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MULTIPLE SCLEROSIS

Atacicept increases relapse rates in multiple sclerosis

Immunotherapy targeting B-cell populations has been found to slow disease progression in multiple sclerosis (MS). Recently, however, a phase II safety and efficacy trial of atacicept—a recombinant fusion protein that suppresses B-cell function and proliferation—in patients with MS was halted due to an increase in annualized relapse rates. The results highlight the complexity of the immune response in MS and the need for carefully designed safety studies.

B cells are known to have a key role in the pathogenesis of autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, and have also been implicated in MS, where they are thought to produce antibodies against myelin sheaths and axons. In patients with MS, depletion of B-cell populations through targeting of the CD20 receptor with monoclonal antibodies such as rituximab or ocreluzimab has been shown to reduce both the frequency of relapses and the numbers of inflammatory lesions on MRI.

Atacicept binds the cytokines BLyS and APRIL, which are involved in B-cell differentiation, maturation and survival. Ludwig Kappos and his team at University Hospital, Basel, Switzerland, assigned 255 patients with active MS to receive atacicept or placebo for 36 weeks, with the possibility of open-label extension to a total treatment period of up to 5 years.

> “...targeting of cytokines ... might disrupt regulatory B-cell pathways...”

The trial was stopped early after the independent monitoring and safety board reported an increased frequency of relapses in the patients receiving atacicept compared with those given placebo. Relapse rate was initially a tertiary outcome in the trial, and no difference was observed in the primary outcome—mean number of gadolinium enhancing T1 lesions per patient per scan—between the two groups. On termination of the trial, patients were enrolled in a 60-week safety follow-up, during which they received standard MS pharmacotherapy to reduce disease activity.

The fact that not all patients completed the 36-week double-blind phase makes it difficult to draw firm conclusions from this study. Nevertheless, the decrease in mature B-cell numbers clearly paralleled an increase in disease activity, and both B-cell levels and relapse rates returned to pre-dose values once standard therapy was initiated, lending support to the idea that atacicept caused the increase in relapse rate.

Compared with other B-cell targets such as CD20, the targets of atacicept are expressed later in B-cell development, so B-cell progenitors and memory B cells, which might be important in MS pathogenesis, are not depleted by this agent. Furthermore, targeting of cytokines such as BLyS and APRIL with antibodies might disrupt regulatory B-cell pathways, which in turn could stimulate T-cell responses, thereby creating a proinflammatory environment and leading to an increase in relapses. Despite the negative outcome, the results of the Kappos *et al.* study should serve to increase our understanding of the complex role of B cells in MS pathogenesis.

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Original article Kappos, L. *et al.* Atacicept in multiple sclerosis (ATAMS): a randomised placebo-controlled, double-blind, phase 2 trial. *Lancet Neurol.* doi:10.1016/s1474-4422(14)70028-6