Safety and clinical efficacy of Relmacabtagene autoleucel (relma-cel) for systemic lupus erythematosus: a phase 1 open-label clinical trial

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eClinicalMedicine
2025;83: 103229
Published Online xxx
https://doi.org/10.1016/j.eclinm.2025.103229

Summary

Background Systemic lupus erythematosus (SLE) is a classic systemic autoimmune disease mediated by autoantibodies. Chimeric antigen receptor T (CAR-T) cell therapy, known for its success in cancer, has shown promise in achieving durable B cell depletion and long-term remission in SLE. Relmacabtagene autoleucel (relma-cel) is the second anti-CD19 CAR-T product approved for marketing by the National Medical Products Administration (NMPA) in China and demonstrates its long-term efficacy in relapsed/refractory (r/r) large B cell lymphoma (LBCL). We report the results from a phase I open-label clinical trial of relma-cel in treating patients with moderately to severely active SLE.

Methods Eligible patients were aged 18–70 years, a ≥6-month history of SLE, and the disease had to remain active after at least 2 months of stable SLE standard treatment prior to screening. We evaluated four dose levels (DL) of relma-cel in a dose-escalation scheme: total dose of 25×10^6, 50×10^6, 75×10^6, and 100×10^6 anti-CD19 CAR-T cells. All patients received lymphodepletion chemotherapy with fludarabine and cyclophosphamide. The primary endpoints were the incidence of dose-limiting toxicities (DLTs) and adverse events (AEs). Secondary endpoints included the evaluation of standard cellular pharmacokinetic parameters, the SLE Responder Index (SRI) response rate, and changes from baseline in the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI), British Isles Lupus Assessment Group 2004 (BILAG-2004) and Physician's Global Assessment (PGA) scores post-treatment. This trial is registered with ClinicalTrials.gov, NCT05765006.

Findings Between March 28, 2023 and April 8, 2024, a total of 12 patients were screened for study inclusion, of whom 8 patients were enrolled and assigned to different dose levels: 25×10^6 cells (n = 3), 50×10^6 cells (n = 2), 75×10^6 cells (n = 2), and 100×10^6 cells (n = 1). No DLT was observed. The most common AEs included cytopenia (n = 8, 100%), cytokine release syndrome (CRS) (n = 7, 88%) and hypogammaglobulinemia (n = 5, 63%). No Grade 3 or higher immune effector cell–associated hematotoxicity (ICAHT) occurred. No cases of immune effector cell-associated neurotoxicity syndrome (ICANS) were reported. CRS was predominantly grade 1, characterized mainly by mild fever and muscle soreness. A rare severe adverse event, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), was observed in one patient. The median time to reach maximum CAR-T cell expansion (C_{max}) was 9.5 days (range: 8–22 days). The median C_{max} was 18.74 CD3+CAR+ cells/μL (range: 7.94–228.36) by flow cytometry and 81766.5 copies/μg DNA (range: 50,979–1,140,893) by quantitative real-time PCR (qPCR). In all patients treated with relma-cel, CD19+ B cells in peripheral blood were almost completely depleted within 11–15 days and gradually recovered within 2–6 months. All patients achieved SRI response. Four patients achieved Definition of Remission in SLE (DORIS) remission criteria and seven patients reached the Lupus Low Disease Activity State (LLDAS) criteria within 1–4 months following relma-cel infusion.

Interpretation This study preliminarily demonstrated that relma-cel is an effective and safe CAR-T product for the treatment of patients with moderately to severely active SLE, providing valuable clinical insights into the management of rare complications. Further studies with larger sample sizes are warranted.

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Funding National Natural Science Foundation of China.

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Keywords: Systemic lupus erythematosus; Anti-CD19 CAR-T cell; Safety; Clinical efficacy

Research in context

Evidence before this study

We conducted a systematic search of PubMed for clinical trials on the treatment of systemic lupus erythematosus (SLE) published up to January 25, 2025. No restrictions were applied to language, study design, or publication date. The search terms used were: "systemic lupus erythematosus" [Title/Abstract] OR "SLE" [Title/Abstract] AND "anti-CD19 CAR-T" [Title/Abstract] OR "CD19-directed Chimeric Antigen Receptor T Cells" [Title/Abstract]. This search identified two clinical trials evaluating the use of anti-CD19 CAR-T therapy for SLE, along with four case reports. In addition, five anti-CD19 CAR-T products have been approved by the Food and Drug Administration (FDA) and three have been approved by the National Medical Products Administration (NMPA) in China, primarily for hematologic malignancies. However, in the absence of prospective clinical trial data specifically targeting SLE, the safety and efficacy of these approved CAR-T products in SLE remain insufficiently evaluated.

We also search on search on ClinicalTrials.gov using the terms "systemic lupus erythematosus" or "SLE," "recruitment," "adults," "anti-CD19 CAR-T," and "Phase 1, 2, 3," which yielded 27 ongoing clinical trials. Among these, only one trial involves a commercially available CAR-T cell product. Therefore, we are at the forefront of research on the use of commercialized CAR-T products for patients with SLE.

Added value of this study

Relma-cel (JWCAR029) is the second commercial anti-CD19 CAR-T product approved by the NMPA in China and has demonstrated high response rates, reduced CAR-T-associated toxicity and long-term efficacy in the treatment of diffuse large B-cell lymphoma. This Phase I, single-arm, open-label clinical trial showed a good safety profile and preliminary clinical efficacy of relma-cel for patients with moderately to severely active SLE. The majority of adverse events (AEs) were grade 1–2 (mild to moderate). No cases of immune effector cell-associated neurotoxicity syndrome (ICANS) or hepatic and renal functional toxicities have been reported. Cytokine release syndrome (CRS) was predominantly grade 1. One patient experienced a rare adverse event, diagnosed as immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), but ultimately achieved Definition of Remission in SLE (DORIS) remission through our empirical treatment. All patients achieved SLE Responder Index (SRI) response and maintained a medication-free state. These results set the stage for pivotal registration trials to further validate the efficacy and safety of relma-cel in SLE patient.

Implications of all the available evidence

This study provides support for the safety and efficacy of relma-cel for patients with SLE and offers valuable clinical insights into the management of rare complications, which warrant further larger cohorts and extended longitudinal follow-up to evaluate it.

Introduction

Systemic lupus erythematosus (SLE) is a classic systemic autoimmune disease primarily resulting from the breakdown of immune tolerance to associated autoantigens. This leads to the emergence of autoantibodies against dsDNA and other nuclear antigens, triggering immune complex-induced inflammation across various organs, such as the kidneys, heart, lungs, and skin.[1] Patients with SLE typically require lifelong treatment, as standard therapeutic approaches, including immunomodulators, immunosuppressive agents, and biologics, do not cure the disease or address its underlying cause, which necessitates a complete reset of the immune system.[2]

Since B cell reactivity to autoantigens precedes clinical symptoms, blocking B cells is an attractive strategy for treating SLE. Monoclonal antibodies that interfere with B cell activation through B lymphocyte stimulator (BLyS; also termed BAFF) or deplete CD20-targeted B cells have been successfully employed in SLE treatment.[3,4] However, studies indicate that the anti-CD20 monoclonal antibody rituximab has limited ability to penetrate tissues and eliminate B cells within these areas, allowing autoreactive B cells in lymphoid organs and inflamed tissues to persist and thus hindering the effective reset of autoimmune responses. Furthermore, CD20 is absent on plasmablasts and long-lived plasma cells, which also contribute to autoantibody production in systemic autoimmune diseases.[5]

