RHEUMATOLOGY

Review

Takayasu arteritis: advanced understanding is leading to new horizons

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Abstract

Although outcomes in Takayasu arteritis (TAK) are improving, diagnosis is typically delayed and significant arterial injury accrues. While wider use of non-invasive imaging is impacting this, the onus remains with clinicians to consider a diagnosis of TAK earlier. Meanwhile, morbidity and mortality in TAK remains increased. Herein we review the current situation, outline recent advances and summarize remaining challenges. Understanding of disease pathogenesis remains poor. However, recent genetic data and identification of pathogenic cytokines may facilitate the search for biomarkers capable of distinguishing active and inactive disease, inflammatory and non-inflammatory arterial remodelling. Imaging is critical for TAK, and each modality has important strengths and limitations. Dependence upon CS therapy remains too high. However, the impact of combination immunosuppressive therapy is now recognized, biologic therapies are increasingly available and new agents offer promise. Multicentre clinical trials are now required, and these will depend upon development of defined clinical and imaging end-points.

Key words: large vessel vasculitis, Takayasu arteritis, biomarkers, imaging, biologic therapy

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Rheumatology key messages

- Early diagnosis and effective combination therapy including biologics can improve outcomes in Takayasu arteritis.
- Novel biomarkers are required for distinguishing inflammatory and non-inflammatory remodelling in Takayasu arteritis.
- Defined clinical and imaging end-points are required in order to optimize future clinical trials in Takayasu arteritis.

Introduction

Takayasu arteritis (TAK) is a rare, idiopathic systemic inflammatory disease affecting large arteries, including the aorta, its major branches and the pulmonary arteries. TAK is predominantly a disease of the young adult, typically presenting in the second and third decades of life [1], and may also affect children [2]. Arterial inflammation is the core feature of the disease, variably associated with a systemic acute-phase response. Inflammatory lesions are characterized by arterial wall thickening and frequently result in remodelling of the arterial lumen following myofibroblast proliferation. In most series, 90% of patients suffer arterial stenoses, and up to 25% aneurysmal disease (Fig. 1). Six predominant patterns defined by angiography and expanded further by non-invasive imaging have been described [3, 4].

Recent success in the management of other vasculitides and the wider application of non-invasive imaging to large vessel vasculitis (LVV) has led to renewed interest and awareness of TAK. The effectiveness of ANCA-associated vasculitis therapy exposes the limitations in the management of TAK and the relative lack of progress. Significant morbidity persists in TAK. Daily activities are compromised in 74%, while mortality remains up to 5% at 10 years [1] and as high as 27% in the most severely affected [5]. Outcomes are closely aligned to the degree of arterial injury. Although longitudinal data suggests that combination immunosuppression is beginning to impact patient outcomes [6], important shortcomings remain.

This review will address recent areas of improvement in the understanding and management of TAK. These include non-invasive imaging modalities, emerging genetic data, wider use of immunosuppressive drugs early in the

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Fɪɢ. 1 Impact of arterial disease in TAK
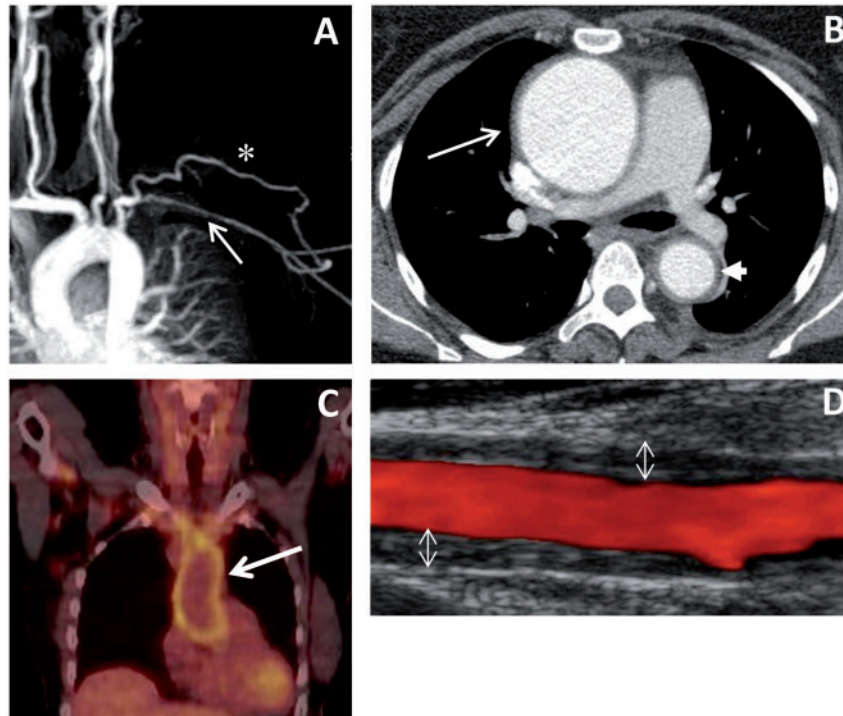
(**A**) Characteristic severe left subclavian artery stenosis (arrow) with associated collaterals (asterisk). (**B**) Large ascending aortic aneurysm (arrow) with cuffing of the aorta by inflammatory tissue seen around the descending aorta (arrowhead). (**C**) ^{18}F-FDG-CT-PET scan showing intense homogenous uptake in the arch of the aorta, consistent with aortitis (arrow). (**D**) Colour Doppler ultrasound study illustrating concentric homogenous thickening of the wall of the common carotid artery. TAK: Takayasu arteritis; ^{18}F-FDG-CT-PET: 2-[18F]-fluoro-2-deoxy-D-glucose-CT-PET.

