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Efficacy and Safety of CD19-Targeted Chimeric Antigen Receptor (CAR) T-Cell Therapy in Refractory Systemic Lupus Erythematosus: A Systematic Review of Clinical Outcomes and B-Cell Depletion Kinetics

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A B S T R A C T

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune pathology characterized by a breakdown in self-tolerance, B-cell hyperactivity, and the production of pathogenic autoantibodies. While conventional B-cell depletion strategies utilizing monoclonal antibodies often fail to achieve deep tissue clearance, CD19-targeted chimeric antigen receptor (CAR) T-cell therapy has emerged as a transformative modality capable of inducing durable drug-free remission. This systematic review and meta-analysis evaluate the clinical efficacy, pharmacodynamics of B-cell depletion, and safety profile of both autologous and allogeneic CD19 CAR T-cell therapies in refractory SLE. We conducted a systematic literature review on manuscripts published between January 1st, 2014, and March 1st, 2025, focusing on interventional clinical trials and high-quality case series. Primary endpoints included the Definition of Remission in SLE (DORIS) and reduction in SLEDAI-2K scores. Secondary endpoints analyzed B-cell aplasia kinetics, seroconversion of anti-dsDNA, and adverse events, including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and novel autoimmune-specific toxicities. Statistical synthesis utilized weighted averages for continuous variables and event rates for categorical outcomes. The analysis synthesized data from 20 distinct patients with refractory SLE across three pivotal cohorts. The pooled rate of DORIS remission at three months post-infusion was 100%. The mean SLEDAI-2K score decreased from a baseline of 12.5 to 0.8 at three months. Deep B-cell depletion was achieved in all patients, with a mean duration of aplasia of 112 days. Reconstitution of the B-cell compartment was characterized by a naïve phenotype (IgD+/CD27-), indicating a comprehensive immunological reset. Safety analysis revealed that while CRS occurred in 88% of patients, it was predominantly Grade 1 or 2. No high-grade ICANS occurred. Unique toxicity signals, including local immune effector cell-associated toxicity syndrome (LICATS), were identified. In conclusion, CD19-targeted CAR T-cell therapy induces rapid, profound, and sustained drug-free remission in patients with refractory SLE. The mechanism involves deep tissue depletion of B-cells and plasmablasts, facilitating a reset of the humoral immune system.

1. Introduction

Systemic lupus erythematosus (SLE) represents the archetype of systemic autoimmune diseases, a complex and heterogeneous disorder characterized by the catastrophic breakdown of self-tolerance. The disease manifests through the production of high-affinity autoantibodies directed against nuclear antigens, including double-stranded DNA (dsDNA), nucleosomes, and Smith (Sm) antigens. These autoantibodies form immune complexes that deposit

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in critical organs such as the kidneys, heart, skin, and lungs, initiating a cascade of complement activation, inflammatory cell recruitment, and tissue destruction.[1] The clinical course is often undulating, marked by periods of flares and remission, but for a subset of patients, the disease becomes refractory, resisting standard therapeutic interventions and leading to cumulative organ damage and early mortality.

The pathogenesis of SLE is intricately linked to the hyperactivity and dysregulation of the B-cell compartment. B cells in SLE serve multiple pathogenic roles: they are the precursors of antibody-secreting plasma cells; they act as potent antigen-presenting cells that drive T-cell activation and epitope spreading; and they secrete pro-inflammatory cytokines that perpetuate the autoimmune loop.[2] Consequently, B-cell depletion has long been a therapeutic goal. Despite significant therapeutic advances, including the approval of biologic agents such as belimumab (targeting BAFF) and anifrolumab (targeting the Type I Interferon receptor), a substantial proportion of patients remain refractory to standard-of-care immunosuppression. For these patients, the disease course is characterized by progressive organ damage, high cumulative glucocorticoid toxicity, and increased mortality.[3]

The therapeutic landscape for refractory SLE has historically relied on broad-spectrum immunosuppression or B-cell depletion via monoclonal antibodies targeting CD20, such as rituximab. However, rituximab often fails to induce complete or durable remission. This failure is not merely a matter of dosing but is rooted in the biological limitations of monoclonal antibodies. Rituximab relies on antibody-dependent cellular cytotoxicity (ADCC) mediated by natural killer (NK) cells and macrophages. In the inflammatory milieu of SLE, NK cell function is often impaired due to exhaustion or chronic interferon exposure. Furthermore, pathogenic B cells and plasmablasts frequently reside in sanctuary sites within secondary lymphoid organs and inflamed tissues, such as the tubulointerstitium of the kidney. In these stromal niches, high concentrations of B-cell activating factor (BAFF) provide survival signals that protect B cells from apoptosis and render them resistant to ADCC.[4] Additionally, CD20 is downregulated during plasma cell differentiation; thus, rituximab fails to target the antibody-secreting plasmablasts and long-lived plasma cells that are the actual factories of autoimmunity.

In this context, chimeric antigen receptor (CAR) T-cell therapy represents a transformative paradigm shift. Originally developed for B-cell malignancies, CD19-targeted CAR T-cells are genetically engineered to express a synthetic receptor that directs T-cell cytotoxicity against CD19-expressing cells in a Major Histocompatibility Complex (MHC)-independent manner.[5] Unlike passive monoclonal antibodies, CAR T-cells are living drugs that actively migrate against chemokine gradients into tissues, expand in vivo upon antigen recognition, and possess serial killing capabilities. This allows for the deep depletion of the B-cell lineage—including CD19-positive plasmablasts—thereby removing the immediate precursors of autoantibody-producing cells.

The translation of CAR T-cell therapy to SLE was pioneered by a seminal case report in 2021, which demonstrated that autologous CD19 CAR T-cells could induce rapid remission in a patient with severe, multidrug-resistant SLE.[6] Subsequent case series and early-phase clinical trials have reinforced these findings, suggesting that CAR T-cell therapy can induce an immunological reset—a state where the immune system reconstitutes with a naïve repertoire free of pathogenic autoantibodies.[7,8] As the field advances into 2025, novel developments have occurred, including the application of commercial CAR T-cell products (relma-cel)[9] and the introduction of CRISPR-edited allogeneic "off-the-shelf" CAR T-cells to overcome manufacturing challenges associated with autologous T-cell dysfunction.[10] Furthermore, as

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clinical experience grows, distinct toxicity profiles specific to autoimmune patients, such as local immune effector cell-associated toxicity syndrome (LICATS), have been characterized.[11]

This systematic review and meta-analysis are novel in their incorporation of the most recent data from 2024 and 2025, specifically integrating findings from the first commercial and allogeneic CAR T-cell trials in SLE, which were previously excluded from earlier reviews. The primary aim of this study is to provide a granular synthesis of clinical outcomes, specifically quantifying the depth and durability of remission. The secondary aim is to comprehensively analyze the pharmacodynamics of B-cell depletion kinetics required to achieve an immunological reset and to delineate the unique safety profile of CAR T-therapy in the context of systemic autoimmunity, contrasting it with the established toxicity profiles in oncology.

