

ORIGINAL ARTICLE

Management of Takayasu arteritis: a systematic literature review informing the 2018 update of the EULAR recommendation for the management of large vessel vasculitis

Ana F Águeda,¹ Sara Monti,^{2,3} Raashid Ahmed Luqmani,⁴ Frank Buttgerit,⁵ Maria Cid,⁶ Bhaskar Dasgupta,⁷ Christian Dejaco,^{8,9} Alfred Mahr,¹⁰ Cristina Ponte,^{11,12} Carlo Salvarani,¹³ Wolfgang Schmidt,¹⁴ Bernhard Hellmich¹⁵

To cite: Águeda AF, Monti S, Luqmani RA, *et al*. Management of Takayasu arteritis: a systematic literature review informing the 2018 update of the EULAR recommendation for the management of large vessel vasculitis. *RMD Open* 2019;**5**:e001020. doi:10.1136/rmdopen-2019-001020

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/rmdopen-2019-001020>).

Received 29 May 2019

Revised 2 August 2019

Accepted 20 August 2019



© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Ana F Águeda;
filipaa729@gmail.com

ABSTRACT

Objective To collect available evidence on management of large vessel vasculitis to inform the 2018 update of the EULAR management recommendations.

Methods Two independent systematic literature reviews were performed, one on diagnosis and monitoring and the other on drugs and surgical treatments. Using a predefined PICO (population, intervention, comparator and outcome) strategy, Medline, Embase and Cochrane databases were accessed. Eligible papers were reviewed and results condensed into a summary of findings table. This paper reports the main results for Takayasu arteritis (TAK).

Results A total of 287 articles were selected. Relevant heterogeneity precluded meta-analysis. Males appear to have more complications than females. The presence of major complications, older age, a progressive disease course and a weaker inflammatory response are associated with a more unfavourable prognosis. Evidence for details on the best disease monitoring scheme was not found. High-quality evidence to guide the treatment of TAK was not found. Glucocorticoids are widely accepted as first-line treatment. Conventional immunosuppressive drugs and tumour necrosis factor inhibitors were beneficial in case series and uncontrolled studies. Tocilizumab failed the primary endpoint (time to relapse) in a randomised controlled clinical trial; however, results still favoured tocilizumab over placebo. Vascular procedures may be required, and outcome is better when performed during inactive disease.

Conclusions Evidence to guide monitoring and treatment of patients with TAK is predominantly derived from observational studies with low level of evidence. Therefore, higher-quality studies are needed in the future.

BACKGROUND

Large vessel vasculitis (LVV), of which giant cell arteritis (GCA) and Takayasu arteritis (TAK) are the major subtypes, represents a group of diseases whose importance has been

Key messages

What is already known about this subject?

- Previous EULAR recommendations for the management of large vessel vasculitis (LVV) were published in 2009, and since then new evidence regarding diagnosis, monitoring and treatment emerged, justifying an update of the previous recommendations.

What does this study add?

- An extensive systematic literature review (encompassing Embase, Medline and Cochrane databases) regarding diagnosis, monitoring and treatment of LVV was produced and used to inform the 2018 recommendations on the management of LVV.
- This study focuses on the data retrieved for Takayasu arteritis.

How might this impact on clinical practice?

- This study offers insight into the available information on Takayasu arteritis monitoring and treatment and potentially impacts daily practice, since it adds information not available when the previous EULAR recommendations were published.

increasingly recognised over the years. Clinical manifestations for these diseases may vary from non-specific constitutional symptoms, such as fever, malaise and weight loss, to more characteristic features, resulting from stenosis/occlusion of the vascular territories involved.

Adequate management requires a correct diagnosis, appropriate monitoring and a tailored treatment strategy. To aid diagnosis and monitoring, new imaging methods have become available, as acknowledged in the new EULAR recommendations for the use of

imaging in LVV,¹ and new biomarkers are currently being evaluated.

The treatment of LVV remains a challenge, with most of the evidence coming from observational studies with limited number of patients and multiple biases, but efforts are being made to improve study quality. Since the 2009 recommendations,² new evidence, including some randomised controlled trials (RCTs), has become available. Thus, an update was needed to explore the new evidence for diagnosis, monitoring, treatment efficacy and safety.

This report will focus on the combined evidence retrieved for TAK and other LVV, excluding GCA.

METHODS

Given the rarity of LVV, the search strategy needed to be comprehensive, allowing varied study designs (RCTs, and observational prospective and retrospective studies). By including high-quality evidence from RCTs, and potentially lower quality evidence from small observational studies such as cohorts or case series, we aimed to ensure that the results better reflect clinical practice.

To maximise results, a wide and indepth search was conducted by two fellows (SM and AFÁ), who performed two independent systematic literature reviews (SLRs), one concerning mainly diagnosis and monitoring and the other concerning efficacy and safety of drug therapies and surgical procedures. The SLRs were conducted encompassing the Medline, Embase and Cochrane libraries, from inception until 31 December 2017, without language restrictions, and allowed all study designs except individual case reports.

The SLRs were conducted according to the EULAR operating procedures for the development of recommendations.³ The research design followed the PICO (population, intervention, comparator and outcome) strategy, although the use of a comparator was not possible given the specifications of the search. Two experienced librarians and the methodologist (RAL) aided the process.

The resulting articles were assessed for eligibility by evaluation of title and abstract and the relevant ones were kept for full-text review. The references of the included articles were screened as well.

Study selection considered agreement to the defined PICO strategy, where the relevant population included patients with a diagnosis of GCA, TAK, or other LVV such as isolated aortitis or IgG4-related disease with vasculitis.

Of note, papers on imaging were included initially. However, given the recently published imaging recommendations for LVV, these were later excluded, and imaging considerations were referred to the EULAR imaging recommendations.¹

The results, in the form of summary of findings tables, were used to summarise the information obtained. According to the EULAR operating procedures, level of evidence (LoE) was attributed according to the 2009 Oxford Centre for Evidence-Based Medicine.⁴ Bias

assessment was performed using the Cochrane risk of bias (RoB) tool⁵ for RCTs, the Newcastle-Ottawa Scale for observational studies,⁶ the revised tool for the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)⁷ and the Quality in Prognosis Studies tool (QUIPS) for prognostic studies.⁸

The results of this process were used to inform the new EULAR recommendations on LVV management and are presented in two supporting SLRs papers according to disease of interest: the current publication focusing mainly on TAK and a separate paper on GCA.

RESULTS

After removal of duplicates, the SLRs relating to diagnosis and monitoring yielded 4389 results and the one focused on treatment yielded 6226 results. Of these, 122 plus 165 papers were kept for full review. The heterogeneity of the methodologies of the studies included precluded a meta-analysis evaluation.

Results are presented according to the general topics of the research questions addressed (available in the online supplementary material).

General management and diagnosis

Disease recognition/patterns

In addition to symptoms resulting from the vascular territories involved, TAK can present with systemic symptoms including fever, weight loss and malaise. Unlike GCA (where a classical cranial pattern of symptoms can be described), in TAK there is no clear pattern of presentation. However, some differences in disease manifestations may occur according to age and gender.

Three observational cohort studies focused mainly on TAK manifestations according to gender (overall LoE 3b), with one paper additionally analysing data according to age of onset. The main conclusions should be interpreted with caution since the methodology varied significantly.

Using an age between 12 and 35 years old plus the 1990 American College of Rheumatology (ACR) classification criteria for TAK as inclusion criteria, Mont'Alverne *et al*⁹ studied 55 patients with TAK (17 males and 38 females). Multivariate analysis showed that male gender was a risk factor for the occurrence of abdominal pain (OR 18.75; 95% CI 2.89 to 121.54) and ascending aortic aneurysm (OR 9.51; 95% CI 1.94 to 46.70).⁹ There were no gender differences regarding the presence of constitutional symptoms, limb claudication, carotidynia, respiratory and articular manifestations, nor the presence of comorbidities.

Watanabe *et al*¹⁰ included 1372 patients (222 males and 1150 females) newly registered (<1 year) in a nationwide Japanese registry and analysed data according to gender and age of disease onset (≤ 40 vs > 40 years). Gender analysis (although limited given the number of males compared with females) showed that, overall, the most common complications were hypertension and aortic

valve regurgitation, with males having more complications than females (ischaemic heart disease, fundoscopic alterations, aortic aneurysm and dissection, renal disorders, renal artery stenosis, and hypertension). The more frequent angiographic patterns were type I in females and type V in males (according to the International TAK Conference in Tokyo 1994 classification).¹⁰ Female patients with disease onset after 40 years of age (vs ≤ 40) had an increased incidence of complications, namely aortic regurgitation, ischaemic heart disease, cataract, renal disorders, hypertension and coronary artery involvement, whereas male patients with disease onset after 40 years of age (vs ≤ 40) had an increased incidence of cataract and hypertension. Angiographic lesions of types I, IIa and IIb were more frequent in patients with younger disease onset, whereas patients with older onset had a higher proportion of type V and coronary artery lesions.¹⁰

Like Watanabe *et al*,¹⁰ Sharma *et al*¹¹ reported higher rates of hypertension (95% vs 68%) and its complications (left ventricular hypertrophy and renal insufficiency) in males, possibly explained by an increased frequency of involvement of abdominal aorta (79.1% vs 53.6%) and renal arteries (right renal artery 67.4% vs 36.2% and left renal artery 65.1% vs 33.3%). However, none of these differences did reach statistical significance, possibly due to the small sample size (43 males vs 89 females) or statistical methodology used, which is not clearly stated.

