CORRESPONDENCE

# CD19-Targeted CAR T Cells in Refractory Systemic Lupus Erythematosus

**TO THE EDITOR:** Systemic lupus erythematosus (SLE) is a severe autoimmune disease that predominantly affects young women. SLE is characterized by the formation of autoantibodies and immune complex–mediated inflammation and organ damage. Although autoreactive B cells play a key role in the pathogenesis of SLE, B-cell depletion by antibodies has only limited therapeutic efficacy.[1] This paradox has been attributed to the inaccessibility and persistence of autoreactive B cells within lymphatic organs and inflamed tissues[2] or the pathologic role of CD20-negative plasma cells, which may act as an additional source of autoantibodies in patients with SLE.[3] Chimeric antigen receptor (CAR)–modified T cells that have been genetically engineered to recognize CD19 and other B-cell surface antigens have emerged as a powerful tool for the treatment of relapsed or refractory B-cell cancers.[4] This technological breakthrough, together with recent convincing data on the role of B cells in disease pathogenesis derived from preclinical lupus models,[5] provides a rationale for the use of CAR T-cell therapies in patients with SLE.

We report here on the use of autologous CD19 CAR T cells in the treatment of an autoimmune disease. A 20-year-old woman with severe and refractory SLE presented with active lupus nephritis (World Health Organization class IIIA, indicating focal proliferative disease with active lesions), nephrotic syndrome, pericarditis, pleurisy, rash, arthritis, and a history of Libman–Sacks endocarditis. Previous treatments with hydroxychloroquine, high-dose glucocorticoids, cyclophosphamide, mycophenolate mofetil, and tacrolimus, as well as the B-cell–targeting therapies belimumab and rituximab, did not control symptoms, deplete B cells, or abrogate autoimmunity (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). All the treatments were stopped before the planned CAR T-cell infusion, and only low-dose prednisolone was administered. CD19 CAR T cells were produced by lentiviral transduction of autologous fresh leukapheresis in the closed automated CliniMACS Prodigy system (Supplementary Methods section in the Supplementary Appendix). After preparatory lymphodepletion with fludarabine at a dose of 25 mg per square meter of body-surface area per day on days −5, −4, and −3 and cyclophosphamide at a dose of 1000 mg per square meter on day −3, an infusion of $1.1\times10^6$ CD19 CAR T cells per kilogram of body weight (ratio of CD4+ to CD8+ T cells, 3:1) was administered on day 0.

In vivo, CAR T-cell numbers rapidly increased (0.31% of the total circulating T cells on day 3 and 27.69% of the total circulating T cells on day 9), followed by a typical decrease, with the circulat-

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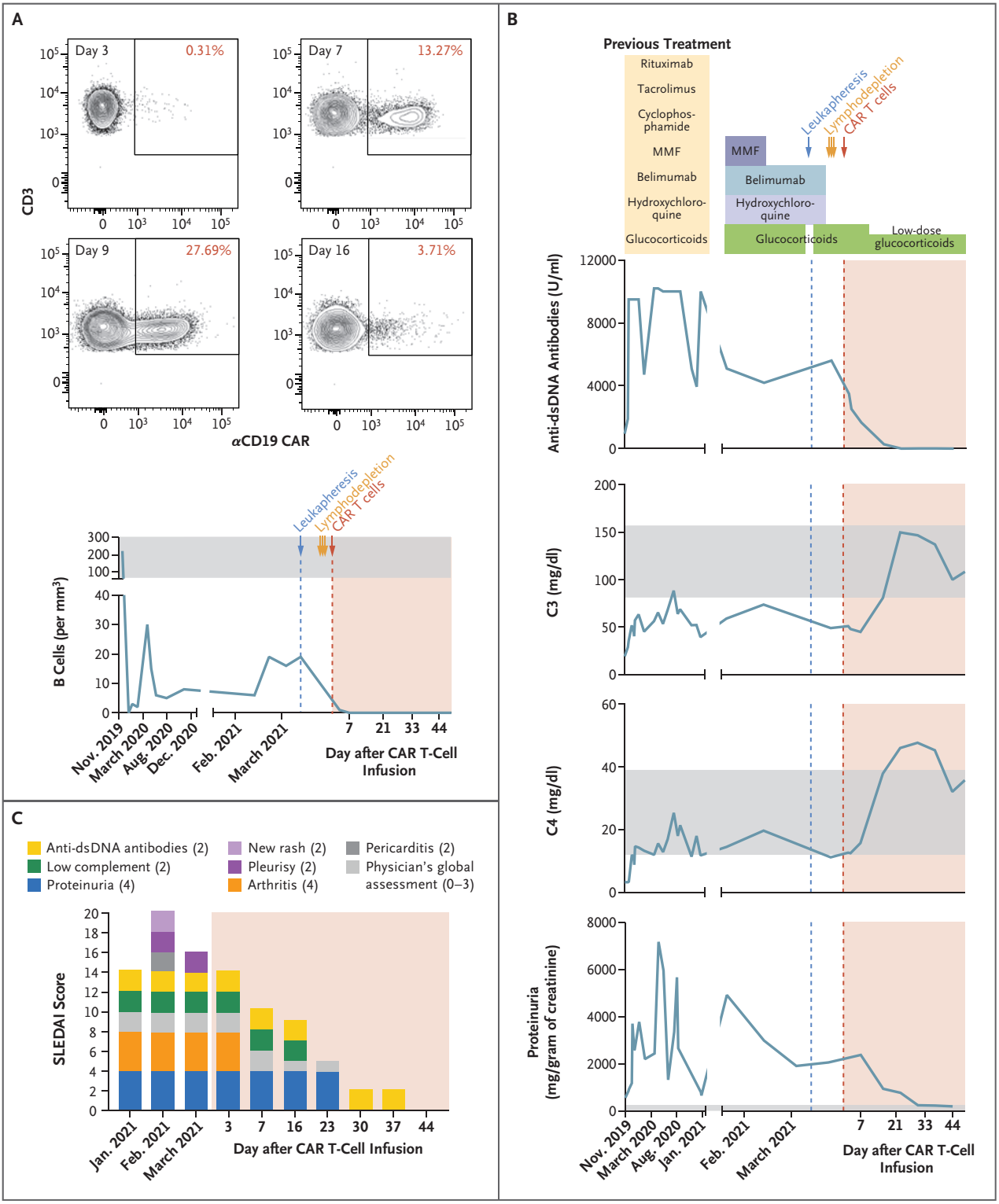

