counts and immunophenotyping, determination of serum immunoglobulin levels, seroconversion rate of HAV and quantification of serum HAV IgG concentration.
Results: Twenty-four (24) healthy subjects were enrolled for the study and 23 completed the study. One subject discontinued prior to completion due to inability to follow study procedures. There were no severe adverse events in subjects who received 3 or 10 mg/kg MGD010. The only serious adverse event reported in t in a subject who had received placebo and was not drug related. There were no CTCAE grade 3 or higher adverse events related to MGD010. Consistent with prior observations (1), ex vivo flow cytometric analysis confirmed dose-dependent MGD010 binding to peripheral B cells without B-cell depletion, accompanied with decreased surface BCR and CD40 expression as well as a moderate decrease in total serum IgM levels. Reduced HAV seroconversion rates were observed in subjects treated with MGD010 as compared to placebo, with significantly lower HAV-specific IgG levels in subjects treated with MGD010 compared with placebo group ($P < 0.05$).
Conclusions: These studies demonstrate that by pharmacologically exploiting the activity of the checkpoint molecule CD32B in combination with the BCR CD79B component, a single dose administration of either 3 or 10 mg/kg MGD010 delivers an immunomodulatory effect that effectively counters B-cell function. Together with a good safety profile, these data provide compelling rationale for further developing MGD010 as a therapeutic modality for autoimmune diseases.
References:
[1] Pandya, N et al., EULAR16–4079.
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Disclosure of Interest: W. Chen Employee of: MacroGenics, S. Shankar Employee of: MacroGenics, J. Lohr Employee of: MacroGenics, X.-T. Yao Employee of: MacroGenics, H. Li Employee of: MacroGenics, X. Chen Employee of: MacroGenics, J. Muth Employee of: MacroGenics, N. Gal-Edd Employee of: MacroGenics, E. Bonvini Shareholder of: MacroGenics, Employee of: MacroGenics, S. Johnson Shareholder of: MacroGenics, Employee of: MacroGenics, N. Pandya Shareholder of: MacroGenics, Employee of: MacroGenics, P. Moore Shareholder of: MacroGenics, Employee of: MacroGenics, J. Wigginton Shareholder of: MacroGenics, Employee of: MacroGenics
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SAT0028 AIOLOS OVEREXPRESSION IN SYSTEMIC LUPUS ERYTHEMATOSUS B-CELL SUBTYPES AND BAFF INDUCED MEMORY B-CELL DIFFERENTIATION ARE REDUCED BY CC-220 MODULATION OF CEREBLON ACTIVITY

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Background: Systemic Lupus Erythematosis (SLE) is an autoimmune disease characterized by alterations in B-cells, autoantibody production, and elevations in circulating B-cell activating factor (BAFF). Aiolos single nucleotide polymorphisms and elevations in Aiolos mRNA are associated with SLE susceptibility. CC-220 is a Cullin Ring Ligase 4 Cereblon (CRL4CRBN) E3 Ubiquitin Ligase Modulator that induces ubiquitination and degradation of Aiolos and Ikaros transcription factors. We investigated the effects of CC-220 in B-cells from SLE patients to assess its impact on Aiolos protein levels and B-cell proliferation, differentiation, and antibody production.
Objectives: Determine the protein levels of the B-cell transcription factors Aiolos and Ikaros in B-cell subtypes of SLE patients and assess the impact of the cereblon modulator CC-220 on Aiolos and Ikaros protein degradation, proliferation, and plasmablast differentiation.
Methods: Peripheral blood mononuclear cells (PBMC) were measured for levels of circulating B-cell subtypes, B-cell activation state, and Aiolos and Ikaros protein levels by flow cytometry. Cell types were defined as: $CD27^-IgD^+$ naive, $CD27^+IgD^-$ switched memory, $CD27^+IgD^+$ nonswitched memory, and $CD27^-IgD^-$ double negative B-cells and $CD20^-CD38^+$ plasmablasts. Measurements of BAFF, IL-2 and IL-21 from plasma and IgG and IgM were done by ELISA. Plasmablast differentiation was induced by BAFF, IL-2, and IL-21 co-stimulation of B-cell cultures for 5 days in the absence and presence of CC-220.
Results: Plasma samples from SLE patients were found to have higher circulating BAFF, similar IL-2 levels, and reduced IL-21 levels relative to healthy individuals. Alterations in circulating B-cell subtypes occur in SLE patients including reduction of memory and elevations of naive and double negative B-cells. Alterations in biomarkers associated with chronic B-cell activation, including elevation of CD95 and reduction of CD21 and CD23 were also observed. Assessment of the B-cell differentiation transcription factors Aiolos and Ikaros in SLE B-cells showed that Aiolos, but not Ikaros is elevated in naive, switched memory, nonswitched memory, and double negative B-cells. CC-220 treatment reduced Aiolos and Ikaros protein levels in both SLE and healthy individuals in all four B-cell subtypes measured. CC-220 treatment was associated with reduced B-cell proliferation, plasmablast differentiation, and secretion of IgG and IgM in cells co-stimulated with BAFF, IL-2 and IL-21. Similarly, CC-220 reduced the expression of genes involved in B-cell differentiation including IRF-4, Xbp-1, Blimp-1, and IgJ indicating an early blockade in B-cell differntiation.
Conclusions: Our observations that SLE is associated with alterations of circulating B-cell subtypes and their activation state, Aiolos overexpression in B-cells, and increases in circulating BAFF support the hypothesis that B-cells play a significant role in SLE pathology. Moreover, these observed changes suggest that B-cells may be predisposed towards plasmablast differentiation and antibody production in SLE. CC-220 administration reduced Aiolos and Ikaros protein levels in B-cells and reduced proliferation, plasmablast differentiation and antibody production at clinically obtainable drug concentrations (<10 nM).
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SAT0029 B CELL DEPLETION AFFECTS CD8 T CELLS IN ANCA-ASSOCIATED VASCULITIS

