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Concise report

Rituximab therapy for Takayasu arteritis: a seven patients experience and a review of the literature

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Abstract

Objectives. To assess the efficacy and safety of rituximab (RTX) in patients with Takayasu arteritis (TAK).

Methods. We conducted a retrospective study on seven TAK patients treated with RTX. Six of the seven patients had a disease refractory to high dose glucocorticoids and conventional immunosuppressive and/or biologic agents. One newly diagnosed, treatment-naïve TAK patient refused glucocorticoids and received RTX alone. Clinical evaluation, laboratory tests and imaging modalities (CT or MR-angiography, and ^{18}F-fluorodeoxyglucose PET/CT) were performed at first RTX administration and every 6 months thereafter. Disease activity was assessed using the Kerr index. We also performed a literature review using PubMed, Ovid MEDLINE and Cochrane library.

Results. Seven patients (6 females) were included in the study. Mean (S.D.) age was 32.4 (17.3) years. At first RTX administration, all patients had active disease according to the Kerr index ($\geqslant$2), and had also evidence of active disease at PET/CT. Despite RTX treatment, four of the seven patients had evidence of persistent disease activity and/or radiographic disease progression during follow-up. Three out of seven patients in whom RTX was employed as rescue therapy achieved complete remission. In the literature review, we identified five papers describing nine patients treated with RTX with good results in eight cases, but short follow-up.

Conclusion. Our data do not support a role for RTX as first line biologic therapy in TAK patients, but it may have a role in some patients as second or third line biologic therapy.

Key words: Takayasu arteritis, rituximab, disease activity

Rheumatology key message

- Rituximab may be effective and safe in Takayasu arteritis refractory to traditional immunosuppressive and biologic agents.

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Introduction

Takayasu arteritis (TAK) is a large vessel vasculitis involving the aorta and its major branches in patients <40 years [1]. Glucocorticoids (GCs) are the mainstay of treatment for TAK, but relapses and GC dependence are seen in more than two-thirds of patients [2].

Increasing evidence supports a role for B cells in the pathogenesis of TAK. Data from immuno-histochemical analyses of aortic wall samples in patients with TAK have shown that B cells are found in the inflamed arterial adventitia [3]. Furthermore, B cell subsets were significantly higher in the peripheral blood of patients with TAK than in matched healthy donors and similar to those found in SLE controls. In particular, a high number

of newly generated plasmablasts were observed [4]. These findings suggest a potential role for B cell depleting therapy in TAK.

Our aim was to assess the efficacy and safety of rituximab (RTX) in a series of seven patients with TAK.

Methods

We conducted a double centre, retrospective study on seven patients diagnosed with TAK who were treated with RTX. All patients satisfied the ACR classification criteria for TAK [5]. Five of seven patients were followed in Reggio Emilia Hospital between 2013 and 2016, and two patients at the Pitié-Salpétrière Hospital of Paris.

Six out of the seven patients had a refractory disease and had received high dose GCs and conventional immunosuppressive (IS) and/or biologic agents before RTX; in all these cases treatment with RTX was given due to lack of efficacy of previous therapies. One newly diagnosed treatment naïve TAK patient refused GCs and received RTX in monotherapy.

RTX was administered according to the RA scheme (two infusions of 1.000 mg, 15 days apart). Clinical evaluation, laboratory tests and imaging modalities were performed at first RTX administration and every 6 months thereafter.

Laboratory tests included ESR and CRP levels. The normal range of ESR was 0–38 mm/1st h. The normal range of CRP was 0.01–0.50 mg/dl.

Imaging studies included contrast-enhanced chest and abdominal computerized tomography angiography (CTA) or magnetic resonance angiography (MRA), and/or whole-body ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography [PET])/computerized tomography (CT)[PET/CT].

Visual analysis of PET/CT was performed in the following 14 vessel segments: ascending aorta, aortic arch, descending thoracic aorta, right carotid artery, left carotid artery, right subclavian artery, left subclavian artery, right axillary artery, left axillary artery, abdominal aorta, right iliac artery, left iliac artery, right femoral artery and left femoral artery.

