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Vasculitis (C Pagnoux and M Walsh, Section Editors)

Current and Future Treatment Options for Takayasu Arteritis and Persistent Therapeutic Challenges

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Opinion statement

Takayasu arteritis is a large vessel vasculitis of unknown aetiology, more common in the tropics. Assessment of disease activity is challenging and evolving, with limitations in the use of conventional inflammatory markers like ESR and CRP resulting in utilization of composite clinical (Kerr criteria, ITAS2010) and imaging (angiography and FDG-PET) modalities. Management is challenging, with a paucity of high-quality evidence to guide therapy. Conventional disease-modifying agents are commonly used, although evidence base is limited, with methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide and leflunomide showing efficacy in open label studies. Role of biologic agents like anti-TNF-alpha agents, tocilizumab and rituximab is based on open label evidence, with a recent randomized trial failing to show significant efficacy of abatacept in reducing disease relapses. Endovascular stenting and open surgical revascularisation, generally done when disease is inactive, help in restoration of blood flow supplied by stenosed segments; however, these may require to be repeated as restenosis is not rare.

Introduction

Takayasu arteritis (TA) is a rare, systemic large vessel vasculitis involving predominantly the aorta and its branches. It was first described by a Japanese ophthalmologist, in 1908, in a young woman with retinal ischemia [1]. TA is a chronic granulomatous vasculitis of unknown aetiology and predominantly effects young women between 20 and 40 years [2]. The pathogenesis of TA is poorly understood but cell mediated mechanisms seem to be predominantly

involved. CD4+ and CD8+ T cells play a role in the pathophysiology of TA. Serum levels of various cytokines like tumour necrosis factor α (TNFα), interferon γ (IFN-γ), interleukin 2 (IL-2), IL-3, IL-4, IL-6, IL-8 and regulated upon activation, normal T cell expressed and secreted (RANTES) and levels of matrix metalloproteinases (MMP2, MMP3 and MMP9) were increased in patients of TA, indicating that they are involved in the pathogenesis of TA [3•]. B lymphocytes are also implicated in the pathogenesis of TA as evidenced/suggested by the presence of anti-aortic endothelial cell antibodies (AAECAs) and anti-annexin V antibodies in patients with TA [4, 5].

The clinical manifestations may vary from an asymptomatic condition with absent peripheral pulses to life-threatening conditions involving the central nervous system, heart and abdomen. The clinical picture can be divided into two phases. The early pre-pulseless phase usually occurs years before the next phase and manifests by non-specific fever, malaise, anorexia, weight loss, arthralgia and skin rashes, and is often missed/not remembered. The subsequent, late occlusive phase, manifests by decreased or absent pulses, claudication, hypertension, stroke, seizures, myocardial infarction, aortic regurgitation, mesenteric ischemia and retinopathy. The diagnosis of TA is mainly clinical and arteriographic as no specific laboratory parameter can help in making the diagnosis.

Disease-activity measures

The important therapeutic challenge is to assess the disease activity of a patient with TA as it helps in determining the treatment strategy. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been shown to be elevated during the active phase of the disease. However, certain studies have shown that in patients with normal ESR and CRP with clinically inactive disease, the aortic biopsies still showed features suggestive of active disease [6-8]. Different studies have identified higher serum levels of cytokines TNFα, IL-6 [9] and IFN-γ [10] in patients with active TA. Pentraxin 3 (PTX3) may be a potential biomarker indicative of active disease as the levels of PTX3 were found to be increased in TA patients with active disease compared to patients with inactive disease [11, 12]. In the absence of sensitive laboratory biomarkers to detect active TA, various criteria and scoring systems were developed to determine the disease activity and help in therapeutic decisions. In 1994, Kerr et al. have proposed a set of four criteria for active disease, which included (1) ESR more than 20 mm/h, (2) constitutional features like fever and malaise, (3) features suggestive of vascular involvement like bruits and pulse loss and (4) angiographic features consistent with TA. The criteria for active disease require new onset or worsening of two out of these four criteria [13]. In a study comparing various disease-activity measures, Kerr criteria had only 74% agreement when compared with physician's global assessment (PGA) for disease activity [14]. In 2005, the Indian Rheumatology Association Core Group on Vasculitis (IRAVAS) devised the Disease Extent Index in TA (DEI.Tak) to assess the disease activity, based on the Birmingham Vasculitis Activity Score (BVAS) [15], scoring items present in the past 6 months irrespective of whether activity or damage. Compared to PGA, DEI.Tak had an agreement of 68% and when compared to imaging findings, 9 out of 19 (47%) patients with progression of disease on imaging had a DEI.Tak score of 0 [14]. A modification of DEI.Tak is the Indian Takayasu's arteritis clinical activity score (ITAS2010), which scores 33 items in six different organ systems [16]. ITAS-A, a modification of ITAS2010, takes into account the acute phase reactants, ESR and CRP. The

