Serial analysis of clinical and imaging indices reveals prolonged efficacy of TNF-α and IL-6 receptor targeted therapies in refractory Takayasu arteritis

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Abstract

Objectives. We analysed a large cohort of patients with Takayasu arteritis, seeking robust clinical evidence for prolonged responses to tumour necrosis factor-α (TNF-α) and interleukin-6 receptor (IL-6R) antagonists in severe refractory disease.

Methods. Case notes from ninety-eight patients with Takayasu arteritis were retrospectively reviewed. Drug treatment, laboratory and serial non-invasive imaging data were analysed, and the Indian Takayasu arteritis activity (ITAS) and damage scores (TADs) calculated.

Results. Nine patients were treated with biologic therapies. All had previously received high dose prednisolone and ≥1 conventional immunosuppressant. Five patients had failed cyclophosphamide. The patients prescribed biologics had more extensive arterial injury than the remainder of the cohort and persistent active disease (ITAS range 2–9, CRP 12–206 mg/L, TADs 3–1). Eight patients were prescribed anti-TNF-α therapy, three IL-6R blockade. The mean duration of anti-TNF-α treatment was 42 months (maximum 8 years). One patient developed new arterial stenoses while receiving anti-TNF-α and subsequently achieved disease remission with tocilizumab. Two patients have now demonstrated sustained responses to IL-6R inhibition at 19 and 20 months. Following introduction of biologic therapy, serial non-invasive imaging has revealed no significant progression in arterial injury. A significant fall in CRP (p<0.01), prednisolone dose (p<0.01) and ITAS (p<0.01) was observed, with no increase in TADs.

Conclusion. We report for the first time sustained responses to both anti-TNF-α and IL6R antagonists in refractory Takayasu arteritis. As 5/9 patients were cyclophosphamide non-responders, we propose that biologics should now be considered ahead of cyclophosphamide in these young patients.

Introduction

Takayasu arteritis is an idiopathic granulomatous vasculitis affecting large- and medium-sized arteries, with a predilection for the aorta and its branches. Affected patients are predominantly female under the age of 40 presenting with systemic symptoms associated with widespread arterial inflammation, necessitating long-term treatment with corticosteroids and other immunosuppressants.

Arterial inflammation is characterised by infiltration of the arterial wall by monocytes, T and B lymphocytes and by the formation of multinucleate giant cells. Pro-inflammatory cytokines secreted by the cellular infiltrate including tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interferon-γ have been implicated in pathogenesis (1, 2). Local release of growth factors, including vascular endothelial growth factor and platelet-derived growth factor, induces myofibroblast proliferation leading to arterial stenosis and occlusion in 90% of patients, while metalloprotease release predisposes to aneurysm formation in up to 25%. The consequences of arterial injury include limb ischaemia, hypertension, stroke, pulmonary hypertension, angina and myocardial infarction.

The majority of patients respond to corticosteroids in combination with an immunosuppressive drug (methotrexate or azathioprine) (2), and this is reflected by recent EULAR and Italian Society of Rheumatology guidelines (3, 4). In those with persistently ac-
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tive disease, the conventional approach has been treatment with oral or pulsed intravenous cyclophosphamide (5). More recently, the role of biologics targeting TNF-α and IL-6R in Takayasu arteritis has been investigated (6, 7), with some evidence for long-term efficacy and improved quality of life (8). However, the majority of these studies, while demonstrating beneficial effects of biologic therapy, include relatively short-term follow-up on biologics and typically 1 year or less. Thus, important questions remain concerning the use of biologic therapy in TA. These include questions regarding which biologic should be used first-line and the optimal duration of treatment. Additionally, concerns have been raised about the efficacy of anti-IL-6R blockade for the modulation of arterial wall inflammation (9, 10).

We have now analysed our use of biologic therapy for the long-term treatment of severe refractory Takayasu arteritis in a cohort followed for 12 years. The biologic-treated group included a substantial proportion of patients who had failed cyclophosphamide therapy, and those in whom cyclophosphamide was not an option due to the need to preserve fertility. All patients were monitored with serial non-invasive arterial imaging. We report the prolonged use of TNF-α antagonists, anti-TNF-α agent switching and extended use of the humanised anti-IL-6R mAb tocilizumab, both as a first-line biologic and following failure of anti-TNF-α therapy.

