

There was no significant difference in measured IMT or plaque between patients in LLDAS-50 and those not in LLDAS-50 for the first year after baseline. However, patients in LLDAS-50 were significantly less likely to have major cardiac events (major stroke, myocardial infarction, positive stress test, angioplasty or percutaneous coronary intervention) or death compared with patients who were not in LLDAS-50, 17.1% and 31.4%, respectively ($p=0.01$).

Conclusions With regard to damage progression, there was significantly less damage at 3 and 5 years among those in LLDAS 50% of the time during the first year after cohort entry. Interestingly, although there were no differences between IMT, presence of carotid plaque, or plaque progression at any of the three time points, there was a statistically significant difference in number of cardiovascular events or deaths in the LLDAS-50 group. This supports LLDAS as a valid predictor of lower overall and cardiovascular damage in SLE patients.

Funding Source(s): NCATS Grant No: UL1TR00188

NIH Grant No: 5R01AR063754-02

Correlation Between LLDAS and Cardiovascular Events or Death. Patients in LLDAS 50% of the time suffer from significantly fewer cardiovascular events or deaths than their non-LLDAS counterparts.

177

DECREASED EXPRESSION OF RENAL MIR-127-3P CONTRIBUTES TO THE OVERACTIVATION OF INTERFERON SIGNALING PATHWAY IN THE KIDNEY OF LUPUS NEPHRITIS

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10.1136/lupus-2019-lsm.177

Background Lupus nephritis (LN) is one of the most serious manifestations of systemic lupus erythematosus (SLE). Overactivation of type I interferon (IFN) signaling pathway is associated with LN pathogenesis, since overexpression of IFN stimulated genes (ISGs) has been found in the kidney of LN and deficiency of IFN receptor alleviates nephritis in lupus prone mice. Abnormal expression of microRNAs in renal tissues is linked to the pathogenesis of LN. However, the functions of these microRNAs and mechanisms for them to participate in the development of LN are largely unknown. In this study, we aimed to investigate the role of LN-associated renal microRNAs in the overactivation of IFN signaling pathway in the kidney of LN.

Methods microRNA expression was measured by Taqman assay. Interferon-stimulated response element (ISRE)-luciferase reporter assay and western blotting were used to investigate the function of candidate microRNAs in IFN signaling pathway. mRNA expression was measured by SYBR green assay. Gene expression profile was done by microarray. Agomir and antagomir (chemical modified microRNA mimics and inhibitors) of the candidate microRNA was used to perform gain and loss of function experiments. Pristane induced lupus mouse model and NZB/NZW F1 mice were used to investigate the *in vivo* function of the candidate microRNA.

Results Among evolutionary conserved differentially expressed renal microRNAs in LN, miR-127-3 p, which was reduced in the kidney biopsies of LN patients, inhibited IFN induced ISRE mediated expression of luciferase reporter gene, as well as the phosphorylation of STAT1 and STAT2. By microarray, we revealed that most of the ISGs were inhibited by miR-127-3 p

in IFN stimulated Hela cells. Consistently, loss of function of miR-127-3 p augmented IFN response in human primary renal mesangial cells, with enhanced ISRE mediated expression of reporter gene, phosphorylation of STAT2 and ISGs expression. Further, we identified JAK1, the upstream tyrosine kinase of STAT1 and STAT2, as a novel target of miR-127-3 p. *In vivo* administration of miR-127-3 p agomir reduced ISGs expression and alleviated pulmonary hemorrhage induced by pristane in B6 mice and proteinuria in NZB/NZW F1 mice.

Conclusions Our study shows miR-127-3 p can inhibit IFN signaling by targeting JAK1. Decreased expression of miR-127-3 p in the kidney contributes to the overactivated IFN response in LN. Subsequent mouse model studies indicate the therapeutic potential of miR-127-3 p in treating lupus associated organ damage.

Funding Source(s): This work was supported by the National Basic Research Program of China (973 program) grant 2014CB541902 and the National Natural Science Foundation of China (No.81401331).

