Case Report

Leflunomide Induced Fevers, Thrombocytosis, and Leukocytosis in a Patient with Relapsing Polychondritis

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ABSTRACT. The most common adverse events reported with the use of leflunomide are hypertension, infections, alopecia, and various gastrointestinal complaints. No fatal adverse hematologic events have been reported in humans, although anemia and leukopenia have been described in animals receiving 20 mg/kg/day. We describe a patient with relapsing polychondritis, in whom treatment failure with glucocorticoids, methotrexate, hydroxychloroquine, and azathioprine led to the institution of therapy with leflunomide at a maintenance dose of 20 mg/day. Two months after the dose of leflunomide had been increased to 30 mg daily, the patient developed high fevers, photophobia, thrombocytosis, and leukocytosis that returned to normal following treatment with cholestyramine and discontinuation of leflunomide. Rechallenge with leflunomide was not attempted and the syndrome did not recur during 14 month followup. (J Rheumatol 2002;29:192–4)

Key Indexing Terms:
LEFLUNOMIDE ADVERSE DRUG REACTION LEUKOCYTOSIS
THROMBOCYTOSIS FEVER RELAPSING POLYCHONDRITIS

Leflunomide is classified as a disease modifying antirheumatic drug (DMARD). It was approved by the FDA in September 1998 for treatment of rheumatoid arthritis (RA) and is an orally administered pyrimidine synthesis inhibitor that is available in 10, 20, or 100 mg tablets. Its immunomodulatory activity comes from its ability to inhibit dihydroorotate dehydrogenase. It also interferes with the phosphorylation of tyrosine kinase[1], and thereby interferes with signal transduction pathways[2]. Its antiinflammatory effects have been documented in one and 2 year studies in RA[3-5].

Leflunomide is metabolized into an active metabolite (A77 1726)[1,6] that is responsible for virtually all its clinical activity. Serum levels peak between 6 and 12 hours after administration. The drug has a long half-life of up to 2 weeks. To reach a steady state quickly, a loading dose of 100 mg/day is given for 3 days. Leflunomide and its metabolites are metabolized in the liver and gastrointestinal tract by an unspecified mechanism. Leflunomide is eliminated by renal (43%) and direct biliary (48%) excretion. Due to the long half-life, cholestyramine (8 g TID for 11 days) may be used to accelerate elimination. Without cholestyramine, it may take up to 2 years to reduce the active metabolite to levels of less than 0.02 mg/l[1].

Relapsing polychondritis is a systemic inflammatory condition first reported by Jaksch-Wartenhorst in 1923[7]. The term relapsing polychondritis was first used in 1960 by Pearson, *et al*, describing 2 cases[8]. The diagnosis is based on the presence of 3 of 6 criteria[9]. Relapsing polychondritis has also been seen in association with various other autoimmune disorders[10-12].

The most common adverse events reported with the use of leflunomide are hypertension, infections, alopecia, and various gastrointestinal complaints[5]. No fatal adverse hematologic events have been reported in humans, although anemia and leukopenia have been described in animals receiving 20 mg/kg/day[13]. We report an adverse drug reaction to leflunomide used in the treatment of refractory relapsing polychondritis.

CASE REPORT

A 50-year-old Caucasian man was diagnosed with relapsing polychondritis in December 1999 based on characteristic symmetrical auricular and nasal cartilage inflammation, decreased hearing acuity, and 2 weeks of polyarthritis. The auricular and nasal inflammation was characterized by erythema, warmth, swelling, and tenderness that developed spontaneously. He had been treated initially with prednisone, which led to the resolution of the polyarthritis. However, satisfactory control of the nasal and auricular symptoms was not achieved and various dosages of prednisone, plaquenil, imuran, and finally methotrexate (MTX) were required. Because of the failure to control the painful, tender erythematous nasal and auricular cartilages with the combination of 20 mg prednisone daily and MTX, MTX was discontinued in May 2000, and leflunomide 100 mg/day was initiated for a 3 day load followed by 20 mg daily. Significant but incomplete resolution of the signs and symptoms were observed after one month of therapy. In an attempt to achieve a more complete suppression of the symptoms the dose was increased to 30 mg daily.

