Case report

A fatal case of acute exacerbation of interstitial lung disease in a patient with rheumatoid arthritis during treatment with tocilizumab

Shin-ya Kawashiri[1], Atsushi Kawakami[1], Noriho Sakamoto[2], Yuji Ishimatsu[2], and Katsumi Eguchi[1]

[1]Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan
[2]Second Department of Internal Medicine, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

Address for correspondence and reprint requests:
Shinya Kawashiri, M.D.
Unit of Translational Medicine,
Department of Immunology and Rheumatology,
Graduate School of Biomedical Sciences, Nagasaki University,
1-7-1 Sakamoto, Nagasaki 852-8501, Japan
Phone: + 81-95-819-7266
Fax: 81-95-849-7270
E-mail: shinya22@nagasaki-u.ac.jp

Abstract

A 68-year-old man, who was an established rheumatoid arthritis (RA) patient with RA-associated interstitial lung disease (RA-ILD) and pulmonary emphysema, began taking tocilizumab. Subsequently, he developed dyspnea parallel to improvement of RA. At ten months after the administration of tocilizumab, he was urgently admitted because of exacerbation of ILD. He died despite receiving steroid pulse therapy and antibiotic therapy on a respirator. This is the first case report to describe the exacerbation of ILD during treatment with tocilizumab in the postmarketing surveillance (PMS) period.

Key words

Tocilizumab, rheumatoid arthritis, interstitial lung disease, pneumocystis pneumonia

Introduction

Tocilizumab is a humanized anti- interleukin-6 (IL-6) receptor monoclonal antibody that blocks IL-6 from binding to its receptor [1]. Japanese [2, 3] and Euramerican [4-7] randomized control trials (RCT) have elucidated the efficacy as well as safety of tocilizumab therapy in rheumatoid arthritis (RA) patients. However, RA patients in RCT had a lower rate of risk factors for adverse effects than in postmarketing surveillance (PMS) in general [8]. Therefore, it is necessary to accumulate clinical information on "real-world" RA cases treated with tocilizumab in Japan starting now.

In this report, we describe an established RA patient with chronic respiratory failure caused by RA-associated interstitial lung disease (RA-ILD) and pulmonary emphysema, who was administrated tocilizumab during PMS. He died of acute exacerbation of ILD during treatment with tocilizumab.

Case report

The patient was a 68-year-old Japanese man who had been diagnosed with RA in 2003, and treated sequentially with salazosulfapyridine (SASP). He also had RA-ILD, and pulmonary emphysema. RA-ILD was classified as usual interstitial pneumonia (UIP) by the transbronchial lung biopsy (TBLB) specimens. He had a history of smoking thirty cigarettes a day for forty years. He was administered home oxygen therapy because of chronic respiratory failure. He was treated with leukocyte aphaeresis against RA in May 2004. Although he began taking etanercept in February 2006, RA disease activity remained high. In July 2008, he was unable to move because of polyarthralgia and was urgently admitted to our hospital. Treatment for his RA was switched from etanercept to tocilizumab. The clinical course after the administration of tocilizumab is shown in Figure 1. Although no therapeutic efficacy was obtained (disease activity score of 28 joints; DAS28 > 5.1), DAS28 and C-reactive protein (CRP) tended to decrease from five months after the administration of tocilizumab. After eight months, a moderate response in the clinical efficacy of tocilizumab according to the criteria set by the European League against Rheumatism (EULAR) was seen, and the CRP levels dropped to negative values. However, he was admitted to our hospital in March 2009 because of increased dyspnea on exertion. Although image findings did not show exacerbation of RA-ILD and pulmonary emphysema, pulmonary function test showed remarkable diffusion disturbance; vital capacity (VC) of 91.8%, forced expiratory volume in 1.0 second ($FEV_{1.0}$) of 79.6%, and diffusion capacity of the lungs for carbon monoxide of 17.9%.

On May 6 2009 he was urgently re-admitted to our hospital because of acute exacerbation of dyspnea. On admission, temperature was 36.4 ℃, pulse 93 /min, respiration 20 /min, and blood pressure 109/70 mmHg. Saturation oxygen by pulse oximetry showed 85% at rest and 70% on exertion in 6 liter/min of oxygen. Fine crackles were heard on the bilateral lung. Edema was not found. The biochemical and serological data are shown in Table 1. The white blood count elevated at 14,000/mm^3, but CRP was negative. KL-6, SP-D and SP-A were elevated. Although β-D glucan slightly elevated at 23.3pg/ml, candida antigen, cryptococcal antigen and aspergillus antigen were all negative. The culture of the sputum and polymerase chain reaction (PCR) for *Pneumocystis jiroveci* of the bronchoalveolar lavage fluid (BALF) were also negative. Chest X-ray (Figure 2A) and computed tonography (CT, Figure 2B) on admission showed no remarkable change. On the following day, he was put on an artificial respirator because of worsening respiratory failure, and chest X-ray (Figure 2C) and CT (Figure 2D) showed exacerbation of interstitial infiltrates in the diffuse bilateral lungs. Steroid pulse therapy and antibiotic therapies were not effective. On May 12, 2009, β-D glucan remarkably elevated at 129.5pg/ml and he died on May 14, 2009.

