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CASE BASED REVIEW

Refractory Takayasu arteritis successfully treated with rituximab: case-based review

Tomoyuki Mutoh[1] · Tomonori Ishii[1] · Tsuyoshi Shirai[1] · Kanae Akita[1] · Yukiko Kamogawa[1] · Yoko Fujita[1] · Hiroko Sato[1] · Yuko Shirota[2] · Hiroshi Fujii[1] · Hideo Harigae[1]

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Abstract

Takayasu arteritis (TAK) is a subtype of the large-vessel vasculitis, affecting the aorta and its major branches. Although T cell-mediated autoimmunity is mainly involved in vascular inflammation, in recent years, accumulating evidence suggests the important role of B cells in the pathogenesis and effectiveness of B-cell-targeted therapy with rituximab (RTX), a chimeric anti-CD20 monoclonal antibody in refractory TAK. Herein, we report for the first time a case involving a 34-year-old man with TAK who was refractory to four different biologic agents, such as one selective T-cell co-stimulation modulator (abatacept), one anti-interleukin-6 receptor monoclonal antibody (tocilizumab), and two tumor necrosis factor-α inhibitors (infliximab and etanercept), but eventually achieved remission with RTX. He received a total of six courses of RTX, and doses of prednisolone and methotrexate were tapered without relapse. The current case provided further evidence to the potential role of RTX therapy in patients with refractory TAK, and its efficacy needs to be validated in a controlled trial.

Keywords Takayasu arteritis · Large-vessel vasculitis · Rituximab · B cells

Introduction

Takayasu arteritis (TAK) is a subtype of the large-vessel vasculitis, affecting the aorta and its major branches [1]. Although T-cell-mediated autoimmunity is mainly involved in the pathogenesis of TAK, B cells are also considered to contribute to the development of vascular inflammation [2]. In fact, increased B-cell subsets in the peripheral blood of active TAK patients and the infiltration of B cells into inflamed aortic walls are reported [3, 4]. In addition, serum levels of B-cell-activating factor of the tumor necrosis factor (TNF) family, essential for survival, differentiation, and isotype switching of B cells [5], are significantly higher in patients with active TAK compared with healthy controls [6], and anti-endothelial cell antibodies have been more frequently found in active compared with inactive TAK [7]. More recently, serum IgG from TAK patients has been found to activate mammalian target of rapamycin pathway, leading to endothelial cell proliferation [8].

To support the pathogenic role of B cells, B-cell-targeted therapy with rituximab (RTX), a chimeric anti-CD20 monoclonal antibody, has been administered to patients with TAK, showing its favorable effect on vascular inflammation in refractory TAK among some case reports and case series [3, 9–16]. Therefore, the potential role of RTX as the therapeutic strategy in refractory TAK is of great interest.

Here, we report a case of TAK that was resistant to one selective T-cell co-stimulation modulator (abatacept), one anti-interleukin (IL)-6 receptor monoclonal antibody (tocilizumab), and two TNF-α inhibitors (infliximab, and etanercept), but eventually achieved remission with RTX therapy that sustained for 36 months. To our best knowledge, this is a first case report of B-cell depletion therapy successfully treated with TAK refractory to biological treatments inhibiting three different immunological pathways. Furthermore, we performed an updated literature review regarding RTX therapy in patients with TAK to investigate the potential role of RTX in the management of TAK in the biological era.

✉ Tomonori Ishii
tishii@med.tohoku.ac.jp

[1] Department of Hematology and Rheumatology, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan

[2] Department of Hematology and Rheumatology, Tohoku Medical and Pharmaceutical University, Sendai, Japan

