CASE REPORT

Montelukast and Churg-Strauss syndrome

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Several cases of eosinophilic conditions including Churg-Strauss syndrome (CSS) have recently been reported in asthmatic patients being treated with antileukotriene receptor antagonists. One patient with CSS who experienced a clinical relapse after treatment with montelukast and two asthmatic patients who developed CSS while receiving montelukast treatment are described. In one case reduction in the dose of oral steroid preceded the onset of CSS. To our knowledge, no case of CSS relapse has previously been reported in association with leukotriene antagonists.

Antileukotriene receptor antagonists are new therapeutic agents that have recently been introduced for the treatment of asthma. These drugs include one enzyme inhibitor of 5-lipoxygenase (zileuton) and three chemically distinct cysteinyl leukotriene type 1 receptor antagonists (zafirlukast, pranlukast and montelukast). The first to be used as a commercial product was zafirlukast which was approved in September 1996 for the treatment of asthma.

Recently, several cases of eosinophilic conditions including Churg-Strauss syndrome (CSS) have been reported in asthmatic patients being treated with zafirlukast,1–6 montelukast,7–10 or pranlukast.11 We describe one patient with CSS who experienced a clinical relapse after montelukast treatment and two asthmatic patients who developed CSS while receiving montelukast treatment. Only in one case did a reduction in oral steroid dose temporally precede the onset of CSS. To our knowledge, no case of CSS relapse has been reported in association with leukotriene receptor antagonists.

CASE REPORT 1

A 54 year old man with a 5 year history of moderate bronchial asthma presented with fever, dyspnoea on exertion, and polyarthralgia. Physical examination revealed a maculopapular rash on the chest and back, small purpuric lesions on both legs and forearms, diffuse ronchi and wheezes and scattered coarse crackles in the bases of both lungs. Laboratory analyses showed an erythrocyte sedimentation rate (ESR) of 65 mm in the first hour and a white cell count of 25 400 × 10⁶/l leucocytes with an absolute eosinophil count of 14 478 × 10⁶/l (23%). The total IgE level was raised (982 IU/l) and antineutrophil cytoplasmic antibodies (ANCA) were positive (57%). The total IgE level was raised (982 IU/l). ANCA were positive (57%) with MPO specificity. The chest radiograph was normal. Neurophysiological studies showed a sensorimotor mononeuritis multiplex involving the left median and cubital nerves and the right common femoral and peroneal nerves with demyelinating features. Biopsy specimens of skin, muscle, and sural nerve disclosed inflammatory perivascular infiltrates with eosinophils and necrotising vasculitis. No granulomas were identified. The prednisone dose was restored (1 mg/kg/day) and the cyclophosphamide dose was increased from 100 mg to 150 mg/day. Gabapentine and capsaicin were added to control pain. The patient’s condition improved progressively. The dosage of prednisone was slowly tapered over the next 6 months with no recurrence of the disease and normalisation of laboratory tests. The patient is currently in complete clinical remission on 10 mg/day prednisone and 100 mg/day cyclophosphamide.

CASE REPORT 2

A 60 year old woman with a long history of type II insulin dependent diabetes mellitus and hypertension was diagnosed with severe asthma at 54 years. She had never smoked. She had a past history of allergic rhinitis and penicillin sensitivity and had been treated with inhaled β agonists, inhaled steroids, and oral theophylline. She had not received systemic corticosteroids. In February 2000 montelukast 10 mg daily
was added to her treatment regime to control asthma with subsequent improvement in her symptoms. After approximately 4 months of treatment with montelukast the patient developed malaise, myalgia, polyarthritis, progressive numbness and pain over her lower and upper limbs, and erythematous exantheme on her forearms. Physical examination revealed diffuse ronchi and wheeze in both lungs, maculopapular exantheme over her trunk and forearms, and palpable purpura with necrotising lesions over her legs. Neurological examination showed muscle strength 1/5 in the right upper limb, 2/5 in the left upper limb, and 3/5 in both lower limbs in an asymmetrical fashion. Deep tendon reflexes were absent in the right upper limb and + in both lower limbs, with flexor plantar responses. There was diminished sensation of pinprick in the right hand and both feet. A complete blood cell count revealed 23,610 × 10⁶/l leucocytes with 13,547 × 10⁶/l (57%) eosinophils. The total IgE level was raised (1183 U/l). The urine was normal. ANA were positive (1/320) with a speckled pattern. Anti-DNA antibodies, anticardiolipine antibodies, hepatitis C and B virus markers, and cryoglobulins were negative. Rheumatoid factor was positive (1/256). ANCA were positive (30 UE) with perinuclear staining (MPO-ANCA). The chest radiograph was normal. Skin biopsy samples showed a leucocytoclastic vasculitis. Neurophysiological studies revealed a sensorimotor mononeuritis multiplex involving the right and left median, right cubital, right sural, and both peroneal nerves with severe active and chronic denervation-reinnervation changes in the muscles innervated by the median and peroneal nerves. Biopsy specimens of skin, muscle and sural nerve showed inflammatory perivascular infiltrates with eosinophils and necrotising vasculitis. No granulomas were identified. Treatment with montelukast was stopped and intravenous corticosteroids (1 mg/kg/day) and monthly pulses of cyclophosphamide (900 mg) were given. The patient’s condition improved progressively with complete resolution of the vasculitic rash and slow resolution of the nerve involvement. All blood parameters including the eosinophil count returned to normal within a few days of starting treatment. The patient remains clinically stable but sensorimotor sequelae persist.

