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Impact of non-immunosuppressive medical therapy on disease progression and complications of Takayasu arteritis: A narrative review

Riccardo Terribili, Edoardo Conticini *, Silvia Grazzini, Luca Cantarini, Bruno Frediani

Department of Rheumatology, Siena University Hospital, Viale Mario Bracci 16, 53100 Siena (SI), Italy

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ABSTRACT

Takayasu's arteritis is a rare large vessel vasculitis typically affecting young Asian women. It causes inflammation of the aorta and its major branches, leading to stenosis and aneurysmal dilations, and increasing cardiovascular morbidity due to accelerated atherosclerosis. Although glucocorticoids are effective for acute disease control and preliminary data on immunosuppressive drugs are promising, standardized treatment protocols are lacking. The use of prophylactic treatments with antihypertensives, antiplatelets, anticoagulants, and lipid-lowering drugs to prevent thrombotic and ischemic complications remains debated. This study reviews the evidence on the effectiveness of non-immunosuppressive medical therapy in Takayasu's arteritis. A search of the PubMed database identified eleven studies involving 204 patients. Antiplatelets: data on 68 patients were mixed, in fact low-dose aspirin did not prevent major cardiovascular events in 36 patients, but higher doses reduced ischemic complications in 24 patients. Anticoagulants: no data on new oral anticoagulants were available, and vitamin K antagonists in 9 patients did not alter cardiovascular complications. Antihypertensives: ACE-inhibitors controlled blood pressure in patients with renovascular hypertension but increased the risk of acute renal function decline, while β-blockers reduced the symptoms and the progression of myocardial hypertrophy in patients with heart failure and aortic regurgitation. Statins: data from two cohorts showed that while statins reduced the recurrence rate of arteritis in 30 patients, they did not affect recurrence rates or cardiovascular complications in 13 patients. Overall, current evidence, although not definitive, supports the use of non-immunosuppressive medical treatments to prevent long-term complications and damage in Takayasu's arteritis, considering the disease's pathophysiological mechanisms and increased cardiovascular risk. Further research is strongly encouraged.

1. Introduction

Takayasu arteritis (TAK) is a Large Vessel Vasculitis (LVV) characterized by the inflammatory involvement of the aorta and its main branches (aortic arch, carotid artery, subclavian artery, abdominal aorta, renal artery but pulmonary arteries and coronaries too).

Its global incidence rate has been reported to be 1.11 per million person-years [1], with the highest prevalence historically observed in Japan. Young females (aged between 20 and 30 years) are typically affected [2].

Clinical presentation usually involves an acute inflammatory phase dominated by symptoms like fever, malaise, and weight loss, followed by a chronic course in which the gradual stenosis/occlusion as well as the thrombotic obliteration or the aneurysmal dilation of the involved vessels lead to a range of complications including secondary hypertension, retinopathy, cerebrovascular events, myocardial infarction, and aortic regurgitation [3]. In fact, inflammation extends from the outer to the inner membrane with marked intimal proliferation and degeneration of the elastic fibers of the media [3].

Although the etiology of TAK remains poorly understood, a combination of genetic, environmental (e.g., infections) and autoimmune factors is believed to ultimately trigger monocyte and lymphocyte activation with subsequent necrotizing granulomatous infiltration of vessels' wall [3].

Currently, the treatment of TAK relies mostly on the use of immunosuppressive drugs, namely glucocorticoids and conventional/biologic Disease Modifying Antirheumatic Drugs (c/bDMARDs) which have proven quite effective in controlling symptoms and slowing disease progression [4], although conclusive and substantial evidence is still lacking.

Interestingly, accelerated atherosclerosis has been documented in TAK and the incidence of carotid atherosclerotic plaques in TAK patients

* Corresponding author.
E-mail address: conticini.edoardo@gmail.com (E. Conticini).

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was found to be higher than in healthy controls [5]. Previous works have outlined that traditional risk factors such as age, dyslipidemia, smoking, etc. are closely related to TAK involvement in coronary artery disease and that inflammation is not the only mechanism of TAK patients involving coronary artery disease (e.g., vascular calcification could also be related to age and the use of glucocorticoids, GCs) [6]; moreover, inflammatory activity in TAK patients is extensive but not necessarily active in the clinical manifestations and while in the clinical disease inactive stage, the vascular disease may still progress [6].

Considering these findings, the use of classes of drugs addressing the major cardiovascular risk factors in patients with TAK would appear reasonable. In this regard, current evidence is however scarce. The 2021 ACR Guidelines for the Management of Giant Cell Arteritis and Takayasu Arteritis conditionally recommend adding aspirin or another antiplatelet therapy for patients with active TAK and critical cranial or vertebrobasilar involvement [7], while 2018 EULAR recommendations suggest using antiplatelet agents based on individual evaluation [8].