advantage of ITAS is that it scores features which are new or worsened in the last 3 months, hence is representative of active disease. Although used in a few recent studies, this measure requires further validation. Various imaging techniques, including conventional digital subtraction angiography, computed tomography angiography (CTA), magnetic resonance angiography (MRA) and ultrasound (US), can detect vessel wall thickening, stenosis, occlusion and aneurysms [17•]. Follow-up imaging may help in determining response to treatment and detect new onset lesions suggestive of disease activity and progression. Recently Sinha et al. have proposed a scoring system based on colour Doppler ultrasound (CDUS-K), which examines 19 vascular regions and scores for stenosis and flow pattern [18]. This scoring also had significant correlation with ITAS, but further studies are required to determine its utility in clinical practice. 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) has also been shown to be useful in assessing disease activity in TA. In a meta-analysis of studies on FDG-PET in TA, the pooled sensitivity and specificity of FDG-PET for determining disease activity were 70.1 and 77.2%, respectively [19]. FDG-PET seems to have utility in detecting active disease at baseline and following immunosuppression; however, activity on PET does not go hand-in-hand with the ESR [20]. A recent study suggests that patients with TA have a unique pattern of uptake on FDG-PET, reflecting lesions in the ascending aorta, arch of aorta, abdominal aorta and carotids, whereas lesions elsewhere may not show uptake on FDG-PET. Interestingly, the uptake of lesions on FDG-PET in this study also did not correlate with ESR or CRP [21]. These findings merit further investigation to exactly delineate the role of FDG-PET in the assessment of TA. Even though many scoring systems were developed to assess disease activity in TA, none of these instruments are validated and in future, there is a strong need to develop a validated and TA-specific disease-activity instrument.

Treatment

Medical management

Conventional disease modifying anti-rheumatic drugs

About 20% of patients with TA have a self-limited, monophasic illness, and the remaining 80% have a progressive or relapsing and remitting disease [13]. Hence, majority of the patients require a long-term immunosuppressive treatment to control disease and prevent long-term damage. Glucocorticoids (GCs) are the mainstay of treatment for TA, even though there are no controlled trials demonstrating the efficacy of GCs compared to placebo. GCs are effective in suppressing systemic symptoms and can arrest and reverse vascular changes in early TA. The European League Against Rheumatism (EULAR) also recommend use of high-dose oral GCs (prednisolone, 1 mg/kg/day) as the initial treatment in TA [22]. It is our usual practice to start oral GCs at 0.5–1 mg/kg/day and continue the dose for 4–6 weeks and then taper to the lowest possible dose, depending on the response of the patient. Even though, GCs are effective in controlling disease, disease relapse may be seen in up to two thirds of the patients, and a second immunosuppressant agent may be required in 46–

84% of patients to sustain disease remission [23••]. Alternate day therapy should be avoided as it is associated with increased relapses [24]. In our experience, most patients with TA would remain on low-dose glucocorticoids for years, even lifelong. There is a need for studies to assess long-term outcomes in those patients with TA on long-term low-dose glucocorticoids versus those not receiving the same, akin to similar studies in small vessel vasculitis such as the TAPIR study (https://clinicaltrials.gov/ct2/show/NCT01933724). Supplementation with oral calcium, vitamin D and prophylactic use of oral bisphosphonates should be considered in all patients, unless contraindicated.

Methotrexate, azathioprine, mycophenolate mofetil (MMF), cyclophosphamide, leflunomide, tacrolimus and TNFα inhibitors (TNFαi) have been used as a second immunosuppressant in steroid resistance or relapses, or even directly from the beginning in order to minimise duration of higher dose glucocorticoid therapy. The EULAR recommends use of second immunosuppressant to achieve control of disease activity and to facilitate reduction of the cumulative dose of GCs [22]. However, there are no randomized controlled trials (RCT) comparing the efficacy of one immunosuppressant with another, and the available data is limited to case series and small open-labelled studies.