disease course and increasing access to biologic therapies. Likewise, persisting limitations, including delayed diagnosis, a paucity of clinical trial data and an unacceptable burden of arterial injury and excessive drug-induced toxicity, will be discussed. Current understanding of disease pathogenesis and the need for novel biomarkers, improved activity and damage indices will also be addressed. Finally, prospects for the future, including novel research areas, will be outlined.

Pathogenesis and genetics

Pathogenic insight into TAK remains poor [7], with direct access to arterial lesions limited to specimens obtained during surgery. Animal models of LVV are confined to: (i) a chimeric model in which sections of temporal artery from patients with GCA are grafted onto an immunodeficient mouse, which is subsequently infused with heterologous human lymphocytes [8], and (ii) IRF-4-binding protein-deficient mice, which develop an IL-17 and IL-21-driven LVV and a rheumatoid-like joint disease [9]. Thus, knowledge of TAK pathogenesis is largely extrapolated from studies in GCA. Arteries from patients with TAK and GCA share many histologic features, leading to the proposition that they may represent a variant of the same disease [10]. However, many important differences in clinical phenotype

exist and it is unknown to what extent pathogenic features described for GCA can be applied to TAK.

Of note, genome-wide association studies have revealed marked genetic differences between GCA and TAK in the *HLA* region, while common susceptibility factors were also revealed within the *IL12B* locus [11]. Genetic data, along with the response to immunosuppressive therapy, support a role for both the adaptive and the innate immune system in TAK (reviewed in [12, 13]). Both Classes I and II *HLA* loci have been associated with TAK (most notably the *HLA-B* locus and the *HLA-B52* allele). Other associated genes include immune-regulatory genes (e.g. *RPS9/LILRB3*, *LILRA3* and *IL38* loci) and inflammatory cytokines (*IL6* and *IL12B* loci) [14–16].

Beyond genetics, recent advances have underlined the importance for health of maintaining arterial integrity and vascular function. Large- and medium-sized arteries are immune-privileged sites, able to blunt immune-inflammatory responses and limit the access of lymphoid cells. Vascular dendritic cells (VDCs) act as gatekeepers. They are present in normal arteries in an inactive state. Studies of GCA implicate VDC activation as an early step in LVV pathogenesis, predisposing to T cell activation, local cytokine release and vascular inflammation [8, 17]. Although the initial pathogenic stimuli are yet to be identified, distinct arterial districts harbour specific populations of VDCs

that exhibit differential expression of activating receptors, including Toll-like receptors [17]. Thus, the local VDC repertoire and specific responses to Toll-like receptor ligands might contribute to the spatial distribution of inflammatory lesions within the arterial tree.

TAK lesions contain macrophages and lymphoid cells ($\alpha\beta$ CD4$^+$ and CD8$^+$ T cells, $\gamma\delta$ T cells, NK cells and B cells). Inflammatory infiltrates lie in close proximity to neoangiogenic *vasa vasora*, which likely represent the portal of access to the arterial wall. The target of the immune response remains elusive, but evidence suggests the local presentation of vasculitogenic antigens, with both priming and maintenance of the immune response occurring in the arterial wall [18]. Indeed, inflamed arteries develop lymphoid follicles and tertiary lymphoid organs, predominantly in the adventitial layer [19]. An important role for Th1 and Th17 responses in the systemic and vascular manifestations of GCA [20] and TAK [21] has been proposed. However, differences in the specific responses seem to exist. Glucocorticoids suppress Th17 cells in GCA, while the Th1 responses typically persist [20]. In contrast, the opposite appears to be true in TAK [21] and further study is required.

In LVV, persistent arterial inflammation predisposes to injury within the vascular stromal compartment, with subsequent remodelling. Studies in GCA suggest that chronic stimulation of myeloid cells (and especially macrophages by lymphocyte-derived cytokines) is a key component [22]. In GCA, multiple changes in arterial wall-infiltrating macrophages have been described, including upregulation of inducible nitric oxide synthase (iNOS) and local release of metalloproteases and growth factors [23–26]. Arteritis in TAK results in neoangiogenesis, leukocytic infiltration with arterial wall oedema, degeneration of smooth muscle and elastic components, fibrosis and hyperplasia of fibroblasts and myofibroblasts. This is accompanied macroscopically by wall thickening and predisposes to arterial stenosis or dilation, which in turn directly impact on clinical features and prognosis (Fig. 2A and B).

Natural history of TAK

Classically TAK is considered triphasic, passing through systemic inflammation and pre-stenotic disease, progressing to stenotic/aneurysmal arterial injury ± pain, and finally to burnt out fibrotic disease (Fig. 1) [27, 28]. However, a systemic inflammatory response is not always detected, and these phases are often difficult to define, with diagnosis typically delayed until the development of phase II and occasionally phase III [27–31].

