RHEUMATOLOGY

Rheumatology 2014;53:793–801
doi:10.1093/rheumatology/ket320
Advance Access publication 4 October 2013

Review

Management of Takayasu arteritis: a systematic review

Gokhan Keser[1], Haner Direskeneli[2] and Kenan Aksu[1]

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 periarterial 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,

[1]Division of Rheumatology, Department of Internal Medicine, Ege University School of Medicine, Izmir and [2]Division of Rheumatology, Department of Internal Medicine, Marmara University School of Medicine, Istanbul, Turkey.

Submitted 11 February 2013; revised version accepted 15 August 2013.

Correspondence to: Gokhan Keser, Division of Rheumatology, Department of Internal Medicine, Ege University School of Medicine, Bornova, 35100 Izmir, Turkey. E-mail: agkkeser@gmail.com

arterial specimens may show histological signs of vasculitis [1, 10].

Imaging modalities are very important for establishing the diagnosis of TA, determining the distribution of lesions and monitoring disease activity [11, 12]. Although conventional radiographic 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, antiplatelet 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. Antiplatelet 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.

Acknowledgements

The authors wish to thank Professor Dr Wolfgang Schmidt, Rheumatology Medical Center, Immanuel

Krankenhaus, Berlin, Germany, for his assistance in writing the imaging section.

Disclosure statement: The authors have declared no conflicts of interest.

References

1 Kerr GS, Hallahan CW, Giordano J *et al*. Takayasu arteritis. Ann Intern Med 1994;120:919–29.

2 Brunner J, Feldman BM, Pascal N *et al*. Takayasu arteritis in children and adolescents. Rheumatology 2010;49:1806–14.

3 Bıçakçıgil M, Aksu K, Kamalı S *et al*. Takayasu's arteritis in Turkey—clinical and angiographic features of 248 patients. Clin Exp Rheumatol 2009;27(Suppl 52):S59–64.

4 Watts R, Al-Taiar A, Mooney J *et al*. The epidemiology of Takayasu arteritis in the UK. Rheumatology 2009;48:1008–11.

5 Saruhan Direskeneli G, Hughes T, Aksu K *et al*. Identification of multiple genetic susceptibility loci in Takayasu arteritis. Am J Hum Genet 2013, Advance Access published 2 July 2013, doi:10.1016/j.ajhg.2013.05.026.

6 Sahin Z, Bicakcigil M, Aksu K *et al*. Takayasu's arteritis is associated with HLA-B*52, but not with HLA-B*51, in Turkey. Arthritis Res Ther 2012;14:R27.

7 Nazareth R, Mason JC. Takayasu arteritis: severe consequences of delayed diagnosis. Q J Med 2011;104:797–800.

8 Mason JC. Takayasu arteritis—advances in diagnosis and management. Nat Rev Rheumatol 2010;6:406–15.

9 Direskeneli H, Aydın SZ, Merkel PA. Assessment of disease activity and progression in Takayasu's arteritis. Clin Exp Rheumatol 2011;29(Suppl 64):S86–91.

10 Salvarani C, Cantini F, Boiardi L *et al*. Laboratory investigations useful in giant cell arteritis and Takayasu's arteritis. Clin Exp Rheumatol 2003;21(Suppl 32):S23–8.

11 Pipitone N, Vesrari A, Salvarani C. Role of imaging studies in the diagnosis and follow-up of large-vessel vasculitis: an update. Rheumatology 2008;47:403–8.

12 Mavrogeni S, Dimitroulas T, Chatziioannou SN *et al*. The role of multimodality imaging in the evaluation of Takayasu arteritis. Semin Arthritis Rheum 2013;42:401–12.

13 Kissin EY, Merkel PA. Diagnostic imaging in Takayasu arteritis. Curr Opin Rheumatol 2004;16:31–7.

14 Andrews J, Mason JC. Takayasu's arteritis—recent advances in imaging offer promise. Rheumatology 2007;46:6–15.

15 Tso E, Flamm SD, White RD *et al*. Takayasu arteritis: utility and limitations of magnetic resonance imaging in diagnosis and treatment. Arthritis Rheum 2002;46:1634–42.