Currently, Chimeric antigen receptor T (CAR-T) cells, known for efficiently and stably eliminating target cells, have gained significant attention in cancer treatment. Studies like ZUMA-1 and TRANSCEND NHL 001 have demonstrated that anti-CD19 CAR T cells can

induce durable responses with long-term efficacy and safety in patients with relapsed/refractory (r/r) large B cell lymphoma (LBCL).[6,7] Since the first successful CD19 CAR-T treatment of SLE in 2021, researchers have increasingly explored CAR-T's therapeutic potential in SLE and a substantial number of clinical trials have been initiated.[8] In these trials, whether traditional CD19 CAR-T or novel BCMA-CD19 compound CAR-T, most patients with SLE who have received CAR-T cell therapy achieved medication-free remission (MFR), significantly enhancing their quality of life.[9,10] Additionally, emerging evidence has shown that in patients with rheumatologic diseases, CAR-T cell therapy not only effectively eliminates B cells in tissues and secondary lymphoid organs but also leads to the corresponding disappearance of follicular dendritic cells (FDCs) and follicular structures within lymph nodes, surpassing the efficacy of CD20 monoclonal antibody therapy.[11]

Relma-cel (JWCAR029) is the second anti-CD19 CAR-T product approved for marketing by the National Medical Products Administration (NMPA) in China. The CAR structure of relma-cel is identical to that of liso-cel, which has demonstrated high response rates and reduced CAR-T-associated toxicity in r/r LBCL in the United States.[12] Furthermore, the pivotal RELIANCE study has confirmed relma-cel's long-term efficacy in r/r LBCL.[13] Given its high target clearance efficiency, long-term persistence, and low toxicity, relma-cel has become the first CAR-T product approved in China for three indications: r/r LBCL, r/r follicular lymphoma, and r/r mantle cell lymphoma.[14]

To further harness these advantages and bring hope for a cure to numerous patients with SLE in China, we have conducted this Phase I investigator-initiated trial (IIT) to preliminarily explore the safe therapeutic dose and clinical efficacy of relma-cel in patients with moderately to severely active SLE.

Methods

Study oversight

We conducted a single-arm, open-label, Phase I dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of relma-cel in subjects with moderately to severely active SLE at the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. The study is registered on clinicaltrials.gov with the identifier NCT05765006.

Ethics

The clinical protocol was reviewed and approved by the Clinical Research Ethics Committee of the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (UHCT22585). All patients provided written informed consent. The study was performed according to the Declaration of Helsinki version 2013 and Good Clinical Practice.

Patient eligibility

Patients were consecutively enrolled between March 28, 2023 and April 8, 2024. The diagnosis of SLE was based on the established practice guidelines.[15]

The inclusion criteria were as follows: patients aged 18–70 years with a ≥6-month history of SLE and persistent disease activity despite first-line standard SLE therapies (glucocorticoids and anti-malarials) and at least one second-line immunosuppressive treatment. Prior to screening, all patients were required to have received at least 2 months of stable standard SLE treatment, defined as consistent use (alone or in combination) of corticosteroids, antimalarials, nonsteroidal anti-inflammatory drugs (NSAIDs), or other immunosuppressive/immunomodulatory agents (azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate, leflunomide, tacrolimus, or cyclosporine). Oral corticosteroids must meet the following requirements:1) Prednisone (or equivalent) ≥7.5 mg/day, and ≤30 mg/day; 2) There is no minimum daily dose requirement for corticosteroids when used in combination with immunosuppressant; 3) At least 8 weeks of treatment prior to screening, and the dose must be kept stable for >2 weeks. In addition, the patient needs to be screened positive for antinuclear antibodies and/or anti-dsDNA antibodies and/or anti-Smith antibodies. And during patient screening, the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score must be ≥8. If there is a score for low complement and/or anti-dsDNA antibodies, the SELENA-SLEDAI score must be ≥6.

The exclusion criteria mainly include having severe lupus nephritis within 8 weeks prior to screening that requires treatment for active nephritis with protocol-prohibited medications, or requiring dialysis, or receiving prednisone ≥100 mg/day or equivalent corticosteroids for ≥14 days. Meanwhile, Patients who received the following treatments before treatment are excluded: 1) therapeutic doses of glucocorticoids (prednisone or equivalent >20 mg/day) within 7 days before leukapheresis or within 72 h before infusion of relma-cel; 2) use of any other clinical investigational drug for SLE within 4 weeks before leukapheresis. However, subjects may be enrolled if the treatment during the study is ineffective or the disease progresses, and at least 3 half-lives have passed before leukapheresis; 3) use of anti-CD20 monoclonal antibodies (e.g., rituximab), telitacicept, or belimumab within 7 days before leukapheresis or 4–6 weeks before infusion of relma-cel; 4) prior CAR-T cell therapy or other genetically modified T cell therapies. Patients with other lupus-related crises, such as active central nervous system lupus, severe lupus pneumonitis, or pulmonary hemorrhage, are also excluded. (more detailed inclusion and exclusion criterias were presented in the Supplementary Material).

Procedures

After enrollment, leukapheresis was performed to collect peripheral blood mononuclear cells (PBMCs), which are then transported to a central manufacturing facility for the production of relma-cel. Relma-cel consists of autologous $CD4^+$ and $CD8^+$ T cells genetically modified to express a CD19-specific CAR and a truncated epidermal growth factor receptor (EGFRt). The CAR construct includes an extracellular single-chain variable fragment (scFv) derived from the murine CD19-specific hybridoma FMC63, linked to intracellular 4-1BB and CD3ζ signaling domains. The T-cells are specifically enriched from apheresis using CD4 and CD8 microbeads. They are then activated with CD3/CD28 microbeads, followed by ex vivo transduction with a self-inactivating (SIN) lentiviral vector encoding the CAR transgene. The transduced T cells are expanded in cell culture, harvested, and resuspended in a cryopreservation medium. The final drug product is a single frozen cell suspension in a cryopreservation medium.

During the manufacturing period of relma-cel (after leukapheresis and before lymphodepletion), if necessary, anti-SLE therapy may be permitted to control disease activity. The bridging therapy regimen consists of a short-term treatment that previously achieved at least disease stabilization in the subject (either corticosteroid monotherapy or corticosteroids combined with immunosuppressants). The use of biologic agents (e.g., belimumab) or investigational drugs is prohibited during the bridging therapy phase, and bridging therapy must be discontinued at least 3 or 7 days before the initiation of lymphodepletion (as specified in Table S1). If corticosteroids are used for bridging therapy, the dosage must be tapered to a physiological replacement level (hydrocortisone $\leq$12 mg/m^2/day or equivalent [prednisone $\leq$3 mg/m^2/day or dexamethasone $\leq$0.45 mg/m^2/day]) at least 3 days before lymphodepletion. Eligibility criteria are reassessed before initiating a three-day lymphodepleting chemotherapy (LDC) regimen, consisting of fludarabine at 25 mg/m^2/day and cyclophosphamide at 250 mg/m^2/day. Following LDC, patients were consecutively assigned to receive a single dose of relma-cel infusion at four dose levels (DLs): 25×10^6, 50×10^6, 75×10^6, and 100×10^6 anti-CD19 CAR-T cells on Day 1 (2–7 days after completing lymphodepletion therapy). All participants underwent approximately two months of inpatient monitoring for safety assessment and management of potential complications. Following discharge, the patient continued with outpatient follow-up to further evaluate efficacy and safety, with ongoing monitoring extending up to 24 months post-treatment.

On Day 29, as well as at 2 months, 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months, clinical performance and treatment efficacy are assessed through reexamination of the proteinuria and indices such as SELENA-SLEDAI score, British Isles Lupus Assessment Group 2004 (BILAG-2004) total score and Physician's Global Assessment (PGA) score. Peripheral blood samples are collected on Days 1, 4, 8, 15, 22, and 29, as well as at Months 2, 3, 6, 9, 12, 18, and 24, for pharmacokinetics (PK), pharmacodynamics (PD), immune effects and safety evaluations following relma-cel infusion (the specific detection methods for various immune parameters, as well as the gating strategies for CAR-T cell and B cell phenotyping, are provided in the Materials & Methods section of the Supplementary Material). All adverse events (AEs) and serious adverse events (SAEs) are recorded within 90 days post-infusion, with only relma-cel-related AEs and SAEs being monitored beyond this period.

