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Deep serological profiling of autoimmune 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 diseases, including myositis and systemic sclerosis (SSc). Initial clinical data demonstrate that adoptive transfer of anti-CD19 CAR T-cells induces a sustained reduction or elimination of disease in SLE, myositis, and SSc patients. However, the mechanisms underlying remission are unclear. Our aim was to elucidate serological factors that are associated with responses in SLE, myositis, and SSc patients following treatment with anti-CD19 4-1BBz CAR T-cells.

Methods

Sera were collected from 8 SLE, 2 myositis, and 3 SSc patients prior to and following anti-CD19 4-1BBz CAR T-cell therapy ($1x10^6$ CAR T-cells/kg following preconditioning with cyclophosphamide 1000 mg on day -3 and fludarabine 25 mg/m2/day on days -5 to -3 as described in Mackensen *et al.*, Nat Med 2022). All patients had severe refractory disease prior to adoptive T-cell transfer and were immunosuppressive-free with up to 29 months of follow-up post-treatment. Sera were evaluated for 25 cytokines and chemokines by electro-chemiluminescence immunoassay (MSD). Sera were also evaluated for 19 SLE-associated antibodies, 24 myositis-associated antibodies, and 14 infectious disease-associated antibodies using a custom developed Luminex-based immunoassay.

Results

Serum levels of the inflammatory cytokines IL-10, IL-6 and TNFα were decreased in most patients post-anti-CD19 4-1BBz CAR T-cell infusion relative to pre-infusion. Levels of IL-7 and BAFF increased between 2 and 7 months post treatment. SLE associated antibodies decreased substantially in most patients following anti-CD19 4-1BBz CAR T-cell infusion. In one patient, SLE associated antibodies either remained stable or increased mildly despite resolution of clinical disease. Only one myositis patient had a substantial decrease in Jo1-associated autoantibodies. Infectious disease associated antibodies typically remained stable or changed minimally following anti-CD19 CAR T-cell infusion.

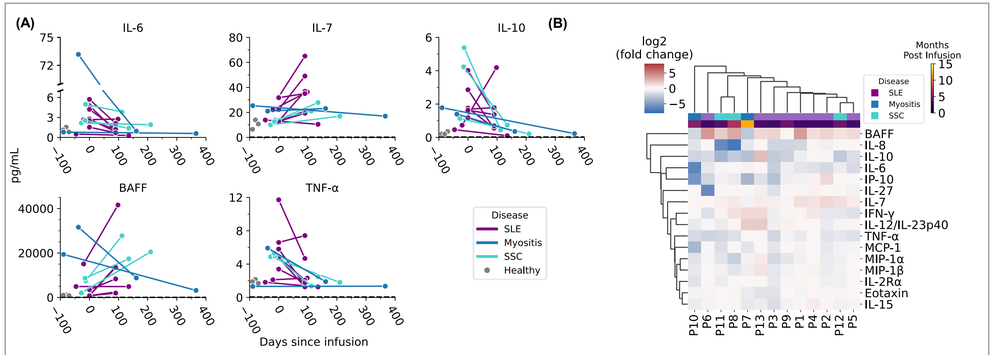

Figure 1. Cytokines. Cytokines were measured by MSD from sera collected prior to and following anti-CD19 4-1BBz CAR T-cell infusion (N=13). (A) Levels of select individual cytokines are plotted against time in days elapsed from CAR T-cell infusion. Dashed lines represent lower limits of quantification for each cytokine. Grey dots represent cytokine levels in sera collected from healthy donors. (B) Heatmap displays the log2 ratio of post-infusion to pre-infusion levels for each cytokine detected. 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 indication or the time elapsed between pre-infusion and the post-infusion samples.