Methods

A retrospective case note review of patients seen at Hammersmith Hospital between 2000-2012 and fulfilling a diagnosis of Takayasu arteritis according to American College of Rheumatology criteria (11) was performed. Disease activity indices used were the CRP level (normal <5 mg/L) and/or ESR (normal <30 mm/hr), and measurement of the Indian Takayasu Activity Score (ITAS) (12). The Takayasu Arteritis Damage Score (TADS) (13), alongside serial non-invasive imaging (magnetic resonance angiography (MRA), computerised tomographic angiography and high resolution ultrasound US) were used to assess disease progression. Patients were analysed for evidence that intervention with biologics modified disease activity and progression using the following end-points: 1. Change in CRP from decision to start biologic to 6 months post-biologic, 2. Change in daily prednisolone dose from biologic start time to the current dose or last dose prior to cessation of biologic, 3. Change in ITAS and TADS from decision to start biologic until the most recent visit or biologic cessation, 4. Change in arterial injury, assessed by non-invasive angiography (new or worsening stenosis, occlusion, dilatation or aneurysm), from decision to start biologic until the most recent visit or biologic cessation. All images were reviewed independently by two radiologists and by JCM.

Statistics

The non-parametric paired two-sided Wilcoxon signed rank test was used to compare variables, using R (14) (www.r-project.org/), with a p-value <0.05 considered significant.

Results

The case notes of 98 Takayasu arteritis patients seen at Hammersmith Hospital between 2000-2012 were reviewed retrospectively. Nine patients treated with biologic agents were identified, eight were female, seven were white and two were Asian (Table I). Median age at diagnosis was 26 years, range 16–34. Mean disease duration prior to biologic therapy was 5 years (range 3 months to 25 years). Non-invasive imaging demonstrated that the patients who received biologics had more extensive arterial involvement than the remainder of the cohort. Eigh had multiple arterial territories involved (mean 7, range 5–9), compared to 3 (range 1–9) in the rest of the cohort. This was reflected in the high TADS score (mean 7.9, range 3–11). All patients had received prednisolone and at least one immunosuppressive drug prior to prescription of biologic therapy (Table I). Six of the nine had received ≥3 immunosuppressant drugs, and importantly five had persistently active disease despite cyclophosphamide therapy. At biologic initiation, all patients were receiving prednisolone and 8/9 were co-prescribed another immunosuppressant (4 methotrexate, 2 azathioprine, 2 mycophenolate mofetil), and these were continued.

Eight patients received anti-TNF-α therapy, with the initial agent used dependent upon considerations including patient preference, tuberculosis risk and assessment of compliance with treatment. One patient was prescribed more than one antagonist. Four patients received infliximab, 2 adalimumab, and 3 etanercept. The mean duration of anti-TNF-α treatment to date is 42 months (range 5 months to 8 years), demonstrating prolonged efficacy, with 3 patients continuing to respond to therapy after more than 5 years. The anti-TNF-α agents have been well tolerated with no serious adverse events reported. There was a significant reduction in the CRP level from pre-treatment to six months post-anti-TNF-α initiation (79 to 28 mg/L, p=0.007813) (Fig. 1A), and this has been sustained (Fig. 2). At the latest assessment, anti-TNF-α therapy had allowed withdrawal of prednisolone therapy in two patients, and a significant reduction in the mean prednisolone dose from 25 to 9.7 mg/day (p=0.02249). TNF-α blockade has also reduced disease activity, with ITAS falling from a mean of 4.6 to 1.3 (p=0.0312). Figure 2 (graphs a-g and i) shows these changes in the CRP level and prednisolone dose in individuals. Case 1 reported below is a short clinical vignette, which demonstrates the efficacy of anti-TNF-α therapy in refractory Takayasu arteritis.