Large-vessel arteritis confined to the arterial wall and without impact on the arterial lumen is heterogeneous in nature and may include patients with: (i) early TAK; (ii) benign causes of arterial inflammation that do not typically trigger luminal remodelling, which may include aortitis associated with an underlying CTD; and (iii) those in whom significant wall thickening is counterbalanced by compensatory outward positive arterial remodelling that prevents luminal narrowing, analogous to that described for atherosclerosis [32]. Distinguishing between these

groups is of paramount importance, as their prognosis and therapy may differ. Moreover, improved understanding of their pathogenesis may ultimately reveal novel therapeutic targets for the prevention of arterial remodelling.

Currently, a pragmatic clinical approach is used to distinguish disease activity, disease remission and burnt-out disease. Evidence suggests that the duration and course of active disease varies between patients. Kerr and colleagues reported a cohort of 60 patients, 20% of whom exhibited a monophasic self-limiting illness, while 80% had a protracted course requiring long-term therapy [29]. In our combined cohort of 220 patients, 12% presented with inactive burnt-out disease and have not relapsed, despite receiving no immunosuppressive therapy. Turning to those with active disease at presentation, Kerr followed 34/60 patients angiographically, and 88% exhibited disease progression [29]. Our recent prospective longitudinal MR angiography study of unselected patients receiving treatment revealed that 40% of vasculitic lesions remained stable, 37% progressed and 23% improved (median 18 months) [33]. A recent study reported 10-year event-free survival, relapse-free survival and complication-free survival rates approaching 48, 70 and 54% respectively [31]. Likewise, other series have reported no progression in 70 and 77%, respectively [30, 34], while higher levels of relapse have been previously reported elsewhere (reviewed in [35]). Although these differences are likely multifactorial and related in part to a variable definition of vascular progression, they may also reflect greater historic dependence upon CS monotherapy.

Disease progression—recognition of heterogeneity

Progressive arterial injury manifesting as stenosis or dilatation/aneurysm is typically considered inflammatory and treated with enhanced immunosuppression. However, progressive dilatation may also represent a mechanical response to intraluminal blood pressure in previously damaged arterial walls, even in the absence of persistent arterial wall inflammation. Likewise, effective blockade of pivotal pro-inflammatory cytokines with agents targeting TNF-α or IL6 does not always arrest progression of stenotic disease, suggesting other pathways/mechanisms may be involved [36–38]. We propose that, on occasion, in TAK new/progressive stenosis may reflect a stereotyped response to long-standing arterial injury, resulting in non-inflammatory stenosis/remodelling driven predominantly by myofibroblast proliferation [39]. Similarly, resolution of inflammation with fibrosis and luminal contraction may result in progressive arterial narrowing. In both scenarios, any response to increased immunosuppression is likely to be minimal.

Current treatment of TAK

Although outcome data for LVV is relatively poor, it is largely accepted that early diagnosis and treatment can improve disease outcomes. A large study from Japan divided patients into those seen before 1999 and those

