Eight-year preservation of knee function with radiographic healing phenomena after anti-tumor necrosis factor-α therapy for a severely erosive knee in a young patient with rheumatoid arthritis

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ABSTRACT

A 23-year-old woman developed rheumatoid arthritis (RA). The pain in her right knee was aggravated and anti-tumor necrosis factor (TNF)-α therapy was selected at the age of 35. The range of motion and Larsen grade were 5º to 120º and 4, respectively. Infliximab and etanercept therapies were quite effective and the pain of the right knee improved. An X-ray at 1 year showed radiographic healing phenomena that included reappearance of a clear visible cortical plane, partial filling-in of erosions and cysts, and sclerosis of the subchondral bone. An X-ray at the age of 43 showed that the radiographic healing phenomena were still preserved after 7 years. The right knee remained pain-free although the Larsen grade was still 4, and the knee function was preserved for 8 years. In conclusion, anti--TNF-α therapy may preserve knee function with radiographic healing phenomena and prevent total arthroplasty of severely erosive knees in young RA patients.

Keywords: Rheumatoid arthritis; Anti-tumor necrosis Factor-α therapy; Radiographic healing; Erosive knee.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease marked by systemic immunologic abnormalities. It mainly affects the synovial joints of the upper and lower extremities and may result in severe damage or destruction of the affected joints[1]. A great deal of progress has been made in biologic treatments for RA, and improvements in disease activity and suppressive effects on bone and joint destruction have been reported[2,3]. Notable effects of anti-tumor necrosis factor (TNF)-α therapy on joint damage can include restoration of joint erosion and radiographic progression inhibition, even in patients who have residual joint inflammation[4,5]. Progression of weight-bearing joint destruction may result in decreased walking ability; however, only a few studies have investigated the suppressive effects of biologics on weight-bearing joints. This case report presents our experience of 8--year preservation of knee function with radiographic healing phenomena after anti-TNF-α therapy in a young RA patient with a severely erosive knee.

CASE REPORT

A 23-year-old woman developed RA in 1992. Although gold sodium thiomalate and auranofin were initially administered, her condition worsened. At the age of 33 years, she consulted our hospital for intensive medical therapy. At the initial visit, her RA was classified radiologically as Larsen grade 4 and functionally as Steinbrocker class III[6]. She had been taking prednisolone (PSL) 7.5 mg/day and bucillamine (BUC) 200 mg/day for 3 years. Laboratory investigations revealed C-reactive protein (CRP) of 0.90 mg/dL, matrix metalloproteinase (MMP)-3 of 267.0 ng/mL, rheumatoid factor of 242 IU/mL, and anti-cyclic citrullinated peptide antibody positivity (21.6 U/mL). Her disease activity score, including a 28-joint count with CRP (DAS28-CRP)[7,8], was 4.85 and her Modified Health Assessment

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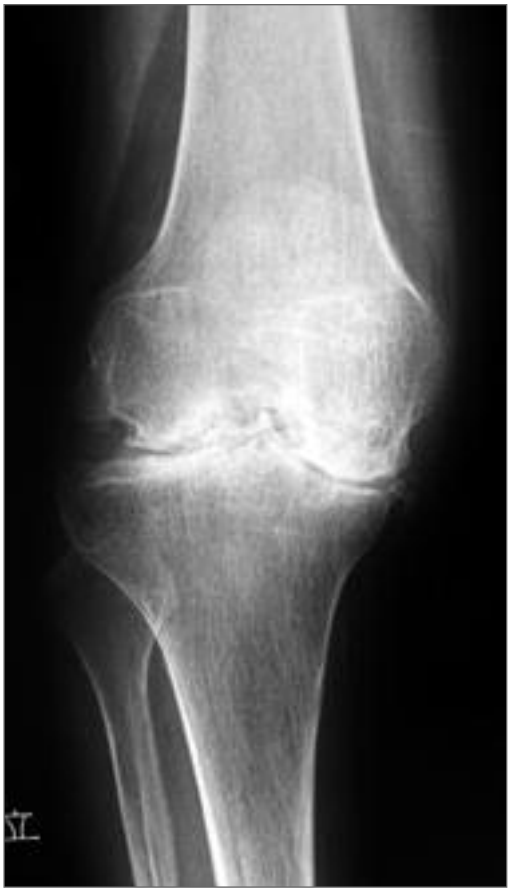

FIGURE 1. Radiograph of the right knee at the initiation of anti-tumor necrosis factor-α therapy shows bony erosion and loss of the bilateral joint space (Larsen grade 4)

Questionnaire (MHAQ) score[9] was 1.250.