Overall, the limited evidence available points towards a more diffuse pattern of vascular lesions and a higher rate of complications in males and in patients with older disease onset (LoE 3b).

Disease patterns in other LVVs: isolated aortitis and chronic periaortitis

Studies focusing on recognition of disease patterns in other LVV are scarce. This SLR retrieved two papers on this subject, one comparing GCA patients with aortitis versus isolated aortitis, and another focusing on IgG4 periaortitis.

Regarding aortitis, Espitia *et al*¹² (n=117) compared clinical and laboratory features and treatment between patients with aortitis in the context of GCA and patients with isolated aortitis (defined as aortitis associated with inflammatory syndrome, without any other ACR criteria for GCA except age, and without any diagnostic criteria for any other causes of aortitis). In this study there were no differences between groups regarding laboratory parameters, location of aortic involvement nor cardiovascular risk factors, although patients with isolated aortitis were younger (65 vs 70 years; $p=0.003$) and more frequently had a history of smoking or currently smoking (43.2% vs 15.1%; $p=0.0007$). Moreover, aortic aneurysms were significantly more common in patients with isolated aortitis (38.6% vs 20.5%; $p=0.03$), and these patients were more likely to require aortic surgery (36.4% vs 13.7%; $p=0.004$). Survival free of aortic events (defined as either

absence of aortic aneurysm or aortic surgery) was better in GCA (LoE 3b).

One small observational study focused on chronic periaortitis (CP), comparing patients with IgG4-related CP with patients with CP not related to IgG4. There were 1245 patients screened but only 61 were included; of these, 10 were classified as IgG4 CP (2011 diagnostic criteria proposed by Umehara *et al*¹³), 25 as non-IgG4 CP (case groups) and the remaining 26 were unclassifiable. Apart from the finding that patients with IgG4 CP were older and had more common pancreatic involvement, (n=3 vs 0; $p=0.018$), there were no differences between groups regarding other variables, namely other clinical manifestations, comorbidities, initial distribution of lesions, clinical course or glucocorticoid (GC) requirements (LoE 3b).¹⁴

Fast-track approach

The consequences of disease progression in TAK may be severe,¹⁵ and a rapid diagnosis and treatment would likely reduce the likelihood of vascular damage, as shown for GCA, where implementation of fast-track clinics leads to an improved prognosis.^{16,17} However, this approach to diagnosis is probably not as relevant in TAK as it is for GCA, and may be difficult to implement, given the usual subacute clinical presentation and pattern of disease progression. No studies regarding such an approach in TAK were found.

Role of histology

Histological evaluation is not routinely performed in TAK since this is only possible if surgery is needed or in the event of death. This SLR did not find relevant papers in this regard.

Prognostic and therapeutic implications of disease patterns, potential biomarkers, comorbidities/complications, disease damage versus activity

Implications of disease activity, damage, comorbidities and complications

TAK arteritis carries a high risk of complications and potentially worse survival (table 1).

The presence of major complications, progressive disease course and older age are unfavourable prognostic indicators, as Ishikawa and colleagues demonstrated in a series of prospective observational studies^{15,18,20}. Ishikawa and Maetani¹⁸ developed a prognostic score with three stages using the following variables: major complications (defined as at least one of the following: microaneurysm formation; severe hypertension; grade 3+ or 4+ aortic regurgitation), progressive disease course and erythrocyte sedimentation rate (ESR) (Westergren method; low <20 mm/hour). This score showed significant differences in survival at 15 years, with a 43% survival rate of patients in stage 3 (major complication, progressive course with or without high ESR). In contrast, patients in stage 1 (patients without major complications nor progressive course with high ESR or patients with only low ESR, or

Table 1 Survival rates in TAK according to specific disease features

Study identification	N	Studied groups (follow-up duration)	Survival rates	P value	RoB QUIPS tool
Ishikawa and Maetani ¹⁸	120	According to prognostic score classification. Stage 1 vs 2 vs 3. (median 13 years and 2 months)	100% vs 83.6% vs 43%	<0.001	Moderate
Ishikawa ¹⁵	81	I+IIa vs IIb+III†. At 5 years and 10 years. (mean 7.4±5.8 years)	100% vs 74.2%	<0.005	Moderate
Soto <i>et al</i> ²²	94	Patients with coronary disease developing between 10 and 19 years vs between 20 and 39 years at 2, 5 and 10 years. Patients with hypertension developing between 10 and 19 years vs between 20 and 39 years at 2, 5 and 10 years. (mean 75±83 months)	50% at each time point vs 88% at each time point 65% vs 87% 57% vs 87% 48% vs 87%	– –	High

*Stages defined according to the presence or absence of three predictors, major complications, progressive disease course or low ESR (<20 mm/hour): stage 1 (0 predictor or only progressive disease or only low ESR), stage 2 (only major complication or progressive disease course and low ESR or major complication and low ESR) and stage 3 (major complication and progressive course or the 3 predictors). †(I) with or without involvement of the pulmonary artery, but all patients had narrowing or occlusion in some region of the aorta or its main branches, or both; (II) one of the following: Takayasu's retinopathy, secondary hypertension, aortic regurgitation, or aortic or arterial aneurysm; if mild or moderate complications (IIa), if severe complications (IIb); (III) two or more of the four complications mentioned above. ESR, erythrocyte sedimentation rate; QUIPS, Quality in Prognosis Studies tool; RoB, risk of bias; TAK, Takayasu arteritis.

patients with progressive disease, high ESR, but without major complications) had 100% survival at 15 years.¹⁸ In this study, peak death rates occurred early, in the first year after diagnosis (n=10/16) and late in the disease course, >10 years after diagnosis (n=5/16). Major causes of death were congestive heart failure, acute myocardial infarction, cerebrovascular accidents and postoperative complications.¹⁸ These results are corroborated by other authors reporting that overall survival^{15 19} decreases in the first 5 years of disease, and event-free survival rates decrease progressively along the years,¹⁵ even more for patients with severe forms of disease (severe or multiple complications)^{15 20} or progressive course and carotidynia²¹ (table 1).

Soto *et al*²² (n=94, Mexican Mestizo patients) verified the decrease in overall survival rates over time, 92%, 81% and 73%, respectively, at 2, 5 and 10 years after diagnosis, and additionally conducted an analysis based on age of onset of complications. Patients with coronary disease developed between 10 and 19 years of age had survival rates at 2, 5 and 10 years that remained stable at 50% at each time point, while for patients with coronary disease developing between 20 and 39 years it was stable at 88% at each time point. The presence of aortic regurgitation decreased survival, when onset was between 10 and 29 years (OR 2.07; 95% CI 1.21 to 3.71), but this effect was not observed for onset over 30 years. Young patients with hypertension had progressively worsening survival at 2, 5 and 10 years (65%, 57% and 48%, respectively), while for patients aged between 20 and 39 years survival was 87% at any point (LoE 4).²²

Relapse-free rates worsened with time (80.1%, 58.6%, 47.7%, 39.6% and 32% at 1, 5, 10, 15 and 20 years, respectively), with multivariate analysis showing that relapses were more common in patients with elevated C reactive protein (CRP), carotidynia and of male gender.²¹ This study had a moderate RoB.

Overall, evidence points towards a worse prognosis in patients with major vascular complications, progressive disease course and older age. Early onset of complications contributes to decreased survival, with most deaths occurring in the first year after diagnosis (overall LoE 4).

Biomarkers for TAK

This SLR identified 40 observational studies analysing potential laboratory biomarkers and their relation to disease outcomes in TAK.

