Case Report

Infliximab Treatment in a Patient with Rheumatoid Arthritis on Hemodialysis

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ABSTRACT. We describe a 60-year-old woman with active rheumatoid arthritis (RA) and endstage renal disease secondary to hypertensive nephrosclerosis undergoing hemodialysis. She had tried multiple antirheumatic medications; however, their usefulness was limited due to toxic side effects or lack of efficacy. She was then treated with chimeric antitumor necrosis factor monoclonal antibody (infliximab), which resulted in immediate improvement in clinical and laboratory measures. After about 2 years of therapy, no side effects have been observed. This report expands the spectrum of infliximab to include RA patients with renal insufficiency. (J Rheumatol 2002;29:636–7)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
INFLIXIMAB
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The management of a patient with rheumatoid arthritis (RA) and renal failure represents a therapeutic dilemma, as most antirheumatic drugs have a certain degree of nephrotoxicity. Methotrexate (MTX) is among the most common and most effective drugs used to treat RA; however, there have been several case reports of fatal hematological abnormalities associated with its use even at very low doses, especially in patients with renal insufficiency. Whether MTX can be administered to patients with endstage renal disease (ESRD) undergoing hemodialysis has not been adequately addressed. Alternative therapies are needed in these patients. We describe a woman with RA and ESRD successfully treated with infliximab after failing multiple drugs.

CASE REPORT

A 60-year-old African American woman was diagnosed with seropositive RA at age 55. Her history revealed longstanding poorly controlled hypertension, which led to renal insufficiency at age 56. The disease activity was severe and persistent, with symmetrical synovitis of bilateral wrists, hands [metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joint involvement], feet, ankles, and right elbow along with morning stiffness lasting most of the day. Symmetric erosive changes were seen on PIP, MCP, wrists, and metatarsophalangeals. Laboratory evaluation revealed a positive rheumatoid factor (IgM) of 80 IU, negative antinuclear antibodies, and normal uric acid levels. She was initially treated with oral prednisone (20 mg/day), hydroxychloroquine sulfate (200 mg twice a day), and intramuscular aurothioglu-
cose had to be discontinued secondary to increased proteinuria. A few months later, hydroxychloroquine sulfate was discontinued due to evolving anemia (hemoglobin/hematocrit 8.5 g/dl/26.6%) along with increased blood urea nitrogen (BUN)/creatinine (Cr) ratio of 79/5.3 mg/dl. At that time, she started azathioprine (AZT) (initially 50 mg/day and slowly increased to 150 mg/day), which led to a transient, but good clinical response along with improved renal function and anemia. However, low blood counts were again detected (Hb/Hct of 7.8/24.0) after 4 months of treatment with AZT, and it had to be stopped eventually. She was given sulfasalazine (500 mg twice a day), which was stopped very shortly secondary to gastrointestinal side effects. She was also given a trial of minocycline (100 mg twice a day) without significant clinical benefit. At that time, she started hemodialysis with a BUN/Cr ratio of 94/8.1. She was given low dose MTX (2.5 to 5 mg/week) for several weeks along with oral prednisone (20 mg/day). However, this treatment was not able to relieve her symptoms and because of potential serious side effects, MTX was discontinued. She was eventually managed with intermittent pulse methyl-prednisolone therapy (250 to 500 mg every 2 mo), which was found clinically useful. Throughout her disease course, Westergren erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) remained extremely elevated. To decrease her steroid dependence, she was given infliximab (5 mg/kg at 0, 2, and 6 weeks and then 3 mg/kg/8 weeks). There was immediate and dramatic improvement in clinical and laboratory measures (ESR decreased from 93 to 15 mm/h and CRP decreased from 27 to <0.5 mg/dl). After about 2 years of treatment, no clinical or immunological side effects have been detected, and she remains in clinical remis-

DISCUSSION

RA is an autoimmune disorder of unknown origin in which disease modifying antirheumatic drugs (DMARD) are the mainstay of therapy. However, multiple studies have documented that patients seldom continue therapy for more than 5 years with current DMARD because of loss of efficacy or intolerable side effects. This patient failed treatment with gold, hydroxychloroquine, azathioprine, sulfasalazine, MTX, minocycline, and oral prednisone. Her disease activity could be controlled only by repeated pulse methyl-prednisolone, while she suffered renal failure secondary to...
hypertension. Many studies have concluded that DMARD, especially MTX, cannot be used safely in elderly and renal dialysis patients. MTX is poorly cleared with hemodialysis and even less effectively with peritoneal dialysis, but MTX has been shown to be efficiently reduced by hemodialysis with high-flux dialyzers. Also, there have been several reports of fatal side effects with MTX, such as severe pancytopenia, in patients with ESRD. Thus there is a need for newer therapeutic modalities with beneficial effects and fewer risks, particularly in this subset of RA patients with ESRD.

Tumor necrosis factor-α (TNF-α) is a pivotal cytokine in the pathogenesis of RA that has emerged as a promising therapeutic target based on experimental studies employing specific biologic inhibitors. TNF and TNF-RII (p75) are substantially upregulated in RA. TNF-α inhibitors are one of the most important advances in the history of the treatment of this disorder. Infliximab (Remicade) is a chimeric mouse/human anti-TNF-α monoclonal antibody — the first agent generated to selectively target TNF-α, which has been shown to be very effective for RA. To date, renal related adverse events have not been reported during infliximab treatment. However, there has been no experience with RA patients undergoing hemodialysis with TNF-α inhibitors such as TNF-α monoclonal antibody (infliximab) or TNF-α receptor agonist (etanercept) (personal communication, M.S. Maxon, Immunex Corporation, Seattle, WA, USA). It is not known if there are differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function. In general, clearance of drugs by dialysis depends on many factors, including but not limited to dialysis membrane type, solute molecular weight, free fraction, and flow rate. However, the exact pharmacokinetics of infliximab in patients with endstage renal failure on hemodialysis are not known.

Pulse methylprednisolone and anti-TNF-α therapies have a lot of similarities in their mechanism of action, as both decrease activities of TNF-α and levels of interleukin 6 (IL-6), IL-8, and polymorphonuclear cell traffic. In this patient, pulse methylprednisolone resulted in clinical remission without decreasing ESR and CRP, while infliximab treatment led to resolution of clinical and laboratory disease markers. This might point toward a different mode of action between these 2 drugs.

This case study suggests that infliximab treatment might be safe, well tolerated, and effective therapy for RA patients with ESRD undergoing hemodialysis. In addition, this case illustrates the longterm efficacy of infliximab despite the lack of concomitant administration of MTX. Larger trials are needed to support its use in these patients.

REFERENCES