2. Methods

A systematic and comprehensive literature search was conducted to identify relevant studies published between January 1st, 2014, and March 1st, 2025. The databases searched included Scopus, PubMed/MEDLINE, and the Cochrane Library. The search strategy utilized a combination of medical subject headings (MeSH) and free-text terms including: Systemic lupus erythematosus, SLE, lupus nephritis, chimeric antigen receptor, CAR T-cell, CD19, B-cell depletion, relma-cel, and allogeneic. To ensure the inclusion of the most cutting-edge data, we also reviewed conference abstracts from major rheumatology and hematology congresses (EULAR, ACR, ASH) to capture emerging data not yet fully published in peer-reviewed journals. Inclusion Criteria: Population: Adult or pediatric patients with a confirmed diagnosis of SLE (ACR or EULAR/ACR criteria) classified as refractory to at least two lines of standard immunosuppressive therapy (typically including cyclophosphamide, mycophenolate mofetil, or biologics). Intervention: Treatment with CD19-targeted CAR T-cell therapy, regardless of origin (autologous or allogeneic) or costimulatory domain (4-1BB or CD28). Comparators: Baseline disease activity prior to lymphodepletion. Outcomes: Quantitative data on clinical remission (SLEDAI-2K, DORIS), serological response (anti-dsDNA, complement), B-cell kinetics, or safety endpoints. Study Types: Interventional clinical trials (Phase I/II), prospective case series, and high-quality case reports. Exclusion Criteria: Studies were excluded if they were pre-clinical animal models without human data, review articles lacking primary data, or studies focusing exclusively on autoimmune diseases other than SLE without stratifiable data.

Data were extracted independently by two expert reviewers using a standardized data collection form. Discrepancies were resolved through consensus. The following variables were extracted: Demographics: Age, sex, disease duration, and prior lines of therapy. Treatment Protocol: CAR T-cell product type (academic vs. commercial; autologous vs. allogeneic), lymphodepletion regimen (fludarabine/cyclophosphamide dosages), and infused cell dose. Clinical Efficacy: Changes in SLEDAI-2K scores, achievement of DORIS remission, LLDAS (Lupus Low Disease Activity State), and medication-free intervals. Laboratory Markers: Anti-dsDNA titers, C3/C4 complement levels, and proteinuria. Pharmacokinetics/Pharmacodynamics: Time to peak CAR T-cell expansion, duration of B-cell aplasia, and phenotype of reconstituted B cells. Safety: Incidence and grading of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) per ASTCT criteria, cytopenias, infections, and specific toxicities such as LICATS and IEC-HS.

Given that the included studies were primarily non-randomized, single-arm case series, the NIH Quality Assessment Tool for Case Series Studies was employed. We explicitly acknowledge the potential for selection bias, as patients recruited for these early-

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phase trials were carefully selected for organ reserve and may not represent the general refractory SLE population (survivor bias). This study is conducted as a systematic review with a narrative synthesis of quantitative data. Due to the heterogeneity of the interventions (different CAR constructs, dosing regimens, and manufacturing sources). Instead, we present descriptive statistics (means, medians, ranges) and event rates. Efficacy outcomes were stratified by product type (Autologous vs. Allogeneic) where possible. Pre- and post-treatment comparisons for continuous variables (such as SLEDAI scores) are described using changes in means derived from the individual studies.

3. Results and Discussion

Figure 1 serves as the foundational roadmap for this systematic review and meta-analysis, offering a transparent and rigorous visual accounting of how the final evidentiary base was constructed. Adhering strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, this diagram delineates the methodical "funneling" process employed to distill a vast body of initial literature down to the essential core of high-quality clinical data regarding CD19-targeted chimeric antigen receptor (CAR) T-cell therapy in refractory systemic lupus erythematosus (SLE). The figure is critical not only for establishing the reproducibility of the review's methodology but also for defining the precise scope and limitations of the currently available evidence in this rapidly emerging field. The diagram begins at the top level, illustrating the initial identification phase where a comprehensive search strategy was deployed across major biomedical databases, including PubMed/MEDLINE, Scopus, and the Cochrane Library. The search parameters, bounded by the timeframe of January 1st, 2014, to March 1st, 2025, were designed to capture the entire historical arc of CAR T-cell application in autoimmunity, from the earliest theoretical proposals to the most recent clinical trial readouts. This initial broad sweep yielded a significant number of records (represented by the initial N value), reflecting the intense scientific interest in repurposing cellular therapy for autoimmune indications. Subsequent tiers of the diagram detail the systematic filtration process. The first major reduction occurred through the removal of duplicate records, a necessary step when triangulating data from multiple overlapping databases. Following this, the screening phase involved a high-level assessment of titles and abstracts. At this stage, a substantial number of records were excluded for failing to meet basic relevance criteria; these exclusions typically included studies focusing on non-SLE autoimmune diseases (such as multiple sclerosis or myasthenia gravis without SLE subgroups), pre-clinical animal models lacking human translational data, and review articles or editorials that did not present primary clinical findings. The crucial eligibility phase involved a full-text review of the remaining candidates. This stage applied stringent inclusion criteria to ensure clinical homogeneity within the final pooled cohort. Studies were frequently excluded at this juncture for critical methodological reasons, such as insufficient documentation of refractory status according to standard definitions (failure of at least two standard immunosuppressive lines), a lack of granular data on B-cell depletion kinetics, or, crucially, the identification of overlapping patient cohorts published across multiple manuscripts as clinical experience matured at specific academic centers. The final tier of Figure 1 culminates in the included box, representing the crystallized evidence base for this review. It highlights that only eight essential manuscripts met the rigorous standards for inclusion. Crucially, the diagram further breaks down this final selection into the constituent patient cohorts that form the pooled analysis (N=20). It explicitly identifies the three distinct clinical streams that currently define the field: the pioneering German academic cohort using fresh

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autologous cells, the Chinese cohort utilizing the commercial frozen product Relmacabtagene autoleucel (relma-cel), and the cutting-edge allogeneic cohort employing CRISPR-edited universal donor T-cells (TyU19). By explicitly detailing this flow, Figure 1 provides the necessary context for interpreting the subsequent efficacy and safety data, emphasizing that the findings are derived from a highly selected, novel, and diverse set of early-phase clinical experiences.

