



Is Takayasu arteritis the result of a *Mycobacterium tuberculosis* infection? The use of TNF inhibitors may be the proof-of-concept to demonstrate that this association is epiphenomenal

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Abstract

Although the association between Takayasu arteritis (TA) and latent or active *Mycobacterium tuberculosis* infection has been suggested for a long time, studies conducted in recent years are challenging this notion. Until recently, the possibility of a pathogenic relationship between TA and tuberculosis (TB) was considered a medical curiosity, but the advent of tumor necrosis factor (TNF) inhibitors as therapy for recalcitrant TA cases, as well as the widespread use of *Bacille Calmette-Guérin* (BCG) for vaccination purposes, has relocated this association as a top priority issue. In an attempt to define whether both diseases are pathogenically linked or if their association is only epiphenomenal in nature, we conduct a thorough literature search on the development of TB in patients with TA receiving TNF inhibitors. From a total of 13 studies that included 214 patients, the occurrence of TB was observed only in two individuals exposed to infliximab. This frequency of 0.93% is similar to that encountered in patients with other rheumatic diseases exposed to TNF inhibitors. Finally, we propose a novel pathogenic model that could reconcile the epidemiological, clinical, and immunological evidence that links TA and TB, while providing rationality for the use of TNF inhibitors in patients with TA.

Keywords Takayasu arteritis · TNF inhibitors · Tuberculosis · Vasculitis

Introduction

Takayasu arteritis (TA) is a granulomatous vasculitis that mainly involves large- and medium- sized arteries, with a particular predilection for the aorta and its main branches. The vascular inflammatory process ends up in intimal thickening, fibrosis, and vessel stenosis, which ultimately results in organ/tissue ischemia and leads to protean clinical manifestations of the disease. In essence, TA is a chronic disorder of

childhood and early adulthood, which predominantly afflicts women and is largely circumscribed to some geographical areas such as East and South Asia, Central and South America, South Africa, and the Mediterranean basin [1]. Nowadays, the main clinical and imaging features of TA are adequately outlined [2].

Although the exact etiology of TA remains obscure, it is clear that the immune system plays a significant role in its pathogenesis and attempts to clarify it are still limited.

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Notably, a potential association between TA and latent or active *Mycobacterium tuberculosis* (*M. tuberculosis*) infection has long been suggested. Shimizu and Sano noted, for the first time, a possible link with tuberculosis (TB) in 1948, based on the presence of Langhans giant cells in the arterial samples from patients with TA, which morphologically resembled those found in TB granulomas [3]. This finding was further strengthened by the results of occlusive lesions in the arterial wall of patients with pulmonary TB, in addition to the existence of pulmonary and extrapulmonary TB foci in TA patients [4]. Apart from epidemiological evidence showing a high prevalence of TA among individuals from countries where *M. tuberculosis* is endemic, these seminal studies laid the groundwork for a thorough analysis of the potential association between both diseases [5].

Evidence linking Takayasu arteritis and tuberculosis

Indirect evidence suggesting a pathogenic connection between TA and TB has been accumulated over decades. An excellent systematic review on this topic has been recently published in Clinical Rheumatology [6]. Briefly, there are many clinical cases of adolescents and adults with TA in which an active TB infection has been demonstrated. Among these patients, the lungs have been the most frequent anatomic site of infection, although there are descriptions of extrapulmonary infections, including tuberculous lymphadenopathy, central nervous system and renal TB, in addition to Bazin's *erythema induratum* (nodular vasculitis) and other cutaneous manifestations associated with TB infection [5]. A large retrospective study conducted in China on 1105 patients with TA reported that 109 (9.9%) of them had evidence of TB infection, including 53 (48.6%) patients diagnosed with TB before the onset of TA, 23 (21.1%) with a simultaneous diagnosis of TA and TB, and 24 (22.0%) patients who developed TB after TA. Pulmonary TB was the most common site of infection, while pulmonary artery involvement and pulmonary hypertension were found most frequently in TA patients with TB infection [7].