FIG. 2 Arterial injury and novel therapeutic targets in TAK
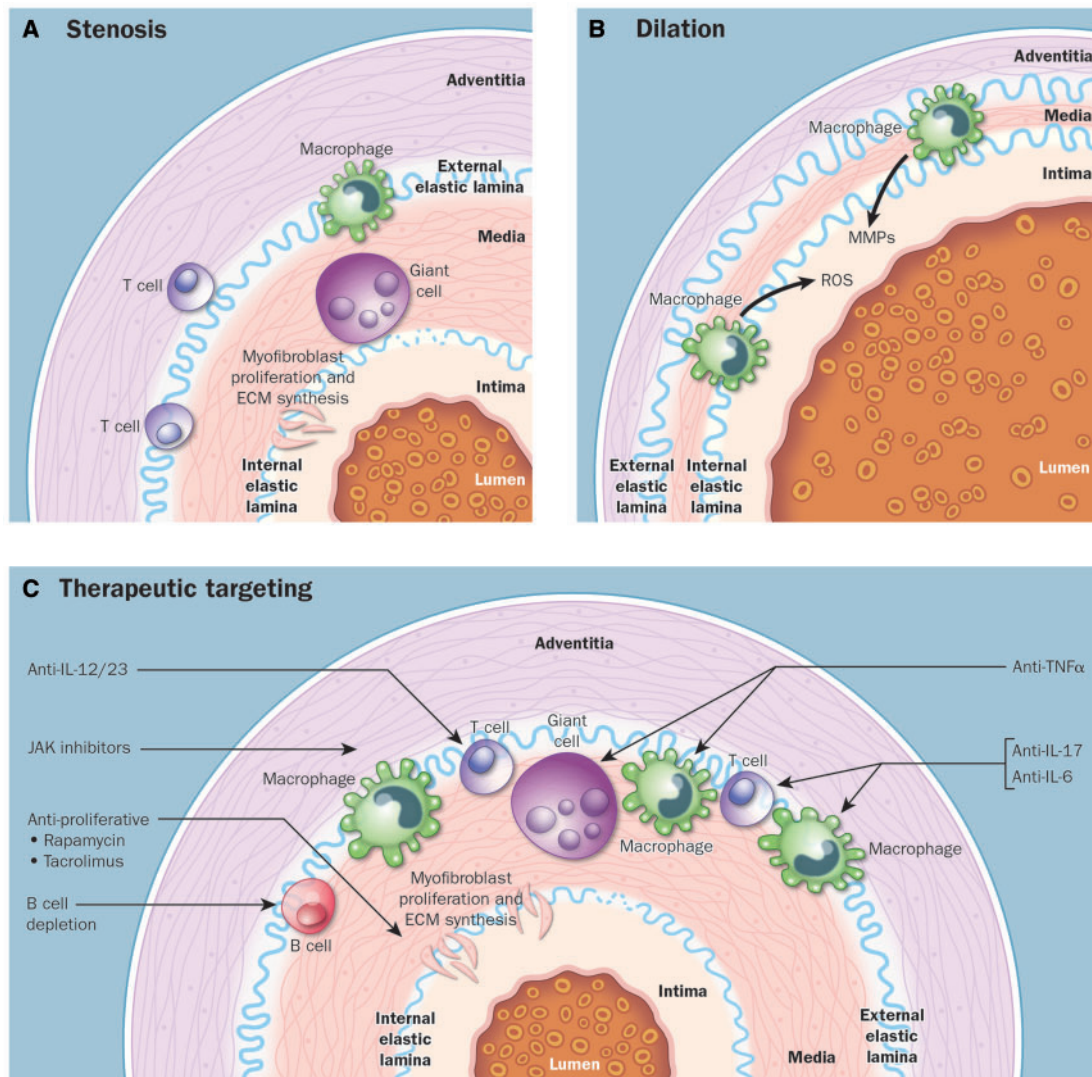
Cartoon illustrating: (**A**) arterial stenosis. This follows invasion of the arterial wall by T cells, B cells and monocyte/macrophages via the *vasa vasorum*, leading to the generation of multinucleate giant cells and fragmentation of the internal elastic lamina. Release of growth factors predisposes to wall oedema, extracellular matrix deposition and the proliferation of myofibroblasts that invade the intima. (**B**) Arterial dilation also follows inflammatory infiltration of the arterial wall by lymphocytes and monocytes. Excessive local release of toxic ROS and MMPs by macrophages is thought to result in degeneration of the tunica media. This predisposes to the death of vascular smooth muscle cells and thinning of the tunica media, disruption of elastin, and weakening and subsequent dilation of the arterial wall. (**C**) The predominant sites of action of current biologic therapies used in TAK and potential novel therapeutic agents and their targets. The diversity of agents and targets raises the prospect of patient stratification and personalized combination therapies for TAK. TAK: Takayasu arteritis; ROS: reactive oxygen species.

after 2000. The latter group were diagnosed earlier, were more likely to have received high-dose combined immunosuppression, and had reduced arterial injury and aortic valve disease [6]. However, the nature of optimal treatment and its duration remain unresolved.

Current treatment options have been covered in detail in recent reviews [36, 40–43] and will be briefly summarized. Although CSs are effective in controlling TAK-associated inflammation and represent the mainstay of therapy, over-

reliance on steroids persists, leading to an unacceptable burden of side-effects. This reflects the relative paucity of controlled clinical trial data [44–46]. Small open-label studies have reported the efficacy of MTX, AZA, MMF, CYC and LEF [47–52]. In those presenting to our centres with active disease, treatment comprises 0.5–1 mg/kg prednisolone plus adjunctive therapy with MTX (maximum dose 15–25 mg/week) or AZA (up to 2 mg/kg/day), with MMF or LEF as alternatives if required. CYC therapy is

largely confined to those with life-threatening disease at presentation or during relapse, including symptomatic cerebral ischaemia or fulminant myocarditis [1, 53].

Biologic therapy in TAK

TAK refractory to conventional immunosuppressive therapy was recently defined [54], and is observed in 15–20% of patients. Although it is widely accepted that TNF-α inhibition [55–59] and IL-6 pathway blockade [60, 61] may control refractory TAK in 60–70% of patients [38, 62], controlled clinical trial data are sparse. This is despite evidence for the potential efficacy of TNF-α and anti-IL-6 antagonists being first reported up to 13 years ago [55, 56, 63]. In the UK, funding for tocilizumab therapy is available for those whose disease is refractory to CSs and at least two immunosuppressants. In many other centres, including those in Italy, a more aggressive approach is adopted, with biologic therapy prescribed after the failure of one immunosuppressive drug [64].

Two trials have demonstrated the efficacy of abatacept and tocilizumab in GCA [65, 66], and two small TAK trials involving these agents have recently been published [67, 68]. The fact that neither trial in TAK met the primary end point likely says more about the challenges of trials in TAK than the efficacy of the drugs. In the abatacept trial, 26 patients were randomized and 18 relapsed. The majority of relapses were symptomatic and, of note, new vascular lesions were only seen in three patients, all of whom were receiving the placebo [67]. In the tocilizumab study, 36 patients with relapsing disease were recruited and randomized into two groups of 18 to receive tocilizumab and CSs or CSs plus placebo. Time to relapse was analysed and a trend towards a positive effect of tocilizumab was reported. Similar trends were reported for disease activity and imaging (CT angiography (CTA) or magnetic resonance angiography (MRA) secondary end-points were used) [68]. Although the time-to-relapse and safety data are encouraging, a longer-term trial with larger numbers and well-defined and quantified vascular outcomes is now required to convincingly show that tocilizumab has a beneficial effect on the vascular outcome of arterial wall inflammation in TAK.