Discussion

The present case was elderly and had established RA with preexisting ILD. He was administered tocilizumab because he was refractory to several DMARDs, but died from exacerbation of ILD at ten months after initiation of the tocilizumab therapy. Differential diagnoses included opportunistic infection, particularly pneumocystis pneumonia (PCP), drug-induced lung injury and exacerbation of RA-ILD. The exacerbation of ILD after administration of anti-tumor necrosis factor (TNF) agents was recently reported [9-11]. Older age and preexisting ILD are risk factors for anti-TNF agent-induced ILD [9]. Although tocilizumab is one of the new biologic DMARDs following anti-TNF agents, the mechanism of action of tocilizumab that improves RA is different from that of anti-TNF agents. In clinical studies such as the SAMURAI trial [2] and SATORI trial [3] in Japan, and the AMBITION trial [6], the TOWARD trial [5] and the RADIATE trial [7] in Europe and the United States, no patient developed ILD including PCP. However, one patient developed ILD and another developed PCP in the OPTION trial [4]. The former patient recovered rapidly on appropriate therapy. The latter patient had a history of chronic obstructive pulmonary disease. The PMS of infliximab and etanercept revealed incidences of PCP in Japanese patients with RA that were higher (0.4% and 0.2%, respectively) than in Western countries [8]. The risk factors of PCP in RA patients treated with infliximab were older age (≧65 years), high dosage of PSL (≧6 mg/day) and pulmonary comorbidities in Japan [12, 13]. Wolfe et al. reported that the risk factors of pneumonia hospitalization in RA patients were prednisolone (PSL) use, older age and the presence of pulmonary comorbidities and diabetes [14]. The RA-ILD is frequent in patients who are older, male, smokers and have a high titer of the rheumatoid factor. The acute exacerbation of RA-ILD results in a high fatality rate regardless of the therapy used. However, disease activity of RA is often uncontrolled when there is an acute exacerbation of RA-ILD. On the other hand, disease activity of RA is often strongly suppressed by treatment when as opportunistic infection and drug-induced exacerbation occur.

In the present case, it was difficult to define the cause of the exacerbation of ILD. Because β-D glucan remarkably elevated during the course of therapy and the patient had many risk factors for PCP, an older age (≧65 years), high dosage of PSL (≧6 mg/day) and pulmonary comorbidities, it is highly possible that PCP caused the exacerbation of ILD. Furthermore, the exacerbation might also be induced by opportunistic infection or drug-induced lung injury, because he had developed respiratory failure parallel to expression of the efficacy of tocilizumab.

References

[1] Mihara M, Kasutani K, Okazaki M, Nakamura A, Kawai S, Sugimoto M, et al (2005) Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other members of IL-6 cytokine family. Int Immunopharmacol 5:1731-40

[2] Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al (2007) Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis 66:1162-67

[3] Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J, et al (2009) Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol 19:12-9.

[4] Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al (2008) TOPTION Investigators. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet 371:987-97

[5] Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al (2008) Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum 58:2968-80

[6] Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, Siri DA, et al (2010) Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The AMBITION study. Ann Rheum Dis 69:88-96

[7] Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al (2008) IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis 67:1516-23

[8] Hagiwara K, Sato T, Takagi-Kobayashi S, Hasegawa S, Shigihara N, Akiyama O (2007) Acute exacerbation of preexisting interstitial lung disease after administration of etanercept for rheumatoid arthritis. J Rheumatol 34:1151-4

[9] Chatterjee S (2004) Severe interstitial pneumonitis associated with infliximab therapy. Scand J Rheumatol 33:276-7

[10] Villeneuve E, St-Pierre A, Haraoui B (2006) Interstitial pneumonitis associated with infliximab therapy. J Rheumatol 33:1189-93

[11] Takeuchi T, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H, et al (2008) Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. Ann Rheum Dis 67:189-94
[12] Harigai M, Koike R, Miyasaka N (2007) Pneumocystis Pneumonia under Anti-Tumor Necrosis Factor Therapy (PAT) Study Group. Pneumocystis pneumonia associated with infliximab in Japan. N Engl J Med 357:1874-6
[13] Komano Y, Harigai M, Koike R, Sugiyama H, Ogawa J, Saito K, et al (2009) Pneumocystis jiroveci pneumonia in patients with rheumatoid arthritis treated with infliximab: a retrospective review and case-control study of 21 patients. Arthritis Rheum 61:305-12
[14] Wolfe F, Caplan L, Michaud K (2006) Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum 54:628-34