The objective of this review is therefore to describe the current knowledge and evidence on non-immunosuppressive therapies in the management of TAK, in order to determine whether they could represent a valuable tool in decreasing disease burden and complications.

A literature review from the electronic database was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations to generate research-based evidence. However, due to the limited availability of appropriate studies, we were compelled to conduct a narrative review instead.

2. Results

Searching PubMed electronic database and screening the results, 11 studies, for a total of 204 patients, were included (Fig. 1). Three papers came from a retrospective analysis of pre-existing cohorts, while one single study was prospectively and longitudinally conducted. The remaining ones were case reports or small case series. Patients' characteristics, design of the studies and main outcomes are summarized in **Table S1**.

2.1. Antiplatelets

Three studies reported the use of antiplatelet agents (aspirin and clopidogrel) in a total of 68 patients. Laurent et al. and De Souza et al. conducted two retrospective studies in which respectively 36 patients and 29 patients received aspirin, but conflicting findings were reported. While low dose aspirin seemed substantially ineffective in preventing vascular complications) [9], a higher dosage (200 mg/daily) led to a reduced incidence of ischemic events) [10]; nevertheless, such a dosage was associated to the occurrence of bleeding in almost 10 % of patients. Similarly, a double treatment (ASA and clopidogrel) resulted effective in two patients with severe, symptomatic, coronary arterial ostial narrowing [11]. No data are available for antiplatelets other than ASA, as only one patient was treated with ticlopidine, and the outcome was not specifically mentioned.

2.2. Anticoagulants

Vitamin K antagonists (warfarin and acenocumarol) were employed in 9 patients without proving efficacy in reducing cardiovascular complications and causing 1 episode of bleeding [9,10].No data have been published yet for oral anticoagulants.

2.3. Anti-hypertensive agents

The use of anti-hypertensive agents has been extensively evaluated in the papers included in this review, but the experience is restricted to ACE-inhibitors (captopril and enalapril) and β-blockers (metoprolol, acebutolol, celiprolol and arotinolol), the first accounting for more than half of the prescriptions. In terms of choice of the treatment, anti-hypertensive drugs were prescribed in patients who already suffered from hypertension and/or presented unequivocal signs or symptoms of organ damage, such as renal insufficiency due to renal artery stenosis) [12–17], or aortic regurgitation) [18]. In the first case, ACE-inhibitors were preferred, while in the latter β-blockers halted the progression of left ventricular hypertrophy.

2.4. Statins

Only two papers (Laurent, Kwon) evaluated the efficacy of statins in preventing disease relapse in TAK, displaying opposing findings. While in the first paper, burdened by a lower numerosity, the co-administration of statins and antiplatelets and/or anti-hypertensive agents did not positively affect the outcome (13 patients) [9], in the second one, comparing treated and untreated patients, statins were

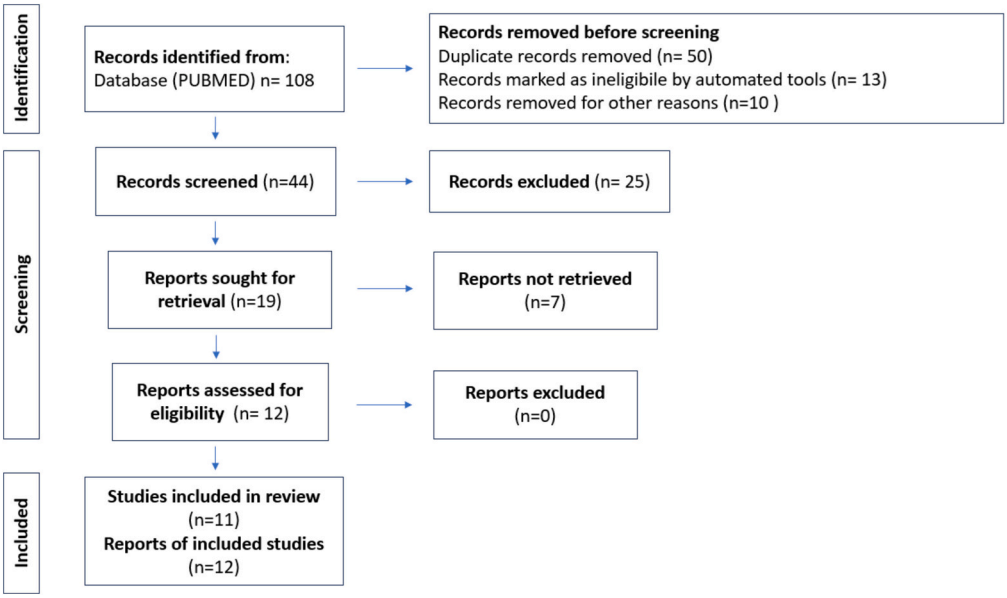

Fig. 1. Flowchart of records screening.

associated to a lower relapse rate (40 patients) [19].