16 Magnoni M, Dagna L, Coli S *et al*. Assessment of Takayasu arteritis activity by carotid contrast-enhanced ultrasound. Circ Cardiovasc Imaging 2011;4:e1–2.

17 Schmidt WA. Imaging in vasculitis. Best Pract Res Clin Rheumatol 2013;27:107–18.

18 Yamazaki M, Takano H, Miyauchi H *et al*. Detection of Takayasu arteritis in early stage by computed tomography. Int J Cardiol 2002;85:305–7.

19 Arnaud L, Haroche J, Malek Z *et al*. Is (18)F-fluorodeoxyglucose positron emission tomography scanning a reliable way to assess disease activity in Takayasu arteritis? Arthritis Rheum 2009;60:1193–200.

20 Lee SG, Ryu JS, Kim HO *et al*. Evaluation of disease activity using F-18 FDG PET-CT in patients with Takayasu arteritis. Clin Nucl Med 2009;34:749–52.

21 Fuchs M, Briel M, Daikeler T *et al*. The impact of 18F-FDG PET on the management of patients with suspected large vessel vasculitis. Eur J Nucl Med Mol Imaging 2012;39:344–53.

22 Karapolat I, Kalfa M, Keser G *et al*. Comparison of F18 FDG PET/CT findings with current clinical disease status in patients with Takayasu's arteritis. Clin Exp Rheumatol 2012;31(1 Suppl 75):S15–21.

23 Pipitone N, Pazzola G, Muratore F *et al*. Assessment of vasculitis extent and severity. Presse Med 2013;42(4 Pt 2):588–9.

24 Sivakumar MR, Misra RN, Bacon PA. The Indian perspective of Takayasu arteritis and development of a disease extent index (DEI.Tak) to assess Takayasu arteritis. Rheumatology 2005;44:iii6–7.

25 Aydın SZ, Yılmaz N, Akar S *et al*. Assessment of disease activity and progression in Takayasu's arteritis with disease extent index-Takayasu. Rheumatology 2010;49:1889–93.

26 Misra R, Danda D, Rajappa SM *et al*. Development and initial validation of the Indian Takayasu clinical activity score (ITAS2010). Rheumatology 2013;52:1795–801.

27 Direskeneli H, Aydin SZ, Kermani TA *et al*. Development of outcome measures for large-vessel vasculitis for use in clinical trials: opportunities, challenges, and research agenda. J Rheumatol 2011;38:1471–9.

28 Numano F, Okawara M, Inomata H *et al*. Takayasu's arteritis. Lancet 2000;356:1023–5.

29 Wen D, Du X, Ma CS. Takayasu arteritis: diagnosis, treatment and prognosis. Int Rev Immunol 2012;31:462–73.

30 Min P-K, Park S, Jung J-H *et al*. Endovascular therapy combined with immunosuppressive treatment for occlusive arterial disease in patients with Takayasu's arteritis. J Endovasc Ther 2005;12:28–34.

31 Liang P, Hoffman GS. Advances in the medical and surgical treatment of Takayasu arteritis. Curr Opin Rheumatol 2005;17:16–24.

32 Schäfer VS, Zwerina J. Biologic treatment of large-vessel vasculitides. Curr Opin Rheumatol 2012;24:31–7.

33 Seyahi E, Ugurlu S, Cumali R *et al*. Atherosclerosis in Takayasu arteritis. Ann Rheum Dis 2006;65:1202–7.

34 Numano F, Shimokado K, Kishi Y *et al*. Changes in the plasma levels of thromboxane B2 and cyclic nucleotides in patients with Takayasu disease. Jpn Circ J 1982;46:16–20.

