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Are CAR T cells the answer to myasthenia gravis therapy?

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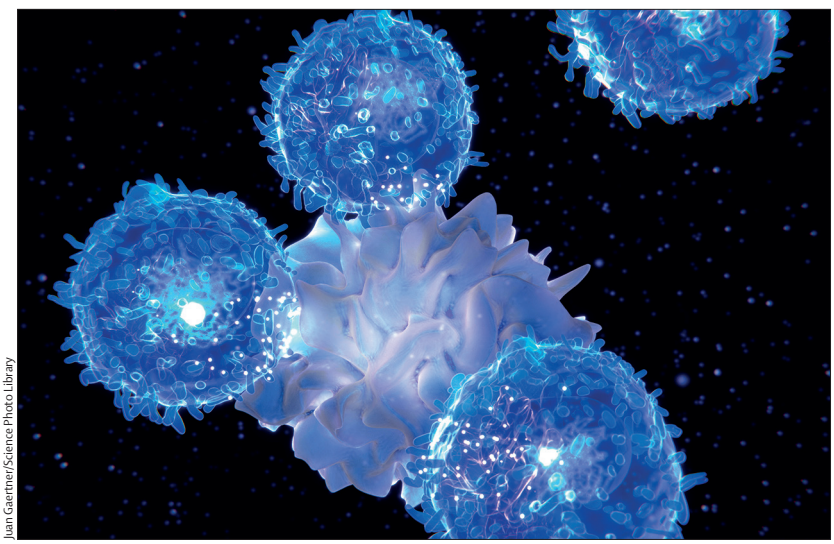
Myasthenia gravis is a chronic autoimmune disorder that is characterised by fluctuating muscle weakness. In people with myasthenia gravis, pathogenic IgG autoantibodies target proteins in the postsynaptic neuromuscular junction, such as the acetylcholine receptor (AChR) or MuSK, thereby impairing the function of skeletal muscles.[1] Myasthenic crisis, a life-threatening manifestation of the disease that involves respiratory failure, affects about 15% of individuals with myasthenia gravis, of whom 12–18% die.[2] Despite the availability of standard therapies, including acetylcholinesterase inhibitors, steroids, steroid-sparing immunosuppressants, and thymectomy, symptoms of myasthenia gravis are unsatisfactorily treated in up to half of individuals over the course of their disease, resulting in a disease burden due in part to lack of efficacy or intolerable side-effects; thus, new treatment approaches are urgently needed.[3-5] Recently, targeted immunotherapy for people with myasthenia gravis has been enabled by the development of C5 and neonatal Fc receptor (FcRn) inhibitors, which can mitigate the attack of autoantibodies against the neuromuscular junction.[1,5] Whereas the C5 inhibitors specifically prevent the complement-dependent membrane attack at the neuromuscular junction, the FcRn inhibitors lead to the reduction of circulating IgG antibodies, including those that are pathological at the neuromuscular junction.[1,5] However, even with these innovative drugs, which have been robustly tested in several landmark phase 3 trials,[6] the ultimate therapeutic goal of complete disease control can be reached only in a subset of people with the disease. Complete elimination of the harmful autoantibodies and their effects is impossible with these therapeutic approaches alone. Therefore, new safe and effective immunotherapies are urgently needed that specifically target the immune machinery that produces the autoantibodies.

In *The Lancet Neurology*, Volkan Granit and colleagues report the results of the prospective, multicentre, open-label phase 1b/2a trial (MG-001) investigating the safety and efficacy of Descartes-08, an anti-B-cell maturation antigen (BCMA, also known as TNFRSF17) autologous RNA chimeric antigen receptor T-cell (rCAR-T) therapy, in individuals with generalised myasthenia gravis.[7] With Descartes-08, Granit and colleagues specifically target plasma cells, which seem to be a reasonable target for autoantibody-mediated diseases. B lymphocytes and plasma cells have already been described as targets for myasthenia gravis therapy, mainly in case series.[5] The anti-CD20 antibody rituximab is likely to have a beneficial effect in people with a rare anti-MuSK-positive generalised myasthenia gravis and might also be of value in the treatment of people in the early course of anti-AChR-positive generalised myasthenia gravis.[5,8]



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MG-001 is a highly innovative proof-of-concept study with some important results. Descartes-08 was designed to specifically recognise and selectively destroy plasma cells using BCMA via the chimeric antigen receptor (CAR) T-cell therapy approach.[7] CAR T cells are a new class of molecularly precise therapies that are becoming increasingly established via their use in the treatment of advanced cancers.[9] The elegant RNA-based approach to CAR T cells used by these investigators has the advantage, over standard DNA-based CAR T-cell therapy, that potentially harmful lymphodepletion chemotherapy is not required for rCAR-T engineering.[7] A major finding is the feasibility of producing rCAR-T from patients with generalised myasthenia gravis treated by standard immunosuppressive therapies. Importantly, Descartes-08 infusions in different dose schemes were well tolerated and not associated with adverse effects that are typical of DNA-based CAR T-cell therapies, such as neurotoxicity, cytokine release syndrome, or haematological adverse effects. Furthermore, most study participants showed clinically meaningful improvements in myasthenia gravis disease severity, as assessed by validated scales, that persisted for months. This improvement coincided with a decrease in plasma cell markers in the blood. Plasma cells were only partly destroyed by rCAR-T, which corresponds with the slightly decreased concentrations of total IgG, vaccine antibodies, and autoantibodies.[7] In terms of susceptibility to infection, this result is positive news. The results are also consistent with the fact that changes in autoantibody concentration and severity of myasthenia gravis correlate only modestly.[10] However, it is too early to confirm the safety and efficacy of Descartes-08 in the treatment of people with myasthenia gravis. The study design was primarily for dose-finding and safety aspects rather than efficacy analysis: the study was not blinded and was too small, with only 14 patients studied.[7] The recent phase 3 trials with C5 and FcRn inhibitors show a comparatively large placebo effect in participants with myasthenia gravis,[6] although the observed improvements after treatment in the MG-001 study appear to exceed the placebo effect.

The results of the MG-001 study provided valuable information for the ongoing phase 2b study (NCT04146051) to further investigate the safety and efficacy of Descartes-08 in individuals with generalised myasthenia gravis. Myasthenia gravis can serve as a model disease for exploring this innovative therapeutic approach, which is also of great interest for other autoantibody-mediated neurological diseases, such as autoimmune encephalitis.

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