Outcomes

The primary objectives were to evaluate the safety and tolerability of relma-cel in subjects with moderately to severely active SLE. The secondary objectives were to assess the expansion and persistence of relma-cel in peripheral blood and the impact of relma-cel on clinical disease activity in SLE.

The primary endpoints included: 1) the incidence of dose-limiting toxicities (DLTs) and 2) the frequency and severity of AEs and SAEs, classified and assessed using version 5.0 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE). Additionally, to better assess bone marrow toxicity (primarily manifested as neutropenia) following CAR-T therapy, we utilized the concept of immune effector cell–associated hematotoxicity (ICAHT) for further characterization.[16] AEs occurring within 28 days post-infusion of relma-cel and meeting any of the predefined criteria (detailed in the Supplementary Materials) will be considered DLTs. Secondary endpoints focused on evaluating the quantity and persistence of CAR-T cells in the blood, including the SLE Responder Index (SRI) response rate, and changes from baseline in the SELENA-SLEDAI, BILAG-2004, and PGA scores at weeks 4, 8, 12, 16, 20, 24, 36, 48, 72, and 96 post-treatment.

Statistical analysis

This IIT is a preliminary study aimed at expanding the indications of relma-cel. The sample size of this study was determined based on practical feasibility considerations and the exploratory nature of this study. Due to the validated safe dose range of relma-cel ($25–100 \times 10^6$ CAR-T cells) in hematologic malignancies[17–19] and the limited sample size, a flexible dose-escalation strategy was adopted to efficiently capture safety signals.

Given the small sample size and uneven dose cohort distribution, no predefined statistical hypothesis testing was performed (e.g., maximum tolerated dose [MTD] estimation or DLT rate comparison). All participants who received relma-cel were included in the safety and clinical efficacy analyses. Descriptive statistics were used to summarize baseline characteristics and 12-month

follow-up data, with medians and means reported as appropriate. Analyses were performed using GraphPad Prism v9.0.

Role of the funding source
The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Patient characteristics
Between March 28, 2023 and April 8, 2024, a total of 12 patients were screened for study inclusion. Of these, two patients were excluded due to failure to meet the eligibility criteria, and one declined participation. Following leukapheresis, one additional patient withdrew consent and was subsequently excluded from the study due to severe infection. Finally, 8 patients proceeded to receive relma-cel infusions at different dose levels: 25×10^6 cells (n = 3), 50×10^6 cells (n = 2), 75×10^6 cells (n = 2), and 100×10^6 cells (n = 1), with ongoing follow-up (Fig. 1). Detailed baseline characteristics for each patient are presented in Table 1. The median age of the enrolled cohort was 27 years (range: 21–36 years), and all participants were female. All patients had moderately to severely active SLE, with median SELENA-SLEDAI, PGA, and BILAG-2004 total scores of 11.5 (range: 8–18), 1.75 (range: 1.00–2.75), and 6.5 (range: 2–10), respectively. All patients had multiorgan involvement, including skin manifestations (n = 8, 100%), joint involvement (n = 5, 63%), kidney abnormalities (n = 5, 63%), and hematologic involvement (n = 7, 88%). The baseline 24-h proteinuria levels ranged from 71 mg to 2512 mg, with a median of 636 mg. Most patients exhibited hematological abnormalities associated with SLE, including decreased levels of hemoglobin and white blood cells. Median baseline values were as follows: hemoglobin 121 g/L (range: 72 g/L–140 g/L), white blood cell count 3.38×10^9/L (range: 2.6×10^9/L–6.88×10^9/L), lymphocyte count 1.39×10^9/L (range: 0.72×10^9/L–1.86×10^9/L), and platelet count 247×10^9/L (range: 143×10^9/L–334×10^9/L). Autoantibody positivity was prevalent among the patients, with all exhibiting elevated baseline levels of anti-dsDNA/anti-Sm/ANA antibodies. The baseline levels of anti-dsDNA ranged from 4 to 192 IU/mL (median: 54.5 IU/mL), the anti-Sm antibody index ranged from 0.2 to 8 (median: 1.8), and the ANA titer ranged from 320 to 3200 (median: 1000). Additionally, baseline C3 levels were low, ranging from 0.355 to 0.875 g/L (median: 0.674 g/L). All patients had received first-line standard therapies for SLE, including glucocorticoids (8/8), hydroxychloroquine (8/8), and at least one second-line immunosuppressive agent, such as mycophenolate mofetil (6/8), cyclophosphamide (3/8), tacrolimus (5/8), or ciclosporin (3/8). Additionally, some patients had been treated with third-line biologic agents, including belimumab (2/8) and telitacicept (3/8).

Pharmacokinetic, pharmacodynamic and immune effect analyses
The expansion and persistence of CAR-T cells were measured by CAR gene copy number and flow cytometry in peripheral blood. CAR-T cell expansion was observed in all patients. The median time to reach maximum CAR-T cell expansion (C_{max}) was 9.5 days (range: 8–22 days). The median C_{max} was 18.74 CD3+CAR+ cells/μL (range: 7.94–228.36) by flow cytometry and 81766.5 copies/μg DNA (range: 50,979–1,140,893) by quantitative real-time

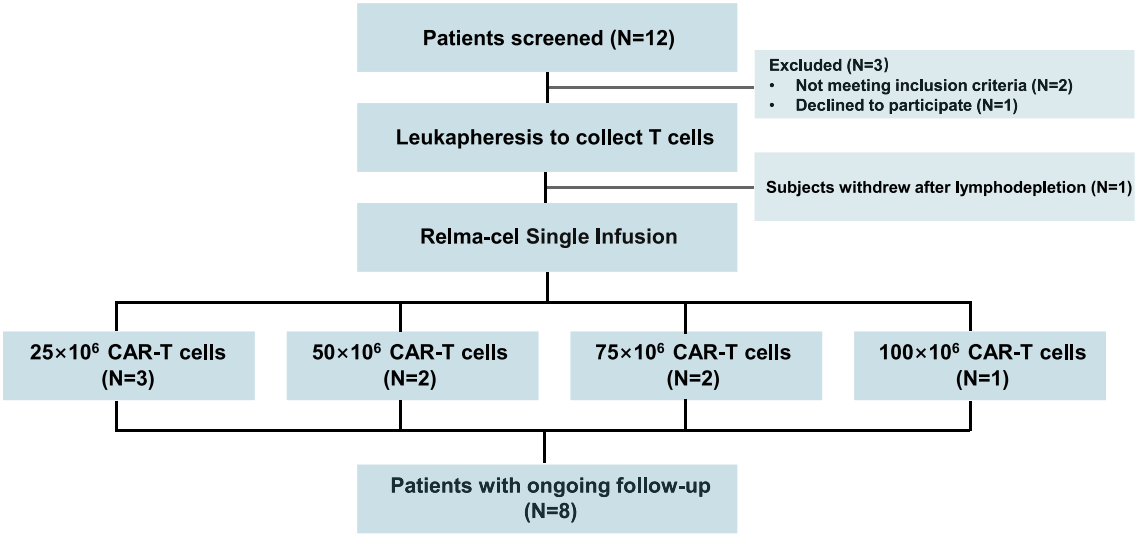

Fig. 1: Study profile and patient flow.