Case 1

A 23-year-old woman with refractory arteritis, despite high dose prednisolone and azathioprine, developed a new left subclavian artery stenosis. Six pulses of intravenous cyclophosphamide were given, followed by methotrexate and further prednisolone. Following a subsequent relapse and despite higher dose corticosteroids and pulsed cyclophosphamide, repeat MRA revealed progressive arterial disease. Control of disease activity was eventually achieved with infliximab 5 mg/kg every
6 weeks, methotrexate 20 mg/week and prednisolone 20 mg/day. The CRP fell to normal and no further arterial injury was seen over 2 years, during which prednisolone was reduced to 11 mg/day. Infliximab and methotrexate were subsequently withdrawn during pregnancy, and post-partum a severe disease relapse occurred. Upon re-introduction of infliximab, methotrexate, and prednisolone at 20 mg/day, disease control was achieved within 6 weeks. However, repeat MR imaging revealed a new saccular thoraco-abdominal aneurysm, most probably a result of the post-partum flare (Fig. 3A). Two years later she remains well on infliximab, prednisolone 10 mg/day and methotrexate 17.5 mg/week, the acute phase response is normal (Fig. 2a) and imaging shows no further disease progression.

At time of analysis, 6/8 patients remain on anti-TNF-α therapy, with the mean duration of therapy 4.4 years and a max-
imum of 8 years (Case 1). Two patients have stopped treatment. One (Fig. 2c), was prescribed a trial of infliximab at the referring hospital due to a slow response to high dose prednisolone. This was discontinued at 4 months due to presumed lack of efficacy. Four years later, she remains well on cyclosporine and low dose prednisolone. The second patient relapsed while receiving anti-TNF-α therapy and is described below.

Case 2
A 16-year-old female was treated at diagnosis with prednisolone 50 mg/day and weekly methotrexate (20mg) with rapid resolution of symptoms. Following modest prednisolone weaning the disease flared. Infliximab 5 mg/kg/month was added and prednisolone gradually reduced to 5 mg daily, at which point the disease flared again. Due to concern over a potential human anti-chimeric antibody response infliximab was switched to adalimumab. However, after 5 months the patient developed arm claudication and MRA revealed new bilateral subclavian artery stenoses (Fig. 3B-C). Adalimumab was withdrawn and tocilizumab (8 mg/kg/month) started, with rapid resolution of constitutional symptoms and acute phase response (Fig. 2b). A repeat MRA following 6 months treatment demonstrated partial regression of the subclavian stenoses, more marked on the left, where at 8 months vascular studies showed that the peak systolic velocity had fallen from 458 to 336 cm/s. These changes were maintained at 1 year. Subsequent imaging at 12 and 18 months has shown no further progression of the arterial disease on tocilizumab and methotrexate therapy (Fig. 3D), and the steroid therapy has now been withdrawn.

Two further patients received tocilizumab, both as first-line biologic therapy after failure of conventional immunosuppressants. In one the CRP was markedly raised (>200mg/l), despite high-dose prednisolone and azathioprine, suggesting predominantly IL-6-driven disease, hence tocilizumab was prescribed. The patient had a rapid and marked symptomatic response. However, two weeks after the first infusion he developed severe necrotising pancreatitis. Although the pancreatitis was most probably associated with prolonged azathioprine or corticosteroid therapy, there is one reported case of pancreatitis in the REACTION tocilizumab for rheumatoid arthritis study (15), and therefore the drug was withdrawn. Following recovery, the patient was prescribed etanercept and by six months there was a marked clinical response (Fig. 2g). The second patient had co-existent dilated cardiomyopathy which precluded the use of anti-TNF-α therapy. She has shown a sustained response to IL-6R blockade at 19 months and a reduction in prednisolone dose from 40 to 5 mg/day (Fig. 2h).

