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Usefulness of MRI and US in Successful Discontinuation of Etanercept in RA Patients: A Report of Two RA Cases

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Abstract

Etanercept (ETN) can induce remission in many patients with rheumatoid arthritis (RA); however, successful cessation is considered difficult. We present two cases with RA treated with ETN and successfully discontinued ETN. Before ETN cessation, we evaluated the presence of synovitis using Magnetic Resonance Imaging (MRI) and ultrasonography (US). Neither patient showed signs of synovitis in these examinations. MRI and US may provide useful indicators in the clinical recommendations for ETN cessation in RA.

Keywords: Ultrasonography; Magnetic resonance imaging; Infliximab; Etanercept

Introduction

The disease activity of most patients with RA is successfully controlled by administering biologics. At present, six biologic agents, Infliximab (IFX), Etanercept (ETN), adalimumab, golimumab, tocilizumab, and abatacept, are available in Japan, and their suppressive effects on disease activity and bone destruction have been established. Regrettably, biological products are expensive, and the economic burden to both patients and the government is large. Many patients with RA who discontinue their use of these biologics experience flare-up of their disease activity. A fraction of these patients have successfully discontinued IFX with no recurrence, and the characteristics of these patients are reported to be early RA and low disease activity with DAS28 [1]. Few cases of successful discontinuation of ETN in patients with RA [2,3]. However, have been reported, although ETN is relatively safe to use and [4] is known as a biologic that is associated with a higher continuing rate [5]. Therefore, establishing a set of drug cessation criteria that must be met before discontinuing ETN is important. Herein, we report two cases of patients with RA who successfully discontinued ETN after achieving low-grade disease activity or remission as evaluated by the DAS28 score. One case involved a patient with a relatively short duration of RA, and the other involved a longstanding established case of RA. Both patients revealed no synovitis before discontinuing ETN as assessed by enhanced magnetic resonance imaging (MRI) or ultrasonography (US). These case studies demonstrate that discontinuation of ETN is possible even in cases of established RA, and that imaging studies, including MRI and US, may be effective tools for evaluating RA activity as predictors of successful discontinuation of ETN.

Case 1

A 70-year-old woman noticed polyarthralgia on her elbow, knee, and jaw, and bilaterally on her wrists, in September 2004. She was diagnosed with osteoarthritis at an open clinic and was prescribed nonsteroidal anti-inflammatory drug therapy. To address her prolonged arthralgia, she visited our hospital in September 2005, where she presented with two swollen joints (bilateral wrists) and four tender joints (right wrist, left elbow, and bilateral knees). The laboratory data showed high CRP levels (4.5 mg/dl), but the rheumatoid factor was negative. X-ray revealed bone erosion at the ossa carpi as well as joint space narrowing at the right fifth metatarsophalangeal joint. We diagnosed her with RA (Steinbrocker stage 2) (Figure 1a) and administered 4 mg of methotrexate (MTX) with prednisolone (PSL) and indomethacin. Despite a gradual increase of MTX to 10.5 mg/wk, her disease activity did not improve (DAS28-CRP 4.05). Therefore, we introduce ETN (25 mg twice/wk) to her treatment in June 2006. Her symptoms gradually improved after 2 weeks; 1 month after initiating ETN treatments, her joint swelling and tenderness disappeared, and the

