CD19 CAR T-Cell Therapy for Refractory Ulcerative Colitis

In recent years, the therapeutic armamentarium for ulcerative colitis (UC) has expanded considerably, largely because of the development of biologics and small molecules targeting key effector mediators involved in disease pathogenesis. Despite these advances, a subset of patients remains resistant to all currently available therapies, ultimately requiring colectomy. In the *New England Journal of Medicine*, Müller and colleagues[1] reported a case of a 21-year-old patient with severe UC resistant to multiple pharmacologic therapies who achieved stable clinical, endoscopic, and histologic remission following administration of autologous chimeric antigen receptor (CAR) T cells targeting CD19. CD19 is a transmembrane protein expressed on both normal and malignant B cells that function as a coreceptor for the B-cell receptor, amplifying intracellular signaling pathways that regulate B-cell activation and responses.[2–4]

Mechanism and Therapeutic Rationale for CD19 CAR T-Cell Therapy

CAR T cells are derived from a patient's circulating T cells and are genetically modified to express synthetic CARs that recognize and bind specific surface antigens on pathogenic cells. These engineered T cells are expanded ex vivo and reinfused into the patient. Initially developed to eradicate malignant B cells in hematologic cancers such as lymphoma, leukemia, and multiple myeloma, CAR T cells are now being explored as potential therapies for autoimmune and inflammatory diseases.[5] CD19-directed CAR T-cell therapy has demonstrated superior and durable B-cell depletion compared with antibody-based strategies in immune-mediated diseases including systemic lupus erythematosus, idiopathic inflammatory myositis, and systemic sclerosis.[6] Because UC-associated mucosal inflammation is characterized by the accumulation of CD19-expressing B cells and plasma cells, and as most current UC therapies do not directly modulate B-cell responses, Müller et al initially treated their patient with blinatumomab, a CD19-directed T-cell engager. However, blinatumomab failed to induce stable resolution of the ongoing mucosal inflammation. Subsequent administration of a single infusion of CD19 CAR T cells led to rapid expansion of CAR T cells, profound B-cell depletion in both peripheral blood and colonic tissue, and complete clinical, endoscopic, and histologic remission at 14 weeks without concomitant immunotherapy. Treatment was well tolerated, with only mild (grade 1) cytokine release syndrome that resolved spontaneously, asymptomatic hypogammaglobulinemia, and a transient episode of neutropenia requiring granulocyte colony-stimulating factor. These encouraging findings suggest that B-cell–targeted therapy may represent a novel therapeutic avenue for certain forms of severe, treatment-refractory UC.

Heterogeneity of Inflammatory Pathways in UC

The molecular mechanisms driving mucosal injury in UC remain incompletely understood. Evidence supported in part by the differential responses to biologics indicates that multiple inflammatory pathways may be activated either simultaneously or at distinct disease stages. Even among patients with similar clinical and endoscopic phenotypes, inflammatory molecular signatures can differ substantially, highlighting disease heterogeneity and explaining the limited efficacy of targeted agents in some subsets.[7,8]

The Müller case, involving severe UC refractory to numerous biologics and small molecules that primarily target antigen-presenting cell or T-cell pathways, suggests that certain aggressive UC phenotypes may be driven predominantly by pathogenic B-cell or plasma cell responses. It remains unclear as to whether these B-cell–mediated processes occur early in disease pathogenesis or arise secondarily, caused by long-term immunomodulatory therapy. If the latter is true, CD19 CAR T-cell therapy may be most effective in patients with long-standing, multidrug-resistant UC.