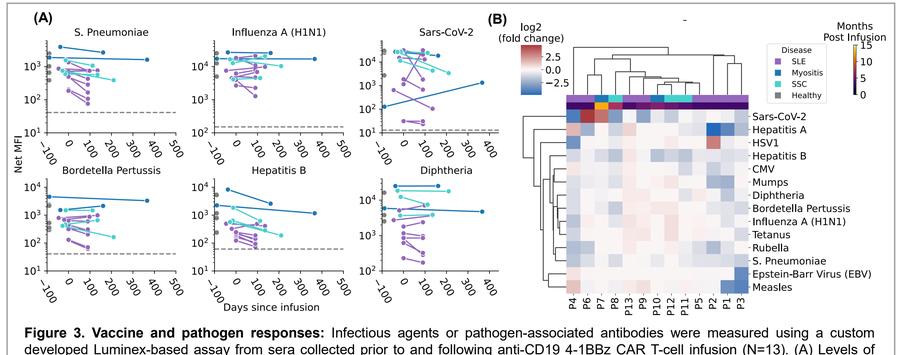

Figure 3. Vaccine and pathogen responses: Infectious agents or pathogen-associated antibodies were measured using a custom developed Luminex-based assay from sera collected prior to and following anti-CD19 4-1BBz CAR T-cell infusion (N=13). (A) Levels of select antibodies are plotted against time in days elapsed from CAR T-cell infusion. Dashed lines represent background fluorescence for each antibody. Grey dots represent antibody levels in sera collected from healthy donors. (B) Heatmap displays the log2 ratios of antibody concentration changes from pre-infusion to post-infusion 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 indication or the time elapsed between pre-infusion and the post-infusion samples. HD, healthy donor control; MFI, mean fluorescence intensity; P, patient.

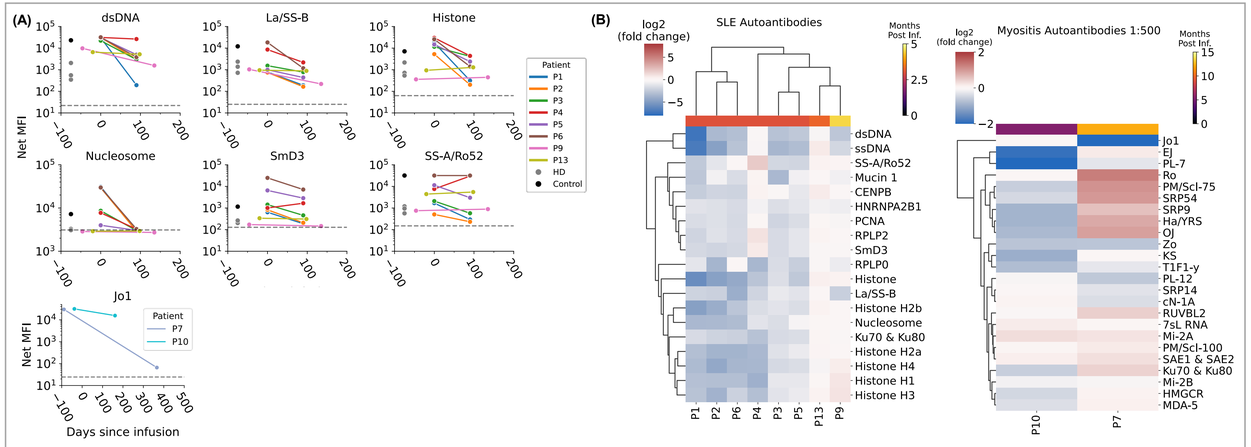

Figure 2. Auto-antibodies SLE-associated (N=8) or Myositis-associated (N=2) autoantibodies were measured using a custom developed Luminex-based assay from sera collected prior to and following anti-CD19 4-1BBz CAR T-cell infusion (N=13). (A) Levels of select antibodies are plotted against time in days elapsed from CAR T-cell infusion. Dashed lines represent background fluorescence for each antibody. Grey dots represent antibody levels in sera collected from healthy donors. Black dot represents pooled sera collected from donors with SLE. (B) Heatmap displays the log2 ratios of antibody concentration changes from pre-infusion to post-infusion 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 indication or the time elapsed between pre-infusion and the post-infusion samples. HD, healthy donor control; MFI, mean fluorescence intensity; P, patient.

Conclusions

- We report on 8 SLE, 2 myositis, and 3 SSc patients following anti-CD19 4-1BBz CAR T-cell therapy showing sustained reduction or elimination of disease off-therapy (Müller *et al.*, NEJM 2024).
- Serum cytokine data suggest that systemic inflammation is consistently decreased at 3 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. A separate panel of Myositis-associated antibodies shows a profound drop in some Myositis-associated antibodies observed in two patients.
- An expanded panel of infectious disease-associated antibodies shows a minimal, if any, impact of anti-CD19 4-1BBz CAR T-cell therapy on pre-existing pathogen humoral immunity.
- The more frequent sampling of serum planned for NCT06359041, NCT06328777, NCT06154252, and NCT06121297 will allow for a deeper understanding of anti-CD19 4-1BBz CAR T-cell therapy in various autoimmune diseases.