EA DV CONGRESS
AMSTERDAM 25-28 SEPTEMBER 2024
EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

Abstract N°: 8058

Allogeneic CD19-targeted CAR-T therapy for refractory systemic lupus erythematosus (SLE)

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Introduction & Objectives:

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease associated with significant morbidity and mortality. It can affect various tissues and organs throughout the body, leading to a broad spectrum of clinical symptoms. The treatment approach for SLE primarily involves immunomodulation and immunosuppression. However, these drugs have considerable toxicity and are not effective in all patients. Conceptually, a deep depletion of CD19+ B cells and plasmablasts could trigger an immune reset in autoimmune diseases. Autologous CD19-targeted CAR-T therapies has been explored in several autoimmune diseases and reported promising efficacy in recent studies. In this study, a healthy donor-derived, multiplex genome-edited allogeneic CD19-targeted CAR-T product (BRL-303) was developed for refractory autoimmune diseases patients. Here we report the efficacy and safety profile of BRL-303 in treating patients with systemic lupus erythematosus (SLE).

Materials & Methods:

This is an investigator-initiated trial evaluated the safety and efficacy of BRL-303 in adult patients with refractory autoimmune diseases (NCT05859997, NCT05988216). Participants were screened and underwent lymphodepletion chemotherapy with cyclophosphamide (300 mg/m^2, day -5 to -4) and fludarabine (25 mg/m^2, day -5 to -3), then BRL-303 infusion at day 0 with a dose level of 1×106 cells/kg. After BRL-303 infusion, each patient underwent safety and systematic follow-up assessments according to the protocol.

Results:

As of August 16, 2024, a total of 6 patients with refractory systemic lupus erythematosus have been treated. These patients were unable to control disease progression despite treatment with corticosteroids and various immunosuppressants. After BRL-303 infusion, CART cells expanded in vivo in all subjects significantly within 7 days and reached a peak around 14-21 days. With expansion of BRL-303, B cells in peripheral blood of patients reached deep and persistent depletion about 1-3 months. The median follow-up time for the 6 subjects was 6 months (range: 1-9 months). After BRL-303 infusion, there was a significant decrease in SLEDAI scores and PGA in all subjects(6/6,100%), and all of them achieved SRI-4 remission. Moreover, all subjects showed a significant decrease in serum autoantibodies and increase in complement. Meanwhile, proteinuria significantly decreased in the subjects with lupus nephritis. In terms of safety, the patient's vital signs remained mostly stable throughout the monitoring period, 2 subjects developed grade 1 CRS on D4 and D5, which recovered soon without tocilizumab and steroid usage. No serious infection (Grade 3/4), no ICANS and GvHD observed in all subjects.

Conclusion:

Overall, SLE subjects treated with BRL-303 achieved significant clinical remission, with a controllable safety profile, offering a potential paradigm shift for SLE patients who are refractory to currently available treatments. Further observation of SLE and more autoimmune disorders treated with BRL-303 are ongoing in our study.

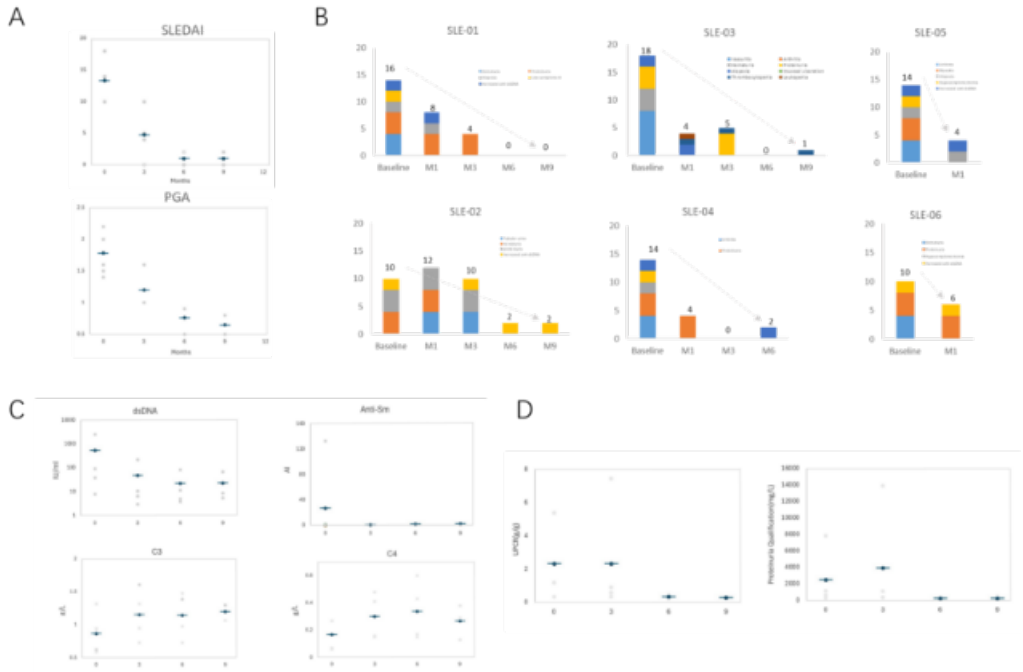

Figure 1 Effects of BRL-303 for SLE patient (A, SLEDAI-2K and PGA change befor and after BRL-303 treatment; B, SLEDAI-2K Score changs; C,Serological changes ; D, Urine protein changes)