**Figure 1 (facing page). Patient with Resistant Systemic Lupus Erythematosus Treated with CD19 CAR T Cells.**

The upper graphs in Panel A show representative flow-cytometric analyses of the percent of circulating anti-CD19 (CD3+ αCD19 chimeric antigen receptor [CAR]+) CAR T cells among total T cells at various days after CAR T-cell infusion. The insets show the gates for CAR T cells and their respective percentage of total circulating T cells. The bottom graph in Panel A shows the B-cell count before and after leukapheresis, lymphodepletion with fludarabine and cyclophosphamide, and treatment with CAR T cells (administered at a dose of $1.1\times10^6$ cells per kilogram of body weight). The gray area indicates the normal range, and the pink area the period after the infusion. Panel B shows anti–double-stranded DNA (dsDNA) antibody levels, serum levels of C3 and C4, and proteinuria with pharmacologic treatment before and after leukapheresis, lymphodepletion, and treatment with CAR T cells. Gray areas indicate the normal range, and pink areas the period after the infusion. MMF denotes mycophenolate mofetil. Panel C shows details of the patient's Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score (with the SELENA [Safety of Estrogens in Lupus National Assessment] modification); the overall score ranges from 0 to 108 points (including up to 3 points for the physician's global assessment). The graph shows the patient's overall scores along with the SLEDAI components with their respective weights (shown in parentheses) during the 3 months before treatment with CAR T cells and up to 44 days after the infusion (pink area).

ing CAR T cells being continuously detectable during the next 7 weeks (Figs. 1A and S2). The patient did not have any adverse events that were considered by the treating physicians to be related to CAR T-cell therapy, such as cytokine release syndrome, neurotoxic effects, or prolonged cytopenia (Fig. S3). Expansion of CAR T cells preceded the complete and sustained depletion of circulating B cells (Fig. 1A). IgG levels were maintained above 5 g per liter without replacement therapy (Fig. S4). The level of double-stranded DNA (dsDNA) autoantibodies decreased rapidly from above 5000 U per milliliter to 4 U per milliliter (indicating a negative status) within 5 weeks, and the low C3 and C4 levels normalized (Fig. 1B). These signs of serologic remission were paralleled by clinical remission with proteinuria decreasing from above 2000 mg of protein per gram of creatinine to less than 250 mg of protein per gram of creatinine (Fig. 1B), and the Systemic Lupus Erythematosus Disease Activity Index score (with the SELENA [Safety of Estrogens in Lupus National Assessment] modification) decreased from 16 at baseline to 0 at follow-up (Fig. 1C).

These data show that CD19 CAR T-cell therapy may induce rapid remission of refractory SLE. The rapid disappearance of dsDNA autoantibodies suggests CD19-expressing plasmablasts as the major source of these antibodies. Given the role of B cells in a variety of severe autoimmune diseases, CAR T-cell therapy that targets B-cell antigens may have wider application.

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

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