LETTERS

Interstitial lung disease guideline

It is a pity that so many eminent societies have sponsored, and *Thorax* has published, a supplement entitled "Guidelines on Interstitial Lung Disease"[1] which is incomplete because no mention is made of children. Interstitial lung disease is a problem at all ages.[2–4] Indeed, genetic disorders such as surfactant protein C deficiency are relevant in adults and children.[5] The supplement should have been entitled "Guidelines on Interstitial Disease in Adults" or, far better, brought together specialists in interstitial lung disease across all ages to achieve the truly comprehensive guideline that the present title erroneously implies.

A Bush

Correspondence to: Dr A Bush, Department of Paediatric Respiratory Medicine, Royal Brompton and Harefield NHS Trust, London SW3 6NP, UK; a.bush@rbh.nthames.nhs.uk

Competing interests: None.

Accepted 26 November 2008

REFERENCES

1. **Wells AU,** Hirani N, British Thoracic Society Interstitial Lung Disease Guideline Group, *et al*. Guidelines on interstitial lung disease. *Thorax* 2008;**63**(Suppl 5):v1–58.
2. **Barbato A,** Panizzolo C, Cracco A, *et al*. Interstitial lung disease in children: a multicentre survey on diagnostic approach. *Eur Respir J* 2000;**16**:509–13.
3. **Deutsch GH,** Young LR, Deterding RR, *et al*. Diffuse lung disease in young children: application of a novel classification scheme. *Am J Respir Crit Care Med* 2007;**176**:1120–8.
4. **Deterding R,** Young L, Dishop M, *et al*. Diffuse lung disease in older children: report of the ChILD network review. *Am J Respir Crit Care Med* 2007;**175**:A148.
5. **Thomas AQ,** Lane K, Phillips J 3rd, *et al*. Heterozygosity for a surfactant protein C gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred. *Am J Respir Crit Care Med* 2002;**165**:1322–8.

Pulmonary rehabilitation and interstitial lung disease

The recent guideline on interstitial lung disease (ILD)[1] has a welcome emphasis on best supportive care, including pulmonary rehabilitation. However, we were disappointed that the guideline states that "… there are no randomised controlled trials of pulmonary rehabilitation" and, as a result, ascribes a low level of evidence (C) to this intervention.

As the authors indicate, the guideline was developed during a time of rapid change and growth in the body of scientific evidence pertaining to management of ILD. Pulmonary rehabilitation is no exception. Last year we published a randomised controlled trial of exercise training for ILD in this journal, which demonstrated short-term improvements in dyspnoea and exercise tolerance.[2] The gain in exercise tolerance was smaller than previously reported in chronic obstructive pulmonary disease, but was accompanied by improvements in quality of life. Also in 2008, Nishiyama and colleagues[3] reported similar findings in a randomised controlled trial of patients with idiopathic pulmonary fibrosis who were diagnosed according to the consensus statement. These findings have since been synthesised in a meta-analysis.[4]

The guideline will be an important aid to diagnosis and management for people with ILD across many settings and countries. However, as the authors point out, there are few data on which to base recommendations in many areas. We suggest that pulmonary rehabilitation is an area where recent evidence may be helpful. Although the benefits attributable to pulmonary rehabilitation may be small and short-lived, there are few treatments which have successfully impacted on symptoms and quality of life in this patient group. We would hope that the growing evidence pertaining to pulmonary rehabilitation for ILD might be included in future editions of this document.

A E Holland,[1] C F McDonald[2]

[1] La Trobe University and Alfred Health, Melbourne, Australia; [2] Institute for Breathing and Sleep, and Austin Health, Melbourne, Australia

Correspondence to: Dr A E Holland, Physiotherapy Department, Alfred Hospital, Commercial Road, Melbourne, Australia 3004; a.holland@alfred.org.au

Competing interests: None.

Accepted 17 December 2008

REFERENCES

1. **Wells AU,** Hirani N, on behalf of the BTS Interstitial Lung Disease Guideline Group. Interstitial lung disease guideline. *Thorax* 2008;**63**(Suppl 5):v1–58.
2. **Holland AE,** Hill CJ, Conron M, *et al*. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. *Thorax* 2008;**63**:549–54.
3. **Nishiyama O,** Kondoh Y, Kimura T, *et al*. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirology* 2008;**13**:394–9.
4. **Holland A,** Hill C. Physical training for interstitial lung disease. *Cochrane Database Syst Rev* 2008;CD006322.

Authors' reply

Thank you for this concise and helpful statement. Plainly, there will be much more to say on this question when the guidelines are eventually revised.

As you may be aware, guideline statements must be approved (in this case by the BTS Standards of Care Committee) and a further time period is then needed for preparation of a guideline supplement. The two studies to which you refer appeared only a month or two before the final publication of the guideline document and their exclusion from consideration was unavoidable. The BTS guideline group had concluded their deliberations very much earlier. Post hoc changes in guideline statements cannot be made by individuals at the proof reading stage.

However, this does highlight a problem with guideline statements: recommendations can be dated within a matter of months. Interstitial lung disease is currently changing rapidly as a speciality and, as the BTS guidelines may not be revised for a further 10 years, there is a strong case for brief updates every 2 years in which changes to the evidence base are summarised. This possibility will be explored.

A U Wells,[1] N Hirani[2]

[1] Royal Brompton Hospital, London, UK; [2] Royal Infirmary Edinburgh, Edinburgh, UK

Correspondence to: Dr A U Wells, Royal Brompton Hospital, London SW3 6NP, UK; a.wells@rbh.nthames.nhs.uk

Competing interests: None.

