The management of autoimmune diseases has improved substantially since the turn of the century, owing largely to the emergence of targeted biologic therapies. Nonetheless, treatment is still considered to be disease-suppressive and lifelong in most cases. In this issue of the Journal, Müller et al. describe a series of 15 patients with systemic autoimmunity treated with a single infusion of CD19-targeted chimeric antigen receptor (CAR) T cells. At a median follow-up of 15 months (range, 4 to 29), all were in remission or had had major reductions in symptoms, along with the disappearance of autoantibodies, and had discontinued all immunosuppressive and antiinflammatory medication, including glucocorticoids. Toxic effects were manageable and mostly mild.

CAR T cells that target the CD19 antigen have provided a paradigm shift in the management of certain B-cell–derived lymphomas and leukemias. These autologous T cells, genetically manipulated to seek out their targets, are also potently cytotoxic. In the short term, treatment may be associated with cytokine-release syndrome and reversible neurotoxic effects; longer-term adverse effects can include B-cell aplasia, hypogammaglobulinemia, and infections. B cells are also central to the pathogenesis of autoimmunity, and B-cell–targeted therapies such as rituximab, which targets CD20-expressing B cells, have been used to treat autoimmunity for several years. Disease remissions occur, but subsequent flares are common. Recent trials of newer agents indicate that efficacy may reflect the depth of B-cell depletion. Müller et al. made these observations in an uncontrolled context in a small heterogeneous series of patients, with limited follow-up. Nonetheless, the findings are remarkable. These patients had serious multisystem disease that was refractory to at least two conventional therapies. Similar outcomes can sometimes be achieved with autologous stem-cell transplantation but with a risk of substantial toxic effects and even death.

Two properties of CD19 CAR T cells may explain their apparent superiority over anti-CD20 monoclonal antibodies. First, CD19 is expressed more broadly than CD20, particularly on plasma blasts and a majority of plasma cells. Whereas rituximab primarily depletes B cells with some secondary loss of plasmablasts, CD19 CAR T cells have direct cytotoxicity for plasmablasts and many plasma cells. Second, CAR T cells are more potently depleting than monoclonal antibodies, probably owing to better tissue penetration and their intrinsic lethality. A key implication of the work of Müller et al. is therefore that at least some B-cell lineage–dependent autoimmunity resides beyond B cells themselves, in plasmablasts and plasma cells. This inference is consistent with current thinking; indeed, plasma cells have been identified as a critical bastion of autoimmunity.

Yet there is relative preservation of protective antibodies, also of plasma-cell origin, after CAR T-cell therapy. In fact, a modest decrease in circulating immunoglobulin levels occurs after therapy, and rare autoantibody specificities persist, which shows that “good” and “bad” antibody production is not completely dissociated, residing in overlapping but mostly distinct niches. For example, some protective antibodies derive from long-lived, CD19-negative plasma cells.

Could CAR T-cell therapy cure autoimmunity? Such cure will require eradication of relevant im-
mune memory from both B-cell and T-cell compartments. B cells that reconstitute blood after treatment resemble a naïve repertoire, with loss of some autoimmunity-associated characteristics. If disease-associated clones have been eradicated, disease recurrence will require their stochastic regeneration and subsequent activation, also requiring cognate T-cell “help.” This interaction is reciprocal, with B cells concurrently activating T cells. Consequently, deep B-cell depletion could cause secondary loss of autoreactive T cells by “neglect,” although some memory T cells are likely to persist. This scenario has further oncologic parallels, in which relapse probability could be determined by the presence or absence of “minimal residual disease.” However, such a concept is an oversimplification and neglects intricacies of our immune system, such as the existence of CD19-expressing regulatory B cells that protect against autoimmunity.

The future trajectory of CAR T-cell therapy for autoimmunity will be driven by efficacy, safety, cost, and acceptability. Diseases such as systemic lupus erythematosus and systemic sclerosis are serious, multisystem, life-threatening conditions. Consequently, if extended follow-up reinforces the current data, the benefit-to-risk ratio is likely to prove acceptable to both physician and patient, at least in certain cases of refractory disease. Therapy is individualized, difficult to scale, and expensive. However, managing chronic autoimmunity with multiorgan failure is also expensive, and the cost of CAR T-cell therapy will decrease with time. If CAR T-cell therapy is truly “tolerogenic,” then discussions will broaden to consider qualitative and quantitative reconstitution of some autoimmunity-associated characteristics. For example, blinatumomab is a bispecific monoclonal antibody that targets T cells to CD19+ cells, although a recent meta-analysis suggested inferiority to CD19 CAR T cells in relapsed or refractory acute lymphoblastic leukemia. It will also be critically important to fully understand potential toxic effects and their minimization. Cases of secondary cancer have recently emerged in the oncologic context, which raises the possibility of insertional mutagenesis. Furthermore, although B-cell depletion has provided a successful therapeutic strategy for autoimmunity, it was associated with poor outcomes after coronavirus disease 2019. Phase 2 trials will therefore be essential to better understand the potential role of CAR T-cell therapy in autoimmunity.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, and the Musculoskeletal Unit, Newcastle upon Tyne Hospitals NHS Foundation Trust, Freeman Hospital — both in Newcastle upon Tyne, United Kingdom.


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