Biologic therapy in supra-aortic Takayasu arteritis can improve symptoms of cerebral ischaemia without surgical intervention

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Key words: Takayasu arteritis, vasculitis, cerebral ischaemia, biologic therapy, inflammation arterial injury.

Key messages:

1. Severe supra-aortic Takayasu arteritis (Tak) may lead to cerebral ischaemia and stroke.
2. Aggressive combined immunosuppression is required in Tak, with early escalation to biologic therapy for non-responders.
3. Optimal disease control may obviate the need for surgery.

Word count: 1996

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Abstract

Background: Takayasu arteritis typically results in severe arterial injury with stenoses, occlusions and occasionally aneurysms. Involvement of the supra-aortic arteries is common, and in its most severe form may compromise cerebral blood supply, resulting in signs of cerebral ischaemia including visual impairment, dysphasia, hemiparesis, loss of consciousness and stroke. In addition to combination immunosuppression, the management paradigm for symptomatic cerebral ischaemia includes revascularisation. The invasive nature of this surgery, the risk of complications and the relatively high rate of re-stenosis is of concern to patients and physicians alike. The aim of this study was to determine whether combined immunosuppression with early escalation to biologic therapy improved outcomes and reduced the need for high risk surgical intervention

Methods: A retrospective review of 145 Takayasu arteritis patients attending Imperial College Healthcare between 2010-2018 was conducted to identify those with cerebral ischaemia secondary to supra-aortic disease and to analyse their treatment and outcomes.

Results: Eight patients (5.5%) were identified. Seven received long-term combined immunosuppressive therapy and six were prescribed biologics. The data revealed a higher than expected comprehensive response to therapy, with significant falls in disease activity, cerebral ischaemia score and prednisolone dose required, over a median follow-up of 37 months. Serial imaging analysis detected no arterial disease progression after the initiation of optimal therapy. Only one patient required surgical intervention for persistent neurological symptoms.

Conclusion: Early use of biologic therapy in those with supra-aortic Takayasu arteritis presenting with cerebral ischaemia may reduce the numbers of patients requiring surgical intervention and improve outcomes.

Introduction

Takayasu arteritis (TAK) is a systemic vasculitis classically affecting large arteries, including the aorta, its major branches and the pulmonary arteries. Granulomatous inflammation involves the arterial wall from the adventitia to the intima. The mononuclear cell inflammatory infiltrate and giant cells release growth factors, which drive myofibroblast proliferation resulting in arterial stenosis and occlusion[1]. The rarity of the condition and the heterogenous clinical features typically result in delayed diagnosis and the risk of extensive arterial injury[2]. Early symptoms of TAK are non-specific and include fever, weight loss and malaise. More obvious signs and symptoms develop following the onset of arterial stenosis and include upper limb claudication, diminished pulses, asymmetrical blood pressure and arterial bruits[3].

The predominant aim of treatment is to suppress arterial inflammation and prevent injury. Corticosteroids remain the mainstay. However, relapse occurs in 50% on weaning and the significant side-effect burden of corticosteroids is well-recognised[2]. Thus, combined immunosuppression with corticosteroids and either methotrexate, azathioprine, mycophenolate mofetil, leflunomide or cyclophosphamide is now commonly employed at diagnosis, with efficacy demonstrated in small open-label studies[4-7]. In approximately 15-20% of patients, TAK remains refractory and biologic therapy is increasingly prescribed, with TNF- α inhibition and IL-6R blockade most commonly used[8-12].

Stenotic lesions affecting the supra-aortic vessels are common in TAK. The subclavian, and common carotid arteries are most frequently involved, followed by the vertebral arteries and internal carotid arteries[3]. In the most severe cases, cerebral perfusion is impaired and signs of cerebral ischaemia appear including visual disturbance, dysphasia, transient hemiparesis, loss of consciousness and stroke. Management decisions in this setting remain extremely challenging for both physicians and patients. On the one hand, there is concern that medical management will prove ineffective and risk stroke, while on the other, anxiety regarding the invasive nature of endovascular and open surgical approaches and their associated risks including stroke are justified.

This study retrospectively reviewed the treatment, outcomes and status of those patients in our cohort who presented with demonstrable signs suggestive of cerebral ischaemia. The findings suggest that appropriate escalation to biologic therapy may lead to significant improvement in symptoms and delay or obviate the need for vascular reconstruction.

