Management of Takayasu arteritis: a systematic review

Gokhan Keser¹, Haner Direskeneli² and Kenan Aksu¹

Abstract

Assessment of the pattern and extent of arterial involvement and measurement of current disease activity are essential for the management of Takayasu arteritis (TA). Since there is no completed, placebo-controlled, randomized clinical trial, the level of evidence for management of TA is low, generally reflecting the results of open studies, case series and expert opinion. The most commonly used agents include corticosteroids and conventional immunosuppressive agents such as MTX, AZA, MMF and LEF. In patients who remain resistant and/or intolerant to these agents, biologic drugs including TNF inhibitors, rituximab and tocilizumab seem to be promising. Antiplatelet treatment may also lower the frequency of ischaemic events in TA. In the presence of short-segment, critical arterial stenosis, balloon angioplasty or stent graft replacement may be useful. On the other hand, long-segment stenosis with extensive periartrial fibrosis or occlusion requires surgical bypass of the affected segment, which is clearly associated with superior results compared with endovascular intervention. As a general rule, both endovascular intervention and surgical procedures should be avoided during the active phase of the disease. Earlier diagnosis, better assessment of disease activity and future clinical trials will obviously improve the management of TA.

Key words: management, Takayasu arteritis, Takayasu vasculitis, large vessel vasculitis.

Introduction

Basic concepts in Takayasu arteritis

Takayasu arteritis (TA) is a large vessel vasculitis (LVV) characterized by granulomatous inflammation of the vessel wall with an unknown etiopathogenesis. TA predominantly affects young females during the second or third decades of life and mainly involves the aortic arch and its primary branches, ascending aorta, thoracic descending aorta and abdominal aorta. Early in the disease course, non-specific constitutional symptoms such as fever, malaise and weight loss may occur. Later, inflammation of the involved arteries progresses, resulting in segmental stenosis, occlusion, dilatation and/or aneurysm. This may cause extremity pain, claudication, bruits, absent or diminished pulses and loss of blood pressure. TA generally follows an insidious course, however, presentation with acute visual loss or stroke may also occur [1-3].

TA may show different patterns of arterial involvement, disease expression and prognosis in different regions of the world [3, 4]. Multiple genetic factors were recently shown by a whole-genome approach in TA and an association between the extent of vascular involvement and the major genetic risk factor HLA-B*52 was reported in Turkish TA patients, suggesting that genetic factors might influence disease severity [5, 6]. The aim of this article is to review the current management of TA, including medical treatment options and endovascular and surgical revascularization procedures.

Why management of TA is not easy

TA is a difficult disease to deal with. First, early diagnosis is difficult and requires clinical awareness and suspicion [7, 8]. Second, and even more important, is the lack of standard and reliable parameters reflecting disease activity [9]. Systemic inflammatory response does not always show a positive correlation with inflammatory activity in the vessel wall. Therefore TA may be active despite a normal ESR and serum CRP level, and vice versa. In patients with apparent clinical and laboratory remission,
arterial modalities are very important for establishing the diagnosis of TA, determining the distribution of lesions and monitoring disease activity [11, 12]. Although conventional radiological angiography [digital subtraction angiography (DSA)] is considered the gold standard for diagnosis of TA, non-invasive imaging methods including magnetic resonance angiography (MRA), colour Doppler ultrasound (CDU), computerized tomography angiography (CTA), PET with 18F-fluorodeoxyglucose (18F-FDG) and 18F-FDG PET/CT [12–22] have recently gained ground on DSA. Since DSA shows only radiological lesions affecting the vessel lumen without giving any information about the vessel wall, it may miss minor, non-occlusive lesions. Besides, it is an invasive method causing exposure to contrast media and radioactivity [11, 12]. MRA, CTA and CDU can visualize the characteristic, homogeneously thickened vessel walls and luminal changes of large arteries. They can demonstrate early inflammatory signs (vessel wall thickening and mural inflammation) as well as late complications (stenoses and aneurysms) [23]. MRA and CTA provide a good overview of the involved vessels in different locations. Ultrasound has the highest resolution, but fails to depict the thoracic aorta unless performed as a transesophageal examination [17]. 18F-FDG PET is a non-invasive imaging method that measures 18F-FDG, which accumulates in hypermetabolic, activated inflammatory cells infiltrating the vessels. 18F-FDG PET/CT combines the functional information from PET and anatomical information from CT. However, vascular uptake on PET is not specific for vasculitis, and discriminating between atherosclerotic and vasculitic lesions may be challenging. Also, PET cannot delineate the vessel wall structure and luminal flow. Radiation exposure is high in CT, particularly in PET-CT [19–22].