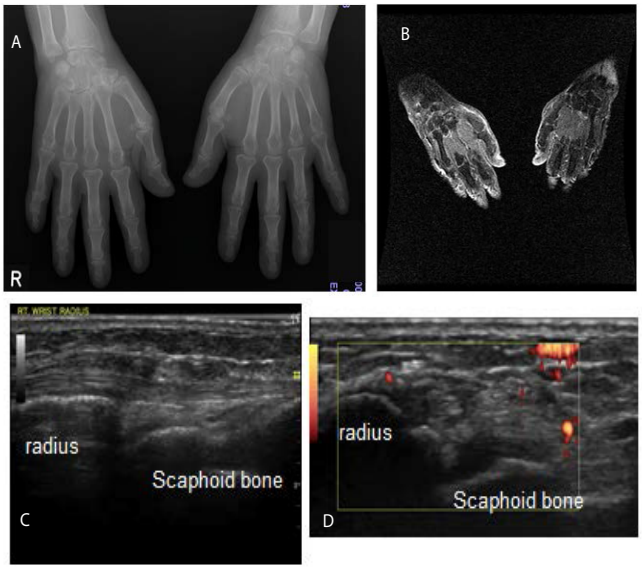

Figure 1: Imaging studies of case 1a). Plain radiograph of the hands revealed soft tissue swelling at bilateral wrists and joint space narrowing at the midcarpal and carpometacarpal joints, but did not show erosion. 1b) Gadolinium-enhanced MRI did not reveal signs of active synovitis or bone marrow edema at bilateral wrist joints. c. US revealed no thickness of synovium with B mode. d. No doppler signal was observed with power doppler at the right radial-scaphoid joint.

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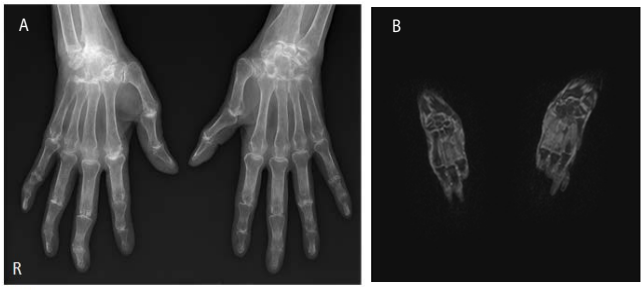

Figure 2: Imaging studies of case. 1a) Plain radiograph of the hands revealed erosion, joint space narrowing and bony ankylosis at the carpal joint, as well as erosion and joint space narrowing at the metacarpophalangeal joints and the proximal interphalangeal joints. 1b) Gadolinium-enhanced MRI revealed no signs of active synovitis or bone marrow edema at bilateral wrist joints.

CRP levels became negative. Thus, her disease activity score achieved remission as evaluated by DAS28-CRP. Although her MTX dose was reduced to 8 mg/wk and prednisolone was discontinued, her disease activity remained in remission. MRI (T1, T2, STIR, or Gd DTPA-enhanced) revealed no evidence of synovitis or bone marrow edema in her hands, bilaterally (Figure 1b). Ultrasonography revealed neither thickness of the synovium nor Doppler signals detecting blood flow as markers of active synovitis (Figure 1c and 1d). With these findings, we recommended discontinuation of ETN with continued MTX treatment in April 2010. Her disease activity has remained in remission with a DAS28-CRP score of 1.29 at her last visit in October 2011. With remission duration of at least 18 months, this case represents a successful discontinuation of ETN.

Case 2

An 81-year-old woman with polyarthralgia at her left shoulder, and bilaterally at her wrists and knee joints, was diagnosed with RA in 1974. Despite treatment with several disease-modifying antirheumatic drugs (DMARDs) (D-penicillamine, MTX, sarazosulfapiridine, gold, and actarit), her disease activity was not fully controlled. We treated her with 150 mg/day of mizoribine and 5 mg/day of PSL; however, her disease activity was still moderate (DAS28-ESR 4.05) before we introduced ETN (25 mg twice/wk) in addition to the former therapy in August 2005 (Steinbrocker stage 4) (Figure 2a). The addition of ETN improved her symptoms and joint swelling dramatically. We tapered the PSL administration in December 2005. Thereafter we diminished ETN to 25 mg/wk in September 2008, and 25 mg/2 wks in January 2009. Her disease activity did not recur, and her DAS-ESR was below 3.0 during the ETN treatment. Because MRI revealed no signs of active synovitis (Figure 2b), we decided to discontinue ETN and treat her with mizoribine alone in October 2009. She did not complain of arthralgia and displayed continued clinical stability without ETN at her last visit in October 2011. With remission duration of at least 24 months, this case appears to be an example of successful ETN cessation in RA.

Discussion

Biologic agents have dramatically improved RA treatment in recent years. However, these agents are associated with increased risk of infectious disease, including increased susceptibility to tuberculosis, and the safety of long-term treatment is not confirmed. Moreover, long-term use of biologics incurs a large economic burden to patients. Therefore, establishing clinical criteria is a matter of great concern for determining when patients who have achieved a good response can discontinue these agents.