Case report

A 34-year-old man with a history of aortic valve replacement for aortic regurgitation (AR) caused by infectious endocarditis was referred to our hospital due to fever and headache with elevated C-reactive protein (CRP) levels (12.9 mg/dL). Although infection was first suspected because of past medical history, antibiotic treatment was not effective in improving his symptoms. The pulse was not palpable in his radial arteries, and contrast-enhanced computed tomography (CT) was performed to determine the cause of inflammation. Computed tomography revealed the wall thickness from the ascending aorta to the arch in addition to the bilateral common carotid artery and left subclavian artery. He was considered to develop TAK, according to the diagnostic criteria established by the Japanese Circulation Society Joint Working Groups [17]. After starting the monotherapy with 30 mg/day of prednisolone (PSL), his symptoms and inflammatory markers were immediately improved. Thereafter, PSL was tapered slowly; however, vasculitis relapsed with systemic symptoms such as fever and arthralgia, carotidynia, and elevated inflammatory markers several times, making it difficult to taper PSL below 10 mg/day. Furthermore, despite adding methotrexate (MTX) on to control vascular inflammation 3 years after the initiation of PSL therapy, it could not completely control the vasculitis.

As shown in Fig. 1, 8 years after the diagnosis, abatacept was administered to suppress further disease progression as contrast-enhanced CT showed the wall thickness in the ascending aorta (Fig. 2a). His general symptoms tended to improve without normalization of inflammatory markers; however, active vasculitis was again detected in contrast-enhanced CT when PSL was tapered to 12.5 mg/day. Therefore, PSL dose was increased to 30 mg/day in combination with 2.5 mg of dexamethasone intermittent infusion to control disease activity. Since abatacept therapy was considered insufficient to resolve continuous inflammation and reduce steroid dose, it was switched to tocilizumab. Levels of inflammatory markers were temporarily significantly decreased, but mild fever and general malaise persisted. His physical status gradually worsened due to uncontrolled vasculitis which caused fever, arthralgia, and increased CRP levels following reduction of the dose of PSL despite combined therapy including MTX and a biological drug; therefore, he was admitted to our hospital.

