LETTERS

Histological appearances of putative montelukast related Churg–Strauss syndrome

Leukotriene receptor antagonists (LTRAs) are widely used in the treatment of asthma. Over the years, case reports have suggested a possible link between their introduction and the development of Churg–Strauss syndrome. The case we describe highlights a strong temporal relationship between the initiation of montelukast and appearance of features suggestive of Churg–Strauss syndrome; our patient went on to have a lung biopsy which confirmed the diagnosis. We speculate that the slightly atypical histological features observed (airway involvement by necrotising granulomas) could indicate changes caused by LTRA induced disease per se.

LTRAs have emerged as useful oral therapeutic adjuncts in the management of persistent asthma. These drugs are usually well tolerated although some reports have suggested a link between LTRAs and the development of Churg–Strauss syndrome. Most (although not all) of these cases have occurred where concomitant prescription of an LTRA has allowed a reduction in dosing of inhaled corticosteroids. Most cases of Churg–Strauss syndrome are associated with leucocytoclastic vasculitis and eosinophilia. We believe that our case is of particular interest because it allows a comparison of the histological appearances of Churg–Strauss syndrome with those described in association with other adverse effects of LTRAs or with montelukast alone.

A non-smoking 40-year-old patient with lifelong atopic asthma presented to the chest clinic with 3 months of very gradually deteriorating asthma control despite regular use of twice daily fluticasone 125 μg/salmeterol 25 μg through an Evohaler plus spacer for well over a year. There was nothing of note in his past medical, occupational or social histories, and he was using no other medication. There were no other symptoms and clinical examination revealed faint bilateral expiratory wheeze alone. At this point his forced expiratory volume in 1 second (FEV1) was 2.5 litres, forced expiratory volume (FVC) 3.8 litres and peak expiratory flow (PEF) 400 l/min. He was started on montelukast 10 mg/day and prescribed 2 puffs twice daily of fluticasone 250 μg/salmeterol 25 μg through an Evohaler plus spacer. Over the next 3–4 weeks, he experienced a dramatic worsening of respiratory symptoms and developed a florid maculopapular rash mainly in the upper body; no other systemic features were present. His lung function had also deteriorated with FEV1 being 2 litres, FVC 3.1 litres and PEF 570 l/min. At this time, the chest radiograph showed widespread bilateral infiltrates, and full blood count showed a raised eosinophil count of 11×10^9/l, having been 2×10^9/l just before institution of montelukast; renal function was normal, and antineutrophil cytoplasmic antibodies (taken approximately 3–4 weeks after initiation of montelukast) and aspergillus serology were negative. A high resolution CT showed widespread airspace opacification predominantly around smaller airways. He was started on high dose oral corticosteroids, advised to continue with fluticasone/salmeterol and montelukast was discontinued, all which resulted in a marked improvement in clinical, laboratory and radiological features. A video assisted thoracoscopic lung biopsy (while instituting montelukast) was responsible although the striking temporal relationship between its introduction and dramatic deterioration in asthma control supports the notion that this drug was probably implicated. It is important to be aware that although fluticasone/salmeterol has also been implicated in Churg–Strauss syndrome, we feel it is unlikely to be responsible in this case, as our patient had been using this combination product for well over a year without adverse effect and in fact improved despite its continuation.

Although clinical features of Churg–Strauss syndrome, whether associated with montelukast or not, are similar, it is conceivable that the slightly atypical histological features (airway involvement by necrotising granulomas) described above may represent changes caused by LTRA induced disease per se. It is important to be aware that there is ongoing uncertainty as to whether LTRAs unmask an already present syndrome or play a more direct causal role by an unknown mechanism. However, when initiating LTRAs, clinicians should remain vigilant in terms of clinical, laboratory and radiological features which may necessitate drug withdrawal and consideration of possible Churg–Strauss syndrome. This report adds to the published literature surrounding the putative association between leukotriene receptor antagonists and development of Churg–Strauss syndrome and in distinction to most other reports, highlights its histological features.

G P Currie,¹ L McKinlay,² K M Kerr²
¹Department of Respiratory Medicine, Aberdeen Royal Infirmary, Aberdeen, UK; ²Department of Pathology, Aberdeen Royal Infirmary, Aberdeen, UK

Correspondence to: Dr G P Currie, Department of Respiratory Medicine, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB2 2DD, UK; gpcurrie@rohs.net

Competing interests: GPC has received funding from MSD and AstraZeneca for attending postgraduate conferences and giving talks, both of whom manufacture LTRAs.