In the majority of papers, patients with active disease presented with higher ESR and CRP levels as compared with patients with stable/inactive disease (ESR ranged 5–115 mm/hour vs 1–43 mm/hour and CRP ranged 0.1–99.1 mg/dL vs 0.06–7.77 mg/dL for active vs stable disease, respectively). Nevertheless, 28.5% of patients classified as being in remission (National Institutes of Health (NIH) criteria) may present with elevated CRP and 23.8% with elevated ESR²³ (overall LoE 4).^{23–29}

In one case–control study (n=120), high-sensitivity CRP was a significant predictor of major cardiac events.³⁰ Adding to cardiovascular risk, patients with TAK present a more atherogenic lipid profile when compared with healthy controls, but not when compared with coronary artery disease controls.^{26 30}

Circulating interleukin (IL)-6^{28 31–33} and IL-18³¹ levels of patients with active disease tend to be higher than of those with stable, inactive disease or healthy controls. In paired samples of patients who had active disease and then evolved to a stable stage, ESR and IL-18 significantly decreased and the changes in ESR correlated well with those of serum IL-18 levels ($r=0.61$, $p<0.001$).³¹ IL-6 correlated positively with ESR and CRP (LoE 4).^{28 33}

Besides their potential use in monitoring disease activity, serum biomarkers have been investigated in relation to treatment response. Goel *et al*²⁴ ($n=32$) verified that in patients responding to GC therapy, with or without additional immunosuppressants, circulating levels of pro-inflammatory cytokines (interferon gamma (IFN- γ), IL-6, IL-23) decreased and anti-inflammatory cytokines (IL-10, transforming growth factor beta) increased from baseline to follow-up, although the difference did not reach statistical significance. Another study of 130 patients with vasculitis, including 41 with TAK, found that circulating Th1 cytokines (IFN- γ , tumour necrosis factor (TNF)-alpha, IL-2) significantly decreased with GC treatment, but the same could not be shown for Th17 cytokines profile (IL-17A, IL-23, IL-1).³⁴ More studies replicating and refining these results are needed in order to prove their utility, superiority versus ESR and CRP, and cost-effectiveness for clinical practice (LoE 4).

Another focus of interest in the field of biomarkers is the role of antiphospholipid antibodies. Of note, in one small retrospective study ($n=22$), vascular complications and need for intervention were increased in patients with TAK with persistent antiphospholipid antibodies positivity (45%, $n=10$, of which 7 required intervention vs 3; $p=0.035$) particularly in those with a positive lupus

anticoagulant. Anticardiolipin antibody titres did not appear to impact on this increased risk (LoE 3b).³⁵

Pentraxin-3 (PTX-3) is a potential biomarker of vascular inflammation in patients undergoing vascular disease progression (LoE 4).³⁶ PTX-3 levels are higher in patients with TAK than in controls,³⁷ but within patients with TAK, differences according to disease activity (NIH criteria, Indian Takayasu Clinical Activity Score (ITAS) or other clinical definitions) are inconsistently found.^{27 36 37} In one study, PTX-3 levels were compared between patients with TAK with active versus inactive disease, and between patients with TAK ($n=57$), healthy ($n=57$) and infection controls ($n=15$). Even though statistical differences were not formally reported, PTX-3 concentrations for healthy and infection controls were reported to be similar, but lower than those of patients with TAK. Receiver operating characteristic (ROC) curve analysis suggested that PTX-3 (Area Under the Curve ROC 0.919 (range 0.847–0.991)), at a threshold of 1 ng/mL, was more accurate than ESR and CRP in distinguishing between patients with active and inactive TAK (LoE 4).³⁷

Disease activity assessment in TAK is difficult and the definition of active and inactive/stable disease is still a matter of debate, making study design difficult, namely regarding biomarkers; therefore, all available results should be carefully interpreted.

Despite the amount of research available regarding biomarkers, some with potential use in the future, evidence comes mostly from studies with low LoE, and further validation/replication of results is needed. For now, ESR and CRP remain as the most useful and widely available laboratory parameters (table 2) (overall LoE 4).

Table 2 Laboratory markers of disease activity in TAK

Study identification	TAK (N)	Circulating laboratorial markers	Studied groups	Results	P value	NOS score
Goel <i>et al</i> ²⁴	32	ESR	Active vs stable	36.5 (range 14.0–70.8) vs 20.0 (range 13.5–43.0)	NS	4
		CRP	Active vs stable	4.5 (range 1.1–33.2) vs 3.4 (range 0.6–11.0)	NS	
		IL-6	Active vs stable	18.2 (range 3.2–46.2) vs 9.6 (range 4.8–16.33)	NS	
de Souza and Ataide Mariz ²⁵	59	ESR	Active vs inactive	54.8±30.9 vs 18.1±15.0	0.015	4
		ET-1	Active vs inactive	1.70±0.46 vs 1.43±0.44	NS	
Park <i>et al</i> ²³	47	ESR	Active vs stable	41.1±18.8 vs 14.4±9.6	0.01	3
		CRP	Active vs stable	1.2±1.1 vs 0.6±0.4	NS	
Park <i>et al</i> ³¹	49	ESR	Active vs stable	44.4±19.0 vs 12.5±8.8	<0.05	3
		IL-6	Active vs stable	54.3±21.2 vs 14.7±5.5	<0.05	
		IL-18	Active vs stable	850.0±211.1 vs 378.7±154.1	<0.001	

This scale assesses the quality of studies based on a 'star/points system' and evaluates studies according to three main considerations: selection of study groups; comparability of the groups; and ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. The maximum score is 9. The RoB decreases inversely to the score.

CRP, C reactive protein in mg/L; ESR, erythrocyte sedimentation rate in millimetre/first hour; ET-1, endothelin-1 in pg/mL; IL-6, interleukin-6 in pg/mL; IL-18, interleukin-18 in pg/mL; NOS, Newcastle-Ottawa Scale; NS, non-significant; TAK, Takayasu arteritis.

Long-term follow-up of patients, including clinical assessment and physical therapy

This SLR could not find any reliable evidence regarding the best timing/frequency of follow-up visits, nor any data regarding the utility of physical therapy.

As for clinical assessment of disease activity, methodologies vary. Most studies use the NIH criteria or the ITAS as disease activity scores. The ITAS showed a modest correlation with ESR in one study but no correlation with CRP.³⁸

Patient education, reported outcome measures and patient-centred care in TAK

This SLR found three cross-sectional studies (overall LoE 4) focusing on this area.

Abularrage *et al*³⁹ (n=158) reported that remission predicted better physical and mental quality of life (QoL) (Short Form (SF)-36 Health Survey), whereas younger age and freedom from immunomodulating medications were predictors of better physical QoL. In the same study, TAK had a relevant impact on the relationship to family members (41% of patients reported improvement, 23% worsening and 35% did not notice a change) and on work status (47% suffered a change in work duties, 46% a change in work hours, and 46% needed more than six consecutive weeks and 31% more than six consecutive months of sick leave from work).³⁹ Worse SF-36 scores correlated with anxiety, depression and high Health Assessment Questionnaire scores.⁴⁰

In addition to the effect of disease activity on QoL, damage is an equally important concept. The Vasculitis Damage Index (VDI) is used by some authors to evaluate damage in TAK, even though its validation included few patients with this condition. Omma *et al*⁴¹ (n=165 patients with TAK and 45 healthy controls) demonstrated that the mental and physical components from the SF-36 negatively correlated with the VDI ($r=-0.23$, $p=0.003$; $r=-0.34$, $p<0.001$). Moreover, resistant disease (persistent disease activity ≥ 6 months despite treatment), cumulative GC dose, age and disease duration were independently related to VDI. In this study, VDI was an independent risk factor for poorer QoL.

No studies were found regarding patient education and its impact on QoL.

Treatment

Role of Glucocorticoids

The SLR did not retrieve any study focusing on the role of GC in TAK or isolated aortitis. The use of GC was protocolised in two RCTs assessing the role of abatacept (ABA) and tocilizumab (TCZ) in TAK,^{42 43} respectively. The trial on TCZ only included relapsing patients receiving different GC regimens at the time of inclusion, but at least 0.2 mg/kg/day. The GC dose was then tapered by 10% per week from week 4 to a minimum of 0.1 mg/kg/day. This taper regimen resulted in a high relapse rate of around 80% during weeks 8–16 in the GC monotherapy arm. In the study on ABA, where newly diagnosed or

relapsing patients received prednisone 40–60 mg/day tapered to 20 mg/day by week 12 and then to 0 mg at week 28, the relapse rate was 60% at month 12. Unlike the Trial of Tocilizumab in Giant cell arteritis (GiACTA trial), these two studies did not include a second arm with a different GC taper protocol. Therefore, these studies do not allow definitive conclusions on the most appropriate GC starting dose and reduction protocol (overall LoE 1b).

Role of methotrexate and other non-biologic immunosuppressive drugs

There are no RCTs published on the role of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) for TAK; therefore, evidence derives from observational cohorts only. There were no eligible studies addressing other types of LVV or isolated aortitis, except for GCA.

Methotrexate (MTX) use in TAK was addressed in an open-label, pilot prospective study (LoE 4) including patients with persistent or GC-refractory TAK.⁴⁴ Weekly MTX (mean dose 17.1 mg) + GC resulted in remission in 13 of 16 (81%) patients. Relapses were frequent after GC discontinuation, but 50% of patients remained in sustained remission for a mean of 18 months. The RoB is high due to the uncontrolled nature of the study.