In the BeSt study, 77 of 120 patients with early RA treated with the anti-TNF agent, IFX, successfully discontinued IFX after a 6-month continuation period with DAS <2.4. Of these patients, 43 were reported to maintain remission during an average follow-up period of 7.2 years [6]. In the RRR study, 56 out of 102 patients with RA maintained remission (DAS28 <3.2) after discontinuation of IFX for 1 year. This patient population included established patients with RA who had continued DAS28 <3.2 for 24 weeks [6,7]. Thus, IFX therapy can be successfully discontinued in about half of the patients for whom IFX induces and maintains low disease activity or remission.

Similar to IFX, ETN is also an agent against TNF. Whereas IFX is a chimerical antibody against TNF-α, ETN is a soluble form of the TNF receptor-IgG Fc fusion protein. ETN is reported to be safer and have a higher persistence rate than other biologic agents, although only a few case studies have reported a successful discontinuation of ETN after remission.

Brocq et al. [2] tried to discontinue ETN for 14 patients with RA who displayed continued DAS <2.6 for 6 months. Of these 14 patients, only 2 maintained remission after 1 year, whereas 11 patients experienced disease flare-up and 1 died. Of the 11 patients experiencing flare-up, 9 had flares within 4 months after discontinuing ETN. In contrast, in the BeSt study conducted on IFX, the average biologics-free duration was 17 months before relapse at the follow-up period of 7.2 years. Mitoma et al. [8] showed that IFX could induce apoptosis to transmembrane TNF-α expressing Jurkat T cells although ETN could not [8]. The functional difference of these biologic agents on TNF-α-producing cells may be related to the biologics-free rate and the period to flare.

In several studies, continued DAS remission was used as an indicator for determining when to withdrawal patients with RA from biologics. Tanaka [1] reported that deeper RA remission, as evaluated with DAS, was associated with successful discontinuation and maintenance of IFX-free remission [1]. In ETN-treated patients, after continued DAS remission (<2.6) for 6 months, most patients with RA flared as early as 4 months. This observation suggests that DAS remission for 6 months alone is inadequate as an indicator for discontinuing ETN.

Recently, MRI and US have been reported to aid in the diagnosis and evaluation of RA activity [7,9-13]. Many patients who appeared to be in clinical remission with no evidence of progression on plain radiograph, revealed continuing synovitis with MRI or US. Brown et al. [13] reported that in 43% of patients with RA having no clinical sign of synovitis, US revealed blood Doppler signal, and in 96.2% of those cases, MRI revealed the thickness of synovium. This subclinical synovitis might progress to joint destruction. Moreover, the power of the Doppler score, rather than the DAS, might be a more accurate indicator to reflect the progression of joint destruction. These facts might suggest that the DAS score alone might not be an accurate predictor of remission since it fails to detect subclinical synovitis in many patients with RA. Therefore, many patients who appear to have clinical remission might experience disease flare when biologics are withdrawn owing to recurred synovitis after discontinuation of these agents.

Herein, we reported two patients who successfully discontinued ETN after continuing low disease activity or remission. MRI and US revealed no sign of active synovitis in one patient who had early RA and clinical remission (DAS28-ESR 0.77). In the other patient with longstanding established RA, joint damage had already progressed severely (Steinbrocker stage 4). Clinically, the patient showed low disease activity (DAS28-ESR 2.96), and MRI revealed no sign of active

synovitis. In both of these cases, we achieved successful discontinuation of ETN, and used MRI and US to confirm the disappearance of synovitis. Because imaging studies such as MRI and US can detect fine erosion of bone or slight synovitis with high sensitivity, they are useful in the diagnosis and evaluation of RA [11-13]. Both imaging techniques, however, have the disadvantage of not to being able to evaluate all of the invaded joints of the whole body, although McQueen et al. [14] reported that the MRI score and the MRI erosion score performed at the dominant wrist correlated with the progression of the total Sharp score [14]. Imaging studies performed at the dominant wrist or the most severely inflamed joint may be representative of other joints in the body, and may serve as predictors for other inflamed joints. Clinical evaluation of disease activity is insufficient to successfully discontinue ETN. Therefore, we suggest the use of imaging studies, such as MRI and US, for predictors of the successful discontinuation of ETN.

This is the first report evaluating synovitis using imaging studies before discontinuing biologics. Future studies determining the optimal imaging techniques will be required to more accurately predict successful discontinuation of ETN for patients with RA.

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