Characteristic	Patient 1 DL:25 × 10^6	Patient 2 DL:25 × 10^6	Patient 3 DL:25 × 10^6	Patient 4 DL:50 × 10^6	Patient 5 DL:75 × 10^6	Patient 6 DL:75 × 10^6	Patient 7 DL:50 × 10^6	Patient 8 DL:100 × 10^6
Demographics								
Age (years)	21	27	22	27	36	33	36	23
Sex	Female	Female	Female	Female	Female	Female	Female	Female
Time since diagnosis (years)	12	12	2	3	21	5	14	5
SELENA-SLEDAI (score)	9	14	8	13	18	10	14	8
PGA (score)	1.2	2	1	2.6	2.75	1.5	2	1.5
BILAG-2004 total scores	5	10	2	7	10	7	6	5
Laboratory values								
Baseline hemoglobin (115–150 g/L)	140	84	115	72	138	127	108	137
Baseline white cell count (3.5–9.5 × 10^9/L)	2.6	2.64	6.88	2.92	3.28	4.56	5.5	3.48
Baseline lymphocytes (1.1–3.2 × 10^9/L)	0.96	0.73	1.86	1.37	0.72	1.4	1.5	1.73
Baseline platelets (125–350 × 10^9/L)	195	143	268	275	211	226	308	334
Baseline anti-dsDNA (IU/ml)	4	192	9	37	53	70	56	130
Baseline anti-Smith (AI)	4.3	2.2	0.2	8	1.4	8	0.4	0.2
Baseline ANA (titer)	1:3200	1:1000	1:320	1:1000	1:1000	1:3200	1:1000	1:3200
Baseline C3 level (g/L)	0.436	0.357	0.758	0.355	0.831	0.62	0.728	0.875
Proteinuria (mg/24 h)	277	2512	71	120	1879	995	1144	121
Treatment before leukaphereis								
First-line								
Glucocorticoids	+	+	+	+	+	+	+	+
Hydroxychloroquine (Sulfate)	+	+	+	+	+	+	+	+
Second-line								
Mycophenolate Mofetil	–	–	+	+	+	+	+	+
Cyclophosphamide	–	–	–	–	+	+	+	–
Tacrolimus	+	+	–	+	+	+	–	–
Ciclosporin	+	–	–	+	–	–	+	–
Third-line								
Belimuzumab	–	+	–	–	–	–	+	–
Telitacicept	–	+	+	–	–	+	–	–
Organ-involvement								
Skin	+	+	+	+	+	+	+	+
Joint	–	–	+	+	+	–	+	+
Kidney	+	+	–	–	+	+	+	–
Hematology	+	+	–	+	+	+	+	+

DL, dose level; SELENA-SLEDAI, Safety of Estrogen in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; PGA, Physician's Global Assessment; BILAG-2004, British Isles Lupus Assessment Group 2004; ANA, anti-nuclear antibody.

Table 1: **Patient demographic and baseline characteristics.**

PCR (qPCR) (Fig. 2A and B). In all patients treated with relma-cel, CD19+ B cells in peripheral blood were almost completely depleted (as low as 0 cells/μL) within 11–15 days and gradually recovered within 2–6 months (Fig. 2C, Table S2).

Analysis of patients' baseline and post-treatment autoimmune antibody profiles showed that after therapy, anti-dsDNA antibodies (normal cut-off: 10 IU/mL), anti-Smith antibodies, anti-nuclear antibodies, and anti-ribosome antibodies (normal cut-off: 1.0 AI for each) were all reduced below pathological thresholds or markedly decreased compared to baseline levels within 3 months (Fig. 2D–G). However, for anti-Ro-52 and anti-SSA/B antibodies (normal cut-off: 1.0 AI for each), several patients did not show any notable improvement (Fig. 2H–J). Moreover, complement levels of C3 (normal cut-off: 0.79–1.52 g/L) and C4 (normal cut-off: 0.16–0.38 g/L) were improved in all patients compared to pre-treatment, and by 3 months, these levels were either normalized or close to the normal range (Fig. 2K and L).

Following B cell reconstitution during the 4–12 months of follow-up, all patients, except P1, did not show any resurgence of antibody positivity or elevation in antibody levels, and complement levels did not show marked decline. Phenotypic analysis of reconstituted B cells revealed that, compared to pre-treatment B cells, the reconstituted B cells were predominantly CD21+CD27– naïve B cells, with few or no CD21+CD27+ memory B cells or CD38+CD20– plasmablasts cells. Additionally, CD11c + CD21lo activated memory B cells, which were expanded in SLE, were absent in the reconstituted B cells

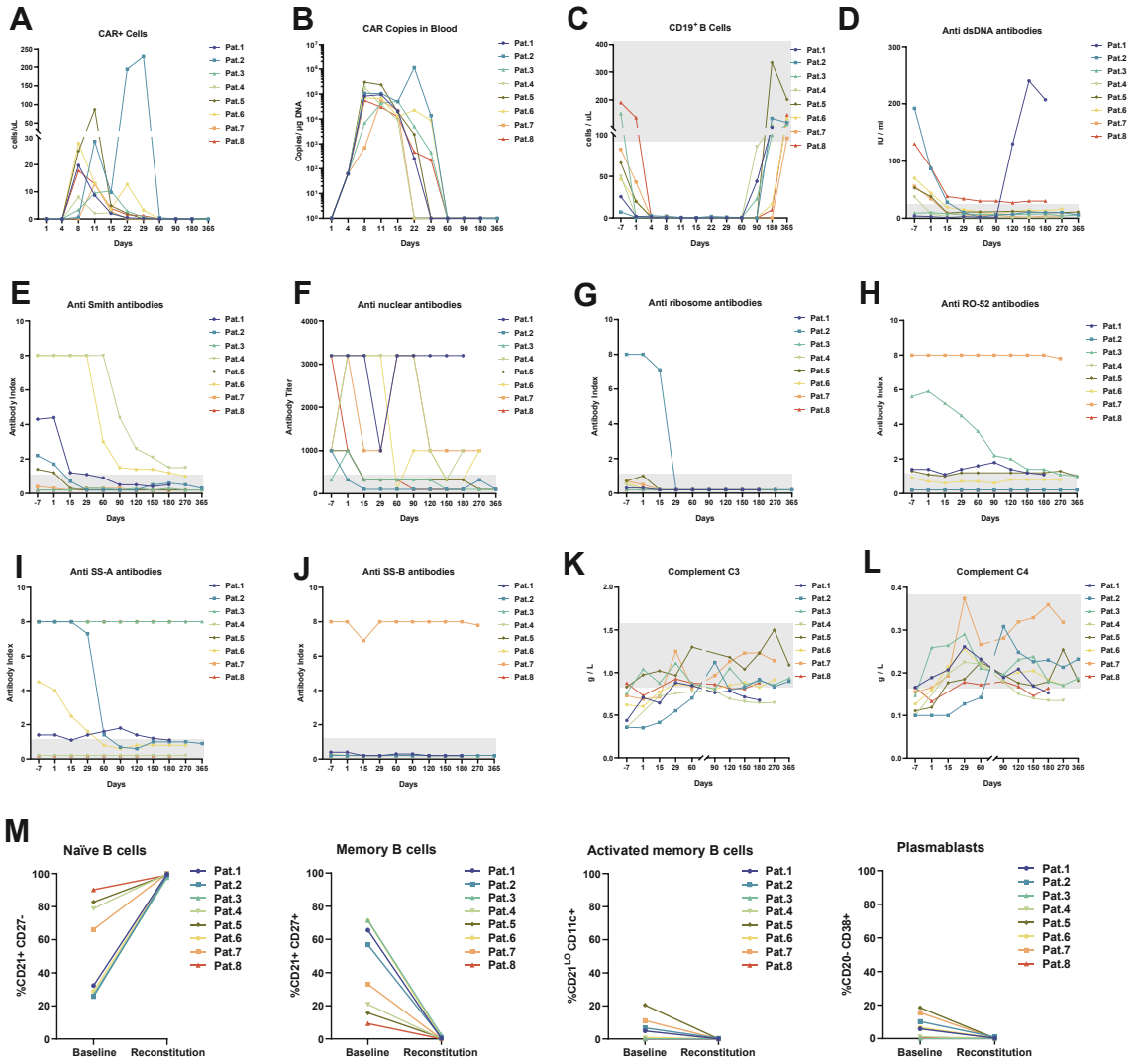

Fig. 2: Pharmacokinetic, pharmacodynamic and immune effects analyses. (A and B) Kinetic of relma-cel in peripheral blood of individual patients measured by flow cytometry and quantitative real-time PCR. (C) The changes in CD19+ B cell counts before and after relma-cel treatment. (D–J) The changes in levels of various SLE-associated autoantibodies before and after relma-cel treatment. (K–L) The changes in complement levels before and after relma-cel treatment. (M) The changes in B cell subsets before and after B cell reconstitution. The gray area represents the normal range.

