

## Infliximab is Effective for Takayasu Arteritis Refractory to Glucocorticoid and Methotrexate

Fumiko Tanaka<sup>1</sup>, Atsushi Kawakami<sup>1</sup>, Nozomi Iwanaga<sup>1</sup>, Mami Tamai<sup>1</sup>, Yasumori Izumi<sup>1</sup>, Kouichiro Aratake<sup>1</sup>, Kazuhiko Arima<sup>1</sup>, Makoto Kamachi<sup>1</sup>, Hideki Nakamura<sup>1</sup>, Mingguo Huang<sup>1</sup>, Hiroaki Ida<sup>1</sup>, Tomoki Origuchi<sup>2</sup> and Katsumi Eguchi<sup>1</sup>

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### Abstract

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We have experienced a Takayasu arteritis (TA) patient, successfully treated with infliximab, who did not respond well to conventional therapy with glucocorticoid and methotrexate. Takayasu arteritis had developed in a 24-year-old woman (March 2003) who had been treated with glucocorticoid including methylprednisolone pulse therapy and methotrexate; however, she relapsed during the tapering of the dosage of oral prednisolone. Nineteen months after the first administration of glucocorticoid, 3 mg/kg of infliximab was introduced to the patient. The therapeutic efficacy of infliximab was markedly demonstrated; the patient's C-reactive protein (CRP) value returned to almost normal range with subsequent tapering of the dosage of oral prednisolone in the absence of further relapse. This is the first case presentation of TA in Japan successfully treated with infliximab.

**Key words:** Takayasu arteritis, infliximab

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### Introduction

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Takayasu arteritis (TA) is an idiopathic systemic granulomatous vasculitis of the large and medium-sized vessels, and tumor necrosis factor (TNF) is important in the formation of granuloma (1). The efficacy of TNF blockers has been described in TA that was not controlled by glucocorticoid therapy or other immunosuppressants in the USA (2); however, successful therapy of TA by TNF blockers has not been found in Japan. Here we present the first case report of Takayasu arteritis in a Japanese patient who was successfully treated by infliximab, a chimeric monoclonal antibody to TNF- $\alpha$ .

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### Case Report

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A 24-year-old woman was admitted to the First Department of Internal Medicine, Graduate School of Biomedical

Sciences, Nagasaki University, because of fever of unknown origin for several months in March 2003. Bruit of the neck and cardiac murmur were pointed out, and elevation of C-reactive protein (CRP) (17.8 mg/ml) and erythrocyte sedimentation rate (ESR) was determined. Magnetic resonance imaging (MRI) study of the chest revealed wall thickening of the aorta, brachiocephalic trunk, left common carotid artery and left subclavian artery (Fig. 1). Magnetic resonance angiography (MRA) simultaneously revealed a marked dilatation of both the ascending aorta and descending aorta (Fig. 2). A diagnosis of TA with aortic valve regurgitation was made, and the patient began treatment with low-dose aspirin and prednisolone including methylprednisolone pulse therapy (500 mg/day).

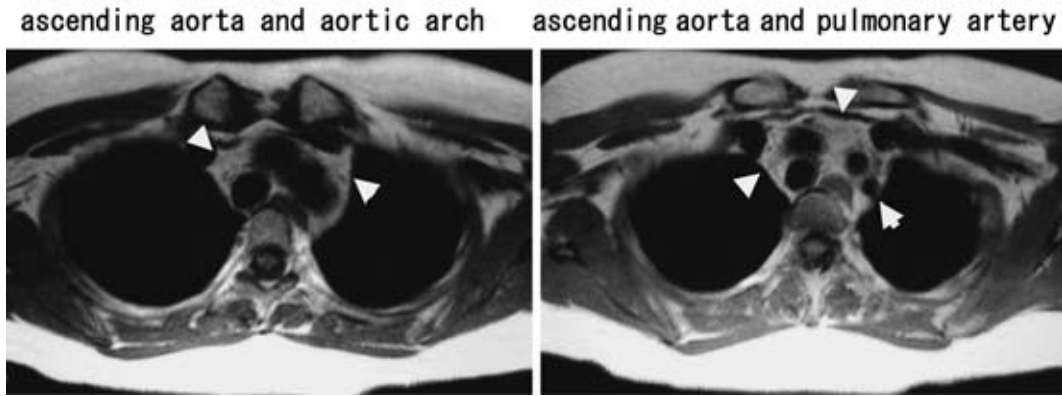
Glucocorticoid therapy was effective, but the patient relapsed after tapering of the prednisolone dosage to 12.5 mg/day, at which point the dosage was again increased to 17.5 mg/day. Methotrexate (up to 8 mg/week) was also introduced during an outpatient clinic visit. Nevertheless, CRP as

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<sup>1</sup> First Department of Internal Medicine, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki and <sup>2</sup> Nagasaki University of Health Sciences, Nagasaki University, Nagasaki

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Correspondence to Katsumi Eguchi, The First Department of Internal Medicine, Graduate School of Biomedical Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501



**Figure 1.** Arterial wall thickening (ascending aorta, aortic arch and pulmonary artery highlighted by arrowheads) determined by MRI.