Regarding the efficacy of methotrexate in TA, the evidence comes from two small prospective studies. Hoffmann et al. used weekly oral methotrexate (mean stable dose of 17.1 mg) in 18 patients who were resistant to GCs [25]. Remission, as assessed by clinical features and angiography, was achieved in 13 (81%) patients, but 7 patients relapsed when GCs were tapered or discontinued, and all responded on retreatment with GCs. Two patients withdrew from the study, and 3 patients did not respond to the treatment with methotrexate and GCs. In another prospective study from India, 36 patients with TA were treated with oral GCs (1 mg/kg/day) and injection methotrexate (15-25 mg/week) for 3 months followed by oral methotrexate for next 3 months [26]. After 24 weeks of therapy, there was a significant reduction in disease activity as measured by ITAS2010, ITAS-A ESR and ITAS-A CRP. These two studies sugggested methotrexate controls disease activity and reduces radiographic progression of disease. Placebo-controlled, randomized studies with large number of patients are required in future to demonstrate the efficacy of methotrexate in TA, whether versus placebo or versus other conventional or biologic DMARDs discussed hereafter.

Another drug commonly used as GCs-sparing drug and used in the management of TA is azathioprine. Azathioprine (2 mg/kg/day) in combination with GCs was used upfront in 15 patients with newly diagnosed TA from India [27]. All patients attained remission by 12 weeks of therapy, and GCs could be tapered to 5–10 mg/day by end of 12 weeks. No new vascular lesions or progression of old lesions were noted on repeat angiography performed after 1 year of therapy. Larger trials are needed to study the efficacy of azathioprine in TA.

Mycophenolate mofetil, recently shown to be effective in lupus nephritis and scleroderma-related interstitial lung disease, has also been used more frequently in treating TA in recent times. The first use of MMF in TA was reported by Daina et al. in 1999, who successfully treated 3 patients with MMF (2 g/day) [28]. Later in 2007, Shinjo et al. reported use of MMF in 10 patients with active TA, 5 of them had unresponsive disease to other immunosuppressants. One patient discontinued MMF due to adverse effects, and the other 9 patients had clinical remission, and the mean dose of prednisolone

could be tapered from 24.5 to 5.8 mg/day. There was also significant reduction in acute phase reactants with MMF therapy [29]. Goel et al. reported the use of MMF in 21 patients with active TA, out of which, 10 patients received azathioprine prior to MMF. One patient discontinued MMF due to skin rash, and among the remaining 20 patients, there was significant reduction in ITAS2010, ESR, CRP and GCs dose at last follow-up [30]. These reports suggest MMF is effective in controlling disease activity in TA, but none of the studies noted the vascular changes with MMF on angiography. In the meta-analysis of these 31 patients, MMF was shown to significantly reduce ESR, CRP, GCs dose and helped in stabilizing the disease [31•]. An open label randomized trial is underway presently and is comparing the efficacy of MMF, methotrexate and GCs with cyclophosphamide and GCs followed by azathioprine (NCT03096275).

The first open label study to use leflunomide (20 mg/day) in TA was published in 2012 by de Souza et al. from Brazil [32]. They included 15 patients with active TA despite being treated with GCs and immunosuppressants. At a mean follow-up of 9.1 months, 80% of patients had clinical improvement and there was significant reduction in GCs dose, ESR and CRP levels. Two patients had new onset vascular lesions on MRA [32]. Long-term follow-up data of 12 patients from this cohort was available, at a mean duration of 43 months. Only 5 (41.6%) patients continued to have remission on leflunomide, and the remaining 7 patients required change of therapy to azathioprine or TNFαi due to relapses or adverse effects [33]. This data indicates that, even though leflunomide was effective initially in controlling disease activity, on long-term, it is not an effective in maintaining remission. A randomized placebo-controlled, double-blind study on efficacy and safety of leflunomide in TA is underway (NCT02981979).

Cyclophosphamide, either oral or intravenous, has also been used as an alternative agent to GCs in patients with TA. Henes et al. treated 4 patients with GCs unresponsive TA with intravenous cyclophosphamide (750 mg/m^2, every 3 weeks) for ten pulses. At follow-up over 6–30 months, all had reduction in activity as evident on FDG-PET [34]. In a retrospective analysis of 23 paediatric patients with TA, Stern et al. used cyclophosphamide (oral or intravenous) upfront in 17 patients. Out of 15 patients whose follow-up details were available, 9 (60%) patients failed cyclophosphamide and 6 patients had remission [35]. Five patients developed opportunistic infections requiring hospital admission. Larger randomized controlled trials need to be conducted to study the efficacy and safety of cyclophosphamide in TA. Tacrolimus was used successfully to control disease activity in TA in isolated case reports [36–39].

