Treating giant-cell arteritis: is IL-6 the cytokine to target?

Giant-cell arteritis is a granulomatous vasculitis affecting medium- and large-sized arteries responsible for cranial symptoms (eg, headaches, jaw claudication, and visual disturbance), polymyalgia rheumatica, and constitutional manifestations. In this population of patients older than 50 years, a still unknown initial trigger activates dendritic cells that will then attract T lymphocytes into the vessel wall. T-helper-1 and T-helper-17 CD4 T cells secrete cytokines, specifically interferon-γ and interleukin-17, which stimulate monocyte and macrophage recruitment. Activated macrophages, in turn, produce and release interleukin-1.
and interleukin-6, which cause constitutional symptoms, and might fuse to form the giant cells that are the hallmark of the disease. In this context, T-regulatory cells are diminished and fail to control inflammation.6

Glucocorticoids, prescribed for months or years, are regarded as the reference treatment for giant-cell arteritis, but are responsible for several and sometimes severe side-effects in as many as 86% of patients with giant-cell arteritis.7 Hence, several randomised studies assessed add-on treatments with an immunosuppressant or biotherapy to prevent relapses and restrict glucocorticoid exposure. However, only methotrexate showed modest efficacy at improving outcome.8

Interleukin-6 is a pleiotropic cytokine that has been linked to giant-cell arteritis activity.9 Blockade of the interleukin-6 receptor might abrogate signs and symptoms of giant-cell arteritis and might also rebalance T-regulatory cells and T-helper-17 cells, thereby supporting its potential place in giant-cell arteritis treatment. Tocilizumab blockade of interleukin-6 receptor quickly lowers the serum C-reactive protein concentration,10 independent of its potential effect on vasculitis. A tocilizumab effect on clinical manifestations and its ability to obtain remission needs to be shown independently of its biologically induced changes. Evaluation of disease activity should be based on clinical symptoms and not biological parameters.

Peter Villiger and colleagues11 report in The Lancet the first randomised trial showing efficacy of tocilizumab in patients with giant-cell arteritis. 30 patients were randomly assigned (2:1) to receive tocilizumab or placebo for 1 year combined with glucocorticoid tapering. At week 12, a significantly higher percentage of patients in the tocilizumab group were in clinical remission without any inflammatory syndrome and with glucocorticoids at 0.1 mg/kg per day, compared with patients in the placebo group (p=0.03). Moreover, at week 52, 85% of patients given tocilizumab achieved relapse-free survival compared with 20% of the placebo group (p=0.001). Furthermore, the cumulative weight-adapted prednisolone dose was significantly lower in patients in the tocilizumab group than in the placebo group (43 mg/kg vs 110 mg/kg, respectively; p=0.0005).

Side-effects were recorded in 75% of patients in the tocilizumab group and 70% in the placebo group. Gastrointestinal complications were more frequent in the tocilizumab group (three vs one serious adverse event in the placebo group) and nine neutropenic episodes were reported in the tocilizumab group. Biotherapy recipients had fewer metabolic complications.

The results of this elegant study strongly support using tocilizumab to treat giant-cell arteritis. However, several points merit mentioning. Glucocorticoid tapering was rapid, emphasising tocilizumab effectiveness at controlling giant-cell arteritis and explains the high rate of relapsing patients in the placebo group. The study aimed to show tocilizumab efficacy but, as recognised by the researchers, was not sufficiently powered to identify and describe all potential side-effects. One question remains open regarding long-term disease evolution after stopping tocilizumab; does tocilizumab cure giant-cell arteritis?

Villiger and colleagues’ results provide definitive evidence that tocilizumab effectively treats giant-cell arteritis. Because of uncertainties regarding long-term efficacy and potential side-effects, its place as first-line treatment replacing or sparing glucocorticoids, relapse therapy, and long-term administration remains a matter of debate.

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AR is investigator in the GIACTA study designed to evaluate the safety and efficacy of tocilizumab for the treatment of giant-cell arteritis. LG declares no competing interests.
