JAK inhibitors as promising agents for refractory Takayasu arteritis

I read with great interest the article 'Successful remission with tofacitinib in a patient with refractory Takayasu arteritis complicated by ulcerative colitis' by Kuwabara *et al*.[1] In this article, the authors reported a patient with both Takayasu arteritis (TAK) and ulcerative colitis (UC) who was successfully treated with tofacitinib, an inhibitor of Janus kinase (JAK). The critical message of this report is that, although inhibitors of tumour necrosis factor α and interleukin (IL)-6 failed to induce remission, symptoms and arterial inflammation on imaging were promptly ameliorated by tofacitinib.[1] Because our group reported the efficacy of JAK inhibitors on experimental large-vessel vasculitis in mice for the first time,[2] I would like to comment on this report.

First, UC is not an uncommon complication in TAK, with a complication rate of approximately 6%.[3 4] However, it has been reported that TAK patients with UC have a different genetic background from TAK patients without UC in HLA-B52:01 positivity, and that the age of TAK onset in the former group is younger than that in the latter.[4] Thus, it may be possible that JAK inhibitors are more likely to be effective in patients with both diseases. It is necessary to test whether JAK inhibitors are efficacious in TAK patients without UC as well.

Second, a genome-wide association study revealed *IL-12B* as a susceptibility gene in TAK, and IL-12 plays a critical role in T helper 1 (Th1) differentiation.[5 6] In addition, patients with TAK have a higher serum concentration of IL-23 than healthy individuals, and IL-23 promotes IL-17 production by $CD4^+$ T cells.[7 8] Both IL-12 and IL-23 are critically involved in the pathophysiology of TAK and activate JAK2 and Tyk2.[9] Because tofacitinib primarily inhibits JAK1 and JAK3, baricitinib, an inhibitor of JAK1 and JAK2, may be a better option in some patients.

Third, the authors seem to believe that the efficacy of tofacitinib is mediated by blocking Th1-derived and Th17-derived cytokines. However, JAK inhibitors, including tofacitinib, target not only $CD4^+$ T cells but also macrophages and natural killer cells,[2 10] which have recently emerged as a promising target in TAK.[11] Because TAK is a multifactorial disease in which many cytokines and cell populations interact with each other in the disease mechanism, multicytokine blockade with JAK inhibitors rather than single cytokine inhibition may be reasonable.

Whether JAK inhibitors can be considered as first-choice immunosuppressive agents added to glucocorticoids (GCs) or even an alternative to GCs for TAK remains unclear. However, although there are some concerns with JAK inhibitors, such as herpes zoster and malignancies, given the significant burden of GCs on patients with TAK, I believe this issue should be discussed in the future.

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