ARTHRITIS & RHEUMATISM
Vol. 44, No. 5, May 2001, pp 1048–1051

Published by Wiley-Liss, Inc.

Leflunomide-Associated Weight Loss in Rheumatoid Arthritis

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Objective. **To determine the frequency of weight loss in patients treated with leflunomide for rheumatoid arthritis at an arthritis referral center.**

Methods. **We queried 35 rheumatologists at the Robert Breck Brigham Arthritis Center to determine if weight loss had occurred as an adverse event in patients treated with leflunomide between November 1998 and January 2000. Five such patients were identified and their clinical course was reviewed.**

Results. **Five of 70 patients who had begun leflunomide therapy had significant weight loss that could not be linked to other identifiable etiologies. The amount of weight loss was substantial in this group of patients, ranging from 19 pounds to 53 pounds. All patients had normal levels of thyroid-stimulating hormone and no other gastrointestinal complaints; evaluation revealed no other cause for the weight loss. Despite the significant weight loss, 4 of the 5 patients continued to take the drug due to its efficacy.**

Conclusion. **Significant weight loss is a potential adverse event in patients with rheumatoid arthritis treated with leflunomide. Awareness of this may obviate the need for extensive medical evaluations.**

Current treatment for rheumatoid arthritis (RA) involves multiple therapies, including nonsteroidal antiinflammatory drugs, corticosteroids, and traditional therapies such as hydroxychloroquine, sulfasalazine, gold salt therapy, and methotrexate (1–3). In the past 2 years, newer therapies have been approved for the treatment of RA, including leflunomide, etanercept, and infliximab. These newer therapies, while very successful, may be associated with side effects that were not entirely appreciated during initial studies. We herein describe 5 cases in which patients had significant weight loss associated with leflunomide therapy, and not associated with other comorbid conditions.

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Submitted for publication May 25, 2000; accepted in revised form January 4, 2001.

PATIENTS AND METHODS

We surveyed via e-mail 35 rheumatologists in the Robert Breck Brigham Arthritis Center to see if clinically significant weight loss was an adverse event of leflunomide treatment for RA. The rationale for this query was that one of the authors (JSC) noted significant weight loss in some of his leflunomide-treated patients. Seventy patients were started on leflunomide regimens between November 1998 and January 2000, and in 5 patients, substantial weight loss was observed. All 70 RA patients in whom leflunomide treatment was initiated were given loading doses from the samples supplied, and their names were recorded. All 5 patients with significant weight loss were treated with leflunomide at a dosage of 100 mg daily for 3 days, followed by 20 mg daily. After identification of patients, medical records were reviewed to ascertain if there were other associated etiologies for the weight loss and what investigations had been undertaken, if any, to ascertain the cause for the weight reduction. All patient records were reviewed for followup after identification of the weight reduction, clinical response to therapy, and whether the patients continued the leflunomide therapy.

RESULTS

The ages of the 5 patients with leflunomide-associated weight loss ranged from 54 years to 77 years. Four of the 5 patients were female. The duration of RA ranged from 6 years to 30 years. The amount of weight loss ranged from 19 pounds to 53 pounds, and this was a 14–26% reduction from baseline. The body mass index significantly fell in all patients. Thyroid-stimulating hormone levels were normal and albumin levels were normal to minimally abnormal in all patients (Table 1).

CASE REPORTS

Patient 1 is a 77-year-old man whose seropositive RA has persisted for >30 years. Prior treatment with disease-modifying antirheumatic drugs (DMARDs) included gold salts, methotrexate, azathioprine, hydroxy-

Table 1. Clinical features of the 5 patients with leflunomide-associated weight loss*

Patient/age/sex	RA duration, years	Pre-leflunomide weight (pounds)/ BMI (kg/m^2)	Post-leflunomide weight (pounds)/ BMI (kg/m^2)	% reduction in weight	Albumin, gm/dl†	TSH, μU/ml‡
1/77/M	30	185/27.5	154/22.9	17	3.7	2.76
2/59/F	8	137/25.3	117/21.5	15	3.9	4.6
3/60/F	20	135/22.5	116/18.4	14	4.4	3.24
4/54/F	6	161/27.8	124/21.4	23	3.5	2.2
5/58/F	20	202/33.7	149/24.9	26	3.6	1.2

* RA = rheumatoid arthritis; BMI = body mass index; TSH = thyroid-stimulating hormone.
† Values at maximum weight loss evaluations. Normal 3.7–5.4 gm/dl.
‡ Values at maximum weight loss evaluations. Normal 0.5–5.0 μU/ml.

chloroquine, sulfasalazine, and demeclocycline. On November 13, 1999, leflunomide therapy was started, at which time his weight was 185 pounds. Two months later, he noted improvement, and his weight was 178 pounds. Four months after starting leflunomide therapy, his weight dropped to 168 pounds. He continued to take prednisone at $\leq$5 mg/day during this entire period of observation, and never experienced diarrhea.

An extensive medical evaluation was undertaken, which included panendoscopy, a chest radiograph, and blood studies. No etiology for his weight loss was ascertained. Leflunomide was stopped when his weight dropped to 154 pounds, a loss of 31 pounds. Etanercept was begun, and his weight has remained stable at 154 pounds.

Patient 2 is a 59-year-old woman with an 8-year history of seropositive RA. DMARD treatment prior to initiation of leflunomide therapy included hydroxychloroquine, sulfasalazine, and methotrexate. She was not treated with corticosteroids. Her medical history was significant for ulcerative colitis, with normal results on repeated colonoscopies in the preceding 5 years. Her weight prior to initiation of leflunomide was 137 pounds. On December 3, 1998, leflunomide therapy was introduced in addition to her background medications, including levothyroxine 0.1 mg daily, celecoxib, and sulfasalazine. Three months after starting therapy, her weight decreased to 118 pounds, a loss of 19 pounds. She had no gastrointestinal complaints, including diarrhea. An extensive evaluation of her weight loss, including chest radiographs, was unremarkable. Due to the excellent response to leflunomide therapy, she elected to continue taking the drug. Her weight has stabilized at 117 pounds.

