

## Rituximab in Takayasu Arteritis, a Case Report

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### Abstract

*Takayasu Arteritis (TAK) is a subgroup of large vessel vasculitis involving major branches of aorta. Corticosteroids are the mainstay of treatment. However, several other steroid-sparing agents are used to control vessel wall inflammation in TAK. Some biologic agents are used as new targeted agents. Several reports denote clinical efficacy of tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin 6 (IL-6) blocking agents in management of TAK. While few studies are devoted to report B cell depletion in inflammation in TAK, we report a 34-year-old woman with established diagnosis of TAK treated with rituximab with good clinical and laboratory control.*

**Keywords:** Takayasu Arteritis (TAK), Vasculitis, Treatment, Biologic agent, Rituximab.

### Introduction

Takayasu Arteritis (TAK) is a type of large vessel giant cell arteritis (GCA) involving major branches of aorta. It usually affects subclavian, brachiocephalic or left common carotid artery. Resultant arterial obstruction leads to absence of distal arterial pulses assigning this disease as 'pulseless disease' or occlusive thromboaropathy. Massive intimal fibrosis and vascular narrowing affecting young or middle-aged women is characteristic feature of the disease.

It is most frequent in Asian descent including Japan [1]. Median age of onset is around 25 years. The real cause of disease is unknown but it appears that autoimmune process may target elastic containing major vessels. Chronic inflammation of these vessels leads to inflammation, thrombosis, fibrosis and finally stenosis. Intimal proliferation evolves into medial thickening, scarring and adventitial fibrosis.

Less than 20% of patients experience self-limit form of the disease; however, remission and exacerbation are frequent. Corticosteroids are the mainstay of the treatment [2]. Initial clinical and laboratory response to glucocorticoids is rather good in most cases, but frequent relapses are the rule in many patients. In almost all cases, additional disease-modifying drugs are needed to spare glucocorticoid side effects. Common therapeutic agents used are methotrexate, azathioprine, mycophenolate mofetil, or cyclophosphamide. Serious side effects associated with cyclophosphamide in young women limited its use in the long-term management of TAK.

Although GCA is the most common systemic vasculitis, prospective randomized trials on steroid-sparing agents are rare and mostly include only small series. No double-blind controlled trial proved any specific drug to be the first choice in this condition [3]. Small case series showed some benefits from biologic agents including anti-TNF agents or B cell depletion therapy.

We report a 34-year-old woman with TAK treated successfully with rituximab.

### Case Report

A 34-year-old Iranian woman with a 9-year history of Takayasu arteritis presented with headache and epistaxis since 6 months before. She was on oral/ intramuscular methotrexate and oral prednisolone for years. She had never experienced complete clinical and/ or laboratory remissions until a year before the presentation. She withdrew therapy due to lack of efficacy and exhaustion. She was complaining occasional epistaxis and daily headache that bothered her for the last 6 months. Over time during last year she was hospitalized and treated with periodic pulsed methylprednisolone and cyclophosphamide (1000 mg each, total 5 gr). Her symptoms did not abate even after this regimen. On the last visit, she presented again with symptoms of throbbing headache and epistaxis accompanied by photophobia. She had neither fever nor nausea or vomiting during the course of disease.

Her physical exam revealed a blood pressure of 800/650 on the right arm. Fever was not detected. Right radial pulse was all right but the left one was not palpable. Heart and lungs were normal on clinical exam. Laboratory investigations revealed a hemoglobin level of 9.5 g/dl with a mean corpuscular volume (MCV) of 75.1 fL. Platelet and white blood cell counts were normal. Erythrocyte

sedimentation rate (ESR) ranged from 74-110 mm/hr, C-reactive protein (CRP) was consistently positive, Prothrombin and Partial thromboplastin times were all within normal limits. Other laboratory tests including liver and kidney function tests were normal as well.

Considering her as a refractory case of TAK she was treated with 500 and 1000 mg rituximab (MabThera, Roche, Switzerland) after single dose of 500 mg methylprednisolone with 15 days' interval. Subsequent follow-ups showed not only remarkable clinical but also laboratory improvement after two doses of rituximab. Her headaches got improved from seven to two episodes in a week and epistaxis was also abolished. Her ESR dropped to 45mm/h1 and CRP to marginal positive titers four weeks after rituximab therapy.

## Discussion

After decades of knowing about giant cell arteritis, no agent is chosen as gold standard of therapy in TAK. Systemic glucocorticoids are the cornerstones of therapy in both temporal arteritis and TAK. Albeit initial good response to systemic glucocorticoids, long term management with these agents carry a considerable risk even with low doses. An important issue other than the adverse effects is the relapse after dose reduction. Plenty of steroid-sparing agents were used in clinical practice to offset these unwanted events [4-8]. Role of microbiological agents in pathogenesis of TAK is noted in some studies; Some investigations indicate the role of some viruses (e.g. varicella-zoster virus) as the etiology of TAK, and successful outcome with antiviral therapy [9]. Several other studies indicate association of Mycobacterium tuberculosis especially in children [10].

Recent advances in discovering basic pathophysiology of TAK led to use of biologic agents. The first ones were TNF-alpha inhibitors -mostly infliximab- with some success [11]. Inadequate clinical response in all cases and establishment the role of IL-6 in mediating inflammation in TAK resulted in use of IL-6 inhibitors (tocilizumab) as the second-line biologic agents [12]. These agents also did not satisfactorily control vessel wall inflammation [13]. Previous studies on the pathophysiology of TAK specifically focused on the role of T cells [14]. In recent years, the role of B cells are more highlighted in pathogenic mechanism of several rheumatic disorders including TAK [15]. Hoyer BF et al. found out that there is an increased number of peripheral blood CD19(+)/CD20(-)/CD27(high) antibody-secreting cells (most of them are new plasmablasts) in patients with active TAK [15]. Whether these biologic agents are lodged in the earlier levels in the treatment algorithm remains to be established [3].

