B lymphocytes may play a significant role in large-vessel vasculitis

Evaluation of: Hoyer BF, Mumtaz IM, Loddenkemper K *et al.* Takayasu arteritis is characterised by disturbances of B cell homeostasis and responds to B cell depletion therapy with rituximab. *Ann. Rheum. Dis.* 71, 75–79 (2012). The novel finding of increased number of circulating, newly differentiated, plasmablasts in Takayasu arteritis and their relationship to disease activity raises interesting questions about the role of B lymphocytes in large-vessel vasculitis. Whether this observation is relevant to the pathogenesis of vascular inflammation in Takayasu arteritis or is only a biomarker of immune activation needs to be investigated. Response of a few patients to B-cell depletion therapy supports an important role of B lymphocytes in vascular inflammation, but needs to be confirmed in clinical trials.

KEYWORDS: B lymphocytes ■ giant-cell arteritis ■ inflammation ■ plasmablasts ■ Takayasu arteritis ■ treatment ■ vasculitis

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Takayasu arteritis (TAK) is a chronic granulomatous vasculitis involving the aorta and its major branches. Due to the tropism of TAK for large arteries, tissue samples are not readily available. Vascular specimens are usually obtained at the time of bypass surgery or death from chronic complications and show predominantly fibrotic changes with various degrees of chronic inflammation. However, during earlier stages of the disease, that the vessel wall is infiltrated by lymphocytes and macrophages that undergo granulomatous differentiation with typical formation of multinucleated giant cells [1]. This pattern, characteristic of a delayed-type hypersensitivity reaction, suggests the predominant participation of Th1-mediated mechanisms in the pathogenesis of vascular inflammation in TAK.

Immunopathology studies have shown that inflammatory infiltrates are mainly constituted by $CD4^+$ T cells and activated macrophages. Adaptive immune response against unknown antigens is thought to play a major role in the pathogenesis of TAK [2,3]. This concept is supported by several observations. Although some heterogeneity exists among studies performed in different geographic areas and ethnicities, genetic risk is associated with polymorphisms in the major histocompatibility complex (MHC) region [2]. Analysis of T-cell receptor Vα–Vβ gene usage shows that infiltrating lymphocytes are oligoclonal, suggesting an antigen-driven immune response [3]. Smooth muscle cells undergo apoptosis and this is thought to be driven by cytotoxic T cells [2,4]. There is evidence that γ/δ T lymphocytes and natural killer cells also contribute to cytotoxicity and several apoptosis-triggering molecules are upregulated in inflammatory infiltrates [4].

More recently, the potential participation of B cells in TAK has attracted some interest. B lymphocytes and plasma cells may be present in TAK lesions, particularly in the adventitia [1]. Antiendothelial cell antibodies can be detected in active patients. Some are addressed to annexin V and may promote endothelial cell apoptosis. The specificities of antiendothelial cell antibodies in patients with TAK appear to be heterogeneous [2]. Recently, antibodies recognizing a 62-kD protein in aortic endothelial cells have been detected in patients with TAK and are able to elicit endothelial cell proinflammatory responses and apoptosis [5]. Although endothelial injury does not seem to be the major pathogenic event in a large-vessel vasculitis,increased endothelial cell proinflammatoy activity may participate in the recruitment of inflammatory cells [6] and endothelial damage may contribute to endothelial dysfunction and premature atherosclerosis observed in TAK patients. Regardless of their precise role in vascular inflammation and injury, the presence of antiendothelial antibodies, observed by several investigators, indicates autoreactive B-cell activation.

Underlining the pathogenic potential of B cells, Hoyer *et al.* have recently reported abnormalities in circulating B-derived cell subsets in patients with TAK [7]. The authors not only found increased numbers of memory ($CD19^+$, $CD20^+$ and $CD27^+$) B cells and decreased numbers of naive ($CD19^+$, $CD20^+$ and $CD27^-$)

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B cells, but also demonstrated increased numbers of plasmablasts ($CD19^+$, $CD20^-$ and $CD27^+$) and, more specifically, activated, newly differentiated plasmablasts identified by strong expression of class II MHC antigens. The presence of newly formed plasmablasts correlated with disease activity. Although less striking, these changes resemble what the same group of investigators has previously found in patients with systemic lupus erythematosus [7]. The authors conclude that disturbance of B-cell homeostasis has a seminal role in the pathogenesis of TAK and suggest that this finding provides a strong conceptual basis for B-cell depletion or B-cell modulation therapy in TAK. The authors prove this concept by successfully treating three patients refractory to standard therapy with the anti-CD20 chimeric monoclonal antibody rituximab. Additional case reports have also shown efficacy of rituximab in inducing remission in patients with TAK [7].