(Fig. 2M). This suggests that the elimination of pathogenic B cells via CD19 CAR-T therapy can promote immune correction in the body.

Clinical efficacy

After receiving relma-cel treatment, all patients experienced significant improvement in clinical symptoms, as evidenced by a reduction in the mean SELENA-SLEDAI score from 11.75 at baseline to 1.625 at 6 months, the mean PGA score from 1.82 at baseline to 0.52 at 6 months, and the mean BILAG total score from 6.50 at baseline to 0.88 at 6 months (Fig. 3A–C). Additionally, throughout the follow-up period, all patients remained off pharmacologic intervention (immunosuppressants or corticosteroids), except when required for severe adverse events (Fig. 3D). Six patients achieved a SELENA-SLEDAI score $\leq$4 within 3 months, three of whom had their scores reduced to 0, meeting the criteria for MFR. Among them, P7 reached MFR within 1 month. All patients achieved SRI response (Fig. 3E), defined as: a) a reduction in SELENA-SLEDAI score by $\geq$4 points; b) no new organ with a BILAG A score or no more than one new organ with a BILAG B score; and c) a change in the PGA score of $\leq$0.3 compared to baseline. Meanwhile, among the eight patients, four achieved Definition of Remission in SLE (DORIS)

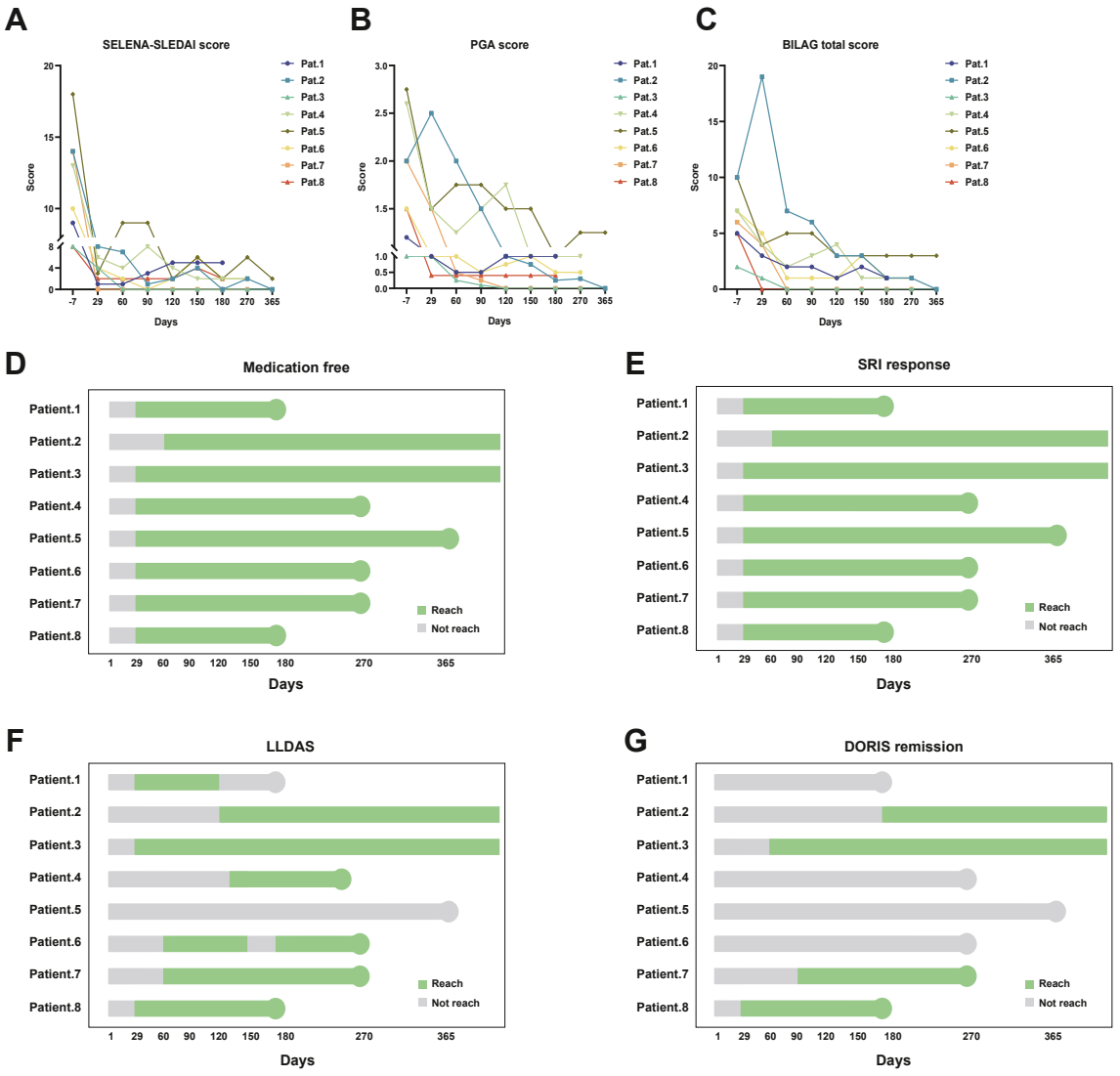

Fig. 3: Clinical efficacy of relma-cel. (A–C) The changes in Safety of Estrogen in Lupus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score, British Isles Lupus Assessment Group (BILAG) total score and Physician's Global Assessment (PGA) score before and after relma-cel treatment. (D) The time to achieve medication-free status and its duration for each patient. (E) The time to achieve SLE Responder Index (SRI) response for each patient and the duration of the response. (F) The time taken for each patient to achieve Lupus Low Disease Activity State (LLDAS) and the duration of LLDAS. (G) The time taken for each patient to achieve Definition of Remission in SLE (DORIS) remission and the duration of DORIS remission.

clinical remission criteria, and seven achieved Lupus Low Disease Activity State (LLDAS) criteria within 1–4 months (Fig. 3F and G). Notably, only P1 experienced serological relapse at three months post-treatment and ultimately withdrew consent at month six.