35 Kasuya N, Kishi Y, Isobe M *et al*. P-selectin expression, but not GPIIb/IIIa activation, is enhanced in the inflammatory stage of Takayasu's arteritis. Circ J 2006;70:600–4.

36 Akazawa H, Ikeda U, Yamamoto K *et al*. Hypercoagulable state in patients with Takayasu's arteritis. Thromb Haemost 1996;75:712–6.

37 Numano F, Maruyama Y, Koyama T *et al*. Antiaggregative aspirin dosage at the affected vessel wall. Angiology 1986; 37:695–701.

38 de Souza AWS, Machado NP, Pereira VM *et al*. Antiplatelet therapy for the prevention of arterial ischemic events in Takayasu arteritis. Circ J 2010;74: 1236–41.

39 Ueno M. Antiplatelet therapy in the treatment of Takayasu arteritis. Circ J 2010;74:1079–80.

40 Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. Arthritis Rheum 2007;56:1000–9.

41 Kötter I, Henes JC, Wagner AD *et al*. 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. Clin Exp Rheumatol 2012;30(Suppl 70):S114–29.

42 Mevorach D, Leibowitz G, Brezis M *et al*. Induction of remission in a patient with Takayasu's arteritis by low dose pulses of methotrexate. Ann Rheum Dis 1992;51: 904–5.

43 Shetty AK, Stopa AR, Gedalia A. Low-dose methotrexate as a steroid-sparing agent in a child with Takayasu's arteritis. Clin Exp Rheumatol 1998;16:335–6.

44 Nakamura S, Morishita M, Yang CL *et al*. An elderly female who survived more than 30 years following a diagnosis of Takayasu's arteritis, complicated by fatal intestinal amyloidosis. Clin Rheumatol 2006;25:907–10.

45 Liang GC, Nemickas R, Madayag M. Multiple percutaneous transluminal angioplasties and low dose pulse methotrexate for Takayasu's arteritis. J Rheumatol 1989; 16:1370–3.

46 Hoffman GS, Leavitt RY, Kerr GS *et al*. Treatment of glucocorticoid-resistant or relapsing Takayasu arteritis with methotrexate. Arthritis Rheum 1994;37:578–82.

47 Ozen S, Duzova A, Bakkaloglu A *et al*. Takayasu arteritis in children: preliminary experience with cyclophosphamide induction and corticosteroids followed by methotrexate. J Pediatr 2007;150:72–6.

48 Kohrman MH, Huttenlocher PR. Takayasu arteritis: a treatable cause of stroke in infancy. Pediatr Neurol 1986;2: 154–8.

49 Brunette MG, Bonny Y, Spigelblatt L *et al*. Long-term immunosuppressive treatment of a child with Takayasu's arteritis and high IgE immunoglobulins. Pediatr Nephrol 1996;10:67–9.

50 Baumgartner D, Sailer-Höck M, Baumgartner C *et al*. Reduced aortic elastic properties in a child with Takayasu arteritis: case report and literature review. Eur J Pediatr 2005;164:685–90.

51 Valsakumar AK, Valappil UC, Jorapur V *et al*. Role of immunosuppressive therapy on clinical, immunological, and angiographic outcome in active Takayasu's arteritis. J Rheumatol 2003;30:1793–8.

52 Edwards KK, Lindsley HB, Lai CW *et al*. Takayasu arteritis presenting as retinal and vertebrobasilar ischemia. J Rheumatol 1989;16:1000–2.

53 Cash JM, Engelbrecht JA. Takayasu's arteritis in western South Dakota. S D J Med 1990;43:5–9.

54 Rodríguez-Hurtado FJ, Sabio JM, Lucena J *et al*. Ocular involvement in Takayasu's arteritis: response to cyclophosphamide therapy. Eur J Med Res 2002;7: 128–30.