Biological disease modifying anti-rheumatic drugs

Even though pathophysiology of TA is unclear, it has been shown that there is increased production of TNFα in TA patients with active disease compared to patients in remission and healthy controls, indicating that TNFα plays a role in the pathogenesis of TA [40]. TNFα inhibitors (TNFαi), a group of monoclonal antibodies against TNFα, are used in the treatment of various autoimmune diseases like rheumatoid arthritis, spondyloarthropathy and inflammatory bowel disease. A word of caution needs to be mentioned here, considering TA is more common in Asian countries where tuberculosis is also common, and

anti-TNF agents have been suggested to predispose towards reactivation of tuberculosis in other rheumatic diseases.

Two systematic reviews analysed the efficacy of TNFαi in TA. In the first review published in 2014, 98 patients of TA treated with biological agents were included for analysis [41•]. Infliximab was used in 75 patients, and clinical remission was achieved in 74.7%, and GCs were discontinued in 32% patients. However, 16 out of 56 patients (28.6%), whose follow-up data was available, had relapse of disease. Etanercept was used in 12 patients, remission was noted in 10 patients, but 9 patients had relapse on follow-up. One patient has sustained remission and response of another patient is not known.

In a systematic review published in 2016, 13 articles, studying the efficacy of TNFαi, were included in the analysis [23••]. Ninety-six patients with TA who were treated with anti-TNFα drugs were analysed (77 received infliximab, 17 etanercept and 5 adalimumab). In most of these patients, these drugs were used in view of refractoriness to or relapse inspite of prior immunosupressant. Fifty-nine patients (61.4%) improved after receiving TNFαi, with reduction in median dose of GCs (tapered and stopped in 38.5 and 39.6%, respectively) and median level of CRP with anti-TNFα therapy. Improvement of vascular lesions on MRA was noted in 3 patients. At a median follow-up of 24 months, 28 relapses were noted and none of the patients expired. Since these two systematic reviews, there was one more case series of 5 patients with TA who were treated with biological agents. Out of these 5 patients, 4 were treated with infliximab and all attained sustained remission at a mean follow-up of 59.6 months [42].

Tocilizumab, a humanised monoclonal antibody against IL-6 receptor, had promising results in TA in recent times. Levels of serum IL-6 were found to be elevated in patients with active TA compared to patients with inactive disease and healthy controls, indicating its role in the pathogenesis of TA [43]. Several small case series suggest that tocilizumab (4–8 mg/kg/month) was effective in treating refractory TA. Systematic review of nine articles on tocilizumab in TA by Ferfar et al. included 24 patients [23••], 21 of whom showed clinical improvement, with reduction or stoppage of GCs in 58.3 and 20.8%, respectively. At a median follow-up of 12 months, 4 patients relapsed but none died. Use of tocilizumab also showed improvement in vascular lesions in 19 patients, as assessed by FDG-PET or MRA or CTA. Osman et al. reported 3 patients with TA treated with tocilizumab and reviewed another 30 TA patients being treated with tocilizumab from the literature [44]. Overall, 27/33 patients achieved remission with tocilizumab therapy but on follow-up, 5 patients developed relapses. Tocilizumab was well tolerated as none of the patients discontinued due to adverse drug events and resulted in significant reduction in GCs dose. In a case series of 11 paediatric TA patients, 4 received tocilizumab and all of them had clinical remission, decrease in ITAS2010 and tolerated the drug well with no new vascular lesions [45]. Loricera et al. showed that tocilizumab was effective in treating 16 patients of refractory aortitis out of which 7 patients had TA [46]. Goel et al. reported the use of tocilizumab in 10 'difficult to treat' TA patients [47] all of whom attained clinical remission with ITAS of 0 by four infusions of tocilizumab; however, most relapsed in stopping tocilizumab requiring rescue with another immunosupressant. Larger

studies with long-term follow-up data are needed to answer the questions on efficacy and safety of tocilizumab in TA.