The results generated by Hoyer *et al.* need to be confirmed in larger series but are challenging and intriguing. If this abnormality is seminal for disease pathogenesis, as suggested, it is noteworthy that abnormalities found in TAK are similar to those found in systemic lupus erythematosus patients, since these diseases have little in common except that they both occur primarily in young females. Perhaps these cells only reflect hyperstimulation of the immune system rather than provide clues about the pathogenic pathways specifically involved in the development of particular diseases. It would have been interesting to test other vasculitis such as ANCA-associated vasculitis, where B-cell disturbances clearly play a role, or giant-cell arteritis (GCA), a closely related large-vessel vasculitis.

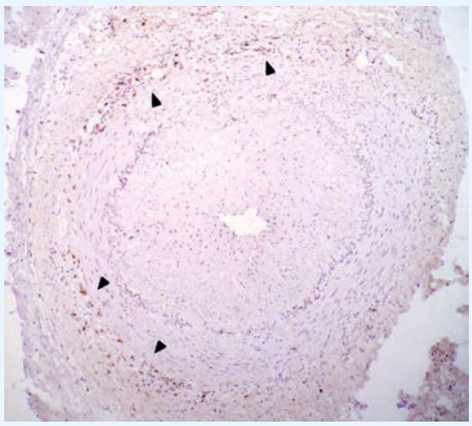

Figure 1. Temporal artery biopsy from a patient with giant-cell arteritis taken after 1 year of corticosteroid treatment.
B lymphocytes, identified by immunohistochemistry using a monoclonal antibody against CD20, can be observed in the adventitia (arrowheads).

Rituximab has no direct effect on antibody-producing plasmablasts since they do not express CD20. However, in other diseases such as systemic lupus erythematosus or rheumatoid arthritis, treatment with rituximab results in decreased circulating plasmablasts by targeting their $CD20^+$ precursors [7,8]. While changes in circulating plasmablasts, if confirmed in large series, may indeed be a biomarker of disease activity, response to rituximab and reduction in circulating plasmablasts upon rituximab treatment cannot be strictly considered a proof of concept of the relevance of circulating plasmablasts to disease pathogenesis. On the one hand, it is not clear that rituximab influences long-lived autoreactive plasma cells retained in inflammatory lesions unless other therapeutic effects reduce the inflammatory microenvironment that creates a favorable niche [8]. On the other hand, and particularly in a disease where T cells undoubtedly play a significant role, rituximab may be affecting B-cell-dependent T-cell activation. Despite limited feasibility given the nature of the vessels involved in TAK, it would have been very interesting to explore changes induced in tissue plasma cells and T-cell activation in tissue.

Another interesting question arising from this study is whether a similar abnormality may be found in patients with GCA, a disease closely related to TAK. GCA and TAK have important similarities. Both involve large vessels and lesions can be indistinguishable. It has even been hypothesized that they are the same disease and differences in phenotype are due to immunosenescence and senescence of the targeted vascular system [9]. However, there are also relevant dissimilarities between these two conditions. In addition to demographic differences, anatomical distribution is not completely alike, although it can be indistinguishable in a subset of patients. In general, GCA frequently involves small vessels in the scalp and distal branches of the ophthalmic artery, whereas TAK invariably involves the main tributaries and the aorta itself and rarely involves small vessels. TAK is primarily a stenosing disease, whereas GCA infrequently leads to symptomatic stenoses requiring re-vascularization procedures [10]. The majority of patients with TAK require adjuvant therapy, whereas most patients with GCA can be treated with glucocorticoids alone. Moreover, while open-label studies suggest efficacy of infliximab

in TAK, a randomized controlled trial did not show benefit over placebo in sustaining glucocorticoid-induced remission in GCA [11]. Although the role of B lymphocytes in GCA has been neglected [12], B cells are indeed present in lesions [13] and, more importantly, may persist after glucocorticoid treatment (Figure 1).

The results generated by Hoyer *et al.*, although preliminary, are challenging and open interesting questions about the pathogenesis of TAK and its related disease GCA. They raise the question of whether B-cell modulators such as the anti-BAFF antibody belimumab may also be useful and whether response to the IL-6 receptor blocking monoclonal antibody tocilizumab reported in case reports of recurrent/refractory TAK and GCA may be, at least partially, a consequence of B-cell modulation.

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Executive summary

- Increased numbers of circulating, newly formed, plasmablasts can be detected in patients with Takayasu arteritis and correlate with disease activity.
- Along with the presence of B cells and plasma cells in lesions observed in immunopathology studies, this finding suggests a previously under-recognized role of B cells in the pathogenesis of Takayasu arteritis.
- The potential relevance of B cells in Takayasu arteritis is supported by several case reports indicating successful treatment of refractory patients with rituximab.
- If confirmed in clinical trials, B-cell-depletion therapy might be a therapeutic option for patients with Takayasu disease refractory to standard therapies.
- An important question raised by this study is whether these findings may also be relevant to giant-cell arteritis, a closely related dirsorder.

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