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Research Article

Immune Therapy in CD19-Positive B-Cell Diseases: A Systematic Review.

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Abstract

Background: CD19 is a lineage-restricted surface antigen expressed on nearly all stages of B-cell development, making it a pivotal target for immune-directed therapy in B-cell malignancies and autoantibody-mediated diseases. Over the past decade, CD19-directed immune therapies—including chimeric antigen receptor (CAR) T cells, bispecific antibodies, monoclonal antibodies, and antibody–drug conjugates—have transformed hematologic oncology and are now extending into autoimmune disorders.

Objective: To systematically review clinical outcomes of CD19-targeted immune therapies across malignant and autoimmune B-cell diseases following PRISMA 2020 guidelines.

Methods: PubMed, Embase, Web of Science, and ClinicalTrials.gov were searched (January 2010–October 2025). Randomized controlled trials (RCTs), phase II/III studies, and pivotal single-arm trials were included. Data were appraised using Cochrane RoB 2 and ROBINS-I.

Results: CD19-directed CAR-T therapies (axi-cel, liso-cel, tisa-cel, brexu-cel) produced high overall response rates and complete response rates in relapsed/refractory large B-cell lymphoma (LBCL), [1,2]. Blinatumomab improved survival and Measurable residual disease (MRD) clearance in newly diagnosed and relapsed B-cell acute lymphoma leukemia (ALL) [3,4,12,13], and early American College of Rheumatology (ACR) 2025 data suggest efficacy in systemic sclerosis [14]. Blinatumomab also led to compete restoration of platelet counts in a patient with refractory immune thrombocytopenia and antiphospholipid syndrome [17]. Tafasitamab–lenalidomide and loncastuximab tesirine achieved durable responses in diffuse large B cell lymphoma (DLBCL) [5,6]. In autoimmunity, CD19 CAR-T therapy induced drug-free remission in systemic lupus erythematodes (SLE) [7].

Conclusions: CD19 has the potential to become a unifying therapeutic target across hematology and immunology. This approach unifies the treatment of many different diseases by one concept. The indication would include all CD 19 positive B cell diseases.

Keywords: CD19; CAR-T; blinatumomab; systemic sclerosis; autoimmunity; lymphoma; leukemia

Introduction

CD19 is a transmembrane glycoprotein essential for B-cell receptor signaling, expressed from the pro-B through plasmablast stages, and absent on hematopoietic stem cells and most long-lived plasma cells. This distribution enables elimination of malignant and autoreactive B cells while preserving regenerative capacity of CD 19 – negative stem cells of

the B lineage system. Therapeutic depletion of $CD19^+$ B cells (e.g., via anti-CD19 CAR T cells or T cell engagers) spares $CD19^-$ hematopoietic stem and progenitor cells (HSPCs) within the bone marrow. Following clearance of pathogenic or autoreactive B cell populations, these progenitors drive de novo B cell lymphopoiesis, leading to gradual reconstitution of the peripheral B cell compartment. Early re-emerging B cells are predominantly transitional and naïve phenotypes, reflecting a "reset" of the B cell repertoire This remodelling process is associated with reconstitution of normal B cells [18,19]. Since 2017, multiple CD19-directed platforms—including CAR-T cells, bispecific antibodies, monoclonal antibodies, and antibody–drug conjugates—have transformed outcomes in B-cell malignancies and are now being applied to autoimmunity [1-7,17]. This systematic review summarizes the evidence across both domains in accordance with PRISMA 2020.

Methods

The review was conducted in accordance with PRISMA 2020. Eligible studies included human clinical trials of CD19-targeted therapies—CAR-T cells, bispecific antibodies, monoclonal antibodies, or antibody–drug conjugates. Preclinical studies, non-English articles, and case series with fewer than five patients were excluded.

Results

Overview of Included Studies

CD19 CAR-T Cell Therapies in B-Cell Malignancies

CD19-directed CAR-T therapies have achieved unprecedented remission rates in relapsed or refractory B-cell malignancies.

- Axi-cel (ZUMA-7) improved two-year event-free survival to ~41 % versus ~16 % with standard salvage therapy and achieved complete response ~65 %, in the experimental arm versus 32% in the control arm [1].
- Liso-cel (TRANSFORM) showed Median event-free survival showed significantly improved median event-free survival in the liso-cel group (10·1 months) versus 2.3 months in the control arm %(2).