Her medications were changed to PSL 7.5 mg/day, methotrexate (MTX) 4 mg/week, and BUC 200 mg/day. Although the dose of MTX was increased gradually to 8 mg/week and BUC 200 mg/day was switched to salazosulfapyridine (SASP) 500 mg/day, her condition did not stabilize. The usual doses of MTX in Japan are typically lower than those in Europe or United States. The dose of MTX in Japan was limited to <8 mg/week until February 2011 because of the lower body weight of Japanese compared with Caucasians. The dose of SASP was reduced from 1000 mg/day to 500mg/day because of nausea at first administration. After 1 year of MTX therapy (patient was 34 years-old), the pain in her right knee did not improve and she received a corticosteroid injection in the knee joint every month for 7 months. Laboratory investigations revealed CRP of 2.40 mg/dL and MMP-3 of 103.0 ng/mL. Her DAS28-CRP score was 4.90 and her MHAQ score was 0.500. Her right knee remained at Larsen grade 410 (Figure 1), and the range of motion (ROM) was 5° to 120°. A total knee arthroplasty (TKA) was planned, but the patient refused the procedure because of her age.

After 1 year of the first corticosteroid injection (patient was 35 years-old), further treatment was discussed with the patient and anti-TNF-α therapy was selected. Infliximab (IFX) therapy was administered in accordance with the Japan College of Rheumatology Guidelines[11]. At the introduction of IFX (3 mg/kg), CRP was 0.90 mg/dL, MMP-3 was 82.5 ng/mL, DAS28-CRP score was 3.90, and MHAQ score was 0.125. IFX therapy was quite effective for the patient; she achieved remission in 6 months and her right knee pain improved. Although she had been taking PSL for 10 years, the PSL dose was gradually decreased from 7.5 mg/day and discontinued at 2 years after the start of anti-TNF-α therapy (patient was 37 years-old). X--rays of her right knee at 1 year after anti-TNF-α therapy (patient was 36 years-old) revealed evidence of radiographic healing, including reappearance of a clearly visible cortical plane, partial filling-in of erosions and cysts, and sclerosis of the subchondral bone (Figure 2). After 2 years of IFX therapy (patient was 37 years-old), its effect diminished, but switching SASP 500 mg/day to tacrolimus (TAC) 3 mg/day maintained the remission. Post-marketing surveillance of TAC in 3,267 Japanese patients with RA demonstrated that TAC is well tolerated by Japanese patients with active RA, including those receiving concomitant MTX, in the real world[12]. After another year and a 3-year remission (patient was 38 years-old), the effect of IFX diminished again and her RA activity increased. Laboratory investigations at that time revealed CRP of 1.42 mg/dL and MMP-3 of 397.0 ng/mL, and her DAS28--CRP and MHAQ scores were 3.24 and 0.000, respectively. The pain in her right knee increased again and IFX was switched to etanercept (ETN)[13]. Low-dose ETN therapy (25 mg every 2 weeks) was very effective and another remission was obtained in 1 month. After 4 years of remission with ETN (patient was 42 years-old), the dose of ETN was increased to 25 mg/week and TAC was gradually decreased and discontinued at 5 years after the start of ETN therapy (patient was 43 years-old). Matsuno[13] reported the efficacy of half-dose treatment with ETN, at 25 mg/week after secondary loss of efficacy of IFX treatment. Owing to the cost problem for the patient, ETN was started at 25 mg