A visual score was assigned to each arterial segment using a four-point scale: 0, no uptake; 1, minimal uptake, less than liver; 2, intermediate uptake similar to liver; and 3, intense uptake higher than liver activity. PET/CT was considered positive for active disease if one or more large vessels showed grade 2 FDG uptake or higher.

Disease activity was evaluated using the Kerr/National Institutes of Health index, which assesses four items: constitutional manifestations, raised ESR and/or CRP, clinical manifestations of vascular ischaemia and angiographic features indicative of vasculitis [1]. Disease is defined as active in the presence of at least two new or worsened items in the previous 3 months. For the purposes of this study, to determine vessel lumen changes we used CTA or MRA instead of conventional digital subtraction angiography.

We defined complete response as resolution of symptoms, absence of new (or worsening of known) arterial lesions on CTA or MRA, low or absent vascular uptake ($\leqslant$1) on PET/CT, a negative Kerr index and the use of $\leqslant$7.5 mg/day of prednisone (or its equivalent).

A detailed literature search was performed to summarize the current evidence published on the RTX use in TAK patients. The following databases were searched since the inception of the database until 24 October 2016: PubMed, Ovid MEDLINE and Cochrane Library. Key words included rituximab and TAK. We also reviewed the reference sections of published studies.

Results

Table 1 summarizes the main results of our study. Seven patients (six females) were included in the study. The mean (S.D.) age at the diagnosis was 27.6 (12.2) years while the mean age at the RTX administration was 32.4 (17.3) years. The mean duration of the disease at the RTX onset was 4.8 (7.7) years.

Prior to RTX therapy six of seven patients had received one or more synthetic anti-rheumatic drugs, namely MTX [5], AZA [3] and MMF [2], while only three of them received other biologic therapies, namely infliximab (IFX) [2], adalimumab [2] and tocilizumab (TCZ) [2]. As mentioned above, one newly diagnosed TAK patient refused GCs and conventional immunosuppressants and received RTX as monotherapy. The mean (S.D.) dose of prednisone (or its equivalent) at the first RTX administration was 25 (19.1) mg/day while the mean (S.D.) dosage 6 months after last RTX administration was 8.7 (5.1) mg/day.

At first RTX administration, all patients had active disease according to the Kerr index ($\geqslant$2) and had also evidence of active disease at imaging evaluations. Despite RTX therapy, 4 out of the 7 patients (RTX was used as first biological therapy after the failure of conventional IS therapy in 2 patients, RTX was used alone in 1 patient, and in the remaining case RTX was used after the failure of conventional IS therapy and 3 biologic agents) had evidence of persistent disease activity and/or radiographic disease progression at follow-up CTA or MRA. Three patients achieved remission where RTX was instead used as rescue therapy after failure of two conventional IS agents in the first, of two conventional IS agents and of two TNF-α blockers in the second, and of two conventional IS agents and TCZ in the third. Two of them experienced long-term remission ($>$30 months to date) after two and four courses of RTX, respectively.

To our knowledge, there are only 10 published cases of TAK patients treated with RTX, which are summarised in Table 2 [6–9]. One of these cases was reported in Croatian and has been excluded.

Eight of nine patients responded with clinical and laboratory remission. Prednisone doses before and after RTX therapy were reported only in two patients, and both patients were able to reduce prednisone to $\leqslant$10 mg/day. Additionally, imaging improvement was observed in two of the four patients with imaging reported before and after RTX treatment. In the two cases described by Caltran *et al.* [6], PET scan was repeated

