Leflunomide-Associated Infections in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine the prevalence of severe infections in patients with rheumatoid arthritis (RA) prescribed leflunomide in North Canterbury, New Zealand.

Methods. A casenote audit of all Christchurch Hospital patients with RA prescribed leflunomide between 2002 and 2006 was performed. The criterion for severe infection was inpatient hospitalization. Relevant reports to the national Pharmacovigilance Centre were also examined.

Results. Since January 2002, 171 patients with RA have commenced taking leflunomide. Ninety-nine of 171 (57.9%) patients were also prescribed prednisone. Combination disease modifying antirheumatic drug therapy was common, with 82/171 (48.0%) taking methotrexate (MTX), 15/171 (8.8%) hydroxychloroquine, 11/171 (6.4%) sulfasalazine, and 8/171 (4.7%) anti-tumor necrosis factor therapy. Eleven patients developed infection requiring hospitalization while taking leflunomide including: lower respiratory tract infections (3), cellulitis (2), disseminated herpes zoster (2), probable TB liver (1), abdominal sepsis (1), mycotic aneurysm (1) and gastroenteritis (1). Nine of the 11 patients were also taking corticosteroids or corticosteroids with MTX. The 171 patients were treated for a total of 4005 months, giving an incidence for severe infection of 3.30/100 patient-years (95% CI 1.65–5.90). Patients at increased risk were those with severe disease and taking concomitant MTX and corticosteroids. The NZ Pharmacovigilance Centre has received 7 additional reports of severe infections in patients with RA taking leflunomide. Reported cases include probable pulmonary TB (1), pneumocystis pneumonia (1), other pulmonary infection (2), and septicemia (3) including a case of infective endocarditis. Four occurred in combination with MTX, one with adalimumab. All 5 patients were also taking corticosteroids.

Conclusion. We believe this observed rate of serious infection is acceptable in the context of optimally treating active RA. Patients with severe disease and taking combination MTX and corticosteroids are at greatest risk. In our experience, once established, infections may rapidly progress in patients with RA taking leflunomide, and early cholestyramine washout is strongly recommended. (First Release Oct 15 2007; J Rheumatol 2007;34:2201-3)

Key Indexing Terms:
RHEUMATOID ARTHRITIS LEFLUNOMIDE INFECTION

Due to lack of central government funding for biological therapies in rheumatoid arthritis (RA) [our only available anti-tumor necrosis factor (TNF) therapy, adalimumab, was not funded until January 2006], RA treatment in New Zealand has relied on disease modifying antirheumatic drug (DMARD) therapy, frequently in combination with other DMARD and with corticosteroids. Although registered in NZ in 2000 for the treatment of RA, leflunomide was rarely used until 2002 following government funding. We report our experience of leflunomide-associated infections requiring hospitalization in RA from 2002 to 2006. Three cases of serious infection in patients taking leflunomide are described, together with our local audit and a summary of national reports.

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MATERIALS AND METHODS

A casenote audit of all Christchurch Hospital patients with RA prescribed leflunomide between 2002 and 2006 was performed. The criterion for severe infection was inpatient hospitalization. Relevant reports to the NZ Pharmacovigilance Centre, the national center for assessing voluntary adverse reaction reports, were also examined.

RESULTS

Cases

Patient 1. A 69-year-old man with stable RA presented with a 2 month history of anorexia, 10 kg weight loss, fever, and night sweats. He had been taking leflunomide 20 mg daily as

monotherapy for 31 months. On examination he was febrile 38°C but had no localizing signs of infection. Investigations revealed elevated C-reactive protein (CRP) 108 mg/l and mildly deranged liver function tests. He was extensively investigated for underlying infection and malignancy, including blood and urine cultures, cytomegalovirus, Epstein-Barr virus and HIV serology, chest radiograph, echocardiogram, and computerized tomography (CT) of the abdomen. These investigations were normal or negative, except the abdominal CT scan, which revealed multiple low attenuation lesions in the liver. Initial liver biopsy was nondiagnostic, revealing only minor changes with no evidence of infection, autoimmune hepatitis, malignancy, or leflunomide toxicity. Because of a high index of clinical suspicion he proceeded to a second liver biopsy, which showed numerous foci of necrotizing caseating granulomatous inflammation highly suspicious of mycobacterial infection. Although *Mycobacterium tuberculosis* culture was negative, due to strong clinical suspicion he was prescribed empiric antituberculous therapy. His condition improved dramatically over subsequent weeks, with resolution of fever and normalization of CRP. At 18 months' review he remains well taking prednisone monotherapy. Although culture negative, a diagnosis of probable mycobacterial infection was made on the basis of typical histological findings on liver biopsy, exclusion of other pathology and prompt response to anti-tuberculous therapy.

Patient 2. A 58-year-old woman with longstanding RA, who was taking leflunomide 20 mg/day and prednisone 5 mg/day, presented with a one day history of abdominal pain. She had a background of a perforated diverticulum 8 years previously for which she had undergone resection of the left colon with end-colostomy formation. At presentation she was febrile, with tenderness and erythema surrounding the stoma. CT scan revealed a parastomal collection and stomach perforation. She proceeded to surgery for drainage of the collection and repair of the perforation. The leflunomide was subsequently stopped and cholestyramine washout given. She required a prolonged hospital stay, with intravenous (IV) antibiotics and total parenteral nutrition.