Abatacept is a fusion protein composed of the fragment crystallisable region of immunoglobulin IgG1 and the extracellular domain of CTLA4 (cytotoxic T-lymphocyte associated protein-4). CTLA4 is expressed in activated T helper cells and competitively binds to CD80/CD86 on antigen presenting cells and then transmits inhibitory signals to T cells. The first randomized controlled trial of abatacept in TA was conducted to study its efficacy in new onset or refractory TA patients [48]. Thirty-four patients with TA were treated with daily prednisolone and intravenous abatacept (10 mg/kg) on day 1, 15, 29 and week 8. At week 12, 26 patients who attained remission were randomized to receive either monthly abatacept or placebo. There was no difference in the relapse free survival at 12 months between abatacept and placebo groups (22 versus 40%, $p = 0.853$). The median duration of remission was also similar between the two groups (5.5 months for abatacept and 5.7 months for placebo). There was no difference in the incidence of adverse events in both the groups. Over all, this study failed to demonstrate abatacept is effective in these patients. However, considering the key role played by T lymphocytes in driving TA, in our opinion, this drug merits further exploration in TA.

Genome-wide association studies (GWAS) has identified IL12B gene as a susceptibility gene for TA, single nucleotide polymorphism in which associates with disease activity and complications of TA [49]. The IL12/23p40 is the common subunit in the receptor for IL-12 and IL-23. IL-23 helps maintain T helper 17 cells in an active state, and recent studies have shown increased T helper 17 cells in TA [50, 51]. With this background, ustekinumab, a monoclonal antibody against IL12/23p40 was studied in a pilot study of 3 patients with active TA [52]. All 3 patients reported improvement in clinical symptoms and tolerated well, but there was no change in vascular wall enhancement on MRA on day 84. Larger studies need to be performed to completely evaluate the efficacy of ustekinumab in TA. Direct targeting of Th17 cells is also a potential therapeutic option in the future. B-cell dysregulation is thought to play a role in the pathogenesis of TA, and B-cell depletion therapy (rituximab) was used successfully in few patients of refractory TA; however, reports are limited to anecdotal reports or case series [53–56].

Recently, two randomized controlled trials were published which studied the efficacy of naturally-occurring TNFα suppressing compounds. Resveratrol, a polyphenol that naturally exists in fruits likes grapes and cranberries, has anti-TNFα activity. In a randomized, placebo-controlled, double-blind trail, 271 patients with acute TA were administered 250 mg resveratrol or placebo daily for 3 months [57]. Resveratrol-treated patients had improvement in disease activity measured by BVAS and had reduction in levels of ESR and CRP. In another randomized trial, curcumin, a naturally-occurring anti-TNFα agent present in turmeric (*Curcuma longa*), was studied for therapeutic efficacy in TA [58]. In this study, 246 patients with acute TA were randomized to receive either daily curcumin or placebo for 4 weeks. Disease activity as measured by BVAS, serum CRP value and ESR values decreased steadily in patients treated with curcumin compared to patients receiving placebo.

Overall, there is a scarcity of high-quality evidence base to guide the management of TA, with very few randomized controlled trials available. Hence, in the existing scenario, there is a definite requirement for multicentric, randomized placebo-controlled trials to generate a solid evidence base to guide the management of TA [59•].

Surgical interventions

Despite the early diagnosis and increased use of combination immunosuppression in the management of TA, surgical therapy has an important role in the management of TA patients. Surgical management may be done in the form of endovascular procedures including percutaneous transluminal angioplasty (PTA) and stent graft placement or open surgery revascularization including surgical bypass grafting, patch angioplasty and endarterectomy. In various studies, the indication for surgical intervention ranged from 17% to more than 50% of TA patients [7, 60–62]. The major indications for surgical intervention are the following: uncontrolled hypertension secondary to renal artery stenosis, aortic regurgitation, ischemic heart disease, symptomatic cerebrovascular disease, severe upper or lower limb claudication, mesenteric ischemia and arterial aneurysms [63••]. There is a seven-fold increased rate of complications at 5 years, if surgical interventions were performed during active inflammation [64]. Surgical intervention is most successful when it is performed in patients with inactive and burnt-out disease. Fields et al. reported 100% patency rates at 5 and 10 years following open surgery in patients with inactive disease and not requiring GCs [60]. In patients with inactive disease but requiring GCs, the patency rates at 5 and 10 years were slightly lower at 95 and 81%, respectively. In patients with active disease and taking GCs, the success rate of procedure at 10 years further decreased to 57% and it was lowest (37%) in patients with active disease and not taking GCs. Perioperative immunosuppression was shown to improve the outcomes on long-term follow-up [60, 61, 64].

