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Deep serological profiling of SLE patients treated with anti-CD19 4-1BBz CAR T-cells

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Background

Anti-CD19 chimeric antigen receptor (CAR) T-cell therapy is a ground-breaking emerging treatment modality for severe refractory systemic lupus erythematosus (SLE) and has shown early promise in other autoimmune diseases. Initial clinical data demonstrate that adoptive transfer of anti-CD19 4-1BBz CAR T-cells induce a durable off-therapy long-term remission in SLE patients. However, the mechanisms underlying remission are unclear. Our aim was to elucidate the serological factors that are associated with responses in SLE patients following treatment with anti-CD19 4-1BBz CAR T-cells. This work expands on the data reported by *Mackensen et al,* in Nature Medicine, 2022 and *Nunez et al*, in Molecular Therapy Methods and Clinical Development, 2023.

Methods

Sera were collected from eight severe refractory SLE patients prior to and following (3 months, 4 months, or 6 months) anti-CD19 4-1BBz CAR T-cell therapy. All patients were in remission off-therapy following adoptive T-cell transfer. Sera were evaluated for 25 cytokines by electro-chemiluminescence immunoassay (MSD). Sera were also evaluated for 17 SLE-associated and 14 infectious disease-associated antibodies using a custom developed Luminex-based immunoassay.

Results

Serum levels of the inflammatory cytokines IL-6 and TNFα were decreased in SLE patients post-CD19 4-1BBz CAR T-cell infusion relative to pre-infusion levels (Figure 1). Over the same period, the B cell memory and homeostatic cytokines IL-7 and BAFF increased (Figure 1). SLE-associated antibodies decreased dramatically in 6 out of 8 patients following anti-CD19 4-1BB CAR T-cell infusion. In 1 out of 8 patients, SLE associated antibodies either remained stable or increased mildly despite resolution of clinical disease. Infectious disease associated antibodies typically remained stable or changed minimally following anti-CD19 4-1BBz CAR T-cell infusion. Lastly, circulating CD19⁺ B-cells were detected in all patients 2 to 7 months following anti-CD19 4-1BBz CAR T-cell infusion (data not shown).

Results

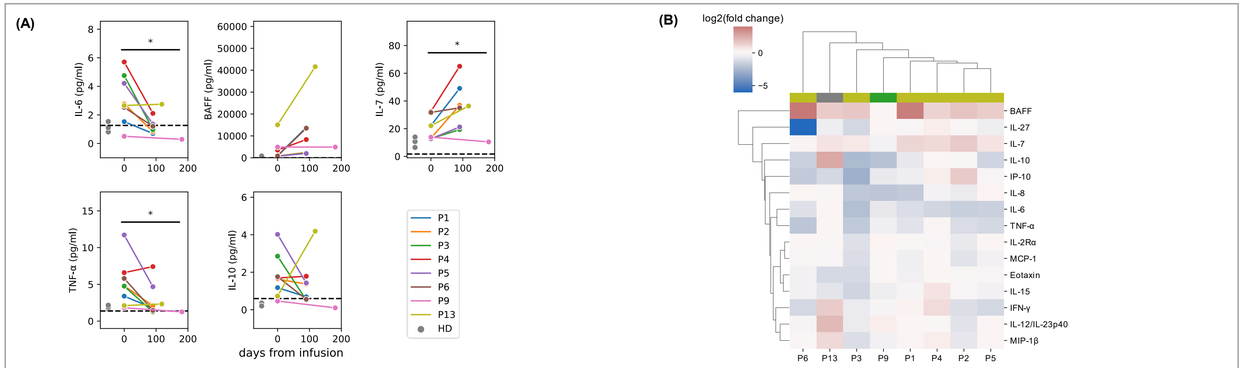

Figure 1. Cytokines. Cytokines were measured by MSD from sera collected prior to and following CAR T-cell infusion. (A) Levels of individual cytokines are plotted against time in days elapsed from CAR T-cell infusion. Dashed lines represent lower limits of quantification for each cytokine. (B) Heatmap displays the log2 ratio of post-infusion to pre-infusion levels for each cytokine analyzed. Hierarchical clustering of these log-transformed ratios was performed using the unweighted pair group method with arithmetic mean (UPGMA) algorithm and Euclidean distance as the distance metric. Color code for each column represents the time elapsed between pre-infusion and the post-infusion samples. Yellow, 3 months; Grey, 4 months; Green, 6 months; HD, healthy donor control; P, patient; *, p < 0.05 calculated using a two-sided paired t-test.