There were three studies (two prospective cohorts and one retrospective series) analysing the efficacy of mycophenolate mofetil (MMF) in patients with TAK (LoE 4), newly diagnosed or refractory to csDMARDs.^{45–47} MMF was variably combined with MTX or azathioprine (AZA) in the longitudinal prospective study from Li *et al*,⁴⁵ with enhanced effectiveness rates compared with MMF alone (80% vs 40%) after a median follow-up of 17 months. Effectiveness was defined by the following: (1) ESR < 20 mm/hour; (2) CRP < 10 mg/L or high-sensitivity CRP < 3 mg/L; (3) stable or improved vascular image studies (by ultrasound); (4) clinical assessment: improved, stable or remission; and (5) GC < 15 mg/day. Improvement in disease activity (NIH definition) was demonstrated by all studies. A meta-analysis (LoE 4) conducted on two of these observational studies concluded that MMF might be an effective alternative csDMARDs drug for TAK (with significant reduction in acute phase reactant values) and with steroid-sparing ability compared with baseline, before starting MMF (mean difference in daily GC dose: -17.96 ; 95% CI -24.89 to -10.4 mg).⁴⁸

A retrospective case series (n=10) evaluated the efficacy (Birmingham Vasculitis Activity Score and positron emission tomography-CT (PET-CT) findings) of GC+pulse cyclophosphamide (Cyc), 750 mg/m²/body surface area every 3 weeks, in patients with severe LVV (large vessel (LV)-GCA or TAK n=4) refractory to GC and/or csDMARDs or with organ/limb-threatening stenosis. Cyc was effective in 9 out of 10 patients; however, despite the use of prophylaxis, *Pneumocystis jirovecii* pneumonia occurred as a complication in 5 patients, warranting caution (LoE 4).⁴⁹

One prospective cohort study (LoE 2b) evaluated the efficacy and safety of GC+Cyc versus GC+MTX in inducing remission (NIH criteria ≤ 1 and GC ≤ 15 mg/kg/day) in TAK without prior exposure to csDMARDs.⁵⁰ Induction treatment was followed by maintenance with MTX or AZA. Remission was achieved by 71.7% vs 75% of patients in the Cyc and MTX groups, respectively. Magnetic resonance angiography (MRA) revealed increased baseline vessel wall enhancement and thickening as well as stenosis in the Cyc compared with the MTX group. After 6 months, vessel wall enhancement decreased only in the Cyc group, while luminal stenosis and wall thickness were unchanged. These data do not provide convincing evidence that induction treatment with Cyc is superior compared with MTX, since baseline data differed significantly.

AZA and leflunomide (LEF) were assessed by one prospective open-label study each (LoE 4).^{51 52} AZA (2 mg/kg/day) + GC (1 mg/kg/day) was associated with an improvement in systemic symptoms and laboratory measures of disease activity. Vascular angiographic progression was halted at 1 year from treatment initiation.⁵¹ The study did not include a control group and the RoB is high. The long-term use of LEF was associated with sustained remission in about half of the patients with good safety profile; however, of 12 patients included, only 5 (41.6%) remained on LEF after a mean of 12 months, with dropouts mainly due to inefficacy.⁵²

In summary, good-quality evidence regarding the use of csDMARDs is still lacking. The available evidence shows variable efficacy for MTX, MMF, LEF, AZA and Cyc, with the latter two showing some evidence of halted angiographic progression. MMF treatment might have some GC-sparing ability. As expected, relapses are more common after GC discontinuation (overall LoE 4).

Role of TCZ, ABA and other bDMARDs

The efficacy and safety of TCZ 162 mg subcutaneously was evaluated in a double-blind, placebo-controlled RCT (LoE 1b), with low RoB, that included 36 relapsing TAK (excluding patients recently treated with csDMARDs). This study did not reach the endpoint of influencing time to relapse (intention-to-treat analysis: HR for time to relapse 0.41, 95% CI 0.15 to 1.10; $p=0.0596$); however, a trend favouring TCZ over placebo was suggested (per protocol set: HR 0.34, 95% CI 0.11 to 1.00; $p=0.0345$). Moreover GC-sparing effect was not proven. There were no safety concerns with the TCZ-treated group.⁵³

Efficacy and safety of intravenous TCZ in refractory TAK have been tested in six case series (LoE 4; two followed prospectively, four retrospective descriptive studies; total $n=89$) suggesting clinical effectiveness but raising concerns about imaging progression (four out of seven patients had worsening radiological damage—assessed by MRA and ultrasound⁵⁴) despite TCZ treatment. Only a temporary effect of treatment was noted, with relapses occurring on drug discontinuation. Abisror *et al* showed no effect of TCZ on radiological activity

(defined as at least two of the following: (1) arterial wall thickening at angio-CT, (2) or arterial wall thickening with mural enhancement on MRI, or (3) by PET-CT) at 6 months, although a significant decrease of arterial fluorodeoxyglucose (FDG) uptake was noted. The RoB of the studies was high.^{47 54–58}

ABA was evaluated in a double-blind, placebo-controlled RCT with low RoB (LoE 1b). In this trial ABA, given to newly diagnosed (all randomised to placebo) or relapsing TAK, did not reduce the risk of relapse compared with GC alone and did not show any GC-sparing effect. There were no safety concerns in the group treated with ABA.⁴² A summary of the RCTs of biologic disease-modifying antirheumatic drugs (bDMARDs) for TAK is shown in table 3.

Evidence for the use of TNF inhibitor (TNFi) in TAK was described in open-label studies only. In a prospective trial, Hoffman *et al*⁵⁹ suggested benefit from TNFi (etanercept (ETA) or infliximab (IFX)) in refractory TAK (despite GC and previous csDMARDs: MTX, Cyc, MMF, AZA, ciclosporin or tacrolimus). However, the use of TNFi was associated with progression of imaging changes (in 4 out of 15 patients) despite apparent complete clinical or partial remission defined as absence of features of active disease, or new lesions on sequential imaging and no GC therapy or with GC dose reduced by $\geq 50\%$.

There were eight retrospective case series assessing the role of TNFi (IFX, ETA, adalimumab), mainly in refractory TAK not responding to previous treatment, demonstrating an overall benefit of TNFi treatment, although the RoB for this evidence is high.^{60–66}

A systematic review of 22 case series (≥ 2 cases) analysed the use of bDMARDs in LVV (95 GCA and 98 TAK).⁶⁷ In 32% of patients with refractory TAK, the use of IFX was associated with improved disease and patients were able to discontinue GC therapy. However, due to the retrospective analysis, parallel use of other drugs and lack of control patients, this observational experience needs to be interpreted with caution. Further analysis was not possible given the heterogeneity of the studies and differences in the definitions of remission applied.

A retrospective multicentre analysis of patients with TAK ($n=49$) treated with TNFi or TCZ found no significant differences in safety and efficacy, even though there was one case of tuberculosis (TB) reactivation in a patient treated with TNFi (IFX).⁶⁸

A descriptive prospective cohort study assessing the effects of escalating therapy with csDMARDs and then with bDMARDs (TNFi or TCZ) in refractory TAK not responding to GC demonstrated that 64% of patients achieved and maintained remission with bDMARD treatment.⁶⁹

There was one retrospective case series ($n=7$) of refractory TAK treated with rituximab as first-line bDMARD, but despite treatment four out of seven patients still had persistent disease at follow-up.⁷⁰

There have not been any important safety concerns from the use of bDMARDs in RCTs even though anecdotal

Table 3 Randomised controlled trials of biologic immunosuppressive agents in TAK

Study identification	TAK subtype	N	Intervention	Control	Primary outcome	Results (I)	Results (C)	P value	RoB
Nakaoka <i>et al</i> ⁶³	Relapse	36: 18 (I) vs 18 (C)	GC (at least 0.2 mg/kg/day) + TCZ 162 mg subcutaneously/week (after ≥1 week from remission after flare)	GC+placebo	Time to relapse	HR, 0.41 (95% CI 0.15 to 1.1)		0.0596	Low
Langford <i>et al</i> ⁴²	New/Relapse	26: 15 (I) vs 11 (C)	PRED 40–60 mg/day → tapered to 20 mg/day at week 12, plus from week 12 if patients in remission: ABA 10 mg/kg intravenously on days 1, 15 and 29, and week 8	GC+ABA intravenously for the first 12 weeks → GC+placebo	Relapse-free survival rate at 12 months	22%	40%	0.853	Low

ABA, abatacept; C, control; GC, glucocorticoid; I, intervention; PRED, prednisone; RoB, risk of bias; TAK, Takayasu arteritis; TCZ, tocilizumab.

reports from observational studies have reported TB reactivation with TNFi treatment.^{65 68} However, in these studies, there is no mention of a prescreening protocol or prophylaxis, as currently recommended when using bDMARDs.

The SLR identified two RCTs testing the role of curcumin or resveratrol (both with a TNFi natural effect) versus placebo in newly diagnosed TAK.^{71 72} The two trials reported some benefits of the two agents. However, disease assessment was unclear, the duration of treatment was very limited (4 and 12 weeks, respectively), there were no data on concomitant treatment, and the RoB was unclear/high for both trials, not allowing robust conclusions regarding efficacy.

