Could abatacept directly target expanded plasmablasts in IgG4-related disease?

Yamamoto et al recently reported the case of a patient with long-standing and relapsing IgG4-related disease (IgG4-RD), who developed secondary resistance to rituximab treatment but subsequently improved under abatacept infusions. This interesting observation drives important questions, regarding both IgG4-RD pathophysiology and abatacept mechanisms of action.

IgG4-RD is a systemic disease of unknown cause, affecting primarily middle-aged men, characterised by swelling of one or several organs (mainly pancreas, salivary and lacrimal glands, lymphadenopathy, retroperitoneal organs) with infiltration of IgG4-positive plasma cells and fibrosis of involved organs, and high serum IgG4 levels in half of the patients. Several diagnostic or classification systems have been proposed. Its pathophysiology is still ill-defined. IgG4-secreting plasmablasts are central players in the disease: they are the main infiltrating cells in affected organs, they are expanded in the circulation, are oligoclonal and may serve as a biomarker to guide therapy. The efficacy of rituximab in IgG4-RD further suggests the major role of B cells as precursors of these expanded plasmablasts. It has been suggested that a shift towards Th2 immune response promotes the initiation of the disease, and that overexpression of IL-21 by Tfh cells leads to the formation of ectopic germinal centres in the target organs and increased IgG4 production. B-cell/plasmablast and T-cell relative contributions in the pathophysiology of IgG4-RD are...
difficult to decipher, as illustrated by the disappearance of a recently described oligoclonal CD4+ cytotoxic T-cell subpopulation after B-cell depletion using rituximab. Abatacept is a fusion protein combining the extracellular domain of CTLA4 with an IgG1 Fc fragment, labelled for the treatment of rheumatoid arthritis (RA). Abatacept has greater binding affinity for CD80/CD86, expressed chiefly on the surface of monocytes, dendritic cells and B cells, than CD28 on the surface of T cells. It is suspected that abatacept acts primarily by impairing CD28-mediated activation of T cells. Therefore, Yamamoto et al suggest that the efficacy of abatacept in their patient is mainly explained by an inhibition of Tfh and subsequent disruption of the formation of ectopic germinal centres.

However, we would like to discuss an alternate explanation to the potential efficacy of abatacept in IgG4-RD: abatacept may also act directly on those expanded plasmablasts observed in the disease. Several observations suggest that abatacept may indeed have a direct effect on CD80/CD86-expressing cells to which it binds. In RA, abatacept increases blood monocyte counts by decreasing their vascular adherence and migratory capacity and binds. In RA, abatacept increases blood monocyte counts by decreasing their vascular adherence and migratory capacity.

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