Reconciling CD19 CAR T-Cell Efficacy With CD20-Targeted Therapy Failure

The benefits observed in the Müller study contrast sharply with previous findings demonstrating that rituximab, a CD20-targeting monoclonal antibody, is ineffective in controlling active UC.[9] However, research in other autoimmune diseases has revealed that rituximab efficiently depletes B cells in peripheral blood but not in solid tissues or mucosal compartments.[10–12] Similarly, in the Müller study, CD19-depleting blinatumomab failed to achieve complete mucosal B-cell clearance or induce durable remission. Thus, the success of CD19 CAR T-cell therapy in UC may reflect its ability to induce profound B-cell depletion within the colonic mucosa and to target both $CD19^+$ and $CD20^+$ B-cell populations.[13]

Pathogenic B-Cell Subsets in UC

Further research is needed to characterize B-cell subpopulations infiltrating the UC mucosa and to elucidate the mechanisms by which they mediate tissue injury. The inflamed UC mucosa is heavily infiltrated by $CD19^+$ plasma cells that produce granzyme B and may directly damage epithelial cells.[14] Single-cell transcriptomic analyses suggest that UC is associated with a plasmablast-skewed humoral response, including an expansion of IgG^+ plasma cells,

interferon-primed naïve B cells, and circulating gut-homing $\beta7^+$ plasmablasts, which correlate with disease activity.[15] Identifying patients with these B-cell signatures may facilitate personalized use of CD19 CAR T-cell therapy.

Immune Reprogramming Induced by CD19 CAR T Cells

Because B cells regulate multiple innate and adaptive immune processes, dissecting the immune reprogramming following CD19 CAR T-cell therapy could yield valuable mechanistic insights. In systemic lupus erythematosus, CD19 CAR T-cell–mediated B-cell depletion not only resets the memory B-cell compartment but also suppresses the pathogenic interferon signature in monocytes and T cells, suggesting a broader immune recalibration beyond B-cell elimination.

Safety Considerations

Currently approved UC therapies, including antitumor necrosis factor (TNF) agents, anti-integrin and anti-interleukin (IL)-23 antibodies, and Janus kinase (JAK) inhibitors, are generally associated with favorable safety profiles, with serious adverse events occurring infrequently and long-term risks manageable in clinical practice.[16–19]

In contrast, CD19 CAR T-cell therapy presents distinct safety concerns arising from both CAR T-cell expansion and lymphodepletion regimens. Patients may experience acute toxicities, such as cytokine release syndrome and immune effector-cell–associated neurotoxicity syndrome, as well as long-term complications from deep and prolonged B-cell depletion: events uncommon with conventional biologics.[20]

Balancing B-Cell Depletion and Cancer Risk

Long-term B-cell depletion may also influence colorectal carcinogenesis, a recognized complication of UC.[21] $CD19^+$ B cells have been reported to suppress tumor aggressiveness in certain cancers, including triple-negative and HER2-positive breast cancer[22] and to enhance antitumor immunity in muscle-invasive bladder cancer.[23] Moreover, $CD20^+$ B cells are enriched in the microenvironment of sporadic colorectal cancers, where their presence correlates with improved prognosis. Experimental depletion of $CD20^+$ B cells promote tumor progression and negates the efficacy of anti–PD-1 immunotherapy in preclinical colon cancer models.[24]

Therefore, although CD19 CAR T-cell therapy offers exciting potential for refractory UC, its long-term implications, particularly regarding oncologic safety, must be carefully evaluated.

Conclusions

The case described by Müller and colleagues provides compelling evidence that B cells may play a more central pathogenic role in UC than previously appreciated. CD19-directed CAR T-cell therapy represents a bold and innovative therapeutic strategy capable of inducing deep remission in otherwise refractory disease. Nonetheless, larger controlled studies are needed to validate these findings, elucidate mechanisms of action, and define the appropriate clinical context for B-cell–targeted therapies in UC.

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Conflicts of interest

These authors disclose the following: Giovanni Monteleone has served as a consultant for First Wave BioPharma and Giuliani SpA and as a speaker for Takeda, Eli Lilly, Abbvie, Galapagos, and Pfizer and has filed a patent related to the treatment of inflammatory bowel diseases with Smad7 antisense oligonucleotides. Irene Marafini has served as a consultant and speaker for Abbvie, Eli Lilly, and Galapagos. The remaining authors disclose no conflicts.

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