CASE STUDY

Suppressed Wound Healing In a Patient with Rheumatoid Arthritis Taking Leflunomide (Arava)

D Miller Wise, MD

Abstract

Although patients with rheumatoid arthritis taking disease-modifying antirheumatic drugs (DMARDs) are monitored for various medication adverse events, DMARDs, and leflunomide in particular, have effects that are not observed clinically, specifically adverse effects on wound healing.

Introduction

Patients with rheumatoid arthritis (RA), while taking newer disease-modifying antirheumatic drugs (DMARDs), are examined clinically for decreases in morning stiffness, in joint swelling or tenderness, and for medication adverse effects. Unfortunately, DMARDs have adverse effects not seen clinically. I believe that DMARDs, and leflunomide (LEF) in particular, have adverse effects on wound healing.[1] When the patients with RA do not heal after surgery, a DMARD may be the cause. I report here the case of a patient with RA whose wound did not heal for three years, most likely because of LEF. Further study is needed to determine safe use of DMARDs for these patients when they undergo surgery.[2]

Case Report

A white woman, age 60 years, with RA of the back, shoulders, knees, and hands had obtained no benefit from nonsteroidal anti-inflammatory drugs, sulfasalazine (Azulfidine), methotrexate, prednisone, or hydroxychloroquine (Plaquenil), alone or combined. LEF (Arava) provided improved control of her RA.

A diagnosis of a large ovarian cyst in our patient led to a total abdominal hysterectomy by Pfannenstiel incision. The fascial repair would not heal, so a vacuum-assisted closure device was applied to her wound. However, an incisional hernia developed. During a period of 2 years, the hernia grew to 30 cm in diameter, and the fascia and skin wound would not heal, despite drainage procedures, mesh repair, mesh removal with repeated fascial repairs, or intermittent use of the vacuum device (Figure 1).

During review of medications and a search of the literature on LEF, I found reports of patients taking LEF for RA or autoimmune vasculitis who developed leg ulcers, poor wound healing, and complications[3–59] (Table 1). Furthermore, some patients' ulcers healed after LEF washout with cholestyramine.[4] A hypothesis grew: LEF is suppressing our patient's healing; stop it, wash it out, and she may heal.[4]

Data for serum LEF level were not available locally; distant results take time. It seemed imprudent to wait for data on serum level after repeated washout procedures and after the patient had lived with an enlarging hernia for more than two years. The patient and I agreed that the benefits of washouts outweighed the risks of waiting to confirm serum LEF level. I did two washouts of LEF with oral cholestyramine, each during a one-week period as described in the literature, and I scheduled a hernia repair with abdominal-wall reconstruction.[4–6]

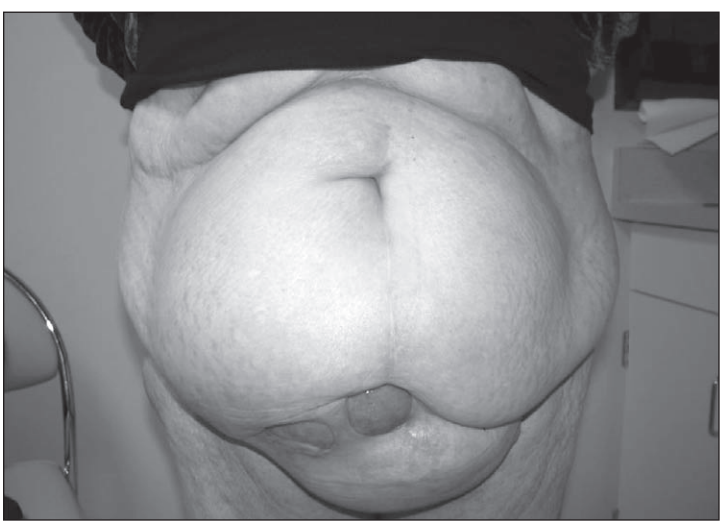

Figure 1. Appearance of wound over hernia at presentation.

