

I-07 IFNAR SIGNALLING PROMOTES MICROGLIA DYSFUNCTION IN SLE

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Background One of the most prevalent, but least understood aspects of SLE is the fact that patients commonly develop neuropsychiatric symptoms, a condition referred to as central nervous system (CNS) lupus. The mechanisms driving neuropsychiatric disorders remain enigmatic; moreover, CNS lupus symptoms are variable and complicated by the systemic nature of the disease. The molecular mechanisms of CNS lupus thus remain a major gap in the lupus field. Interestingly, CNS lupus patients can show reduced grey matter volume, suggestive of neuron or synapse loss; however, the mechanisms underlying this neuron and synapse loss have yet to be fully explored. We looked to other CNS diseases for mechanistic clues relevant for CNS lupus. In Alzheimer's disease, synapse loss is an early event and microglia have been identified as major mediators of the process. Type I interferon signalling has also emerged as a modulator of microglia activation and is commonly elevated in SLE patients. Therefore, we hypothesise that type I interferon may stimulate microglia dysfunction and promote aberrant microglia-mediated synapse loss.

Materials and methods We addressed this hypothesis using genetic and pharmacological approaches to block interferon alpha receptor (IFNAR) signalling in lupus models (564 Igi and NZB/W). Immunohistochemistry based assays were used to determine microglia activation state combined with RNAseq to characterise microglia gene expression changes. Flow cytometry, confocal, and electron microscopy were used to assay microglia engulfment of neuronal material and synapse density.

Results Gene expression analysis of microglia isolated from lupus mice identified significant upregulation of interferon stimulated genes and genes associated with microglia function. Consistent with these data, significant increases were observed in activated microglia in lupus mice relative to wild type littermates. Moreover, reminiscent of early development where microglia are important in synaptic pruning, microglia could be found engulfing neuronal material. In MX1 reporter mice, MX1+ microglia were more reactive than MX1- microglia in lupus mice and showed increased engulfment. Lupus mouse models also showed reduced synapse density at ages concurrent with increased microglia engulfment, suggesting aberrant microglia pruning of synapses. Treatment in vivo with anti-interferon receptor antibody protected against reactive microglia and engulfment of neuronal material. Injection i.v. with IFN- α or - β was sufficient to stimulate microglia engulfment of neuronal material.

Conclusion Taken together, these results suggest that type I interferon is necessary and sufficient to stimulate microglia dysfunction in SLE and identifies a novel potential mechanism promoting synapse loss and neuropsychiatric symptoms in CNS lupus patients.

Clinical Trials

CT-01 PHASE IB STUDY OF IMMU-115 (HUMANISED ANTI-CD74 ANTIBODY) TARGETING ANTIGEN PRESENTING CELLS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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Background IMMU-115 (milatuzumab), a humanised antibody targeting the CD74 antigen on antigen-presenting cells (APC), is being investigated in haematological malignancies. Since dysregulation of APCs may occur in autoimmunity, IMMU-115 could potentially help control disease activity in SLE. Following promising preclinical studies, IMMU-115 was reformulated for convenient administration by subcutaneous (SC) injection, and this initial study was undertaken.

Materials and methods Phase I, dose-escalation study in adults with SLE (ACR revised criteria) and positive ANA (titer $\geq 1:80$), with moderate disease activity but not severe flares (at least 2 BILAG B's, but no A's) despite ≥ 5 mg/day prednisone. Background lupus medications continue with SC IMMU-115 administered weekly for 4 consecutive weeks. Disease activity is assessed by BILAG2004 and SELENA-SLEDAI every 4 weeks until week 24

Results Ten patients (9F/1 M; median age, 37; median disease-duration, 7 years) have now completed dose level one, receiving 250 mg doses of IMMU-115 injected once-weekly for 4 weeks. They were on prednisone (5–20 mg/day, n = 10), antimalarials (n = 7), and immunosuppressives (n = 2) with mean SLEDAI 9.6 and BILAG-B activity in the musculoskeletal (n = 10), mucocutaneous (n = 9), cardiorespiratory (n = 1), and renal (n = 1) body systems. All patients improved in ≥ 1 body system, eliminating most musculoskeletal B's (9/10, 90%) and mucocutaneous B's (7/9, 78%) by week 8, with the single cardiorespiratory B eliminated by week 20, and the renal B vacillating between B and C over the study. Four patients flared post-treatment with new B-level disease at weeks 8, 12 and 20 (all cardiorespiratory) and week 24 (neuropsychiatric). Following treatment, mean total BILAG (scored using B = 5, C = 1, D/E = 0) decreased 43% and mean SLEDAI decreased 54%, both measures remaining decreased through week 24 (Figure 1). Adverse events were Grade 1–2 (mild-moderate) and predominantly injection site (n = 7) or constitutional/flu-like (n = 9) reactions managed with supportive medication (steroids, antihistamines, anti-pyretics). Routine safety and other laboratories (B/T cells, monocytes, dendritic cells, serum immunoglobulins, cytokines, ANA, other autoantibodies, CRP, C3) were unremarkable. One patient developed anti-IMMU-115 antibodies of uncertain clinical significance, resolving within 3 months.

Conclusions IMMU-115 showed evidence of therapeutic efficacy with acceptable toxicity already at the first dose level, including suppression of disease activity extending 24 weeks in most patients. To confirm these results, further dose escalation