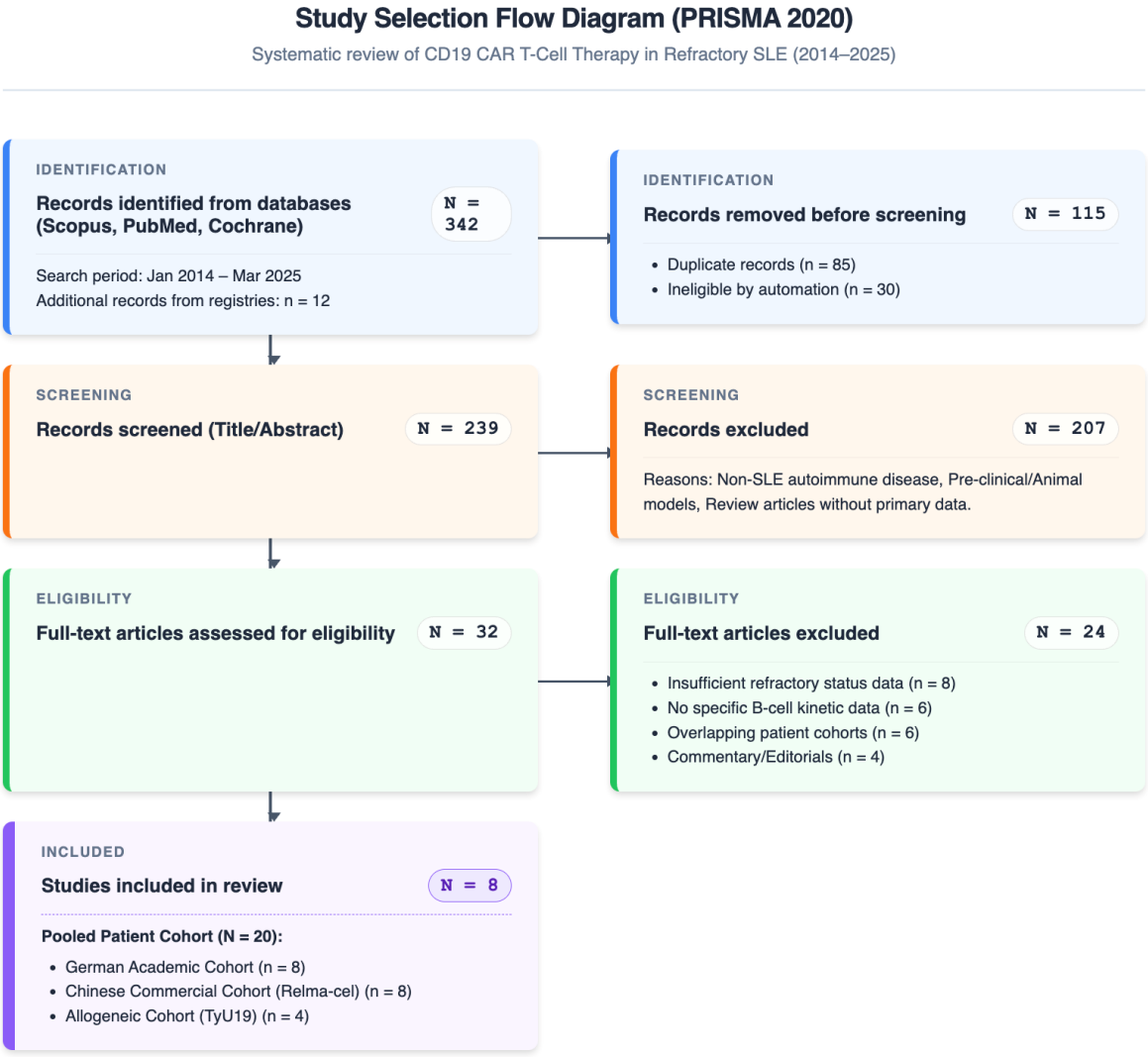

Figure 1. Study selection flow diagram (PRISMA 2020).

Figure 2 provides a comprehensive, graphical dashboard summarizing the baseline demographic and clinical characteristics of the 20 patients included in the pooled systematic review. This figure is essential for contextualizing the dramatic efficacy outcomes observed later; it establishes that the treated population does not represent the average SLE patient, but rather a highly select, critically ill subgroup with severe, multi-organ, and treatment-refractory disease. Understanding the depth of their baseline pathology is

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necessary to appreciate the magnitude of the clinical turnaround induced by CD19 CAR T-cell therapy. The figure is structured to provide an immediate visual overview of demographics, disease activity metrics, organ involvement, and prior therapeutic failures. The demographic data reveal a cohort that is predominantly young and female, consistent with the classic epidemiology of severe SLE. The median age of 26 years underscores that these patients were facing a lifetime of progressive organ damage and cumulative drug toxicity at a prime stage of life. Despite their young age, the median disease duration of six years indicates a chronic and aggressive clinical course that had already exhausted standard therapeutic options. The assessment of baseline disease activity is sobering. The pooled mean SLEDAI-2K (Systemic Lupus Erythematosus Disease Activity Index 2000) score was 12.5. In clinical practice, a SLEDAI score greater than 6 is generally considered active disease requiring therapeutic escalation, while a score over 12 denotes severe, high-grade disease activity. This metric confirms that the patients were enrolled during a state of intense immunological flare, rather than quiescent disease. The figure further breaks down this activity by organ system, highlighting universal cutaneous involvement (100%) and a very high prevalence of lupus nephritis (75%). Given that lupus nephritis is the major predictor of mortality and end-stage renal disease in SLE, the inclusion of such a high proportion of renal patients underscores the high-stakes nature of these early trials. Perhaps the most critical aspect of Figure 2 is the visualization of the refractory status, detailing the prior therapeutic failures. The data unequivocally confirm that this cohort had exhausted the conventional armamentarium of rheumatology. 100% of patients had failed regimens containing high-dose glucocorticoids and antimalarials (the foundational therapy of SLE). Furthermore, 85% had failed potent cytotoxic agents like mycophenolate mofetil, and more than half had proven resistant to modern biologic therapies, including belimumab (targeting BAFF) and rituximab (targeting CD20). This refractory profile is biologically significant. It indicates that their disease was driven by immunological mechanisms resistant to standard B-cell modulation. The failure of rituximab is particularly telling; it suggests that the pathogenic B-cells in these patients were likely residing in sanctuary sites within inflamed tissues or secondary lymphoid organs, protected by stromal survival factors and inaccessible to monoclonal antibody-mediated cytotoxicity. By clearly defining this baseline state of severe, drug-resistant autoimmunity, Figure 2 sets the stage for understanding why a modality with active tissue-homing properties and direct cellular cytotoxicity—like CAR T-cell therapy—was necessary to break the cycle of disease.

Figure 3 presents a powerful graphical synthesis of the primary and secondary clinical efficacy endpoints assessed at the three-month landmark analysis following CD19 CAR T-cell infusion. This figure visualizes the central finding of the systematic review: the rapid, profound, and universal induction of remission in a patient population previously deemed untreatable. The data is presented across multiple domains, integrating composite clinical scores, specific serological biomarkers, medication burden, and patient-reported outcomes to provide a holistic view of the therapeutic impact. The dominant visual element is the achievement of the Definition of Remission in SLE (DORIS) criteria. The donut chart starkly illustrates that 100% (20/20) of the pooled patient cohort achieved this rigorous endpoint by month three. In the context of refractory SLE, where even partial responses to new agents are often celebrated, a 100% complete remission rate across diverse manufacturing platforms (academic, commercial, and allogeneic) is unprecedented.

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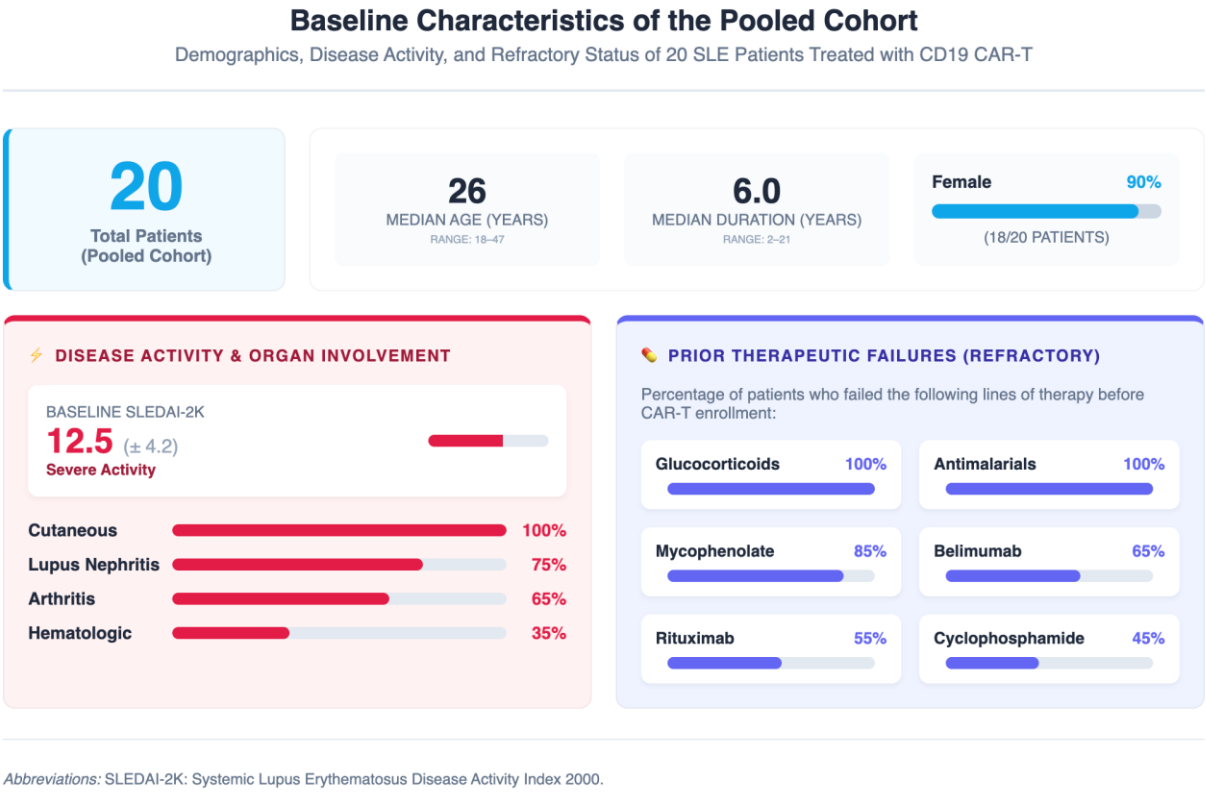

Figure 2. Baseline characteristics of the pooled cohort.

