

Case Report

Leflunomide therapy-associated tuberculosis infection

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Leflunomide is a new type of immunosuppressive agent for treatment of rheumatoid arthritis and good efficacy has been obtained in clinical practice. These past years, leflunomide has been used for treatments of not only rheumatoid arthritis but also glomerulonephritis and ankylosing spondylitis. A case is presented that a male patient diagnosed ankylosing spondylitis and treated with leflunomide experienced tuberculosis of lymph nodes. The side effects of leflunomide were suspected and a literature review is followed. It was concluded that tuberculosis infection in this case might be a result of leflunomide therapy partly. Clinical concern should be put to inpatients treated with leflunomide.

Key words: tuberculosis, leflunomide, side effect.

INTRODUCTION

Leflunomide is a new anti-rheumatic medication of the disease-modifying anti-rheumatic drug (DMARD) type (Dougados et al., 2005). It is used in active moderate to severe rheumatoid arthritis (RA) in the earlier years, which is a progress of the treatment of RA (Katayama and Matsuno, 2009). Now leflunomide has been used more widely and has got a good clinical therapeutic effect evaluation. These past years, leflunomide is used for not only treatment of systemic lupus erythematosus (SLE) but also treatment of glomerulonephritis (Lou et al., 2006) and ankylosing spondylitis (AS) (Haibel et al., 2005). Leflunomide is a pyrimidine synthesis inhibitor, which is chemically and pharmacologically heterogeneous (Pinto et al., 2006). So it is a new immunosuppressant. It is known that patients with immunosuppressant therapy often undergo bacteria, tuberculosis and virus infection. The side-effects of leflunomide affect quite a number of organ systems, including liver damage ranging from jaundice to hepatitis, myelosuppression with

leukopenia and/or hypoplastic anemia, and/or thrombocytopenia, interstitial lung disease, and infections (Pinto et al., 2006). But the report of leflunomide associated tuberculosis is rare. A clinical case of a patient who developed tuberculosis of lymph nodes during treatment with leflunomide is presented and followed by a literature review.

CLINICAL DATA

This is a 32 old male patient, who was hospitalized for 2 year lumbar and back pain with one year right knee joint swelling and pain, and stiffness in the middle part of the spine as well as have a family history of AS. His body temperature was 36.9°C, pulse rate 77 beats per minute (bpm), blood pressure 125/70 mmHg taken with mercurial sphygmomanometer. There were no swollen superficial lymph nodes were found. Examination of chest and abdomen showed no abnormality. Swelling right knee and bilateral positive "4" signs were observed. After examination, the following laboratory test results were obtained: HLA-B27 positive, ESR 51 mm/h, CRP 112 mg/L, WBC 11.8×10^9 /L, PLT 412×10^9 /L, OT test negative,

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normal hepatic function. CT scan showed bilateral sacroiliitis, and ultrasonography showed no enlarged superficial and abdominal lymph nodes, and chest X-ray films showed no abnormality.

A diagnosis of AS was made. Then the patient was administered salicylazosulfapyridine (SASP) 1.0 bid po, leflunomide 20 mg qd po and diclofenac sodium 75 mg qd po. The symptoms were improved after 6 weeks with CRP 10 mg/L, ESR 26 mm/h and normal hepatic and renal function.

Three months later, the patient was given SASP 1.0 bid po and leflunomide 10 mg qd po. After 6 months, right side enlarged cervical lymph node occurred with low fever, night sweat. Ultrasonography showed multiple bilateral enlarged cervical lymph node, and the largest one on right side was approximately 18mm×16mm. Blood routine tests showed WBC 8.7×10^9 /L, N 70%, PLT 316×10^9 /L, ESR 49 mm/h, and CRP 120 mg/L. OT showed a titre of 1:2000 (++++). Biopsy of lymph node showed caseous necrosis and acid-fast bacillus was found.

The patient was diagnosed with lymphoid tuberculosis. Leflunomide was stopped. He was treated with Isoniazid, rifampicin, pyrazinamide and para-salicylic acid at once. The symptoms were improved significantly after 6 weeks and lymph nodes were reduced in size after 3 months.

The patient with AS was diagnosed tuberculosis and it was through the side effect of leflunomide. It was concluded that tuberculosis infection in this case might be a result of leflunomide therapy partly.

DISCUSSION

Leflunomide is a new type of isoxazole immunosuppressive agent with anti-proliferative activity. It inhibits the activity of pyrimidine of lymphocyte by suppressing the activity of dihydrogen L-lactate dehydrogenase. Both *in vivo* and *in vitro* trials have suggested that leflunomide has anti-inflammatory effect (Savage, 2010). Currently, leflunomide has been used for the first-line therapy of RA and gradually applied to the treatment of SLE (Zhang et al., 2009), glomerulonephritis (Lou et al., 2006) and AS (Haibel et al., 2005).

Like other immunosuppressive agents, leflunomide also has side effects including decrease in leucocyte and damage of immune function of human body. Among which, hepatic impairment is more common (Suissa et al., 2006), and pulmonary fibrosis is induced sporadically (Wong et al., 2007). Literatures have reported that leflunomide leads to infectious diseases such as skin infection, upper respiratory tract infection and vaginal candidiasis (Grover et al., 2006), and leflunomide-related tuberculosis infection has been also reported sporadically (Hocevar et al., 2006). SASP is generally considered to be a typical

anti-rheumatic drug which does not cause tuberculosis infection although there have been report of SASP-induced decrease in leukocyte.

The patient in this report was diagnosed AS. His symptoms were improved and both ESR and CRP were decreased after treatment with SASP and leflunomide. This indicated the efficacy of leflunomide on large limb arthritis of AS. The patient showed no evidence of tuberculosis infection before he received leflunomide (OT test was negative, no enlarged cervical lymph node was found, and chest X-ray films showed no signs of tuberculosis). However, he was diagnosed with confirmed tuberculosis with lymph node enlargement after 6 months. This was possibly related to AS treatment-associated damage to immune function, and most likely associated with leflunomide. Since there are rare relevant literature reports and no direct evidence showing that tuberculosis infection was induced by leflunomide in this case, the causality between leflunomide and tuberculosis infection needs further investigation.

Since the incidence of tuberculosis has been prone to increasing globally in recent years, the disease has attracted more and more attention. People attach much importance to the risk of tuberculosis in patients receiving biological agents, especially tumor necrosis factor antagonists (Bray et al., 2010). However, the immunosuppressive agent is one of the most common causes of tuberculosis infection in patients with auto-immune diseases. Therefore, more concern should be put to the risk of tuberculosis in patients receiving new immunosuppressive agent.

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