An enhancement in humoral and cellular immune responses directed toward cell stress proteins such as the mycobacterial 65 kDa heat shock protein (HSP) and its human homolog 60 kDa HSP has been consistently found in patients with TA [8, 9]. There is also a delayed hypersensitivity to tuberculin in TA patients, with a higher frequency than that observed in their counterparts without TA, in both children and adult populations [10]. Moreover, a Mexican study evaluated the presence of *IS6110* and *HupB* genes in aortic tissue specimens from autopsies of patients with TA, pulmonary TB, or atherosclerotic aortic disease [11]. The *IS6110* sequence is shared by several members of the *M. tuberculosis* complex, and the *HupB* gene encodes a histone-like protein that can differentiate *M. tuberculosis* and *M. bovis*. In this study,

IS6110 and *HupB* sequences were detected in 70% of TA tissue samples, 82% in TB, and 32% of aortic atherosclerosis samples. Importantly, as incidental findings during necropsy, tuberculous lesions were found adjacent to the aorta or elsewhere in 48% of TA patients; additionally, 32% of individuals with atherosclerosis, which were included as negative controls, yielded positive results for the *IS6110* and *HupB* sequences. Considering the prevalence of TB in Mexico, these results are highly significant [11]. Based on these data, the authors speculated that *M. tuberculosis* could take advantage of the high concentration of oxygen in the aorta, evade the immune system, and proliferate in its wall [11]. Said otherwise, this hypothesis offers an explanation of how arteritis might be the result of a TB infection directly in the vessel wall.

If TA is the result of *M. tuberculosis* infection, either directly in the arterial wall or away from the actual location of the mycobacterium infection, is not a minor issue due to the risk of pulmonary reactivation and disseminated TB associated with the use of tumor necrosis factor (TNF) inhibitors, which are increasingly prescribed as therapy in large vessel vasculitis [12], as well as the increasing use of *Bacille Calmette-Guérin* (BCG) for vaccination purposes worldwide [5, 12]. In this regard, studies developed in recent years have begun to challenge the physiopathogenic connection between TA and TB, suggesting the association is a purely epiphenomenal matter. It has been discussed that intradermal delayed hypersensitivity tuberculin tests could be a misinterpretation of active TB infection particularly in individuals from countries where routine BCG vaccination is performed early in life, although this issue has been partially settled with the advent of functional tests known as interferon-gamma release assays (IGRA) [13]. These assays are able to identify latent and active *M. tuberculosis* infection in a highly specific manner; in this regard, a Turkish study showed that patients with TA have a similar IGRA response compared to controls (22.3% versus 22.4%) despite having a significantly higher frequency in the positivity to the tuberculin test (62.5% versus 41.4%, respectively) [14]. Likewise, studies based on molecular techniques and even on the direct demonstration of the presence of *M. tuberculosis* in aortic tissues of patients with TA also point to a lack of pathogenic association between both entities. A recent study in Brazil compared the presence of mycobacterial DNA measured by three different sequences, including the *IS6110*, the *HSP65* gene, and the 16S ribosomal RNA gene in peripheral blood from 32 TA patients and in arterial specimens from 10 patients with TA; untreated individuals with active TB and healthy blood donors were included as controls [15]. No mycobacterial nucleic acid sequences were found in blood samples from patients with TA or healthy blood donors, while the *IS6110* sequence was found in peripheral blood of 78.5% of individuals with active TB. In addition, the *IS6110* sequence was detected in the arterial sample of a single patient with arterial TB, but it could not be found in any of the tissue

samples obtained from patients with TA [15]. Similarly, a French study evaluated the presence of *M. tuberculosis* by acid-fast and auramine-fluorochrome staining, mycobacterial cultures in Lowenstein-Jensen media, and amplification of 16S ribosomal RNA in arterial specimens (aorta and carotid arteries) from 10 patients with TA undergoing surgery. Histological examination showed active TA lesions in arterial samples from five patients, but none of the diagnostic technologies used were able to detect *M. tuberculosis* in any of the arterial specimens [16].