Methods

Study population

The Imperial College Healthcare NHS Trust TAK database (2010-2018) was retrospectively reviewed. Of the 145 patients seen, those with evidence of severe supra-aortic disease and symptoms of cerebral ischaemia were identified. Analysis of the medical records was performed and the clinical signs and symptoms at presentation, imaging reports, laboratory results and subsequent medical and surgical management were recorded. Laboratory measures were conducted as part of routine clinical care using conventional methods. This research was approved by Imperial College Healthcare and informed written consent for inclusion in the research programme was obtained from all participants.

Clinical assessment

The baseline clinical assessment data and that from the most recent post-treatment follow-up visit were included in the analyses. TAK disease activity was evaluated using the Indian Takayasu arteritis activity score (ITAS-2010)[13]. The stenotic lesions in the pre-treatment imaging studies (MRA or CTA) and the most recent post-treatment study were assessed separately by (i) a vascular radiologist and (ii) at the Rheumatology/Radiology multi-disciplinary meeting. Radiological assessments defined disease evolution as improved if ≥ 1 artery improved and none progressed, stable if all arteries were unchanged, or worsened if ≥ 1 artery progressed.

An 8-point cerebral ischemia score was developed. One point was allocated for the presence of each of the following: 1. Intermittent spontaneous visual disturbance; 2. Persistent visual impairment; 3. Visual impairment on exertion; 4. Dizziness on standing; 5. Transient hemiparesis; 6. Sudden onset loss of consciousness; 7. Dysphasia; 8. Completed stroke.

Statistical analysis

Data grouped according to treatment stage were analysed using GraphPad Prism version 6.0. Differences between pre- and post- treatment were determined using a Mann Whitney test and a value of $p < 0.05$ was considered significant.

Results

One hundred and forty-five patients attended the large vessel vasculitis clinic during the study period. Eight (5.5%) suffered severe supra-aortic TAK with neurological signs and symptoms consistent with cerebral ischaemia. All were female. Mean age at presentation was 26 years (range 20-32). One patient was excluded from further analysis as, for personal reasons; she did not wish to consider a change in treatment from prednisolone 5 mg daily. Although her symptoms including significant visual impairment did not improve, no clinical progression was observed over 4 years. The clinical details of the remaining 7 patients are summarised in the Supplementary Table.

Presenting symptoms

In addition to the presence of more common TAK symptoms, those suggesting significant neurological impairment were present. These included visual disturbance (n = 7), dizziness, often worse on standing (n = 3), unilateral hemiparesis (n = 5), dysphasia (n = 5) and sudden loss of consciousness (n = 5). Patterns of visual disturbance were variable and included amaurosis fugax, transient visual dimming on minimal exertion secondary to a steal effect, transient complete visual loss and persistent reduction in visual acuity (n=2), with one complicated by retinal neovascularisation. On occasion patients reported having to lie flat with their legs raised to aid visual recovery. Prior to the prescription of biologic therapies, the disease was active in all patients as evidenced by a raised ESR (60 mm/hr, IQR 32-65), CRP (27.8 g/L, IQR 12-72) and ITAS score (9, IQR 8-14).

Imaging findings

The predominant vascular imaging modalities used were contrast-enhanced MR and CT angiography of the supra-aortic vessels and Circle of Willis. In all cases, while the Circle of Willis remained patent, extensive arterial stenoses and occlusions of the supra-aortic vessels were present. The pattern of involvement varied between patients and the vessels affected included the brachio-cephalic, common carotid, vertebral and subclavian arteries (Figure 1 and Supplementary Table 1). In addition, stenoses affected the more proximal intracranial arteries (internal carotid arteries, the anterior, middle and posterior cerebral arteries) in 3 patients. Figure 1A shows marked inflammation with concentric thickening of the wall of the arch of the aorta, which extends to involve the supra-aortic vessels including the brachiocephalic, left subclavian and common carotid arteries. Figure 1B-D illustrates the extent of the arterial injury revealed by MRA in patients 3, 4 and 6. In order to assess the impact of treatment, an eight point cerebral ischemia score incorporating the presence of key

signs and symptoms was used. The maximum score recorded was 7/8, median score 4 (IQR 4-6).