Non-invasive imaging methods are essential for monitoring disease activity and response to treatment in TA. Increased vessel wall thickness, vessel wall oedema and mural contrast enhancement are usually considered evidence of active disease [12]. Vessel wall oedema, mural contrast enhancement or 18F-FDG uptake may decrease with successful immunosuppression. A decrease in wall thickness provides information about whether the disease has been well controlled over months or years. However, these findings are not always reliable [11, 12, 15]. Using echocardiography, the heart should also be monitored for the presence or progression of aortic regurgitation or left ventricular hypertrophy due to hypertension in TA [12].

Taken together, monitoring disease activity in TA may be accomplished by the integrated use of non-invasive imaging methods, patient symptoms, clinical findings and acute phase reactants. There is no single imaging modality that can provide all the information required and each method has distinct and complementary roles in monitoring. The use of non-invasive procedures providing a good overview of the involved vessels without radiation exposure, such as MRA, is recommended if available [12].

There are also criteria defined for assessing disease activity in TA. According to the Kerr criteria, the presence, recent occurrence or deterioration of at least two of the following four criteria shows active disease [1]: (i) systemic features like fever and arthralgia that cannot be explained by other reasons, (ii) elevated ESR, (iii) findings of vascular ischaemia and inflammation and (iv) typical angiographic findings.

In 2005 the Disease Extent Index–Takayasu (DEI-Tak) was defined for the follow-up of TA by assessing only new clinical findings within the past 6 months without the requirement for imaging techniques or acute phase reactants [24]. The DEI-Tak was shown to be a practical and valuable tool to assess disease activity and progression in a Turkish TA series [25]. Recently a new version of the DEI-Tak, the Indian Takayasu’s Arteritis Score (ITAS) was introduced [26]. The OMERACT Vasculitis Working Group also performs a Delphi exercise for the assessment of disease activity in LVV to develop a core set of validated outcome measures [27].

Another problem in the management of TA is the low level of evidence. The relative rarity of TA and the lack of ideal outcome measures are barriers in conducting placebo-controlled, randomized clinical trials in TA. Current evidence reflects the results of open studies, case series and expert opinion [9].

Methods

We conducted a comprehensive review of the literature for English articles published between 1966 and 2012, using PubMed as the database. The key words Takayasu arteritis and Takayasu’s arteritis were searched in combination with the following key words: treatment, management, endovascular intervention, bypass surgery, corticosteroid (CS), anti-platelet agents, anticoagulant agents and immunosuppressive (IS) agents. Each of the IS agents that are currently used, or has the potential to be used, for the treatment of TA, i.e. MTX, AZA, cyclophosphamide (CYP), ciclosporin A (CSA), MMF, LEF and tacrolimus, were also used as additional key words. Among biologic agents, TNF inhibitors (anti-TNF agents), rituximab (RTX), tocilizumab and abatacept were selected as key words. We also manually searched the references of the selected articles for any relevant articles that we might have missed.

Management of TA

General principles

Patient education and cooperation between the doctor and the patient are essential. The rationale of the medical treatment is to suppress systemic and vascular inflammation using CS and IS agents. When the CS dose cannot be lowered and conventional IS agents remain ineffective, or when these agents can no longer be used due to adverse events, biologic agents may be tried. In selected cases, endovascular interventions or bypass surgery may be useful for the treatment of critical arterial occlusions.
However, these interventions should not be performed during the active phase of the disease [28–32].

Supportive measures

Diet, low salt intake, calcium and vitamin D supplementation and regular exercise are essential to reduce the metabolic side effects of CS agents. Monitoring and control of blood pressure may be difficult in cases with absent or reduced pulses in some extremities. Blood pressure measurements should be made in the unaffected extremities. In some patients with unreliable measurements, the presence of hypertensive retinopathy may be a warning sign for the clinician. In the presence of treatment-resistant hypertension, the possibility of renovascular hypertension should be considered, which may be treated with endovascular interventions or surgery [29].

Similar to other inflammatory diseases, atherosclerosis risk is also increased in TA, and preventive measures should be considered [33]. There are some basic studies favouring the use of antiplatelet agents in TA [34–36]. In the limb affected by arterial stenosis, more platelet aggregation and higher levels of thromboxane were reported, and these findings were shown to improve after 80 mg/day aspirin treatment. A recent retrospective observational study [38] suggested that antiplatelet therapy was associated with a lower frequency of ischaemic events in patients with TA [38]. However, the relative efficacy of this treatment between different angiographic stages of TA is not known [39].

