



Re-administration of abatacept for the control of articular symptoms of rheumatoid arthritis during anti-tuberculous therapy



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ABSTRACT

This case report describes the re-administration of abatacept to successfully reduce the articular symptoms of a patient with rheumatoid arthritis during the intensive phase of anti-tuberculous therapy. A 75-year-old man developed active pulmonary tuberculosis during the administration of abatacept for rheumatoid arthritis. The patient experienced a paradoxical reaction and exacerbation of rheumatoid arthritis that caused us to discontinue the abatacept. Later re-administration of abatacept along with anti-tuberculosis treatment led to well-controlled rheumatoid arthritis without exacerbation of the tuberculosis. This case shows that re-administration of abatacept may be much safer than TNF inhibitor to treat patients who are infected with mycobacteria during the treatment of immunological diseases such as rheumatoid arthritis with biological agents.

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1. Introduction

Biological agents such as abatacept are widely used in patients with moderate-to-severe active rheumatoid arthritis (RA). However, biological agents increase the risk of reactivation of the latent tuberculosis (TB) infection [1]. The American College of Rheumatology proposes that biological agents can be re-administered to patients with active TB after completion of anti-TB therapy [2]. The British Society of Rheumatology recommends that patients who are treated with biological agents should receive full anti-TB chemotherapy if clinically indicated [3].

Stopping treatment with biological agents increases the risk of exacerbating the disease attributable to the recovery of the biological agent-dependent inflammation. When RA patients are treated with biological agents that exacerbate pre-existing tuberculous lesions or cause the development of new lesions, this is termed a paradoxical reaction. Patients with a paradoxical reaction typically show fever, pulmonary infiltrates, and hypoxemia [4]. It is

necessary to control the active TB as well as the RA in a paradoxical reaction.

Here, we describe a RA patient who developed active TB during the initiation of abatacept, which is not an anti-tumor necrosis factor (TNF) agent, and whose RA and TB were successfully controlled by the re-administration of abatacept after anti-TB treatment.

2. Case report

A 75-year-old man was diagnosed as having RA 2 years ago because of polyarthralgia and increases in inflammatory reactions, rheumatoid factor and anti-cyclic citrullinated peptide antibody. At first, prednisolone (PSL) was prescribed at 5 mg per day, and salazosulfapyridine and methotrexate were added shortly thereafter because his RA was not under good control. After half a year, abatacept was also added because the above-mentioned medicines were still not enough to control the RA. After the addition of abatacept, his RA had been well controlled.

Two years later, he complained of a cough and slight fever. Laboratory data indicated increased inflammatory reaction, and a chest X-ray and computed tomography (CT) scan revealed consolidation in the right upper field lung (Fig. 1A and B). The patient's

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previous physician suspected bacterial pneumonia, discontinued the abatacept, and prescribed new quinolone antibiotics. However, the patient's pulmonary symptoms and laboratory data did not improve, and his RA was getting worse. Thereafter, *Mycobacterium tuberculosis* was confirmed by polymerase chain reaction and culture of his sputum. The isolated *M. tuberculosis* was susceptible to all anti-TB drugs. The result of a T-SPOT® TB test was indeterminable, and his C-reactive protein and matrix metalloproteinase 3 levels were elevated (Table 1).

After the diagnosis of TB, an anti-TB regimen comprising isoniazid, rifabutin, ethambutol and pyrazinamide was initiated. His cough improved although he still had a slight fever after the anti-TB regimen. On the 21st day of therapy, he experienced breathlessness, and oxygen at 2 L was necessary to maintain his blood oxygen level. A chest X-ray and CT scan showed progression of consolidation in the right upper lung field and new consolidation in the left upper lung field (Fig. 2A and B). A paradoxical reaction was suspected because consolidation in the pre-existing lesions had worsened and a new lesion appeared even though his clinical symptoms had improved with the anti-TB regimen. We added steroid pulse therapy (methylprednisolone at a daily dose of 1000 mg for 3 days) to the ongoing anti-TB therapy, after which his chest X-ray, oxygen saturation and RA symptoms immediately improved. After steroid pulse therapy, PSL 60 mg per day was used as steroid

Table 1

Laboratory data on admission.

