Conclusions B cell phenotypic abnormalities precede the onset of clinical disease in ANA+ individuals and have a pattern suggesting ongoing activation through T-B collaboration.

Background The primary B cell receptors for antigen-bound complement C3 fragments are complement receptor 1 (CR1/CD35) and complement receptor 2 (CR2/CD21). In mice, as opposed to humans, CR1 and CR2 are derived through alternative splicing from a common gene designated Cr2. CR1 is the primary receptor for the C3b and C4b fragments of C3 and C4, respectively, while CR2 binds the TED domain within C3d and iC3b. The absence of CR1/Cr2 in Gr2-/- mice impairs immunological responses to foreign antigens due to the lack of CR2/C3d costimulatory signals on B cells and impaired antigen retention on follicular dendritic cells. One might expect a similar humoral autoimmune enhancing role for CR1 and CR2 in systemic lupus erythematosus (SLE) through amplification of B cell responses to C3b/C3d-bound self-antigens. However, studies in murine models of SLE performed on a Gr2-/- background have demonstrated enhanced lupus-related autoimmunity. One potentially confounding factor with use of Gr2-/- mice is that CR1 is a high affinity receptor for C4b, which is itself necessary to maintain tolerance on follicular dendritic cells. One might expect a similar humoral autoimmune enhancing role for CR1 and CR2 in systemic lupus erythematosus (SLE) through amplification of B cell responses to C3b/C3d-bound self-antigens. However, studies in murine models of SLE performed on a Gr2-/- background have demonstrated enhanced lupus-related autoimmunity. One potentially confounding factor with use of Gr2-/- mice is that CR1 is a high affinity receptor for C4b, which is itself necessary to maintain tolerance on follicular dendritic cells.

Materials and methods Previously, only rat anti-mouse monoclonal antibodies (mAbs) to CR2/CR1 have been available, which are immunogenic in mice. We have developed novel non-immunogenic mouse anti-mouse mAbs targeted to CR2-specific ligand-receptor interaction. The first is a non-B cell depleting mAb that recognises and blocks CR2 interactions with C3d without directly affecting CR1 interactions with C4b or C3b. The second mAb recognises the C3d fragment and blocks its interaction with CR2 without directly affecting C3b or C4b interactions with CR1.

Results Using the MRL/lpr model of SLE, we have found that treatment with anti-CR2 mAb does not provide clinical benefit. Conversely, a single injection of anti-C3d mAb durably reduced anti-dsDNA antibody production (mean 383 R.U. in mAb 3d8b injected mice and 949 R.U. in control PBS injected mice, p < 0.05) and proteinuria (mean 13115 mg albumin/dL/creatinine (g/dL) compared to 101759 in PBS injected mice, p < 0.05). The reduction correlated with reduced kidney damage and reduced BUN levels (46 ± 10 compared to 72 ± 38, p < 0.05). Notably, mice injected with anti-C3d mAb exhibited higher levels of CR1 and CR2 expression and trends toward normalisation of the splenic B cell compartment.

Conclusions Blocking C3d/TED domain interactions with its receptor(s) through ligand-directed interruption of binding represents a potential new therapeutic approach in patients with SLE. Whether interruption of C3d:CR2 interactions through targeting of CR2 itself will provide similar clinical benefit requires additional study.

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