55 Shelhamer JH, Volkman DJ, Parrillo JE *et al*. Takayasu's arteritis and its therapy. Ann Intern Med 1985;103:121–6.

56 Talwar KK, Chopra P, Narula J *et al*. Myocardial involvement and its response to immunosuppressive therapy in nonspecific aortoarteritis (Takayasu's disease)—a study by endomyocardial biopsy. Int J Cardiol 1988;21:323–34.

57 Kötter I, Daikeler T, Amberger C *et al*. Autologous stem cell transplantation of treatment-resistant systemic vasculitis—a single center experience and review of the literature. Clin Nephrol 2005;64:485–9.

58 Daina E, Schieppati A, Remuzzi G. Mycophenolate mofetil for the treatment of Takayasu arteritis: report of three cases. Ann Intern Med 1999;130:422–6.

59 Shinjo SK, Pereira RM, Tizziani VA *et al*. Mycophenolate mofetil reduces disease activity and steroid dosage in Takayasu arteritis. Clin Rheumatol 2007;26:1871–5.

60 Goel R, Danda D, Mathew J *et al*. Mycophenolate mofetil in Takayasu's arteritis. Clin Rheumatol 2010;29:329–32.

61 Horigome H, Kamoda T, Matsui A. Treatment of glucocorticoid-dependent Takayasu's arteritis with cyclosporine. Med J Aust 1999;170:566.

62 Ujiie H, Sawamura D, Yokota K *et al*. Pyoderma gangrenosum associated with Takayasu's arteritis. Clin Exp Dermatol 2004;29:357–9.

63 Fullerton SH, Abel EA, Getz K *et al*. Cyclosporine treatment of severe recalcitrant pyoderma gangrenosum in a patient with Takayasu's arteritis. Arch Dermatol 1991;127: 1731–2.

64 Fearfield LA, Ross JR, Farrell AM *et al*. Pyoderma gangrenosum associated with Takayasu's arteritis responding to cyclosporine. Br J Dermatol 1999;141:339–43.

65 Yokoe I, Haraoka H, Harashima H. A patient with Takayasu's arteritis and rheumatoid arthritis who responded to tacrolimus hydrate. Intern Med 2007;46: 1873–7.

66 Unizony S, Stone JH, Stone JR. New treatment strategies in large-vessel vasculitis. Curr Opin Rheumatol 2013;25: 3–9.

67 Haberhauer G, Kittl EM, Dunky A *et al*. Beneficial effects of leflunomide in glucocorticoid- and methotrexate-resistant Takayasu's arteritis. Clin Exp Rheumatol 2001;19:477–8.

68 de Souza AW, da Silva MD, Machado LS *et al*. Short-term effect of leflunomide in patients with Takayasu arteritis: an observational study. Scand J Rheumatol 2012;41:227–30.

69 Park MC, Lee SW, Park YB *et al*. Serum cytokine profiles and their correlations with disease activity in Takayasu's arteritis. Rheumatology 2006;45:545–8.

70 Tripathy NK, Gupta PC, Nityanand S. High TNF-α and low IL-2 producing T cells characterize active disease in Takayasu's arteritis. Clin Immunol 2006;118:154–8.

71 Della Rossa A, Tavoni A, Merlini G *et al*. Two Takayasu arteritis patients successfully treated with infliximab: a potential disease modifying agent? Rheumatology 2005; 44:1074–5.

72 Jolly M, Curan JJ. Infliximab responsive uveitis and vasculitis in a patient with Takayasu arteritis. J Clin Rheumatol 2005;11:213–5.

73 Karageorgaki ZT, Mavragani CP, Papathanasiou MA *et al*. Infliximab in Takayasu arteritis: a safe alternative? Clin Rheumatol 2007;26:984–7.

74 Tanaka F, Kawakami A, Iwanaga N *et al*. Infliximab is effective for Takayasu arteritis refractory to glucocorticoid and methotrexate. Intern Med 2006;45:313–6.