Hematology	
White blood cells	8170/ μ L
Hemoglobin	12.4 g/dL
Platelets	28.3×10^4 / μ L
Serology	
Albumin	3.4 g/dL
AST	19 U/L
ALT	18 U/L
Creatinine	0.78 mg/dL
C-reactive protein	6.3 mg/dL
Hemoglobin A1c	6%
Biochemistry	
Anti-CCP antibody	783.4
MMP-3	300.4
RF	228.3 IU/mL
T-spot TB	
	Indeterminable

AST, aspartate aminotransferase; ALT, aspartate aminotransferase; CCP, cyclic citrullinated peptide; MMP-3, matrix metalloproteinase 3; RF, rheumatoid factor; TB, tuberculosis.

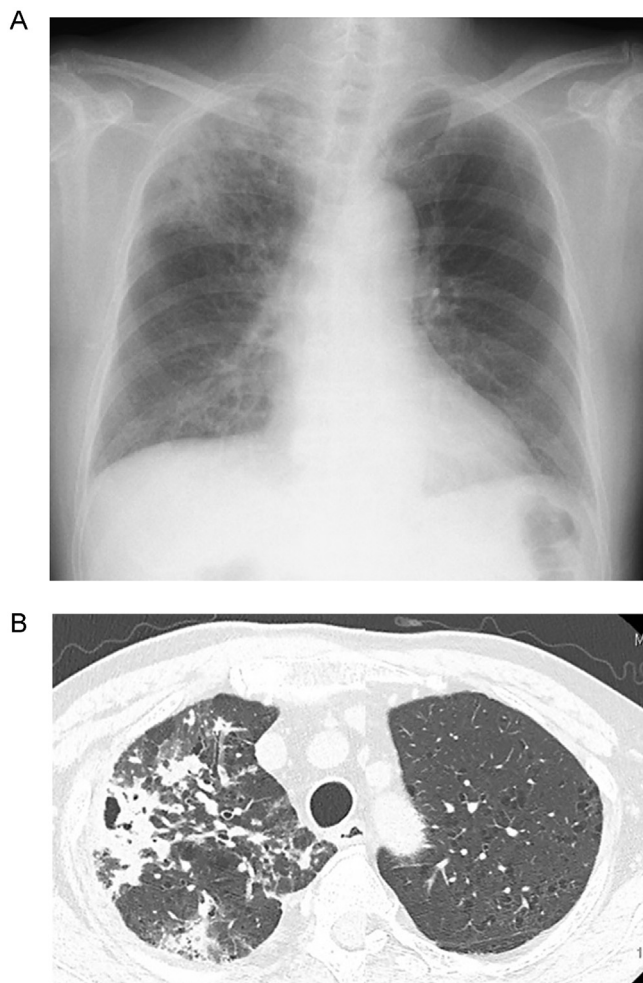


Fig. 1. (A) Chest X-ray shows consolidation in the right upper lung field and ground glass opacity in the bilateral lung bases. (B) Chest computed tomography shows emphysema, consolidation and granular shadows in the right upper lobe.