Rituximab is a chimeric antibody that binds to CD20(+) B-lymphocytes depleting circulating B cells for a long period of time. Rituximab is widely used in the management of several kinds of lymphoma and ANCA-associated vasculitides. Recent studies suggested rituximab as the initial therapy in granulomatosis with polyangiitis (GPA) [16]. However, only a few cases has been reported regarding the use of B cell depletion therapy in case of TAK [17]. Caltran E et al. published a case-based review in 2014

covering two cases with newly diagnosed TAK with successful results and complete hampering of inflammatory markers confirmed with PET scan [18]. Putting all together, we can conclude that an orchestra of mediators and cell types are interactively taken into motion in the pathophysiology of TAK and blockade each of them may interrupt the vicious cycle of the disease individually.

Chronic drug use and frustrating remission-exacerbations are important issues in the management of TAK. Accordingly, long-lasting effect of rituximab is another advantage to other therapeutic options in chronic inflammatory conditions.

Further studies are needed to confirm safety and efficacy of rituximab in management of TAK.

## Conclusion

Rituximab could be a good candidate biologic agent in case of refractory TAK in selected cases.

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## References

1. Parra JR, Perler BA (2003) Takayasu's disease. *Semin Vasc Surg* 16: 200-208.
2. Kotter I, Henes JC, Wagner AD, Loock J, Gross WL (2012) Does glucocorticosteroid-resistant large-vessel vasculitis (giant cell arteritis and Takayasu arteritis) exist and how can remission be achieved? A critical review of the literature. *Clinical and experimental rheumatology* 30: S114-29.
3. Clifford A, Hoffman GS (2014) Recent advances in the medical management of Takayasu arteritis: an update on use of biologic therapies. *Current opinion in rheumatology* 26: 7-15.
4. Audibert Mena L, Gallego Beuter J, Gutiérrez Marcos F (1991) [Colchicine treatment of Takayasu arteritis]. *Rev Clin Esp* 188: 430-431.
5. Yamaguchi K, Yamamoto Y, Murashima A (2004) Clarithromycin reduces prednisolone requirements for treatment of intractable Takayasu arteritis. *Clinical and experimental rheumatology* 22: S102.
6. Daina E, Schieppati A, Remuzzi G (1999) Mycophenolate mofetil for the treatment of Takayasu arteritis: report of three cases. *Ann Intern Med* 130: 422-426.
7. Hoffman GS, Leavitt RY, Kerr GS, Rottem M, Sneller MC, et al. (1994) Treatment of glucocorticoid-resistant or relapsing Takayasu arteritis with methotrexate. *Arthritis Rheum* 37: 578-582.
8. Yamazaki H, Nanki T, Harigai M, Miyasaka N (2012) Successful treatment of refractory Takayasu arteritis with tacrolimus. *J Rheumatol* 39: 1487-1488.
9. Gilden D, White TM, Nagae L, Gurdin WH, Boyer PJ, et al. (2015) Successful Antiviral Treatment of Giant Cell Arteritis and Takayasu Arteritis. *JAMA Neurol* 72: 943-946.

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10. Soto ME, Del Carmen Avila-Casado M, Huesca-Gomez C (2012) Detection of IS6110 and HupB gene sequences of Mycobacterium tuberculosis and bovis in the aortic tissue of patients with Takayasu's arteritis. BMC infectious diseases 12: 194.
  11. Lv N, Dang A, Zhu X (2011) The role of tumor necrosis factor-alpha promoter genetic variation in Takayasu arteritis susceptibility and medical treatment. The Journal of rheumatology 38: 2602-2607.
  12. Bravo Mancheno B, Perin F, Guez Vazquez Del Rey Mdel M, Garcia Sanchez A, Alcazar Romero PP (2012) Successful tocilizumab treatment in a child with refractory Takayasu arteritis. Pediatrics 130: e1720-e1724.
  13. Xenitidis T, Horger M, Zeh G, Kanz L, Henes JC (2013) Sustained inflammation of the aortic wall despite tocilizumab treatment in two cases of Takayasu arteritis. Rheumatology 52: 1729-1731.
  14. Arnaud L, Haroche J, Mathian A, Gorochov G, Amoura Z (2011) Pathogenesis of Takayasu's arteritis: a 2011 update. Autoimmun Rev 11: 61-67.
  15. Hoyer BF, Mumtaz IM, Loddenkemper K, Bruns A, Sengler C, et al. (2012) Takayasu arteritis is characterised by disturbances of B cell homeostasis and responds to B cell depletion therapy with rituximab. Ann Rheum Dis 71: 75-79.
  16. Niles J (2011) Rituximab in induction therapy for anti-neutrophil cytoplasmic antibody (ANCA) vasculitis. Clin Exp Immunol 164 Suppl 1: 27-30.
  17. Caltran E, Di Colo G, Ghigliotti G, Capecchi R, Catarsi E, et al. (2014) Two Takayasu arteritis patients successfully treated with rituximab. Clin Rheumatol 33: 1183-1184.
  18. Caltran E, Di Colo G, Ghigliotti G, Capecchi R, Catarsi E, et al. (2014) Two Takayasu arteritis patients successfully treated with rituximab. Clin Rheumatol 33: 1183-1184.

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