Anti-CD19 chimeric antigen receptor T cell therapy achieved rapid and sustained remission in a patient with systemic lupus erythematosus-associated refractory immune thrombocytopenia

Sirs,

Systemic lupus erythematosus (SLE) is featured by widespread inflammation and damage in multiple tissues and organs (1). SLE exhibits heterogeneous clinical manifestations, including haematologic disorders such as anaemia and immune thrombocytopenia (ITP) (2). Standard therapeutic regimens typically include glucocorticoids, immunosuppressants, and biologic agents such as rituximab and belimumab (3). However, some refractory SLE patients exhibit suboptimal responses to monoclonal antibody therapy (4). Chimeric antigen receptor T (CAR-T) cell therapy as an emerging therapeutic approach, has shown promising potential in the management of refractory SLE. A recent clinical study has shown that part of patients with refractory SLE-ITP can benefit from CAR-T cell immunotherapy (5). However, CAR-T cell therapy for refractory SLE-ITP lacks robust evidence, with unconfirmed safety and long-term efficacy requiring further investigations. (6-8). This report evaluated the long-term efficacy and safety of CAR-T cell therapy in a patient with refractory SLE-ITP, providing clinical evidence for its therapeutic application.

A 37-year-old female subject with a 15-year history of SLE presented autoimmune haemolytic anaemia initially which remained stable after proper treatment with glucocorticoids and immunosuppressants, although there were several fluctuations. She had developed recurrent haemorrhagic episodes five years ago. The lowest platelet count was 1×10^9/L, and severe anaemia, even with a haemoglobin level of 50g/L, along with persistently low complement levels and high total bilirubin levels. Bone marrow smear examination was performed to confirm megakaryocyte maturation disorder and rule out other haematologic diseases. The patient was diagnosed with SLE-ITP. She received a high dose of intravenous glucocorticoids (including pulse therapy) and intravenous immunoglobulin (IVIG) at each episode, and subsequently oral glucocorticoids and immunosuppressants. However, despite trying nearly all immunosuppressants and biologic agents, the prednisone dosage could not be reduced to less than 30 mg/day. She suffered pelvic bone fracture and experienced several episodes of bacteria, fungi, and virus infections in lungs and intestinal tract because of long-term use of glucocorticoids and immunosuppressants. This female patient underwent uterine and splenic artery embolisation to control vaginal bleeding and needed thrombopoietin receptor agonist (TPO-RA) or recombinant human thrombopoietin injections (rh-TPO) to sustain platelet counts. Prior treatments, including glucocorticoids pulse, hydroxychloroquine sulfate, cyclosporine, mycophenolate mofetil, tacrolimus, sirolimus, immunoglobulin, rh-TPO, rituximab, belimumab, and TPO-RA (Fig. 1A) did not yield satisfactory outcomes. Anifrolumab has been proposed as a potential therapeutic option for SLE-ITP, but it was not used in this case due to its lack of regulatory approval in China (9).

