Conclusions: was observed in S100A9. Treatment were also greater than S100A8 low group. A trend similar to S100A8 significantly higher in the S100A8 high group. Cytokine changes after HCQ ing serum cytokines and adipokines, serum IL-1ra and resistin levels were greater in the S100A8 high group after 3 months of HCQ treatment. Regard-

DAI and SLE-DAS in the S100A8 low group (Figure 1). The C3 increase was 3 months of HCQ treatment. There was no significant improvement in SLE-

group, 56.3%). SLEDAI and SLE-DAS improved in the S100A8 high group after more likely to achieve LLDAS after HCQ treatment (high group, 76.9 % vs. low

complement titer (C3) and white blood cell count. The S100A8 high group was more likely to have a history of lupus nephritis and active skin lesions. The S100A8 low group had a low serum S100A8 and S100A9 protein levels. The high and low groups were analyzed

ing serum S100A8 and S100A9 protein and adipokines (adiponectin, leptin, and VEGF-A, and MIP-1a) were measured by the multiplex Luminex assay, and

resistin) by ELISA.

Methods: SLE patients with different serum S100 protein levels. In a previous study, we found that hydroxychloroquine (HCQ), which regulates IFN activity,

ular pattern factor, has been associated with interferon (IFN) [1]. In a previous study, we found that hydroxychloroquine (HCO), which regulates IFN activity,

regulates serum IFN activity, modulates serum S100 protein in SLE patients [2].

Objectives: This study determined if the therapeutic effect of HCO is altered in SLE patients with different serum S100 protein levels.

Methods: This single-center, prospective, exploratory study evaluated patients before HCQ treatment and every 3 months for a year. SELENA-SLE-

DAI, SLE-DAS, and the Lupus Low Disease Activity State (LLDAS) scale measured disease activity. Serum cytokines (TNF-α, IL-6, IL-8, MCP-1, IL-1ra, VEGF-A, and MIP-1a) were measured by the multiplex Luminex assay, and serum S100A8 and S100A9 protein and adipokines (adiponectin, leptin, and resistin) by ELISA.

Results: Sixty-seven patients (63 females, mean age 41.8 years) were divided into three groups, namely, high, intermediate, and low, according to baseline S100A8 and S100A9 protein levels. The high and low groups were analyzed (Table 1). The S100A8 high group was more likely to have a history of lupus nephritis and active skin lesions. The S100A8 low group was more likely to achieve LLDAS after HCO treatment (high group, 76.9 % vs. low group, 56.3%). SLEDAI and SLE-DAS improved in the S100A8 high group after 3 months of HCQ treatment. There was no significant improvement in SLE-

DAI and SLE-DAS in the S100A8 low group (Figure 1). The C3 increase was greater in the S100A8 high group after 3 months of HCQ treatment. Regarding serum cytokines and adipokines, serum IL-1ra and resistin levels were significantly higher in the S100A8 high group. Cytokine changes after HCQ treatment were also greater than S100A8 low group. A trend similar to S100A8 was observed in S100A9.

Conclusion: SLE patients with high serum S100 protein levels respond better to HCQ therapy. This finding suggests that serum S100 protein levels may predict the response to IFN inhibitor therapy.

References:
Objectives: To evaluate the impact of UPA and ABBV599 on immunologic pathways associated with SLE pathogenesis.

Methods: SLE patients (n = 205) were randomized to (placebo [PBO]; n = 75; UPA 30mg QD; n = 62; ABBV599 n = 68). At screening, patients were stratified by their SLE Disease Activity Index 2000 (SLEDAI-2K) score, corticosteroid dose (> 10mg prednisone or no), immunosuppressant and IFN score. Proteomic analyses were performed on the plasma samples using a commercial proximity-extension immunoassay. A repeated mixed linear model was used to compare changes in biomarkers vs PBO and Pearson’s correlation was tested to compare protein biomarkers, IFN score, and SLEDAI-2K scores. All analyses were corrected for multiple testing using the Benjamini–Hochberg method. Enrichment analyses were performed to elucidate the biological pathways associated with changes in protein biomarkers.

Results: As expected, elevated IFN gene expression at baseline was associated with higher SLEDAI 2K disease activity scores, increased anti-double stranded DNA titers, and lower levels of complement components. Expression of serum proteins related to the IFN pathway, such as CXCL10, sialic acid binding immunglobulin-like lectin 1, IFN gamma, and ZBP1, positively correlated with the IFN score. Treatment with UPA monotherapy or the combination ABBV599 significantly reduced the IFN gene scores compared with PBO at weeks 4 and 24 (P ≤.0001). Proteomic analyses revealed 301 protein biomarkers differentially modulated at weeks 2, 12, and 24 compared with PBO, including significant down-regulation of Type I IFN pathway proteins. There were additional impacts of UPA and ABBV599 on T-cell-associated cytokines, B cells, macroglobules, and innate response markers. These effects were similar with UPA and ABBV599, suggesting that the main effect was attributable to activity of UPA.

Conclusion: These results suggest that the clinical benefit demonstrated by UPA in patients with SLE includes the modulation of Type I IFN with impact on several core pathogenic pathways involved in SLE. The main biomarker effects of UPA and ABBV599 were driven by UPA.