Corticosteroids

In the presence of active disease, standard initial treatment of TA is high-dose (1 mg/kg/day) prednisolone or its equivalents. Generally, two-thirds of the total daily dose is given early in the morning and the rest of the dose in the evening after meals. The response to high-dose prednisolone is generally favourable, but relapses may occur while gradually tapering the dose and adverse effects of long-term treatment can cause problems. Therefore many physicians tend to start conventional IS agents together with the initial CS treatment or while tapering the CS dose [40, 41].

Conventional IS agents

In TA there is no randomized study comparing the efficacy of different IS agents, therefore there is no evidence showing which IS agent is superior in the treatment of TA. Since MTX is an inexpensive, easily available and relatively safe agent that is widely used in rheumatology, it is the first choice of many physicians. However, the data regarding MTX use in TA is limited and generally is in the form of case reports and few small open studies [42–47]. Hoffman et al. [46] reported 16 patients with TA given standard CS treatment plus MTX. Thirteen patients (81%) went into remission and eight patients (50%) remained in remission for a mean period of 18 months.

AZA is another IS agent widely used for the treatment of TA. Besides case reports [48–50], there is only one open study from India [51]. In this study, 65 patients with TA who had not received any IS agent previously were given 2 mg/kg/day AZA in addition to CS treatment for 1 year. Acute phase responses were significantly reduced, no adverse events occurred and control angiography showed no progression. However, long-term follow-up of these patients was not reported.

CYP is a very potent and effective IS agent, generally used for the treatment of systemic vasculitis in the presence of severe life and/or vital organ-threatening conditions. Most of the case reports with CYP use in TA include severe cases with at least one of the following conditions: retinal vasculitis, pulmonary artery involvement with or without aneurysm, severe aortic regurgitation or myocarditis [52–54]. In a prospective study in TA, seven patients resistant to CS treatment were additionally given 2 mg/kg/day oral CYP [55]. After a mean period of 27.5 months, no clinical or radiological progression was observed in these patients. Haemorrhagic cystitis developed in two patients, herpes zoster in one and oligomenorrhoea in seven. In another open study, eight patients with myocardial involvement were reported to have clinical haemodynamic and morphological improvement using CS plus CYP treatment [56]. There is also a case report of a resistant TA patient treated with autologous stem cell transplantation with CYP [57].

MMF, which is widely used for the treatment of lupus nephritis, is also a promising agent in TA. In a single case series of three TA cases resistant to CS plus MTX, MMF treatment (2 g/day) for at least 1 year prevented both clinical and radiological progression [58]. In the first open MMF study, 10 patients with treatment-resistant TA were given MMF for a mean period of 23 months, resulting in significant reductions in acute phase proteins [59].

Recently the data of 21 consequent Indian TA cases using MMF for 9.6 ± 6.4 months were reported [60]. Previously 10 patients had been receiving AZA treatment in addition to CS. Improvement in disease activity was shown using ITAS and physician global assessment. The CS requirement was also reduced. The only adverse event was skin rash in a single patient. This study is notable in that it reflects MMF data for the largest TA series with favourable efficacy and safety profiles.

CSA [61–64], tacrolimus (FK-506) [65] and LEF [66, 67] were also tried in selected cases with successful results. CSA may also be effective in some cases in the treatment of pyoderma gangrenosum complicating TA [62–64]. In a prospective open-label study of LEF, 15 TA patients with treatment-resistant active disease were given 20 mg/day LEF with a mean follow-up of 9.1 months. The short-term results showed a favourable clinical response in 12 (80%) of the patients. No patients discontinued therapy due to adverse effects. However, two patients developed new angiographic lesions in the follow-up MRA [68].

Definition of refractory disease in TA

Although there is no universally accepted consensus definition, in previous studies refractory disease was accepted if disease activity increased following reduction of the CS dose or persisted despite use of at least one...
conventional IS agent [46]. The Turkish TA Study Group defined refractory disease [5] as angiographic or clinical progression despite treatment or the presence of any of the following characteristics: (i) prednisolone dose >7.5 mg/day after 6 months of treatment, despite administration of conventional IS agents; (ii) new surgery due to persistent disease activity; (iii) frequent attacks (more than three per year) and (iv) death associated with disease activity.

