{NO} is raised in chronic obstructive pulmonary disease and severe asthma, even when treated with inhaled corticosteroid.[2] Forced manoeuvres and bronchial challenge are known to reduce FE_{NO} measurements;[1] however, changes in CA_{NO} after challenge have not been reported.

Forty-eight patients with mild to moderate asthma performed fractionated exhaled nitric oxide before methacholine challenge and again after the methacholine concentration provoking a fall in forced expiratory volume in 1 s (FEV_1) of 20% or more (PC_{20}) or 8 mg/ml had been reached. Participants had a physician diagnosis of persistent asthma and were receiving treatment with $\leqslant$1000 μg/day beclometasone or equivalent. Spirometry was performed using a SuperSpiro spirometer (Micro Medical, Chatham, Kent, UK). Exhaled nitric oxide was performed on a NIOX chemiluminescence analyser (Aerocrine AB, Solna, Sweden) at three flow rates (50, 100 and 200 ml). A linear regression equation was applied to derive values for FE_{NO}, CA_{NO} and bronchial flux (J_{NO}).[3] Nitric oxide values were logarithmically transformed to achieve Gaussian distribution prior to analysis.

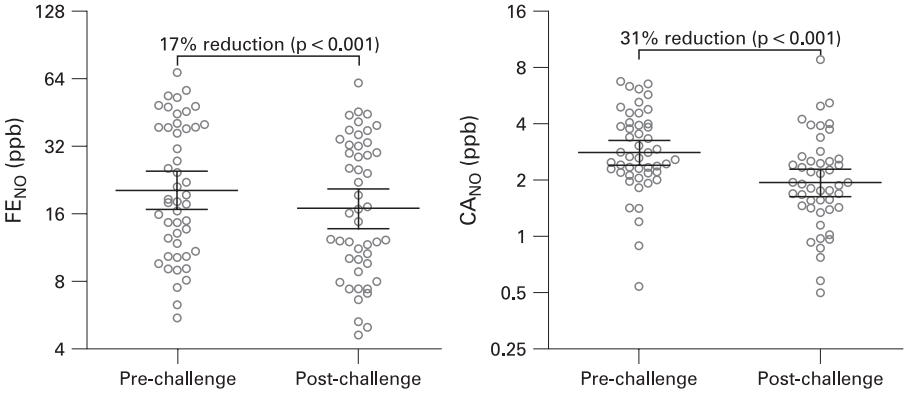

Figure 1 Scatter plots for effect of methacholine challenge on exhaled nitric oxide (FE_{NO}) and the contribution of the alveolar compartment to exhaled nitric oxide (CA_{NO}). Individual data points are shown with geometric means and 95% confidence intervals.