D Miller Wise, MD, is a Plastic Surgeon at the Walnut Creek Medical Center in California. E-mail: david.m.wise@kp.org.

Within 10 days of the first washout, empiric evidence of healing appeared: The lower wound bled for the first time in 2 years, the granulation tissue was redder and thicker, and the lower epithelial wound border advanced 1 cm.

At surgery, the chronic wound was peeled off the bowel, and then the hernia was reduced with no enterotomies. Poorly vascularized abdominal skin was removed. We placed a single-layer underlay of AlloDerm acellular dermal matrix, with the reticular dermal side up against the peritoneum and musculofascial layer.[47–50] The AlloDerm was sutured under tension to the laterally pulling oblique muscles, taking tension off the midline closure. The rectus abdominis muscles and fascia were closed in the midline under mild tension, with no change in pulmonary compliance. Skin and subcutaneous tissue were closed without tension over suction drains.

After surgery we observed no loss of pulmonary domain, no oxygen desaturation, no supplemental oxygen need, early ambulation, no infection, no dehiscence, and no ileus. Within six months, the patient remained healed until, after minor activity, she felt a tearing in the pubic area and presented with a new suprapubic hernia.

Protein and iron stores, hemoglobin level, and hematocrit were all normal. Because LEF has been reported to leech out of bone and other tissues for up to two years after stopping the drug, and because of our empirical experience with healing during the first washouts, I elected to repeat cholestyramine washout two times, and then to repair the hernia.

During surgery, I found that the first AlloDerm repair was intact and reperitonealized with no adhesions. The new tear was several inches caudal to the AlloDerm at the rectus origin from the symphysis pubis. The repopulated AlloDerm was stronger than the rectus origin from bone. I created an underlay of another piece of AlloDerm secured into the symphysis periosteum and caudal rectus fascia, and then closed the musculofascial layer over the AlloDerm. The patient healed rapidly and has remained healed for five years (Figure 2). Unfortunately, hydroxychloroquine, etanercept (Enbrel), and newer DMARDs are now used for her severe RA.

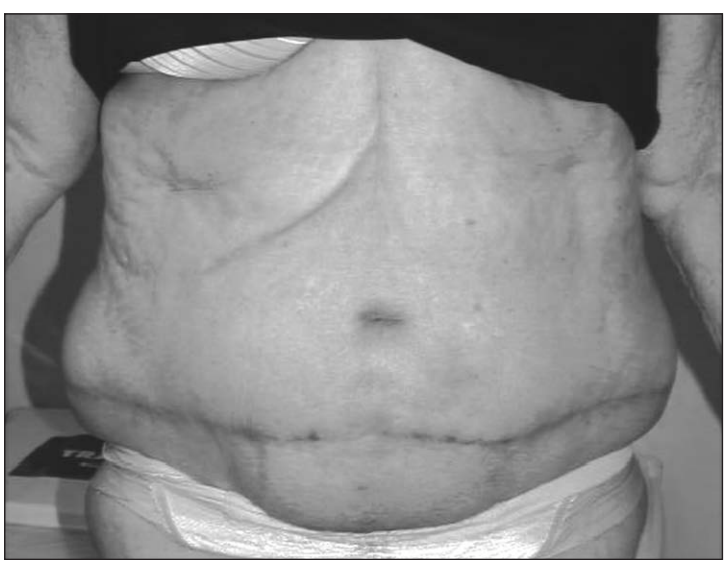

Figure 2. After surgery, the patient remained healed.