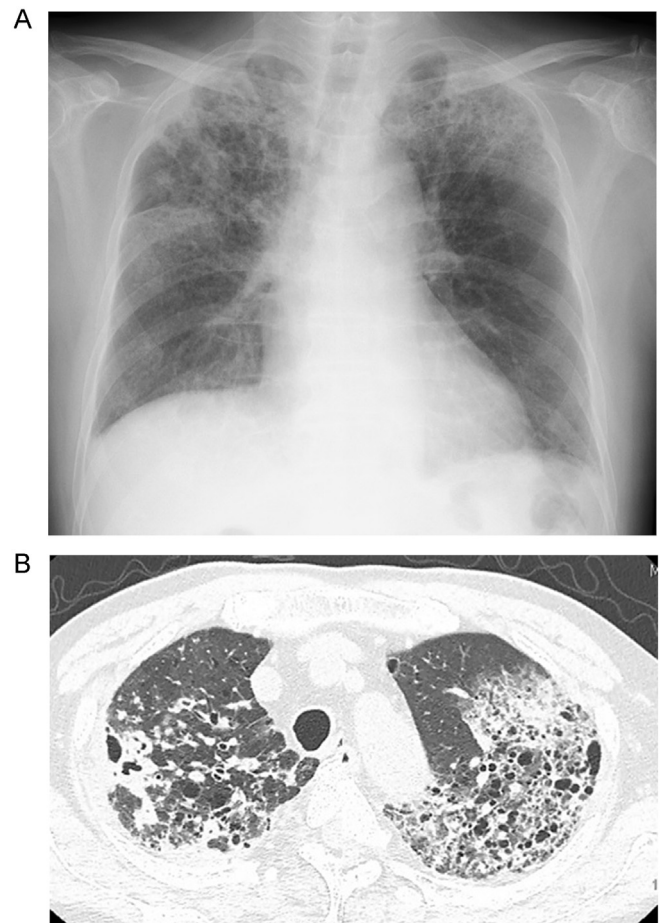


Fig. 2. (A) Chest X-ray shows exacerbation of the consolidation in the right upper lung field and the spread of consolidation to the left upper lung field. (B) Chest computed tomography shows the spread of consolidation in the bilateral lung lobes.

maintenance therapy. After steroid therapy for one month, almost all consolidations in the bilateral upper lung fields had disappeared (Fig. 3). We began to gradually taper the dose of PSL every week because his clinical course was uneventful.

When the PSL was reduced to 15 mg per day, he experienced exacerbation of left knee joint pain, and was no longer able to walk.



Fig. 3. Chest X-ray shows improvement of the consolidation in the bilateral lung fields.

His RA was thought to have recurred, so we increased the PSL to 20 mg per day. However, his symptoms were little improved. Because a high dose of PSL was needed to control his RA, we implemented a policy of re-administering abatacept to promote RA control.

After re-administration of abatacept, his symptoms improved gradually, and we succeeded in reducing the PSL by 2.5 mg every two weeks. He was discharged under good control of RA with PSL at 10 mg per day and has continued to maintain a good clinical course after discharge (Fig. 4).

With regard to TB, culture of his sputum was positive only once

after admission. However, liver function disorder, a drug rash and bleary eyes occurred as adverse events. The anti-TB regimen was therefore changed to the combination of isoniazid, rifampicin and levofloxacin, with the ethambutol and pyrazinamide eliminated (Fig. 4). He is currently being treated with anti-TB therapy without relapse of his *M. tuberculosis* infection.

3. Discussion

Keane et al. [5] reported the onset of tuberculosis during the administration of TNF inhibitors or biological agents that are commonly used in a large number of RA patients. From 2004 to 2012 in Japan, the onset of TB during the administration of biological agents was reported in 408 patients, 13 of whom died [6]. Thus, tuberculosis treatment should be kept in mind when biological agents are administered.

Some reports [7,8] indicated that reinstatement of infliximab and adalimumab was effective in controlling bacteriological infection in cases in which paradoxical reaction was observed. One report showed that the group undergoing high doses of steroid or etanercept treatment during the first month had a significantly better negative bacterial infection rate than the group treated with usual medical treatment [9], and another report stated that reinstatement of infliximab resulted in good control of RA in addition to TB treatment [10]. Although the prevailing opinion is that treatment with biological agents should be stopped during active pulmonary tuberculosis, we would like to propose the possibility of administering a biological agent carefully along with TB treatment. However, further studies will be required to obtain evidence of the effectiveness of parallel treatment with biological agents and anti-TB medicine.