One month later in July 2000 the patient developed daily fevers to 103°F associated with photophobia and a burning sensation of his face and eyes. A suspected sinusitis was treated with levofloxacin 500 mg daily for 6 days. Meanwhile, the prednisone taper was continued and the leflunomide dose was

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maintained at 30 mg/day. Ocular steroids were prescribed but ENT evaluation and computerized tomographic (CT) scan of the sinuses failed to document sinusitis. During the same time period, platelet, C-reactive protein (CRP), and leukocyte counts rose steadily while the hematocrit fell (Figure 1). Levofloxacin and leflunomide were discontinued, cholestyramine was administered, and prednisone was increased to 20 mg BID. CRP (normal 0–4.9) rose from 11.4 on May 23, 2000 to 426 on July 18. Other serum tests were normal, including liver function and basic chemistries. Hematologic evaluation included a bone marrow aspiration. The marrow was found to be hypercellular and all elements normally found were appropriately represented.

By mid-August, one month after discontinuation of leflunomide the patient became symptom-free and the hematologic abnormalities normalized. However, ear and nasal cartilage inflammation recurred in September 2000 and treatment was initiated with etanercept 25 mg twice weekly and risedronate sodium 30 mg once weekly. The dose of prednisone was tapered. In October, symptoms of mild ear tenderness, swelling, and erythema began to increase. MTX was added to the above regimen at a dose of 12.5 mg/week. His symptoms remained limited and less severe.

Since October 2000, the signs and symptoms of polychondritis have been mild and there has been no recurrence of fever. The prednisone dose was tapered to 15 mg/day in January 2001. At that time MTX was increased to 15 mg/week as a steroid sparing measure. Etanercept was continued at 25 mg SQ twice a week. In early February, a moderate flare of cartilaginous symptoms and blurred vision required an increase in prednisone to 40 mg/day. The symptoms resolved over the following 3 weeks and the prednisone dose was reduced to 30 mg/day by March and to 17.5 mg daily when last examined in August 2001.

DISCUSSION

We describe a serious hematologic adverse event attributable to leflunomide that has not been reported previously in humans. An English language search of the Medline revealed no reports of leflunomide induced or associated thrombocytosis/leukocytosis. A prior study of leflunomide[14] described fever in patients with advanced solid malignancies at dosages ranging between 15 and 443 mg/m^2. In animal studies, hematologic abnormalities have been reported, but in higher doses (20 mg/kg/day) than the dose used in human subjects.

We believe that the temporal relationships described in our case report between the increased dose of leflunominde and the occurrence of fever, photophobia, leukocytosis, and thrombocytosis is compelling evidence of a causative association of leflunomide and the clinical syndrome. The immediate reduction of fever and photophobia and the return to normal of the hematological abnormalities in conjunction with the discontinuation of leflunomide and treatment with cholestyramine leads us to conclude that the events were linked to the use of leflunomide and were dose related.

Although an infection cannot be excluded with certainty, an infectious process could not be identified clinically or with a CT scan of the sinuses. The syndrome showed no signs of response to treatment with levofloxacin and the hematologic evaluation that included a bone marrow aspiration biopsy was interpreted as being a reactive marrow.

Accordingly, we believe clinicians should be alerted to the syndrome reported here. Careful dosing and periodic monitoring of patients treated with leflunomide are recommended.