2.5. Tadalafil

The use of anti-phosphodiesterase 5 has been evaluated only in one paper conducted in vitro. Tadalafil, administered in association with tacrolimus in peripheral blood mononuclear cells, proved to reduce the levels of several inflammatory cytokines and lymphocytes, particularly those, such as Th17, involved in the development of fibrosis [20].

3. Discussion

In our review, which is the first one specifically addressing the question whether non-immunosuppressive drugs should be employed in TAK, interesting, but conflicting data arose. Hypertension is one of the most frequent and characteristic features of TAK, with an estimated prevalence of 33–83 % among patients, according to the available data from large cohorts [21]. Moreover, it is regarded to represent a crucial drive for the development of cardiovascular complications, heavily affecting the morbidity and mortality of this pathological condition. Interestingly, although crucial for the induction of remission of the disease, and effective in reversing arterial stenosis, with beneficial effect on blood pressure [22], steroid treatment likely poses the threat to favor and maintain a hypertensive state, making the handling of this complication even more challenging.

More in detail, the causes of hypertension in TAK are attributable to the narrowing of the lumen of the vessels (due to acute and chronic inflammation and subsequent endothelial disfunction), loss of elasticity, and reduction of baroreflex sensitivity [23]. In particular, renovascular hypertension, caused by the stenosis of renal arteries with increased activation of the Renin-Angiotensin-Aldosterone System (RAAS) represents the most common complication in TAK [3,9,24].

ACE inhibitors, particularly captopril, are highly effective in managing refractory hypertension by inhibiting RAAS but must be used with caution in cases of bilateral stenosis or single kidney due to the risk of acute renal failure [14,15]. Similarly, caution should be exercised also in patients with descending thoracic aorta or suprarenal abdominal aorta involvement; in this setting, in which renal hypoperfusion mimics a bilateral artery stenosis, the administration of ACE-inhibitors may be associated with an abrupt decrease in GFR [25].

Moreover, ACE-inhibitors also show potential in modulating nitric oxide metabolism, offering intriguing insights on the possibility to exploit their indirect antiproliferative and antimitogenic activity to halt arterial narrowing [26] [26].

In TAK systemic hypertension is additionally reported to be associated with aortic regurgitation and cardiac hypertrophy, ultimately leading to progressive hearth failure [27,28]. Although their known negative inotropic, chronotropic and dromotropic effects, β-blockers have been shown to be effective in slowing and even reversing left ventricular hypertrophy in TAK patients with refractory/severe hypertension complicated by moderate or severe aortic regurgitation, with overall improvement of the clinical status [18].

Additionally, TAK patients display elevated thrombotic markers, including TXB2 and platelet activation factors, indicating an active thrombotic system even in inactive disease stages [29,30]. Indeed, Akazawa et al. observed that plasma levels of platelet factor 4 (PF4) and β-thromboglobulin (β-TG) (markers for platelet activation), and D-dimer (marker of fibrinolysis) were higher in patients with TAK indicating an activated thrombotic system, with no correlation with active or inactive inflammation and in the absence of significant endothelial injury [31].

Furthermore, atherosclerosis is extensively documented in TAK patients [32,33]. Atherosclerosis is also common in TAK, with both traditional risk factors and disease-related inflammation contributing to its development [34]. Additionally, neutrophil-derived myeloperoxidase and its oxidants [35], T cells and autoantibodies such as anti-endothelial cell antibodies and anti-cardiolipin antibodies are known to contribute to the genesis of atherosclerosis in vasculitis [36–38]. In patients with systemic vasculitis, HDL cholesterol levels are reduced, and pro-inflammatory HDL is often observed, especially during corticosteroid therapy, which also raises total, LDL, and HDL cholesterol levels. [39]. Lastly, it has been observed that total cholesterol, LDL cholesterol and HDL cholesterol all increase during corticosteroid therapy [40], and that pro-inflammatory HDL is increased during prednisolone therapy of >7.5 mg day [39].

These findings suggest that antiplatelet agents and statins could help lower thrombotic risk and prevent cardiovascular complications in TAK.

