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Spotlight

Therapeutic intersections: Expanding benefits of CD19 CAR T cells from cancer to autoimmunity

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Anti-CD19 CAR T cells were among the last decade's scientific breakthroughs, achieving remarkable remissions in patients with B cell leukemias and lymphomas. Now, the engineered cell therapies are traversing disease indications into autoimmunity and resolving disease symptoms in patients with systemic lupus erythematosus (SLE), idiopathic inflammatory myositis, and systemic sclerosis.[1]

Autoimmune diseases, defined by the loss of tolerance against self-antigens, encompass a wide array of disorders based on antigen reactivity as well as symptoms. Even though the entire immune system is involved in disease pathogenesis, targeting of autoreactive B cells either by inhibition of cell activation or by complete aplasia has been an effective way to induce remission. For example, belimumab and ianalumab are used to treat systemic lupus erythematosus (SLE) by inhibiting B cell activating factor (BAFF).[2,3] B cell depletion is often achieved with the anti-CD20 monoclonal antibody rituximab, currently FDA approved for the treatment of rheumatoid arthritis, Wegener's granulomatosis, microscopic polyangiitis, and pemphigus vulgaris.[3] Rituximab has also been used to treat patients with B cell malignancies, such as non-Hodgkin's lymphoma and chronic leukocytic leukemia.[4] Although typically effective in the short term, current therapies for autoimmune disorders do not achieve long-lasting drug-free remission, with patients prone to relapse when their B cells repopulate. In a recent issue of *The New England Journal of Medicine*, Müller et al. pursue durable remissions in a variety of autoimmune diseases using $CD19^+$ B cell-depleting chimeric antigen receptor (CAR) T cells.[1]

CAR T cells are a class of immunotherapy currently FDA approved to treat patients with B cell leukemias, lymphomas, and multiple myeloma. Engineered with an anti-CD19 single-chain variable fragment tethered to a 4-1BB costimulatory domain and CD3zeta signaling domain, CD19 CAR T cells are effective at depleting all $CD19^+$ B cells and maintaining complete aplasia.[4] Since the first clinical trial was published in 2011, CD19 CAR T cells have been successful at inducing lasting remission in leukemia patients resistant to other B cell-depleting therapies, including rituximab.[4] CAR T cell treatment improves on the short duration of current therapies, as patients maintain complete B cell aplasia with circulating CAR T cells detectable even a decade after treatment.[5] This improved therapy shows promise not only in treating various cancers but also for sustained ablation of autoreactive B cells in patients with autoimmune diseases without the need for continuous treatment.

Following an initial report in which five patients were successfully treated for SLE with CD19 CAR T cells (MB-CART19.1),[6] Müller et al. now report on the treatment of fifteen patients across three autoimmune diseases with MB-CART19.1. Most patients had SLE, but the trial also included patients with idiopathic inflammatory myositis and systemic sclerosis.[1] All patients had severe disease burden, including glomerulonephritis, and lack of sustained remission with multiple therapies, including B cell ablation (rituximab) and BAFF inhibition (belimumab).[1]

MB-CART19.1 was inserted into patient $CD4^+$ and $CD8^+$ T cells via lentiviral transduction, and following expansion, T cells were infused back into the patient.[1] Interestingly, patients who were previously treated with rituximab had a smaller percentage of CD19 CAR-positive cells and reduced T cell proliferation compared to patients who had not received rituximab.[1] This effect was not described in the original CD19 CAR T cell trials, in which patients had received rituximab therapy several times prior to CAR T cell infusion.[4] All patients who received MB-CART19.1 achieved B cell aplasia an average of 5.9 days after treatment and resolved disease symptoms.[1] Interestingly, despite sustained remission, B cell aplasia only lasted an average of 112 days, and only one patient still maintained aplasia at the time of publication.[1] Lack of CAR T cell persistence is a departure from early trials of CAR T cells, which showed persistence continuing for more than a decade[5] rather than only a few months, likely owing to the utilization of a 4-1BB costimulatory domain in the CD19 CAR[4] also used by MB-CART19.1. With phase I clinical trials ongoing for MB-CAR19.1 in the treatment of leukemia, it remains to be seen whether lack of persistence is specific to autoimmune diseases or due to the MB-CART19.1 construct itself.

Autoimmune diseases are often initially triggered by an inflammatory event, such as pneumonia. This inflammatory event stimulates the immune system and triggers loss of tolerance, resulting in autoreactive B cells and symptomatic disease.

Current therapies induce remission by eliminating these B cells to reset the immune system and restore tolerance.[2] These therapies are often successful, allowing patients to cease therapy and remain disease-free for a short time. However, relapses often occur after another unrelated inflammatory event that once again triggers loss of tolerance. CAR T cells should offer an advantage over traditional therapies because, historically, they persist for years rather than months and remain on patrol during inflammatory events to correct loss of tolerance before it becomes symptomatic disease. Therefore, it is surprising that patients treated with MB-CART19.1 have, to date, remained in remission despite both lack of persistence of CAR T cells and occurrence of inflammatory events, including pneumonia.[1] The authors hypothesize that this could be due to a complete reset of the immune system, resulting in class switching of antibodies and depletion of plasmablasts.[1] Future follow-ups will determine whether remission will continue in these patients past the two-year endpoint of the study.

Cytokine release syndrome (CRS) is common in B cell cancer patients treated with CD19 CAR T cells.[7] Therefore, patients receiving MB-CAR19.1 were monitored for toxicity following infusion. Patients had only mild CRS with grade 1 and 2 fevers, a milder response than seen with CD19 CAR T cell trials in leukemia patients.[1] Symptoms of CRS were treated with the IL-6 inhibitor tocilizumab.

One concern with anti-CD19 CAR T cell therapy is an increased risk of infection and potential destruction of protection from lifetime vaccinations due to elimination of B cells and humoral immunity. However, although protection against COVID-19, pneumonia, and coronavirus were lost, Müller et al. found that protection gained from some vaccinations, such as tetanus and measles, was unaffected by MB-CART19.1 therapy.[1] These findings align with results from CD19 CAR T cell trials in cancer patients and are explained by the existence of a population of CD19-negative long-lived plasma cells that reside in the bone marrow, where protection induced by some vaccines is retained.[8,9]

CAR T cell therapy shows immense promise in improving the treatment of autoimmune diseases. MB-CART19.1 induces sustained drug-free remission thus far, despite lack of persistent B cell depletion. Specific targeting of autoreactive B cells is one way that we can further advance treatment of autoimmune diseases. Chimeric autoantibody receptor T cells achieve B cell depletion using the autoantigen itself to eliminate only autoreactive B cells, leaving the rest of the B cell population unharmed and humoral immunity intact. This advanced class of immunotherapy has been developed for the treatment of pemphigus vulgaris and is currently being evaluated in a phase I clinical trial.[10] In summary, CD19 CAR T cell therapy improves the treatment of autoimmune diseases by inducing lasting drug-free remission and provides a roadmap for the development of autoimmune-disease-specific therapies in the future.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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