**Title**

**Author(s)**
Ishikawa, Yuki; Yukawa, Naoichiro; Ohmura, Koichiro; Hosono, Yuji; Imura, Yoshitaka; Kawabata, Daisuke; Nojima, Takaki; Fujii, Takao; Usui, Takashi; Mimori, Tsuneyo

**Citation**
Clinical rheumatology (2010), 29(5): 563-566

**Issue Date**
2010-05

**URL**
http://hdl.handle.net/2433/120949

Right
The original publication is available at www.springerlink.com; この論文は出版社版ではありません。引用の際には出版社版をご確認ご利用ください。This is not the published version. Please cite only the published version.

**Type**
Journal Article

**Textversion**
author

Kyoto University
Etanercept-Induced Anti-Jo-1-Antibody-Positive Polymyositis in a Patient with Rheumatoid Arthritis: A Case Report and Review of the Literature

Yuki Ishikawa1, MD; Naoichiro Yukawa1,2, MD; Koichiro Ohmura1,2, MD, PhD; Yuji Hosono1, MD; Yoshitaka Imura1,2, MD; Daisuke Kawabata1,2, MD, PhD; Takaki Nojima1,2, MD, PhD; Takao Fujii1,2, MD, PhD; Takashi Usui1,2, MD, PhD; Tsuneyo Mimori1,2 MD, PhD

Department of Rheumatology and Clinical Immunology, 1Kyoto University Hospital and 2Graduate School of Medicine, Kyoto University, Kyoto-city, Kyoto, Japan.

Correspondence to Naoichiro Yukawa, Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawahara-cho, Sakyoku, Kyoto-city, Kyoto, 606-8507, Japan

e-mail: Naoichiro Yukawa (naoichiy@kuhp.kyoto-u.ac.jp)
Tel. +81-75-751-4380, Fax.+81-75-751-4338

Key Words: Polymiositis, Dermatomyositis, Anti-Jo-1 antibody, Anti-synthetase antibodies, Anti-TNF therapy, Rheumatoid arthritis,
Abstract

Anti-tumor necrosis factor (TNF) therapy has been associated with adverse immunologic events including systemic lupus erythematosus. However, the development of polymyositis (PM)/dermatomyositis (DM) associated with anti-TNF therapy is extremely rare. We experienced a case of a 48-year-old female with rheumatoid arthritis (RA) who had anti-Jo-1 antibodies and interstitial lung disease but no previous history of PM/DM, and who developed PM soon after the initiation of etanercept (ETN) therapy for RA. The patient recovered upon withdrawal from ETN and corticosteroid (CS) therapies. Only four reports of PM/DM associated with anti-TNF therapy for RA could be found in the literature. The patients described in three of the four reports were positive for anti-Jo-1 antibodies before the initiation of anti-TNF therapy, and in all the cases, recovery occurred after the cessation of anti-TNF-agent administration and CS therapy. These results suggest a relationship between the onset of PM/DM with anti-Jo-1 antibody and anti-TNF therapy for RA.
Therapy directed at blocking tumor necrosis factor (TNF) is effective in the treatment of rheumatoid arthritis (RA) [1]. Because TNFα has recently been recognized as an important cytokine in the pathophysiology of idiopathic inflammatory myopathies (IIMs) [2], a therapeutic benefit from blocking TNF has been surmised in IIMs, and several case reports have supported the use of anti-TNF agents in refractory IIMs [3–5]. The use of TNF antagonists has also been associated with adverse immunologic events including the development of antinuclear antibodies (ANAs), anti-dsDNA antibodies, and lupus-like illnesses [6]. However, reports of polymyositis (PM) or dermatomyositis (DM) in association with TNF-antagonist therapy have been extremely rare. In this report, we describe a patient treated with etanercept (ETN) for seropositive RA, who subsequently developed PM. We could find only four cases described in the literature in which the use of anti-TNF agents for patients with RA led to the development of inflammatory myopathy. Interestingly, the majority of patients were positive for anti-Jo-1 antibodies.

