Case Report

Treatment of Felty's Syndrome with Leflunomide

FREDERICK TALIP, NANCY WALKER, WASEEM KHAN, and BERNARD ZIMMERMANN

ABSTRACT. Felty's syndrome (FS) is a rare manifestation of severe rheumatoid arthritis (RA). It is an immune mediated inflammatory process, usually treated with standard disease modifying antirheumatic drugs. We describe a case of severe FS that developed in a patient receiving methotrexate therapy for RA. Treatment with etanercept resulted in severe allergic cutaneous reactions. The patient subsequently responded to treatment with leflunomide. The response included dramatic improvement of leukopenia and neutropenia as well as excellent control of his arthritis. Leflunomide has recently been used effectively for the treatment of RA and may be useful for the management of patients with FS. (J Rheumatol 2001;28:868–70)

Key Indexing Terms:
FELTY'S SYNDROME RHEUMATOID ARTHRITIS LEFLUNOMIDE

Patients with severe rheumatoid arthritis (RA) may develop extraarticular manifestations of neutropenia, splenomegaly, and leg ulcers, which is called Felty's syndrome (FS). There appear to be multiple factors involved in the predisposition to FS. The pathogenetic mechanisms of neutropenia in FS are not clearly understood, but probably involve multiple abnormalities of white blood cell kinetics as well as interaction of immune complexes, antineutrophil antibodies, cytokines, and growth factors. Patients with FS are at increased risk for infection, especially if the neutropenia is severe. Medical therapies for FS including corticosteroids, gold, methotrexate, and recombinant human granulocyte colony stimulating factors have been reported, with variable results. Splenectomy has been advocated by some, but recurrent neutropenia and infections are common after splenectomy.

We describe a patient with severe RA and profound neutropenia due to FS. Treatment with leflunomide resulted in dramatic improvement in his white blood cell count, absolute neutrophil count, and the articular manifestations of his RA. The pathogenesis of FS is reviewed and reports regarding therapy for FS are discussed. We are not aware of previous reports of the use of leflunomide for treatment of FS.

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CASE REPORT

A 58-year-old white man with a 26 year history of seropositive nodular RA presented to the Providence Veterans Affairs Medical Center Rheumatology Clinic in October 1998 for routine followup. He was noted to have cutaneous ulcers on his anterior tibial surfaces and splenomegaly. Complete blood count showed white blood cells (WBC) 1500/mm^3 (neutrophils = 9, lymphocytes = 65, monocytes = 26) and absolute neutrophil count (ANC) of 145/mm^3. No large granular lymphocytes were seen. A diagnosis of FS was made based on the findings of leukopenia with neutropenia, splenomegaly, and leg ulcers in a patient with longstanding RA. He had received several disease modifying antirheumatic drugs (DMARD) including hydroxychloroquine and parenteral gold, which resulted in transient leukopenia and thrombocytopenia. He was maintained on weekly methotrexate (MTX) up to 15 mg for 5 years prior to development of leukopenia and 10–15 mg daily prednisone. At the time of his visit, MTX was discontinued due to leukopenia and neutropenia. Leucovorin was given, without improvement. He was treated with recombinant human granulocyte colony stimulating factor (rG-CSF) when his ANC was 32/mm^3, with transient response. Etanercept (Enbrel; Immunex, USA) was given for 5 doses but was discontinued because of large erythematous pruritic rashes at the injection sites. There was no significant improvement in his neutropenia after 2 weeks of etanercept therapy.

He was prescribed leflunomide (Arava; Aventis Pharmaceuticals, USA) starting in September 1999. His ANC was 272/mm^3 and WBC count 1700/mm^3 prior to initiation of leflunomide therapy. The usual loading dose (100 mg/day orally for 3 days) was given and treatment was continued with 10 mg daily. Serial ANC and WBC counts were noted to increase gradually over the next 6 months (Figure 1). Improvement of his pain and morning joint stiffness was noted and his leg ulcers gradually healed. After 175 days of leflunomide treatment, ANC was 1602/mm^3 and WBC count was 3000/mm^3. Prednisone was tapered and discontinued.

DISCUSSION

Felty's syndrome is a well recognized but uncommon complication of RA. This syndrome was first described by Augustus Felty in 1924, who noted "5 cases, strikingly similar in their essential features, presenting an unusual but unmistakable clinical picture, characterized by arthritis, splenomegaly, and leucopenia"[1]. Although the classic triad of FS comprises its diagnostic criteria, it has also been associated with severe joint disease and extraarticular features of