178

PHASE 2 TRIAL OF INDUCTION THERAPY WITH ANTI-CD20 (RITUXIMAB) FOLLOWED BY MAINTENANCE THERAPY WITH ANTI-BAFF (BELIMUMAB) IN PATIENTS WITH ACTIVE LUPUS NEPHRITIS

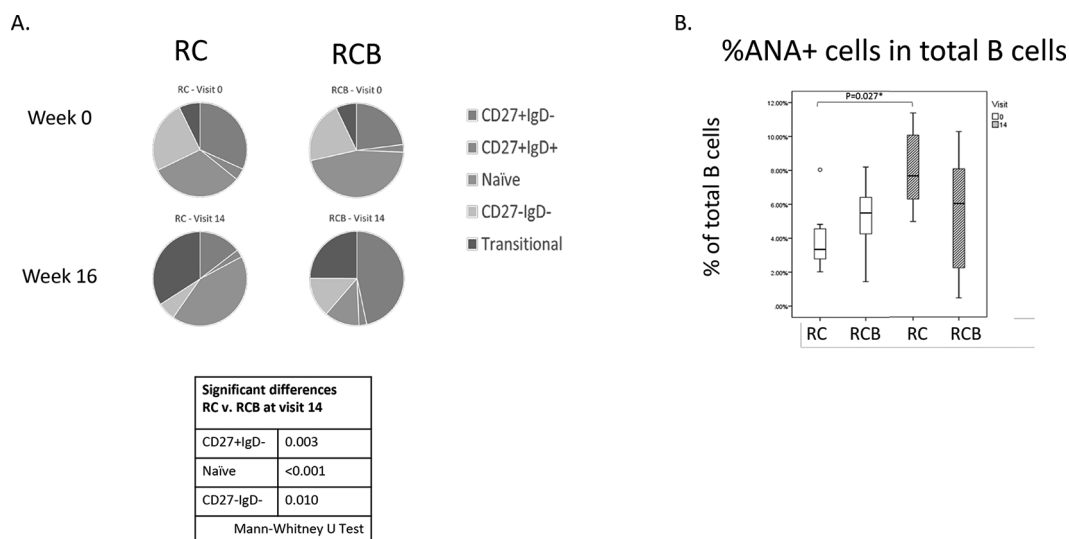
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10.1136/lupus-2019-lsm.178

Background Despite case series suggesting efficacy, controlled trials of anti-CD20 in lupus and lupus nephritis (LN) have not meet their primary endpoints (Arthritis Rheum 2012;64:1215 and 2013;65:2368). A potential explanation is the observation that serum BAFF levels are elevated after treatment with rituximab and may lead to disease flare by facilitating maturation of and re-population with autoreactive B cells. The CALIBRATE study (NCT 02260934) was designed to test this hypothesis, to determine whether addition of anti-BAFF (belimumab) could enhance the clinical effects of anti-CD20 (rituximab), and assess safety of the combination.

Methods Forty-three patients with active LN despite conventional treatment were enrolled in a prospective randomized open-label trial that compared two therapeutic strategies. All subjects received iv rituximab (1000 mg), CTX (750 mg), and methylprednisolone (100 mg) at wks 0 and 2, followed by 40 mg/d prednisone with taper to 10 mg/d by wk 12. At wk 4, subjects were randomized to belimumab (10 mg/kg iv at wks 4, 6, 8 and then every 4 wks) plus prednisone (n=21) (RCB) or prednisone alone (RC) (n=22). Complete response (CR) was defined as: (i) urine protein:creatinine ratio (UPCR) <0.5; (ii) eGFR 120 or, if <120, eGFR >80% of screening; and (iii) prednisone dose of 10 mg/d. Partial response (PR) differed only in the UPCR criterion (>50% reduction).