Overall, evidence for bDMARDs favours the use of TCZ and TNFi in relapsing/refractory disease, when csDMARDs fail (LoE 4). More studies are needed to prove the efficacy and safety of other bDMARDs.

Specific treatment and organ complications

Good-quality information on this topic is lacking. The SLR identified a retrospective longitudinal study (LoE 4) evaluating the preliminary surgical experience in the management of stroke caused by cervical arterial lesions in 49 patients with TAK. This supported a percutaneous transluminal angioplasty (PTA) as first choice, even though recurrence rates were high. Arterial rupture, cerebral reperfusion syndrome and thrombotic complications are a serious concern. The study has a high RoB and did not provide details on concomitant medical treatment.⁷³

Management of hypertension in patients with TAK due to multifactorial causes (renal arteries or aortic stenosis) was retrospectively described in a cohort of 381 patients (LoE 4),⁷⁴ with many patients requiring intensive medical treatment with ≥3 different antihypertensive drugs combined with immunosuppressive agents (GC and/or csDMARDs) and revascularisation procedures.

Revascularisation procedures (aneurysm and stenosis treatment)

The SLR identified one prospective cohort (n=11) evaluating the safety and efficacy of PTA for symptomatic pulmonary stenosis in TAK. This study showed improved symptoms and improvements in several objective variables. Mean pulmonary arterial pressure (PAP) decreased immediately after the intervention (p<0.001). After an average of 29 months of follow-up, the New York Heart Association functional class and 6 min walking distances improved, while mean PAP measured by echocardiography decreased significantly (compared with baseline, all p<0.01). Two patients died, one had reperfusion pulmonary injury, dying of respiratory insufficiency 3 days after the procedure, and the other 28 months after the procedure, following a pulmonary infection and cardiac shock.⁷⁵

Evidence supporting the surgical management of arterial stenosis in TAK arises from several retrospective case series (LoE 4), with variable baseline characteristics of

the patients included, different involved vascular sites and variable concomitant medical treatment.^{76–108} Indications for referral, when specified, mainly comprised symptomatic arterial stenosis (eg, renovascular uncontrolled hypertension, transient ischaemic attack, limb claudication, syncope, vertigo, angina). Some authors considered referral in the presence of a stenotic vessel >70% of normal diameter or with a peak systolic gradient >50mm. The recurrent finding across studies was the need for good clinical control of disease activity at the time of surgery, using GC and/or immunosuppressive drugs (ensuring normal ESR and CRP values during the months following surgery).

Antiplatelet agents were prescribed in most patients and continued for at least 3–12 months after surgery, sometimes indefinitely.

A retrospective small case series (n=10 LV-GCA or TAK) analysed the safety and effectiveness of PTA for occlusive arterial disease with results in line with previous evidence. Overall technical success was better for stenotic lesions than for occlusive lesions. Cumulative primary clinical success rate was 67.6%. Despite the risk of arterial injury during PTA, the rate of this complication is low (LoE 4).¹⁰⁹

A meta-analysis of seven observational studies (266 patients and 316 lesions treated) compared the outcome between balloon angioplasty and stenting in TAK with several anatomical sites involved (LoE 2a).¹¹⁰ Results state that balloon angioplasty can yield better results in renal artery interventions compared with stenting. The restenosis rate was not different between the two procedures for all other anatomical sites. While the clinical efficacy of improving renal hypertension was similar, acute vascular complications were less frequent in patients who were stented compared with those undergoing balloon angioplasty (OR 0.007; 95% CI 0.02 to 0.29; p<0.001); however, this was at the expense of efficacy, with higher rates of restenosis in renal artery stenting procedures (OR 4.4; 95% CI 2.14 to 9.02).

Restenosis has been described in 17%–60% of patients (usually higher for stenting procedures compared with angioplasty).^{78 83 84 89 92}

Efficacy during follow-up of PTA treatment decreases to 80%–90% after 2–5 years,^{83,90} and significantly different outcomes have been reported according to the type of intervention, 5-year patency: 91.7% (angioplasty) vs 33.3% (unassisted stent) vs 55.6% (primary assisted stent).⁹²

Independent variables for arterial patency after surgical procedures for any site of vascular involvement have been reported to be interventions performed during a stable stage of the disease (HR 0.30 for restenosis), and interventions followed by GC and immunosuppressive treatments (csDMARDs) (HR 0.41).⁸³ Freedom from the need for revision after 5 and 10 years from surgery has been reported to range from 100% for patients with inactive disease and drug-free remission not requiring

GC therapy, to 33% for patients with active disease at the time of surgery and without adequate GC treatment.¹¹¹

Management of aneurysms in TAK was specifically assessed in a retrospective case series including 10 patients with thoracic or thoracoabdominal aneurysms. Surgical therapy aiming at definitive repair is recommended whenever possible because the rate of recurrence is very high in palliative procedures not ensuring a radical surgical resolution of the lesion. The RoB of this study is high.¹¹² Evidence from other retrospective cohorts (LoE 4) combining surgery for stenotic and/or aneurysmal complications in TAK supports the need to control inflammation and disease activity before and after the surgical intervention to prevent complications and ensure a good long-term outcome. Recurrent late aneurysmal dilatation is frequently reported in aortic surgery.^{111 113–126}

Overall, there is evidence (LoE 4) to support the use of revascularisation techniques both for stenosis and aneurysm. Perioperative GC treatment for inflammation control is crucial. As for the preferred surgical procedure, balloon angioplasty appeared superior to stenting for renal artery interventions even though the restenosis rate was similar.

Role of adjunctive therapy, prophylaxis and physical exercise

A protective role of antiplatelet therapy against acute ischaemic events was reported in a retrospective case series analysis with 48 patients (HR 0.55; 95% CI 0.06 to 0.514) (LoE 4).¹²⁷ Cardiovascular disease was present in 44 patients (91.7%), with hypertension, high low-density lipoprotein and obesity being the most common comorbidities (77.1%, 45.8% and 16.7%, respectively). In this study, antiplatelet therapy was used by 62.5% and anti-coagulants by 12.5%, and it was noted that patients with ischaemic events used significantly less antiplatelet agents (14.3%) than those without events (82.4%) (p<0.0001). There were no differences for patients on anticoagulant therapy.

There was one small prospective cohort study (n=11) assessing the effects of physical exercise on inflammatory markers and symptoms of TAK, suggesting a potential immunomodulatory role and improvement of strength and function in these patients (LoE 4).¹²⁸

There were no studies addressing the role of infectious screening or prophylaxis for TAK. However, therapeutic trials and observational studies have reported few cases of TB, underlying the need to consider screening and preventive measures in at-risk individuals.

DISCUSSION

The 2009 LVV recommendations were an important landmark,² providing guidance in an area where information was still scarce. However, given recent advances, namely in treatment, new recommendations with updated and added information were needed. The results in this paper reflect the findings for TAK and should be considered together

with the online supplementary tables in the online supplementary material, where more information is available.

The comprehensive research strategy adopted for the SLRs had the advantage of providing a large amount of results. However, these studies were mostly observational with low LoE and moderate to high RoB, requiring extra care when interpreting results.

By contrast with the 2009 recommendations, we were able to retrieve data on prognosis relating to patients' characteristics. Namely, it was noted that male patients, carotidynia and high CRP related to higher relapse rates, and prognosis in general was worse in the presence of older age, major complications and a somewhat weaker inflammatory response.

Regarding treatment, only two RCTs specifically addressing treatment of TAK were identified. While one study on ABA was negative, the other trial provided some evidence of the potential efficacy of TCZ, although the primary endpoint was not achieved. In both RCTs, assessment of disease activity was largely symptom-based and therefore subject to potential bias. Both RCTs did not use systematic imaging for assessment of disease activity and extent. Therefore, for future studies in TAK, the development of validated instruments to assess disease activity, use of imaging for assessment of vascular inflammation and progression of vascular lesions, and implementation of study designs that also address steroid-sparing properties of the drugs under study are desirable. ESR and CRP are extensively used as biomarkers of disease activity despite not being fully reliable for this purpose.

With the exception of a few case reports, evidence on types of LVV other than GCA and TAK, such as isolated aortitis or IgG4-related LVV, is lacking. Multicentre registries could be a first step to gather knowledge on these less common forms of LVV.

In summary, recommendations on the management of TAK can only be based on an overall low LoE, and more high-quality research on TAK and other less common forms of LVV is needed.