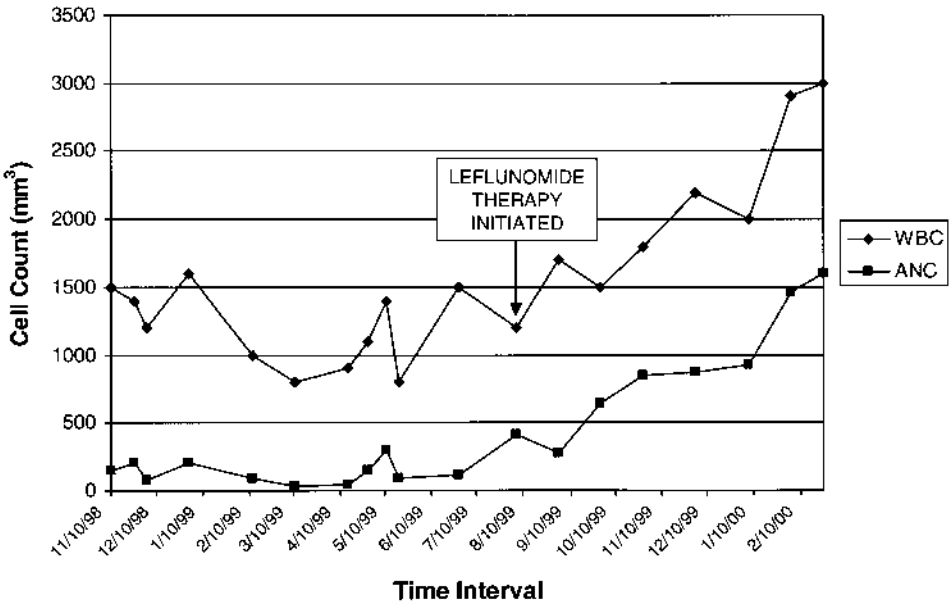

Figure 1. White blood cell count (WBC) and absolute neutrophil count (ANC) over time show response to initiation of leflunomide therapy.

RA including vasculitis, Sjögren's syndrome, cutaneous ulcers, rheumatoid nodules, and lymphadenopathy[2]. It is estimated that FS occurs in 1–4% of patients with RA[2,3]. Sixty to seventy percent of patients are women. One review of reported cases found a mean age of onset of 55–65 years, with 10–15 years' duration of arthritis before the onset of leukopenia and splenomegaly[3]. The decreased WBC count characteristically found in FS is attributed mainly to immune mediated neutropenia. High occurrences of both major and minor infections are reported in FS. The most important factor influencing the risk of infection appears to be the degree of neutropenia. Absolute neutrophil counts below $0.1 \times 10^3/mm^3$ have been associated with an increased incidence of infections[4]. Sepsis was shown to be the major cause of death in 25% of patients with FS in one study[5].

Several pathophysiologic mechanisms for the neutropenia of FS have been proposed, involving both humoral and cellular immune mechanisms. Defective granulopoiesis and excessive margination of neutrophils have been described in FS[3]. The presence of antineutrophil antibodies has also been shown[6]. However, current evidence mainly supports the role of neutrophil bound and neutrophil ingested immune complexes causing increased splenic sequestration or peripheral destruction of neutrophils[3,7]. It is still debated whether neutrophil dysfunction plays a role in the occurrence of infections in FS[8]. Systemic immunosuppressive treatment is considered the most appropriate form of therapy for FS, but it is not extremely effective. High dose corticosteroid therapy may elevate the peripheral WBC count, but this effect is not maintained when the steroid dose is reduced. Parenteral gold has been reported to be useful therapy for FS in retrospective studies[9]. Several case reports observed that low dose methotrexate (MTX) may improve the neutropenia of FS[10-12]. Cyclophosphamide has been utilized in patients refractory to other DMARD but should be used cautiously due to its potential for serious side effects. The use of recombinant granulocyte colony stimulating factor (rG-CSF) has also been shown to be effective[13-15]. Therapy with rG-CSF has been reported to be useful during acute infections, but cost and side effects limit its longterm use. Splenectomy does improve neutropenia but has little effect on the incidence of infection[2]. Neutropenia improves postsplenectomy in up to 80% of patients after 6 months of followup. However, there is a 12% incidence of fatal infections after splenectomy regardless of hematologic response and there is an inherent risk from the procedure itself[16]. Traditional therapy for FS has focused on treatment of the underlying disease. A more fundamental understanding of the pathogenesis of RA has allowed the development of more focused therapies. It is likely that these newer treatments will also be effective for extraarticular manifestations of the disease.

Etanercept is a tumor necrosis factor (TNF) receptor fusion protein that binds and neutralizes circulating TNF and reduces its availability to stimulate the immunoinflammatory cascade. In randomized double blind studies of RA, treatment with etanercept resulted in statistically significant improvement in American College of Rheumatology criteria compared to placebo after 3 and 6 months[17,18]. We could

find no report of attempts to treat FS with etanercept. Our patient had severe cutaneous allergic reaction to the drug, presumably unrelated to his FS.

Leflunomide is an immunoregulatory drug that is believed to cause G1 phase arrest in the cell cycle of autoimmune lymphocytes by inhibiting uridine monophosphate synthesis as well as preventing *in vitro* proliferation of T cells. It has been shown to be effective in an array of autoimmune animal models including adjuvant and collagen arthritis[19]. To date, a small number of studies have described its benefit for use in RA, including improvement in clinical measures of inflammation, function, and health related quality of life[20,21]. Combination therapy with MTX and leflunomide in RA has also been shown to be effective without significant drug interactions[22].

Clinical observations of patients with RA treated with leflunomide indicate that it provides antirheumatic activity at doses that are not associated with significant leukopenia, thrombocytopenia, or mucositis. This implies a preferential inhibitory effect of leflunomide on autoimmune lymphocytes rather than on continuously dividing cells of hematopoietic lineage and gastrointestinal tract[19]. A randomized placebo controlled phase 2 study on the safety and effectiveness of leflunomide in treatment of active RA showed no incidence of leukopenia or neutropenia[23]. The ability of this drug to effect immunoregulation without significant depression of hematopoietic cells suggested to us that it may be reasonable to use in the treatment of FS.

Our patient's dramatic recovery of WBC and ANC coupled with improvement of his arthritis while taking leflunomide indicates an overall clinical improvement of his disease. He has had 6 months of leflunomide therapy without side effects and has been able to discontinue prednisone. His leg ulcers have completely resolved and he has had no further infection except a transient bronchitis. This experience suggests that leflunomide may be a useful therapeutic agent in patients with severe FS.

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