Results We describe novel and selective small molecule non-oligonucleotide TLR7/8 antagonists for the treatment of SLE. They exhibit potent activity in vitro in TLR-specific reporter systems (IC_{50} of ~100 nM) and in primary human blood cells (IC_{50} of 50–500 nM across various ligands and cytokine readouts), suppressing TLR7 and TLR8 but with no activity against TLR9 or other TLRs tested. Exploration of mechanism of action shows direct interaction of the lead compound with the external domain of TLR8. The compounds are orally available and active in a mouse model of R848 challenge. When tested in long-term dosing in pristane-induced or spontaneous NZB/W disease the compounds slow the advance of nephritis and associated proteinuria.

Conclusions We have identified novel small molecule antagonists of human TLR7 and TLR8 with beneficial activity in mouse models of systemic lupus.

Background and aims Auto-antibodies to nuclear constituents

Binding of CD40 ligand (CD40L) to

Evidence suggests CD40L blockade might provide an effective

Results Ixazomib suppressed the time-dependent increase in anti-dsDNA IgG antibodies, resulting in 73% (p<0.01) inhibition of autoantibodies at the end of treatment versus vehicle. In ELISpot assays, ixazomib decreased the number of anti-dsDNA IgG antibody-secreting cells in spleen by 25% (p<0.01). In addition, FACS analysis revealed that ixazomib decreased both splenic plasma cells by 39% (p<0.001) and plasmacytoid dendritic cells (pDCs) by 38% (p<0.01), with treatment.

Conclusions These findings suggest that ixazomib may be an effective agent for treating antibody-mediated diseases such as SLE by depleting both plasma cells the source of pathogenic antibodies and pDCs the main source of type I IFN production.

An ongoing randomised, double-blind phase Ib study is investigating multiple rising doses of Ixazomib (MLN9708) for the treatment of patients with SLE. We have previously demonstrated that TLR7 and TLR8 are significantly up-regulated in peripheral blood mononuclear cells (PBMCs) of systemic lupus erythematosus (SLE) patients and can be further induced with oestrogen treatment. It has recently been shown that specific micro-RNA (miR) sequences packaged in extracellular vesicles can stimulate these receptors in addition to the conventional activation by binding single-stranded RNA of viral origin. The aim of this study was to explore the feasibility of using miR antagonists to block TLR7 and TLR8-mediated inflammatory pathways.

Methods Human-mouse chimeraes were generated by adoptively transferring PBMCs from active SLE patients into immunodeficient NOD-scid IL-2γ (null) mice using a modified protocol that we previously established in Sjögren’s syndrome. Prior to transfer, SLE patient PBMCs were treated either with a cocktail of locked nucleic acid antagonists targeting several miRs or nonsense, scrambled controls. At 21 days post-transfer, blood was collected for flow cytometry and cytokine analysis; tissues were processed for histopathological examination by H and E and immunohistochemistry.

Results The phenotypic characteristics of various immune cells were similar in both experimental groups; however, inhibition with miR antagonists reduced levels of human IL-2, IL-6, IL-10, and TNF-α relative to scramble (control) treatment. Histopathological analysis revealed that miR antagonists inhibited the robust responses detected with control treatment in the small intestine, liver, and kidney. Further characterisation of infiltrates confirmed the presence human CD3+ T-cells.

Conclusions These data establish a novel model to study SLE and provide experimental evidence that TLR7 and TLR8 targeted miR antagonists have therapeutic potential in SLE.

Background and aims We have previously demonstrated that toll-like receptor (TLR)7 and TLR8 are significantly up-regulated in peripheral blood mononuclear cells (PBMCs) of systemic lupus erythematosus (SLE) patients and can be further induced with oestrogen treatment. It has recently been shown that specific micro-RNA (miR) sequences packaged in extracellular vesicles can stimulate these receptors in addition to the conventional activation by binding single-stranded RNA of viral origin. The aim of this study was to explore the feasibility of using miR antagonists to block TLR7 and TLR8-mediated inflammatory pathways.

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