75 Calderon R, Estrada S, Ramírez de la Piscina P *et al*. Infliximab therapy in a patient with refractory ileocolic Crohn's disease and Takayasu arteritis. Rev Esp Enferm Dig 2010;102:145–6.

76 Buonuomo PS, Bracaglia C, Campana A *et al*. Infliximab therapy in pediatric Takayasu's arteritis: report of two cases. Rheumatol Int 2011;31:93–5.

77 Maffei S, Di Renzo M, Santoro S *et al*. Refractory Takayasu arteritis successfully treated with infliximab. Eur Rev Med Pharmacol Sci 2009;13:63–5.

78 Filocamo G, Buoncompagni A, Viola S *et al*. Treatment of Takayasu's arteritis with tumor necrosis factor antagonists. J Pediatr 2008;153:432–4.

79 Nunes G, Neves FS, Melo FM *et al*. Takayasu arteritis: anti-TNF therapy in a Brazilian setting. Rev Bras Reumatol 2010;50:291–8.

80 Tato F, Rieger J, Hoffmann U. Refractory Takayasu's arteritis successfully treated with the human, monoclonal anti-tumor necrosis factor antibody adalimumab. Int Angiol 2005;24:304–7.

81 Hoffman GS, Merkel PA, Brasington RD *et al*. Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. Arthritis Rheum 2004;50:2296–304.

82 Molloy ES, Langford CA, Clark TM *et al*. Anti-tumor necrosis factor therapy in patients with refractory Takayasu's arteritis: long-term follow-up. Ann Rheum Dis 2008;67:1567–9.

83 Schmidt J, Kermani TA, Bacani AK *et al*. Tumor necrosis factor inhibitors in patients with Takayasu arteritis: experience from a referral center with long-term follow-up. Arthritis Care Res 2012;64:1079–83.

84 Comarmond C, Plaisier E, Dahan K *et al*. Anti TNF-α in refractory Takayasu's arteritis: cases series and review of the literature. Autoimmun Rev 2012;11:678–84.

85 Quartuccio L, Schiavon F, Zuliani F *et al*. Long-term efficacy and improvement of health-related quality of life in patients with Takayasu's arteritis treated with infliximab. Clin Exp Rheumatol 2012;30:922–8.

86 Galarza C, Valencia D, Tobon GJ *et al*. Should rituximab be considered as the first-choice treatment for severe autoimmune rheumatic diseases? Clin Rev Allergy Immunol 2008;34:124–8.

87 Ernst D, Greer M, Stoll M *et al*. Remission achieved in refractory advanced Takayasu arteritis using rituximab. Case Rep Rheumatol 2012;2012:406963.

88 Hoyer BF, Mumtaz IM, Loddenkemper K *et al*. Takayasu arteritis is characterized by disturbances of B cell homeostasis and responds to B cell depletion therapy with rituximab. Ann Rheum Dis 2012;71:75–9.

89 Nishimoto N, Nakahara H, Yoshio-Hoshino N *et al*. Successful treatment of a patient with Takayasu arteritis using a humanized antiinterleukin-6 receptor antibody. Arthritis Rheum 2008;58:1197–200.

90 Salvarani C, Magnani L, Catanoso M *et al*. Tocilizumab: a novel therapy for patients with large-vessel vasculitis. Rheumatology 2012;51:151–6.

91 Salvarani C, Magnani L, Catanoso MG *et al*. Rescue treatment with tocilizumab for Takayasu arteritis resistant to TNF-α blockers. Clin Exp Rheumatol 2012;30(Suppl 70):S90–3.

92 Unizony S, Arias-Urdaneta L, Miloslavsky E *et al*. Tocilizumab for the treatment of large-vessel vasculitis (giant cell arteritis, Takayasu arteritis) and polymyalgia rheumatica. Arthritis Care Res 2012;64:1720–9.

93 Bredemeier M, Rocha CM, Barbosa MV *et al*. One-year clinical and radiological evolution of a patient with refractory Takayasu's arteritis under treatment with tocilizumab. Clin Exp Rheumatol 2012;30:S98–100.