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Background: In anti-neutrophil cytoplasmic antibodies associated vasculitis (AAV), several clues suggest that the efficacy of B cell depletion therapy lies beyond the suppression of ANCA-producing cells and may involve the suppression of B-T cell crosstalk. However, little if any data are available regarding the impact of rituximab on CD4, regulatory T and CD8 T cells in this setting.
Objectives: To compare the effect of conventional immunosuppressants (CIS) and rituximab (RTX) on 3 T cells compartments in AAV. To assess the impact of patients B cells and that of B cell depletion on CD8 T cell cytokine production.
Methods: Thorough cross-sectionnal immunophenotypic analysis of CD4, regulatory T and CD8 cells of 53 patients with AAV, using polychromatic flow cytometry. A multiplex Luminex immunoassay was used to measure Cytokine/chemokine production of in vitro stimulated CD8 T cells. Active untreated AAV patients' B cells and/or CD8 T cells were cocultures for 72h with Staphylococcal Enterotoxin (Autologous and criss-cross experiments), and CD8 T cells cytokine production was then measured by flow cytometry.
Results: Among CD4 T cells, we found that frequency of naïve and memory subsets and the expression of CCR5, CCR4 and CD161 were not influenced by maintenance treatment type. Similarly, total Treg frequency and Treg subsets including CD161+, Helios+, resting (CD45RA+) and memory (CD45RA-FoxP3hi) Tregs were comparable among RTX and CIS treated patients. By contrast, the type of maintenance treatment markedly influenced the CD8+ T cell compartment. Patient under B cel depletion therapy had less TEMRA (CD45RA+CCR7-) and more TEM cells than those receiving CIS, and ressembled those in long term remission off therapy. CMV seropositivity did not explained the observed diifferences. Longitudinal data confirmed that B cell depletion significantly decreased TEMRA (CD45RA+CCR7-) CD8 T cell frequency ($p<0.001$), whereas CIS had the opposite effect. Furthermore, we found that in vitro stimulated CD8 T cells from B cell depleted patients produced less pro-inflammatory cytokine/chemokine than those from patients treated with CIS. In coculture with B cells and SEB, patients CD8 cells coculture produced higher level of inflammatory cytokines than those from controls, but only when they were stimulated with patients' B cells.
Conclusions: B cell depletion therapy has a significant impact on the CD8 T cell compartment in terms of phenotype and function. B cell can promote pro-inflammtory function of CD8 T cell in vitro. CD8 T cell are found in vasculitis lesions. These observations raise the question whether the disruption of B cell help to CD8 T cells could contribute to the dramatic efficacy of RTX. Further studies are needed to demonstrate the implication of patients' CD8 T cell in tissue damage.
Disclosure of Interest: None declared
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SAT0030 BREACH OF AUTOREACTIVE B-CELL TOLERANCE BY POST-TRANSLATIONALLY MODIFIED FOREIGN PROTEINS

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Background: Autoimmunity in Rheumatoid arthritis (RA) patients is characterized by a spectrum of anti-modified protein antibodies (AMPA) directed against post-translationally modified (PTM) proteins. The best-known AMPA in RA are anti-citrullinated protein antibodies (ACPA). Much less is known about the occurrence and aetiology of other AMPA responses in RA such as autoantibodies directed to malondialdehyde-acetaldehyde (MAA) adducts, acetylated antigens, and carbamylated proteins. Anti-carbamylated protein (anti-CarP) autoantibodies recognize carbamylated proteins containing a homocitrulline, a PTM structurally similar to citrulline. With the presence of various AMPA responses in RA, PTM proteins have been implicated in the breach of autoreactive B-cell tolerance