Renal artery stenosis (RAS) with uncontrolled hypertension is the most common indication for surgical intervention in TA patients [63••]. Both endovascular and open surgery are effective in controlling blood pressure. Angioplasty is the preferred procedure for RAS, with a 5-year patency rate of 91.7 compared to 55.8% with stenting and 79% with renal artery bypass grafting [65, 66]. The restenosis rate was also less with angioplasty (8%) compared to stenting (66%) and bypass graft (16%). In patients with common carotid lesions, aorto-carotid bypass is the preferred procedure due to better efficacy. Restenosis rate with aorto-carotid bypass surgery was 12.5 compared to 53.4% with angioplasty [67]. Surgical intervention for subclavian artery stenosis or occlusion may be required for severe disabling claudication or critical ischemia. Both angioplasty and bypass procedures have good early outcomes, but restenosis rates are high, up to 21.7% [67, 68]. For coronary artery lesions in TA, coronary artery bypass grafting (CABG) is the preferred method of treatment with an overall survival rate of 81.4% at 10 years and cardiac event free survival rate of 72.6% [69]. Drug-eluting stents were reported to have short-term efficacy, but restenosis is common at 4–5 years [70]. In patients with aortic regurgitation, aortic valve and root replacement is required as aortic

regurgitation is frequently complicated by aortic root dilatation [63••]. Aortic aneurysms can be managed with open repair with prosthetic graft replacement or endovascular aneurysm occlusion [71, 72].

Conclusion

Figure 1 summarizes disease-activity assessment and management options in TA. Early detection and initiation of therapy is important in preventing long-term sequela of TA. Determining the disease activity is essential in therapeutic decision-making. There are no sensitive and specific laboratory parameters to determine the disease activity. ITAS2010 is a comprehensive tool developed recently to determine the disease activity in TA, but further validation of the tool is needed from larger cohorts. Imaging techniques like MRA, FDG-PET and CDUS may provide additional information on disease activity. The limited data suggests that methotrexate (15–25 mg/week), azathioprine (2 mg/kg/day) and mycophenolate mofetil (2 g/day) are efficient in controlling disease activity and preventing relapses and help in reducing GCs dose. Leflunomide could control disease initially but did not prevent relapses on long-term. Cyclophosphamide may be reserved for those patients who are unresponsive to other immunosuppressants. Among the biologicals, tocilizumab and agents targetingTNFα were shown to be effective in controlling disease in small case series. B-cell depletion therapy and drugs targeting IL12/23p40 pathway need to be studied in detail for their efficacy in treating TA. Surgical intervention in the form of endovascular procedure or open surgery may be needed in some patients to manage the sequelae of occlusive vascular disease. Results are better when the surgical interventions are performed during inactive phase of the disease. In

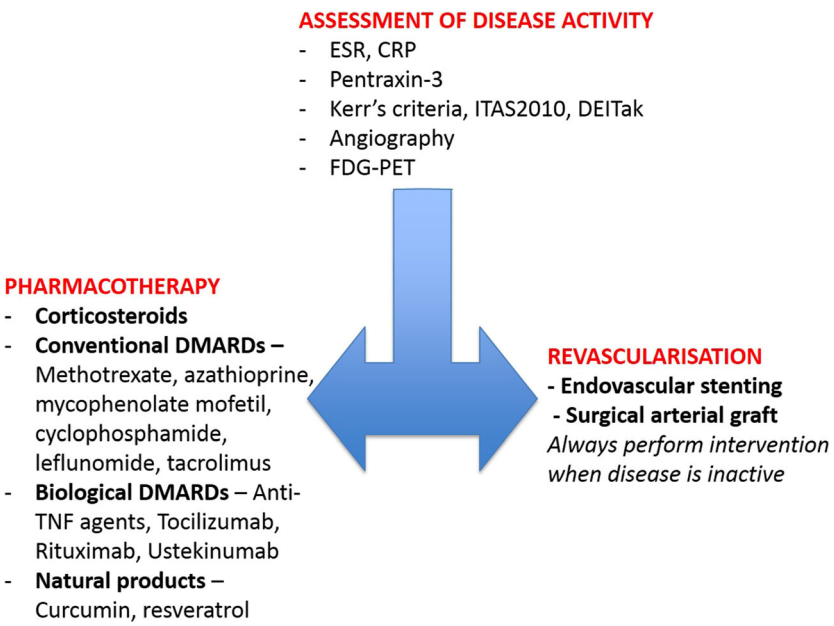

Fig. 1. Summary of options to assess disease activity and therapeutic strategies in Takayasu arteritis.

future, there is a need to conduct large, multicentre randomized controlled trails to generate high-quality evidence for the management of TA.

Compliance with Ethical Standards

Conflict of Interest
GSRSNK Naidu, Durga Prasanna Misra and Aman Sharma have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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