Successful treatment of sarcoidosis with leflunomide

SIR, Leflunomide (Arava) is an inhibitor of pyrimidine synthesis that has immunomodulating/immunosuppressive properties. Although currently approved for the management of patients with rheumatoid arthritis, it has been used with some success in several other autoimmune
Our patient is a 30-yr-old African American male who presented initially in 1998 with recurrent sinusitis and non-productive cough. Evaluation revealed hilar lymphadenopathy and granulomatous inflammation of his sinus mucosae, with biopsy positive for non-caseating granuloma, consistent with sarcoidosis. Symptoms and signs persisted despite initial treatment with prednisone 20 mg/day and methotrexate up to 15 mg/week. During this period, he also developed a facial rash consistent with cutaneous sarcoidosis. Methotrexate was discontinued because of gastrointestinal symptoms and headache. Subsequent therapy with azathioprine had to be stopped because of gastrointestinal intolerance and insufficient clinical response. Hydroxychloroquine 400 mg/day was also used without success. When first evaluated in our arthritis clinic in November 2001, he had a persistent skin rash involving his face and continued symptoms of sinusitis and cough. He remained on hydroxychloroquine 400 mg/day but had chosen to stop prednisone 6 weeks before his visit. His review of symptoms and medical, social and family history provided no new pertinent information. On examination, he had normal vital signs and general appearance. His physical examination was remarkable for facial rash, which was erythematous, maculopapular with areas of plaques consistent with sarcoidosis skin involvement, tenderness of maxillary and frontal sinuses, and scattered ronchi on lung auscultation. His laboratory values showed an elevated serum angiotensin-converting enzyme level of 160 IU/dl, mild normocytic anaemia with haemoglobin 12.3 g/dl, sedimentation rate 45 mm/h and C-reactive protein 2.3 g/dl. Complete blood count and routine blood chemistry studies were within normal limits.

He was started on leflunomide at 20 mg/day because of significant disease activity on the basis of his clinical findings and laboratory markers. He refused further prednisone therapy. Follow-up evaluation in March and April 2002 revealed complete resolution of sinus symptoms and cough and marked improvement of his skin rash. The angiotensin-converting enzyme level had decreased to 80 IU/dl, anaemia had resolved, serum sedimentation rate had improved to 30 mm/h and C-reactive protein was normal at 0.5 mg/dl. He had had no adverse clinical or biochemical effects of leflunomide therapy.

Sarcoidosis is a multisystem granulomatous disorder characterized pathologically by the presence of non-caseating granulomas in the organs involved. Although sarcoidosis most frequently involves the lung, extrathoracic manifestations, including cutaneous involvement, are common [1]. Corticosteroids remain the mainstay of treatment of sarcoidosis and are started at a daily dose of 20–80 mg tapering to 5–15 mg. Several cytotoxic agents have been used to treat sarcoidosis and are clearly of value in selected patients, though controlled studies are lacking. On the basis of safety and efficacy, methotrexate and azathioprine are often the preferred agents [2, 3]. Cyclophosphamide [3] should be reserved for refractory cases. Other agents that have been used with varying success include chloroquine and hydroxychloroquine [4], cyclosporin [5] and pentoxifylline [6]. Leflunomide probably acts as an immunomodulatory agent by interfering with the de novo synthesis of pyrimidines, and is a specific inhibitor of T-cell proliferation [7]. Leflunomide is 80% bioavailable orally and is rapidly converted by the liver and intestinal wall to the active metabolite, A77-1726, which itself has a half-life of about 15 days. The effect of leflunomide is selective for proliferating lymphocytes and is reversible, accounting for an improved toxicity profile. In addition to its use in rheumatoid arthritis, leflunomide has been an effective alternative in the treatment of other autoimmune diseases, such as Sjögren syndrome and Wegener’s granulomatosis, and has also produced beneficial effects in several animal models of autoimmunity, including systemic lupus erythematosus and myasthenia gravis [8, 9]. A poor therapeutic response and intolerance to the usual immunosuppressive agents led to the use of leflunomide in our patient. A convincing improvement of his disease without concurrent corticosteroid therapy was a satisfactory result.

In the case described here, a favourable response to leflunomide in a patient with otherwise rather refractory sarcoidosis suggests that leflunomide may prove to be a safe and effective alternative to currently accepted therapies for sarcoidosis. Results in this initial case suggest that further clinical trials to establish the efficacy of leflunomide in the treatment of sarcoidosis are warranted.

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