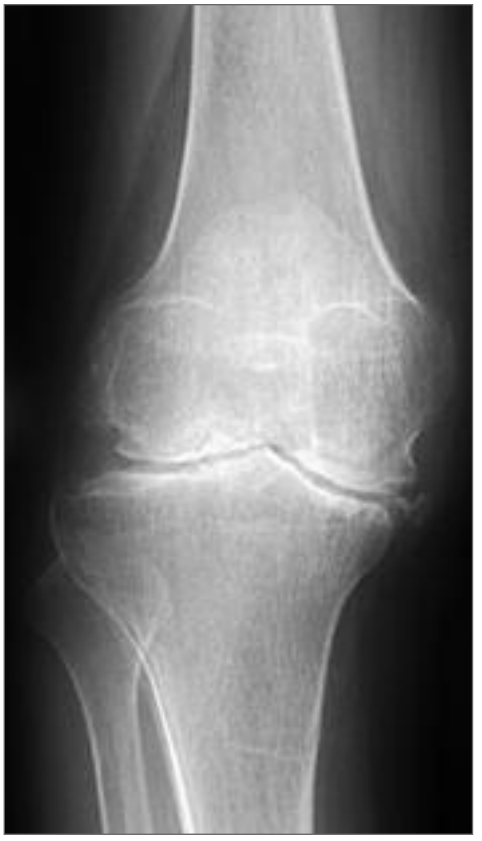

FIGURE 2. Radiograph of the right knee at 1 year after the initiation of anti-tumor necrosis factor-α therapy shows healing phenomena including reappearance of a clearly visible cortical plane, partial filling-in of erosions and cysts, and sclerosis of the subchondral bone

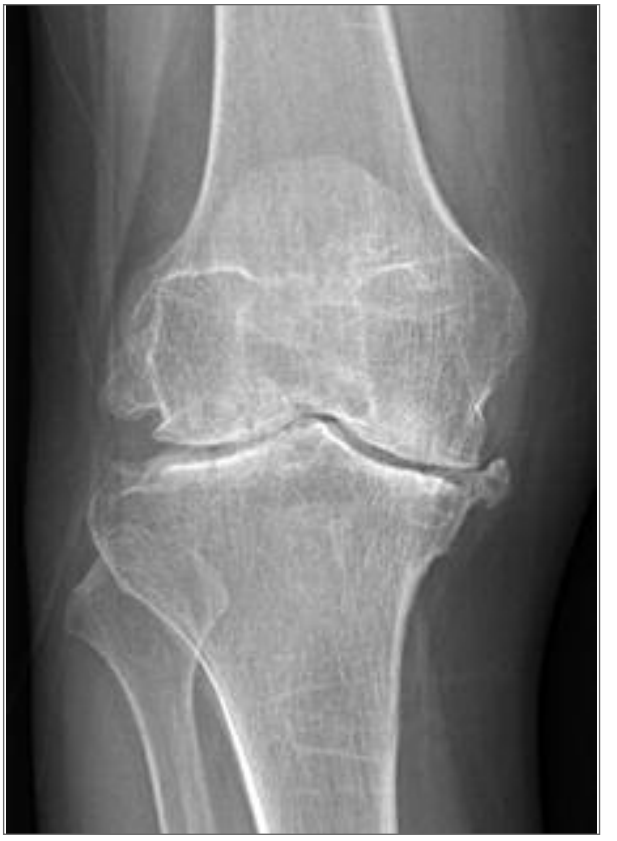

FIGURE 3. Radiograph of the right knee at 8 years after the initiation of anti-tumor necrosis factor-α therapy shows that the radiographic healing phenomena was maintained for 7 years

every 2 weeks and increased to 25 mg/week after reduction of efficacy.

Her second RA remission has been maintained for more than 5 years. An X-ray of her right knee joint at 8 years after the start of anti-TNF-α therapy (patient was 43 years-old) revealed that the radiographic healing phenomena were still maintained for 7 years (Figure 3). Her current medication is MTX 8 mg/week and ETN 25 mg/week. Her most recent evaluation revealed CRP of 0.01 mg/dL, MMP-3 of 39.1 ng/mL, DAS28-CRP score of 1.57, and MHAQ score of 0.000. The right knee had a ROM of 10° to 115°, and pain-free.

