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CASE REPORT

Treatment with Etanercept in a Patient with Rheumatoid Arthritis-Associated Interstitial Lung Disease

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Abstract: We report a case of a 52-year-old woman with a 1-year history of rheumatoid arthritis-associated interstitial lung disease referred to hospital because of aggravated pulmonary symptoms in spite of intensive treatment including prednisone, azathioprine and triptergium glycoside. We subsequently initiated treatment with 25 mg of etanercept, subcutaneously injected twice weekly. Following 6 months of therapy with this agent, sustained improvement in dyspnea, cough was reported by the patient and respiratory function test showed marked improvement. The improvement was confirmed by reduced middle and lower lung markings on chest radiography and high-resolution CT scan. This report suggests etanercept may be effective in the treatment of rheumatoid arthritis-associated interstitial lung disease.

Keywords: rheumatoid arthritis, interstitial lung disease, etanercept

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Introduction

Although tumor necrosis factor (TNF)-α inhibitors have been used for the treatment of patients with rheumatoid arthritis for more than a decade,[1–3] their effect on RA-associated ILD (rheumatoid arthritis—associated interstitial lung disease) have been rarely reported.

TNF-α is one of most important cytokines in the early immune response to a variety of inflammatory disorders, and is a critical mediator in the pathogenesis of pulmonary fibrosis.[4] TNF-α can directly stimulate the secretion of matrix proteins, increase fibroblast proliferation, and promote induction of matrix-degrading gelatinases that can facilitate fibroblast migration to site of injury.[5] Increased expression of TNF-α gene is observed in fibrotic human lungs as well as animal models of lung fibrosis, and inhibition of TNF-α expression can significantly reduce the incidence of pulmonary fibrosis.[6] Therefore, TNF-α inhibitors have potential for the treatment of RA-associated ILD.

Here we report a case of RA-associated ILD whose condition was improved after etanercept (a recombinant TNF- α blocker) treatment.

Case Report

A 52-year-old woman first experienced knee pain and swelling bilaterally in May 2002, followed by gradual emergence of pain and swelling in wrist, metacarpophalangeal and proximal interphalangeal joints in both hands, with morning stiffness lasting more than one hour. In August 2002, rheumatoid arthritis was confirmed. Methotrexate (MTX) (10 mg/w) plus leflunomide (10 mg/d) were used to control her disease. Approximately a year later the patient stopped her drugs because of relieved joint symptoms. She was admitted to hospital in June 2006 for aggravation of joint symptoms with irregular low heat, cough during the preceding two months.

Physical examinations disclosed fine moist rales in the lower location of the lungs, tenderness and swelling at both knees and both wrists, and toe joints deformities. Laboratory testing demonstrated an erythrocyte sedimentation rate of 66 mm/h, a C-reactive protein of 50.30 mg/L, a rheumatoid factor of 21.9 IU/mL, an anti-CCP antibody of 58 RU/mL, but negative for antinuclear antibodies. High-resolution CT scan of the chest showed lung markings increased, part of the grid-like changes, interlobular septa thickening, and patchy density- enhanced shadow. Pulmonary function tests demonstrated a slight restrictive ventilation dysfunction with severe small airway obstruction, but the diffusing capacity was normal. The patients had no history of pulmonary disease and had no other medical problems. There was no history of exposure to any known occupational irritant or birds. She had no history of smoking, and denied a history of illicit drug use or alcohol abuse a diagnosis of RA-associated ILD was made.

The patient received the following medications at presentation: prednisone, 30 mg/d; azathioprine 100 mg/d, triptergium glycoside 30 mg/d. After leaving hospital prednisone dosage gradually reduced to 10 mg/d. Her joint's condition was improved, but the symptoms of cough and expectoration were not improved. In January 2007, the patient was admitted to hospital again because of a repeated cough with. On examination of the lungs there were moderate moist sounds at both bases. High-resolution CT scan of the chest showed bilateral lung interstitial lesions and emphysema, mediastinal lymphadenopathy. Pulmonary function tests revealed mixed ventilatory disorder, severe obstruction in small airway function (VC 73.0%, FEV 69.2%), small reduction in diffusing capacity (TLCO/VA 69.2%).