Table 1: Reported adverse effects of leflunomide (Arava)

Hematologic
Leucopenia[59]
Anemia[59]
Pancytopenia[9,59]
Fever, thrombocytosis, leukocytosis, and relapsing polychondritis[10]
Potentiation of warfarin[11]
Dermatologic
"Skin disorder"[59]
Skin discoloration[59]
Maculopapular rash[59]
Skin ulcers[4–6,59]
Alopecia areata[12]
Erythema multiforme[13]
Exfoliative dermatitis[14]
Lichenoid eruptions[15,16]
Cutaneous lupus erythematosus[17–20]
Dermatomyositis[21]
Acute necrotizing vasculitis[7,46]
Nonhealing surgical wounds[3]
Pulmonary
Acute interstitial pneumonia, elevated liver enzymes, hypertension[59]
Lethal pneumonitis[22]
Pulmonary hypertension[23]
Pulmonary abscess[24]
Pulmonary aspergillosis[25]
Mycobacterium abscessus infection[26]
Pulmonary tuberculosis[27]
Rheumatoid lung nodulosis and osteopathy[28]
Atypical *Mycobacterium* pneumonia[29]
Infectious
Opportunistic infections[59]
Fatal sepsis[59]
Propionibacterium acnes endophthalmitis[30]
Pulmonary tuberculosis[27]
Brain abscess[31]
Postsurgical osteomyelitis[32]
Cardiovascular
Hypertension[59]
Hypertriglyceridemia[33]
Inhibition of neointima proliferation[34]
Gastrointestinal
Hepatotoxicity[59]
Diarrhea[59]
Acute, fatal hepatitis[35,36]
Liver failure[37]
Colitis[38]
Neurologic
Aseptic meningitis[39]
Brain abscess[31]
Cystoid macular edema[40]
Peripheral neuropathy[41–44]
Severe axonal sensorimotor polyneuropathy[44]
Musculoskeletal
Rhabdomyolysis[15]
Osteomyelitis[32]

Discussion

LEF, a potent anti-inflammatory, antiproliferative, and antineoplastic drug, is one of a new generation of DMARDs for use in patients with severe RA, a group of drugs that includes etanercept, infliximab (Remicade), and adalimumab (Humira).

Normal white blood cell (WBC) function and normal fibroblast function are necessary for a normal inflammatory response and wound healing. Multiple reports show that WBC and red blood cell precursor cell lines' intra- and intercellular biochemical reactions are blocked by LEF. LEF is reported to suppress or block proliferation of multiple normal WBC lines: leukocyte phagocytic antigen-presenting cells,[51] leukocyte dendritic cells,[52,53] and lymphocyte T-cells[54–57] (Figure 3). DMARDs should be considered immunosuppressive drugs, of a different class from corticosteroids.

Pyrimidine synthesis, blocked by LEF, is a key process in synovial cell production and in fibroblast collagen production. LEF therefore affects proliferation and functions of normal cell lines. LEF alters fibroblast-like synovial cell proliferation, halting progression of RA; it appears in this case to affect true fibroblasts the same way, blocking wound fibrosis and healing.

Milder adverse effects of LEF—that are not apparent clinically until the patient has a reported complication—may be treated by stopping and then restarting LEF once signs decrease.[58] However, stopping LEF is not enough to prevent suppression of wound healing after surgery. LEF leaches out of tissues for up to 2 years.[59] Surgeons should optimize conditions for wound healing, including cessation of smoking or harmful medications and the washout of suppressive DMARDs before surgery. Hernia recurrences increase with each hernia repair after the first.

