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

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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.

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.

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 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) tool[5] 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, funduscopic 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 Maetani[18] 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 *et al*[22]	94	Patients with coronary disease developing between 10 and 19 years vs between 20 and 39 years at 2, 5 and 10 years.	50% at each time point vs 88% at each time point	–	High
		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)	65% vs 87% 57% vs 87% 48% vs 87%	–	

*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 carotidynia[21] (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 ESR[23] (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-18[31] 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 proinflammatory 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).[27]

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 *et al*[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 *et al*[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 *et al*[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/m^2/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 jiroveci* 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 ultrasound[54]) 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 arterialfluorodeoxyglucose (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 ≥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 *et al*[53]	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 *et al*[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 >50 mm. 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,[8390] 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 anticoagulants 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.

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