Anti-cytokine treatment for Takayasu arteritis: State of the art

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Takayasu arteritis (TA) is a rare and idiopathic large-vessel arteritis typically affecting young women which has important morbidity and mortality. There are no animal models of TA and pathogenesis is still mysterious. Clinical assessment lacks accurate activity indexes and is based on the integration of clinical, laboratory and radiological data. TA rarity has hampered randomized clinical trials and the achievement of high-quality evidence to guide clinical activity. Prevention of vascular progression, with progressive vessel wall remodelling and hyperplasia, is the main therapeutic goal. Medical therapy remains the mainstay of management and comprises traditional immunosuppressive agents and anti-inflammatory drugs, such as steroids and blockers of pivotal cytokines, TNF-\alpha and IL-6. These strategies however only partially limit vascular progression, indicating that local molecular events are involved. Here we discuss recent data suggesting that selected cellular components of TA lesions should be evaluated as novel therapeutic targets.

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Takayasu arteritis (TA) is an idiopathic inflammatory disease, typically affecting young women which has important morbidity and mortality (1-8). Although TA is a systemic disease, inflammation primarily localizes in the large arteries, such as the aorta, the pulmonary artery and their major branches (7,9). Traditionally, the TA course is subdivided into the early, active phase and the late, chronic phase (10). Although the active phase can be mono- or oligo-phasic, a chronic-relapsing course is more common, needing long-term treatment (1,3,7).

The outcome of the deregulated inflammatory process can be an irreversible fibrosis of the vessel wall. On occasion, vasculitis can result in aneurism formation secondary to the action of various enzymes involved in extracellular matrix remodelling, such as metalloproteinases. Although aneurysms are reported in about 10-25\% of patients, stenotic or occlusive lesions occur in more than 90\% (1,5,7,11-14). In addition to sequelae associated with cerebral, organ and limb ischemia and to expanding aneurysms, patients develop arterial hypertension, accelerated atherosclerosis and heart failure.

TA is a rare and truly orphan disease: ample areas of TA pathogenesis and disease activity assessment are still poorly known. There are no animal models of the disease. Studying TA is further complicated by difficulties in obtaining tissues from living patients. Histology reveals focal panarteritis with macrophages, lymphocytes and dendritic cells, frequently in a granulomatous organization (15). The local production of growth factors, including platelet-derived growth-factor (PDGF) and vascular endothelial growth factor (VEGF), drives local vessel wall changes responsible for arterial thickening and progressive lumen narrowing (16).

In the absence of accurate markers, activity definition is based on the integration of clinical, laboratory and radiological data and it is frequently established \textit{a posteriori} on an already-occurring progression of vascular involvement as assessed by radiologic or clinical evaluation. To date, our capacity to identify the processes undelaying vascular progression is very poor ((7) and unpublished data).

TA rarity has prevented controlled comparative clinical trials. Accordingly, the evidence to guide clinical management is poor (17) and no definitive
treatment advice can be given as to dosing, duration and choice of therapeutic agents. Clinical or laboratory systemic inflammatory response is variably associated with disease activity and thus it cannot be used as a reliable therapeutic target. Vascular complications are the events that most clearly impinge on the clinical outcome (5). Therefore we believe that the main therapeutic goal in TA is prevention of vascular progression through control of vascular inflammation and remodelling. Accordingly, vascular imaging is crucial for monitoring TA course. There is no single imaging modality that can provide all the information required and each method has distinct and complementary roles in monitoring disease activity (18).

TA treatment is based on medical and operative (endovascular or surgical) therapies (19). Medical therapy is the cornerstone of early, active TA and it is primarily based on high-dose corticosteroids (19,20). Unfortunately, 55-90% of patients relapse when corticosteroids are tapered and need to enhance steroid and immunosuppressive treatment (1,4,7,21,22).

The addition of immunosuppressive agents (methotrexate, azathioprine, mycophenolate mofetil and leflunomide) often allows better disease control and further steroid reduction in steroid-resistant or -dependent patients. Nonetheless, clinical relapses and progression of vascular involvement remain frequent (19). Patients with uncontrolled disease with immunosuppressive agents can benefit from biologic therapy. Tumor Necrosis Factor-α (TNF)-inhibitors are the most widely studied biologic agents in TA. TNF is involved in granuloma formation and blood levels of TNF are increased in TA patients (23). In five major observational uncontrolled cohorts, TNF-inhibitors were studied in overall 90 refractory TA patients (24-28). Complete or partial response was observed in 85-90% of patients, with a relapse rate of 33-60%. Four studies documented radiological follow-up, although with different modalities, and new lesions were observed in 16-33% of patients. Dose escalation of TNF-inhibitors was often required to maintain remission (29). TNF-inhibitors control TA without curing the disease: disease relapsed in 13 of the overall 14 patients with suspended biologic treatment after longstanding-remission (24-26). A satisfactory response was observed after resuming TNF-blockers.