From an epidemiological point of view, although the number of incident TB cases is slowly decreasing worldwide, the frequency of TA (or at least its detection) seems to be increasing in several countries around the world. According to the Global Tuberculosis Report 2019 (World Health Organization), an estimate of 10.0 million (range, 9.0 to 11.1 million) of people fell ill with TB in 2018, with the majority of cases occurring in the regions of Southeast Asia, Africa, and the Western Pacific [17]. The global average rate of decline in TB incidence rate was 1.6% per year in the 2000–2018 period, and 2.0% per year between 2017 and 2018 [17]. In contrast, data collected from the Korean National Health Insurance have shown a steady increase in the age-standardized prevalence of TA from 15.4 per million (95% confidence interval, 14.3 to 16.5) in 2006 to 28.9 per million (27.4 to 30.3) in 2013 [18]. Likewise, an epidemiological study conducted in Norway in the period 1999–2012 (based on a population denominator of 2.8 million) reported an unusual prevalence of 22.0 cases of TA per million, with a striking doubling of the average annual incidence rate in the second half of the study period (2008–2012) [19].

Tuberculosis reactivation in patients with Takayasu arteritis using TNF inhibitors

Reliable clinical and laboratory strategies focused on resolving whether TA and TB are pathogenically linked or if their association is only epiphenomenal in nature have not yet been developed. However, the key role that TNF plays in catalyzing tissue damage in TA, as well as in keeping the inflammatory mechanisms that limit the spread of latent *M. tuberculosis*, has been adequately established [20]. Indeed, TNF is involved in several processes including macrophage activation and recruitment of natural killer cells, granulocytes, fibroblasts, and T cells to sites of chronic inflammation, which in turn leads to the formation of granulomas, the hallmark of TA and TB [20]. In TB infection, granulomas are composed of inflammatory cells and viable *M. tuberculosis*, so its conservation is critical for the adequate containment of mycobacteria [20]. That partly explains why TNF inhibition may interfere with protective, physiological inflammatory responses mediated by TNF, causing disruption of formed granulomas and the consequent release of viable mycobacteria [21]. After

therapy with TNF inhibitors, the risk of TB is increased up to 25 times, depending on the clinical setting and the type of TNF antagonist used [20]. Most cases of TB occur shortly after the initiation of TNF inhibitors, and the reactivation of latent *M. tuberculosis* infection shows a characteristically rapid progression [20, 21]. Consequently, we speculate that reactivation and dissemination of *M. tuberculosis* from latent foci of infection in patients with TA who receive TNF inhibitors may be the proof-of-concept necessary to settle the dispute.

In order to better understand the possible pathogenic association between TA and TB, we conducted a comprehensive literature search in PubMed to identify all published studies related to the use of TNF inhibitors in patients with TA. The full text of each study was reviewed, and the occurrence of TB infection was thoroughly investigated. It should be noted that we exclude single-case reports to minimize possible perception bias. Table 1 summarizes all available studies on the subject until October 2019. A total of 13 studies were selected and reviewed, which in total included 214 patients with TA [22–34]. As expected, most of the included patients were women from geographic areas with a high incidence of TA, such as those from the Mediterranean basin or South Korea, as well as from countries with high migratory mobility, such as the USA or France. All studies had a follow-up period of at least 9 months. With the exception of golimumab, all commercially available TNF inhibitors were used, and the most commonly prescribed drug was infliximab. Notably, the occurrence of TB was observed only in two individuals exposed to TNF inhibitors, for a total frequency of 0.93%. The first case, from a retrospective series of 15 cases, corresponded to a pulmonary infection due to *M. tuberculosis* fortuitously discovered due to a cavitation of the upper right lobe in a French patient who received infliximab; TB screening before initiation of anti-TNF therapy was not performed [26]. The second case, from a retrospective series that included 49 patients studied by the same group of researchers, corresponded to a pulmonary tuberculous reactivation associated with the use of infliximab [30].