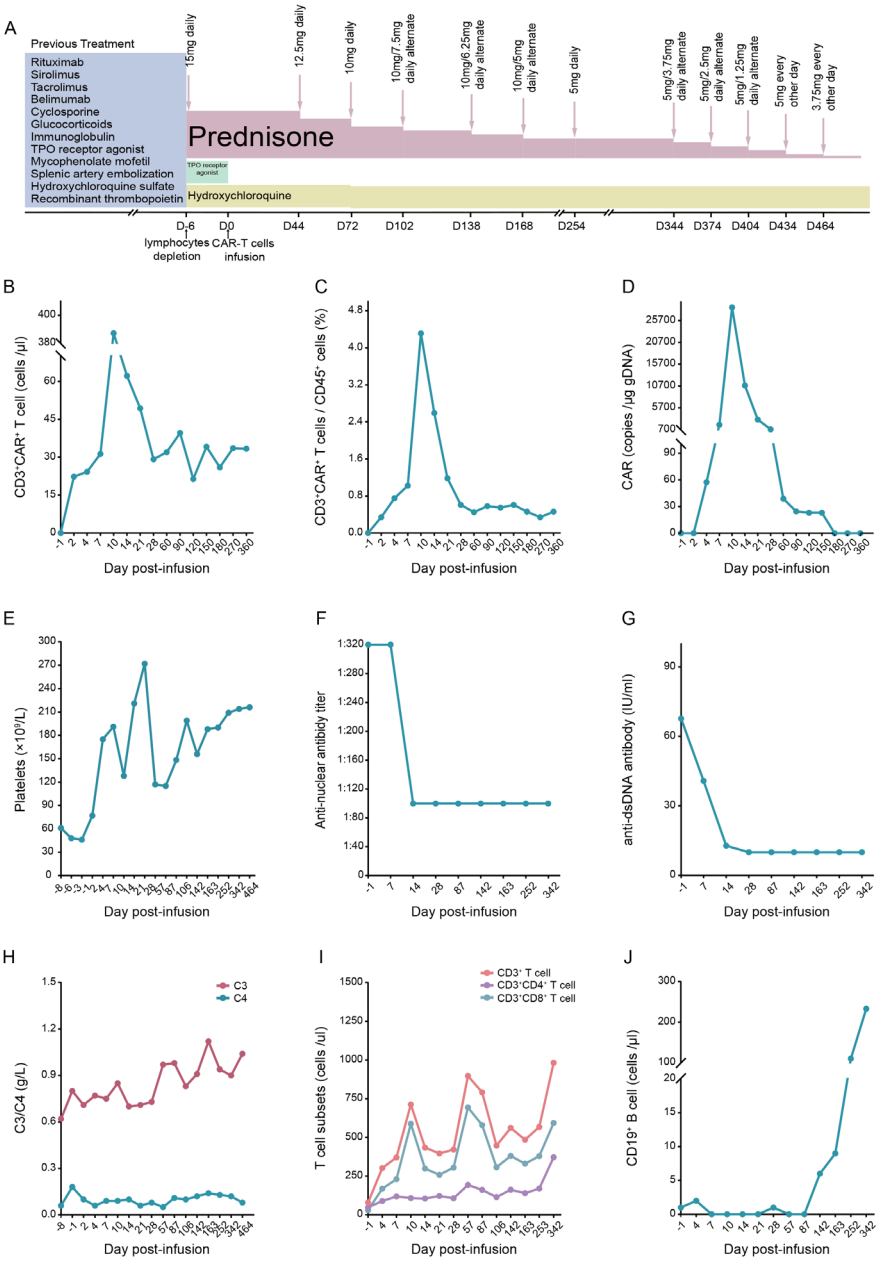

Fig. 1. The patient with refractory SLE-ITP was administrated by CAR-T cell therapy. The patient's medication therapy process (**A**). The CAR-T cell total number (**B**), the CAR-T cell proportion of CD45+ cells (**C**) and the CAR copies (**D**) were monitored in peripheral blood. Platelet count (**E**), the titre of antinuclear antibodies (**F**), the anti-dsDNA antibodies (**G**), complement C3 and C4 (**H**), T cell subsets (**I**) and circulating B cell numbers (**J**) were changed in peripheral blood before and after CAR-T cell infusion.

We recorded the outcomes of the patient using anti-CD19 CAR-T cell (Inaticabtagene Autoleucel) therapy in treating refractory SLE-ITP. Anti-CD19 CAR-T cells were produced through lentiviral transduction of autologous fresh lymphocytes. At the time of lymphocytes depletion, the patient was taking TPO-RA, hydroxychloroquine and prednisone and stopped other medications. Prior to the CAR-T cell infusion, only hydroxychloroquine and prednisone were administered (Fig. 1A). Following the infusion of cyclophosphamide (519 mg) and fludarabine (43.25 mg) on Day -6 and Day -5 respectively, 30.15×10^6 CAR-T cells were

infused on Day 0. On Day 2 the CAR-T cell count was 22.34 cells /μl in the peripheral blood (Fig. 1B-C), and peaked at 387.11 cells /μl on Day 10 with the CAR copies increased to the maximum 28700 copies /μg gDNA concurrently (Fig. 1D). The CAR-T cell persisted up to one year in the peripheral blood post-infusion (flow cytometry methodology). And the patient did not exhibit any symptoms of cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS) following CAR-T cell therapy. After administrating the CAR-T cell, the platelet count rapidly increased, maintaining a normal level since Day 2 (Fig. 1E). Furthermore, the anti-nuclear antibody titre decreased to 1:100 within 2 weeks and remained negative (Fig. 1F), accompanied by a sustained decline in anti-dsDNA antibody levels (Fig. 1G) and restoration of complement C3 and C4 to normal ranges (Fig. 1H). Additionally, T cell subsets exhibited an obvious rise compared with the baseline. Both $CD3^+$T cell count and $CD3^+CD8^+$T cell count had normalised (Fig. 1I). The B cell number in peripheral blood returned to normal level by the 9 months after CAR-T cell infusion (Fig. 1J). On Day 254 the patient fulfilled the Doris (Definition of Remission in SLE) remission criteria. In subsequent follow-ups, the therapeutic effects above still existed and were maintained for over one year. Currently the prednisone dosage gradually tapered to 3.75 mg every other day (Fig. 1A).

We described a female patient with refractory SLE-ITP who achieved sustained remission following CAR-T cell therapy after demonstrating resistance to multiple conventional treatments. The CAR-T therapy exhibited a favourable safety profile, with no observed instances of ICANS, CRS, or other adverse events. More significantly, our patient demonstrated a completely normalised platelet count with glucocorticoid tapering during the follow-up period after CAR-T therapy. In this case, CAR-T cells demonstrated prolonged persistence (over one year) in peripheral blood, longer than previously reported (5).

The critical pathogenic mechanism of SLE is closely associated with hyperactivation of B cells and production of pathogenic autoantibodies by plasma cells and plasmablasts. The overactive B-cell response contributes to disease progression through multiple mechanisms, including the secretion of inflammatory cytokines and serving as antigen-presenting cells that activate T lymphocytes (10). Consequently, strategies aimed at depleting B cells have become central to therapeutic. Although some clinical trials support B cell-targeting therapies with belimumab and rituximab for refractory SLE, a subset of patients remains unresponsive to them (4). The limited efficacy of rituximab may be attributed to unresponsive CD20negative plasmablasts or long-lived plasma cells and insufficient elimination of B cells in tissue and marrow (6, 7). In our data, repeated administration of rituximab and belimumab failed to prevent platelet decrease or overcome glucocorticoid and immunosuppressant reliance. Preclinical studies utilising anti-CD19 CAR-T cell in mouse models have demonstrated effective clearance of B lymphocytes and improved prognosis (11). However, our study found that auto-antibodies remained undetectable in peripheral blood, with sustained clinical remission after B-cell counts normalised. Some researches suggest that CAR-T cells may migrate to lymphoid organs and tissues, facilitating comprehensive B cell depletion, which particularly targets $CD19^+$ plasma cells and plasmablasts that produce autoantibodies (12, 13).

In summary, our study demonstrates that anti-CD19 CAR-T cell therapy can lead to sustained and safe remission in refractory SLE-ITP, providing clinical evidence that anti-CD19 CAR-T therapy may induce durable disease control in refractory SLE-ITP.

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