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FOUND IN TRANSLATION

CD19-directed T cell–engaging antibodies for the treatment of autoimmune disease

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Jennifer S. Michaelson, Chief Scientific Officer at Cullinan Oncology, and Patrick A. Baeuerle, scientific advisor to Cullinan Oncology and honorary professor in immunology at Ludwig Maximilians University Munich, discuss the use of CD19-specific T cell–engaging antibody therapies (TCEs) as therapeutics for autoimmune diseases.

T cell–engaging antibody therapies (TCEs) are designed to transiently connect cytotoxic T cells with cancer cells to mediate redirected lysis (van de Donk and Zweedman, 2023). This is achieved by bispecific binding of the TCE to the invariant CD3ε subunit of the T cell receptor on T cells and to a cell surface antigen on target cells. TCEs have experienced an unparalleled upsurge in the industry. Whereas 2 years ago only one TCE, namely blinatumomab, was on the market treating relapsed/refractory acute lymphoblastic leukemia (ALL), today eight Food and Drug Administration (FDA)–approved TCEs additionally treat uveal melanoma, non-Hodgkin's lymphoma (NHL), and multiple myeloma (MM).

A therapeutic modality providing an alternative approach to TCEs is autologous chimeric antigen receptor (CAR)-T cell therapies (Finck et al., 2022). To generate CAR-T cell products, T cells are isolated from patients and reprogrammed, typically with a virally delivered cDNA encoding the CAR, which allows the genetically engineered T cells to recognize a cell surface antigen on cancer cells. The autologous CAR-T cells are administered to patients following a lymphodepleting chemotherapy regimen necessary to promote engraftment and survival of the CAR-T cells. A total of six such therapies have been FDA approved for treatment of ALL, NHL, and MM, targeting CD19 or B cell maturation antigen (BCMA).

CD19-specific CAR-T cells have exquisite potency for eliminating both normal and malignant B cells. This prompted researchers to investigate the therapeutic potential of autologous CD19-specific CAR-T cells in systemic lupus erythematosus (SLE), an autoimmune disease driven by autoreactive B cells. A single CAR-T cell administration led to durable drug-free remissions in all patients with severe SLE treated (Mackensen et al., 2022). Similar data were recently reported for a limited number of patients with idiopathic inflammatory myopathies and systemic sclerosis (Müller et al., 2024). Several biotech companies developing CD19-specific CAR-T cell therapies have since pivoted from oncology toward autoimmune diseases (Arnold, 2024). Here, we propose exploration of CD19-specific TCEs as an alternative approach and compare TCEs and CAR-T cells for their potential as therapeutics for autoimmune diseases. The key differences are summarized in Table 1.

A fundamental difference between TCE and CAR-T cell therapies relates to manufacturing. The currently approved commercial autologous CAR-T therapies require individual manufacturing for each patient, with on-demand production being very costly (Khang et al., 2023). Off-the-shelf, allogenic CAR-T and CAR–natural killer cell therapies are being developed but most are still early in clinical development. By contrast, TCEs are produced like monoclonal antibodies, and are available as off-the-shelf treatments for immediate therapeutic use.

A single intravenous (IV) infusion of CAR-T cells is typically sufficient to treat leukemia and lymphoma and was also sufficient to achieve the deep remissions observed in a small number of autoimmune disease patients (Mackensen et al., 2022; Müller et al., 2024). It is not known yet whether a defined duration of CD19-specific TCE therapy can achieve the same outcome, but it may be advantageous that a TCE treatment can be repeated until a robust therapeutic effect is achieved. TCEs also afford the option of re-treatment if needed upon potential future relapse. While it is hard to predict the robustness and longevity of a single CAR-T cell therapy, the pharmacokinetics (PK) of TCEs are predictable.

Endogenous T cell activation by TCEs and activation of CAR-T cells typically comes with the release of proinflammatory primary and secondary cytokines, like TNF-α and interleukin-6 (IL-6), respectively. This can lead to life-threatening cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS). Prophylactic steroids, anti-IL-6 monoclonal antibody, and antihistamines are frequently employed to curb cytokine release. An advantage of TCEs over CAR-T cell therapies is the option for step-up

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Table 1. **Comparison of CD19/CD3-bispecific TCE and autologous CD19 CAR-T cells**