Treatment

All patients initially received pulsed intra-venous methylprednisolone (1 gram x 3) followed by oral prednisolone (40-60 mg daily). Conventional synthetic disease-modifying therapies (csDMARD) were prescribed to all prior to biologic therapy (range 1-4). These included methotrexate (5), mycophenolate mofetil (2) azathioprine (2) and intra-venous cyclophosphamide (1). Six patients who failed to respond sufficiently to csDMARDs, as evidenced by return of clinical symptoms, rising ITAS score and/or arterial disease progression, required biologic therapy; 5 tocilizumab 2 infliximab, with 1 patient on tocilizumab switched to infliximab due to a new additional diagnosis of Crohn's disease.

Patient 7, concerned about the potential side-effects of corticosteroids and immunomodulators initially declined treatment. Following worsening of disease she suffered a stroke. Despite the subsequent addition of corticosteroids, azathioprine and infliximab, the arterial disease progressed. Infliximab was replaced with tocilizumab and disease control was achieved. However, in light of persistent ischaemic neurological signs, she underwent a successful aorto-bicarotid bypass.

At the time of analysis the median duration on treatment across the seven patients was 37 months (IQR 23-80). Four patients remain on low dose corticosteroids + csDMARD + biologic, one patient remains on csDMARD + biologic. Patient 7 is prescribed tocilizumab monotherapy by request. Patient 3 has been successfully withdrawn from all medication following long-term remission (total treatment 80 months).

Outcome data

To achieve suppression of disease activity, biologic therapy was required in 6/7 patients. The ESR fell in all patients from a pre-treatment median of 60 mm/hr to a post-treatment value of 8 mm/hr (IQR 2-14) (Figure 2A). Likewise, the mean CRP fell from a pre-treatment median of 27.8 mg/L (IQR 12-72) to a post-treatment level of 0.2 mg/L (0.2-0.5). However, control of disease activity was best illustrated by a marked fall in the ITAS 2010 score, with the median ITAS 2010 falling from 9 (IQR 8-14) to 1 (IQR 0-2) (Figure 2B). These responses allowed a significant and important reduction in the prednisolone dose in all patients. The median pre-treatment dose was 20 mg daily (IQR 15-40). At the latest clinic visit the median dose was 5 mg daily (IQR 0-6), with corticosteroids withdrawn in three patients.

A marked fall in the cerebral ischaemia score was seen in all patients ($p < 0.001$) (Figure 2C). In three patients, there has been complete resolution of their neurological symptoms. Patients 2 and 6 have residual infrequent transient visual disturbance and Patient 4 occasional drop attacks, which in all cases have reduced in frequency. Patient 7 has persistent visual disturbance and dysphasia following a stroke. The Takayasu arteritis damage score has remained stable, pre-treatment median 10 (IQR 10-11), post-treatment 11 (IQR 10-11), range 7-13. Two independent radiological assessments of the pre-treatment and most recent MRA or CTA scans, graded the arterial disease as stable in six patients. In patient 2, remodelling with improved patency was seen in the right common carotid artery. Importantly, aside from patient 7 who initially declined therapy, no endovascular or open surgical intervention has been required.

Discussion

Stenoses affecting the supra-aortic arteries sufficient to cause cerebral ischaemia and a heightened risk of stroke, is one of the most feared complications of TAK. While rare, this pattern of disease remains a major indication for surgical intervention in TAK[14]. In light of the severity of the symptoms and signs in the patients described herein, the initial aim was to gain control of disease activity prior to surgical intervention. Endovascular and open surgical approaches have been successfully adopted for supra-aortic TAK. A Korean study reported that 10% of their patients with supra-aortic arterial stenoses required surgical intervention. During a mean follow-up period of ~40 months, 53% of lesions treated with angioplasty and 12.5% of bypass grafts re-stenosed. Serious complications, although rare, were more common after open surgery and included intracerebral haemorrhage and cardiac tamponade[15].