The development of TB in approximately 1% of patients with TA after the use of TNF inhibitors is similar to that observed in other rheumatic diseases. A recently published systematic review analyzed the incidence of TB in patients receiving TNF inhibitors for various rheumatic conditions, including 52 observational studies. A total of 947 cases of TB were documented, with a cumulative incidence of 9.62 cases per 1000 exposed patients [35]. Similarly, the “Brazilian Registry of Biological Therapies in Rheumatic Diseases” recently described the occurrence of 5 cases of TB among 942 patients with RA who received anti-TNF therapies (infliximab, adalimumab, and etanercept), which corresponds to a frequency of 0.53% [36]. Likewise, the “Adalimumab Pregnancy Exposure Registry”, an observational cohort study conducted in North America, described the occurrence of 63

Table 1 Main studies on the use of tumor necrosis factor (TNF) inhibitors in Takayasu arteritis and the occurrence of tuberculosis (TB)

Cases (female)/study design	Age/disease duration	Country (ethnicity)	TNF inhibitor	Follow-up	TB development	Reference
15 (95%) prospective	26 y (17–48 y) / 6 y (2–16 y)	USA (Caucasian and Indian)	INF, ETN	21.7 m (3–51 m)	None	Hoffman et al., 2004 [22]
25 (88%) retrospective	35 y (15–64 y) / 116 m (39–344 m)	USA (Caucasian, Asian and Hispanic)	INF, ETN	28 m (2–84 m)	None	Molloy et al., 2008 [23]
20 (95%) retrospective	Mean 33 ± 10.2 y / 15.9 m (IQR, 2–37 m)	USA (Caucasian, Asian, African, American and Native American)	INF, ETN, ADA	54 m (IQR, 34–82 m)	None	Schmidt et al., 2012 [24]
5 (60%) case series	51 y (19–58 y) / 3 y (6 w–13 y)	France (Caucasian, African, Arabic)	INF	9 m (3–72 m)	None	Comarmond et al., 2012 [25]
15 (87%) retrospective	41 y (17–61 y) / 37 m (6–365 m)	France	INF	43 m (4–71 m)	1 case (pulmonary)	Mekinian et al., 2012 [26]
15 (NA) retrospective	28 y (16–65 y) / 12 m (0–96 m)	Italy	INF	74 m (10–162 m)	None	Quartuccio et al., 2012 [27]
9 (100%) case series	29 y (19–37 y) / 74 m (30–168 m)	Russia	INF, ADA	36 m (16–112 m)	None	Novikov et al., 2013 [28]
5 (80%) prospective	36 y (34–40 y) / NA	Italy	INF, ADA	34 m	None	Serra et al., 2014 [29]
49 (80%) retrospective	42 y (20–55 y) / NA	France (Caucasian, African, other)	INF, ETN, ADA	24 m (2–95 m)	1 case (pulmonary reactivation)	Mekinian et al., 2015 [30]
32 (~90%) population-based cohort	NA	Norway (Caucasian, Asian, African)	INF, ETN, ADA	NA	None	Gudbrandsson et al., 2017 [31]
11 (100%) case series	Mean 46.8 ± 13.5 y / Mean 4.4 ± 5.2 y	South Korea	INF biosimilar CT-P13	54 w	None	Park et al., 2018 [32]
10 (100%) retrospective	31 y (18–35 y) / 12 y (3–23.5 y)	Russia (Caucasian, Turkish)	CZP	10 m (3–28 m)	None	Novikov et al., 2018 [33]
3 (100%) case series	42 y (33–46 y) / 9 y (6–10 y)	Turkey	INF, CZP	12 m (8–26 m)	None	Ataş et al., 2019 [34]

Data are presented as median (minimum to maximum range) unless otherwise specified

TNF tumor necrosis factor, IFN infliximab, ETN etanercept, ADA adalimumab, CZP certolizumab pegol, y years, m months, w weeks, IQR interquartile range, NA not available