Author affiliations

¹Rheumatology, Centro Hospitalar do Baixo Vouga EPE, Aveiro, Portugal

²Rheumatology, IRCCS Policlinico S. Matteo Foundation, University of Pavia, Pavia, Italy

³University of Pavia, PhD in Experimental Medicine, Pavia, Italy

⁴Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Science (NDORMS), University of Oxford, Oxford, UK

⁵Rheumatology and Clinical Immunology, Charité University Medicine Berlin (CCM), Berlin, Germany

⁶Vasculitis Research Unit, Department of Autoimmune Diseases, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

⁷Rheumatology, Southend University Hospital, Westcliff-on-Sea, UK

⁸Rheumatology, Department of Rheumatology, South Tyrol Health Trust, Hospital of Bruneck, Bruneck, Italy

⁹Rheumatology, Medical University Graz, Graz, Austria

¹⁰Internal Medicine, Hospital Saint-Louis, University Paris Diderot, Paris, France

¹¹Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal

¹²Rheumatology, Centro Hospitalar de Lisboa Norte, EPE, Hospital de Santa Maria, Lisboa, Portugal

¹³Rheumatology, Università di Modena e Reggio Emilia and Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy

¹⁴Medical Centre for Rheumatology, Klinik für Innere Medizin, Rheumatologie und Klinische Immunologie Berlin-Buch, Immanuel Krankenhaus, Berlin, Germany

¹⁵Klinik für Innere Medizin, Rheumatologie und Immunologie, Vaskulitis-Zentrum Süd, Medius Kliniken, – Akademisches Lehrkrankenhaus der Universität Tübingen, Kirchheim-unter-Teck, Germany

Acknowledgements The authors wish to thank the librarians Chiara Rebuffi, Grant Office and Scientific Documentation Center, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, and Helena Donato, Documentation Unit, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal, for advice and assistance during the SLR.

Contributors AFÁ and SM conducted the SLRs. AFÁ drafted the first version of the current manuscript and subsequent revisions. All authors reviewed and approved the final version of the manuscript.

Funding This project was funded by EULAR.

Competing interests SM received speaker fees and consultancies from Roche and Chugai. FB received grants from Horizon and Mundipharma, and speaker fees and/or consultancies from Horizon, Mundipharma, Roche and Sanofi. MC received lecturing fees from Boehringer Ingelheim and Vifor, consulting fees from Roche, Janssen, AbbVie and GSK, and research agreement from Kiniksa. CD received a grant from Celgene, and speaker fees and/or consultancies from AbbVie, BMS, Lilly, MSD, Pfizer, Novartis, UCB, Roche and Sanofi. WS received a grant from Roche, and speaker fees and consultancies from Chugai, GSK, Novartis, Roche and Sanofi. BH received speaker fees and/or consultancies from AbbVie, Boehringer, Chugai, Celgene, MSD, Pfizer, Novartis and Roche. All other authors have no competing interests.

Patient consent for publication Not required.

Ethics approval Since this project was an SLR and did not use individual patient data, ethical approval was not deemed necessary.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

- Dejaco C, Ramiro S, Duftner C, *et al*. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis* 2018;77:636–43.
- Mukhtyar C, Guillemin L, Cid MC, *et al*. EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis* 2009;68:318–23.
- van der Heijde D, Aletaha D, Carmona L, *et al*. 2014 update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8–13.
- CEBM. Oxford centre for evidence-based medicine – levels of evidence (March 2009). Available: <http://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
- GSe HJPT. Cochrane handbook for systematic reviews of interventions version 5.1.0. In: *The Cochrane collaboration*, 2011.
- Wells G, Shea BJ, O'Connell D, *et al*. *The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*, 2000.
- Whiting PF, Rutjes AWS, Westwood ME, *et al*. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529–36.
- Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 2006;144:427–37.
- Mont'Alverne ARdeS, Paula LEde, Shinjo SK. Features of the onset of Takayasu's arteritis according to gender. *Arq Bras Cardiol* 2013;101:359–63.

10. Watanabe Y, Miyata T, Tanemoto K. Current clinical features of new patients with Takayasu arteritis observed from Cross-Country research in Japan: age and sex specificity. *Circulation* 2015;132:1701–9.
11. Sharma BK, Jain S. A possible role of sex in determining distribution of lesions in Takayasu arteritis. *Int J Cardiol* 1998;66(Suppl 1):S81–S84.
12. Espitia O, Samson M, Le Gallou T, et al. Comparison of idiopathic (isolated) aortitis and giant cell arteritis-related aortitis. A French retrospective multicenter study of 117 patients. *Autoimmun Rev* 2016;15:571–6.
13. Umehara H, Okazaki K, Masaki Y, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 2012;22:21–30.
14. Kim IY, Eun YH, Jeong H, et al. Clinical characteristics and outcomes of 61 patients with chronic periaortitis including IgG4-related and non-IgG4-related cases. *Int J Rheum Dis* 2017;20:1751–62.
15. Ishikawa K. Survival and morbidity after diagnosis of occlusive thrombooaortopathy (Takayasu's disease). *Am J Cardiol* 1981;47:1026–32.
16. Patil P, Williams M, Maw WW, et al. Fast track pathway reduces sight loss in giant cell arteritis: results of a longitudinal observational cohort study. *Clin Exp Rheumatol* 2015;33(2 Suppl 89):S-103–6.
17. Diamantopoulos AP, Haugeberg G, Lindland A, et al. The fast-track ultrasound clinic for early diagnosis of giant cell arteritis significantly reduces permanent visual impairment: towards a more effective strategy to improve clinical outcome in giant cell arteritis? *Rheumatology* 2016;55:66–70.
18. Ishikawa K, Maetani S. Long-term outcome for 120 Japanese patients with Takayasu's disease. Clinical and statistical analyses of related prognostic factors. *Circulation* 1994;90:1855–60.
19. Yang L, Zhang H, Jiang X, et al. Clinical manifestations and longterm outcome for patients with Takayasu arteritis in China. *J Rheumatol* 2014;41:2439–46.
20. Ishikawa K. Patterns of symptoms and prognosis in occlusive thrombooaortopathy (Takayasu's disease). *J Am Coll Cardiol* 1986;8:1041–6.
21. Comarmond C, Biard L, Lambert M, et al. Long-term outcomes and prognostic factors of complications in Takayasu arteritis: a multicenter study of 318 patients. *Circulation* 2017;136:1114–22.
22. Soto ME, Espinola N, Flores-Suarez LF, et al. Takayasu arteritis: clinical features in 110 Mexican Mestizo patients and cardiovascular impact on survival and prognosis. *Clin Exp Rheumatol* 2008;26(3 Suppl 49):S9–15.
23. Park M-C, Park Y-B, Jung SY, et al. Anti-Endothelial cell antibodies and antiphospholipid antibodies in Takayasu's arteritis: correlations of their titers and isotype distributions with disease activity. *Clin Exp Rheumatol* 2006;24(2 Suppl 41):S10–16.
24. Goel R, Kabeerdoss J, Ram B, et al. Serum cytokine profile in Asian Indian patients with Takayasu arteritis and its association with disease activity. *Open Rheumatol J* 2017;11:23–9.
25. de Souza AWS, Ataíde Mariz H, Torres Reis Neto E, et al. Risk factors for cardiovascular disease and endothelin-1 levels in Takayasu arteritis patients. *Clin Rheumatol* 2009;28:379–83.
26. Wang X, Chen B, Lv N, et al. Association of abnormal lipid spectrum with the disease activity of Takayasu arteritis. *Clin Rheumatol* 2015;34:1243–8.
27. Dagna L, Salvo F, Tiraboschi M, et al. Pentraxin-3 as a marker of disease activity in Takayasu arteritis. *Ann Intern Med* 2011;155:425–33.
28. Arraes AED, de Souza AWS, Mariz HA, et al. [¹⁸F]-Fluorodeoxyglucose positron emission tomography and serum cytokines and matrix metalloproteinases in the assessment of disease activity in Takayasu's arteritis. *Rev Bras Reumatol* 2015. doi:10.1016/j.rbr.2015.03.009. [Epub ahead of print: 30 Jul 2015].
29. Ma J, Luo X, Wu Q, et al. Circulation levels of acute phase proteins in patients with Takayasu arteritis. *J Vasc Surg* 2010;51:700–6.
30. Wang X, Dang A, Lv N, et al. High-sensitivity C-reactive protein predicts adverse cardiovascular events in patients with Takayasu arteritis with coronary artery involvement. *Clin Rheumatol* 2016;35:679–84.
31. 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.
32. Noris M, Daina E, Gamba S, et al. Interleukin-6 and RANTES in Takayasu arteritis: a guide for therapeutic decisions? *Circulation* 1999;100:55–60.
33. Kong X, Sun Y, Ma L, et al. The critical role of IL-6 in the pathogenesis of Takayasu arteritis. *Clin Exp Rheumatol* 2016;34(3 Suppl 97):S21–7.
34. Saadoun D, Garrido M, Comarmond C, et al. Th1 and Th17 cytokines drive inflammation in Takayasu arteritis. *Arthritis Rheumatol* 2015;67:1353–60.
35. Jordan NP, Bezanahary H, D'Cruz DP. Increased risk of vascular complications in Takayasu's arteritis patients with positive lupus anticoagulant. *Scand J Rheumatol* 2015;44:211–4.
36. Tombetti E, Di Chio MC, Sartorelli S, et al. Systemic pentraxin-3 levels reflect vascular enhancement and progression in Takayasu arteritis. *Arthritis Res Ther* 2014;16.
37. Alibaz-Oner F, Aksu K, Yentur SP, et al. Plasma pentraxin-3 levels in patients with Takayasu's arteritis during routine follow-up. *Clin Exp Rheumatol* 2016;34(3 Suppl 97):S73–6.
38. Goel R, Nair A, Kabeerdoss J, et al. Study of serial serum myeloid-related protein 8/14 as a sensitive biomarker in Takayasu arteritis: a single centre study. *Rheumatol Int* 2018;38:623–30.
39. Abullarrage CJ, Slidell MB, Sidawy AN, et al. Quality of life of patients with Takayasu's arteritis. *J Vasc Surg* 2008;47:131–7.
40. Yilmaz N, Can M, Oner FA, et al. Impaired quality of life, disability and mental health in Takayasu's arteritis. *Rheumatology* 2013;52:1898–904.
41. Omma A, Erer B, Karadag O, et al. Remarkable damage along with poor quality of life in Takayasu arteritis: cross-sectional results of a long-term followed-up multicentre cohort. *Clin Exp Rheumatol* 2017;35 Suppl 103:77–82.
42. Langford CA, Cuthbertson D, Ytterberg SR, et al. A randomized, double-blind trial of abatacept (CTLA-4lg) for the treatment of Takayasu arteritis. *Arthritis Rheumatol* 2017;69:846–53.
43. Nakaoka Y, Isobe M, Takei S, et al. Long-Term efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis treated continuously over 52 weeks: results from phase 3, randomized, double-blind, placebo-controlled trial and open-label extension in Japan. *Arthritis Rheum* 2017;69.
44. Hoffman GS, Leavitt RY, Kerr GS, et al. Treatment of glucocorticoid-resistant or relapsing Takayasu arteritis with methotrexate. *Arthritis Rheum* 1994;37:578–82.
45. Li J, Yang Y, Zhao J, et al. The efficacy of mycophenolate mofetil for the treatment of Chinese Takayasu's arteritis. *Sci Rep* 2016;6:38687.
46. Shinjo SK, Pereira RMR, Tizziani VAP, et al. Mycophenolate mofetil reduces disease activity and steroid dosage in Takayasu arteritis. *Clin Rheumatol* 2007;26:1871–5.
47. Goel R, Danda D, Mathew J, et al. Mycophenolate mofetil in Takayasu's arteritis. *Clin Rheumatol* 2010;29:329–32.
48. Dai D, Wang Y, Jin H, et al. The efficacy of mycophenolate mofetil in treating Takayasu arteritis: a systematic review and meta-analysis. *Rheumatol Int* 2017;37:1083–8.
49. Henes JC, Mueller M, Pfannenber C, et al. Cyclophosphamide for large vessel vasculitis: assessment of response by PET/CT. *Clin Exp Rheumatol* 2011;29(1 Suppl 64):S43–8.
50. Sun Y, Ma L, Ma L, et al. Cyclophosphamide could be a better choice than methotrexate as induction treatment for patients with more severe Takayasu's arteritis. *Rheumatol Int* 2017;37:2019–26.
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. de Souza AW, de Almeida Agustinelli R, de Cinque Almeida H, et al. Leflunomide in Takayasu arteritis - A long term observational study. *Rev Bras Reumatol* 2016;56:371–5.
53. Nakaoka Y, Isobe M, Takei S, et al. Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study). *Ann Rheum Dis* 2018;77:348–54.
54. Tombetti E, Franchini S, Papa M, et al. Treatment of refractory Takayasu arteritis with tocilizumab: 7 Italian patients from a single referral center. *J Rheumatol* 2013;40:2047–51.
55. Zhou J, Chen Z, Li J, et al. The efficacy of tocilizumab for the treatment of Chinese Takayasu's arteritis. *Clin Exp Rheumatol* 2017;35 Suppl 103:171–5.
56. Nakaoka Y, Higuchi K, Arita Y, et al. Tocilizumab for the treatment of patients with refractory Takayasu arteritis. *Int Heart J* 2013;54:405–11.
57. Loricera J, Blanco R, Hernández JL, et al. Tocilizumab in patients with Takayasu arteritis: a retrospective study and literature review. *Clin Exp Rheumatol* 2016;34(3 Suppl 97):S44–53.
58. Abisror N, Mekinian A, Lavigne C, et al. Tocilizumab in refractory Takayasu arteritis: a case series and updated literature review. *Autoimmun Rev* 2013;12:1143–9.