Patient 3. A 61-year-old woman with severe RA taking leflunomide 20 mg alternate days and prednisone 10 mg/day presented with cellulitis of the left foot not responding to oral amoxycillin/clavulinic acid. *Staphylococcus aureus* was isolated from a plantar ulcer. Despite appropriate IV antibiotic therapy the infection progressed rapidly and she developed necrosis of the left foot. She proceeded to surgical debridement with forefoot amputation and skin graft. On Day 4 of admission, leflunomide was discontinued and cholestyramine washout administered. She had a prolonged hospital stay requiring 5 further debridement procedures.

Local audit

The Christchurch Hospital Rheumatology Department has a catchment population of approximately 450,000. Since January 2002, 171 patients with RA have commenced taking leflunomide with an average dose of 16.8 mg/day (range 5–20 mg). Of these 171 patients, 99 (57.9%) were also prescribed prednisone. Combination DMARD therapy was common, with 82/171 (48.0%) taking methotrexate (MTX), 15/171 (8.8%) hydroxychloroquine, 11/171 (6.4%) sulfasalazine, 8/171 (4.7%) anti-TNF therapy, and 3/171 (1.8%) IM gold.

The mean duration of leflunomide therapy was 23.4 months. Seventy-one patients ceased treatment due to lack of efficacy (13), diarrhea (14), infection (9), abnormal liver function tests (7), nausea (6), hypertension (4), rash (3), neutropenia (2), pneumonitis (2), entering a TNF study (1), leg ulcers (1), mouth ulcers (1), and planned pregnancy (1). In 7 patients the reason for stopping leflunomide was unclear from the clinical records.

Eleven patients developed infection requiring hospitalization while taking leflunomide (Table 1). The 171 patients were treated for a total of 4005 months, giving an incidence for severe infection of 3.30/100 patient-years (95% confidence interval 1.65–5.90).

New Zealand reports

The NZ Pharmacovigilance Centre has received 7 additional reports of severe infections in patients with RA taking leflunomide. Reported cases include probable pulmonary tuberculosis, septicemia (3 cases including 1 with infective endocarditis), and lower respiratory tract infection (3 cases including pneumocystis carinii). Four of 7 cases occurred in combination with MTX, 1 with adalimumab, and 2 with leflunomide monotherapy. Five patients were also taking corticosteroids. Two patients with septicemia (1 with infective endocarditis) died, and a further patient with lower respiratory infection subsequently died although the cause of death was attributed to diabetes mellitus complications.

DISCUSSION

It is generally accepted that patients with RA have a higher risk of infection, in particular those with more active disease and other comorbidities[1]. Interest in infectious risk has been heightened by the advent of anti-TNF therapy. Our local audit of serious infections with leflunomide has shown a similar rate (3.3 cf. 4.1/100 patient-yrs) to that of a recent UK register comparing DMARD and anti-TNF-treated patients[2]. Although earlier studies have shown minimal increased infectious risk with standard DMARD, relatively few patients were taking leflunomide[3,4]. More recent case reports have documented leflunomide–associated infections in RA[5,6]. It is likely that a number of serious infections are not noted by the NZ Pharmacovigilance Centre, which relies on voluntary reporting.

Our audit does not prove a cause and effect relationship between leflunomide and serious infection. It has highlighted an association and it is likely that other factors including RA disease activity and severity, other comorbidities, and combination therapy with DMARD, particularly MTX and cortico-

Table 1. Severe infections in patients with RA taking leflunomide.

Patient Sex/age(yrs)	Leflunomide Dose, mg/day	Other DMARD	Prednisone (Y/N)	Infection
M/69	20	—	N	Probable liver TB
F/58	20	—	Y	Abdominal sepsis
F/61	20	—	Y	Cellulitis with local necrosis
F/64	20	MTX	Y	Mycotic aneurysm
F/54	20	MTX	Y	Disseminated herpes zoster
M/34	20	MTX	Y	Bronchitis
F/73	20	—	Y	Gastroenteritis
F/55	10	MTX	Y	Pneumonia
F/68	20	—	N	Cellulitis
M/65	10	MTX	Y	Infected lung bullae
F/76	20	—	Y	Disseminated herpes zoster

RA: rheumatoid arthritis; DMARD: disease modifying antirheumatic drugs; TB: tuberculosis; MTX: methotrexate.

steroids, substantially increase this risk. Our use of leflunomide and MTX in combination is relatively high in view of known side effects with this combination including hepatotoxicity. This reflects lack of access to alternative (i.e., biological) therapies, and will likely continue, as funding of these agents is restricted to patients who prove intolerant or refractory to DMARD combinations including leflunomide and MTX. We believe the locally observed rate of serious infection is acceptable in the context of optimally treating active RA. However, it has been our experience that once established, infections may progress rapidly in patients with RA taking leflunomide and early cholestyramine washout is strongly recommended.

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