Although biologic therapy is effective [59], relapse is still common, particularly if treatment is withdrawn [42]. Moreover, effective suppression of systemic inflammation and its associated symptoms does not necessarily equate to resolution of arterial wall inflammation [38, 69, 70], and detailed follow-up with arterial imaging is required, initially every 6 months, to exclude progressive arterial disease [37].

The presence of B cells in TAK lesions has led to investigation of the anti-CD20 mAb rituximab in refractory TAK. Results are preliminary and somewhat conflicted. Hoyer and colleagues [71] used flow cytometry to identify three patients with clinically active TAK and an expansion of plasmablasts in peripheral blood. Remission was achieved in all three patients following B cell depletion with rituximab and, similarly, treatment of a further eight refractory patients has suggested rituximab efficacy [72].

In contrast, four out of five patients with refractory TAK exhibited persistent disease activity ± progressive arterial disease despite B cell depletion [73]. Further prospective evaluation of B cell depletion is clearly warranted.

Surgical intervention

Although medical therapy plays the predominant role in TAK, endovascular and open surgical intervention should be considered in specific circumstances [74, 75]. While endovascular approaches are now more commonly applied, the duration of benefit of open surgery tends to be longer [76]. Whenever possible, disease remission should be obtained prior to surgery, with immunosuppression continued during and after surgery [76, 77].

Challenges associated with TAK phenotyping and assessment

Differentiation of TAK from other large vessel vasculitides

The classification of the LVVs, and particularly TAK and GCA, is undergoing further consideration and debate [78–80]. Our ongoing comparative analysis of arterial involvement in TAK and large vessel GCA (LV-GCA) shows intrinsic differences between the two, although the vascular phenotype of some patients with LV-GCA overlaps with that for TAK [81]. The distinction between TAK and GCA is traditionally based on the age at disease onset. Differences in the natural course of disease, histologic features [82], response to immunosuppressive agents, genetics of the HLA region [11] and a stronger association of GCA with intense systemic inflammation further supports this division. However, there are patients who do not fit into the prototypic TAK or GCA classification, or who satisfy criteria for both diseases [82]. Age is not an absolute discriminator, as onset after 40 years of age is reported in 15–20% of patients with TAK [83]. Post-mortem data [84] and, more recently, the increased use of non-invasive imaging has revealed aortic disease and involvement of extra-cephalic branches in up to 60–85% of those with GCA [85–87]. These observations have led to the description of a large-vessel GCA subset (LV-GCA) with a low frequency of cephalic involvement [88, 89], and accordingly novel classification criteria for GCA have been proposed [44]. Likewise, a late-onset TAK classification (>40 years at onset) has been proposed. These patients are phenotypically similar to patients with traditional TAK and more likely to exhibit aortic regurgitation, carotid, subclavian and iliac artery involvement than those classified as GCA [83].

This discussion represents more than an academic debate. In our opinion, effort should be made to reach a global classification for all LVVs. Thus, conditions with potential overlap with TAK and GCA, such as isolated aortitis and giant cell aortitis [90, 91], should be incorporated into a new classification wherever possible. Accurate phenotyping of LVV subtypes is required in order to obtain

homogeneous groups for research studies and clinical trials, and ultimately for optimal clinical care [92].

Analysis of TAK disease activity

Definition and assessment

Although the physician global assessment is a central component of therapeutic decisions in TAK, this is multi-faceted and far from straightforward [93–95]. Assessment includes measurement of systemic inflammation, typically using analysis of acute-phase reactants such as ESR and CRP, alongside review of extra-vascular features such as carotidynia, fever and arthralgia. Additionally, imaging may be used to search for inflammation in the arterial wall and the presence or absence of vascular progression, defined as progressive stenosis or dilatation. However, none of these measures are perfect and often fail to correlate with one another. Indeed, persistent arterial wall inflammation was present in up to 44% of patients undergoing vascular surgery and thought to have inactive disease on the basis of currently available activity measures [29]. Moreover, vascular progression with appearance of new arterial lesions was observed in 61% of patients thought to be inactive [29, 35].

Efforts have been made to address these limitations through the development of the National Institute of Health (NIH) score [29], the Indian Takayasu Activity score (ITAS) and disease-extent index [96] and Takayasu arteritis damage score (TADs) [97], and by the work of the OMERACT working group. NIH score, ITAS (including ITAS-CRP and ITAS-ESR) and TADs, although not fully validated, are readily applied. ITAS and TADs also incorporate cardiovascular weighting when compared with the BVAS and the vasculitis damage index. However, they also have a number of limitations [93]. These are summarized in Table 1, and perhaps foremost among them is the need for the further incorporation of imaging data.

