often unknown by the physician and since no predictive clinical or biological factors were identified, our results suggest the benefits of testing to detect severe non-adherence, to identify the patients at risk.

Thursday 06 October 2022 from 13:00 to 14:10

Po.1 E- poster session 1: animal models, omics in lupus, major organ involvement inclucing npsle, organ damage and survival

PO.1.1 AFIMETORAN, A POTENT AND SELECTIVE INHIBITOR OF HUMAN TOLL-LIKE RECEPTOR 7 (TLR7) AND TLR8, PROVIDES ROBUST EFFICACY IN A MURINE LUPUS MODEL OF ADVANCED DISEASE

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Purpose TLR7 and TLR8 (TLR7/8) are members of the Toll-Like Receptor family that recognize single strand RNA. Activation of TLR7/8 within immune cells elevates pro-inflammatory cytokines and type I/III interferons and promotes steroid resistance. TLR7/8 have been implicated in the initiation and progression of lupus, a disease associated with defects in the clearance of apoptotic debris which can activate these receptors. However, the effects of TLR7/8 inhibition in advanced lupus remain unclear. Afimetoran (BMS 986256) is a potent, selective, and orally bioavailable inhibitor of TLR7/8 currently in clinical development for immune mediated diseases. Previously, we observed that afimetoran inhibited the production of both interleukin-6 and interferon alpha in a dose-dependent manner in mice challenged with a TLR7 agonist. In this study, we examined the therapeutic efficacy of afimetoran in a murine model of advanced lupus.

Methods NZB/W mice with advanced lupus (proteinuria > 100 mg/dL) were treated orally, once daily, with vehicle or afimetoran and/or prednisolone. The effects of treatment on survival, proteinuria, kidney histology, glomerular IgG deposition, cytokine-secreting cells, and circulating cytokines were measured.

Results Afimetoran treatment resulted in near complete (92%) survival in the advanced lupus model, reaching 100% when combined with low-dose prednisolone; survival was 47% in mice treated with vehicle only (Table 1). In the advanced lupus model, afimetoran treatment reversed kidney tissue damage and proteinuria in all surviving animals. In contrast, treatment with low-dose prednisolone alone did not show significant modulation of proteinuria. Treatment with afimetoran reversed both the number of IgG-positive glomeruli and the amount of glomerular IgG deposition, and also reduced cytokine secreting cells and secreted cytokines to a greater extent than low-dose prednisolone alone.

Conclusions Afimetoran displayed robust efficacy in a murine model of advanced lupus. Treatment with afimetoran led to improved survival, reversal of proteinuria and glomerular IgG deposition, suppression of kidney injury markers, and reductions in the proportion of cytokine-secreting cells and circulating cytokine levels. These results indicate that afimetoran, now being investigated in a phase 2 clinical trial (NCT04895696), may offer a novel therapeutic approach to the treatment of lupus.

Abstract PO.1.1 Table 1 Afimetoran alone and in combination with prednisolone improved survival of mice in the NZB/W model of lupus with advanced disease

Treatment Group	Dose (mg/kg)	Survival (%)
Vehicle	NA	47
Prednisolone	1	67
Prednisolone	10	83
Afimetoran	0.25	92
Afimetoran + prednisolone	0.25 + 1	100

PO.1.2 BANK1 HAS A DETERMINANT ROLE IN THE PRESENCE OF AGE-ASSOCIATED B CELLS IN AUTOIMMUNITY

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10.1136/lupus-2022-elm2022.36

Systemic Lupus Erythematosus (SLE) is a multisystemic autoimmune disease characterized by the hyperactivity of B cells and the production of autoantibodies. Previous studies in our group described the genetic association between SLE and the B cell-specific gene BANK1. The role of BANK1 in disease progression remains unclear. Bank1 deficiency in mice ameliorates the lupus phenotype. It also reduces numbers of CXCR4hi T cells, known as extrafollicular T helper cells (Tefh), which are involved in autoantibody production. A B cell subpopulation rare in normal mice named known as Age-associated B cells (ABC) has been implicated in autoimmunity in both mice and humans (T-bet+ or DN2 cells). This population is thought to be driven by TLR7 signaling, secretes autoantibodies and increases with age. These ABC cells are expanded in lupus-prone mice while DN2 cells in lupus patients.

The main objective of this study was to determine the effect of Bank1 deficiency on the appearance of ABCs in an SLE model and the relationship of ABCs with Tefh. This project aims to define exactly which cells are producing the excess of proinflammatory cytokines and autoantibodies and what the role of BANK1 in this process is. In order to do that, we worked with two murine lupus models crossed with the knockout for Bank1, (Bank1-/-): a transgenic model of the TLR7 gene (TLR7.tg), and a TLR7 pathway-induced disease model with Imiquimod (Imiquimod-induced model).

The results showed that Bank1 deficiency, in both models, decreased the total percentage of ABCs and Tefh. The lack of Bank1 also ameliorates signs of autoimmunity such as splenomegaly and the production of autoantibodies. Besides, it restores to normal the cellular phenotypes in the spleen modified by the autoimmune process.

Bank1 deficiency improves the development of the disease in both models and has an effect on the production of ABCs. In the absence of Bank1, the ABC number decreases and this reduction correlates positively with Tefh levels. Ongoing experiments are focused on understanding the role of Bank1 on the generation and differentiation of ABCs by in vitro and single-cell transcriptome assays.