Table 1 Parameters of disease activity before and after rituximab treatment

Case	Age/ Sex	Disease duration, years	Previous therapy	ESR/ CRP at first RTX, mm/h, mg/dl	PDN dose at first RTX (mg/day)	Concomitant IS therapy	RTX courses	ESR/CRP 6 months after last RTX, mm/h, mg/dl	Imaging (CTA/MRA) 6 months after last RTX	PET/CT 6 months after last RTX	Kerr index 6 months after last RTX	Outcome 6 months after last RTX	PDN 6 months after last RTX	Therapeutic changes	Follow-up, months
1	20/F	2	MTX	38/6.2	25	MTX 20 mg/ weekly	2	68/4.7	No disease progression	Positive	Positive	Active disease	5	Stop RTX, start ADA	12
2	32/F	0	None	49/4.6	0	None	1	61/3.4	Disease progression	Positive	Positive	Disease progression	12.5	Stop RTX, start PDN +TCZ	12
3	21/F	1	MMF	12/2.7	50	MMF 2 g/day	1	16/2.8	Disease progression	Positive	Positive	Disease progression	5	Stop RTX, start ADA	12
4	60/M	22	MTX, MMF, ADA, IFX	66/2.0	25	MMF 2 g/day	2	18/0.5	No disease progression	Negative	Negative	Remission	7.5	PDN tapering	36
5	19/F	5	MTX, AZA, TCZ, IFX, ADA	98/11.5	50	None	2	78/4.0	Disease progression	Positive	Positive	Disease progression	18.75	Stop RTX, start MMF	24
6	22/F	1	AZA, MTX	MD/4.4	10	None	4	MD/0.3	No disease progression	ND	Negative	Remission	2.5	No changes	72
7	54/F	3	MTX, AZA TCZ	MD/1.1	15	None	3	MD/0.2	No disease progression	ND	Negative	Remission	10	PDN tapering No changes	60

ADA: adalimumab; CTA: computerized tomography angiography; IFX: infliximab; IS: immunosuppressive; MD: missing data; MRA: magnetic resonance angiography; ND; not done; PDN: prednisone; RTX: rituximab; TCZ: tocilizumab.

Table 2 Characteristics of the published cases of Takayasu arteritis treated with rituximab

Author	Number of patients	Disease duration, months	Previous therapy	PDN dose pre-RTX, mg/day	Concomitant IS therapy	Number of RTX courses	Number of responders	PDN dose after RTX, mg/day	Follow-up, months	Imaging improvement after RTX
Hoyer *et al.* [4]	3	36/48/ 120	PDN (3), MTX (1), MPA (1), CYC (1), ADA (1), HCQ (1)	10/5/7.5	NS	NS	3/3	NS	NS	In 1 patient, PET after the second cycle of RTX: marked decrease in vascular FDG uptake, NS for 2 patients
Galarza *et al.* [7]	2	84/96	MTX (2), anti-TNFα (2) (not specified)	NS	0	NS	1/2	NS	NS	NS
Ernst *et al.* [8]	1	NS	PDN, CYC, AZA	30	NS	3	1/1	5	14	1/1 MRA 14 months after RTX: no active vasculitis and no further stenoses
Caltran *et al.* [6]	2	NS	PDN (2), CYC (2), MTX (1), ADA (1), IFX (2)	NS	MMF	2 in both patients	2/2	5	42 for both patients	2/2 PET 18 months after first RTX: active vasculitis in both of 2 patients, after retreatment NS
Walters *et al.* [9]	1	3	PDN, MTX	40	MTX (discontinued during RTX)	1	1/1	10	At least 3 months	NS
Total	9						8/9			2/4

ADA: adalimumab; IFX: infliximab; IS: immunosuppressive; MD: missing data; MPA: mychophenolic acid; NS: not stated; PDN: prednisone; RTX: rituximab.

18 months after starting RTX and in both cases showed the presence of active vasculitis. The two patients were retreated with RTX and 2 years later they were in clinical and laboratory remission, but imaging evaluation was not repeated. No side effects were reported during RTX treatment in our cases and in the published nine cases.

Discussion

GCs remain the cornerstone of the therapy in large vessel vasculitis. However, they are frequently associated with serious side effects and relapses. GC dependence is seen in more than two-thirds of patients when GCs are tapered or withdrawn [2]. Thus, between 46 and 84% of TAK patients will need a second agent to achieve sustained remission with acceptable GC dosages [2].

In the last decades, several synthetic conventional IS drugs have been employed as GC-sparing agents in TAK, mainly MTX, MMF, AZA and CYC [10, 11]. However, these studies were open-label pilot studies and their results were limited by the low number of patients involved.