Feature	CD19/CD3-bispecific TCE	Autologous CD19 CAR-T cell therapy
Manufacturing	• Standard antibody manufacturing • Off-the-shelf availability	• Individualized CAR-T cell production; delayed treatment • High cost and complexity
Mode of action	• Can potentially engage all T cells in a patient for redirected target cell lysis • Potential to eliminate cells expressing very low levels of CD19	• Redirected target cell lysis relies on limited number of genetically engineered T cells
PK/pharmacodynamics (PD)	• Antibody construct with well-defined PK/PD properties	• "Living drug" with difficult-to-predict PK/PD
Administration	• IV or SC administration with potential for self-administration • Ability to re-treat if required	• Onetime treatment • IV route only
Safety	• CRS and ICANS • SC administration and step-up dosing have potential to limit CRS and ICANS to grade 1 or 2	• Risk for grade 3 and higher CRS and ICANS • Adverse events from lymphodepletion • Risk of secondary T cell malignancies
Experience with modality	• Eight FDA-approved TCEs (five targets)	• Six FDA-approved CAR-T cell products (two targets)

dosing to potentially mitigate first-dose adverse events and enable higher subsequent dosing with reduced risk of CRS. Subcutaneous (SC) administration of TCEs is another option to potentially mitigate cytokine release via reduced Cmax relative to IV administration. By application of step-up dosing and SC administration, most FDA-approved TCEs show limited CRS of grade 1 or 2 (Falchi et al., 2023).

Administration of CAR-T cells, but not TCEs, requires pre-conditioning of patients by lymphodepletion with chemotherapy, which may add complexity, toxicities, and additional risks in the autoimmune disease setting. Integration of the CAR gene into the T cell genome by lentiviral delivery is emerging as a novel risk that can lead to secondary malignancies (Verdun and Marks, 2024). A recent analysis of 449 patients receiving commercial CAR-T cell therapies projected a 5-year cumulative incidence of 15.2% and 2.3% for solid and hematological secondary malignancies, respectively (Ghilardi et al., 2024). While this may not limit the use of CAR-T cell therapies for treating deadly malignancies, this risk may not be appropriate for treating patients with chronic autoimmune diseases.

The therapeutic success in treating lupus and other autoimmune diseases is thought to require profound depletion of the B cell compartment. This likely hinges upon three factors: deep tissue penetration of the therapeutic, high potency of target B cell depletion, and selection of the optimal B cell target. While CD19 CAR-T cells have seemingly achieved deep tissue penetration and B cell depletion in patients with severe lupus, one can envision similar activity for TCEs given their successful treatment of various B cell malignancies. For instance, the CD19/CD3-bispecific TCE blinatumomab has shown rapid depletion of normal and malignant B cells in ALL patients, and also showed profound activity in NHL patients where deep penetration into malignant lymph nodes is required for efficacy (Goebeler et al., 2016). Likewise, efficacy of CD20-specific TCEs in NHL in terms of complete response rates and response duration is relatively comparable to that of CD19-specific CAR-T cells (Falchi et al., 2023).

Several B cell lineage markers can be considered as target antigens for elimination of autoreactive B cells in autoimmune diseases, including CD19, CD20, and BCMA. All three B cell markers are targeted by FDA-approved TCEs and CAR-T cell products effectively treating B cell malignancies such as ALL, NHL, and MM, respectively. CD19 stands out given its expression in the earliest as well as latest stages of B cell development (Clatworthy, 2011). Unlike CD20 and BCMA, CD19 is expressed on pro- and pre-B cells. And, like BCMA and unlike CD20, CD19 is expressed on antibody-producing plasma blasts. Unlike BCMA, CD19 targeting may not deplete long-lived plasma cells, thereby conserving protective immunity to pathogens (Müller et al., 2024). Given the recent CAR-T cell therapy data, CD19 is emerging as the B cell target with the highest potential to achieve durable treatment-free remissions for patients with severe autoimmune diseases.

While several CD19 CAR-T cell therapies are commercially available for treating ALL and NHL, these will require new clinical studies for their establishment as a therapy for autoimmune diseases, and safety considerations may limit their use to patients with severe disease. The only approved CD19-specific TCE, blinatumomab, may also have limited utility for autoimmune diseases given the requirement for continuous IV infusion and a response rate in pediatric ALL that is lower than that seen for CD19 CAR-T cell therapies. Currently, there are only two additional CD19-specific TCEs in clinical development in the U.S., namely TNB-486 and CLN-978. Both are being developed in B cell NHL and have shown high potency and specificity in preclinical studies (Malik-Chaudhry et al., 2021; Meetze et al., 2023). TNB-486 is administered by IV infusion, and recently, issues with CRS in NHL patients required the introduction of a double step-up dosing regimen (Gaballa et al., 2023). CLN-978 is given by SC administration, which showed safety advantages over the IV route in preclinical studies while delivering comparable B cell depletion and anti-tumor activity (Meetze et al., 2023). Furthermore, CLN-978 is optimized for elimination of target cells expressing very low copy numbers of CD19 (Meetze et al., 2023), which may have particular utility for removal of pathogenic B cells with low levels of CD19 expression.

The encouraging early proof-of-concept studies with CD19-directed CAR-T cell therapies in severe lupus patients gives promise for CD19-specific TCEs as a potent, off-the-shelf, patient-friendly, and potentially safer therapy. T cell engagement by TCEs may achieve deep and durable

responses for a potentially wide range of autoimmune disease indications where pathogenic B cells play a key role in disease.

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