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.[1] These drugs include one enzyme inhibitor of 5-lipoxygenase (zileuton) and three chemically distinct cysteinyl leukotriene type I 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,[2–6] 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 antagonist therapy.

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 erthrocyte sedimentation rate (ESR) of 65 mm in the first hour and a white cell count of $25\,400 \times 10^6$/l leucocytes with an absolute eosinophil count of $14\,478 \times 10^6$/l (57%). The total IgE level was raised (982 IU/l) and antineutrophil cytoplasmic antibodies (ANCA) were positive (41 UE) with specificity for myeloperoxidase (MPO-ANCA). ANA, rheumatoid factor, cryoglobulins, and hepatitis virus B and C markers were negative. A skin biopsy showed a perivascular lymphocytic infiltrate with eosinophils, and dermal necrosis with eosinophils and thrombi in superficial blood vessels. Over the following 4 days the patient developed fever up to 38.9°C, tachycardia of 110 beats/min, and severe dyspnoea with a respiratory rate of 32/min and oxygen saturation of 80% while breathing air. A chest radiograph showed diffuse opacities in both lungs and a high resolution CT scan of the thorax revealed bilateral pulmonary alveolar opacities. An echocardiogram showed no abnormalities. The patient subsequently underwent bronchoscopic examination. The bronchoalveolar lavage fluid disclosed an alveolar haemorrhage with 10% eosinophils; no acid-fast bacilli, fungi, or parasites were seen. Aspergillus precipitins and anti-glomerular basement membrane antibodies were negative. Blood culture and sputum culture specimens were sterile. Progressive hypercapnia and hypoxaemia required tracheal intubation and ventilatory assistance. Treatment was started with intravenous hydrocortisone (1 g) and cyclophosphamide (1 g) with subsequent improvement in the patient's symptoms. After 6 weeks of treatment with oral prednisone (60 mg/day) and cyclophosphamide (100 mg/day) the dosage of prednisone was slowly tapered over the next 6 months to a maintenance dose of 10 mg/day with no recurrence of the disease and normalisation of laboratory tests.

Twelve months after the diagnosis of CSS, while the patient was in complete clinical remission, he experienced an increase in asthmatic symptoms and a 1 week trial of montelukast 10 mg/day was started at the suggestion of his general practitioner. During the next 2 weeks the patient experienced malaise, polyarthralgia, cutaneous purpura and, finally, progressive and painful paraesthesia in both legs. He was referred to our outpatient department and readmitted. On physical examination there were diffuse wheezes and ronchi and purpuric lesions involving the lower limbs. Neurological examination showed hypoaesthesia of the left hand and lower limbs in an asymmetrical fashion. The deep tendon reflexes were ++ and symmetrical with flexor plantar responses. Blood tests on admission showed an ESR of 9 mm in the first hour, white cell count of $13\,800 \times 10^6$/l with an absolute eosinophil count of 3200×10^6/l (23%). The total IgE level was raised (989 IU/l). ANCA were positive (80 UE) 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 the 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

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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, polyarthralgia, progressive numbness and pain over her lower and upper limbs, and erythematous exanthema on her forearms. Physical examination revealed diffuse ronchi and wheeze in both lungs, maculopapular exanthema 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 × 10^6/l leucocytes with 13 547 × 10^6/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-reinervation 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 polyposis. 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 fluticasone propionate. Montelukast 10 mg daily was added to her treatment regime in March 1999 with good control of her asthma symptoms. Ten days after beginning montelukast the patient developed general malaise, myalgia, swollen ankles, polyarthralgia, and palpable purpura over both legs. Blood tests showed a white cell count of 11 × 10^6/l with 10% eosinophils. ANA, rheumatoid factor, hepatitis C virus markers, and cryoglobulins were negative. ANCA were positive (40 UE) with MPO specificity. A chest radiograph showed pulmonary infiltrates in both lung bases. Skin biopsy samples showed inflammatory perivascular infiltrates with eosinophils and necrotising vasculitis. Montelukast was discontinued and treatment with prednisone (1 mg/kg/day) was initiated. The patient's symptoms reversed rapidly, the chest radiograph resolved, and the eosinophil count returned to normal within a few days of starting treatment.

DISCUSSION

Antileukotriene receptor antagonists are new therapeutic agents that counteract the inflammation, bronchospasm, and airway oedema caused by leukotrienes. Clinical studies have shown that they are safe and effective in the treatment of asthma, although no guidelines for their clinical use in asthmatic patients have been produced.[1 12] Several cases of CSS have recently been reported in asthmatic patients being treated with these drugs. Most appeared in patients treated with zafirlukast,[2–6] but similar cases have recently been described in patients treated with montelukast[7–10] and pranlukast.[11] The first reported cases were eight asthmatic patients who developed CSS after treatment with zafirlukast when oral corticosteroids were tapered off.[2] All of the patients had discontinued systemic corticosteroid use within 3 months of presentation and all developed the syndrome within 4 months of zafirlukast initiation. For this reason, the authors suggested that CSS development was not directly the result of leukotriene antagonist therapy but, rather, occurred as part of the natural course of the disease.[2] They speculated that patients who developed CSS while treated with leukotriene receptor antagonists suffered from a primary CSS that was unmasked when steroids were withdrawn. Similarly, other authors suggested that patients who develop CSS during leukotriene therapy are forme fustre variants of the eosinophilic vasculitis that become apparent when leukotriene receptor antagonists are added to the asthma therapy and corticosteroids are tapered off.[2 13] Recently, Wechsler *et al* reviewed all the cases reported in the literature and concluded that, in the majority of patients, the introduction of leukotriene antagonists allowed significant steroid dose reduction, thereby unmasking previously controlled CSS.[14] However, CSS has also been reported after beginning zafirlukast or montelukast therapy in asthmatic patients not treated with oral steroids.[5 8]

In our series, despite the fact that two patients had required intermittent courses of corticosteroids to control asthma, only one patient 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.[4–8] It is suggested by the clear temporal relationship between the use of these drugs and the development of CSS symptoms 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[14 15] 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.[16]

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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 an imbalance in leukotriene receptor stimulation in patients with an underlying eosinophilic disorder, as previously suggested by other authors.[5 7 15] Cysteinyl leukotriene type I receptor antagonists block the synthesis of LTC4, LTD4, and LTE4 but have no effect on the receptors for LTB4 which has been shown to be a potent chemoattractant for eosinophils and neutrophils.[12 15] Unopposed LTB4 activity may precipitate the phase of the illness characterised by eosinophilic infiltrates or life threatening vasculitis. Moreover, LTB4 may also induce neutrophil activation[12 15] which seems to be an important feature in patients with highly active CSS.[17] In addition, it has recently been shown that the leucocytes of asthmatic patients who are not receiving oral corticosteroids produce significantly more LTB4 than those of patients treated with steroids.[18] 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*[14] 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.

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