List of Abbreviations used

CRP: C-reactive protein

CT: computed tonography

DAS: disease activity score

ILD: nterstitial lung disease

PCP: pneumocystis pneumonia

PMS: postmarketing surveillance

PSL: prednisolone

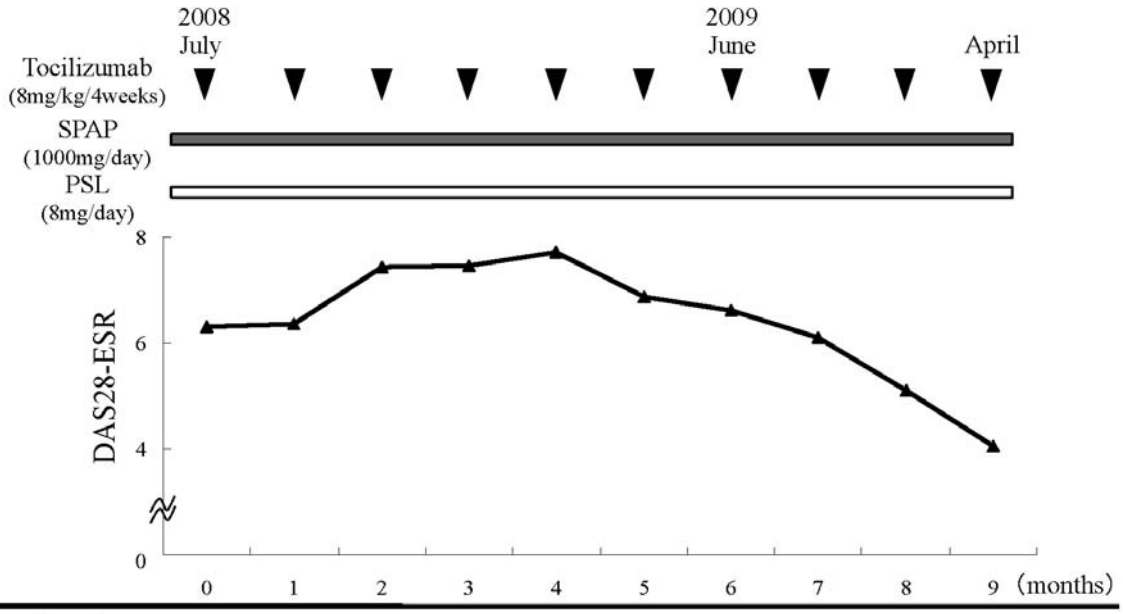
RA: Rheumatoid arthritis

RCT: randomised control trial

TNF: tumor necrosis factor

UIP: usual interstitial pneumonia

Figure Legends



WBC ($\times 10^3/mm^3$)	7.0	9.8	10.3	8.8
Hb (g/dl)	8.4	9.3	8.8	8.2
PLT ($\times 10^3/mm^3$)	34.9	36.1	25.3	29.3
CRP (mg/dl)	10.7	5.1	1.0	0.0
ESR (mm/hr)	119	61	26	11
IgG (mg/dl)	2,560	—	1,810	1,730
MMP-3 (ng/ml)	320	306	310	280
IgM-RF (IU/l)	2,580	—	1,170	692
KL-6 (U/ml)	1,088	—	974	1,073
β-D glucan (pg/dl)	18.3	10.9	16.1	12.4

Fugure 1

Clinical course after administration of tocilizumab.