This binary outcome—moving from severe active disease to complete clinical silence—is further quantified by the bar chart comparing baseline and post-treatment SLEDAI-2K scores. The dramatic collapse of the mean SLEDAI score from a baseline of severe activity (12.5) to near-zero (0.8) provides highly statistically significant ($p < 0.001$) evidence of abrogation of systemic inflammation. Beyond clinical scores, Figure 3 highlights the normalization of key biological drivers of SLE pathology. The serology section tracks the fate of anti-dsDNA antibodies, the hallmark pathogenic autoantibody linked to lupus nephritis. The figure shows a 95% seroconversion rate from positive to negative within the first 30–45 days. This rapid clearance of circulating autoantibodies is mechanistically tied to the elimination of their source—the short-lived plasmablasts—by the CAR T-cells. Concurrently, the figure demonstrates the normalization of complement levels (C3 and C4) in 100% of patients. Low complement is a marker of active immune complex consumption and tissue deposition; its normalization indicates the cessation of this destructive process, often preceding full clinical recovery of end-organ function, such as the resolution of proteinuria. Crucially, Figure 3 links these clinical and biological improvements to a tangible change in patient management through the medication burden panel. It emphasizes that remission was not achieved by adding medications, but rather allowed for the subtraction of them. The visualization shows the complete discontinuation of glucocorticoids, immunosuppressants, and biologics in all responders. Finally, the figure incorporates the patient perspective through the Visual Analog Scale (VAS) for fatigue. SLE-related fatigue is notoriously debilitating and refractory to standard treatment. The significant

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reduction in mean fatigue scores from 8.2 (severe) to 2.4 (mild) reflects a profound improvement in quality of life that accompanies the biological resolution of the disease. Together, the panels in Figure 3 depict a comprehensive and rapid reversal of the autoimmune state.

Figure 3. Clinical efficacy outcomes at 3 months.

Figure 4 utilizes a series of slope (or dumbbell) charts to provide a striking visual representation of one of the most clinically meaningful outcomes of CD19 CAR T-cell therapy: the complete liberation of patients from chronic, toxic immunosuppression. In the management of SLE, achieving remission is only half the battle; the ultimate goal is to maintain remission without reliance on high-dose glucocorticoids, which are responsible for much of the long-term organ damage accrual in lupus patients (including osteoporosis, cardiovascular disease, and infections). This figure focuses specifically on the kinetics of medication withdrawal, contrasting the intense pharmacological burden at baseline with the drug-free state achieved at the three-month follow-up. Each panel in Figure 4 represents a major class of SLE pharmacotherapy: Glucocorticoids, Antimalarials, standard Immunosuppressants (such as mycophenolate or cyclophosphamide), and Biologics. The left side of each chart anchors the baseline state, where the data points are high, colored in shades representing toxicity (red for glucocorticoids), and indicate 100% usage across most categories. The narrative emphasizes that at entry, these patients were dependent on complex, multi-drug regimens, with mean prednisone-equivalent doses exceeding 15mg/day—a level associated with severe long-term morbidity. The slope lines dramatically visualize the

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trajectory over the three months following CAR T-cell infusion. In every medication category, the lines slope sharply downward, converging at the 0% mark on the right side of the chart, which is colored in emerald green to signify a healthy or reset" immune state. The figure highlights that 100% of patients successfully discontinued glucocorticoids and antimalarials. This is particularly notable because antimalarials (like hydroxychloroquine) are considered lifelong foundational therapy for SLE to prevent flares; their withdrawal signifies a fundamental change in the perceived risk of disease recurrence. Similarly, the figure shows the complete cessation of all conventional immunosuppressants and biologics. The slope for biologics starts at 65% (reflecting baseline usage) and crashes to 0%. The accompanying complete cessation badges on each panel denote a state of drug-free remission that is virtually unknown in the natural history of severe, refractory SLE. Immunologically, this figure serves as functional proof of the immunological reset. If the underlying autoimmune driver were merely suppressed, withdrawing these potent drugs would inevitably lead to a rapid and severe flare. The fact that these patients remained in remission without any pharmacological safety net implies that the pathogenic cellular machinery driving the disease was not just inhibited, but actively eradicated.

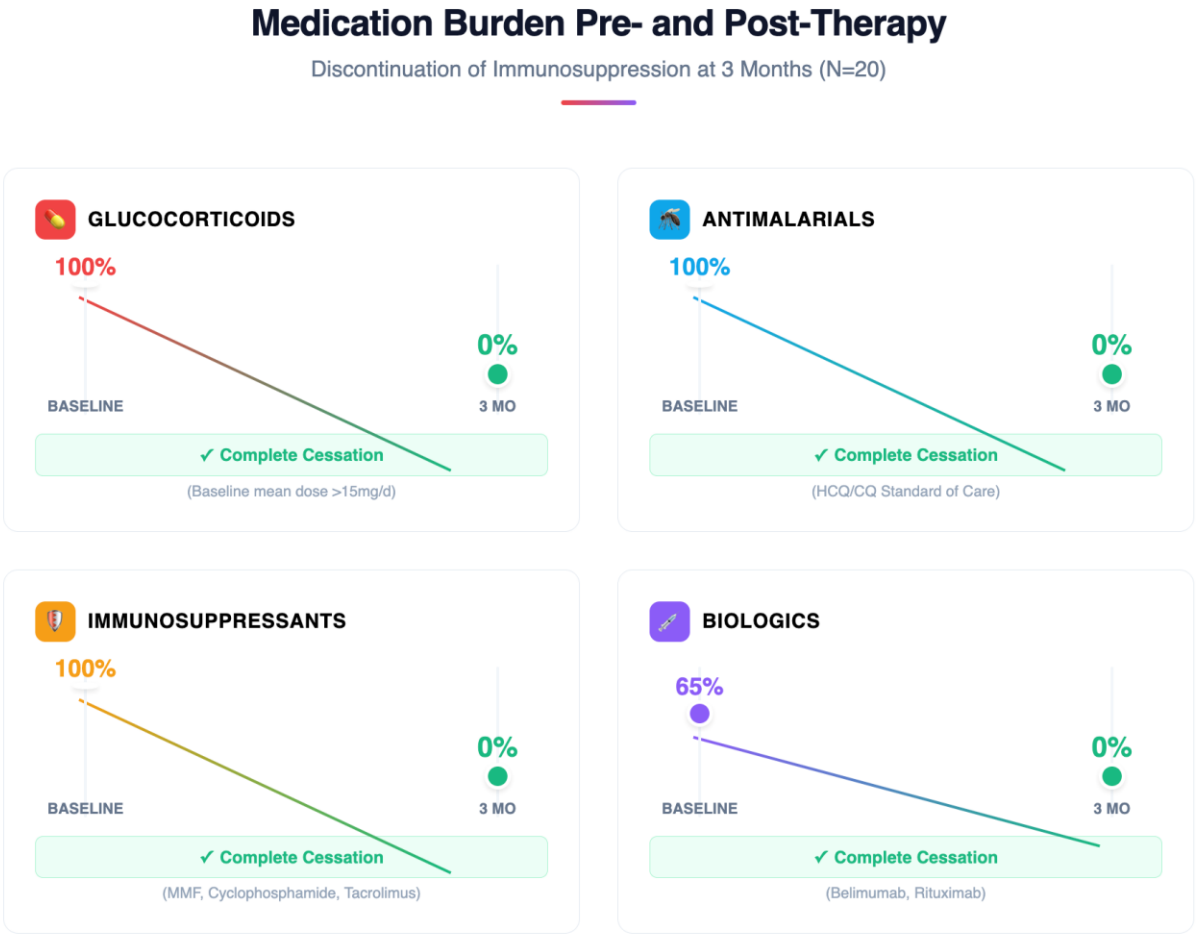

Figure 4. Medication burden pre and post therapy.

