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

Hironori Kawamoto, M.D. a,*, Jin Takasaki b, Satoru Ishii b, Manabu Suzuki b, Eriko Morino b, Go Naka b, Motoyasu Ikura b, Shinyu Izumi b, Yuichiro Takeda c, Haruhito Sugiyama b

a Division of Respiratory Diseases, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan
b Division of Respiratory Diseases, Department of Internal Medicine, National Center for Global Health and Medicine, Tokyo, Japan
c Division of Respiratory Diseases, Department of Internal Medicine, Kohnodai Hospital, National Center for Global Health and Medicine, Tokyo, Japan

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.

© 2017 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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 tuberculosis 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 polyarthritis 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
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 cul-
ture of his sputum. The isolated *M. tuberculosis* was susceptible to
all anti-TB drugs. The result of a T-SPOT® TB test was indetermin-
able, and his C-reactive protein and matrix metalloproteinase 3
levels were elevated (Table 1).

After the diagnosis of TB, an anti-TB regimen comprising isoni-
azid, 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 breathless-
ness, and oxygen at 2 L was necessary to maintain his blood oxygen
level. A chest X-ray and CT scan showed progression of consolid-
ation in the right upper field lung and new consolidation in the left
upper field lung (Fig. 2A and B). A paradoxical reaction was sus-
ppected 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
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.

---

**Table 1**

| Laboratory data on admission. |
|-------------------------------|
| **Hematology**                |
| White blood cells             | 8170/μL                  |
| Hemoglobin                    | 12.4 g/dL                |
| Platelets                     | 28.3 × 10⁴/μL            |
| **Seroology**                 |
| 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.
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 reinstitution 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 reinstitution 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...
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, CH2, and CH3) 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 report 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 needed to establish the role of abatacept in the treatment of RA and other immunological diseases.

References

[1] R.S. Wallis, Tumour necrosis factor antagonists: structure, function, and tuberculosis risks, Lancet Infect. Dis. 8 (2008) 601–611.

[2] A.A. Singh, D.E. Furst, A. Bharat, et al., 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis, Arthritis Care Res. 64 (2012) 625–639.

[3] T. Ding, J. Ledingham, R. Luqmani, et al., BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies, Rheumatology 49 (2010) 2217–2219.

[4] A.C. Carvalho, G. De Iaco, N. Salemi, et al., Paradoxical reaction during tuberculosis treatment in HIV-seronegative patients, Clin. Infect. Dis. 42 (2006) 893–895.

[5] J. Keane, S. Gershon, R.P. Wise, et al., Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent, N. Engl. J. Med. 345 (2001) 1098–1104.

[6] T. Matsumoto, Incidence and number of reported deaths due to tuberculosis during treatment with biologic agents in Japan, J. Infect. Dis. Ther. 2 (2014) 4.

[7] R.S. Wallis, C. van Vuuren, S. Potgieter, Adalimumab treatment of life-threatening tuberculosis, Clin. Infect. Dis. 48 (2009) 1429–1432.

[8] T.K. Blackmore, L. Manning, W.J. Taylor, et al., Therapeutic use of infliximab in tuberculosis to control severe paradoxical reaction of the brain and lymph nodes, Clin. Infect. Dis. 47 (2008) e83–e85.

[9] R.S. Wallis, Reconsidering adjuvant immunotherapy for tuberculosis, Clin. Infect. Dis. 41 (2005) 201–208.

[10] T. Matsumoto, T. Tanaka, I. Kawase, Infliximab for rheumatoid arthritis in a patient with tuberculosis, N. Engl. J. Med. 355 (2006) 740–741.

[11] J.M. Kremer, M. Dougados, P. Emery, et al., Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iiib, double-blind, randomized, placebo-controlled trial, Arthritis Rheum. 52 (2005) 2263–2271.

[12] P.S. Linsley, W. Brady, M. Urnes, et al., CTLA-4 is a second receptor for the B cell activation antigen B7, J. Exp. Med. 174 (1991) 561–569.

[13] P.I. Mapp, M.C. Grootveld, D.R. Blake, Hypoxia, oxidative stress and rheumatoid arthritis, Br. Med. Bull. 51 (1995) 419–436.

[14] J.L. Flynn, M.M. Goldstein, J. Chan, et al., Tumor necrosis factor-alpha is required in the protective immune response against Mycobacterium tuberculosis in mice. Immunity 2 (1995) 561–572.

[15] C.L. Bigbee, D.G. Gonchoroff, G. Vratsanos, et al., Abatacept treatment does not exacerbate chronic Mycobacterium tuberculosis infection in mice, Arthritis Rheum. 56 (2007) 2557–2565.