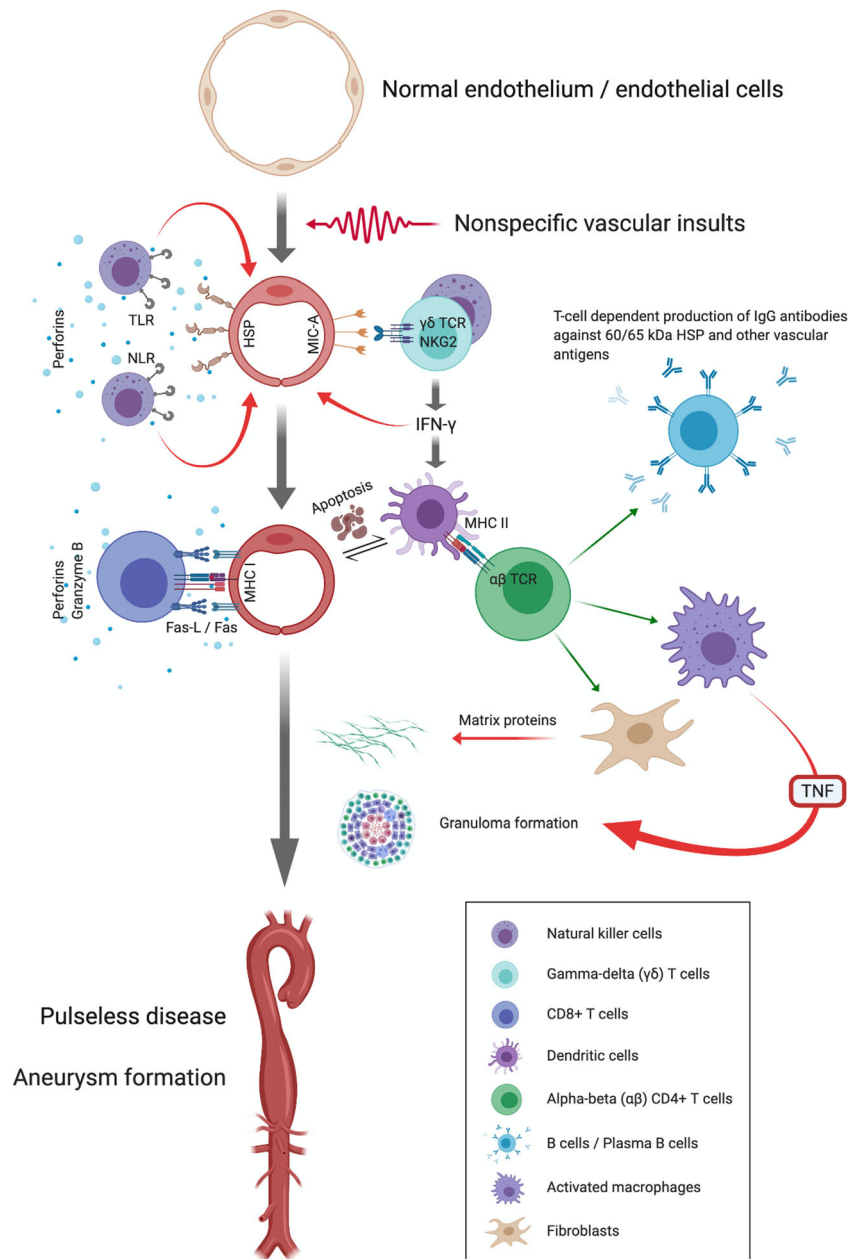
cases of active TB in a cohort of 15,152 women with RA (frequency of 0.41%) in treatment with adalimumab during pregnancy [37]. In adult patients with moderate to severe chronic plaque psoriasis, the use of adalimumab was associated with the development of tuberculosis in 16 of 3723 individuals (frequency of 0.42%) exposed to the drug [38]. Also, in a Portuguese cohort of 765 individuals with different inflammatory diseases, including rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel disease, 25 patients (3.26%) had TB associated with the use of TNF inhibitors for a period of observation covering from 2001 to 2012 [39]. Finally, the appearance of active TB was observed in 16 individuals undergoing TNF inhibition (infliximab and

adalimumab), out of a total of 376 Korean patients with inflammatory bowel disease [40]. It is worth noting a higher incidence of TB among patients exposed to TNF inhibitors from countries in South America and Asia compared to those from North America and Europe [35].