More recently, biologic agents have been employed in the treatment of refractory TAK.

Although there are not randomized clinical trials on the use of anti-TNFα inhibitors in TAK patients, several open studies and case reports have shown efficacy of anti-TNFα drugs in treating disease and reducing GC requirements in patients with longstanding, relapsing disease [12]. A recent literature review reported the efficacy of anti-TNF inhibitors (mainly IFX) in inducing remission in 70–90% of TAK patients unable to achieve or maintain remission with GC and traditional immunosuppressant alone; over 40% of these patients have been able to discontinue GC while relapses are described in nearly 40% [12].

TCZ may be an effective GC-sparing agent in patients with TAK. Loricera *et al.* [13] in the largest case series of TAK patients treated with TCZ showed that this biologic agent was effective in the management of patients with vasculitis refractory to GCs and/or conventional IS drugs. Several case series and case reports confirmed that TCZ may be effective in relapsing or refractory TAK patients in whom it has been difficult to taper GCs to an acceptable level, even despite therapy with additional agents [14–16].

There is increasing evidence supporting a role of B cells in TAK: in particular the presence of B cell infiltrates in inflamed vessels and anti-endothelial antibodies suggest a pathogenic role of B cells [3, 17, 18]. Furthermore patients with active TAK show elevated B cell-activating factor levels, which play a role in survival, differentiation and isotype switching of B cells [19], and a markedly increased number of newly generated plasmablasts, similarly to SLE active patients, as shown in a recent study [4]. The same study reported three cases of refractory TAK patients successfully treated with RTX, as assessed by clinical, laboratory and imaging modalities. These data may suggest that the B cell homeostasis could play a role in the pathogenesis of TAK and that RTX may thus represent an option in treating refractory TAK patients.

Furthermore, RTX was demonstrated to be effective in chronic periaortitis refractory to conventional treatments or with contraindications to standard dose GCs. Similarly to TAK, this condition is characterized by a chronic inflammatory infiltrate rich in CD 20^+ B cells, particularly pronounced at the level of adventitial vasa vasorum of the aortic wall [20].

Four case reports described six additional patients with active relapsing/remitting TAK despite multiple IS agents, including anti-TNFα agents, that have been treated with RTX with good reported outcomes in five of six cases [6–9]. However (Table 2), in the majority of cases the response criteria were not specified, and in particular, imaging response criteria were not uniformly reported. Furthermore, the use of concomitant medications compounds the assessment of efficacy of RTX. Finally, in most patients the duration of follow-up remains short. These limitations significantly hamper the assessment of the real efficacy of RTX and may contribute toward explaining the discrepancies between our findings and those of previous studies.

In fact, in our series a response to RTX was observed in less than half of cases. Three out of seven patients, previous unsuccessfully treated with traditional immunosuppressant and biologic therapy, after 6 months of RTX therapy experienced clinical improvement along with a decreased level of acute phase reactants and an absence of disease progression, verified by imaging techniques. In all these cases prednisone was tapered to an acceptable dosage.

Conversely, in the remaining four cases, when RTX was used as first line biologic therapy (two patients) or in a naïve patient (one patient), we observed a persistently active disease with radiological progression. This last patient with newly diagnosed TAK was treated in an early phase with RTX alone and had an unfavourable response. We observed a persistent disease activity and radiological progression also in the fourth case in which RTX was employed as third line biologic therapy.

RTX was well tolerated by all patients. In particular, no serious adverse events such as severe infections or infusion-related reactions occurred.

Considering our results and those previously reported, we think that RTX may be a potentially effective and safe therapeutic option in patients with TAK refractory to standard IS and biologic drugs, while our data do not support a role of RTX as a first line biologic therapy. Hoyer *et al.* [4] suggested that circulating plasmablasts could be a useful biomarker of disease activity and a tool for selecting appropriate candidates for B cell depletion in TAK. However, the efficacy and safety of the RTX in TAK patients and the potential role of plasmablasts in monitoring disease activity should be assessed in prospective controlled clinical trials with long-term follow-up.

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