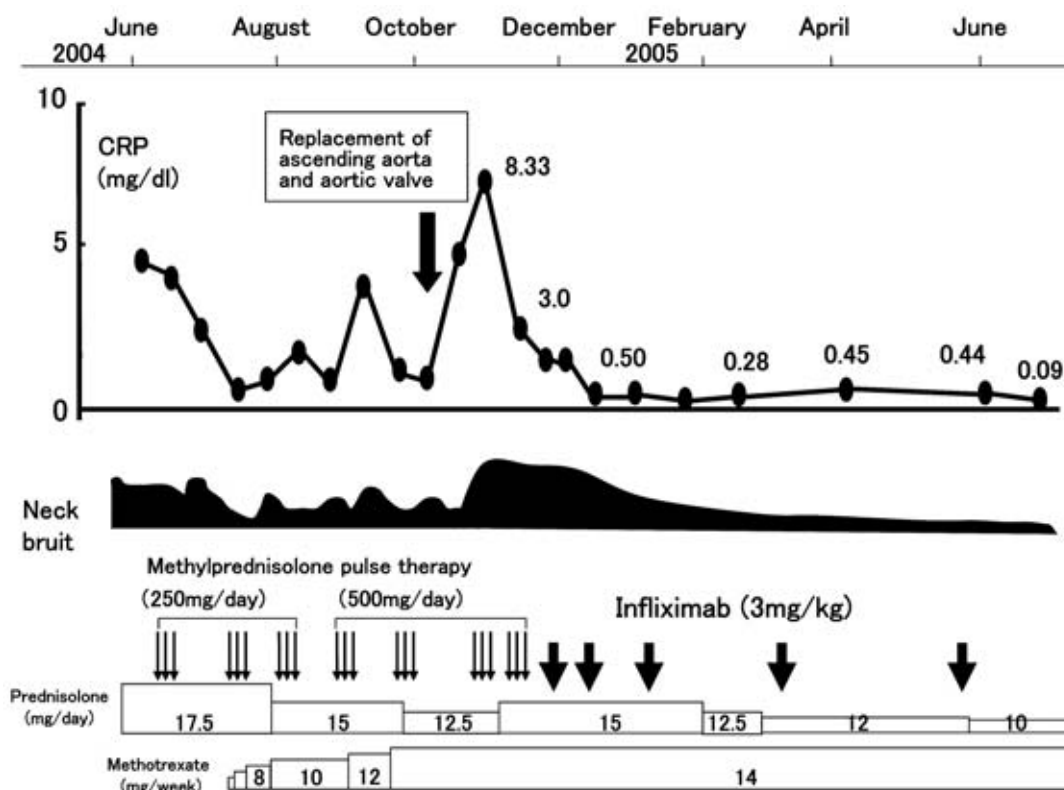
**Figure 2.** Dilatation of both the ascending aorta and the descending aorta determined by MRA. The arrowhead indicates the portion.

well as ESR remained continuously elevated, so the patient was admitted again to our hospital in July 2004. Although she suffered from a fever during the first visit, elevated temperature was not remarkable during the treatment with prednisolone and methotrexate, thus the relapse of TA was judged by the increment of bruit as well as that of inflammatory reactions.

The patient's clinical course after the second admission is summarized in Fig. 3. Laboratory studies on the second admission showed the elevation of CRP (4.33 mg/dl) and ESR (47 mm/h). Enhanced computed tomography (CT) of the chest showed a marked dilatation of the ascending aorta, and furthermore, small thrombus of the right pulmonary artery was determined (data not shown). Compression of the right pulmonary artery by the ascending aorta was consid-

ered to be the cause of thrombosis. The ultrasonography of the heart showed moderate aortic valve regurgitation, but cardiac ejection fraction (EF) was preserved (EF; 65%), thus replacement of both the ascending aorta and the aortic valve was scheduled. The methotrexate dosage was increased gradually to 14 mg/week, and methylprednisolone pulse therapy (2 times of 250 mg/day and 3 times of 500 mg/day) was also administered for a total of 5 times, leading to the decrement of the oral prednisolone dosage to 12.5 mg/day.

