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Invited Article

Biological treatments in giant cell arteritis & Takayasu arteritis

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ABSTRACT

Giant cell arteritis (GCA) and Takayasu arteritis (TAK) are the two main large vessel vasculitides. They share some similarities regarding their clinical, radiological and histological presentations but some pathogenic processes in GCA and TAK are activated differently, thus explaining their different sensitivity to biological therapies. The treatment of GCA and TAK essentially relies on glucocorticoids. However, thanks to major progress in our understanding of their pathogenesis, the role of biological therapies in the treatment of these two vasculitides is expanding, especially in relapsing or refractory diseases. In this review, the efficacy, the safety and the limits of the main biological therapies ever tested in GCA and TAK are discussed. Briefly, anti TNF-α agents appear to be effective in treating TAK but not GCA. Recent randomized placebo-controlled trials have reported on the efficacy and safety of abatacept and mostly tocilizumab in inducing and maintaining remission of GCA. Abatacept was not effective in TAK and robust data are still lacking to draw any conclusions concerning the use of tocilizumab in TAK. Furthermore, ustekinumab appears promising in relapsing/refractory GCA whereas rituximab has been reported to be effective in only a few cases of refractory TAK patients. If a biological therapy is indicated, and in light of the data discussed in this review, the first choice would be tocilizumab in GCA and anti-TNF-α agents (mainly infliximab) in TAK.

1. Introduction

Giant cell arteritis (GCA) and Takayasu arteritis (TAK) are the two main large vessel vasculitides [1]. It has been suggested that TAK and GCA may be different phenotypes of a single disease [2–4] since they share some similarities regarding their clinical, radiological and histological presentations, both being granulomatous vasculitides involving the aorta and its major branches [1]. However, some pathogenic processes in GCA and in TAK are activated differently [5–7]. Furthermore, GCA can be distinguished from TAK by several epidemiological, clinical, arterial distribution and therapeutic features [2]. GCA occurs in people over 50 years and its incidence increases progressively after 50 years with a peak occurring between 70 and 80 years [8,9]. Women are affected two to three times more frequently than men. GCA is very rare in African, Arabic and Asian countries [10–14], whereas the highest prevalence is observed in Caucasian people, especially in Scandinavian countries and in Olmsted County, Minnesota, where the population has a similar ethnic background [15]. Assessment of GCA activity usually relies on clinical symptoms, erythrocyte sedimentation rate (ESR) and acute-phase reaction proteins – mainly C-reactive protein (CRP) and fibrinogen – which are increased in > 95% of cases and closely related to disease activity [16]. By contrast, TAK occurs in patients < 40 year old and is much rarer than GCA, accounting for 1–3 cases per million per year. In 90% of cases, patients affected by TAK are women. TAK has been described in all ethnic groups around the world but is more frequent in Asian countries and in northwest Turkey [17]. It is more challenging to assess disease activity in TAK than in GCA since TAK seems to be a more chronic and insidious disease. Particularly, a substantial number of patients with active disease have normal levels of acute phase reaction proteins and ESR. This situation has led to the proposal of scores to assess TAK activity: the National Institute of Health (NIH) criteria (or Kerr criteria) [18] and more recently the Indian Takayasu Clinical Activity Score (ITAS2010) [19].

In both diseases, glucocorticoids (GC) remain the cornerstone of treatment. They are very effective in inducing remission but relapses are common when doses are tapered. Immunosuppressive drugs,

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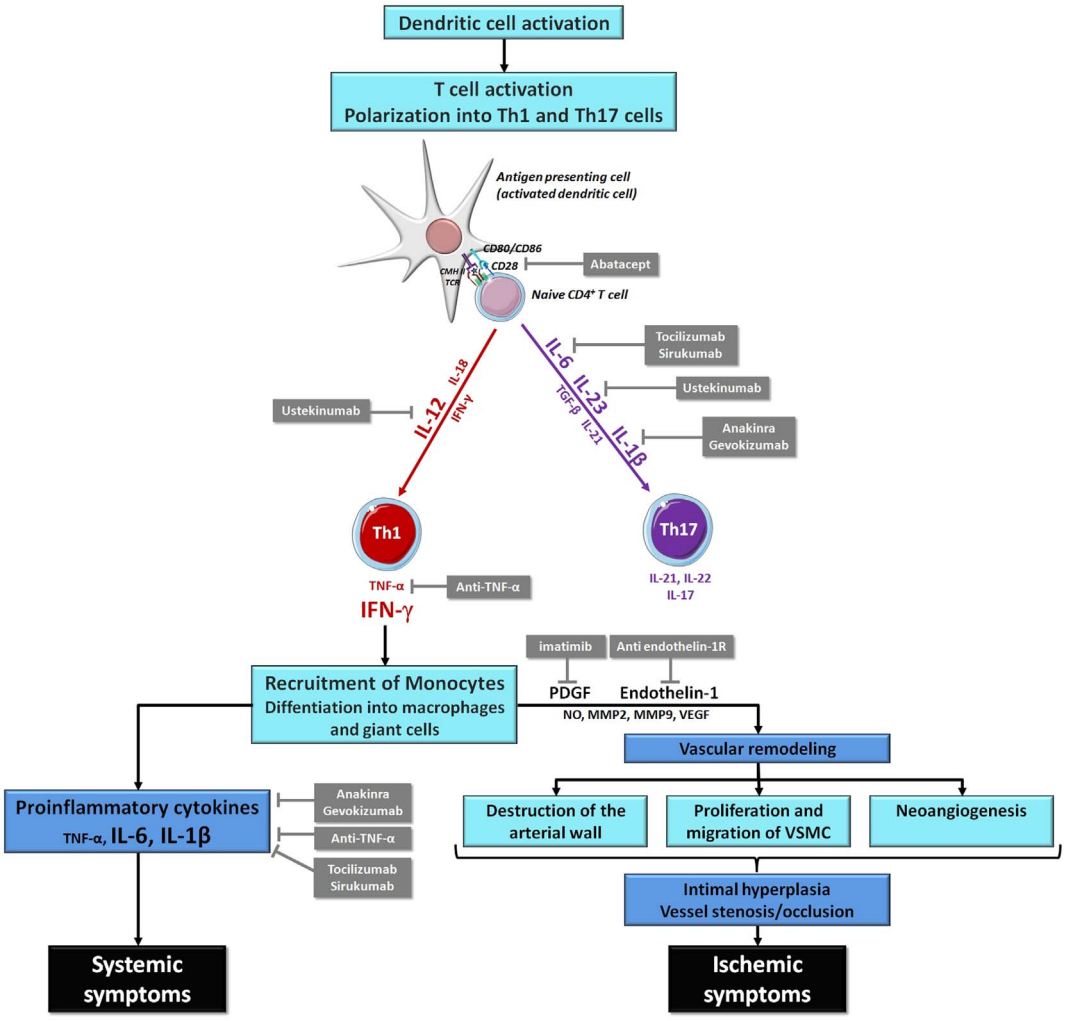