Analysis of surgical outcomes in Takayasu arteritis have emphasised the necessity, whenever possible, to gain adequate control of disease activity prior to intervention [16, 17]. For six patients, the addition of biologic therapy was required to control disease activity as measured by ITAS, and to halt radiological progression. However, the degree of improvement in the neurological symptoms observed far exceeded that expected. A fact reflected by the significant fall in the cerebral ischaemia score. Therefore, to date six patients have not required surgery. Instead, for between 13-80 months, they have been closely monitored in the clinic with serial imaging. The therapeutic benefit has been maintained. Moreover, the corticosteroid dose has been significantly reduced. Patient 7 suffered a stroke prior to receiving adequate therapy. Once the disease was suppressed by combination therapy, some neurological symptoms persisted and she received an aorto-carotid bypass graft, which remains patent 80 months post-surgery.

The mechanism underlying the marked improvement in cerebral ischaemia remains unknown. One hypothesis is that optimal therapy is sufficient to reduce arterial wall inflammation and the associated oedema, leading to a small increase in the vessel lumen diameter. According to Poiseuille's equation, this would result in an increase in cerebral blood flow equivalent to the change in radius to the power four. Alternatively, suppression of systemic inflammation may act at the microvascular level. Cytokines driving systemic inflammation including IL-1, IL-6 and TNF- α have been linked to cerebral and coronary microvascular dysfunction, at least in part through increased synthesis of the vasoconstrictor endothelin-1[18]. Furthermore, TNF- α antagonism can restore coronary microvascular function in psoriasis[19]. We have recently reported improvements in arterial stenoses in Tak[20], and in further studies, we propose to monitor changes in cerebral perfusion to monitor treatment efficacy, making use of nuclear medicine and transcranial Doppler techniques.

Limitations of this study include its retrospective nature, the small number of patients and the lack of an appropriate control group. Thus, the conclusions are made with caution. However, we believe that this initial cohort analysis has demonstrated that combined immunosuppression at the outset, with early escalation to biologic therapy where appropriate, is required in those with supra-aortic TAK presenting with cerebral ischaemia. This approach may reduce the numbers of patients requiring surgical intervention and improve outcomes in those that have persistent symptoms and undergo surgery.

Conflicts of Interest: JC Mason has participated in medical board meetings with Roche/Chugai. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Funding: This work received infrastructure support from the Imperial College, National Institute for Health Research Biomedical Research Centre scheme.

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Figure legends

Figure 1. Supra-aortic Takayasu arteritis.

A. CT angiogram of patient 6 demonstrates inflammation affecting the aortic arch which extends to the supra-aortic vessels (brachiocephalic trunk, left common carotid (CCA) and subclavian arteries (SCA) (arrows)), with stenosis of the left SCA (star). **B.** Shows the MR angiogram (MRA) for patient 6, with stenosis/occlusion of the right CCA and left SCA (arrows). The star marks the occlusion of the left CCA and proximal narrowing of the left vertebral artery (VA). **C.** In patient 3, the MRA reveals occluded right and left SCAs (large arrows), occluded CCAs (stars), with an occluded left VA (small arrow) and hypertrophied right VA. **D.** Patient 4 has occlusion of the left SCA (black arrow), stenosis of the left CCA, right SCA and left VA (stars), with tight proximal stenosis of the right CCA (white arrow).

Figure 2. The response to therapy.

The ITAS 2010 score, ESR, cerebral ischaemia score and prednisolone dose were recorded immediately prior to the start of biologics therapy and at the latest clinic visit. **A.** Shows a significant fall in disease activity as measured by ITAS 2010. **B.** The ESR fell in all patients. **C.** An eight point cerebral ischaemia score revealed marked neurological impairment at baseline and a significant fall in response to biologic therapy. **D.** Reveals a significant reduction in prednisolone dose in response to optimal therapy. ** $p < 0.01$, *** $p < 0.001$.