**Case Report**

A 58-year-old woman who had non-specific interstitial pneumonia (NSIP) and RA was admitted to our hospital because of sub-acute muscle weakness and pain in the upper and lower extremities.

Two months before admission, ETN administration had been initiated for the treatment of RA. Although ETN was effective, the patient began to experience muscle weakness, mainly in the proximal upper and lower extremities, shortly after initiation of the therapy; this weakness then got progressively worse. Although laboratory tests initially revealed a normal level of creatine kinase...
(CK) (66 IU/L), the muscle weakness persisted and muscle pain also appeared. ETN was administered ten times in total, initially at a dose of 25 mg weekly, which was then increased to 25 mg twice-weekly. At the follow-up subsequent to the last injection, a dramatically increased CK level (611 IU/L) was detected. Although ETN administration was thought to be effective for RA, the patient was withdrawn from the treatment because a relationship between the ETN therapy and the onset of myositis was suspected.

The patient was positive for anti-Jo-1 antibodies and fluorescent ANAs (FANAs) with a nucleolar pattern since six years prior to the onset of muscle symptoms, at the time of the NSIP diagnosis. NSIP had been successfully treated with a moderate-to-low dose of prednisolone (PSL). The patient had never experienced any muscle or skin manifestations compatible with PM/DM and had been negative for other autoantibodies including anti-U1RNP, anti-dsDNA, and anti-SS-A/Ro antibodies. CK and aldolase (ALD) levels had been in the normal range, and electromyogram results had also been normal. Three years before the initiation of ETN treatment, morning stiffness lasting at least one hour and intermittent arthralgia in both hands had appeared, and gradually became worse. About one year after the onset of joint swelling and pain, the diagnosis of RA was established on the basis of the morning stiffness, symmetrical polyarthritis (wrists, MCPs, PIPs, and knees), typical X-ray findings including joint space narrowing at both wrists, and positive test results for serum anti-cyclic citrullinated peptide (CCP) antibodies (> 100 IU/mL). 300 mg of bucillamine and 3 mg of tacrolimus were partially effective, but the control of arthritis was insufficient, and X-ray findings had been
progressively worse, which led to the initiation of ETN therapy.

Upon admission, muscle weakness and tenderness of the proximal lower and upper extremities were noted, but skin rashes were not observed. After cessation of ETN treatment, arthritis recurred at the wrists, MCPs, PIPs, knees, and ankles. Joint X-rays showed bone erosion and joint space narrowing at the wrists and ankles. Electromyograms revealed a typical myogenic pattern at both quadriceps femoral muscles. A muscle biopsy of the left quadriceps femoris lateralis muscle showed myopathic changes including variation in the size of fibers, regenerative changes of myocytes, and mild inflammatory cell infiltrates around the muscle bundles. Anti-Jo-1 antibodies were positive (239 IU/mL), and FANA showed the titer of 1:320 with a speckled and nucleolar pattern, although IgG-anti-dsDNA antibodies were negative. The diagnosis of PM was established, and in view of the long-term absence of muscle symptoms prior to the initiation of ETN therapy, the possibility existed that ETN administration might have triggered its onset. The patient was orally administered 45 mg (1 mg/kg) of PSL daily, which resulted in a marked improvement in muscle symptoms. After two weeks of initial treatment, semi-pulse-steroid therapy (500 mg of methyl-prednisolone for 3 consecutive days) was inserted because of a minor relapse of PM. Thereafter, PSL dose was carefully tapered and clinical remission of PM was achieved. CK levels decreased from a peak of 1,538 IU/L to a normal value at the time of discharge. Prior to discharge, 50 mg of cyclosporine twice a day was also added to control both RA and PM.

Discussion
Several studies have indicated that TNFα has prominent roles in the pathogenesis of PM/DM [7], and there have been studies that focused on the testing of anti-TNF agents on patients with PM/DM, especially in cases refractory to conventional therapies; however, only controversial results have been reported until now. The results of some studies indicated the efficacy of anti-TNF therapy for PM/DM [3-5], but others failed to prove its efficacy, especially for patients that were positive for anti-Jo-1 antibodies [8-10]. These results also suggested that anti-TNF therapy for patients with anti-synthetase antibodies, including anti-Jo-1 antibodies, might not be effective, and might even be harmful.