In this regard, Numano et al. evaluated the effect of the administration of 40 or 80 mg of aspirin in patients with TAK and increased levels of mean plasma levels of TXB2 and ADP-induced platelet aggregation but normal CRP and ESR, showing a significant reduction in TBX2 levels with the 80 mg regimen, thus demonstrating a preventive effect against the aggregation of platelets that have just passed along a rough-surfaced arterial wall [41].

On the other hand, statins have proved to increase the activity of the enzyme paraoxonase [42], whose low activity has been found in patients with vasculitis [43], and, more importantly, has been linked to the HDL proinflammatory phenotype [44]. Moreover, Atorvastatin has displayed immunomodulatory properties, especially in terms of Th1/Th2 imbalance regulation and minimization of proinflammatory cytokines [45–47].

However, studies on aspirin and statins in TAK have yielded mixed results. De Souza et al. found a protective effect of 200 mg aspirin [10], while Laurent et al. did not confirm these results [9]. Similarly, they did not find a reduced risk of disease relapse in patients receiving statins, while Kwon et al. outlined the efficacy of statins in reducing relapse rate after achieving remission [19]; details on the type of statin administered were not given in both studies.

The variation in aspirin's effects could be due to dosage differences, as Numano et al. found 80 mg to be effective.

Aside from the evidence about efficacy, it must be underlined how patients receiving higher dosage of aspirin tended to report a greater risk of bleeding, and, even if not univocal, case studies and retrospective analysis suggested an association between the use of statin and an increased risk of developing and/or flaring up of autoimmune diseases [48–52].

Data on anticoagulants in TAK are limited, but a small study showed no significant effect on ischemic events, though bleeding complications were reported [10].

These findings suggest platelet activation plays a significant role in TAK-related thrombosis, while the coagulation cascade is less involved.

TAK is strongly associated with accelerated atherosclerosis and cardiovascular complications, with an increased risk of stroke and of myocardial infarction [53]. Moreover, a cohort study investigating the relationship between TAK and ischemic heart disease reported that these patients show a higher prevalence of ischemic heart disease, and a lower 15-years survival rate compared to control group [54], while a multicenter study of 318 patients showed that 50 % of patients with TAK will relapse and experience a vascular complication <10 years from diagnosis [55]. Coronary artery calcification (CAC) is common in TAK, particularly in patients on glucocorticoids and statins [56,57]. However, studies have reported that statin use is linked to an increased rate of conversion from coronary atherosclerosis to high-density calcium, and that statins' effect of reduction of the progression of atherosclerotic plaques is also related to a change in the composition and micro-architecture of the plaque itself, possibly through an increase of micro-calcium deposits [58].

Lastly, there is evidence of a higher prevalence of conventional risk factors for atherosclerotic coronary disease in patients with TAK [6] and both inflammation and traditional factors likely drive coronary artery disease progression. However, it remains challenging to assess their relative impact, as hypercoagulability in TAK is only partially linked to inflammation, and endothelial injury is minimal compared to other

vasculitis. Despite efforts, reliable cardiovascular predictor scores for rheumatic patients are still unavailable.

4. Conclusions

To our knowledge, this is the first paper to comprehensively review the available scientific literature regarding the suitability and efficacy of non-immunosuppressive medical treatment in TAK. Several limitations were encountered, mostly due to the rarity of the disease and consequent lack of prospective interventional studies. The main source of evidence is indeed represented by retrospective analysis and isolated case series or case reports, with heterogeneous and scarcely comparable outcomes and forms of intervention. However, data seem to support the use of antihypertensives, antiplatelet agents and statins to achieve better control of symptoms (ACE-inhibitors for renovascular hypertension and β-blockers in moderate-severe aortic regurgitation) and improve cardiovascular outcomes over time, with uncertain effects on the reduction of disease relapse. Nonetheless, immunosuppressive treatment plays a decisive role as well in the management of cardiovascular risk in TAK patients, since aside from controlling acute and chronic inflammation and reducing damage accrual, it can both positively (eg. metothrexate, anti-TNF agents, tocilizumab etc.… [59,60]) and negatively (GC) affect the development of cardiovascular disease. In this respect, the early employment of GC-sparing agents should be pursued, if not contraindicated.

In conclusion, until further evidence would clarify the peculiar etiopathogenesis of cardiovascular disease in TAK, and more randomized clinical trials are available, medical non immunosuppressive treatment in TAK patients should be individually evaluated based on disease presentation and traditional cardiovascular risk factors. Indeed, a more precise identification of prognostic factors predicting disease complications as well as the development of adjusted scores for cardiovascular risk in vasculitis would represent valuable tools for the development of an effective targeted treatment.

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Declaration of competing interest

None.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2024.103656.

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