Recently, interleukin-6 (IL-6) has been assessed as a therapeutic target for TA. IL-6 is a pleiotropic cytokine with local and systemic actions. IL-6 influences the function of many cell types present in TA arterial lesions: IL-6 is important for B- and T-lymphocyte differentiation, generation of Th17 cells, fibroblast proliferation and hepatic synthesis of acute-phase proteins, including C-reactive protein (CRP) (30). IL-6 is expressed in TA aortic lesions and serum IL-6 levels are elevated in TA, particularly during active phases (23,31,32). Very preliminary experience proposed that tocilizumab, a humanized anti-IL6 receptor antibody, could be another option for refractory TA (33-38). Very recently, a meta-analysis observed a steroid-sparing activity of tocilizumab with a good clinical and laboratory response (39). Even if arterial 18F-fluorodeoxyglucose (18F-FDG) uptake at PET examination was reduced after tocilizumab therapy, radiological activity did not apparently significantly decrease (39). Tocilizumab was effective in several patients refractory to TNF-inhibitors and relapses were frequent after its discontinuation, needing long-term maintenance therapy. Major limitations in this work are the heterogeneity in radiological follow-up between different studies and a median follow-up of tocilizumab after nine months, which is quite short considering that TA frequently has a chronic-relapsing course.

After this meta-analysis, three unicentric cohorts of TA patients treated with tocilizumab were published: Goel et al. reported that six of ten patients treated with tocilizumab for six months remained radiologically stable as evaluated by angiography or Doppler ultrasonography (40). Nekaoka et al. reported four patients (two of which previously received only steroids) on tocilizumab therapy for more than two years followed with both Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) (41). They observed imaging stabilization in two patients and improvement in the other two. Interestingly, serum IL-6 levels initially increased and then gradually were reduced concordantly with improvement of arterial thickened lesions, suggesting progressive reduction of IL-6 production.

We recently reported our experience with seven refractory patients treated with tocilizumab for a median of 14 months (42). All patients were followed with regular high-resolution ultrasonography and MRI. Each arterial lesion was assessed individually at radiological follow-up. Three out of our seven patients had a complete response and imaging evidence of stabilization or improvement of all arterial lesions. However, we had big difficulties in assessing TA activity, because tocilizumab causes normalization of acute-phase markers, such as CRP and erythrocyte sedimentation velocity (ESR) and resolution of systemic inflammatory symptoms (fever and malaise). This might not necessarily reflect an effective action of the agent on the actual pathway responsible for vessel progression, but only interference with the systemic pleiotropic function of the cytokine.

This implies that inflammatory reactants might be biased when assessing activity during tocilizumab therapy. Similarly, the accuracy of disease activity indices, such as the National Institutes of Health (NIH) criteria or the Indian Takayasu Activity Score (ITAS) may be compromised. Regular morphologic vascular imaging with MRI, CT and Doppler ultrasonography is thus fundamental for assessment of response and
TA activity using tocilizumab (42,43). If functional imaging (and \(^1^8\)F-FDG-PET in particular) can overcome this problem and allow identification of progression is still an open issue. Similarly, it is unknown if therapy with tocilizumab or other biological agents influences the accuracy of functional imaging. We feel that these points should receive greater attention before relying on functional imaging for clinical decisions.

Our study also raises questions about the mechanism of vascular progression, which we observed in 4/7 patients despite adequate therapy targeting the pivotal proinflammatory pathway of IL-6 and in the absence of systemic inflammatory reaction. Probably other local inflammatory pathways cooperate in the process. Locally-produced inflammatory molecules whose generation is independent of IL-6, such as pentraxin-3 (a long pentraxin produced directly within the sites of arterial inflammation), have indeed been shown to detect TA activity other than ESR and CRP (44). In addition to secreted molecules such as cytokines, also infiltrating leukocytes and resident cells likely represent important factors of this local inflammatory response. This cellular component may represent promising therapeutic targets for TA. Examples of this strategy are the anti-CD20 antibody rituximab and the fusion molecule abatacept. However, experience with these agents for refractory TA are still very embryonic (45).

Inflammation and damage perturb tissue homeostasis evoking responses that may lead to tissue remodelling. As such, local reparative responses are likely activated at the sites of arterial lesions. Alterations in blood flow and shear stress may further modulate arterial remodelling. Currently, arterial wall response to inflammation, damage and alteration of shear stress in TA has been a neglected issue.

Peculiar tissue remodelling responses have been advocated in the observation that operative (endovascular or surgical) therapies have worse long-term patency rates in TA than in occlusive arteriosclerotic disease (19). This constitutes the major pitfall of operative therapies in TA. Current (scarce) evidence reports that myointimal hyperplasia is the main cause of restenosis and long-term failure. Structural characteristics of TA lesions in comparison to atherosclerosis, such as longer length and lower arterial wall compliance, may result in suboptimal dilatation and in more mechanical damage due to higher inflating pressures and may partly explain the observed worse long-term results (19). However, the TA inflammatory milieu probably influences post-interventional arterial wall remodelling (8,46–49), because a lower restenosis rate is observed when vascular interventions are carried out during remission (18,50) and when post-interventional immunosuppressive therapy was added onto steroid regimens used to control disease activity (50).

These observations suggest that local arterial inflammation and arterial wall remodelling may cooperate for vascular progression and account at least partially for the inaccuracy of the systemic inflammatory markers in addressing TA activity and in the heterogeneity of response to biologic agents that block pivotal proinflammatory pathways such as TNF and IL-6. Further research is needed to clarify the pathogenesis of this still orphan and mysterious disease.

References

14. Park MC, Lee SW, Park YB, Chung NS, Lee SK. Clinical characteristics and outcomes of Takayasu's arteritis: Analysis of 108 patients using standardized criteria


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