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Topical Review

Takayasu's arteritis

Durga Prasanna Misra *, *Vir Singh Negi*

Department of Clinical Immunology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605006, India

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ABSTRACT

Takayasu's arteritis (TA) is a granulomatous large vessel vasculitis more common in India. We review recently published literature in this field over the past year. Multiple reports based on genetic data and studies in peripheral blood of patients with TA suggest perturbation of the Th17-IL17 axis in these patients, which may be amenable to targeted therapy. Abnormal pro-atherogenic lipid profiles in TA (increased LDL-C and Apo A1, decreased HDL-C and Apo-B) may drive disease process in TA. Clinically inactive TA at diagnosis has been shown to relapse and progress angiographically on follow-up. TA seems to be associated with poorer pregnancy outcomes. Recent papers on 18 fluoro-deoxyglucose positron emission tomography and contrast-enhanced magnetic resonance angiographic scoring of TA suggest the need to incorporate these techniques into clinical assessment tools to delineate the actual extent of vascular involvement in TA. Recent advances in therapeutics indicate that leflunomide may be an effective disease-modifying agent in TA, whereas a large retrospective French cohort suggests relatively safety and efficacy of biologic agents targeting tumour necrosis factor alpha or interleukin-6 in patients with TA.

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1. Introduction

Takayasu's arteritis (TA) is a large vessel vasculitis (LVV) more common in India than the West. We shall review recent advances in TA.

2. Search strategy

The strategy for writing narrative reviews advocated by Gasparyan et al.[1] was adopted. The Scopus database (which also includes articles from Medline) was searched using the search words ''Takayasu's arteritis'' or ''Takayasu arteritis'',

* *Corresponding author.*
E-mail address: durgapmisra@gmail.com (D.P. Misra).

Abbreviations: Apo, apolipoprotein; CRP, serum C-reactive protein; ESR, erythrocyte sedimentation rate; FDG-PET, 18-fluorodeoxyglucose positron emission tomography; GCA, giant cell arteritis; GWAS, genome-wide association study; HDL-C, high-density lipoprotein-cholesterol; IFN-γ, interferon gamma; IL, interleukin; ITAS2010, Indian Takayasu Clinical Activity Score; LDL-C, low-density lipoprotein-cholesterol; LILRB3, leucocyte immunoglobulin-like receptor subfamily B group 3; LVV, large vessel vasculitis; OR, Odd's ratio; PTA, percutaneous transluminal angioplasty; SNP, single nucleotide polymorphism; TA, Takayasu's arteritis; Th17 cells, T helper 17 cells; USA, United States of America; VAS, visual analog scale.

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for articles published from 2015 onwards. After screening abstracts and titles of 211 articles, 17 articles were selected for review.

3. Pathogenesis

3.1. *Role of Th17-IL-17 axis in TA- from genetics to therapeutics*

A genome-wide association study (GWAS)[2] involving 559 Turkish patients and 134 European-American patients reported predisposition to TA in the presence of polymorphisms in interleukin (IL)-6 (which is pro-inflammatory and drives differentiation of naïve T helper cells towards Th17 cells), leucocyte immunoglobulin-like receptor subfamily B group 3 (which dampens responses induced by MHC class I molecules) and a gene near chromosome 21p22. Matsumura et al.[3] found that patients expressing the variant A allele of IL12B gene (SNP rs6871626) had a greater chance of developing severe TA, defined by younger age of disease onset (before 20 years), requirement for immunosuppressive agents other than glucocorticoids, or clinical or angiographic relapse (Odd's ratio – OR 1.94 for heterozygotes and 3.75 for homozygotes). IL12B encodes the common p40 subunit of IL-12 and IL-23, respectively driving the T helper (Th1) and Th17 differentiation. Two papers from France[4] and India[5] have shown increased circulating Th17 cells and serum IL-17 in patients with TA compared to healthy controls. The former study[4] showed higher levels of IL-17 expression in aortic biopsies from patients with TA. The latter study[5] also showed higher levels of serum IL-23 in patients with TA compared to healthy controls. Interestingly, while the former study[4] reported no differences in levels of Th17 cells in those patients with respect to glucocorticoid therapy, the latter[5] study reported no significant decreases in Th17 cells or serum IL-17 and IL-23 in a sub-group before and after immunosuppression (for 3 months) with steroids and methotrexate. This is in contrast to the classical findings in giant cell arteritis (GCA), wherein Th17 cells have been shown to be expanded, but responsive to glucocorticoid therapy.[6] This may suggest fundamental differences in the pathogenesis of GCA and TA, and merits further exploration. Involvement of the Th17 pathway in TA could also have translational relevance, considering a recent case series[7] of favourable responses to ustekinumab (a monoclonal antibody blocking the common p40 subunit of IL-12 and IL-23) in 3 patients with TA. Table 1 summarises these studies on Th17-IL-17 axis in TA. Fig. 1 illustrates how the findings from these studies affect the Th17-IL-17 axis at different levels.

3.2. *Novel biomarkers*

Chakravarti et al.[8] identified a novel antigen, 14-3-3, in the aortic wall, against which antibodies were detected in the sera of patients with LVV (including TA) to a greater extent than in healthy or disease controls. Wang et al.[9] found increased levels of apolipoprotein (Apo) B and lower ApoA1 and high-density lipoprotein-cholesterol (HDL-C) in patients with TA. The ratio of ApoB:ApoA1 predicted higher disease activity and higher levels of circulating C-reactive protein (CRP). Another Indian study

Table 1 – Summary of recent studies on perturbations of Th17-IL-17 axis in TA.

Reference number	Country of origin	Type of study	Key results
2	Turkey, USA	GWAS	Polymorphisms in IL-6, LILRB3 and a gene on chromosome 21p22 predispose to development of TA.
3	Japan	Case–control study	Presence of variant A allele (SNP rs6871626) of IL12B gene predisposes to develop severe TA (OR 1.94 – heterozygotes; 3.75 – homozygotes).
4	France	Observational	Patients with TA have higher circulating Th17 and Th1 cells, to a greater extent in active disease. Serum derived from patients with TA stimulated production of IL-17A and IFN-γ from CD4+ lymphocytes derived from healthy controls. Patients with active TA demonstrated higher expression of IL-6, IL-17A and IFN-γ in aortic wall biopsies than those in remission. Patients on glucocorticoids did not have reduction in Th17 cytokines.
5	India	Observational	Patients with TA have increased circulating Th17 cells and serum IL-17A and IL-23. No differences were noted in sub-groups with respect to disease activity or medication intake. A sub-group of immunosupressant-naïve patients followed longitudinally over 3 months did not show differences in Th17 cells or serum IL-17A or IL-23 before or after immunosuppression with glucocorticoids and methotrexate.
7	Japan	Case series	3 patients with TA refractory to conventional immunosuppressive drugs, carrying variant allele of IL12B (SNP rs6871626), showed favourable responses to ustekinumab 45 mg on day 0 and 28. They had improvement in patient VAS in all three and significant reductions in ESR and CRP when followed upto 100 days.

CRP, serum C-reactive protein; ESR, erythrocyte sedimentation rate; GWAS, genome-wide association study; IFN-γ, interferon gamma; IL, interleukin; LILRB3, leucocyte immunoglobulin-like receptor subfamily B group 3; OR, Odd's ratio; SNP, single nucleotide polymorphism; TA, Takayasu's arteritis; Th17 cells, T helper 17 cells; USA, United States of America; VAS, visual analog scale.

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