Montelukast and Churg-Strauss syndrome

I read with interest the case report by Tuggey and Hosker where Churg-Strauss syndrome was associated with the use of montelukast in an asthmatic patient in whom there was no recent exposure to oral corticosteroids. However, it is worth noting that the patient was using a high dose of inhaled fluticasone propionate (1.5 mg/day) via a large volume spacer prior to the introduction of montelukast. In this respect, a large volume spacer has been shown to double the systemic bioavailability of fluticasone propionate compared with a metered dose inhaler, in terms of its protein binding for adrenal suppression. In a dose ranging study in asthmatic patients a comparison was made between inhaled fluticasone propionate via a 750 ml large volume spacer (Volumatic) and oral prednisolone. Regression analysis showed significant (p<0.05) dose-response relationships with both drugs for suppression of peripheral blood eosinophils (fig 1), in keeping with their systemic bioavailability. At the highest doses studied for prednisolone (20 mg/day) and fluticasone propionate (2 mg/day nominal dose) there was a 1.5-fold (95% CI 0.8 to 2.7) greater suppression of blood eosinophils with fluticasone propionate than with fluticasone although, as indicated by the confidence interval (which included unity), this did not represent a significant difference between the drugs. Our data are in keeping with those of Tuggey et al who also showed dose related suppression of blood eosinophils with inhaled budesonide and oral prednisolone.

It is therefore evident that a high dose of inhaled fluticasone via a spacer, as reported in the case of Tuggey and Hosker, might have been suppressing the eosinophil count and therefore masking previously undiagnosed Churg-Strauss syndrome prior to starting montelukast. Indeed, it has been shown in a previous meta-analysis of 13 studies that, in terms of relative systemic bioactivity for producing suppression of early morning plasma cortisol, mg inhaled fluticasone is approximately equivalent to 10 mg oral prednisolone. The learning point here is that high doses of inhaled corticosteroid may exhibit sufficient systemic bioactivity to suppress previously undiagnosed Churg-Strauss syndrome in the same way as low doses of oral corticosteroids. Furthermore, in a dose ranging study in asthmatic patients a comparison was made between inhaled fluticasone propionate (as Flovent, GlascoWellcome Inc, Research Triangle Park, North Carolina, USA) now has an insertion in the section on precautions and adverse reactions stating that “in rare cases patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome”. These events usually but not always have been associated with the reduction and/or withdrawal of oral corticosteroids following the introduction of fluticasone propionate. A causal relationship between fluticasone propionate and these underlying eosinophilic conditions has not always been associated with suppression of peripheral blood eosinophil count.

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AUTHORS’ REPLY We are grateful to Professor Lipworth and Dr Wilson for their interest in our case report. Their main point seems to be that the dose of inhaled fluticasone via a Volumatic might have suppressed the eosinophil count and masked previously undiagnosed Churg-Strauss syndrome before starting treatment with montelukast. Several points can be made against this argument: (1) the blood eosinophil count was normal before the patient received any systemic or inhaled steroids (including fluticasone); (2) there was no reduction in inhaled fluticasone before the symptoms of systemic symptoms and profound peripheral eosinophilia; and (3) the features of vasculitis developed very rapidly with a close temporal relationship to the commencement of montelukast therapy.

Montelukast sodium in cystic fibrosis

Many older patients with cystic fibrosis (CF) describe a component of their condition as an "asthma" despite a lack of objective bronchial lability. We undertook a therapeutic trial of the leukotriene antagonist montelukast sodium in one such patient and observed a marked improvement in symptoms and peak expiratory flow rate (PEFR). Subsequently...

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Professor Lipworth and Dr Wilson also point out that montelukast is normally associated with suppression of the peripheral blood eosinophil count. However, this does not preclude the possibility of an eosinophilic vasculitis developing as a consequence of montelukast therapy.