Patient 3 is a 60-year-old woman who has had seropositive RA for $>$20 years. Prior DMARD therapy included hydroxychloroquine, gold salt therapy, methotrexate, sulfasalazine, and azathioprine. On December 2, 1998, leflunomide therapy was initiated. Her weight was 135 pounds. Over the next year, her weight progressively fell to 116 pounds, a decrease of 19 pounds. She had no diarrhea, nausea, or vomiting. Extensive evaluations included panendoscopy, abdominal and pelvic computed tomography scans, and chest radiographs, with no abnormalities discovered. Her prednisone dosage remained unchanged at $\leq$10 mg/day during this period of observation. She has continued to take leflunomide because of the beneficial effect of this therapy.

Patient 4 is a 54-year-old woman with 6 years of seropositive RA, who previously was treated unsuccessfully with gold salts, hydroxychloroquine, sulfasalazine, azathioprine, and methotrexate. Her current medications included prednisone, ranging from 5 mg to 12.5 mg/day, and naproxen. Nine months prior to leflunomide therapy, the patient underwent an anterior sigmoid colon resection for diverticulitis, with an end sigmoid colostomy performed. Due to persistent synovitis, leflunomide was started in May 1999. One month after the initiation of leflunomide therapy, her weight was 161 pounds. Over the next 6 months, her weight dropped steadily to 124 pounds, a loss of 37 pounds. She described an increased loss of appetite, but there was no change in her stools. Evaluations included chest computed tomography, laboratory studies, stool guaic tests, and an upper gastrointestinal examination followed by assessment of the small bowel. The patient elected to continue taking leflunomide despite the weight loss, because of her good clinical response.

Patient 5 is a 58-year-old woman who has had RA for $\sim$20 years. Prior DMARD therapy included hydroxychloroquine, gold salts, azathioprine, and cyclosporin A. Despite ongoing therapy with methotrexate at 17.5 mg per week and 4 mg per day of prednisone, she continued to have polyarthritis. When leflunomide was started, her weight was 202 pounds. Over the next 3 months, she noticed less pain and swelling in her joints. The pred-

nisone was tapered and later discontinued entirely. She noted a reduction of weight to 149 pounds, a 53-pound weight loss. She denied having any gastrointestinal symptoms, including anorexia and diarrhea. Results of laboratory studies, including a complete blood cell count as well as assessment of liver, renal, and thyroid function, were all within normal limits. She has continued taking methotrexate and leflunomide without further weight loss.

DISCUSSION

Leflunomide is a new immunomodulatory drug approved by the Food and Drug Administration in October 1998 for the treatment of RA. It is a novel isoxazole drug that has demonstrated immunosuppressive and antiproliferative properties. Its mechanism of action differs from that of other DMARDs. It inhibits dihydroorotate dehydrogenase, an enzyme required for de novo pyrimidine synthesis, resulting in an inhibition of actively dividing lymphocytes (4–6). In a phase II randomized, placebo-controlled trial, leflunomide at a dosage of 10 mg and 25 mg once daily was shown to be significantly superior to placebo in all outcome measures (7). Its efficacy has been confirmed in phase III studies (8).

In those 2 studies, the amount of weight loss did not differ significantly from that in the placebo group (7,8). While other reports did mention weight loss as an adverse event with leflunomide therapy (9), subsequent studies have not revealed that weight loss is a prominent feature of treatment with leflunomide, used either as a single agent or in combination with methotrexate (8,10). In fact, in the package insert for leflunomide, weight loss is mentioned in an accompanying table as occurring as often as that in methotrexate-treated patients in active-controlled trials (11). In other studies, weight loss was not mentioned as a side effect of leflunomide therapy when compared with other disease-modifying drugs (12,13).

One mechanism by which leflunomide may induce weight loss may be by interfering with oxidative phosphorylation and ATP generation in the mitochondria. Dihydroorotate dehydrogenase is a flavin-linked enzyme that typically catalyzes specialized oxidoreduction that is not in the mainstream of electron transport (5). However, like other flavin-linked enzymes, it may nonspecifically inhibit the mitochodrial electron transport chain by uncoupling oxidative phosphorylation. Two other agents known to cause weight loss, fluoxetine and the newly described $\beta 3$ agonist I-755, 507, increase energy expenditure via this mechanism (14,15). Further studies are necessary to determine whether leflunomide-associated weight loss is the result of increased catabolism from inefficient ATP generation in the mitochondria.

We have presented 5 of 70 patients (7.1%) who initiated leflunomide therapy in our center and developed significant weight loss. In all of these patients, there was no explanation for the weight loss other than leflunomide therapy. Table 1 outlines the characteristics of our patient population with leflunomide-associated weight loss. The magnitude of the weight loss varied between 19 pounds and 53 pounds, resulting in a 14–26% loss of weight compared with baseline weights. None of the patients intentionally tried to lose weight. One of the patients began to gain weight once leflunomide was stopped, and the others continued to take the drug because of a favorable response to therapy.

We propose that weight loss associated with leflunomide is independent of the occurrence of diarrhea or other gastrointestinal side effects, may be related to an increased metabolic requirement, and is a more common adverse event than is currently recognized. Awareness of this side effect may obviate the need for significant investigative evaluations in those patients with RA who have had weight loss in the setting of leflunomide therapy.

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