Safety and tolerability

During treatment, all patient groups experienced one or more AEs. Table 2 summarizes the incidence and severity of AEs during the treatment period, while Table 3 provides detailed information on specific AEs for each group. The majority of AEs were grade 1–2 (mild to moderate). The incidence and severity of AEs were comparable across different dose groups, and no DLTs were observed, indicating that the maximum tolerated dose was not reached. The most common AEs included cytopenia (n = 8, 100%), cytokine release syndrome (CRS) (n = 7, 88%) and hypogammaglobulinemia (n = 7, 88%). No cases of immune effector cell-associated neurotoxicity syndrome (ICANS) or hepatic and renal functional toxicities have been reported. Except for P2, whose ICAHT grading reached a

	DL:25 × 10^6 (N = 3)	DL:50 × 10^6 (N = 2)	DL:75 × 10^6 (N = 2)	DL:100 × 10^6 (N = 1)	Total (N = 8)
Any CRS, n (%)	2 (67)	2 (100)	2 (100)	1 (100)	7 (88)
≥Grade 3 CRS, n (%)	1 (33.3)	0 (0)	0 (0)	0 (0)	1 (13)
Any NT, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
≥Grade 3 NT, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAE, n (%)	1 (33)	1 (50)	0 (0)	0 (0)	2 (25)
AESI, n (%)	3 (100)	2 (100)	2 (100)	1 (100)	8 (100)
≥Grade 3 Infection, n (%)	1 (33)	0 (0)	0 (0)	0 (0)	1 (13)
≥Grade 3 Immunoglobulin Reduction (IgA/IgG/IgM), n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
≥ Grade 3 Cytopenia after infusion, n (%)	3 (100)	2 (100)	2 (100)	1 (100)	8 (100)
≥Grade 3 early ICAHT (day 0–30), n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
≥Grade 3 late ICAHT (after day +30), n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
DLT, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

DL, dose level; CRS, cytokine release syndrome; NT, neurotoxicity; SAE, serious adverse event; AESI, adverse events of special interest; DLT, dose-limiting toxicity; ICAHT, immune effector cell-associated hematotoxicity.

Table 2: **The occurrence of adverse events.**

maximum of grade 2, other patients experienced at most grade 1 ICAHT. No patients received granulocyte colony stimulating factor (G-CSF). Similarly, apart from P2, who received corticosteroids for grade 3 CRS, other patients experienced no more than grade 1 CRS, primarily presenting with low-grade fever and muscle soreness. Consequently, no corticosteroids or tocilizumab were administered to the remaining patients and they were managed symptomatically with NSAIDs.

One patient (P2) in the 25 × 10^6 dose group, compared to others, experienced persistent and severe complications. On day 6 post-infusion, the patient developed persistent fever (>39 °C) accompanied by hypotension, hypoxemia, fatigue, nausea, vomiting, palpitations, chest tightness, dyspnea, and edema of the face and lower limbs. Elevated IL-6 and ferritin levels were also detected (Fig. 4B and C). Based on these manifestations, the patient was diagnosed with grade 3 CRS. Oxygen therapy and methylprednisolone (40 mg/day) were subsequently initiated, resulting in rapid symptom relief. The methylprednisolone was then tapered to 10 mg/day, but symptoms recurred on day 11. At that time, the first CAR-T cell expansion peak was observed, and ultrasound revealed bilateral pleural effusion and pericardial effusion with CAR-T cell infiltration detected in the pleural fluid, indicating localized CRS. The methylprednisolone dosage was increased back to 40 mg/day, resulting in alleviation of the patient's symptoms again.

However, between days 15 and 22, the patient experienced recurrent fever accompanied by concurrent COVID-19 and bacterial infections, coinciding with another CAR-T expansion peak, which was nearly 8 times higher than the first peak. Persistent cytopenia was observed (Fig. 4I-L, Figure S1), along with markedly elevated ferritin (9783.6 μg/L), soluble CD25 (6095.74 U/mL), triglycerides (4.81 mmol/L), and hemophagocytosis identified on bone marrow examination (Figure S2), meeting six out of eight HLH-2004 diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH).[20] A comprehensive treatment regimen was initiated, including dexamethasone (20 mg/day), antimicrobial and antiviral agents, intravenous immunoglobulin (IVIG), plasma exchange and blood transfusions, resulting in symptom improvement (the detailed treatment and clinical course are presented graphically in Figure S5).

Following multiple treatments, the patient exhibited a marked response. Anti-dsDNA and anti-SM autoantibody levels fell below pathological thresholds by days 60 and 14, respectively, while C3 and C4 levels returned to normal by day 60. Serological signs of remission aligned with clinical remission, evidenced by a SELENA-SLEDAI score reduction from 14 to 0 and a significant decrease in proteinuria from >2500 mg/24 h to <250 mg/24 h (Figure S3).

In contrast, other patients demonstrated relatively stable overall responses. All experienced grade ≥3 cytopenia, which resolved in approximately three months post-treatment (Fig. 4I–L, Figure S1). Inflammatory markers (C-reactive protein [CRP], ferritin) initially rose during CAR-T expansion but subsequently declined to normal levels (Fig. 4A and B). Corresponding inflammatory cytokines (such as IL-6, IFN-γ, TNF-α, etc.) generally mirrored with the CAR-T expansion time points (Fig. 4C–E, Figure S4), with a small number of patients not showing complete correspondence due to adverse events (P2) or disease progression (P1). Apart from P2, cytokine peaks in other patients were relatively low, consistent with lower CRS grades. All patients who received CAR-T therapy experienced a decline in immunoglobulin levels (IgA, IgG, and IgM), with recovery initiating around 2–3 months post-treatment and approaching baseline by six months (Fig. 4F–H). Hypogammaglobulinemia, defined as serum IgG <7 g/L,

Adverse event	DL:25 × 10^6 (N = 3)			DL:50 × 10^6 (N = 2)			DL:75 × 10^6 (N = 2)			DL:100 × 10^6 (N = 1)			Total (N = 8)		
	Number of cases (%)	CTCAE classification		Number of cases (%)	CTCAE classification		Number of cases (%)	CTCAE classification		Number of cases (%)	CTCAE classification		Number of cases (%)	CTCAE classification	
		<3	≥3		<3	≥3		<3	≥3		<3	≥3		<3	≥3
AE haematologic															
Leucopenia	3 (100)	0	3	2 (100)	0	2	2 (100)	0	2	1 (100)	1	0	8 (100)	1	7
Eosinopenia	1 (33)	1	0	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0	1 (13)	1	0
Anaemia	2 (67)	1	1	0 (0)	0	0	2 (100)	2	0	1 (100)	1	0	5 (63)	4	1
Thrombocytopaenia	1 (33)	0	1	1 (50)	1	0	1 (50)	1	0	0 (0)	0	0	3 (38)	2	1
Lymphocytopenia	3 (100)	0	3	2 (100)	0	2	2 (100)	0	2	1 (100)	0	1	8 (100)	0	8
Monocytopenia	1 (33)	1	0	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0	1 (13)	1	0
AE gastrointestinal															
Nausea and vomiting	1 (33)	1	0	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0	1 (13)	1	0
Abdominal pain upper	1 (33)	1	0	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0	1 (13)	1	0
Constipation	0 (0)	0	0	0 (0)	0	0	1 (50)	1	0	0 (0)	0	0	1 (13)	1	0
AE infectious										0 (0)					
Upper respiratory infection	0 (0)	0	0	1 (50)	1	0	0 (0)	0	0	0 (0)	0	0	1 (13)	1	0
COVID infection	1 (33)	1	0	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0	1 (13)	1	0
Pneumonia	1 (33)	0	1	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0	1 (13)	0	0
Bacterial infection	1 (33)	1	0	0 (0)	0	0	1 (50)	1	0	0 (0)	0	0	2 (25)	1	0
Immune system disorders															1
Cytokine release syndrome	2 (67)	1	1	2 (100)	2	0	2 (100)	2	0	1 (100)	1	0	7 (88)	6	1
Hypogammaglobulinaemia	2 (67)	1	1	1 (50)	1	0	2 (100)	2	0	0 (0)	0	0	5 (63)	4	1
Hypersensitivity	1 (33)	1	0	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0	1 (13)	1	0
AE other															
Fever	2 (67)	2	0	2 (100)	2	0	2 (100)	2	0	1 (100)	1	0	7 (88)	7	0
Hypertension	1 (33)	1	0	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0	1 (13)	1	0
Hepatobiliary disorders	1 (33)	1	0	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0	1 (13)	1	0
Arthralgia	1 (33)	1	0	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0	1 (13)	1	0
Myalgia	1 (33)	1	0	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0	1 (13)	1	0
Hypocalcaemia	0 (0)	0	0	1 (50)	1	0	0 (0)	0	0	0 (0)	0	0	1 (13)	1	0
Hypokalaemia	1 (33)	1	0	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0	1 (13)	1	0
Blood fibrinogen decreased	1 (33)	1	0	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0	1 (13)	1	0
Tachycardia	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0	1 (100)	1	0	1 (13)	1	0
Neurologic toxic effect	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0	0 (0)	0	0

DL, dose level; AE, Adverse event; CTCAE, common terminology criteria for adverse events.