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We read with interest the case report by Tuggey et al of a woman who developed Churg-Strauss syndrome associated with montelukast therapy in the absence of corticosteroid withdrawal. We have recently seen a similar case of a 65 year old man who was admitted acutely to hospital with malaise, general polymyalgia, and weakness associated with a dry cough. He was known to have nasal polyps and asthma for which his general practitioner had started treatment with montelukast 10 mg daily four months previously due to poor control, despite treatment with beclometasone 400 μg daily. He was not on oral prednisolone and had not received any courses previously. Clinical examination revealed a fever of 37.8°C and generalised muscle tenderness. The rest of the examination was unremarkable. Blood tests revealed a raised white cell count of 15×10⁹/L of which the eosinophil count was 8×10⁹/L. The chest radiograph showed left basal infiltration. Discontinuation of montelukast brought about temporary improvement, but he then deteriorated with severe myalgia and paraesthesia in his toes and soles of the feet. Chest examination revealed basal crepitations. The eosinophil count had increased to 13.8×10⁹/L and he had a moderate positive P-ANCA (titre of 1/160) against myeloperoxidase. The clinical and biochemical tests were in keeping with the diagnosis of Churg-Strauss syndrome which we believe to be associated with montelukast therapy in this asthmatic patient in whom prednisolone had not been previously used. He was started on prednisolone 40 mg/day with prompt clinical improvement and his eosinophil count decreased to 1.5×10⁹/L. We would like to reinforce the message of Tuggey et al that clinicians need to be vigilant in patients developing systemic symptoms after starting treatment with a leukotriene antagonist.

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Table 1  Subjective and objective changes during observation and montelukast treatment periods

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Run in</th>
<th>Change with montelukast</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise tolerance</td>
<td>5.6 (1.0 to 10.0)</td>
<td>1.4 (0.0 to 3.8)</td>
<td>0.008</td>
</tr>
<tr>
<td>FEV1 (l/min)</td>
<td>2.4 (0.7 to 4.2)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>PEFR morning (l/min)</td>
<td>390 (180 to 545)</td>
<td>22.8 (1.0 to 63.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Diurnal PEFR variability (l/min)</td>
<td>34.3 (8.3 to 101.0)</td>
<td>-10.3 (-4.0 to 0.0)</td>
<td>0.008</td>
</tr>
<tr>
<td>Day to day variability in morning PEFR (l/min)</td>
<td>24.0 (5.7 to 68.0)</td>
<td>-9.1 (-4.0 to 1.4)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Values are mean (95% confidence interval). The statistical analysis was made using Wilcoxon signed rank test.

we performed an open label study in adult patients attending the Hull Adult Cystic Fibrosis Clinic.

Eleven patients (eight male) of mean (range) age 25.9 (16–44) years with stable CF and no pulmonary infective exacerbations for at least four weeks entered a two week observation period during which they recorded a daily symptom score on a scale of 1–10 and twice daily PEFR. Each patient was also asked to define a desirable and achievable individual outcome from the new therapy. After the observation period patients received montelukast sodium 10 mg nightly (Singulair; Merck Sharp & Dohme, Herts, UK) for a further two weeks.

In the new study without adverse events. There was a significant augmentation in subjective symptoms score, with most pronounced improvement in exercise tolerance. Morning PEFR and PEFR variability were significantly improved (table 1). There was a positive correlation (Spearman’s correlation coefficient \( r_s = 0.834 \)) between the improvement in the day to day morning PEFR variability and percentage change in forced expiratory volume in one second (FEV1) following montelukast (\( p=0.01 \)). Eight patients achieved their objective aims. Five of these patients had a positive immunological response to Aspergillus fumigatus and FEV1, of less than 65% of predicted.

Montelukast is a specific LTD4, receptor antagonist which has been shown to reduce symptoms and improve lung function in several large randomised controlled trials in asthma. Leukotrienes have been found in the sputum of patients with CF.1-3 Cysteinyl leukotrienes were also shown to be correlated with the severity of pulmonary disease in CF.1 Our study suggests that LTD4 may have a clinically important role in the pathophysiology of CF. That the patients who benefited the most had positive Aspergillus serology provides further evidence as to a possible mechanism. Two thirds of adults with CF develop an immune response to Aspergillus, usually by the IgE, mast cell, eosinophil system.1 It has been hypothesised that intrinsic respiratory epithelium in CF allows access of aeroallergens and the presence of Aspergillus fumigatus in the mucus may stimulate the immunological response by activating local immune cells including T helper 2 (Th2) cells.