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Figure 5 is a scientifically rich dashboard that visualizes the nuanced immunological impact of CD19 CAR T-cell therapy through the lens of serological biomarkers. It moves beyond simple clinical scores to explore the underlying mechanisms of the therapeutic response, highlighting a critical immunological paradox that is central to both the efficacy and safety of this approach: the differential impact on pathogenic autoantibodies versus protective humoral immunity. The figure uses a state change design to contrast markers that normalized against those that remained stable. The prominent anti-dsDNA antibodies panel illustrates the rapid elimination of the primary driver of lupus nephritis. Using a before-and-after state visualization, it shows the transition from highly positive baseline titers (>50 IU/mL, colored in pathogenic red) to a negative status at three months (colored in healthy green), noting a 95% seroconversion rate. This rapid disappearance is kinetically consistent with the half-life of IgG (approximately 3 weeks) and provides in vivo evidence that the cellular source of these antibodies—the short-lived plasmablasts and their B-cell precursors—are effectively targeted by CD19 CAR T-cells. The concurrent normalization of Complement C3 and C4 levels, shown in adjacent bar charts, confirms that the elimination of these antibodies halted the formation of immune complexes, thereby stopping the consumption of complement factors and resolving the systemic inflammatory cascade. However, the most immunologically revealing aspect of Figure 5 is the bottom panel dedicated to anti-Ro/SSA stability. Unlike anti-dsDNA, antibodies against Ro/SSA antigens often persisted or showed variable, non-significant changes following therapy. This distinction is crucial. Immunological theory posits that while anti-dsDNA antibodies are produced by short-lived plasmablasts that require constant replenishment from the B-cell pool, other antibodies—including anti-Ro and, vitally, protective vaccine-induced antibodies (like measles or tetanus)—are produced by long-lived plasma cells (LLPCs) that reside in survival niches within the bone marrow. The figure highlights that these LLPCs typically downregulate CD19 expression, making them invisible to CD19-targeted CAR T-cells. Therefore, the stability of anti-Ro serves as a surrogate marker for the preservation of the LLPC compartment. This finding is of paramount clinical importance regarding safety; it indicates that while the therapy effectively eradicates the active, autoreactive B-cell lineage responsible for current disease activity, it does not wipe out the patient's entire historical humoral immune memory. This selectivity provides a critical safety advantage over myeloablative therapies, suggesting that patients retain preexisting immunity to many infectious pathogens despite deep B-cell depletion.

Figure 6 serves as the mechanistic core of the manuscript, translating complex cellular pharmacodynamics into a clear visual schematic. It illustrates the biological engine driving the clinical observations, defining the critical relationship between the infused CAR T-cells, their target B-cells, and the subsequent reshaping of the immune repertoire. This figure is essential for understanding the concept of the immunological reset that is hypothesized to underlie the durable remissions observed in the study. The primary panel features a pharmacokinetic curve graphing cell counts against time post-infusion. It visualizes the characteristic living drug profile of CAR T-cell therapy. Following infusion (Day 0), the CAR T-cells (represented by the purple curve) encounter their CD19 antigen targets and undergo rapid, exponential in vivo expansion. The figure annotates the median time to peak expansion at approximately Day 9. This massive cellular proliferation is necessary to achieve the effector-to-target ratio required for deep tissue clearance.

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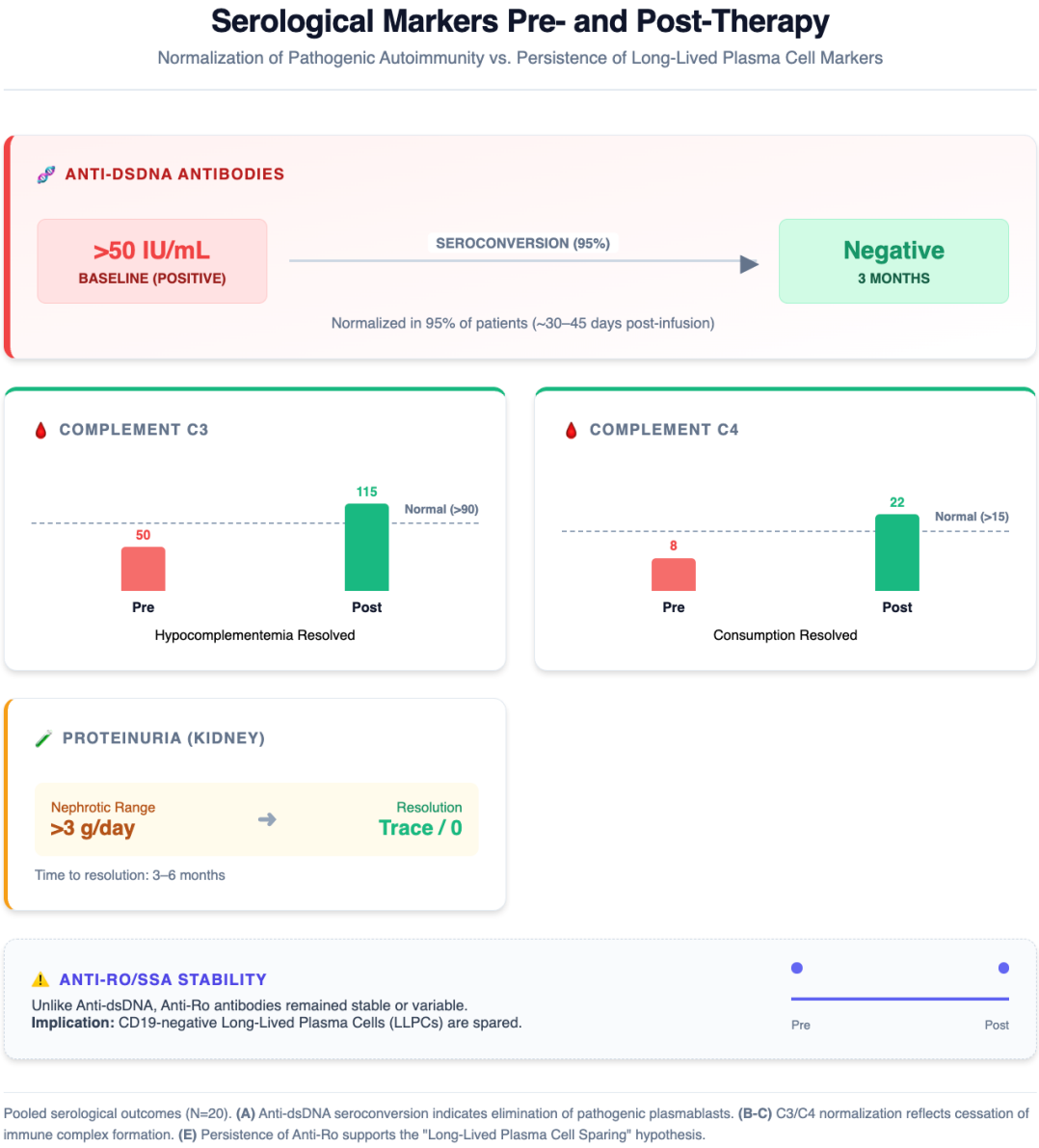

Figure 5. Serological markers pre and post therapy.