Table 3: **The occurrence of adverse events of varying severity in different systems during patient treatment.**

occurred in five out of eight patients, among whom P2 developed Grade 3 hypogammaglobulinemia (IgG <4 g/L) and required IVIG replacement therapy. The remaining patients exhibited milder reductions and did not take intervention.

Discussion

Safety is the key focus of this clinical trial. No DLT, neurotoxicity, or hepatotoxicity and nephrotoxicity were observed. Most AEs were grade 1–2, demonstrating that relma-cel therapy for SLE is generally safe and well-tolerated. However, it is noteworthy that CAR-T cell therapy for SLE differs from that for malignancies due to the unique features of SLE. Compared to hematologic malignancies, patients with SLE often have poor baseline conditions and immune dysregulation, which predispose them to a higher risk of macrophage activation syndrome (MAS)[21,22] During our clinical trial, we observed the world's first case of MAS with features of a secondary haemophagocytosis (also known as immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome, IEC-HS) in a patients with SLE treated with CAR-T cells. This syndrome is characterized by: 1) macrophage activation/HLH features, 2) attribution to immune effector cell therapy, and 3) association with disease progression or newly emerging cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia, and/or transaminitis.[23] The occurrence of this severe complication may be due to concurrent severe CRS and serious infections. The clinical manifestations of IEC-HS resemble those of CRS or an excessive inflammatory response following CAR-T cell expansion, and HLH-like features are more commonly observed in patients with severe CRS. However, IEC-HS tends to have a delayed onset, typically developing during or after CRS

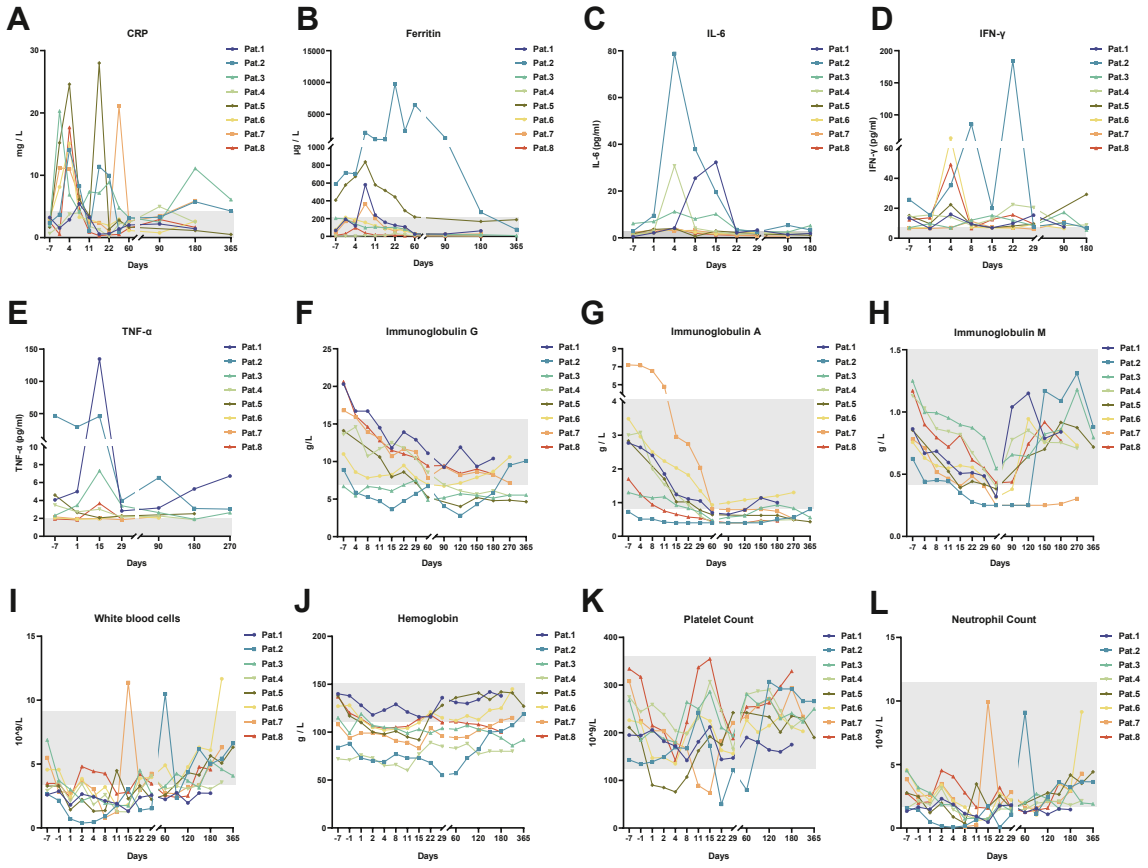

Fig. 4: Various safety parameters of patients following treatment. (A and B) The changes in inflammatory marker levels, including C-reactive protein (CRP) and ferritin, before and after relma-cel treatment. (C–E) The changes in inflammatory cytokine levels (IL-6, IFN-γ, TNF-α) before and after relma-cel treatment. (F–H) The changes in the levels of three immunoglobulins (IgG, IgA, and IgM) before and after relma-cel treatment. (I–L) The changes in peripheral blood hemoglobin and blood cell levels (including white blood cells, platelets and neutrophils) before and after relma-cel treatment. The gray area represents the normal range.

resolution. According to current guidelines for the treatment of IEC-HS, initial therapy can start with anakinra ± corticosteroids.[23] For patients with significantly worsening inflammatory parameters and more severe manifestations of IEC-HS, a higher-dose dual therapy is recommended. In cases of rapid disease progression, the addition of other agents, such as ruxolitinib, should be considered. However, as there are currently no reported cases of IEC-HS in patients with SLE undergoing CAR-T therapy, our treatment approach was not entirely guideline-based but was instead adapted according to the clinical experience of our medical center. We found that, in addition to timely intervention with high-dose corticosteroids, sustained intravenous immunoglobulin administration, fibrinogen supplementation, and prompt plasma exchange are also critical for effective management in these patients.

In this clinical trial, although we observed a higher incidence of cytopenia compared to other studies, no definitive association with CAR-T cells has been established. From both structural perspective and clinical trial outcomes, relma-cel exhibits relatively lower toxicity. Relma-cel separates the costimulatory domain from the CD3 signaling domain, mimicking the natural T-cell receptor signaling pathway and thereby reducing excessive T-cell activation, ultimately lowering the risks of CRS and neurotoxicity. In the RELIANCE study for LBCL, the incidence of Grade ≥3 CRS and neurotoxicity associated with relma-cel was 5.1% and 3.4%,[13] respectively, which were lower than those reported for the Food and Drug Administration (FDA)-approved commercial CAR-T products axicabtagene ciloleucel and tisagenlecleucel.[24,25] Therefore, we believe that these observed adverse events are more likely attributable to patients' poor baseline conditions. Among them, most patients experienced spontaneous recovery of neutrophils (including Grade 2 ICAHT) and platelets within 28 days without pharmacological intervention, while lymphocyte and hemoglobin recovery was relatively slower. The delayed recovery of lymphocytes is primarily

attributable to the physiological process of B-cell reconstitution, whereas hemoglobin levels were partially influenced by patients' baseline conditions, as some had pre-existing chronic anemia prior to enrollment.