Biologic agents

Serum TNF-α levels are increased in TA and T cells from patients with active TA had higher TNF-α production compared with those in remission or healthy controls [69, 70]. Therefore anti-TNF agents, mostly infliximab (IFX), were tried in refractory TA patients. There are many case reports and series showing beneficial effects in both adult and paediatric patients [71–80]. In 2004, data from 15 refractory TA patients from three medical centres were reported [81]. Anti-TNF therapy resulted in improvement in 14 of 15 patients and remission was sustained in 10 patients despite discontinuation of CS therapy. Adverse events were seen in three patients. In 2008 the same group retrospectively reported 25 cases with refractory TA from a single centre [82]. Treatment duration was up to 7 years. CS treatment was discontinued in 15 patients and was successfully tapered to <10 mg/day in 7 patients. Adverse events were seen in four patients.

The results of long-term follow-up of anti-TNF treatment were reported in another case series of 20 refractory TA patients from a single centre [83]. IFX was the most frequently used agent. The median duration of treatment was 23 months. Remission was achieved in 90% of patients and CS treatment could be discontinued in 50% patients. However, 33% of patients relapsed and 20% discontinued treatment because of adverse events.

Recently Comarmond et al. [84] reported five new patients and reviewed the data of 79 patients previously reported in the literature. Most patients received IFX together with MTX or AZA. While 37% of patients achieved complete remission, 53.5% showed a partial response. CS treatment could be discontinued in 40% of the patients. However, <10% of patients remained resistant and side effects were observed in 20% of patients, including mainly infections and hypersensitivity reactions. In another recent study, IFX was reported to show a sustained clinical improvement in the long-term in TA, with significant benefits in health-related quality of life [85].

RTX, which is a chimeric monoclonal antibody binding to CD20 expressed on the surface of B cells, was also tried in TA. There are case reports showing good clinical response to RTX treatment in refractory TA patients [86, 87]. RTX treatment not only resulted in clinical remission, but also reduced the expansion of newly generated plasmablasts in TA cases [88].

Since IL-6 is highly expressed within inflamed arteries and serum levels correlate with disease activity, blocking IL-6 may be effective in TA [66, 69]. Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor, and the first report of successful use of tocilizumab in a patient with refractory TA was published in 2008 [89]. Later, nine additional cases of TA treated with tocilizumab 8 mg/kg every 4 weeks were reported [90–95]. In the majority of the cases, disease activity improved and CS doses were discontinued or tapered. However, a single TA case showed radiological progression [93]. Also, another patient relapsed after 8 months of treatment while still receiving tocilizumab [94]. Abatacept is another promising biologic agent inhibiting the co-stimulation of T cells, and is currently being investigated in the first randomized, placebo-controlled trial of LVV patients including TA [96].

After summarizing the available data about medical treatment options in TA, a practical approach that also reflects our personal experiences may be recommended. At the time of diagnosis, we generally start conventional IS agents together with the initial CS treatment. Since there is no evidence showing which IS agent is superior for the treatment of TA, the choice of initial and subsequent IS agents generally reflects the previous experiences of the clinician. We start with oral MTX, which is an inexpensive, easily available and relatively safe agent. If oral MTX seems to be ineffective, we try parenteral MTX. We also use AZA as an alternative IS agent in patients who cannot tolerate MTX. If the disease remains resistant to MTX or AZA, we tend to switch to LEF or MMF treatment. In refractory disease we generally combine two IS agents before switching to biologics. Our most frequent combination is MTX plus LEF, which requires close observation to avoid adverse effects. We use CYP for TA patients with severe life- and/or vital organ-threatening conditions for a short-term treatment, later switching to another less toxic IS agent. If the patient remains resistant to all these treatments, we use biologics.

Invasive interventional radiology and surgery

In the chronic stages of TA, one of the principles of treatment is revascularization of the affected organs either by surgery or endovascular interventions, including balloon angioplasty, stent and stent graft replacement. As a general rule, both endovascular interventions and surgery should be tried only after the suppression of inflammation in the vessel wall. Post-interventional IS treatment is also recommended [97–100].

The success rate and outcome of endovascular interventions depend upon the site, length and stage of the arterial stenosis. Being a less invasive and safe method, percutaneous transluminal angioplasty (PTA) was widely used for relief of short-segment arterial stenotic lesions, and initial reports revealed excellent results ranging from 81 to 100% [101–105]. However, restenosis occurring in up to 77.3% of the procedures in the long term appeared to be a major problem with PTA [106]. Therefore PTA is not cost effective and may be better used only in selected cases.