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NOVEL APPROACH TO TREAT SYSTEMIC LUPUS ERYTHEMATOSUS, BY TARGETING THE "ROOT CAUSE": B CELLS AND PLASMA CELLS, USING BCMd-CD19 COMPOUND CAR

Keywords: Autoantibodies, Systemic lupus erythematosus, Clinical trials


Background: Systemic lupus erythematosus (SLE) is a heterogeneous multi-system autoimmune disease characterized by the production of autoantibodies produced by the “root cause” B and plasma cells. Autoantibody depletion has been attempted by targeting B cells, however no such treatment addresses both B and plasma cells.

Objectives: We assess the safety and efficacy of dual resetting B and plasma cell populations using our novel BCMd-CD19 cCAR T (cCAR) in an open label phase I clinical trial.

Methods: We constructed a cCAR composed of a complete BCMd-CD19 CAR fused to a complete CD19-CAR, separated via self-cleaving P2A peptide. The cCAR functional activity was assessed in co-culture assays with multiple cell lines and mouse models. T cells from peripheral blood obtained viapheresis were transplanted to create cCAR. Cessation of steroids and immunosuppressing medications was followed by conditioning. Patients received monthly IgG until B cells recovered. Patients were dosed from 1.5×10^6 cCAR cells/kg body weight and monitored. P1 and P2: 20-year history of managed SLE and received cCAR as compassionate use for B cell lymphoma. P1 and P2 achieved complete remission (CR). After 1-year follow up demonstrated CR of SLE, hospital approved additional SLE/Lupus Nephritis (LN) patients for treatment. Baseline Characteristics: 12 patients received cCAR treatment, 7 SLE and 5 LN. Patient ages range 3-58. Ten of 12 were female. P1 and P2: SLEDAI-2K score 4, and 8, respectively. Patient 3-12: SLEDAI-2K baseline score mean 11 range 6 to 16. All of patients (3-12) had LN on kidney biopsy between IV to V with failure of standard therapy.

Results: Safety: Overall cCAR has been well tolerated to date. There have been no severe adverse events (SAE) or infections attributed to cCAR, no CRES and no CRS above Grade 1. All patients with >3 weeks follow up had a mild fever (CRS grade 1) which resolved with supportive care. Onset of mild fever occurred between days 3 to 14 and resolved within a week of onset. Efficacy: B cells were entirely depleted in peripheral blood 3-14 days post cCAR. Three patients treated >6 months in CR (SLEDAI-2K = 0, all autoantibodies negative, and normal complement). P1 and P2 maintain drug free CR and with no autoantibodies post-cCAR approximately 40 and 20 months respectively. All B cells recovered within 2-6 months with no indications of relapse. At 1-4 months post-treatment 9 patients were negative, for anti-dsDNA autoantibody, anti-nuclear autoantibody, anti-SSA/Ro52 autoantibody, anti-SSA/Ro60 autoantibody, anti-ribosomal P, and anti-U1-snRNP. Among 9 patients rapid improvement within 1 month after cCAR, mean SLEDAI-2K dropped from 8.7 mean at baseline to 2 at 1 month (7 patients no symptoms), and mean drop to 0.88 within 6 months (9 patients no symptoms). All patients achieved 100% response and are maintaining medication free recovery (no immunosuppressives or glucocorticoids). An immune “reset” was observed via flow cytometry showing that most of recurring cells are naïve B cells, and further observed in BCR deep sequencing (patients 3-4), whereby IgG and IgA clonotypes are absent and non-class-switched BCR repertoires are generated with 95% IgM heavy chain.

Conclusion: These data on the 12 patients treated with cCAR demonstrate that the intervention is well tolerated. Initial data suggests immune system “reset” with long-term remission is possible as cCAR treats the “root cause” of disease by depleting autoantibody produced by plasma cells and memory B cells. This approach can be extended to other B and/or plasma-cell mediated autoimmune disorders. The full dataset will be updated at the meeting.

Acknowledgements: Patients and their families.


Keywords: Autoantibodies, Systemic Lupus Erythematosus

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Background: Pediatric Antiphospholipid Syndrome (APS) is an autoimmune disease characterized by venous and/or arterial thrombotic events (TE) associated with 2 consecutive positive determinations (at least 12 weeks apart) of antiphospholipid antibodies (aPL), IgG/IgM anticardiolipin (aCL), IgG/IgM [Ig2-glycoprotein I (a1)2GPI] and/or lupus anticoagulant (LA). Recent data suggests that aPL levels may decrease over time due to the natural history of the disease or to treatments. Therefore, monitoring of aPL levels may represent a strategy to evaluate disease activity and response to treatment.

Objectives: To investigate the trend over time of aPL titers in children with APS, comparing patients under immunomodulatory therapies and those without them.

Methods: A descriptive, observational, cross-sectional study was carried out in children with APS. aPLs testing was carried out in all patients from diagnosis every 3-4 months for 2 years. Interferon Gene Signature (IGS) was assessed as described by Crow[1]. Laboratory parameters, clinical and demographic data was retrieved and analyzed. Statistical analysis was performed with software R_v.4.0.3.

Acknowledgements: Patients and their families.


Keywords: Antiphospholipid syndrome, Autoantibodies

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