59. 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.
60. Gudbrandsson B, Molberg Øyvind, Palm Øyvind. Tnf inhibitors appear to inhibit disease progression and improve outcome in Takayasu arteritis; an observational, population-based time trend study. *Arthritis Res Ther* 2017;19.
61. Novikov PI, Smitienko IO, Moiseev SV. Tumor necrosis factor alpha inhibitors in patients with Takayasu's arteritis refractory to standard immunosuppressive treatment: cases series and review of the literature. *Clin Rheumatol* 2013;32:1827–32.
62. Schmidt J, Kermani TA, Bacani AK, *et al.* Tumor necrosis factor inhibitors in patients with Takayasu's arteritis: experience from a referral center with long-term followup. *Arthritis Care Res* 2012;64:1079–83.
63. Molloy ES, Langford CA, Clark TM, *et al.* Anti-tumour necrosis factor therapy in patients with refractory Takayasu arteritis: long-term follow-up. *Ann Rheum Dis* 2008;67:1567–9.
64. 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.
65. Mekinian A, Neel A, Sibilia J, *et al.* Efficacy and tolerance of infliximab in refractory Takayasu arteritis: French multicentre study. *Rheumatology* 2012;51:882–6.
66. Karageorgaki ZT, Mavragani CP, Papatheasiou MA, *et al.* Infliximab in Takayasu arteritis: a safe alternative? *Clin Rheumatol* 2007;26:984–7.
67. Osman M, Pagnoux C, Dryden DM, *et al.* The role of biological agents in the management of large vessel vasculitis (LVV): a systematic review and meta-analysis. *PLoS One* 2014;9:e115026.
68. Mekinian A, Comarmond C, Resche-Rigon M, *et al.* Efficacy of biological-targeted treatments in Takayasu arteritis: multicenter, retrospective study of 49 patients. *Circulation* 2015;132:1693–700.
69. Ohgashi H, Tamura N, Ebana Y, *et al.* Effects of immunosuppressive and biological agents on refractory Takayasu arteritis patients unresponsive to glucocorticoid treatment. *J Cardiol* 2017;69:774–8.
70. Pazzola G, Muratore F, Pipitone N, *et al.* Rituximab therapy for Takayasu arteritis: a seven patients experience and a review of the literature. *Rheumatology* 2017. doi:10.1093/rheumatology/kex249. [Epub ahead of print: 18 Jul 2017].
71. Shao N, Jia H, Li Y, *et al.* Curcumin improves treatment outcome of Takayasu arteritis patients by reducing TNF- α : a randomized placebo-controlled double-blind clinical trial. *Immunol Res* 2017;65:969–74.
72. Shi G, Hua M, Xu Q, *et al.* Resveratrol improves treatment outcome and laboratory parameters in patients with Takayasu arteritis: a randomized double-blind and placebo-controlled trial. *Immunobiology* 2017;222:164–8.
73. Gu YQ, Wang ZG. Surgical treatment of cerebral ischaemia caused by cervical arterial lesions due to Takayasu's arteritis: preliminary results of 49 cases. *ANZ J Surg* 2001;71:89–92.
74. Qi Y, Yang L, Zhang H, *et al.* The presentation and management of hypertension in a large cohort of Takayasu arteritis. *Clin Rheumatol* 2018;37:2781–8.
75. Dong H, Jiang X, Peng M, *et al.* Percutaneous transluminal angioplasty for symptomatic pulmonary stenosis in Takayasu arteritis. *J Rheumatol* 2014;41:1856–62.
76. Qin L, Hong-Liang Z, Zhi-Hong L, *et al.* Percutaneous transluminal angioplasty and stenting for pulmonary stenosis due to Takayasu's arteritis: clinical outcome and four-year follow-up. *Clin Cardiol* 2009;32:639–43.
77. Dong H, Che W, Jiang X, *et al.* An unrecognised presentation of Takayasu arteritis: superficial femoral artery involvement. *Clin Exp Rheumatol* 2017;35 Suppl 103:83–7.
78. Gülcü A, Gezer NS, Akar S, *et al.* Long-Term follow-up of endovascular repair in the management of arterial stenosis caused by Takayasu's arteritis. *Ann Vasc Surg* 2017;42:93–100.
79. Hinojosa CA, Anaya-Ayala JE, Gomez-Arcive Z, *et al.* Factors associated with need for revascularisation in non-coronary arterial occlusive lesions secondary to Takayasu's arteritis. *Eur J Vasc Endovasc Surg* 2017;54:397–404.
80. Qureshi MA, Martin Z, Greenberg RK. Endovascular management of patients with Takayasu arteritis: stents versus stent grafts. *Semin Vasc Surg* 2011;24:44–52.
81. Lee B-B, Laredo J, Neville R, *et al.* Endovascular management of Takayasu arteritis: is it a durable option? *Vascular* 2009;17:138–46.
82. Joh J-H, Kim D-K, Park K-H, *et al.* Surgical management of Takayasu's arteritis. *J Korean Med Sci* 2006;21:20–4.
83. Park MC, Lee SW, Park YB, *et al.* Post-interventional immunosuppressive treatment and vascular restenosis in Takayasu's arteritis. *Rheumatology* 2006;45:600–5.
84. 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.
85. Liang P, Tan-Ong M, Hoffman GS. Takayasu's arteritis: vascular interventions and outcomes. *J Rheumatol* 2004;31:102–6.
86. Sharma BK, Jain S, Bali HK, *et al.* A follow-up study of balloon angioplasty and de-novo stenting in Takayasu arteritis. *Int J Cardiol* 2000;75(Suppl 1):S147–S152.
87. Hong S, Ghang B, Kim Y-G, *et al.* Longterm outcomes of renal artery involvement in Takayasu arteritis. *J Rheumatol* 2017;44:466–72.
88. Peng M, Ji W, Jiang X, *et al.* Selective stent placement versus balloon angioplasty for renovascular hypertension caused by Takayasu arteritis: two-year results. *Int J Cardiol* 2016;205:117–23.
89. Kinjo H, Kafa A. The results of treatment in renal artery stenosis due to Takayasu disease: comparison between surgery, angioplasty, and stenting. A monocentric retrospective study. *G Chir* 2015;36:161–7.
90. Pang N, Xie C, Yang M, *et al.* Clinical efficacy of percutaneous transluminal renal artery stenting for the treatment of renovascular hypertension associated with Takayasu arteritis. *Ann Vasc Surg* 2015;29:816–21.
91. Shao P, Qin C, Meng X, *et al.* Hybrid laparoscopic technique for renal artery Takayasu arteritis. *Eur J Vasc Endovasc Surg* 2011;42:803–8.
92. Park HS, Do YS, Park KB, *et al.* Long term results of endovascular treatment in renal arterial stenosis from Takayasu arteritis: angioplasty versus stent placement. *Eur J Radiol* 2013;82:1913–8.
93. Feng R, Wei X, Zhao Z, *et al.* Aortorenal bypass with autologous saphenous vein in Takayasu arteritis-induced renal artery stenosis. *Eur J Vasc Endovasc Surg* 2011;42:47–53.
94. Weaver FA, Kumar SR, Yellin AE, *et al.* Renal revascularization in Takayasu arteritis-induced renal artery stenosis. *J Vasc Surg* 2004;39:749–57.
95. 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.
96. Sharma S, Saxena A, Talwar KK, *et al.* Renal artery stenosis caused by nonspecific arteritis (Takayasu disease): results of treatment with percutaneous transluminal angioplasty. *AJR Am J Roentgenol* 1992;158:417–22.
97. 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.
98. Luo XY, Wu QH, Zhang FX. Open and endovascular management of severe cerebral ischemia in Takayasu's arteritis. *Ann Vasc Surg* 2017;42:101–10.
99. Wang X, Dang A, Lv N, *et al.* Long-term outcomes of coronary artery bypass grafting versus percutaneous coronary intervention for Takayasu arteritis patients with coronary artery involvement. *Semin Arthritis Rheum* 2017;47:247–52.
100. Yang Y, Tian T, Yang K, *et al.* Outcomes of percutaneous coronary intervention and coronary artery bypass grafting in patients with Takayasu arteritis. *Int J Cardiol* 2017;241:64–9.
101. Na KJ, Lee K-H, Oh SJ, *et al.* Anaortic off-pump coronary artery bypass grafting in patients with Takayasu's arteritis. *Korean J Thorac Cardiovasc Surg* 2013;46:274–8.
102. Endo M, Tomizawa Y, Nishida H, *et al.* Angiographic findings and surgical treatments of coronary artery involvement in Takayasu arteritis. *J Thorac Cardiovasc Surg* 2003;125:570–7.
103. Xiao Y, Zhou J, Wei X, *et al.* Outcomes of different treatments on Takayasu's arteritis. *J Thorac Dis* 2016;8:2495–503.
104. Ozpak B, Ilhan G. Biosynthetic versus polytetrafluoroethylene graft in extra-anatomical bypass surgery of Takayasu arteritis patients with supra-aortic disease. *J Cardiovasc Thorac Res* 2015;7:101–6.
105. Kim Y-W, Kim D-I, Park YJ, *et al.* Surgical bypass vs endovascular treatment for patients with supra-aortic arterial occlusive disease due to Takayasu arteritis. *J Vasc Surg* 2012;55:693–700.
106. Kim HJ, Lee C-S, Kim JS, *et al.* Outcomes after endovascular treatment of symptomatic patients with Takayasu's arteritis. *Interv Neuroradiol* 2011;17:252–60.
107. Chen B, Yu HX, Zhang J, *et al.* Endovascular revascularization for carotid artery occlusion in patients with Takayasu arteritis. *Eur J Vasc Endovasc Surg* 2015;49:498–505.
108. 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.