Currently, there are several biological agents for RA in the world. Biological agents except abatacept are contraindicated in patients

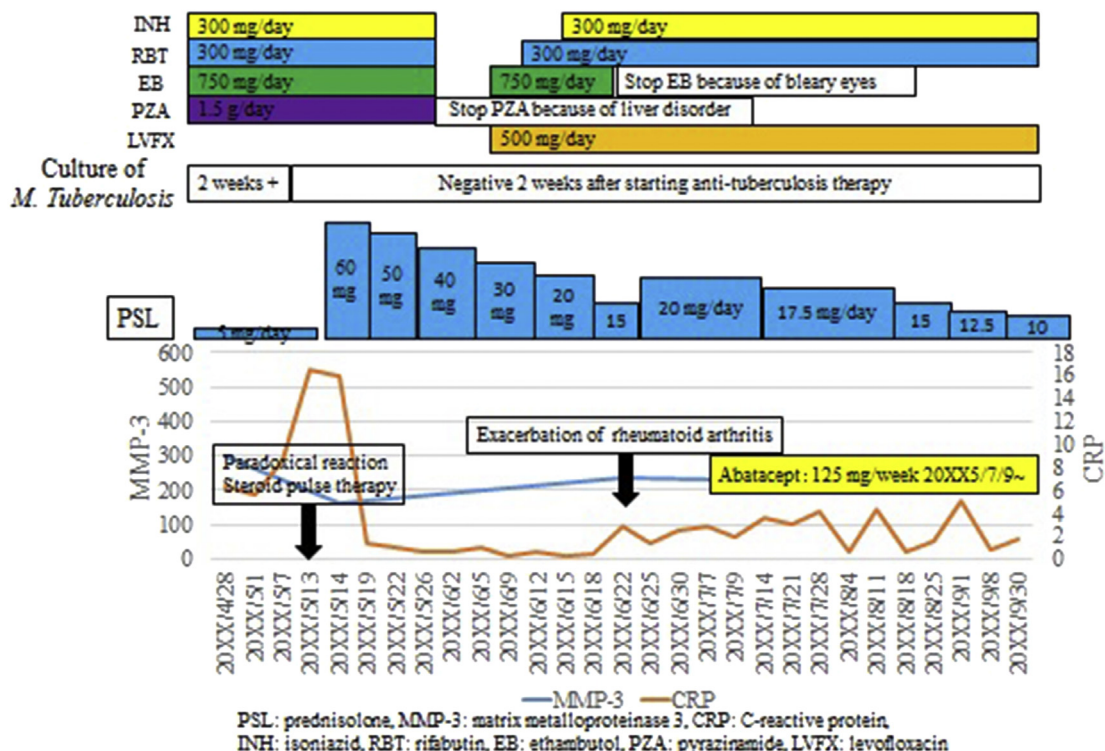


Fig. 4. Clinical course of the patient's rheumatoid arthritis. The doses of prednisolone, the period of abatacept treatment, and changes in the patient's C-reactive protein and matrix metalloproteinase 3 values are shown. And clinical course of anti-tuberculosis treatment and *Mycobacterium tuberculosis* infection.

with active pulmonary tuberculosis. In contrast, only abatacept is permitted to be carefully administered according to the medical package insert as the first new class agent for RA treatment because it has a fundamentally different mechanism of action than other anti-TNF therapies. The mechanism of action for abatacept selectively modulates the CD80/CD86-mediated CD28 costimulatory signal required for full T-cell activation and is a fusion protein that consists of the extracellular domain of human CTLA-4 linked to the modified Fc (hinge, C_H2, and C_H3) protein of human IgG1 [11,12]. Therefore, it is an immunomodulator and may affect the host response to opportunistic infections, including TB.

TNF is an important cytokine for the formation of granulomas [13]. There is a report that TB infection caused by the administration of TNF inhibitors decreased the survival rate of TNF receptor knockout mice [14]. In mice with chronic TB infection, no significant difference was observed in survival rate or weight loss between the abatacept group and placebo. However, the group with TNF inhibited had a significantly shorter survival rate and lost more weight than the abatacept group [15]. The cause of these results remain unclear [15].

This reports highlights the possibility that re-administration of abatacept is much safer than a TNF inhibitor to treat patients infected with mycobacteria during the treatment of an immunological disease such as RA with biological agents. Additional clinical studies are need to establish the role of abatacept in the treatment of RA and other immunological diseases.

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