In February 2007, she began receiving 25 mg of etanercept, subcutaneously injected twice weekly, along with prednisone (10 mg/d). During six –month treatment she was followed up monthly. We found that her right-side basilar moist rales disappeared and left-side basilar moist rales could still be detected. Chest radiography showed middle and lower lung markings were reduced and the marked improvements were also confirmed by high-resolution CT. In July 2007 pulmonary function tests suggested a slight restrictive ventilation dysfunction, with moderate small airway function obstruction (VC 76.7%, FEV 72.9%) and normal diffusion capacity (TLCO/VA 89.2%). Before and after the treatment of etanercept, her arthritis activity has been quiescent.

Discussion

This is the first report documenting RA-associated ILD treated with etanercept in China. We found that pulmonary function in a female patient with RA-associated ILD was improved after etanercept

treatment for 6 months. Symptoms and signs were also ameliorated.

ILD is the most common manifestation of pulmonary disease in rheumatoid arthritis which severely affects prognosis of rheumatoid arthritis, and its secondary pulmonary fibrosis is one of the causes of death. However, the conventional treatments of ILD associated to RA are not effective, and some new drugs such as interferon-γ, pirfenidone, acetylcysteine, endothelin receptor antagonist, 5-lipoxygenase inhibitor are still in the stages of clinical trials.[7]

In 2002, Vassallo et al[8] first treated a patient with RA-associated ILD for 1 yr with anti-tumor necrosis factor-α infliximab. The patient is a 71-year-old man with a 3-year history of seropositive rheumatoid arthritis. Approximately a year following the onset of joint symptoms, progressive dyspnea and dry cough appeared. Lung examination revealed fine Velcro-type crepitations at the bases of both lungs. Laboratory testing demonstrated a PO_2 at rest of 75 mm Hg, which declined to 51 mm Hg following mild exercise. Chest radiography and high-resolution CT scan show pulmonary fibrosis with honeycombing. Following 1 year of therapy with infliximab, along with the improvement in joint symptoms, the patient sustained improvements in dyspnea, dry cough, and exercise tolerance. Pulmonary function demonstrated a normal saturation at rest and a saturation decline to only 90% following mild exercise.

In 2004, Bargagli et al[9] also reported a patient with rheumatoid arthritis and pulmonary fibrosis whose condition was improved after 15 months of infliximab treatment. Lung function tests (LFT) showed increases of 17% in TLCO (from 65% to 82%), and 11% in VC (from 73% to 84%); in contrast, high-resolution CT scan of the chest, which showed bibasilar mantellar fibrosis with honeycombing, was not altered after 15 months of therapy. Similar to our case, these results suggests a tumor necrosis factor-α inhibitor may be more effective on acute exudative lesions of RA-associated ILD by improving lung function, but has poor effects on chronic pulmonary fibrosis. It is expected to have a better efficacy if used at the early stage of RA-associated ILD.

It has been documented that methotrexate (MTX) can induce ILD whose frequency is around 1%–5%.[10] MTX induced- ILD is characterized by the occult onset after MTX use and improvement after stopping while recurrence of lung symptoms after repeated use. It is difficult to distinguish it from RA-associated ILD from clinic and imaging feathers. Although having a history of MTX treatment, our patient was treated only for 1 year, 2 years before receiving a diagnosis of RA-associated ILD. It is clear that MTX use cannot explain the occurrence of ILD, because MTX had been stopped for nearly 4 years, and the patient's diffuse capacity had not been improved until using etanercept.

It has been reported that etanercept can induce ILD or its aggravation.[11] However, our patient have ILD before etanercept, and her condition improved markedly after etanercept. Triptergium is a chinese herb which is used in chronic inflammatory disorders, we have not find any article reporting triptolide can induce ILD or its aggravation through a MEDLINE search.

In conclusion, this study suggests etanercept may be effective in the treatment of RA-associated ILD. This needs to be confirmed by future double-blind, randomized controlled trials.

Conflicts of Interest

Yu Wang, Sheng-qian Xu, Jian-hua Xu, Changhai Ding declare that there are no conflicts of interest.

Disclosure

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest. Written consent was obtained from the patient's daughter for publication of this study.

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