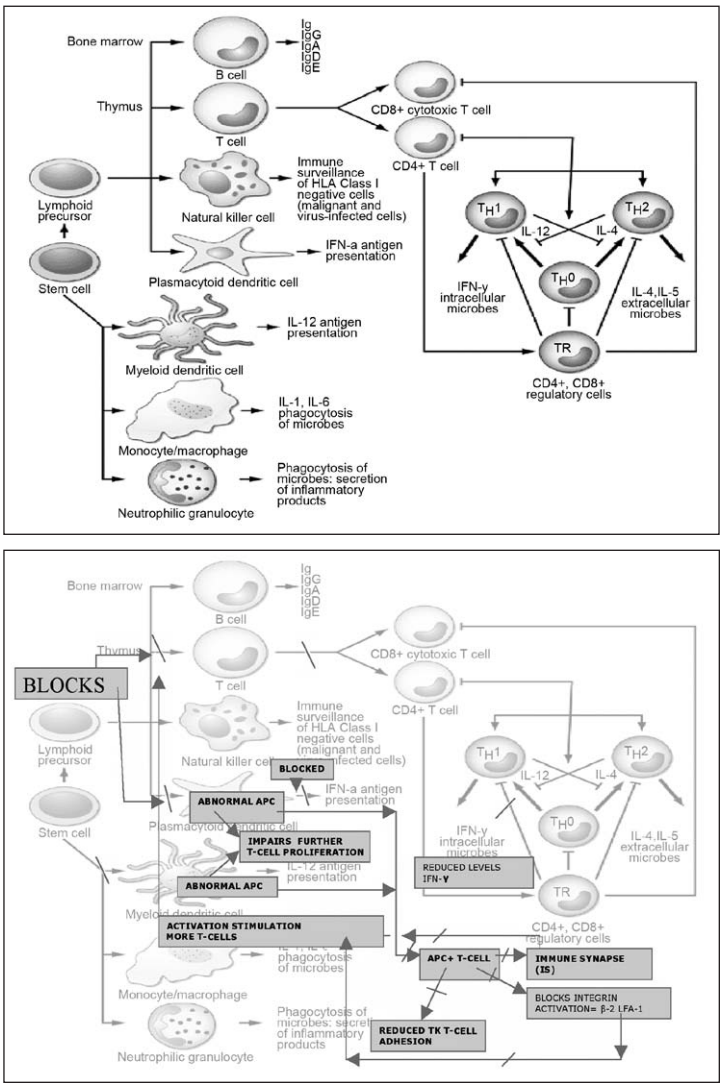

Figure 3. Normal cellular immune function (top) and adverse cellular effects of Arava (bottom).

APC = antigen-presenting cell; HLA = human leukocyte antigen; IFN = interferon; Ig = immunoglobulin; IL = interleukin; LFA = lymphocyte function-associated antigen. (Modified with permission from Part 13: disorders of the immune system, connective tissue, and joints. In: Kaspar DL, Braunwald E, Fauci AS, Hansen SL, Longo DL, Jameson JL, editors. Harrison's principles of internal medicine. 16th ed. New York: McGraw-Hill Professional; 2005. p 1923.)

Recurrence is even higher in patients with associated comorbidities such as smoking or chronic obstructive pulmonary disease, massive obesity (a body mass index >35 kg/m^2), and immunosuppression. This patient had no comorbidities other than RA treated with LEF. Her body mass index was 32 kg/m^2, and she did not smoke or have chronic obstructive pulmonary disease. She was immunocompromised by LEF.

Any patient taking DMARDs must be made aware of potentially fatal adverse effects, give informed consent, and then be closely monitored for hepatic, gastrointestinal, hematologic, infectious, pulmonary, dermatologic, and neurologic adverse effects.[3–46] The 59th edition (2005) of the *Physicians'*

Desk Reference provided little information on the adverse effects of LEF.[59] Serious adverse effects are typically learned from after-market reports[3–59] (Table 1). In 2010, the US Food and Drug Administration added a black-box warning to LEF about hepatic injury and failure. Box warnings of all serious adverse effects belong on data sheets of all DMARDs, similar to after-market warnings added in the past for chloramphenicol (marrow suppression) and for oral contraceptives (thromboembolism).

When a patient with RA needs surgery, how do the surgeon and rheumatologist manage medications to improve the likelihood of healing? The case I presented here is of a patient with RA whose lack of wound healing was most likely caused by the DMARD LEF. That hypothesis led to washout of LEF with cholestyramine. Clinical examination findings confirmed the effectiveness of LEF washout. Today, rapid local assays for serum LEF levels are available to confirm readiness for surgery.[60] I believe that further studies are needed both to define the effects of DMARDs on WBC cell lines, fibroblasts, and wound healing and to help guide the prudent management of DMARDs—or their washout—in these patients with complex needs who must undergo surgery.[2] ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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