Accepted 22 January 2009

Statins and cancer in patients with asthma

Imamura and colleagues[1] found that pravastatin attenuated allergic airway inflammation through suppression of interleukin 17 in the lungs of ovalbumin-sensitised mice. However, in the accompanying editorial,[2] Rubin pointed out that, in clinical practice, it is unlikely that adding a statin to an appropriate dose of inhaled corticosteroids might provide any additional benefit for patients with asthma, highlighting that in this setting statin therapy can represent a "snake oil panacea". We concur with Rubin,[2] and further suggest that statin drugs might actually be harmful in patients with asthma.

In healthy individuals, immune responses to allergens include a dominant regulatory element. There is mounting evidence that the function of regulatory T cells (Tregs) may be defective in patients with allergy and asthma.[3] Indeed, as Imamura and colleagues reported,[1] there is a reciprocal developmental pathway for the generation of pathogenic Th17 cells and protective Tregs in the immune system, depending on the state of the innate immune system.

On the other hand, some of the well-known immunomodulatory effects of statins are mediated through an increase in the peripheral numbers and functionality of Tregs[4] by the induction of the transcription factor forkhead box P3. However, an increase in Treg numbers and functionality may impair the host antitumour immunity via the suppression of tumour-specific effector T cell responses and the development of immune tolerance to neoplastic cells.[4]

Interestingly, epidemiological evidence suggests that a history of allergy is associated with a decreased overall risk of cancer.[5] It is plausible that the defective function of Tregs in subjects with allergic disease could reduce the cancer risk by

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.

L Mascitelli,[1] F Pezzetta,[2] M R Goldstein[3]

[1] Comando Brigata Alpina "Julia", Medical Service, Udine, Italy; [2] Ospedale di Tolmezzo, Tolmezzo, Italy; [3] Fountain Medical Court, Bonita Springs, Florida, USA

Correspondence to: Dr L Mascitelli, Comando Brigata Alpina "Julia", Medical Service, 8 Via S. Agostino, Udine 33100, Italy; lumasci@libero.it

Competing interests: None.

Accepted 18 January 2009

REFERENCES

1. **Imamura M,** Okunishi K, Ohtsu H, *et al*. Pravastatin attenuates allergic airway inflammation by suppressing antigen sensitisation, interleukin 17 production and antigen presentation in the lung. *Thorax* 2009;**64**:44–9.
2. **Rubin BK.** Statins for the treatment of asthma: a discovery well, dry hole or just snake oil. *Thorax* 2009;**64**:4–5.
3. **Larché M.** Regulatory T cells in allergy and asthma. *Chest* 2007;**132**:1007–14.
4. **Goldstein MR,** Mascitelli L, Pezzetta F. The double-edged sword of statin immunomodulation. *Int J Cardiol* 2008 May 15 [Epub ahead of print].
5. **Prizment AE,** Folsom AR, Cerhan JR, *et al*. History of allergy and reduced incidence of colorectal cancer, Iowa Women's Health Study. *Cancer Epidemiol Biomarkers Prev* 2007;**16**:2357–62.

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.

M Imamura, M Dohi

Department of Allergy and Rheumatology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

Correspondence to: Dr M Dohi, Department of Allergy and Rheumatology, Graduate School of Medicine, University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan; mdohi-tky@umin.ac.jp

Competing interests: None.

Accepted 16 February 2009

REFERENCES

1. **Cholesterol and Recurrent Events Trial Investigators**. The effects of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;**335**:1001–9.
2. **West of Scotland Coronary Prevention-Study Group**. Long-term follow-up of the West of Scotland Coronary Study. *N Engl J Med* 2007;**357**:1477–86.
3. **Mo H,** Elson CE. Studies of the isoprenoid-mediated inhibition of mevalonate synthesis applied to cancer chemotherapy and chemoprevention. *Exp Biol Med* 2004;**229**:567–85.
4. **Rubin BK.** Statins for the treatment of asthma: a discovery well, dry hole or just snake oil. *Thorax* 2009;**64**:4–5.
5. **Barners PJ.** New molecular targets for the treatment of neutrophilic diseases. *J Allergy Clin Immunol* 2007;**119**:1055–62.
6. **Imamura M,** Okunishi K, Ohtsu H, *et al*. Pravastatin attenuates allergic airway inflammation by suppressing antigen sensitisation, interleukin 17 production and antigen presentation in the lung. *Thorax* 2009;**64**:44–9.

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.

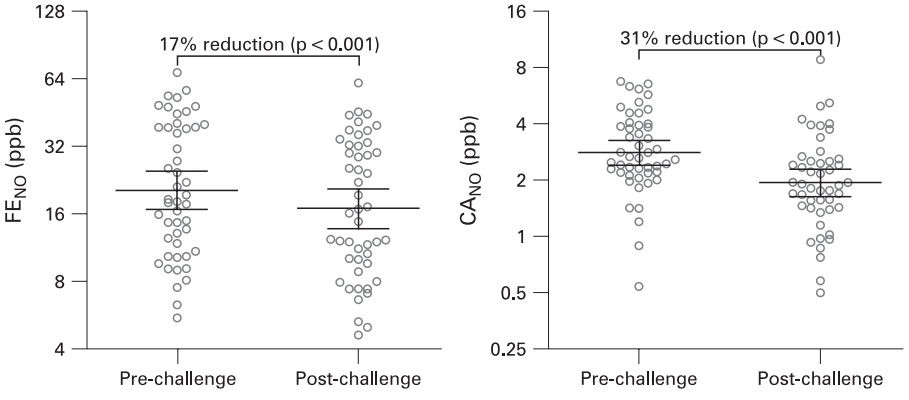

Figure 1 Scatter plots for effect of methacholine challenge on exhaled nitric oxide (FE_{NO}) and the contribution of the alveolar compartment to exhaled nitric oxide (CA_{NO}). Individual data points are shown with geometric means and 95% confidence intervals.