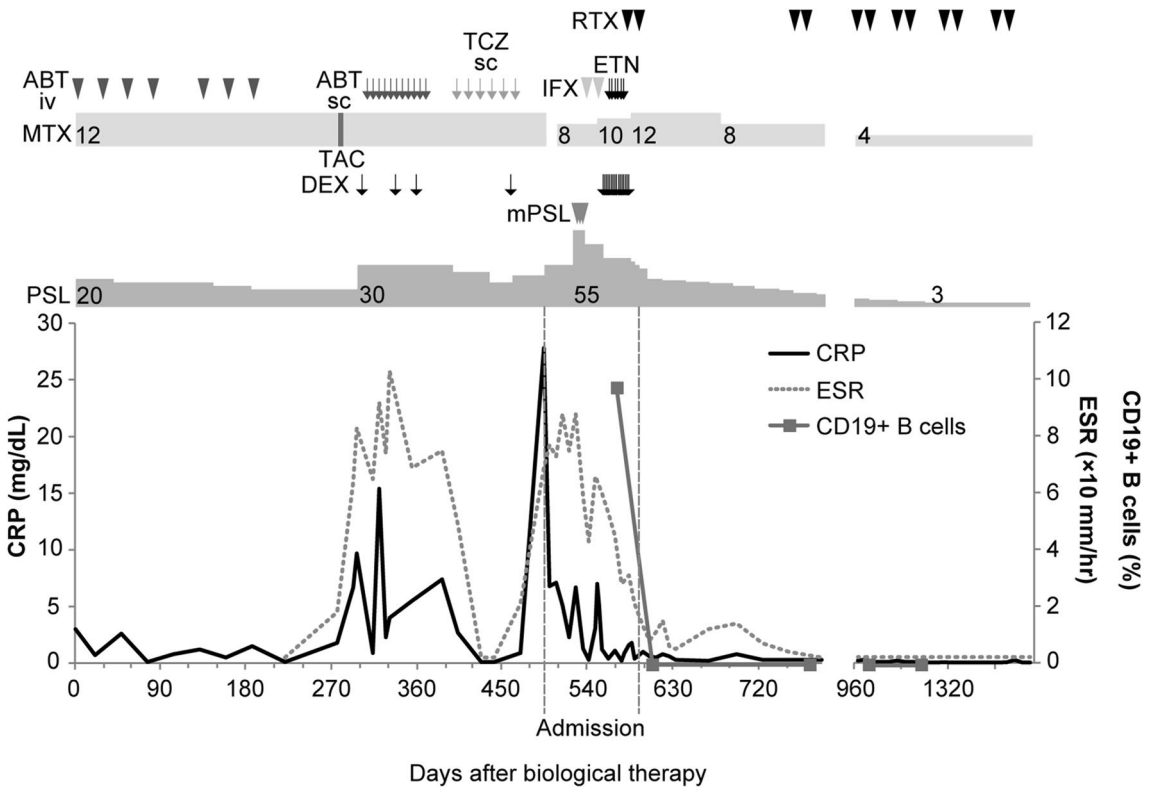

Fig. 1 The clinical course after biological therapy. *ABT* abatacept, *CD* cluster of differentiation, *CRP* C-reactive protein, *DEX* dexamethasone, *ESR* erythrocyte sedimentation rate, *ETN* etanercept, *IFN* infliximab, *iv* intravenously, *mPSL* methylprednisolone, *MTX* methotrexate, *PSL* prednisolone, *RTX* rituximab, *sc* subcutaneously, *TAC* tacrolimus, *TCZ* tocilizumab

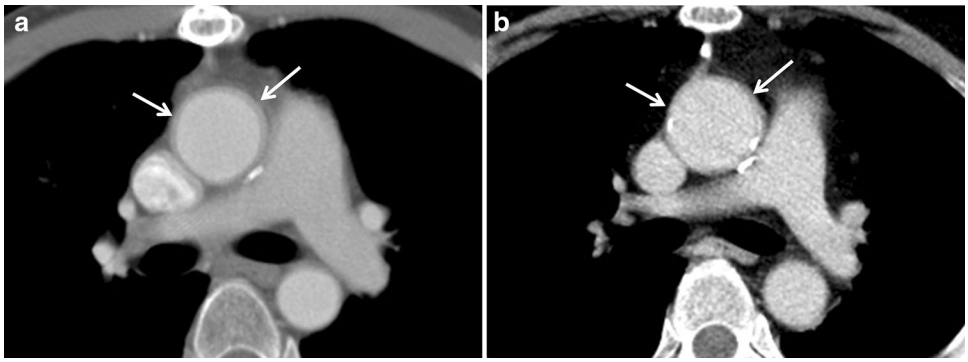

Fig. 2 Imaging improvement. **a**, **b** Contrast-enhanced computed tomography shows reduced wall thickness in the ascending aorta (**a**: 2 years before RTX therapy, **b**: 3 years after RTX therapy). *RTX* rituximab

On admission, he had vertigo and headache. His consciousness was clear, body temperature was 36.8 °C, blood pressure was 123/50 mmHg without any difference between the upper limbs, heart rate was 82/min, and oxygen saturation was 99% at room air. Physical examination showed no heart murmur and neck or abdominal bruit, and neurological findings were normal. Laboratory tests revealed significantly elevated CRP levels and erythrocyte sedimentation rate (ESR) (27.8 mg/dL and 69 mm/h, respectively). We did not detect autoimmune antibodies, such as anti-nuclear antibodies (Ab), anti-dsDNA Ab, anti-cardiolipin Ab, proteinase three anti-neutrophil cytoplasmic antibodies (ANCA), myeloperoxidase ANCA, and rheumatoid factor. The serum complement levels were increased. TSPOT and β-D-glucan test results were negative. Blood cultures did not detect bacteria or fungi. Other extensive infection work-ups were negative. Human leukocyte antigen was not investigated. Contrast-enhanced CT showed circumferential mural thickening of the ascending aorta. Echocardiography revealed no deterioration of AR, cardiac dysfunction, or vegetation. A diagnosis of relapsed TAK was established according to the National Institutes of Health criteria [18], satisfying the following components: systemic symptoms, elevated inflammatory markers, and typical angiographic features. Clinical course after admission is shown in Fig. 3. Prednisolone dose was increased from 22.5 mg/day to 30, but his symptoms