Fig. 1. Schematic pathogenesis of GCA and TAK and main targets of biological therapies. The detection of pathogen associated molecular patterns (PAMPs) or other danger signals by Toll like receptors (TLR) induce dendritic cell (DC) activation. Activated DC modify their morphology, express high levels of major histocompatibility complex class-II (MHC-II), costimulatory molecules such as CD80 and CD86, and produce chemokines such as CCL19, CCL20 and CCL21, which makes them able to recruit, activate and polarize $CD4^+$ T cells into Th1 and Th17 cells. T cell activation relies on the addition of a first signal resulting from the interaction of the T cell receptor (TCR) and MHC-II/peptide complex, the latter being presented by antigen presenting cells (APC) which are mainly DC. Then, the second signal depends on other molecular interactions between APC and T cells, in particular through an interaction between CD80 and CD86, which are expressed by APC, and CD28 which is expressed by T cells. This second signal is blocked by abatacept, a fusion protein composed of the crystallizable fragment of a human IgG_1 and the extracellular domain of CTLA-4, whose affinity for CD80/86 is higher than that for CD28. After their activation, T cells proliferate and are polarized in different subsets of T helper (Th) cells depending on the cytokines produced in their microenvironment. Th1 and Th17 cells are the two main pathogenic subsets involved in GCA and TAK, whereas a quantitative deficit in Treg is observed. Tocilizumab and sirukumab block the IL-6 pathway, thus inhibiting Th17 polarization. Furthermore, tocilizumab has been shown to restore the Treg compartment. By blocking IL-1β effects, anakinra and gevokizumab are potential inhibitors of Th17 cells. IL-12 and IL-23 share a common subunit (p40), which allows ustekinumab, a humanized anti-p40 monoclonal antibody, to target both IL-12 and IL-23 pathways, thus disrupting Th1 and Th17 immune responses. IFN-γ induces the production of several chemokines by vascular smooth muscle cells. Among them, CCL2 leads to the recruitment of monocytes which express its receptor (CCR2) and then differentiate into macrophages and multinucleated giant cells. Macrophages of the adventitia produce IL-6, IL-1β and TNF-α, which are responsible for systemic symptoms of GCA and TAK. In the media, macrophages activated by IFN-γ differentiate into multinucleated giant cells, which produce reactive oxygen species (O^-), nitric oxide (NO) and matrix metalloproteinases (MMP), which induce media destruction and internal elastic lamina digestion. IFN-γ-activated macrophages and giant cells also synthesize growth factors: vascular endothelial growth factor (VEGF) triggers neovascularization, which increases immune-cell homing, while platelet-derived growth factor (PDGF) and endothelin-1 induce the migration and proliferation of VSMC, thus generating intimal hyperplasia, leading to vascular occlusion and the ischemic symptoms of GCA and TAK. The blockade of the PDGF pathway by imatimib or of endothelin-1 receptors decreases the proliferation and/or migration of VSMC. However, their use is limited to *in vitro* or *ex vivo* studies.

especially methotrexate, are therefore used to spare GC and/or prevent further relapse(s), but have not shown a major benefit [20]. Therefore, biologics are often used in GCA or TAK after failure of GC tapering despite the use of conventional immunosuppressive drugs. This review focuses on recent data available about the use of biologics in large-vessel vasculitis, and highlights the differences between GCA and TAK with regard to these treatments.

2. Anti-TNF-α drugs (Fig. 1)

a. GCA

By comparing the mRNA levels of interleukin-1beta (IL-1β), tumour necrosis factor-alpha (TNF-α) and IL-6 in temporal artery samples from 36 patients with biopsy-proven GCA and 11 controls, Hernández-Rodríguez et al. demonstrated that the tissue expressions of these three