DISCUSSION

Although joint inflammation and poor control of disease activity in RA can progress to joint destruction, recent studies have demonstrated the effectiveness of anti-TNF-α therapies for inhibition of radiographic progression. The ASPIRE study reported reduced radiographic progression with MTX and IFX therapy compared with MTX monotherapy over 54 weeks[4]. The BeSt study demonstrated that initial combination therapy with anti-rheumatic medication and IFX resulted in earlier functional improvement and less radiographic damage compared with anti-rheumatic drug monotherapy after 1 year[14]. Suppression of joint destruction progression was reported to be greater with MTX plus ETN therapy than with MTX monotherapy over a 2-year period in the TEMPO study[3]. In these studies, radiographic joint damage was assessed by changes in the modified Sharp/van der Heijde score[15], but only small joints (hands and feet) were evaluated; large joints, especially weight-bearing joints, were not assessed. Destruction of weight-bearing joints decrea-

ses walking ability, which limits the performance of activities of daily living and reduces quality of life. Therefore, it is quite important to limit joint destruction and restore the function of knee joints, but only a few studies have investigated the suppressive effects of biologics on weight-bearing joints.

Seki *et al.*[16] reported a suppressive effect on joint destruction in weight-bearing joints such as the hip, knee, and ankle at 1 year after anti-TNF-α therapy, demonstrating that, even in patients with a good response, damaged weight-bearing joints (Larsen grades 3 and 4 at baseline) showed progression of joint damage. However, the study only reported short-term results. In our case, at the introduction of IFX therapy, the patient's knee was classified as Larsen grade 4. According to the above study by Seki *et al.*[16], this condition placed our patient at risk for progression of joint destruction, but in fact she showed radiographic healing of her knee joint and loss of knee symptoms at 1 year after initiating anti-TNF-α therapy and has maintained these effects for 7 years. The difference between our case and Seki's study was patient age; the average age of the patients in their study was over 55 years, while our patient was 35 years-old. Imagama *et al.*[17] reported on knee joint destruction after 94 weeks of anti-TNF-α therapy, demonstrating no difference in the progression of knee joint destruction between baseline Larsen grades 0-2 and 3-4. They found that residual symptoms of swelling and tenderness were observed significantly more frequently in the group that experienced progression of knee joint destruction and concluded that the presence of residual symptoms was a risk factor for knee joint destruction after anti-TNF-α therapy. In our case, after introduction of anti-TNF-α therapy, the loss of symptoms in the patient's knee has been maintained for at least 7 years, and this condition was similar to the study by Imagama *et al.*[17]. In fact, her radiographic healing phenomena have been maintained for 7 years after initiating anti-TNF-α therapy. We attribute her increased healing ability to her young age and continued absence of local symptoms.

Although the long-term results of TKA in RA patients are excellent[18], TKA is associated with potential risks of delayed wound healing and infection as a result of immunosuppressive medications, and atrophy of the skin and subcutaneous tissues[19]. Although the prosthesis survival rate is estimated to be >90% at 10 years, with revision as the endpoint in RA[20,21], multiple revision surgeries are expected for young RA patients (<60 years-old). Crowder *et al.*[22] reported excellent long-term results of TKA in 32 young RA patients aged 55 years or younger (average age 43 years). The Kaplan–Meier estimated survival to revision was 100% at 15 years and 93.7% at 20 years of follow-up; however, the Kaplan–Meier graph also indicated that the survivorship of prostheses was 60% at 25 years of follow-up. Certainly, similar cases may not follow the same course as that of our patient; however, it is important to avoid TKA through the use of anti-TNF-α therapy in young patients.

In conclusion, we report a case of 8-year preservation of knee function with radiographic healing phenomena after anti-TNF-α therapy for a severely erosive knee in a young RA patient. Anti-TNF-α therapy should be attempted in young RA patients with severely erosive knees, even those with severities as high as Larsen grade 4, to avoid TKA.

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