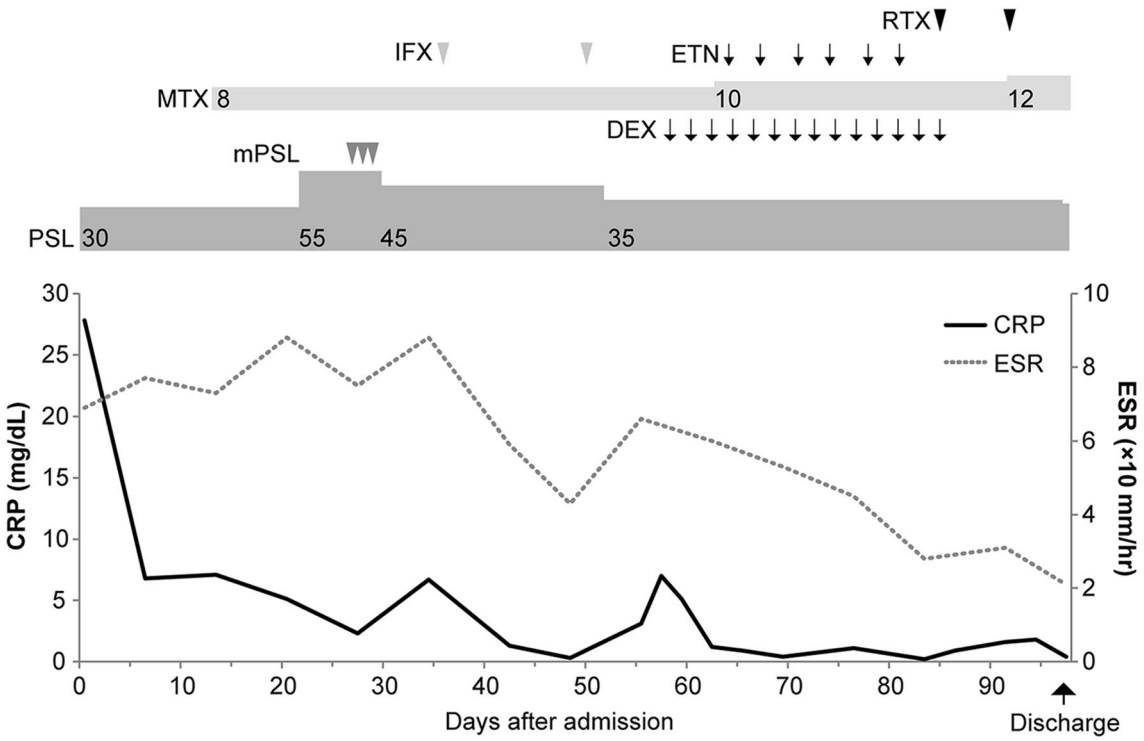

Fig. 3 The clinical course during admission. *CRP* C-reactive protein, *DEX* dexamethasone, *ESR* erythrocyte sedimentation rate, *ETN* etanercept, *IFN* infliximab, *mPSL* methylprednisolone, *MTX* methotrexate, *PSL* prednisolone, *RTX* rituximab

persisted. This dose was considered to be too low to control vascular inflammation; hence, it was increased to 55 mg/day equivalent to 1 mg/kg/day on day 21 from admission. Nevertheless, his symptoms did not completely disappear with increased CRP levels and ESR. Thus, methylprednisolone pulse therapy at a dose of 1000 mg/day was administered for three consecutive days, followed by 45 mg/day of PSL. CRP levels and ESR were not normalized, and another potent immunosuppressant was necessary to stabilize disease activity and to decrease the required PSL dose. Since anti-TNF-α agents had been used with some success in refractory TAK [19], infliximab was initiated on day 35 from admission. CRP levels and ESR once decreased; however, they started to increase again even under high dose of PSL (45 mg/day). To inhibit further vascular damage, infliximab was replaced with etanercept (50 mg/week) with dexamethasone (2.5 mg intravenously, every other day), because elevated levels of inflammatory markers caused by TAK did not become negative, showing no complete resolution of vasculitis.