94 Seitz M, Reichenbach S, Bonel HM *et al*. Rapid induction of remission in large vessel vasculitis by IL-6 blockade: a case series. Swiss Med Wkly 2011;141:w13156.

95 Bravo Mancheno B, Perin F, Guez Vázquez Del Rey Mdel M *et al*. Successful tocilizumab treatment in a child with refractory Takayasu arteritis. Pediatrics 2012;130:e1720–4.

96 http://clinicaltrials.gov/show/NCT00556439 (1 October 2013, date last accessed).

97 Liang P, Tan-Ong M, Hoffman GS. Takayasu's arteritis: vascular interventions and outcomes. J Rheumatol 2004;31:102–6.

98 Giordano JM. Surgical treatment of Takayasu's arteritis. Int J Cardiol 2000;75(Suppl 1):S123–8.

99 Saadoun D, Lambert M, Mirault T *et al*. Retrospective analysis of surgery versus endovascular intervention in Takayasu arteritis: a multicenter experience. Circulation 2012;125:813–9.

100 Park MC, Lee SW, Park YB *et al*. Postinterventional immunosuppressive treatment and vascular restenosis in Takayasu's arteritis. Rheumatology 2006;45:600–5.

101 Dev V, Shrivastava S, Rajani M. Percutaneous transluminal balloon angioplasty in Takayasu's aortitis: persistent benefit over two years. Am Heart J 1990;120:222–4.

102 Joseph S, Mandalam KR, Rao VR *et al*. Percutaneous transluminal angioplasty of the subclavian artery in nonspecific aortoarteritis: results of long-term follow-up. J Vasc Interv Radiol 1994;5:573–80.

103 Fava MP, Foradori GB, Garcia CB *et al*. Percutaneous transluminal angioplasty in patients with Takayasu arteritis: five-year experience. J Vasc Interv Radiol 1993;4:649–52.

104 Lee BB, Laredo J, Neville R *et al*. Endovascular management of Takayasu arteritis: is it a durable option? Vascular 2009;17:138–46.

105 Sharma S, Gupta H, Saxena A *et al*. Results of renal angioplasty in nonspecific aortoarteritis (Takayasu disease). J Vasc Interv Radiol 1998;9:429–35.

106 Qureshi MA, Martin Z, Greenberg RK. Endovascular management of patients with Takayasu arteritis: stents versus stent Grafts. Semin Vasc Surg 2011;24: 44–52.

107 Visonà A, Tonello D, Zalunardo B *et al*. Antithrombotic treatment before and after peripheral artery percutaneous angioplasty. Blood Transfus 2009;7:18–23.

108 Tepe G, Zeller T, Albrecht T *et al*. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. N Engl J Med 2008;358:689–99.

109 Isobe M. Takayasu arteritis revisited: current diagnosis and treatment. Int J Cardiol 2013;168:3–10.

110 Ogino H, Matsuda H, Minatoya K *et al*. Overview of late outcome of medical and surgical treatment for Takayasu arteritis. Circulation 2008;118:2738–47.

111 Miyata T, Sato O, Koyama H *et al*. Long-term survival after surgical treatment of patients with Takayasu's arteritis. Circulation 2003;108: 1474–80.

112 Fields CE, Bower TC, Cooper LT *et al*. Takayasu's arteritis: operative results and influence of disease activity. J Vasc Surg 2006;43:64–71.

113 Kieffer E, Piquois A, Bertal A *et al*. Reconstructive surgery of the renal arteries in Takayasu's disease. Ann Vasc Surg 1990;4:156–65.

114 Tyagi S, Verma PK, Gambhir DS *et al*. Early and long-term results of subclavian angioplasty in aortoarteritis (Takayasu disease): comparison with atherosclerosis. Cardiovasc Intervent Radiol 1998;21: 219–24.