

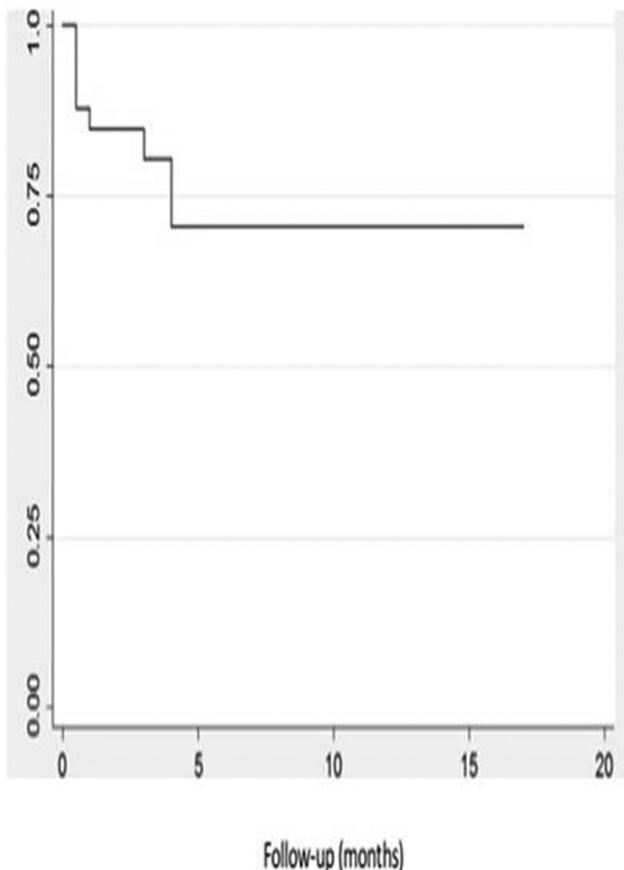
Abstracts

was to investigate safety of belimumab in patients with active SLE in daily clinical practice.

Methods We included patients with diagnosis of SLE (ACR criteria) treated at Medicarte IPS from March 2015 to October 2016. Medicarte is a referral centre for the integral medical care and pharmaco-surveillance of patients under biologic therapies in 13 cities in Colombia. Clinical information was obtained from electronic records. Adverse events (AE) were carefully evaluated during treatment.

Results Thirty three patients (all female) with active SLE were included. Mean age was 38.0 ± 11.8 years, and mean disease duration was 10.6 ± 9.2 years. Main refractory manifestations were musculoskeletal (100%), renal (45%), and mucocutaneous (42%). Background medications included MMF (87%), antimalarials (84%), MTX (72%), azathioprine (39%) and RTX (33%). Mean follow-up under belimumab treatment was 7.9 ± 5.6 cycles. Mean prednisone doses were 12.0 ± 11 mg/d. Only 8 (24%) out of 33 patients developed any AE. With a mean exposure time of 5.72 months, AE incidence rate, expressed as events per 100 p/months was 4.2 (Figure 1). The most common AE were: infusion reactions (3), urinary (2), and respiratory infections (1), herpes zoster (1) and mild pancytopenia (1). None of the patients stopped belimumab due AE.

Conclusions Belimumab was safe in clinical practice setting; only a few number of mild side AE were recorded. None of the patients discontinued belimumab treatment due AE.



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MESENCHYMAL STEM CELLS INDUCE LYMPHOCYTES APOPTOSIS INDEPENDENT OF BIM AND BCL-XL IN LUPUS MICE

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10.1136/lupus-2017-000215.86

Background and aims Mesenchymal stem cells (MSCs) have recently been used successfully in humans to control a lot of diseases. However, the mechanisms involved in their immunomodulatory effects remain a matter of debate. Here we explored whether lymphocytes apoptosis involved in the therapeutic effects of UC-MSCs in lupus mice.

Methods 1×10^6 of human UC-MSCs were injected into B6.lpr mice via tail vein and 6, 24 hours and 4 weeks later, all the mice were sacrificed, the apoptosis of lymphocyte in peripheral blood and spleen tissues as well as the expressions of Bim and Bcl-xL were detected by FACS, the immune cell subpopulations and cytokines in serum were also examined at 6 and 24 hours, respectively. The curative effects were assessed 4 weeks later.