The insufficient responsiveness to abatacept, tocilizumab, infliximab, and etanercept prompted us to choose blockade of the alternative immune response such as B cells. Thus, etanercept was switched to RTX (500 mg, once weekly, for 2 weeks) based on rheumatoid arthritis (RA) protocol on day 84 from admission. Three weeks later, inflammatory markers eventually improved within normal range without intermittent infusion of dexamethasone, and contrast-enhanced CT showed improvement in the enhancement in the ascending aorta. In addition, the percentage of CD19 + B cells decreased below the detection limit (< 0.1%) from 9.7%, which was before RTX treatment. He was discharged on day 100 from admission. Subsequently, we administered six courses of RTX therapy and then the doses of PSL and MTX were tapered without relapse. At 36 months after RTX administration, the patient remains in remission with the dose of PSL tapered to 3 mg/day and low dose of MTX (4 mg/week) (Fig. 1). Importantly, improvement in wall thickness in the ascending aorta on contrast-enhanced CT has been observed (Fig. 2b), and progressive narrowing, stenosis, and aneurysms formation of affected arteries are currently undetected with no elevated inflammatory marker levels.

Search strategy

To analyze recently increasing data regarding the treatment response with RTX in TAK patients, we searched PubMed and Scopus databases using the following keywords: "Takayasu arteritis" and "Rituximab", according to the search strategy recommended for writing a narrative review [20]. Until June 2019, four case reports and five open studies [3, 9–16] have reported a total of 26 cases covering TAK treated with RTX. All the reported cases and our case, which are summarized in Table 1, were included for detail analysis.

Discussion

Glucocorticoids (GCs) are a mainstay treatment for patients with TAK, but its prolonged use is associated with significant adverse events [21]. In European League Against Rheumatism, recommendations for the management of large-vessel vasculitis, an immunosuppressive agent should be considered as adjunctive therapy to improve disease control and reduce cumulative steroid doses [22]. In recent years, accumulating evidence has indicated biological agents are effective for relapsed TAK. Clifford et al. [19] reviewed the effectiveness of TNF-α inhibitors (mainly infliximab) in 70–90% of patients with TAK who were resistant to conventional therapy. Decker et al. [23] reported that among the 105 patients including 76 refractory cases (72.4%), 90 patients (85.7%) had an initial clinical response and radiological improvement after the treatment with tocilizumab was observed in 43 out of 66 patients (65.2%) for which imaging assessment was performed. Moreover, the initial favorable outcome after B-cell depletion therapy with RTX in relapsed TAK has been reported in several small cohorts over the past years [3, 15, 16].

As shown in Table 1, RTX was administered to 27 cases, and 26 of them showed persistent vasculitis even after intensive immunosuppression with MTX, azathioprine, cyclophosphamide, cyclosporine A, mycophenolate mofetil, or hydroxychloroquine in combination with GCs. Among the 26 refractory cases, 4 patients (15.4%), 1 patient (3.8%), and 13 patients (50%) were treated with tocilizumab, abatacept, and TNF-α inhibitors (infliximab in 8 patients, adalimumab in 5, and etanercept in 2), respectively. The clinical response assessed by both clinical signs/symptoms and laboratory findings after RTX therapy was observed in 19 patients (73.1%). Meanwhile, radiographic findings before and after RTX therapy were investigated in 13 of 26 cases (50%), and imaging improvement was reported in 9 of 13 cases (69.2%). These favorable outcomes are not likely to be far behind from treatment results of anti-TNF-α [19] or anti-IL-6 agents [23] described above. Taken together, these data suggest that treatment targeting B cells, which could play important roles in chronic vessel wall inflammation, might be a useful option for TAK resistance to conventional immunosuppressive drugs.