The OMERACT group recently reported on a detailed Delphi exercise involving 92 experts. Important conclusions were reached, including proposal of a preliminary core set of domains in LVV, which include TAK-specific domains [98]. For the assessment of disease activity, development of new indices that incorporate patient-reported outcomes and imaging data is recommended. The OMERACT group have also tested a new damage index. Preliminary results suggest that damage in TAK is predominantly related to the primary disease rather than to treatment-related side-effects [98]. They also identify a critical need, namely for the development of standardized assessment of arterial imaging modalities such as MRI, CT and PET, which is essential for future clinical trials.

Current role of non-invasive imaging

The cardinal role of non-invasive imaging in the management of TAK has been reviewed in detail [99–103]. Response to therapy is typically monitored by MRA or CTA every 6–12 months for the first 2 years. Once disease control has been achieved, the CS dose is gradually weaned to ≤5 mg/day. This is maintained for 6 months, prior to initiating cautious CS withdrawal in those considered clinically inactive, bearing in mind the risk of relapse [29, 35]. Patients are closely monitored and undergo annual MRA. Following 12 months CS-free clinical remission and imaging evidence of stable arterial disease, immunosuppression is gradually weaned. The ultimate aim is treatment withdrawal, typically 5 years from initiation.

The demonstration of arterial wall thickening, multiple arterial lesions and/or luminal abnormalities in the right clinical setting is highly suggestive of TAK. In addition, morphologic assessment aids prediction of vascular complications and prognosis, the evaluation of arterial disease progression and the planning of interventional procedures. The different imaging modalities are conceptually divided into those that analyse arterial morphology (luminal changes and/or wall thickening) and those techniques that functionally characterize vasculitic lesions (Table 2). Unenhanced colour Doppler US, digital subtraction angiography and MRI-based angiographic studies belong to the former, with PET and PET/CT in the latter category (Fig. 1). Contrast-enhanced US (CEUS), CTA and MRI can assess both vascular morphology and identify arterial wall enhancement.

Arterial wall imaging may reveal the presence of oedema or contrast enhancement. More acute changes, including the presence of oedema, may be reversible with treatment [104–106]. However, the link between arterial wall oedema or enhancement and clinical measures of disease activity or subsequent disease progression with luminal encroachment has not been conclusively demonstrated [107, 108].

2-[^{18}F]-fluoro-2-deoxy-D-glucose PET (^{18}F-FDG-PET) co-registered with CT is widely applied in TAK [103]. Its principal role is in diagnosis, where the identification of enhanced metabolic activity may improve diagnostic accuracy and influence therapeutic decisions [109]. However, during follow-up the precise role of ^{18}F-FDG-PET is less clear [110, 111]. Cumulative radiation exposure is a concern, and the accuracy of ^{18}F-FDG-PET/CT for the detection of low-grade relapsing or partially treated arteritis is limited and study data variable [112–115]. On occasion, increased arterial FDG uptake may provide additional information. However, in the absence of correlative biopsy data, interpretation of low-level arterial FDG uptake is complex as it may reflect a variety of processes, including arterial wall inflammation, non-inflammatory myofibroblast proliferation, vascular remodelling, active fibrosis or atherogenesis.

Two recent studies have considered further the role of ^{18}F-FDG-PET/CT in identification of disease activity and prediction of progression. The first conducted a detailed analysis of arterial wall lesions using both ^{18}F-FDG-PET/CT and MRI. The data revealed no correlation between arterial wall FDG uptake and either systemic inflammation or disease activity measured using the NIH score [110]. However, the thickness of FDG-avid arterial lesions correlated with their maximum standardized uptake values (SUV$_{max}$). The findings suggest that ^{18}F-FDG-PET/CT may be useful for the identification of active local arterial wall inflammation and/or remodelling in those with

Table 1 Assessment of current disease activity and damage indices for Takayasu arteritis

Tool	Assessment	Pros	Cons
NIH criteria [29]	Disease activity	Multi-item score, assessing different disease features. Practical, easy to apply. Includes imaging data.	Relies on new/worsening disease features: inaccurate for first assessment or infrequent visits. Cut-off for individual items undefined. Inappropriate for persistent active disease. Includes only on angiographic data. Not validated.
ITAS ITAS-CRP ITAS-ESR [92]	Disease activity	Multi-item score, assessing different disease features. Allows grading of disease activity. Distinguishes features of active and inactive vasculitis. Allows grading according to the number of worsening vessels. Cardiovascular weighting.	Relies on new/worsening disease features: inaccurate for the first assessment or infrequent visits. Inappropriate for persistent active disease. Imaging data not included. Limited validation (to PGA and NIH). Dependence on the location of vascular lesions; the same lesions can affect multiple items (e.g. a new subclavian artery occlusion leading to pulse inequalities, claudication and loss of more than one pulse).
TADS [93]	Disease damage	Multi-item score, assessing different disease features. Allows grading of severity using a multi-item score. Weights cardiovascular damage. Accounts for vascular procedures.	Cannot identify damage present for <6 months. Relative underscoring of the splanchnic arteries. Limited inclusion of imaging data. Lack of validation, especially for longitudinal analysis.
DEI-Tak [92]	Disease extent	Multi-item score, assessing different disease features. Reflects both features of activity and damage.	Time-consuming. Relevance for assessment of disease extent remains to be confirmed. The same arterial lesions can affect multiple items (e.g. a new subclavian artery occlusion leading to pulse inequalities, claudication and loss of more than one pulse). Does not take into account imaging or laboratory data. Limited validation (to PGA and NIH).