Anti-TNF therapy is linked to autoimmune phenomena including the development of ANAs, anti-dsDNA antibodies, drug-induced lupus, and multiple sclerosis; however, the development of PM/DM is extremely rare. We could find only four case reports of PM/DM associated with anti-TNF therapy on MEDLINE (Table 1). Harald et al. reported the development of DM with anti-Jo-1 antibodies six months after the initiation of ETN therapy in a patient with seronegative RA [11]. The patient improved upon the withdrawal of ETN and treatment with CS. AZP and MTX were later introduced upon recurrence, which resulted in clinical remission. Musial et al. described the development of anti-Jo-1-antibody-positive PM soon after the initiation of therapy with infliximab (IFX) in a patient with seropositive RA [12]. This patient also improved upon the withdrawal of IFX and CS administration. The patient showed positive anti-dsDNA antibodies, ANAs, and anti-Jo-1 antibodies. Previously obtained and stored sera were positive for anti-Jo-1 antibodies, but negative
for anti-dsDNA antibodies. In another case, Urata et al. reported the development of PM with anti-Jo-1 antibodies, anti-dsDNA antibodies, and ANAs nine months after the initiation of IFX therapy for long-standing RA with pulmonary fibrosis [13]. Sera obtained before IFX therapy also showed positive anti-Jo-1 antibodies, but negative anti-dsDNA antibodies, and exhibited a homogenous and speckled ANA patterns. The latter two reports strongly suggest that IFX may induce autoimmune phenomena in individuals with some background risks (anti-Jo-1 antibodies, ANAs). Kiltz et al. reported a case of long-standing seropositive RA, in which the patient developed PM six weeks after ETN therapy. The patient initially received ETN for a few months two years before the onset of PM and ceased for some months because of well-controlled RA activity. But arthritis recurred and ETN therapy re-started, which might have triggered the onset of PM. Samples from the patient were positive for ANAs (1:160), but the titer dramatically increased to 1:2560 in four years. Profiles of anti-Jo-1 antibodies were not described. Withdrawal from ETN therapy and administration of CS and intravenous cyclophosphamide led to a considerable improvement in muscle strength [14]. In addition to the possible relationship between anti-TNF therapy and the onset of PM/DM, it should be noted that anti-Jo-1 antibodies were found in most of the patients described in the above reports.

Anti-Jo-1 antibodies are one of the six anti-aminoacyl-tRNA synthetase antibodies. They recognize hystidyl tRNA synthetase in many cells including myocytes, but their pathophysiological role in IIMs has yet to be clarified [15]. Although suggested mechanisms must explain the generation
of anti-synthetase antibodies and pre-myositis immunologic conditions, the patients described in the reports above were positive for anti-Jo-1 antibodies long before the onset of PM/DM. Additional triggers that lead to subsequent self-perpetuating inflammatory responses are still unclear. On the basis of the observed relationship between anti-Jo-1 antibodies and the onset of PM/DM after anti-TNF therapy, interactions between anti-synthetase antibodies and TNF$\alpha$ seem to play critical roles in the pathogenesis.

In contrast to that for RA, the efficacy of anti-TNF therapy for treating PM/DM remains unclear. But present case and the reported four cases pose one speculative explanation that anti-TNF therapy induces clinical overt myositis in patients with underlying or subclinical PM/DM, which is characterized by the presence of anti-Jo-1 antibodies, but the absence of muscle symptoms. The frequency of RA patients with anti-Jo-1 antibodies is unclear. However, as a precaution, tests for anti-Jo-1 antibodies should be carried out prior to the administration of TNF-blocking agents if a patient presents characteristic symptoms of anti-synthetase syndrome. Furthermore, if tests for anti-synthetase antibodies are found to be positive, the patient should be carefully monitored so that treatment can be stopped as soon as findings suggestive of PM/DM become apparent.
References