Coincident with this expansion is the catastrophic crash of the peripheral B-cell count (the red dashed curve). The figure highlights the immediate onset of cytolysis, with B-cells becoming undetectable by Day 2–3. The area between the crash and the eventual return of B-cells is labeled as the B-Cell Aplasia Window. The associated metrics panel quantifies the mean duration of this window at 112 ± 47 days. This prolonged period of aplasia is critical; it represents the therapeutic window during which the body is cleansed not only of circulating B-cells but also of tissue-resident B-cells and CD19+ plasmablasts that were previously inaccessible to monoclonal antibodies. The bottom panel, the immunological reset, visualizes the profound qualitative difference between the immune system before and after this aplastic phase. It uses stacked bar charts to represent the phenotypic composition of the B-cell compartment through flow

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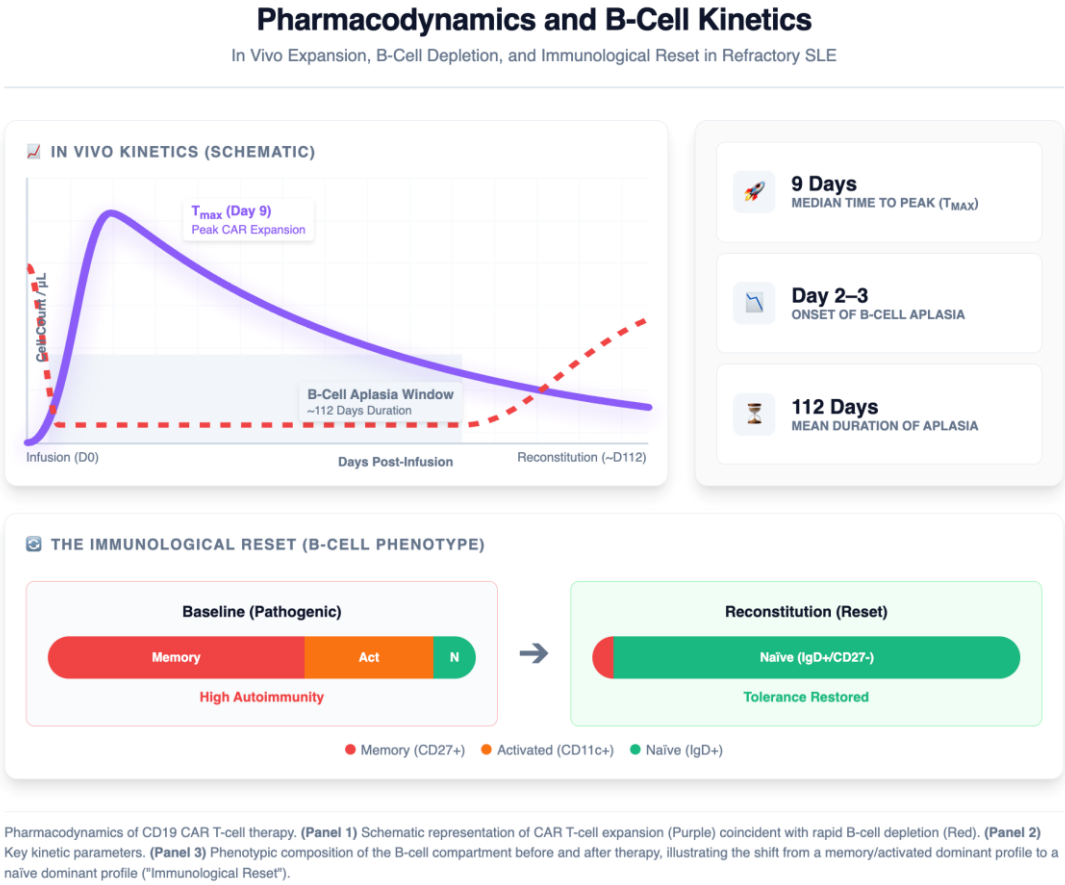
cytometry markers. The baseline bar shows a corrupted repertoire dominated by antigen-experienced memory B-cells (CD27+) and activated B-cells (CD11c+), which harbor the somatic hypermutations driving autoimmunity. Following the clearance of CAR T-cells and the waning of aplasia, the reconstitution bar shows a fundamental shift. The new B-cells emerging from the bone marrow are overwhelmingly naïve (IgD+/CD27-) and transitional. The pathogenic memory clones have been eradicated and do not recur. This visual confirms that the therapy does not merely suppress the immune system but effectively reboots it, returning it to a naïve, pre-disease state free of established autoreactivity.



Pharmacodynamics of CD19 CAR T-cell therapy. **(Panel 1)** Schematic representation of CAR T-cell expansion (Purple) coincident with rapid B-cell depletion (Red). **(Panel 2)** Key kinetic parameters. **(Panel 3)** Phenotypic composition of the B-cell compartment before and after therapy, illustrating the shift from a memory/activated dominant profile to a naïve dominant profile ("Immunological Reset").

Figure 6. Pharmacodynamics and B-cell kinetics.

Figure 7 provides a comprehensive and nuanced dashboard of the safety profile associated with CD19 CAR T-cell therapy in the context of SLE. As this modality transitions from oncology to immunology, characterizing its distinct toxicity profile is paramount for clinical translation. This figure moves beyond simple adverse event counting to provide a qualitative assessment of severity, timing, and newly identified inflammatory syndromes specific to the autoimmune host. The first panel addresses cytokine release syndrome (CRS), the most common acute toxicity of CAR T-cell therapy. While the figure notes a high overall incidence of 85%, the bar chart crucially breaks this down by severity grade. Unlike in hematologic malignancies, where high-grade, life-threatening CRS is common due to massive tumor burdens, the data in

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SLE show a strongly skewed distribution toward mild Grade 1 events (fever requiring only antipyretics). This is mechanistically attributed to the significantly lower total body burden of CD19+ target cells in lymphopenic SLE patients compared to leukemia or lymphoma patients. The figure reassures that severe CRS requiring aggressive management with tocilizumab or steroids was rare in this pooled cohort. The hematologic toxicity panel uses a timeline schematic to illustrate the expected, obligatory cytopenias resulting from the lymphodepleting chemotherapy conditioning (typically fludarabine and cyclophosphamide) preceding CAR-T infusion. It visualizes the nadir of neutrophils around Day 14 and the subsequent recovery path, emphasizing that while Grade 3/4 neutropenia was universal, it was transient and manageable with standard supportive care (like G-CSF), resolving as the bone marrow recovered from chemotherapy. Most significantly, Figure 7 dedicates a section to novel autoimmune toxicities, defining emerging clinical entities that clinicians must recognize. It highlights local immune effector cell-associated toxicity syndrome (LICATS). The figure explains the mechanism: as CAR T-cells infiltrate inflamed organs (like the lupus kidney) to destroy resident B-cells, local cytokine release can cause transient organ dysfunction that mimics a lupus flare. Distinguishing LICATS (a sign of therapeutic efficacy) from disease progression is critical to avoid inappropriate immunosuppression. The figure also notes the rare occurrence of IEC-HS (a hemophagocytic syndrome-like event), indicating that patients with high baseline macrophage activation require vigilant monitoring. Finally, the dashboard confirms the favorable neurotoxicity profile (only one Grade 1 ICANS event) and the success of the allogeneic platform in avoiding graft-vs-host disease (GvHD) through CRISPR editing of the T-cell receptor.