Due to its mechanism of action, tocilizumab completely suppresses CRP, therefore analysis of CRP reduction would not be an indicator of clinical response. In addition, the small number of patients receiving tocilizumab (n=3) precluded further specific statistical analysis. Therefore, the data was combined with that from the anti-TNF-α cohort to allow overall assessment of the introduction of biologic therapy in patients with refractory disease. This analysis revealed a significant reduction in the mean prednisolone dose from 25.4 mg/day at the start of biologic treatment to 8.4 mg/day at time of analysis (p=0.00903) (Fig. 1B). Figure 4A shows individual data points for ITAS pre- and post-biologic therapy, and demonstrates a significant fall in the biologic-treated population from 4.4 to 1.4 (p=0.0078). Likewise, analysis of TADs in the population as a whole revealed no significant increase in the score following introduction of biologics (p=0.500) (Fig. 4B). In light of the marked suppression of acute phase markers following initiation of biologic therapy, particularly tocilizumab, and the fact that arterial disease may progress in the face of a normal acute phase response, all patients underwent regular MRA. Detailed review of serial MRAs confirmed that only Cases 1 and 2 exhibited progressive arterial injury after biologic initiation, with a new saccular aneurysm and bilateral subclavian artery stenoses identified, respectively.

**Fig. 1. Response to biological therapy.**
A. Mean CRP levels pre- and 6 months post-anti-TNF-α therapy.
B. Mean prednisolone dose pre- and post-biologic therapies (anti-TNF-α and tocilizumab). Error bars represent the standard error of the mean, p-values were calculated using a paired two-sided Wilcoxon test, **p<0.01.**
Discussion

Although the efficacy of biologic therapy in Takayasu arteritis has been reported in case series, the ability of anti-TNF-α and anti-IL-6R therapies to control refractory disease in the long-term is not yet established and outstanding questions remain. Our data is from a retrospective analysis of 98 Takayasu arteritis patients seen at our tertiary referral centre. Nine patients received biologics, representing those with the most severe refractory disease. All were serially monitored using MR angiography. We have demonstrated prolonged efficacy of biologic therapy in this cohort, with mean duration of treatment 42 months, maximum of 8 years. Three patients (33%) have been withdrawn from prednisolone and in the remainder the dose has now been reduced to ≤10 mg daily. Although corticosteroid therapy alone may achieve clinical remission in 60% of patients, most relapse when corticosteroids are tapered, raising the question of how prolonged remission can be best achieved (16). Thus, it is our practice to start steroid-sparing immunosuppressive drugs at the onset of treatment. Despite this, up to 10% of patients had persistently active disease and were considered for anti-TNF-α therapy. TNF-α levels are
Raised in the serum of Takayasu patients (1) and TNF-α has been implicated in pathogenesis (17). Our results support the initial effectiveness of TNF-α blockade in refractory Takayasu arteritis and also demonstrate prolonged efficacy, well illustrated by Case 1. Despite the severity and refractory nature of their disease, two patients receiving anti-TNF-α have now ceased corticosteroid therapy and the remainder have achieved dose reduction to ≤10 mg prednisolone/day. In our series, 7/8 initially responded to anti-TNF-α and six continue on therapy. Sustained reductions in prednisolone dose, CRP and ITAS were seen, with no significant change in TADs or arteriographic imaging appearances, and no adverse events. Importantly, benefit extended to those in whom cyclophosphamide, the standard approach to refractory arteritis, had failed. A recent review of all reported cases of Takayasu arteritis treated with TNF-α antagonists found complete disease remission in 37%, partial remission in 53.5%, with 9.5% non-responders. Corticosteroids were tapered in 52% and withdrawn in 40%, and the median duration of follow-up was 10 months (18). Using the absence of active disease features and prednisone withdrawal for at least 6 months as the definition of complete remission, Hoffman reported that 16/25 patients treated with etanercept or infliximab achieved complete remission. In this study, the first evidence for long-term efficacy was reported, with median duration of 28 months and a maximum duration of 7 years follow-up (6). Schmidt reported 20 patients prescribed anti-TNF-α with a median duration of treatment of 23 months. Disease remission was achieved in 90% and sustained in 50%. However, 33% relapsed on treatment and 20% discontinued due to adverse events (19). Mekinian also reported a significant response to infliximab in 73% at one year (20), while prolonged efficacy and improved quality of life has also been reported with infliximab (8). Thus, open-label studies suggest that TNF-α antagonism is an important therapeutic option in refractory disease and may result in long-term disease control. Although clinical trials are needed, we propose that there is now sufficient data to suggest that TNF-α blockade should be considered ahead of cyclophosphamide, and particularly in patients of child-bearing age. Furthermore, their efficacy also leads to the question of whether TNF-α antago-

Fig. 3. Magnetic resonance angiographic monitoring. A. 3-D reconstruction of the MR angiogram of Case 1 revealing the development of a new saccular aortic aneurysm following a post-partum disease flare, and shown in close up in 2-D in the inserted panel. B-D. Serial MRA monitoring of Case 2, showing the initial MRA (B), new bilateral subclavian artery stenoses developed while receiving anti-TNF-α therapy (C), and no further progression of disease 1 year post-initiation of tocilizumab (D).