Results The clinical outcome at wk 48 was similar in both groups: CR was 38% in the belimumab group (RCB) and 32% in the control group (RC). The frequency of subjects with serious infections was also similar between groups. B cell depletion occurred in both groups by wk 12, but the pace of repopulation was delayed in the RCB group. However, median IgG levels remained within the normal range in both



Abstract 178 Figure 1

groups. Mechanistic analyses of circulating B cells at week 48 showed differences in the relative proportions of B cell subpopulations between RC and RCB groups and fewer ANA +B cells in the RCB group (figure 1).

Conclusions Treatment with anti-BAFF following anti-CD20 did not improve clinical outcome at week 48; (ii) anti-BAFF delayed blood B cell reconstitution following B cell depletion; (iii) anti-BAFF following anti-CD20 was not associated with hypogammaglobulinemia or an increase in serious infections and (iv) the reconstituted B cell populations differed between the RCB and RC groups. Further analyses at 96 weeks will address how anti-BAFF therapy affects quantitative and qualitative recovery of B cells as well as long-term clinical outcome.

Funding Source(s): Conducted by ITN with support from NIAID (UM1AI109565) and Genentech.

179

KZR -616, A SELECTIVE INHIBITOR OF THE IMMUNOPROTEASOME, ATTENUATES THE DEVELOPMENT OF MURINE LUPUS

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10.1136/lupus-2019-lsm.179

Background The proteasome inhibitor bortezomib, which inhibits both the constitutive proteasome and immunoproteasome, has been used successfully to treat patients with systemic lupus erythematosus (SLE), but adverse effects limit its use. The immunoproteasome is a distinct class of proteasome found predominantly in immune effector cells. KZR-616 selectively inhibits the LMP7 and LMP2 subunits of the immunoproteasome and is currently being studied in patients with SLE and lupus nephritis (LN). Here we describe the clinical, cellular, and molecular effects of KZR-616 in a mouse model of SLE.

Methods Immunoproteasome inhibition was measured in mice following administration of KZR-616 by quantitation of proteasome active site occupancy. The therapeutic effect of KZR-616 treatment was examined in the NZB/W F1 model of SLE. The degree of proteinuria (0-4 scale) was used to evaluate the severity of nephritis. Serum anti-double-stranded deoxyribonucleic acid (dsDNA) was measured by enzyme-linked immunosorbent assay (ELISA). Kidneys were harvested and

stained with hematoxylin and eosin (H and E) and anti-immunoglobulin G (IgG). Ribonucleic acid (RNA) was extracted from spleens and kidneys and examined by RNA sequencing analysis.

Results KZR-616 administration mice resulted in selective inhibition of LMP7 and LMP2 by 91% and 71%, respectively, similar to levels of inhibition seen *in vitro*. KZR-616 treatment in diseased mice resulted in complete resolution of proteinuria and statistically significant reductions in anti-dsDNA production and an absence of renal IgG deposition compared to vehicle treated animals. Proteinuria levels did not significantly increase 8 weeks after KZR-616 treatment discontinuation. Histologic analysis following 12 weeks of treatment revealed complete prevention of glomerular nephritis and sclerosis. Immunoproteasome inhibition decreased expression of genes involved in plasma cell differentiation, antibody secretion, and glomerular and tubulointerstitial renal pathology in diseased mice treated with KZR-616.

Conclusions KZR-616 effectively blocks disease progression in a mouse model of SLE. Durable disease remission in animals was achieved at well-tolerated doses. Inhibition of the immunoproteasome attenuated gene expression associated with immune effector cell function and glomerular injury. These experimental data support the ongoing clinical evaluation of KZR-616 in patients with LN.

Funding Source(s): None

180

EXAMINING THE TRANSCRIPTIONAL IMPACT OF LIGANDED ESTROGEN RECEPTOR ALPHA IN THE INFLAMMATORY MILIEU OF SYSTEMIC LUPUS ERYTHEMATOSUS

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10.1136/lupus-2019-lsm.180

Background Systemic lupus erythematosus (SLE) disproportionately affects females (9:1) over males. Despite significant research effort, the exact mechanisms behind this compelling sex bias are undefined. Our prior studies demonstrate a significant role for estrogen receptor alpha (ER) mediated