The treatment regimen of RTX is one important issue. Its optimal dose, the interval of administration, and the number of courses have not yet been determined for the clinical management of TAK; however, two protocols have been widely used: one is RA protocol (1000 mg, every other week × 2) and the other is vasculitis protocol (375 mg/m^2,

Table 1 The previous literature and the present case of Takayasu arteritis treated with rituximab

References	Number of patients	Median age (years)	IS before RTX	IS with or after RTX	RTX dose and interval in first cycle	Median number of RTX cycles	Clinical response	Imaging response
Galarza [9]	2	27	MTX: 2, TNFi: 2 (details: NR)	NR	NR	NR	1/2	NR
Hoyer [3]	3	18	MTX: 2, CYC: 3, MMF: 2, HCQ: 1, TNFi: 2 (ADA: 1, the other: NR)	MMF: 2, CYC: 1	500 mg biweekly × 2:1, 1000 mg biweekly × 2:2	2	3/3	1/1 (NR in 2 cases)
Ernst [10]	1	25	CYC, AZA	AZA	1000 mg biweekly × 2	2	1/1	1/1
Walters [11]	1	16	MTX	MTX	1000 mg biweekly × 2	1	1/1	NR
Caltran [12]	2	32.5	CYC: 2, MTX: 1, IFX: 2, ADA: 1	MMF: 2	1000 mg biweekly × 2:2	2	2/2	2/2
Ahmed [13]	1	42	AZA, CYC, ETN, TCZ	NR	NR	NR	0/1	0/1
O'Connor [14]	1	39	None	AZA	375 mg/m^2 weekly × 4	1	1/1	1/1
Pazzola [15]	7	22	AZA: 2, MTX: 5, MMF: 2, IFX: 2, ADA: 2, TCZ: 2	MTX: 1, MMF: 2	1000 mg biweekly × 2:7	2	3/7	4/7
Nakagomi [16]	8	38	AZA: 6, CYC: 4, MTX: 4, MMF: 3, CYA: 1, IFX: 3, ADA: 1	AZA: 2, MTX: 1	1000 mg biweekly × 2:7, 375 mg/m^2 weekly × 4:1	1.5	7/8	NR
Our case	1	34	MTX, ABT, TCZ, IFX, ETN	MTX	500 mg weekly × 2	6	1/1	1/1

ADA adalimumab, *AZA* azathioprine, *CYA* cyclosporine A, *CYC* cyclophosphamide, *ETN* etanercept, *HCQ* hydroxychloroquine, *IFX* infliximab, *IS* immunosuppressants, *MMF* mycophenolate mofetil, *MTX* methotrexate, *NR* not reported, *PSL* prednisolone, *RTX* rituximab, *TCZ* tocilizumab, *TNFi* tumor necrosis factor inhibitor

every week × 4). As shown in Table 1, the former regimen was administered to 20 cases, in which 15 cases showed good clinical response, and the latter was to 2 cases, all of which achieved clinical remission. In the current case, RTX dose was 500 mg (weekly × 2), a half of dose in the standard RA protocol, but no relapse had been observed during the follow-up period of 36 months. In addition, RTX cycles in this case are more frequent compared with those in previous cases (6 times vs. 1–2 times). We speculate that long-term infusion of RTX may contribute to achievement of persistent remission, despite the use of relatively low-dose of RTX.

Conversely, no clinical response was reported in seven cases [9, 13, 15, 16]. Particularly, five cases provided the information about the treatment detail [15, 16]. Three cases received RTX only based on the RA protocol [15, 16] as immunosuppressive therapy, one case was administered to only one cycle of RTX combined with mycophenolate mofetil [15], and the remaining case was treated with two courses of RTX in addition to MTX [15]. Vasculitic lesions detected by CT angiography or magnetic resonance angiography did not deteriorate 6 months after the last RTX therapy in only one case, although the clinical response was insufficient. Our case received concomitant MTX and six cycles of RTX. Therefore, these findings indicate that two or more cycles of RTX with additional immunosuppressive agents could be important to control vascular inflammation. Further studies are necessary to explore the appropriate RTX treatment strategies targeting sustained remission in TAK.

In conclusion, B-cell-targeted therapy could effectively manage TAK that was a difficult-to-control disease despite treatment with four different biologic agents, such as two TNF-α inhibitors, one selective T-cell co-stimulation modulator, and one anti-IL-6 receptor monoclonal antibody. The current case provided further evidence to the potential role of RTX therapy in patients with refractory TAK. To validate long-term efficacy and safety of RTX, a randomized clinical trial is essential.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Informed consent Written informed consent was obtained from this patient.

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