In addition to adverse reactions, another noteworthy phenomenon observed during treatment is the unusual biphasic expansion of CAR-T cells in P2 and to a lesser extent P6, despite B-cell depletion. We hypothesize that this specific phenomenon is primarily driven by infection. Specifically, P2 experienced severe viral and bacterial infections, where pathogen-associated molecular patterns (PAMPs) could activate the innate immune system, inducing monocytes/macrophages to secrete pro-inflammatory cytokines such as IL-6 and IFN-γ.[26] These cytokines may establish a positive feedback loop, further promoting CAR-T cell proliferation and activation. Additionally, the secondary expansion of CAR-T cells can create a highly inflammatory microenvironment, potentially leading to IEC-HS, persistent ICAHT, and immune dysfunction,[27] which are consistent with P2's clinical manifestations. However, for P6, no definitive cause has been identified. The patient exhibited no apparent infectious symptoms during the secondary expansion, and inflammatory markers remained largely within normal ranges. We hypothesize that latent viral reactivation may be a key contributing factor. The reactivation of latent viruses could stimulate CAR-T cells through the T-cell receptor (TCR) signaling pathway, leading to delayed expansion.[28,29]

Following administration of varying doses of relma-cel, SRI response was achieved in all patients within 1–2 months. During the follow-up, B cell reconstitution occurred in most patients within three months after infusion. Notably, despite immune reconstitution, most patients maintained relatively normal complement levels throughout the 12-month follow-up periods and anti-dsDNA and anti-Smith antibodies remained below or close to the pathological threshold. One patient (P1) experienced serological relapse at month 3. However, at the time of follow-up discontinuation (M6), the patient remained in clinical remission, as evidenced by reduced proteinuria and resolution of malar rash, resulting in an improved quality of life. Regarding the resurgence of dsDNA and ANA levels in this patient, we hypothesize that it is due to the lowest dose may not be sufficient to fully deplete pathogenic cells. Additionally, some patients exhibited persistent positivity or no decline in anti-Ro-52 and anti-SSA/SSB antibodies throughout the treatment course. We speculate that these antibodies are predominantly produced by therapy-resistant CD19-autoreactive antibody-secreting cells,[10] yet their presence does not seem to compromise the overall therapeutic efficacy.

Existing studies have demonstrated that BCMA-CD19 dual-target CAR T cells achieve superior long-term antibody clearance in the treatment of SLE. However, the deeper depletion of B cells associated with this approach increases the risk of infections compared to CD19 CAR-T therapy.[9] Meanwhile, in our study, even at the lowest dose administered, one patient (P2) experienced grade 3 CRS. This patient had a history of multiple immunosuppressive and B cell-depleting therapies, resulting in low baseline peripheral B cells at enrollment. However, the patient still presented with active organ inflammation and multiple organ damage at the time of enrollment. We hypothesize that substantial infiltration of autoreactive, antibody-producing B cells persisted in the inflamed tissues and organs, and the patient's limited functional organ reserve may have exacerbated the acute adverse reactions, leading to more severe organ dysfunction during CRS. Therefore, considering the overall therapeutic efficacy of relma-cel and the need to balance its potential benefits and risks, future clinical trials evaluating relma-cel for SLE should prioritize refining inclusion and exclusion criteria in accordance with the latest international guidelines on CAR-T cell use in autoimmune diseases.[30] Patients exhibiting active organ inflammation with minimal or no existing organ damage may represent an ideal cohort.

Moreover, another crucial consideration for patients with SLE undergoing CAR-T therapy is the lymphocyte depletion regimen. Lymphodepletion therapy is a critical element for the application of CAR-T therapy in SLE. Unlike patients with hematologic malignancies, patients with SLE typically possess an intact, often hyperactivated T-cell system and a normal bone marrow reserve capable of competing with CAR-T cells, as evidenced by the rapid disappearance of CAR-T cells post-infusion and the reappearance of B cells within an average of three months.[10] Lymphodepletion reduces the competition of CAR T cells for cytokines with other cells, facilitating the homeostatic proliferation of a limited number of adoptively transferred CAR T cells and enabling profound depletion of B cells throughout the body. The inadequate CAR T cell acquisition, quantity, and/or functionality may impede the achievement of this goal.[31,32]

However, the choice of drugs and dosages for the lymphodepletion regimen still requires careful consideration. In this trial, we employed the most commonly used lymphodepletion regimen, consisting of fludarabine at 25 mg/m^2/day and cyclophosphamide at 250 mg/m^2/day (Flu/Cy) administered over three days. This dosage is lower than that used in the majority of international lymphodepletion regimens for CAR-T therapy in SLE.[9,10,33] Nonetheless, one enrolled patient developed a severe infection following lymphodepletion and ultimately had to withdraw from the study. We hypothesize that this was due to the patient's already compromised immune function from extensive prior immunosuppressive therapy, with lymphodepletion further exacerbating immunosuppression, leading to infection. Therefore, it is imperative to explore the

minimum effective lymphodepletion dose or whether the lymphodepletion duration can be shortened in patients with SLE without compromising CAR-T cell expansion and therapeutic efficacy.

The limitations of this study include a non-standardized dose-escalation design and the small sample size, leading to uneven cohort distribution. However, relma-cel is a commercial product with a favorable safety profile, having been thoroughly validated in patients with hematologic malignancy at doses ranging from 25 to 150 × 10^6 CAR-T cells. This supports the expectation that our dose range would retain an acceptable safety margin in SLE. Moreover, as an exploratory IIT assessing feasibility for potential label expansion, the primary aim was to detect early safety signals in SLE rather than to determine the MTD. Upon completion of this limited-size cohort, no DLTs were observed across all dose groups, consistent with its expected safety profile.

In conclusion, this study preliminarily demonstrated that relma-cel is a safe and effective CAR-T product for the treatment of moderately to severely active SLE. It also provides valuable clinical insights into the management of rare complications such as IEC-HS observed during CAR-T treatment in SLE. Larger cohorts and extended longitudinal follow-up are warranted to further validate and contextualize these findings.

Contributors

H.M. and Y.H. conceptualised and designed the study. H.M. and J.S. wrote this article. H.M., Y.H. and J.S. accessed and verified the data. H.M., Y.H., W.X., C.M., and K.S. enrolled and treated patients. J.S., W.X., A.R., M.M. and Z.Z. collected, analysed and interpreted the data, and critically reviewed and approved the final version of this report. All authors reviewed and commented on the manuscript before publication. All authors accept responsibility to submit for publication.

Data sharing statement

The study protocol and individual deidentified participant data that underlie the results reported in this Article, will be available to researchers who provide a reasonable method proposal. For meta-analysis purposes, individual participant data will become available between 9 months and 36 months after Article publication, and proposals should be directed to hmei@hust.edu.cn. To gain access, data requestors will need to sign a data access agreement.

Declaration of interests

All co-authors declare no competing interests. *JW Therapeutics (Shanghai) Co., Ltd.* provided the investigate drugs (relma-cel) and financial support throughout the clinical trial, such as patient compensation and the examination costs. The other work in this clinical trial, including study design, data collection, data analysis, data interpretation and writing of the report et al. were jointly conducted by authors. The company has no objection to the contributions described in the manuscript, and there are no conflicts of interest between the company and all co-authors.

Acknowledgements

This work was supported by Grants from the National Natural Science Foundation of China (82425003, 82330005) and the National Key R&D Program of China (2023YFC2507805). The authors would like to thank all the study investigators and coordinators.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103229.

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