Surgical replacement was successfully accomplished on October 7, 2004, and the thrombus of the right pulmonary artery spontaneously disappeared during the operation. Tissue specimens of the ascending aorta obtained during the operation showed a remarkable thickening of adventitia with the presence of giant cells, considered to be typical for TA



**Figure 3.** The clinical course of patients during infliximab treatment.

(data not shown). Seventeen days after the operation, CRP was elevated to 8.33 mg/dl, in comparison of 0.3 mg/ml before the operation, with the increment of neck bruit. Exacerbation of TA was the most likely cause. When oral prednisolone was increased to 15 mg/day with two subsequent sessions of methylprednisolone pulse therapy (500 mg/day), disease activity was still not suppressed (CRP 3.0 mg/dl, after 2 sessions of methylprednisolone pulse therapy).

Considering the therapeutic time course, this patient appeared to be suffering from TA refractory to glucocorticoid therapy and methotrexate therapy. A protocol for therapy with infliximab for the patient was approved by the Institutional Review Board of Nagasaki University, and infliximab therapy was scheduled according to the same sequential regime as is used in rheumatoid arthritis. The patient's skin test toward purified protein derivative for tuberculin was negative, and computed tomography of the chest did not show pulmonary nodules. Intravenous injection of 3 mg/kg of infliximab was started at November 29, 2004. The therapeutic efficacy of infliximab was significant; CRP was reduced from 3.0 mg/dl to 0.5 mg/dl after 7 days of initial infliximab injection. After 24 weeks of infliximab administration, CRP remained at less than 0.5 mg/dl, and the dosage of oral prednisolone was reduced to 10 mg/day. Bruit of the neck tended to be decreased, and no adverse events have been found to date. During the follow-up period, neither the laterality of arterial pulsation nor pulselessness was found in this patient.

## Discussion

The pathogenesis of TA includes vessel injury due to products from activated T cells, natural killer cells,  $\gamma\delta$  T cells and macrophages (1). One of the important humoral factors is TNF- $\alpha$ , the molecular target for human autoimmune diseases (1, 3-5). Glucocorticoid therapy is usually introduced for TA, but glucocorticoid alone is sometimes not efficient; Kerr et al reported that about half of active TA patients did not respond well to glucocorticoid alone (6). In addition to glucocorticoid, an immunosuppressive regime such as cyclophosphamide, methotrexate and azathioprine has been used to treat TA (6-8); however, some patients are refractory to both glucocorticoid and immunosuppressants. Hoffman et al have recently reported the efficacy of TNF blockers toward TA refractory to conventional glucocorticoid therapy and immunosuppressants (2). The present case is the first demonstration of TA successfully treated with infliximab in Japan.

Patient selection criteria described by Hoffman et al include: 1] required toxic doses of glucocorticoids to maintain remission, and 2] either experienced multiple relapses while receiving conventional and experimental therapy or refused re-treatment with glucocorticoids following relapses. All the cases described by Hoffman et al were negative for skin test toward purified protein derivative for tuberculin. Our present case met the above criteria, and infliximab was administered according to the same regime as is used to treat rheumatoid arthritis. As stated in the article by Hoffman et al

(2), infliximab therapy could reduce the dosage of prednisolone, which occurred in our case. Hoffman et al found that, among 15 refractory cases of TA treated with TNF blockers (8 patients were treated with infliximab and 7 patients with etanercept), 10 out of 15 patients achieved complete remission sustained for 1- to 3.3-year observation periods without glucocorticoid therapy, and 4 patients achieved partial remission, with more than 50% reduction of glucocorticoid requirement. However, in spite of the excellent therapeutic response, the authors have also reported that an increase of TNF blockers dosage was required to sustain the remission in 9 of the above 14 responders (2). Nevertheless, they have found 2 cases of relapse after interrupting the TNF blockers (2). The duration of our case was only 24 weeks of observation, thus a careful follow-up will be necessary. In addition, repeated imaging of MRI and MRA is also recommended in our case since TNF blockers promote not only the clinical

remission but the improvement of arterial wall thickening (2). In our case, MRI and MRA of the ascending aorta after infliximab therapy at 3 months did not show remarkable changes; however, these images did not show the appearance of new lesions (data not shown). Further serial radiographic examinations are required to characterize the effect of infliximab in this case.

Anti-TNF treatment schedules for TA proposed by Hoffman et al are the same as those for rheumatoid arthritis (2). The present observation is a preliminary case report at 24 weeks follow-up after infliximab administration that shows the adjunct therapeutic application of infliximab toward a patient with TA refractory to treatment via a conventional regime.

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