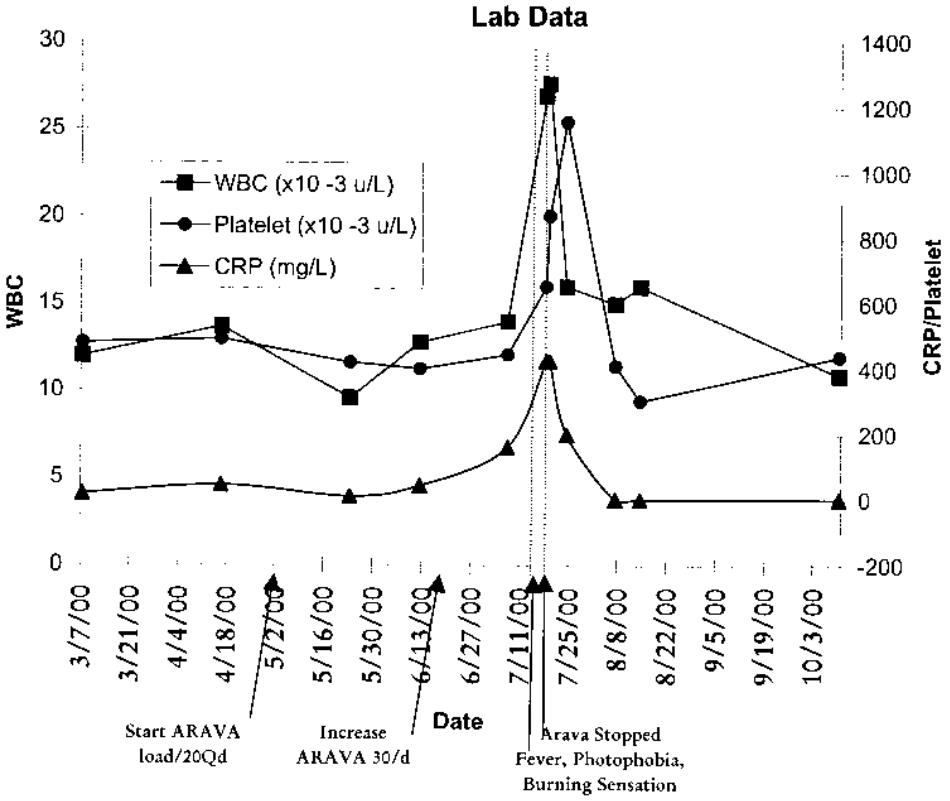

Figure 1. Platelet, CRP and leukocyte measures at start and withdrawal of leflunomide (Arava) therapy.

This is especially important where leflunomide is used in the treatment of conditions or diseases for which it has not been specifically approved by drug regulatory agencies such as the US Food and Drug Administration (FDA), and at doses not currently used for the treatment of RA. RA is at present the only condition for which leflunomide is FDA approved and its efficacy has been adequately documented.

Interestingly, despite the adverse reaction, our patient had a clinically significant reduction in the clinical signs and symptoms of the polychondritis while taking leflunomide. Thus further evaluation of this agent for this condition would appear to be appropriate.

REFERENCES

1. Product information: Arava™, leflunomide. Kansas City: Aventis, Inc.; 2000.
2. Kraan M, Reece R, Barg E. Modulation of inflammation and metalloproteinase expression in synovial tissue by leflunomide and methotrexate in patients with active rheumatoid arthritis: Findings in a prospective, randomized, double-blind, parallel design clinical trial in 39 patients at two centers. Arthritis Rheum 2000;43:1820-30.
3. Emery P, Breedveld FC, Lemmel EM. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. Rheumatology 2000;39:655-65.
4. Smolen JS, Kalden JR, Scott DL. Efficacy and safety of leflunomide compared with placebo and sulfasalazine in active rheumatoid arthritis: a double-blind, randomized multi-center trial. European Leflunomide Study Group. Lancet 1999;353:259-66.
5. Strand V, Cohen S, Schiff M. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Arch Intern Med 1999;159:2542-50.
6. Chong A, Huang W, Liu W. In vivo activity of leflunomide: Pharmacokinetic analyses and mechanism of immunosuppression. Transplantation 1999;68:100-9.
7. Jaksch-Wartenhorst R. Polychondropathia. Wien Arch Med 1923; 6:93-100.
8. Pearson CM, Kline HM, Newcomer VD. Relapsing polychondritis. N Engl J Med 1960;263:51-8.
9. McAdam LP, O'Hanlan MA, Bluestone R. Relapsing polychondritis: Prospective study of 23 patients and a review of the literature. Medicine 1976;55:193-215.
10. Tishler M, Caspi D, Yaron M. Classical rheumatoid arthritis associated with nondeforming relapsing polychondritis. J Rheumatol 1987;14:367-8.
11. Hager MH, Moore ME. Relapsing polychondritis syndrome associated with pustular psoriasis, spondylitis and arthritis mutilans. J Rheumatol 1987;14:162-4.
12. Michet CJ. Vasculitis and relapsing polychondritis. Rheum Dis Clin North Am 1990;16:441-4.
13. Yuh DD, Gandy KL, Morris RE, et al. Leflunomide prolongs pulmonary allograft and xenograft survival. I. J Heart Lung Transplant 1995;14:1136-44.
14. Eckhardt SG, Rizzo J, Sweeney KR, et al. Phase I and pharmacologic study of the tyrosine kinase inhibitor SU101 in patients with advanced solid tumors. J Clin Oncol 1999;17:1095-104.