Results 104 patients were randomized. In the efficacy evaluative population, 42% of XmAb5871-treated subjects reached Day 225 without LOI vs 28.6% of the placebo group (p=0.18) with 40.4% vs 23.1% (p=0.06) achieving this endpoint in the ITT population. In those with LOI, no (0%) XmAb5871 patients vs 9 (30%) placebo had SLE-DAI increase 7 with 3 (13%) vs 7 (23%) developing BILAG A scores. Six XmAb5871-treated patients were withdrawn for infusion-related events. The efficacy evaluative population excluded 10 placebo patients vs 2 XmAb5871 for other reasons, increasing placebo response proportions compared to the ITT population. Time to LOI was significantly longer in XmAb5871-treated patients than placebo (p=0.025, see figure 1).

The most common AEs in XmAb5871-treated patients were transient, infusion-related gastrointestinal side effects during the 1st or 2nd infusion. There were 8 SAES in 7 XAb-treated subjects, 5 in 4 placebo patients, no opportunistic infections, and no deaths. Infection rate was low compared to other SLE trials.

Conclusions Results from this small trial, designed to maximize interpretability, supports further evaluation of XmAb5871 in SLE.

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Background  Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterized by high morbidity and mortality and its treatment remains challenging. Inflammatory dendritic cells (DCs) have been shown to participate in the initiation and perpetuation of lupus pathogenesis, and tolerogenic DCs have a potential for cell-based therapy in this condition. The mannose receptor (MR, CD206) is a C-type lectin expressed by DCs and its cross-linking induces anti-inflammatory immunosuppressive effects. D-Mannose is a C-2 epimer of glucose that exhibit immunoregulatory effect in models of autoimmune diseases, such as type 1 diabetes and lung airway inflammation. However, the function of D-Mannose treatment in lupus remains unknown.

Methods  B6.MRL-Fas(lpr) (B6.lpr) mice at 4 months of age were treated with D-Mannose in drinking-water for 2 months. Autoantibody production and immune cell activation were compared between the two groups. In vitro, GM-CSF bone marrow-derived dendritic cells (BMDCs) from non-autoimmune B6 mice were cultured for 5 days to generate mature dendritic cells. On day 5, BMDCs were treated with 10 mM glucose (G10) or 10 mM Mannose (M10) for 24 hour and pulsed with LPS for an additional 4 hour. Surface markers and cytokines secretion of BMDCs were analyzed.

Results  The D-Mannose treatment significantly decreased serum anti-dsDNA antibody at week 4. It also increased the percentage of naïve T (Tn) cells and decreased CD4 +T cell activation measured as CD44 +expression. Follicular helper T (TFH) cells/follicular regulatory T (TFR) cells ratio was reduced after D-Mannose treatment. The low frequency of regulatory T (Treg) cells in B6/lpr mice was also expanded after treatment. Besides, D-Mannose treatment increased CD206 expression on splenic DCs. In vitro experiments showed that D-Mannose promoted a tolerogenic phenotype in BMDCs by decreasing the expression of activation markers (CD40, CD80, CD86) and promoting that of inhibitory markers (CD206 and CD64) expression in B6 mice. Additionally, D-Mannose reduced inflammatory cytokine secretion in BMDCs.

Conclusions  D-Mannose ameliorates the development of lupus-like disease in the B6/lpr mouse model, which may be due to the induction of tolerogenic DCs.

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