CASE REPORT

Improvement of Rheumatoid Arthritis and Autoimmune Hepatitis in a Patient Treated with the Tumor Necrosis Factor Inhibitor, Etanercept

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Abstract

We report a case of rheumatoid arthritis (RA) with autoimmune hepatitis (AIH) and Sjogren syndrome (SjS) that was treated with the tumor necrosis factor (TNF) inhibitor, etanercept (ETN). Both RA activity and transaminase levels improved as a result of treatment. Follow-up liver biopsy showed improvement of hepatitis. Although the efficacy of anti-TNF for RA patients with AIH remains controversial, this case suggests that treatment with ETN may result in a favorable clinical course in a certain subset of patients with RA and AIH.

Key words: autoimmune hepatitis, rheumatoid arthritis, anti-TNF therapy


Introduction

Tumor necrosis factor (TNF) is thought to play a critical role in the pathogenesis of chronic inflammatory diseases, such as rheumatoid arthritis (RA) (1). Several biologic agents such as etanercept (ETN), a soluble TNF receptor, and infliximab, an anti-TNF-α antibody, inhibit the function of TNF and improve the quality of life of patients with RA (2). Anti-TNF therapies are now used not only for RA, but also for chronic inflammatory diseases like Crohn’s disease and ankylosing spondylitis (3).

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease. AIH results from a complex interaction involving a triggering factor, autoantigens, genetic predisposition, and immunoregulatory networks (4, 5). Corticosteroid and immunosuppressants are generally effective in AIH (4, 6, 7). When inflammation can not be controlled, however, progression from chronic hepatitis to cirrhosis is frequently seen and hepatocellular carcinoma may appear at the end stage (4).

The imbalance of Th1/Th2 cytokines has been associated with the pathogenesis of AIH, with researchers reporting that Th1 cytokines such as TNF-α are more predominant than Th2 cytokines in the liver of patients with active AIH (8-10). Therefore, anti-TNF agents can be one of the options for AIH treatment theoretically; however, a case of AIH suspected of resulting from anti-TNF agents has also been reported (11). The contribution of cytokines such as TNF to the pathogenesis of AIH may be complex and the efficacy of anti-TNF agents for AIH remains controversial.

Here, we report that administration of ETN to a patient with RA and AIH resulted in improvement of both RA and AIH, which suggests that ETN can result in a favorable clinical course in a certain subset of patients with RA and AIH.

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A 52-year-old woman presented to our hospital in 1987 complaining of morning stiffness, multiple joint and bilateral parotid gland swelling. She was diagnosed as having RA and Sjogren syndrome (SjS). Because her transaminase levels were moderately elevated (AST 95 IU/mL, normal range 9-32; ALT 84 IU/mL, normal range 5-46), liver biopsy was performed. Results showed a mild inflammation, prompting a pathological diagnosis of non-specific reactive hepatitis due to RA and/or SjS. She was treated with lobenzarit disodium. In 1992, tests revealed the elevated levels of AST (319 IU/mL) and ALT (312 IU/mL). The patient tested positive for anti-nuclear antibody (1 : 160, homogenous type) and anti-smooth muscle antibody. Her serum IgG was elevated (3,540 mg/dL). Anti-mitochondrial antibody (AMA) was negative. Serological markers of viral hepatitis (hepatitis C virus antibody, hepatitis B surface antigen and hepatitis B surface antibody) were negative. Laparoscopy revealed multiple nodular change on the liver surface. Liver biopsy showed piecemeal necrosis with the infiltration of plasma cells in portal areas. Based on these data and reference to the criteria established by the Japanese Ministry of Health, Labour and Welfare Research Committee on AIH in 1992, a diagnosis of AIH was made (12). The AIH was treated with oral prednisolone (PSL) (30 mg/day) and serum transaminase levels decreased to normal limits (AST 12 IU/mL and ALT 9 IU/mL). Low-dose PSL (6-10 mg/day) was continued from 1993 to 2004. Lobenzarit disodium proved ineffective in controlling RA activity, and the patient was administered several different anti-rheumatic drugs, such as auranofin, bucillamine, salazosulfapyridine, and mizoribine. However, administration was discontinued due to liver and renal dysfunction. Methotrexate was rejected in consideration of the underlying AIH, and the patient was placed on a low-dose PSL. A minimum of 6 mg/day was required to prevent the increase of AST and ALT. In 2006, RA activity increased gradually.