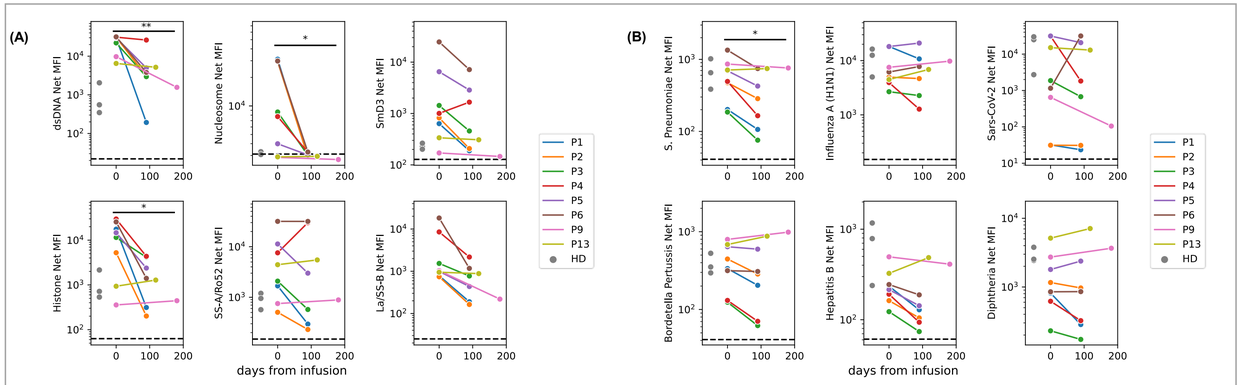

Figure 2. Auto-antibodies and pathogen responses (A) SLE-associated and (B) infectious agents or pathogen-associated antibodies prior to following anti-CD19 4-1BBz CAR T cell infusion. Quantification of antibodies against double-stranded (ds) DNA, total histone, Sjogren's syndrome (SS)-A/Ro52, SS-B/La, Nucleosome, SmD3, Streptococcus Pneumoniae, Influenza A (H1N1), Sars CoV-2, Bordetella Pertussis, Hepatitis B and Diphtheria (N = 8). HD, healthy donor control; MFI, mean fluorescence intensity; P, patient. Dashed black line depicts lower limit of antibody quantification. *, p < 0.05, **, p < 0.01 calculated using a two-sided paired t-test.

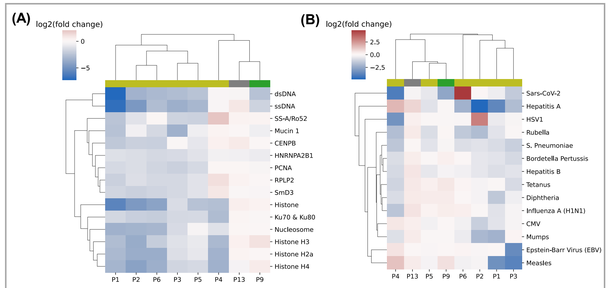

Figure 3. Auto-antibody and pathogen responses – Heatmaps: (A) SLE-associated and (B) infectious agents or pathogen-associated antibodies prior to and following anti-CD19 4-1BBz CAR T-cell infusion. Values displayed are the log2 transformed ratios of antibody concentration changes from pre-infusion to the third month after infusion (log2 fold change). Antibodies are ordered based on hierarchical clustering of these log-transformed ratios performed using the unweighted pair group method with arithmetic mean (UPGMA) algorithm and Euclidean distance. Color code for each column represents the time elapsed between pre-infusion and the post-infusion samples. Yellow, 3 months; Grey, 4 months; Green, 6 months.

Conclusions

- We report on 8 SLE patients following anti-CD19 4-1BBz CAR T therapy showing sustained remission off-therapy.
- Serum cytokine data suggest that systemic inflammation (IL-6 and TNFα) is consistently decreased at three to 6 months post infusion.
- An expanded panel of SLE-associated antibodies shows a profound drop in some SLE-associated antibodies observed in most patients and supports the idea of an immune reset following CAR T therapy.
- An expanded panel of infectious disease-associated antibodies shows a minimal, if any, impact of anti-CD19 4-1BBz CAR T therapy on pre-existing pathogen humoral immunity.
- These studies support the continued exploration of anti-CD19 4-1BBz CAR T cell therapy in SLE and in other autoimmune diseases.