Stent grafts are better than uncovered metal stents or PTA in terms of the patency period and occurrence of restenosis in TA patients. Since the inner layers of the
vessel wall derive nutrition from the luminal blood flow, placement of a stent graft may disturb luminal blood flow, leading to a decrease in chronic inflammation and less severe fibrotic reaction on the luminal side, with a lower incidence of restenosis [106]. In a retrospective study analysing the outcome of endovascular interventions including stent replacements performed in the inactive stage of TA, the restenosis rate was reported as 17% after a mean follow-up period of 23.7 ± 18.4 months [30].

To decrease the occurrence of restenosis, antplatelet treatment should be used before and after endovascular interventions in TA. As was also used in a recent randomized clinical endovascular trial for peripheral arterial disease [107, 108], some authors administer loading doses of 300 mg of aspirin and clopidogrel 12 h before the procedure, then continue with aspirin (100 mg/day) indefinitely and clopidogrel (75 mg/day) for 4 weeks after the intervention.

Indications for surgery in TA include critical cerebrovascular or coronary artery ischaemia, extremity claudication and severe renal artery stenosis. Progressive aneurysm enlargement with a tendency for dissection or rupture, severe aortic regurgitation and aortic coarctation also require surgery. Surgical interventions not only reduce the complications caused by TA, but may increase long-term survival [98, 99, 109].

In the presence of long-segment stenosis with extensive periarterial fibrosis or occlusion, surgical bypass of the affected segment is clearly associated with superior results compared with endovascular intervention [109–112]. According to recent literature, occlusion or restenosis after bypass grafting occurs in 8–31% of cases after a follow-up period of 3–6 years [109]. In a retrospective, multicentre study analysing the results and outcomes of 79 consecutive patients with TA who underwent 104 surgical and 62 endovascular procedures, the frequencies of complications were 37.5% and 50%, respectively, after a follow-up of 6.5 years [99]. Kieffer et al. [113] also reported satisfactory early and long-term outcomes in 24 patients with TA who underwent surgery for renal artery stenosis. During the 61.3-month follow-up, repeated renal artery revascularization procedure was required in only four patients. Hypertension was cured in 63% and improved in 31% cases.

Despite better results compared with endovascular intervention, the results of bypass surgery in TA are worse than in atherosclerotic occlusive disease [114]. The presence of longer and more fibrotic vessels and the possible persistence of vessel wall inflammation despite clinical and laboratory remission may reduce the success of surgery in TA [114].

Since TA patients are generally immunosuppressed and often obese as the result of chronic CS therapy, surgical procedures carry additional risks. In particular, surgery for aortic aneurysms has a high morbidity and mortality. Surgical complications such as restenosis, graft occlusion and anastomotic site aneurysm may be related to the progressive inflammatory nature of TA. Anastomotic detachment may occur anytime in the long term, however, the use of synthetic suture material was reported to reduce this complication [109–112].

**Conclusion**

The diagnosis of TA should preferably be made before a critical stenosis or occlusion occurs in the involved arteries. Assessment of the pattern and extent of arterial involvement and measurement of current disease activity are essential for the management of TA. As acute phase responses are not always reliable, non-invasive imaging methods are used to monitor disease activity. However, there is no single imaging method that provides all the information required and each method has distinct and complementary roles in assessing disease activity and vascular inflammation. As a rule, the information obtained from non-invasive imaging methods should be integrated with patient symptoms, clinical findings and acute phase reactants to adjust the dose of IS agents and the duration of treatment.

Since there is no completed, placebo-controlled, randomized clinical trial, the level of evidence for the management of TA is low, generally reflecting the results of open studies, case series and expert opinion. The most commonly used therapeutic agents include CS and conventional IS agents, such as MTX. In patients who remain resistant and/or intolerant to these agents, biologics, including anti-TNF agents, RTX and tocilizumab, seem promising. Antplatelet treatment may lower the frequency of ischaemic events in patients with TA.

In the presence of a critical short-segment arterial stenosis causing life-threatening conditions, the principle of treatment is mainly revascularization of the affected organs by endovascular interventions including balloon angioplasty or stent graft replacements. On the other hand, long-segment stenosis with extensive periarterial fibrosis or occlusion requires surgical bypass of the affected segment, which is clearly associated with superior results compared with endovascular intervention. Both endovascular interventions and surgical procedures should be avoided during the active phase of the disease. Post-interventional IS treatment is recommended. Earlier diagnosis, better assessment of disease activity and future clinical trials will help improve the management of TA.

### Rheumatology key messages

- Assessing disease activity is essential for tailoring treatment in Takayasu arteritis.
- Biologics should be tried in treatment-resistant Takayasu arteritis patients.
- Revascularization procedures may be performed during the inactive phase of Takayasu arteritis.

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