The patient was admitted to our hospital for treatment with anti-TNF agents in June, 2007 (Fig. 1). Disease Activity Score in 28 joints (DAS28) was high at 6.4 (Table 1). SjS symptoms such as dry eyes and mouth were minimal. Serum transaminase levels were slightly increased (AST 59 IU/mL and ALT 58 IU/mL). Liver biopsy performed to assess the status of liver damage before starting anti-TNF agent treatment. Pathological examination of liver showed inflammation of periportal areas with infiltration of plasma cells and piecemeal necrosis suggesting active AIH (Fig. 2-a, b). The patient was exhibiting high RA activity and severe symptoms; however, due to concern about administering anti-TNF treatment to a patient with active AIH, ETN (25 mg, twice a week) was started after obtaining informed consent. PSL dosage was the same before and after ETN treatment. The signs and symptoms of RA quickly improved. DAS28 and C-reactive protein (CRP) values decreased, as did transaminase and serum IgG levels, though more gradually (Fig. 1, Table 1). In May 2008, forty-four weeks after the start of ETN, DAS28 became 2.3. Most of the symptoms of RA had disappeared. This patient com-

**Figure 1.** Clinical course. AST: aspartate aminotransferase, ALT: alanine aminotransferase, DAS28: disease activity score in 28 joints, CRP: C-reactive protein
plained only morning stiffness after ETN treatment. The dosage of PSL was decreased to 5 mg/day and serum transaminases values remained low. Follow-up liver biopsy was performed and marked improvement of inflammation to periportal areas was noted (Fig. 2-c, d). In July 2010, 126 weeks after the start of ETN, RA and AIH were in remission even though the dosage of PSL had been decreased to 3 mg/day. The minimal symptoms of dry eyes and mouth, noted prior to the start of ETN treatment in 2007, remained unchanged.

Discussion

A case of active RA with AIH and SjS was treated with ETN. RA activity in the patient decreased quickly and clinical remission (DAS28<2.6) has continued for 3 years without other anti-rheumatic drugs. SjS symptoms were unaffected by ETN treatment.

In addition to AIH, several possible causes exist for the liver dysfunction seen in the present case, including liver manifestations of RA or SjS and drug-induced liver dysfunction. In this case, it was difficult to differentiate AIH and reactive or non-specified hepatitis associated with RA or SjS initially, because patients with RA or SjS frequently show positive ANA and an increased level of IgG, which are important in the diagnosis of AIH. Therefore, histology obtained from liver biopsy was important in the present case (13-15). The histology of hepatic lesions due to SjS or RA has been reported as non-specific inflammation with infiltration of mononuclear cells and with fatty change (13, 16, 17). SjS is also known to be associated with primary biliary cirrhosis (16, 18). However, the present case tested positive for anti-smooth muscle antibody, but negative for AMA. Moreover, liver biopsy of this case revealed the interface hepatitis with infiltration of plasma cells and piecemeal necrosis in the periportal area. These results supported the diagnosis of AIH in this case. Drug-induced liver dysfunction was also considered unlikely in light of the clinical course and histology of the liver.

The liver biopsy in 2008 revealed the mild infiltration of mononuclear cells, however, the degree of inflammation was much less than that in 2007. In addition, the levels of transaminases decreased even after the dosage of PSL had been decreased to 3 mg/day. Therefore, improvement of AIH after ETN treatment was suggested.

The role of TNF in the pathogenesis of AIH remains unclear. Th1 cytokines, such as TNF-α were reported to be predominant in the liver of patients with AIH (6). TNF-α has been reported to activate cytotoxic T lymphocytes and/or macrophages, and their cellular autoimmunity results in hepatocellular injury (6, 7, 9, 10). These activated cells were also reported to produce B-cell activating factor belonging to the tumor necrosis factor family (BAFF), which stimulates B-cell inducing humoral autoimmunity (19). In theory, therefore, TNF inhibitor may be effective in the treatment of AIH; however, no reports have been published to date showing TNF inhibitor to be clinically useful as a treatment for AIH. On the contrary, development of AIH in a patient with ankylosing spondylitis treated with infliximab, an agent of anti-TNF-α antibody, has been reported (20). Another report showed that a patient with active RA and SjS, treated with ETN developed liver dysfunction and was diagnosed as AIH (11). These reports suggest that caution is necessary in the treatment of autoimmune diseases with AIH using anti-TNF agents.

In conclusion, the anti-TNF agent, ETN was effective in
References in patients with active RA and AIH.

Further study is required on ETN treatment did not exacerbate AIH and it was possible the treatment of active RA in a patient with SjS and AIH.

The authors state that they have no Conflict of Interest (COI).

References