Accepted 13 July 2008

REFERENCES


Optimal treatment for idiopathic pulmonary fibrosis

The recent review series on interstitial lung disease has created a great deal of interest. However, the review by Williams and Wilson of novel treatments and lung transplantation in pulmonary fibrosis does not reflect recent developments in clinical and translational research in idiopathic pulmonary fibrosis (IPF).

The belief that inflammation is the primary driver of fibrosis in IPF has been superseded by newer pathogenetic paradigms that emphasise...
the role of aberrant wound healing in the evolution of fibrosis. The pathogenetic importance of inflammation has been downgraded. Furthermore, greater diagnostic accuracy has led to a better understanding of IPF disease behaviour. It is now appreciated that patients with IPF may have periods of remarkable disease stability interspersed by acute exacerbations, during which time fibrosis progresses rapidly, often with fatal consequences. Better understanding of the pathogenesis of IPF has led to the development of treatments directed at various elements of the wound healing cascade. Additionally, treatment strategies that aim to modify IPF disease behaviour and prevent acute exacerbations have been investigated. Consequently, there has been a recent striking increase in clinical trials in IPF. Among these trials, a number of key results not covered by the review of Williams and Wilson stand out.

In a 9-month study of 107 patients, Azuma and colleagues found that the pluripotent antifibrotic agent pirfenidone improved vital capacity and reduced the incidence of acute exacerbations compared with placebo.1 Kubo et al in a relatively small group of patients, all of whom were initially hospitalised with acute exacerbations of IPF, found that treatment with warfarin and prednisolone improved survival and reduced subsequent exacerbations compared with prednisolone alone.2 In the recently reported placebo controlled BUILD-1 study, no treatment effect was demonstrated for bosentan in the whole cohort, although a statistically significant effect was evident in the subgroup of biopsyed patients.3

In the most important recent trial, the IFIGENIA study, Demedts et al demonstrated that the addition of N-acetylcysteine (NAC) 600 mg three times daily to standard therapy of prednisolone and azathioprine significantly slowed disease progression in IPF compared with prednisolone and azathioprine alone.4 While questions have been raised concerning both the clinical significance of this finding and the mechanism by which NAC exerts a beneficial effect, this paper represents a landmark in the treatment of IPF. For the first time, primary end points have been clearly met in this relentless disease in a well-performed placebo controlled study.

In contrast to these trials, a large phase III study of interferon-γ1b, a compound that had previously shown promise as a treatment for IPF, was definitively negative with mortality (the primary end point) minimally higher in the treatment arm.5

The ongoing expansion in the number of new drugs being trialled in IPF offers the realistic hope that effective disease-modifying therapy may become available in the foreseeable future. Given the rapid development of novel therapies, we would urge that patients with IPF should be enrolled in clinical trials whenever possible. When this is not possible, we believe that the results of the IFIGENIA study provide a rationale for treatment in IPF.6 NAC is non-toxic and the benefits of treatment, although uncertain in magnitude, exceed the negligible risk. In a lethal disease it does not appear logical to withhold a cheap non-toxic treatment shown to have a beneficial functional effect, even if the exact clinical significance of this effect remains uncertain.

T M Maher, A U Wells
Interstitial Lung Disease Unit, Department of Respiratory Medicine, Royal Brompton Hospital, London, UK
Correspondence to: Dr T M Maher, Interstitial Lung Disease Unit, Department of Respiratory Medicine, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK. t.maher@ucl.ac.uk

Competing interests: None.
Accepted 29 July 2008

REFERENCES

Authors’ reply
The response to our article identifies the hazard of reviewing a topic in the middle of a paradigm shift, and was helpful in identifying pirfenidone and acetylcysteine as other potential agents for the management of idiopathic pulmonary fibrosis (IPF).1 Our review was aimed at identifying immunologic mechanisms underlying the remodelling process and did not suggest optimal management, which is at present not clear. In fact, a recent BTS study of IPF management still highlighted the importance of anti-inflammatory therapy in achieving better clinical responses.2 Furthermore, uncertainty in the rapidly changing area of antifibrotic therapy has resulted in significant delays in producing guidelines to support clinicians.3 We look forward to confirmation of promising early clinical trials of pirfenidone and acetylcysteine and their translation into clinical practice. Our optimism is tempered by experience with “false Messiahs” noted by Maher and Wells in their letter.

T J Williams, J W Wilson
Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital and Monash University, Melbourne, Victoria, Australia
Correspondence to: Dr J W Wilson, Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital and Monash University, Commercial Road, Melbourne 3004, Victoria, Australia; john.wilson@med.monash.edu.au

Competing interests: None.
Accepted 6 August 2008

REFERENCES