Figure 1

Figure 2

								CRP (mg/L)		ESR (mm/hr)		Steroid dose (mg)		Cerebral Ischaemia Score	
Case	Sex	Age at presentation	Presenting symptoms	Imaging findings	Treatment received	Duration of treatment	Progress	Pre Tx	Post Tx	Pre Tx	Post Tx	Pre Tx	Post Tx	Pre Tx	Post Tx
1	F	32	Sudden loss of consciousness Exercise induced visual disturbance. Left hemiparesis Dysphasia	Right & Left CCA stenosed Right & Left SCA stenosed Right & Left VA stenosed	IV Methylprednisolone followed by: Prednisolone 60mg & methotrexate 20mg. Subsequent flare on weaning → infliximab.	Remains on prednisolone, methotrexate and infliximab after 2 years	Resolution of loss of consciousness and visual disturbance Nil further hemiparesis/dysphasia No significant interval change on recent CT angiogram	72	0.2	60	14	35	8	5	0
2	F	29	Right sided facial weakness Dysphasia Visual disturbance	Right CCA stenosed Left ICA occluded Right & left SCA occluded Right & Left VA patent	IV Methylprednisolone followed by prednisolone 60mg Methotrexate. 2 years later flared, treated with cyclophosphamide Switch to azathioprine maintenance. Persistent neurological symptoms after 8 years → tocilizumab.	Remains on azathioprine and and tocilizumab.	Initially, further episodes of dysphasia and visual disturbance. Resolved after switch to IV tocilizumab. No progression of arterial disease, and improved Rt CCA on recent MRA.	6.7	0.5	56	2	20	0	4	1
3	F	23	Sudden loss of consciousness. Watershead infarct. Visual disturbance	Right & Left CCA occluded Right & Left SCA occluded Right VA patent Left VA occluded	IV Methylprednisolone followed by prednisolone 60mg and methotrexate maintenance for 5 years	Prednisolone 4 yrs and methotrexate 5 years. Now successfully weaned off treatment and stable at 2 years.	No further loss of consciousness, dysphasia or visual symptoms. Weaned off Methotrexate and prednisolone No significant interval change on recent MR Angiogram	71	0.2	65	3	5	0	6	0
4	F	26	Drop attacks with loss of consciousness on exertion Visual loss on exertion Light headed on standing	Right CCA occluded Left CCA stenosed Right SCA patent Left SCA occluded Right VA patent Left VA occluded	IV Methylprednisolone followed by prednisolone 60mg and methotrexate 25mg. Flare treated with IV methylprednisolone & cyclophosphamide (8 months). Maintenance with mycophenolate mofetil Persistent symptoms 6 months later → tocilizumab therapy.	Remains on tocilizumab, prednisolone and MMF	Intermittent drop attacks persist Visual loss on exertion resolved Stable appearances of arterial disease on recent MR angiogram	27.8	0.5	98	33	20	7	3	1
5	F	20	Visual disturbance Dysphasia Light headed on standing	Right CCA occluded Left CCA stenosed Right VA stenosed Left VA retrograde filling Right & Left SCA stenosed	IV Methylprednisolone followed by prednisolone 60mg and methotrexate 25mg for 3 months. Progressive stenosis on MRA → tocilizumab. Subsequent diagnosis of concomitant Crohn's disease led to switch to Infliximab.	Remains on Prednisolone, methotrexate and infliximab.	Nil further episodes of dysphasia or visual loss. Stable MRA imaging.	12	1.7	32	8	40	5	4	0

6	F	26	Left arm weakness, hypertension, Visual disturbance. Sudden loss of consciousness.	Right CCA stenosed Left CCA occluded Right & Left VA patent Right and Left SCA patent Right and Left ICA stenosed	IV Methylprednisolone followed by - prednisolone 60mg methotrexate 20mg Flare after 1 year, mycophenolate added Persistent symptoms at 6 mths tocilizumab commenced and mycophenolate withdrawn.	Remains on low dose prednisolone, methotrexate and tocilizumab	Very occasional visual disturbance. Stable MRA imaging.	13.8	0.2	25	2	15	5	4	1
7	F	30	Visual disturbance. Transient ischaemic attacks. Sudden loss of consciousness. Stroke, dysphasia and hemiparesis.	Right CCA stenosed Left ICA occluded Right SCA patent Left SCA occluded Right VA patent Left VA stenosed	IV methylprednisolone followed by prednisolone 60mg and azathioprine maintenance. Flare → addition of infliximab. Disease progression after 6 mths led to switch to tocilizumab	Remains stable on tocilizumab monotherapy	Recurrent CVA. Predominantly aphasic.	62.2	0.2	65	14	40	0	7	2

Supplementary table: showing patient characteristics, investigations performed, treatment and outcomes.

Key CCA – Common carotid artery ICA – Internal carotid artery VA – Vertebral artery SCA – Subclavian artery