SASP, salazosulfapyridine ; PSL, prednisolone

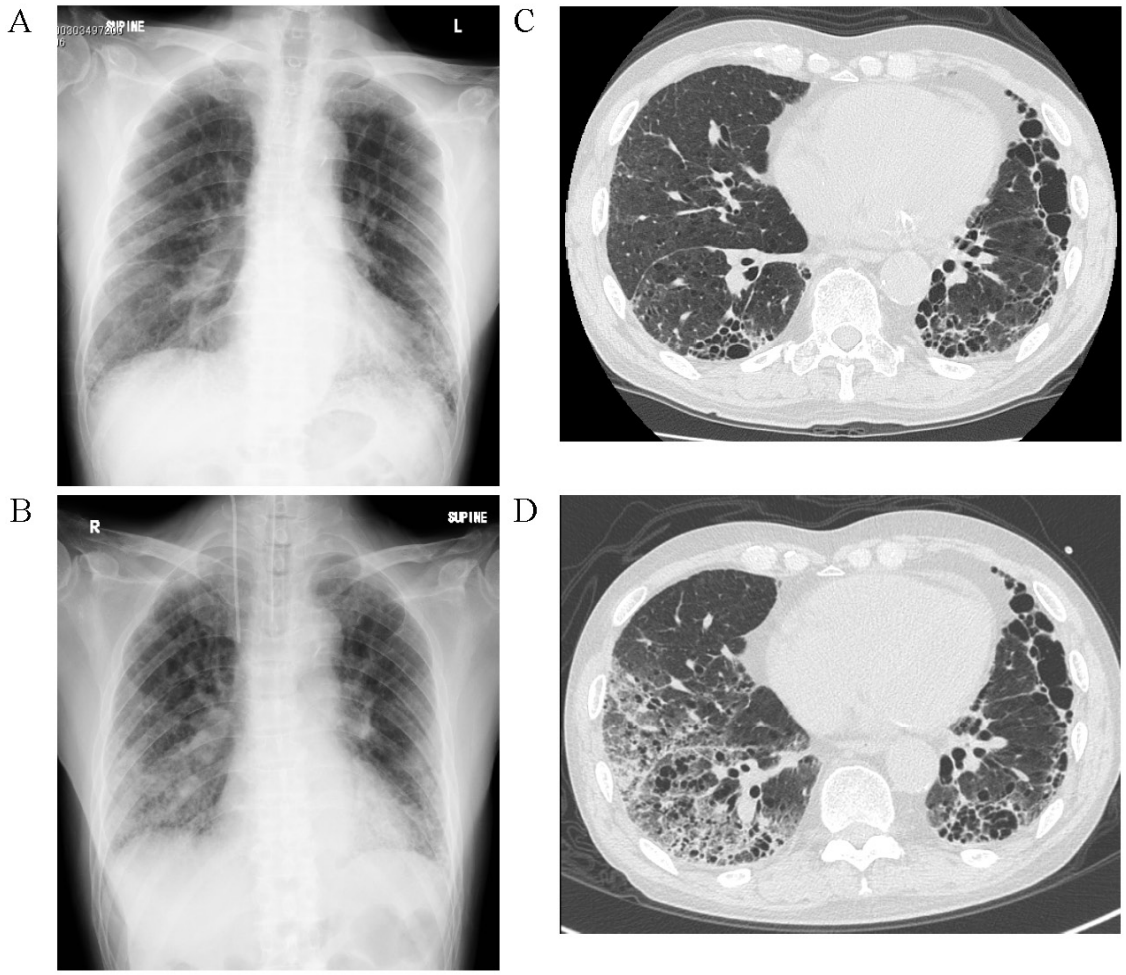


Figure 2

Chest radiograph and computed tomography (CT) obtained on admission (A, B) and on the following day (C, D).

A. Chest X ray (May 6), B. Chest CT (May 6); Interstitial infiltrates with honeycombing, which is the pattern of usual interstitial pneumonia (UIP), and emphysematous change are observed in the bilateral lungs.

C. Chest X ray (May 7), D. Chest CT (May 7); Diffuse bilateral ground-glass opacity appears in the bilateral lungs.

Table 1

Biochemical and serological evaluation

Laboratory test	Result	Laboratory test	Result
White cell count	14,000 /mm^3	C reactive protein	0.03 mg/dl
Neutrophils	10,780 /mm^3	IgA	401 mg/dl
Lymphocytes	2,520 /mm^3	IgG	1,500 mg/dl
Monocytes	560 /mm^3	IgM	172 mg/dl
Eosinophils	140 /mm^3	KL-6	1,339 U/ml
Hemoglobin	7.9 g/dl	SP-A	55.1 ng/ml
Platelets	26.8×10^4 /mm^3	SP-D	533 ng/ml
Sodium	137 mEq/l	β-D glucan	23.3 pg/dl
Potassium	3.8 mEq/l	Candida antigen	Negative
Chloride	107 mEq/l	Cryptococcus antigen	Negative
BUN	14.0 mg/dl	Aspergillus antigen	Negative
Creatinine	0.82 mg/dl	Mycoplasma antibody	Negative
AST	40 IU/l	Urinary S.pneumoniae antigen	Negative
ALT	22 IU/l	Urinary Legionella antigen	Negative
LDH	276 IU/l		
Total protein	6.7 g/dl	Arterial blood gas (O_2 6L/min)	
Albumin	3.6 g/dl	pH	7.41
Glucose	71 mg/dl	$PaCO_2$	30.2 mmHg
		PaO_2	89.7 mmHg
		HCO_3^-	18.8 mmol/l
		Base Excess	-4.8 mmol/l