In most patients with CF, however, in our small study population, there is insufficient bronchial lability to meet the diagnostic criteria for asthma. These patients also do not meet the diagnostic criteria for allergic bronchopulmonary aspergillosis. We believe that colonisation of the CF airway by Aspergillus stimulates Th2 inflammation and thus leukotriene synthesis. Such a Th2 mediated immune response is a feature of asthma. The confirmation of this hypothesis in randomised studies of leukotriene antagonists may have important implications for the treatment of this large subgroup of patients with CF.

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Declining incidence of episodes of asthma

With great interest we read the thoughtprovoking comments by Fleming et al on general practice consultation patterns for asthma.1 We would like to offer some alternative viewpoints to those posed by the authors. First of all, we wonder whether the choice of statistical techniques obscure the view of what happened to respiratory morbidity. Given the sudden rise in asthma episodes at the end of 1991 and the subsequent fall after 1994, a step function would be more appropriate. Besides, the amplitude within the years studied appears to increase during the period 1991–4. This can be modelled by adding an interaction term season*time to the model. Furthermore, given the nature of the data, Poisson regression would be preferable to linear regression techniques.

Secondly, it is unclear whether the trend is specific for asthma and bronchiolitis or is relevant for all respiratory morbidity or, even broader, applies to all morbidity. In the discussion paragraph the authors point out that the broader category of respiratory infections shows the same trend, but they fail to explore the possible implications of this finding. How do their data compare with hospital data over the years? How about general practice consultation patterns?

Thirdly, the distinction between new episodes and repeat consultations may be a difficult one, especially for chronic diseases like asthma. Subtle changes in registration routines may have affected the outcome of the data. Apart from practice nurses, we wonder whether the introduction of asthma facilitators3 may be possible causes for the trends that are shown.

The authors suggest that the observed trends are due to fluctuations in prevalence. There is no evidence for this. The rise in consultations in the years 1991–4 could be due to a temporary increase in community consultation rates, the same number of prevalent asthma patients.

We invite the authors to explore these and other alternative hypotheses to explain or elucidate their findings.

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I was particularly interested to read the paper by Fleming and colleagues in which they described giving some further indirect support to our hypothesis. My colleagues and I are currently investigating the influence of maternal diet during pregnancy on allergy in the child, including in these studies fatty acids as well as antioxidants. We believe that a dietary hypothesis for the aetiology of asthma is more susceptible to allergy, and that this was the explanation for the increases in the prevalence of asthma observed worldwide. Since then we have published three studies, all different but all showing evidence of a 3–7-fold increase in risk of wheezy illness in relation to the lowest intakes of foods containing antioxidant vitamins. A poor diet does indeed appear to be an important risk factor for asthma.

In the final sentence of our original paper we stated “...if the dietary hypothesis is correct, the favourable trend in eating habits between 1984 and 1991 may already be having a beneficial effect”. The trend we referred to was a clear increase in intake of the three foods referred to above, as recorded in the annual national household food consumption and expenditure surveys. We had in mind a decrease in the prevalence of asthma in 10–12 year olds from about the mid 1990s.

The paper by Fleming and colleagues seems to give some further indirect support to our hypothesis. My colleagues and I are currently investigating the influence of maternal diet during pregnancy on allergy in the child, including in these studies fatty acids as well as antioxidants. We believe that a dietary hypothesis for the aetiology of asthma is worthy of very serious scientific investigation, not least because it points to an obvious and simple public health strategy for prevention.

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CORRECTION

In the reply by Becklake and Kauffman to the letter by Morice et al entitled “Gender differences in airway behaviour” which appears on page 629 of the July 2000 issue of Thorax, an error occurred in the second paragraph. This paragraph should have read: “We thank them for their references. Of particular interest to us was the observation that the cough was higher in postmenopausal than in premenopausal women, an observation in line with our own findings”. The authors apologise for this error.
Montelukast and Churg-Strauss syndrome

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