CASE REPORT 3

A 62 year old woman with a 20 year history of moderate to severe aspirin sensitive and corticosteroid dependent bronchial asthma was referred to the internal medicine outpatient department. She also had recurrent sinusitis and nasal polypsis. She had received multiple courses of corticosteroids to control asthma, the last of them 2 months before starting montelukast treatment. She was also receiving salmeterol and montelukast treatment. She was on oral steroid maintenance when montelukast was initiated. The first reported patient diagnosed with CSS 1 year ago was in complete clinical remission taking 10 mg/day prednisone and 100 mg/day cyclophosphamide when montelukast was initiated. The prednisone dose was not modified. Over the next 2 weeks the patient experienced a severe clinical relapse consistent with purpuric rash and mononeuritis multiplex with ANCA positivity and an increase in the eosinophil count. To our knowledge, there has been no previous report of a patient diagnosed as having CSS who had a clinical relapse while being treated with a leukotriene antagonist. The second reported patient had not received systemic corticosteroids. These drugs were avoided because the patient had long term diabetes. Instead, fluticasone propionate was being used to control asthma and its dosage was not modified after starting treatment with montelukast. Only in the third case were systemic steroids discontinued 2 months before montelukast was started. Thus, corticosteroid withdrawal was not clearly implicated in CSS development or relapse in our patients. Instead, montelukast would appear to have played a causative role in the pathogenesis of this syndrome independent of withdrawal of corticosteroids.

A causative role for leukotriene antagonists in the development of CSS has been suggested by other authors. It is suggested that the temporal relationship between the use of these drugs and the development of CSS in all the reported cases. In addition, the fact that CSS has developed not only with montelukast, but also with zafirlukast and pranlukast, suggests that the syndrome may be related to the effect of antileukotriene drugs on leukotriene receptors. Finally, the documented increase in the incidence of CSS since leukotriene receptor antagonists have been approved for the treatment of asthma also suggests that these drugs have been directly involved in the development of CSS. Over the last year four patients have been diagnosed with CSS in our department, three of whom have been related to the use of leukotriene modifiers. This represents a clear increase in our annual incidence of 1–2 new cases of CSS per year; a total of 32 patients have been diagnosed at our institution during the last 20 years.
Many hypotheses have been put forward as to the cause of CSS. However, because the factors underlying eosinophil activation and proliferation in CSS are poorly understood, no clear mechanistic link between CSS and the use of leukotriene modifiers has yet been found and any link remains speculative. We consider that this syndrome may result from the phase of the illness characterised by eosinophilic infiltrates or life threatening vasculitis. Moreover, LTB4 may be a potent chemoattractant for eosinophils. Thus, tapering of corticosteroids in patients treated with leukotriene modifiers may result in an even greater leukotriene imbalance with a clear predominance of LTB4 activity. This is supported by the fact that no cases of CSS have so far been reported in the literature in association with the use of zileuton, the 5-lipoxygenase inhibitor that blocks the synthesis of all the leukotrienes including LTB4, even though Wechsler et al. referred to a patient reported to the FDA who developed a systemic eosinophilic condition in association with the use of this drug.

Although these case reports do not prove that montelukast has a causative role in the development and relapse of CSS, they further support the hypothesis that leukotriene antagonists are indeed involved in the generation of this serious disease. It therefore seems prudent to be vigilant to the emergence of new symptoms in asthmatic patients previously treated with oral corticosteroids who start treatment with leukotriene modifiers, particularly when the corticosteroid dose is tapered off. Close monitoring of rising eosinophil counts or pulmonary infiltrates is recommended in these patients. Similarly, it seems prudent to avoid the use of leukotriene modifiers in patients with CSS. Further data will be necessary to confirm whether or not leukotriene modifiers are directly involved in the development of this condition.

References

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