Fig. 4. Disease activity and damage indices. A. Indian Takayasu activity score (ITAS) and B. Takayasu arteritis damage score (TADs), pre- and post-treatment with biologics. "p<0.01, calculated using a paired two-sided Wilcoxon test.
nists should be used earlier, becoming the first choice therapy for those with progressive arterial injury despite treatment with prednisolone and a first-line immunosuppressant. While anti-TNF-α is effective in refractory disease, 10–30% of patients do not respond and up to one third relapse on treatment, as seen in Case 2. This had led to interest in therapeutic targeting of IL-6, circulating levels of which are raised in Takayasu arteritis. IL-6 may drive local synthesis of matrix metalloproteinases by mononuclear cells and hence contribute to arterial injury (1, 21). Thus, tocilizumab offers an exciting alternative therapeutic approach. Recent case series of IL-6R inhibition in large vessel vasculitis have included 1–2 Takayasu patients each, demonstrating the apparent efficacy of tocilizumab and suppression of arterial wall inflammation as measured by 18F-Fluorodeoxyglucose CT-PET (22-25). Of the nine Takayasu patients treated with tocilizumab and reported in the literature, the majority were treated for ≤6 months (21) and one for up to 41 months (6, 7). However important practical and theoretical caveats concerning the efficacy of anti-IL-6R inhibition remain. A lack of constitutional symptoms and suppression of CRP synthesis in those receiving tocilizumab complicates disease monitoring and may be falsely reassuring. This is illustrated by the case of a young female who, while well on tocilizumab treatment with a suppressed acute phase response, developed new arterial stenoses over 12 months (9). A recent report describes 2 further patients in whom persistent enhancement of the arterial wall was found by contrast-enhanced MRA despite tocilizumab therapy. This arterial wall signal may represent sustained inflammation, despite a fall in the acute phase markers and the disease activity score (10). Although this potential lack of efficacy is likely multifactorial, it implies that while inhibition of circulating IL-6 is sufficient for effective suppression of CRP and systemic symptoms, it may not adequately control arterial wall inflammation. It has also been suggested that IL-6 may in fact exert a direct protective effect on the arterial wall, with elevated IL-6 levels associated with a reduced incidence of ischemic complications in giant cell arteritis (26). Therefore, we advocate careful arterial monitoring including MRA, assessments of peripheral pulses, limb blood pressures and arterial flow, initially every six months. Decisions to taper co-prescribed corticosteroid/immunosuppressants should be based on imaging data and not purely on the CRP level and resolution of systemic symptoms. Using this approach we now report sustained efficacy at up to 20 months in 2 patients treated with tocilizumab, one who failed anti-TNF-α therapy and another in whom tocilizumab was used as a first line biologic. Since the introduction of tocilizumab, neither patient has suffered any further demonstrable arterial injury, as evidenced by serial contrast-enhanced MRA.

In conclusion, the use of TNF-α and IL-6R blockade has yielded encouraging results in refractory Takayasu arteritis, with emerging evidence of prolonged efficacy. Based on currently available data, we advocate TNF-α antagonists as the first line biologic treatment. Nevertheless, there is no clinical trial data and outstanding questions remain. The optimal TNF-α antagonist and the duration of biologic treatment required are unresolved. The strengths and weaknesses of alternative approaches including IL-6R inhibition and B cell depletion need to be determined, and prospective controlled clinical trials are required (2, 21). Ideally, these should be multina- tional and include assessment by non-invasive imaging and clinical scoring indices such as ITAS and TADS.

References

19. SCHMIDT J, KERMANI TA, BACANI AK,