Toward a new model that could unify the evidence linking Takayasu arteritis with tuberculosis

Acknowledging that studies conducted in recent years consistently show the absence of mycobacteria directly in arterial tissue, as well as the absence of latent infection with *M. tuberculosis* through highly specific ex vivo functional

Fig. 1 A novel model on the pathogenesis of Takayasu arteritis that may explain the alleged association with *Mycobacterium tuberculosis* infection



tests, we have already formulated a hypothesis about a model of pathogenesis based on the loss of self-tolerance against stress-induced cell molecules, with the innate immune system as the main culprit in the onset, amplification and progression of the inflammatory response observed in TA [5, 41]. This novel pathogenic model seems to unify the fundamental epidemiological, inflammatory, and immunogenic evidence that links TA and TB. This model has already been published in extended format [5], but is briefly presented in the following paragraphs (Fig. 1):

- At an early non-self-reactive stage, nonspecific insults such as infections, shear stress, imbalance of the redox environment, and other inflammatory stimuli could induce endoplasmic reticulum stress in vascular endothelial cells, which in turn would lead to increased expression of stress-induced proteins such as HSP and unfolded proteins. These “warning of danger” molecules could be detected by innate cytotoxic cells (i.e., natural killer cells and $\gamma\delta$ T cells) through Toll-like and NOD-like receptors. After recognition, cytotoxic cells would be activated, promoting apoptosis of vascular endothelial cells and thereby increasing the stress on the cellular environment.
- In a subsequent innate self-reactive stage, stressed vascular endothelial cells could activate transcription of the *MIC-A* gene. MIC-A molecules on the endothelium could be recognized by NKG2D receptors on infiltrating natural killer cells and oligoclonally expanded $\gamma\delta$ T cells, which in turn would result in cytolytic responses against endothelial targeted-cells expressing MIC-A molecules. The production of large amounts of interferon-gamma by infiltrating lymphocytes would enhance and amplify the expression of class II and I major histocompatibility complex (MHC) molecules. Co-expression of MHC proteins and vascular antigens (perhaps muted or misfolded self-antigens) could lead to a massive vascular homing of $\alpha\beta$ CD4+ and CD8+ T cells.
- Finally, in a self-reactive adaptive immune stage, oligoclonally expanded and self-reactive $\alpha\beta$ CD4+ T cells could boost the progression and perpetuation of the inflammatory/immune response. In genetically susceptible individuals, different T cell subsets could provide help for the switch to IgG isotype and the production of “arteritic” autoantibodies such as anti-endothelial and anti-60/65 kDa HSP antibodies. In addition, T cell subsets might modulate the expansion and effector functions of infiltrating macrophages, driving its transformation into Langhans giant cells with the consequent granuloma formation. Late in the disease course, infiltrating CD4+ and CD8+ T cells would promote the massive deposition of collagen and matrix proteins by active fibroblasts, which

would lead to arterial wall fibrosis, typical of the pulseless phase of chronic TA.

Concluding remarks

An accumulation of indirect evidence has suggested an intriguing potential association between TA and TB. Until recently, the possibility of the aforementioned association was only a matter of academic and research interest. However, the advent of cytokine-targeted therapies, particularly TNF inhibition, has placed the potential association as a matter of top priority.

Growing evidence shows that patients with TA have no greater risk of developing TB than individuals with other rheumatic diseases when they are exposed to TNF inhibitors. The absence of mycobacterial reactivation may be the proof-of-concept to confirm that the association between TA and TB is simply an epiphenomenal matter, not a causal one. Although speculative, we propose a novel pathogenic model that reconciles laboratory evidence with epidemiological and clinical information, while providing rationality for a judicious use of TNF inhibitors in TA.

Compliance with ethical standards

The manuscript does not contain clinical studies or patient data.

Disclosures None.

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