NIH: National Institute of Health; ITAS: Indian Takayasu Activity Score; TADS: Takayasu arteritis Damage Score; DEI-Tak: Disease Extent Index-Takayasu; PGA: Physician Global Assessment.

TABLE 2 Conceptual classification of imaging techniques for TAK assessment

Morphological depiction of arteries		Functional characterization of the arterial wall
Arterial lumen	**Arterial wall**	
CDUS	CDUS	CDUS (halo sign), CE-US
CT-angiography	CT-angiography	CE-CT
MR-angiography	Vessel wall MRI	T2-weighted MRI sequences, CE-MRI
Digital subtraction angiography		PET, PET/CT and PET/MRI

CE-CT/MRI: contrast enhanced-CT/MRI; CE-US: contrast-enhanced ultrasonography; CDUS: colour Doppler ultrasonography.

clinically active disease, so revealing a subset potentially at risk of disease progression. The second study generated rare prospective data regarding the use of ^{18}F-FDG-PET/CT in patients with TAK and in a comparator group with diseases mimicking LVV [116]. A qualitative score was developed (PETVAS), based on global arterial FDG uptake. ^{18}F-FDG-PET/CT proved most sensitive and specific in those with clinically active disease. Interpretation of the uptake in 58% of positive scans of those with clinically inactive disease proved more challenging. However, preliminary evidence suggests that these patients were more at risk of disease relapse, and similarly a PETVAS cut-off of ⩾20 also seemed to be a useful predictor [116].

Current thinking suggests that luminal assessment and arterial wall analyses, either morphologically or functionally, are complementary. The former provides the most clinically relevant data concerning disease extent, disturbances to blood flow and the risk of end-organ ischaemia. The latter may provide insight into pathogenic events occurring early in the arterial wall and facilitate diagnosis of pre-stenotic/pre-angiographic disease. Ultimately, it may also aid assessment of disease activity and predict vascular remodelling. However, further studies are needed to verify whether characterization of arterial wall thickness and enhancement can predict vascular outcomes [103].

Reflecting this uncertainty and in light of resource restrictions, a pragmatic approach is often adopted in the clinic, so that MRI studies during follow-up are often limited to assessment of the arterial lumen. This approach requires a much shorter MRI acquisition time than detailed assessment of changes in the arterial wall. Furthermore, we have shown that monitoring in this way with MRI allows accurate assessment of disease extent and phenotype and long-term monitoring of disease evolution [33].

Recent exciting discoveries, future prospects and challenges

Novel plasma biomarker discovery

The multiple unresolved issues in the management of TAK highlight the need for novel biomarkers to aid clinical decision-making. Identification of these is no small task. Biomarkers are needed for the identification of LVV subsets, for accurate assessment of disease activity, as predictors of response to specific therapies or risk of future relapses. Additional biomarkers are required for

distinguishing inflammatory and non-inflammatory remodelling. Recent research has focused on disease activity biomarkers [117]. However, advances have been minimal, with the new biomarkers variably associated with acute-phase reactants or with activity indices. In the last year, soluble HLA-E, serum amyloid-A, IL-6 and soluble IL6-receptor have been associated with current activity indices [118–120]. Previous studies have explored the relationship between plasma biomarkers, arterial wall inflammation and vascular progression [121, 122]. Pentraxin-3 (PTX3) is directly released at sites of inflammation and exhibits multiple functions, including the modulation of tissue repair/remodelling. PTX-3 levels were shown to correlate with vascular progression but not with systemic inflammation as assessed by CRP and ESR [122]. A subsequent study also reported higher PTX-3 in patients with TAK than in healthy controls, although there was no association with disease activity [123]. Thus, PTX-3 may represent a marker of increased risk of progressive arterial injury, and further research is needed to define its potential clinical utility in TAK management.

New approaches to imaging

Imaging biomarkers offer significant potential because they allow serial non-invasive assessments. Although it remains to be determined how closely imaging data reflects arterial wall inflammation and the subsequent risk of luminal remodelling, an optimal clinical assessment based upon imaging biomarkers reflecting local pathogenic events, combined with clinical and plasma biomarker data is a valid aspiration. Novel and predominantly research-based imaging techniques are improving identification of pathology associated with tissue inflammation. When compared with colour Doppler US, a study of both TAK and GCA reported that microbubble CEUS optimizes assessment of arterial wall lesions and detects neovessel development [124]. Further evidence suggests that CEUS is able to quantify disease activity and monitor treatment responses in TAK-associated carotid arteritis [125, 126].