T-Cell–Redirecting Bispecific Molecule: Blinatumomab

Blinatumomab, a CD19×CD3 bispecific T-cell engager, has become integral across the ALL continuum. In the TOWER trial, median overall survival was 7.7 months with blinatumomab vs 4.0 months with chemotherapy [3]. In patients with MRD-positive remission, MRD clearance was achieved in ~80 % with 2-year relapse-free survival 54 %(6). In newly diagnosed adult B-ALL (E1910), 3-year overall survival was 85 % vs 68 % with chemotherapy [12]; COG AALL1731 demonstrated similar benefits in pediatric/AYA populations [13]. Beyond malignancy, the first human experience in diffuse cutaneous systemic sclerosis (American College of Rheumatology (ACR) 2025) showed near-complete depletion of $CD19^+$ B cells, median mRSS reduction 35 %, and stabilization of lung function (ΔFVC +6 %) with only grade 1–2 CRS and no neurotoxicity [14]. Blinatumomab also restored platelet counts completely with sustained effect and normalized anti-glycoprotein (GP) IIb/IIIa-, anti-cardiolipin- and 2-glycoprotein I antibody titers in a patient with refractory immune thrombocytopenia and antiphospholipid syndrome [9].

Monoclonal Antibody: Tafasitamab Plus Lenalidomide

In DLBCL tafasitamab-cxix, an Fc-enhanced anti-CD19 monoclonal antibody, combined with lenalidomide in the L-MIND study achieved ORR 60 %, CR 43 %, and median OS 33 months with mainly hematologic toxicity [5].

Antibody–Drug Conjugate: Loncastuximab Tesirine

In LOTIS-2 in DLBCL, loncastuximab tesirine demonstrated ORR 48 % and CR 24 %, with median DOR 10 months and OS ~10 months [6]. Myelosuppression and edema were the most common adverse events.

CD19-Directed Therapies in Autoimmune Diseases

Autologous CD19 CAR-T therapy induced drug-free remission in refractory SLE [7]. The ACR 2025 SSc blinatumomab series expanded CD19 targeting to fibrotic autoimmunity with clinically meaningful improvement and low-grade toxicity [14].

Discussion

CD19-positive B-cell disorders have entered an era of immune precision. CAR-T therapy remains the most potent modality for salvage treatment, achieving durable remissions and, in early-relapsed LBCL, superiority over transplant-based salvage [1, 2]. Construct-specific differences—CD28 vs 4-1BB costimulation and product composition—shape efficacy-toxicity profiles. Relapse mechanisms include CD19 antigen loss [10], CAR-T exhaustion, and immunosuppressive microenvironments; next-generation dual-target, armored, and allogeneic platforms aim to overcome these challenges [15].

Blinatumomab has reframed ALL management by prioritizing molecular remission. Across TOWER [3], E1910 [12], and AALL1731 [13], it achieved deep MRD negativity and survival gains while maintaining manageable toxicity. Its continuous-infusion dosing allows precise immune engagement absent in cellular therapies.

Translational progress now extends CD19 targeting beyond oncology. Autologous CAR-T therapy achieved long-term drug-free remission in SLE [7], while blinatumomab produced early improvement in fibrotic parameters in systemic sclerosis [14]. Collectively, these therapies illustrate a continuum: transient modulation (blinatumomab), sustained depletion (inebilizumab, tafasitamab), and durable immune reset (CAR-T). Tailoring interventions along this spectrum enables alignment with disease biology, patient comorbidity, and therapeutic intent.

Future Directions

Step-Up Dosing to Prevent and Mitigate Neurologic Toxicity (ICANS)

In patients with prior neurotoxicity blinatumomab successfully uses an initial low-dose infusion and step-up escalation for retreatment, in order to prevent neurotoxicity [16].

Limitations

Heterogeneity among trial designs and follow-up durations precluded quantitative meta-analysis. Autoimmune cohorts were small, with short observation periods. The systemic-sclerosis data [20] remain preliminary and hypothesis-generating pending controlled validation.

Conclusions

CD19-targeted immune therapies have transformed management of B-cell malignancies and are rapidly extending into autoimmune and fibrotic diseases. Blinatumomab's evolution from salvage to frontline therapy in

ALL and its initial success in systemic sclerosis underscore CD19 as a unifying therapeutic target across hematology and immunology. Future investigations should validate durability, optimize sequencing within combination regimens, and ensure equitable access to these transformative modalities.

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