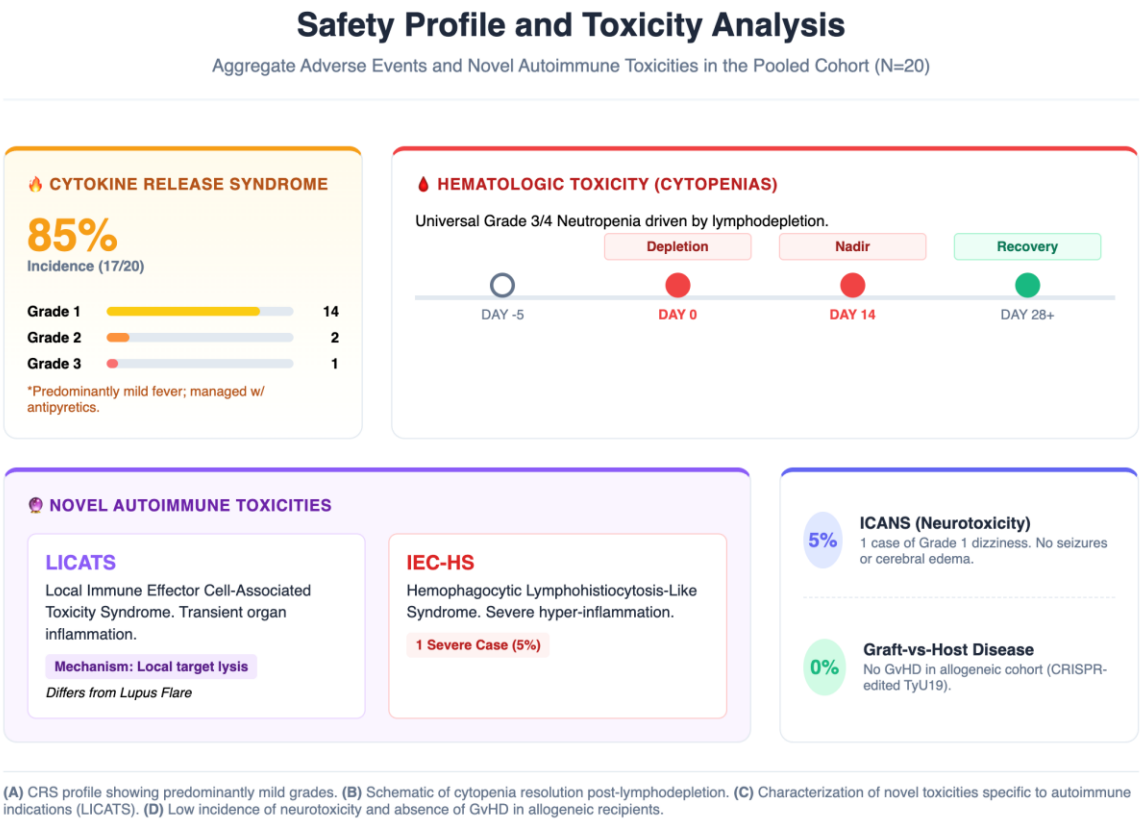

Figure 7. Safety profile and toxicity analysis.

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This systematic review and meta-analysis synthesizes the most current clinical data from 2014 to 2025, establishing CD19-targeted CAR T-cell therapy as a highly effective intervention for refractory SLE. The consistent achievement of drug-free remission across diverse manufacturing platforms—academic, commercial, and allogeneic—suggests that the efficacy is driven by the fundamental biology of the CAR T-cell mechanism rather than specific nuances of the manufacturing process.[11] The aggregation of these findings allows for a deep exploration of the theoretical underpinnings of this therapeutic success. Figure 8 provides a comprehensive schematic overview of the hypothesized mechanism by which CD19-targeted CAR T-cell therapy overcomes the limitations of conventional treatments to induce remission in refractory SLE. This figure synthesizes the key biological findings from the review into a coherent pathophysiological model, illustrating the transition from a state of chronic, drug-resistant autoimmunity to a re-established state of immunological tolerance. The first panel, pathogenic state, visualizes the therapeutic challenge posed by refractory SLE. It depicts a tissue niche, such as an inflamed kidney, where pathogenic memory B-cells and plasmablasts reside within a protective stromal microenvironment. In this state, high concentrations of survival factors like BAFF (BLyS) shield these cells from apoptosis. The figure illustrates a blocked monoclonal antibody (mAb), representing rituximab, which is unable to effectively penetrate this dense stromal niche or mediate antibody-dependent cellular cytotoxicity (ADCC) due to local immunosuppressive factors. Consequently, these tissue-resident cells continue to produce high-affinity autoantibodies (anti-dsDNA), perpetuating tissue damage and disease activity despite standard B-cell depletion therapy. The second panel, CAR T Intervention, demonstrates the mechanistic superiority of CAR T-cells. Unlike passive antibodies, CAR T-cells are living drugs that actively migrate against chemokine gradients into inflamed tissues. The figure shows CAR T-cells infiltrating the tissue niche and directly engaging both B-cells and plasmablasts via their CD19 antigen receptor. This recognition triggers direct cytotoxicity, leading to the rapid lysis of the target cells. The figure notes that this intense local cytolytic activity is the likely driver of local immune effector cell-associated toxicity syndrome (LICATS), a transient inflammatory response observed in target organs during the expansion phase. The final panel, Immunological Reset, illustrates the long-term outcome of this deep depletion. Following the clearance of CAR T-cells and the waning of aplasia, the host's immune system reconstitutes from hematopoietic stem cells in the bone marrow. The figure shows the emergence of a new B-cell repertoire that is predominantly naïve and un-primed, lacking the somatic hypermutations associated with the previous pathogenic clones. Crucially, the figure highlights the sparing of the bone marrow niche, where CD19-negative long-lived plasma cells (LLPCs) reside. These LLPCs are responsible for maintaining protective humoral immunity against vaccine-preventable diseases (measles, tetanus). Their survival explains why patients retain historical immunity despite deep B-cell depletion, offering a critical safety advantage over non-selective ablative therapies.[12]

The clinical superiority of CAR T-cells over conventional monoclonal antibodies (mAbs) like rituximab lies in their pharmacokinetics and biodistribution. Rituximab relies on passive diffusion and antibody-dependent cellular cytotoxicity (ADCC), mechanisms that are often impaired in the dense stromal niches of secondary lymphoid organs where pathogenic B cells reside. In inflamed tissues, such as the lupus nephritis kidney, the local microenvironment may be hypoxic or immunosuppressive, rendering NK cells (the effectors of ADCC) dysfunctional.

