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Commentary

Dual targeting of plasma cells and B-cells to treat systemic lupus erythematosus

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Abstract

Autoimmune disorders, such as systemic lupus erythematosus, are associated with significant morbidity that is often ultimately refractory to current treatment modalities. To targetthe role of autoantibodies in disease pathogenesis, biologics have been designed for selective targeting of B-cells. However, results have been disappointing as these modalities are unable to deplete long-lived plasma cells that can continue to produce autoreactive antibodies. To target both B-cells and plasma cells, a BCMA-CD19 compound CAR (cCAR) was tested in a patient with 20-year-history of SLE. Despite cessation of immunosuppressant therapy, cCAR alone led to the normalization of complement and antinuclear antibody levels, indicating an effective response to the therapy. This success of cCAR demonstrates that SLE and other antibody-mediated disorders may benefit from dual resetting of both B-cell and plasma cell populations.

Keywords: Antibody-producing cells; B-cells; Plasma cells; BCMA-CD19 CAR; CD19 cCAR; Autoimmune disorders; Systemic lupus erythematosus (SLE)

Introduction

Systemic lupus erythematosus (SLE) is a debilitating autoimmune disorder with an estimated prevalence of approximately 200,000 people in the United States [1]. B-cells and plasma cells, antibody-producing "root" cells, have critical roles in the pathogenesis of SLE through the production of autoantibodies, such as anti-nuclear antibodies (ANA), leading to immune complex deposition, complement activation, and organ damage. Current treatment options, such as corticosteroids, limit disease manifestations and progression through non-specific immunosuppressive effects. However, disease course may be unresponsive to these agents, and toxicity has been associated with prolonged use of these drugs, increasing the need for new treatment modalities.

Alternative Treatment Strategies

To avoid the toxicity associated with general immunosuppression, trials have been developed using biologics aimed at selective B-cell depletion [2-4]. Most of these trials, however, have given disappointing results [2-4]. B-cell depletion has also been studied using CD19 chimeric antigen receptor (CAR) T-cells in murine models of lupus [5,6]. While CD19 CAR T-cells demonstrated benefit in disease progression, circulating levels of immunoglobin remained elevated [5,6]. Additionally, autoantibodies remained detectable when therapy was applied later in disease progression [6]. In contrast, a recent report demonstrated that CD19 CART-cell infusion led to reduction of ANA to undetectable levels in a patient with refractory SLE [7]. However, B-cell numbers remained undetectable throughout the study so it is unclear if eventual B-cell recovery would lead to renewed ANA production.

The failure of biologics and CD19 CAR T-cells in murine models of lupus might be dueto the failure to target all antibody-producing cells. While B-cell depletion may prevent the formation of new plasma cells, it is not effective in reducing levels of long-lived plasma cells that secrete antibodies even in the absence of B-cells [8-10]. Long-lived plasma cells commonlyreside in survival niches in bone marrow and inflamed tissues, rendering them more resistant toimmunosuppressive therapy [9,11,12]. These plasma cells contribute to the production of autoantibodies that potentiate autoimmune disease and lead to refractory disease in patients treated with anti-B-cell therapy alone [12-14].

To reset the antibody-producing cells of the immune system, hematopoietic stem cell transplantation (HSCT) has been used to protect against self-reactivity through the eradication of lymphoid cells and memory immune cells responsible for the longevity of self-reactivity.

However, the conditioning regimen of high-dose chemotherapy or chemoradiotherapy used in HSCT is unlikely to completely deplete the population of memory immune cells and may not be practical given the severity of its toxicity. While allogeneic HSCT has also been shown to induceremission in lupus-like autoimmune disease in animal models [15], it can have a mortality rate as high as 20%, can be associated with severe negative effects on the patient's quality of life, and may not be the optimal method for an immune system reboot.

Benefits of CAR Approach

In contrast, CAR T-cells might provide an optimal avenue for resetting the antibody-producing population of the immune system. The use of CAR T-cells instead of antibodies or drug inhibitors has several benefits. While antibodies and drug inhibitors have limited biodistribution, CAR T-cells can overcome that limitation by traveling within the tissue and bypassing endothelial barriers to achieve more widespread distribution [16]. Therefore, CAR T-cells might be more successful in targeting long-lived plasma cells that reside in the bone marrow and tissues. While concentrations of antibodies and chemical drugs decrease over time and require multiple dosing to maintain therapeutic levels, CAR T-cells can have expansion ratesof 10^4-fold in patients, limiting the need for repeated doses [17,18]. As complement levels are typically low in SLE patients due to chronic consumption, antibody-based approaches, such as Rituximab, may have limited effect as they exhibit complement-dependent cytotoxicity [19].

Alternatively, CAR T-cells are capable of lysing target cells independent of complement levels. Additionally, compound CAR T-cells containing two individual CAR targets have previously demonstrated potent cytotoxic effects against two distinct cell populations [20,21]. A compound CAR could therefore enable simultaneous targeting of both B-cell and plasma cell populations to eradicate autoantibody-producing cells.

CAR-related toxicities largely revolve around cytokine-release syndrome (CRS), which results from widespread immune activation resulting in elevated levels of inflammatory cytokines. It has been demonstrated that the degree of toxicity due to CRS is related to the tumorburden at the time of CAR infusion [22]. While CRS is an important consideration in patients with malignant hematologic cells that have undergo extension expansion, it is less likely to lead to adverse effects in patients suffering from autoimmune disorders who do not have abnormally expanded populations of cells. With minimal toxicity expected from CRS in CAR-based approach, CAR T-cells offer an opportunity to reboot the immune milieu without the severe toxicities associated with HSCT.

CD19-BCMA cCAR

To deplete both plasma cells and B-cells, we created a CD19-BCMA compound CAR (cCAR) that targets CD19 on B-cells and BCMA on plasma cells. We reported the results of a patient with stage IV diffuse large B-cell lymphoma (DLBCL) and 20-year history of SLE who received cCAR [23]. cCAR led to a profound depletion of B-cells, which remained undetectable until Day 198 post-cCAR. However, the aplasia was temporary, and B-cells returned to baseline 9 months post-cCAR. Despite discontinuation of immunosuppressant therapy, the patient's complement levels remained within normal limits, indicating absence of complement activation. In addition, measured ANA levels were undetectable by Week 28 post-cCAR. ANA remained undetectable at Week 37 despite the recovery of B-cells to normal levels, indicating that cCAR had effectively "reset" the immune population. Additionally, the patient achieved complete remission based on bone marrow biopsy and positron-emission tomography computed tomography (PET-CT) analysis after cCAR T-cell infusion. cCAR was demonstrated as safe in the patient, who did not display any signs of CRS-related toxicity during treatment. Twenty-threemonths post-cCAR, the patient's SLE remains stable and DLCBL in remission.

Future Direction

Additional clinical trials of cCAR are currently ongoing to further elucidate the safety and efficacy of this treatment option in SLE and other related conditions. As autoimmune disorders encompass a wide range of clinical conditions mediated by autoantibodies, the benefits of B-cell and plasma cell depletion by cCAR might be extended beyond SLE treatment.

Additionally, as acute organ transplant rejection is dependent on preformed antibodies to donor markers, cCAR may be an effective pretreatment strategy to deplete any potential damaging antibodies and increase successful organ transplantation. These ongoing trials will better explore the potential of cCAR as an emerging therapy for various antibody-mediated conditions through resetting dual antibody-producing populations.

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