In another small study of 12 patients with TAK or GCA, conventional ^{18}F-FDG-PET-CT was compared with ^{18}F-FDG-PET-MRI. The latter compared favourably with ^{18}F-FDG-PET-CT, and in addition demonstrated enhanced soft-tissue resolution and proved optimal for determining disease extent [127]. As a glucose analogue, FDG is taken up by any metabolically active tissue and

hence lacks specificity for inflammatory cells. Thus, additional PET ligands are being sought for the detection of different phases of arterial disease in TAK. [^{11}C]-PK11195 binds the translocator protein (TSPO) which is highly expressed by activated monocytes and macrophages. [^{11}C]-PK11195-PET demonstrated arterial wall uptake in all six symptomatic LVV (GCA and TAK) patients and in none of the asymptomatic controls [128]. Second-generation TSPO ligands circumvent many of the technical issues associated with [^{11}C]-PK11195 [129]. However, ligand binding is significantly reduced by a common TSPO polymorphism (rs6971), with a minor allele frequency of up to 30%. Therefore genotyping is required or alternative ligands for TAK need to be identified that are not affected by rs6971 [130]. The latter might include ligands shown to bind activated macrophages in atherosclerotic plaque, such as those targeting the integrin $\alpha_V\beta_3$ [131] and somatostatin receptor subtype-2 [132].

PET imaging using novel and more specific ligands, co-registered with images derived from the more powerful and sensitive 7 T MRI scanners [133], may eventually offer accurate assessment of both disease activity and arterial injury. PET-MRI may prove to be the approach that overcomes the challenge of detecting persistent low-grade arterial wall inflammation or early relapse.

Novel approaches to therapy

The paucity of clinical trial data in TAK has a direct impact on patients and leaves funding agencies reluctant to endorse reimbursement for biologic therapies. Although further controlled clinical trials are urgently needed, the design and conduct of clinical trials in TAK is challenging, and recruitment of sufficient numbers with active disease within a specific time-frame necessitates multicentre trials [45]. Moreover, TAK disease activity indices, including ITAS and the NIH score, require further optimization and as yet there are no validated biomarkers for distinguishing active arteritis and arterial damage [117].

Clinical trials in LVV have typically focused upon end-points measuring systemic inflammation as an index of disease activity, which may not be a true measure of arterial wall inflammation or the likelihood or presence of arterial disease progression [95]. Arterial, injury and remodelling predispose to stenoses and aneurysms and are directly linked to prognosis in TAK (Fig. 2A and B). Thus, prevention of arterial disease progression is the fundamental therapeutic goal. Incorporation of imaging end-points of disease activity (^{18}F-FDG-PET) or arterial involvement (MRS/CTA) into clinical trials is desirable. However, these modalities remain very expensive and not universally available. Furthermore, standardized methods for quantifying imaging data also remain to be developed. We and others are investigating novel approaches for image analysis [33, 81, 134]. Similarly, the OMERACT working group is working towards development of a core set of outcomes for LVV, incorporating imaging data [93, 98].

The plethora of biologic agents, their emerging biosimilars and oral targeted disease-modifying therapies aimed at inflammatory arthritis also offer promise for LVV [135] (Fig. 2C). Recent advances in our understanding of disease pathogenesis will aid selection of the most appropriate agents [21, 136–138]. Similarly, identification of novel biomarkers that can distinguish active arterial wall inflammation from non-inflammatory progressive vascular remodelling is essential. While targeting IL-6, TNF-α, IL-12/23 or IL-17 might be optimal for targeting active arterial inflammation, anti-proliferative agents such as rapamycin or calcineurin inhibitors might be required for the latter. Clinical trials of all these agents are required. The common susceptibility factors for GCA and TAK at the *IL12B* locus, and early clinical data indicating that the IL-12/23 antagonist ustekinumab may be effective in refractory GCA [139, 140], suggests that this agent is worthy of trial in TAK [141]. Similarly, the novel Janus kinase (JAK) inhibitors tofacitinib, an inhibitor of JAK1 and 3, and baricitinib (JAK1/2) offer exciting possibilities in LVV. Numerous upstream pro-inflammatory cytokines and types I and II IFNs signal via members of the JAK family. Tofacitinib and baricitinib are approved for use in RA and are being investigated in a variety of other chronic inflammatory diseases [142].

Important and often overlooked aspects of treatment in TAK are those in which the patient can take control. These include cardiovascular risk factor management, such as maintaining a healthy diet, cessation of smoking and regular exercise. For example, in those with limb claudicant symptoms, regular exercise encourages the development of a collateral circulation and offers symptom relief. A recent report shows that 12 weeks of aerobic exercise reduces circulating TNF-α and increases the pro-angiogenic cytokines VEGF and PDGF-AA, leading to enhanced muscle strength and function [143]. Although no change in quality of life was seen in this short study, it sets an important precedent regarding the safety of exercise and the biologic plausibility of its effects.

Conclusion

Recent evidence suggests that increased recognition of LVV, rapid development of non-invasive imaging, the early use of combined immunosuppression and increased availability of biologic therapy may be improving outcomes in TAK. Future challenges include the need to reduce the burden of steroid toxicity, to improve understanding of disease pathogenesis, and to identify novel biomarkers for each phase of the disease and defined end-points for future clinical trials. The ultimate aim in TAK is to find a therapeutic combination capable of controlling all aspects of disease. These include its effects in the macro- and microcirculation and its propensity to induce pulmonary arterial hypertension. The most effective combination therapy is likely to reflect the nature of TAK, a condition at the crossroads between immune-mediated rheumatic disease and cardiovascular medicine.

Acknowledgements

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