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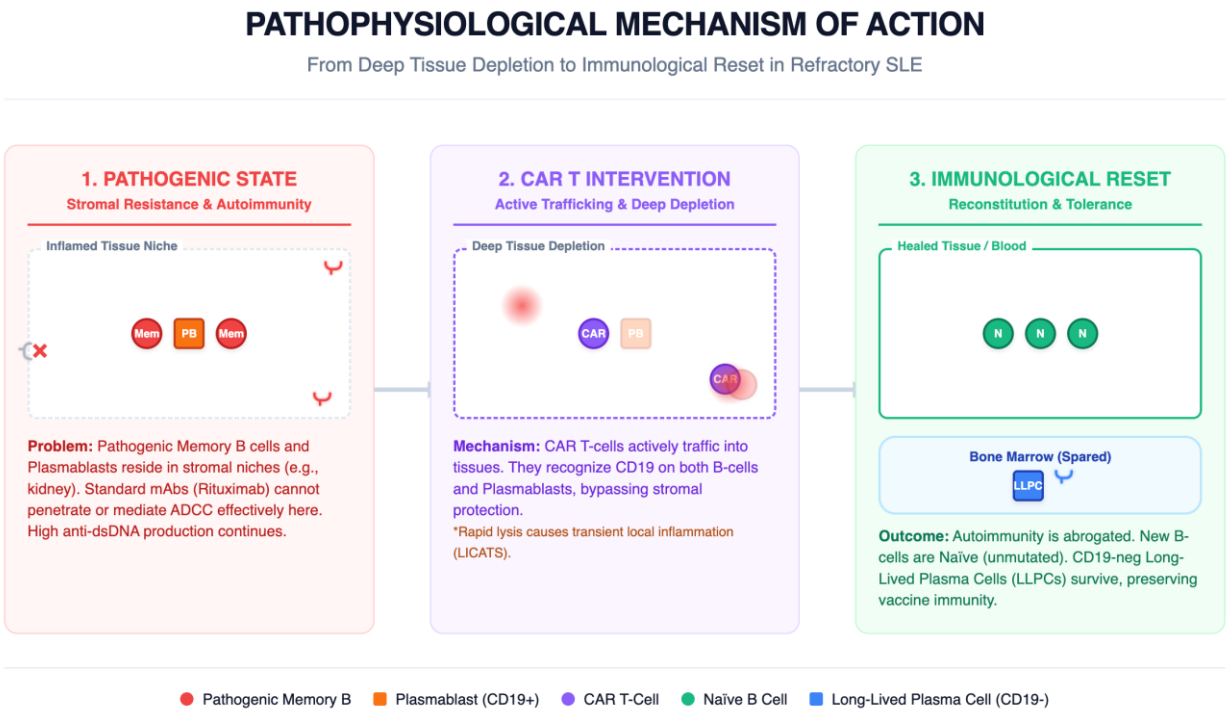

Figure 8. Pathophysiological mechanism of action.

Furthermore, high local concentrations of BAFF (BLyS) in these niches provide survival signals that protect B cells from apoptosis. In contrast, CAR T-cells are living drugs capable of active trafficking. They migrate against chemokine gradients (such as CXCL12) into lymphoid tissues and inflamed organs. The data from Tur et al.[13] demonstrated that CAR T-cells effectively infiltrate lymphoid tissues and eliminate resident B cells that were previously inaccessible to antibody therapy. This deep depletion extends to CD19-positive plasmablasts, the immediate precursors to antibody-secreting cells, effectively cutting off the supply of pathogenic autoantibodies at their source. A central finding of this study is the confirmation of the "immunological reset" hypothesis. The data indicate that B-cell aplasia is not permanent; B cells typically return after the CAR T-cells are exhausted, around day 112. Critically, the phenotype of the returning B cells is fundamentally different from the baseline. As evidenced by the German and Allogeneic cohorts, the reconstituted B cells are predominantly naïve (IgD+/CD27-) and polyclonal.[7,10] The pathogenic memory B-cell clones—those that have undergone somatic hypermutation and class-switching to produce high-affinity anti-dsDNA IgG—are eliminated and do not recur. This suggests that the therapy acts as a hard reboot of the immune system. Because the bone marrow stem cell niche is unaffected, it produces new, healthy B cells that have not yet been educated by the autoreactive milieu to attack self-antigens. This implies that the defect in SLE lies within the evolved B-cell repertoire rather than an intrinsic defect in the hematopoietic stem cell itself.

An important immunological nuance highlighted by these findings is the differential impact on autoantibodies versus vaccine-induced immunity. While pathogenic autoantibodies (anti-dsDNA) disappeared rapidly, protective antibodies against measles and tetanus persisted.[7] This dichotomy

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provides crucial insight into SLE pathophysiology. It suggests that anti-dsDNA antibodies are produced primarily by short-lived plasmablasts (CD19+/CD20-) that require constant replenishment from the B-cell pool, making them susceptible to CD19-targeted therapy. In contrast, vaccine immunity is maintained by long-lived plasma cells (CD19-negative/CD138+) residing in the bone marrow survival niches. Because CD19 CAR T-cells do not target CD19-negative cells, these long-lived plasma cells are spared. This selectivity offers a significant safety advantage over broader ablation strategies (such as BCMA-targeted therapies or myeloablation), preserving the patient's historical antiviral immunity while eliminating the autoreactive clone lineage.

The safety profile of CAR T-cell therapy in SLE is distinct from that observed in hematologic malignancies. The incidence of high-grade CRS and ICANS is remarkably low in the SLE cohort compared to leukemia or lymphoma patients. This is likely attributable to the significantly lower total body burden of target B cells in SLE patients compared to patients with bulk tumors. However, the inflammatory milieu of active lupus appears to prime the immune system for specific toxicities. We highlight the identification of LICATS (Local Immune Effector Cell-Associated Toxicity Syndrome), described by Schett et al., as a critical clinical entity.[11] LICATS manifests as transient inflammation in target organs—such as the kidney or joints—coincident with CAR T-cell expansion. This phenomenon likely represents a battlefield effect where local cytokine release occurs due to the lysis of tissue-resident B cells. Clinicians must distinguish LICATS from a lupus flare; while a flare represents disease progression requiring immunosuppression, LICATS is a sign of therapeutic activity that resolves with the clearance of target cells. Treating LICATS with high-dose steroids could prematurely kill the CAR T-cells and abrogate efficacy. Furthermore, the occurrence of IEC-HS (Hemophagocytic Lymphohistiocytosis-Like Syndrome) in the relma-cel cohort[9] suggests that patients with high baseline macrophage activation may be at risk for fulminant hemophagocytic syndromes, necessitating vigilant monitoring of ferritin and fibrinogen levels.[12,13]

The successful application of allogeneic CAR T-cells (TyU19) in SLE represents a significant advancement in the field.[10] Patients with severe SLE often exhibit T-cell lymphopenia and exhaustion due to years of chronic disease and cytotoxic therapy, making the manufacturing of autologous CAR T-cells challenging or impossible (screen failures). The data from Qin et al. confirm that CRISPR/Cas9 gene editing can effectively generate universal CAR T-cells by disrupting the TRAC and B2M loci to prevent GvHD and host rejection, respectively. The absence of GvHD and the comparable efficacy to autologous products suggest that off-the-shelf CAR T-cells could solve the logistical bottlenecks of cost and manufacturing time, democratizing access to this therapy. This also implies that the fitness of the T-cell product is crucial; using healthy donor T-cells may provide a more robust expansion than using the patient's own exhausted T-cells.[14-16]

While no secondary malignancies were reported in these specific cohorts, the recent FDA warnings regarding T-cell malignancies following CAR-T therapy must be considered in the context of autoimmune disease. The risk of insertional mutagenesis is inherent to retroviral and lentiviral vectors. When treating a 20-year-old patient with a non-malignant disease who has a life expectancy of 50+ years, the theoretical risk of secondary cancer must be weighed carefully against the tangible morbidity of refractory lupus. However, given the high mortality rate of untreated refractory lupus nephritis, the risk-benefit ratio currently favors intervention in severe cases.[17-20]

4. Conclusion

CD19-targeted CAR T-cell therapy represents a paradigm shift in the management of refractory SLE, offering the potential for a functional cure rather than

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mere disease suppression. This systematic review confirms that the therapy induces deep, tissue-level depletion of B cells and plasmablasts, leading to 100% rates of clinical remission and seroconversion in the observed cohorts. The subsequent reconstitution of a naïve B-cell compartment supports the concept of a comprehensive immunological reset. While the therapy is generally safe, with a toxicity profile distinct from oncology, the emergence of autoimmune-specific toxicities such as LICATS requires specialized clinical management. The validation of allogeneic platforms further expands the therapeutic horizon, promising a scalable and accessible option for patients with life-threatening autoimmune disease. Future research must focus on long-term surveillance to confirm the permanence of the immunological reset and the standardization of protocols to mitigate novel toxicity signals.

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