Results UC-MSCs ameliorated disease progression of lupus mice at 4 weeks, increasing the percentage of Treg while downregulating Tfh, plasma cells and Th1 cells, decreasing spleen weight and repairing kidney lesion. UC-MSCs promoted lymphocyte apoptosis in peripheral blood and spleen at 6 and 24 hours, and reduced serum TGF-β1 levels, but did not affect Bim and Bcl-xL expressions in CD4+ and CD8+ T cells. Meanwhile, the percentage of Treg was significantly increased in the MSCT group at both 6 and 24 hours. Reductions in the proportions of plasma cells, Th1, Th2 cells were also evident at 24 hours after MSCs infusion.

Conclusions UC-MSCs exhibit extensive pro-apoptosis properties against lymphocytes in B6.lpr mice, which may offer a form of immunomodulatory therapy for lupus.

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SELECTIVE AND ORALLY AVAILABLE SMALL MOLECULE INHIBITORS OF TLR7 AND 8 FOR THE TREATMENT OF LUPUS

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10.1136/lupus-2017-000215.87

Background and aims The toll-like receptors (TLRs) are critical participants in vertebrate innate immune recognition of pathogen-associated molecular patterns (PAMPs). Diverse ligands act as “danger signals” detected by this component of the innate immune system. TLR7 and 8 are located in the endosomes of specific immune subpopulations, and are activated by single-stranded RNA from viruses or by autologous RNA fragments bound to immune complexes, inducing the generation of cytokines such as interferons (specifically IFN-alpha) and IL-6. Strong genetic evidence supports variants in TLR7 as contributors to development of systemic lupus erythematosus (SLE).

Methods *In vitro* and *in vivo* assays were used to guide development of potent and specific small molecule inhibitors.

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 read-outs), 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 autoantibody titers and efficiently suppress development 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.

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IXAZOMIB, AN ORAL PROTEASOME INHIBITOR, DEPLETES PLASMA CELLS REDUCING AUTOANTIBODIES AND PDCS IN PRE-CLINICAL MODEL OF SYSTEMIC LUPUS ERYTHEMATOSUS

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10.1136/lupus-2017-000215.88

Background and aims Auto-antibodies to nuclear constituents and type I Interferons (IFN) such as IFN- α play key roles in pathogenesis of Systemic Lupus Erythematosus (SLE). Ixazomib, an oral proteasome inhibitor, approved in the US and Canada for use in combination with lenalidomide and dexamethasone in patients with multiple myeloma who have received at least 1 prior therapy. Proteasome inhibitors like ixazomib that may deplete plasma cells and cellular sources of IFN- α are also attractive for autoimmune diseases like SLE. To investigate the potential of ixazomib the MRL/lpr model was used as it has extensively been shown to replicate many features of SLE.

Methods MRL/lpr animals received oral ixazomib twice a week for 4 weeks.

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 ISN/RPS class III, IV or V lupus nephritis who have not responded adequately to current therapy.

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TLR7 AND TLR8 TARGETED MICRO-RNAS INHIBIT SIGNALLING AND SUPPRESS INFLAMMATION IN A NOVEL HUMAN-MOUSE CHIMERIC MODEL OF SYSTEMIC LUPUS ERYTHEMATOSUS

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10.1136/lupus-2017-000215.89

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.

Methods Human-mouse chimaeras were generated by adoptively transferring PBMCs from active SLE patients into immunodeficient NOD-scid IL-2r γ (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.

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SAFETY, EFFICACY AND TRANSCRIPTIONAL CHANGES FOLLOWING REPEATED ADMINISTRATION OF DAPIROLIZUMAB PEGOL IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: RESULTS FROM A PHASE I STUDY

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10.1136/lupus-2017-000215.90

Background and aims Binding of CD40 ligand (CD40L) to CD40 activates B cells, antigen-presenting cells and platelets. Evidence suggests CD40L blockade might provide an effective treatment for systemic autoimmune disorders, including