109. Both M, Jahnke T, Reinhold-Keller E, *et al.* Percutaneous management of occlusive arterial disease associated with vasculitis: a single center experience. *Cardiovasc Intervent Radiol* 2003;26:19–26.
110. Jeong HS, Jung JH, Song GG, *et al.* Endovascular balloon angioplasty versus stenting in patients with Takayasu arteritis: a meta-analysis. *Medicine* 2017;96:e7558.
111. 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.
112. Sasaki S, Kubota S, Kunihara T, *et al.* Surgical experience of the thoracic aortic aneurysm due to Takayasu's arteritis. *Int J Cardiol* 2000;75(Suppl 1):S129–34.
113. Rosa Neto NS, Shinjo SK, Levy-Neto M, *et al.* Vascular surgery: the main risk factor for mortality in 146 Takayasu arteritis patients. *Rheumatol Int* 2017;37:1065–73.
114. Labarca C, Makol A, Crowson CS, *et al.* Retrospective comparison of open versus endovascular procedures for Takayasu arteritis. *J Rheumatol* 2016;43:427–32.
115. Perera AH, Youngstein T, Gibbs RGJ, *et al.* Optimizing the outcome of vascular intervention for Takayasu arteritis. *Br J Surg* 2014;101:43–50.
116. 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.
117. Matsuura K, Ogino H, Matsuda H, *et al.* Surgical outcome of aortic arch repair for patients with Takayasu arteritis. *Ann Thorac Surg* 2006;81:178–82.
118. Matsuura K, Ogino H, Kobayashi J, *et al.* Surgical treatment of aortic regurgitation due to Takayasu arteritis: long-term morbidity and mortality. *Circulation* 2005;112:3707–12.
119. Tyagi S, Kaul UA, Nair M, *et al.* Balloon angioplasty of the aorta in Takayasu's arteritis: initial and long-term results. *Am Heart J* 1992;124:876–82.
120. Kaku Y, Aomi S, Tomioka H, *et al.* Surgery for aortic regurgitation and aortic root dilatation in Takayasu arteritis. *Asian Cardiovasc Thorac Ann* 2015;23:901–6.
121. Nishimura S, Toubaru T, Ootaki E, *et al.* Follow-up study of aortic-valve replacement surgery in patients with Takayasu's disease complicated by aortic regurgitation. *Circ J* 2002;66:564–6.
122. Amano J, Suzuki A, Tanaka H, *et al.* Surgical treatment for annuloaortic ectasia in Takayasu arteritis. *Int J Cardiol* 1998;66(Suppl 1):S197–S202.
123. Ando M, Kosakai Y, Okita Y, *et al.* Surgical treatment for aortic regurgitation caused by Takayasu's arteritis. *J Card Surg* 1998;13:202–7.
124. Taketani T, Miyata T, Morota T, *et al.* Surgical treatment of atypical aortic coarctation complicating Takayasu's arteritis--experience with 33 cases over 44 years. *J Vasc Surg* 2005;41:597–601.
125. Ham SW, Kumar SR, Rowe VL, *et al.* Disease progression after initial surgical intervention for Takayasu arteritis. *J Vasc Surg* 2011;54:1345–51.
126. 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.
127. 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.
128. Oliveira DS, Shinjo SK, Silva MG, *et al.* Exercise in Takayasu arteritis: effects on inflammatory and angiogenic factors and disease-related symptoms. *Arthritis Care Res* 2017;69:892–902.