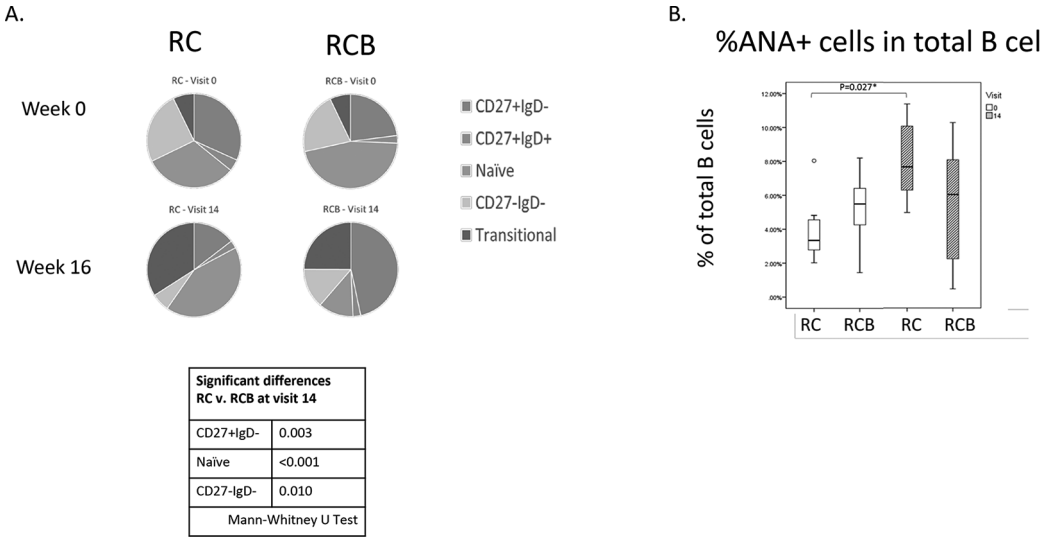


| Significant differences RC v. RCB at visit 14 | |
|---|---|
| CD27+IgD- | 0.003 |
| Naïve | <0.001 |
| CD27-IgD- | 0.010 |
| Mann-Whitney U Test | |

**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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**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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**Background** Systemic lupus erythematosus (SLE) disproportionally 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

inflammation in the pathogenesis of disease. NZM2410 lupus prone mice, expressing a truncated ER functional knockout, survived longer and had significantly reduced renal disease. Yet, a complete knockout of ER was not protective, suggesting the truncated isoform may be protective with the full-length gene necessary for disease. These findings underscore the importance of defining the role of ER in lupus.

**Methods** While the hormonal impact of estrogen and ER is well studied, less is known about the transcriptional impact of ER in immunity. Our goal is to identify the molecular mechanisms utilized by liganded ER in regulating the inflammatory milieu. To accomplish this, we have identified ER associated target genes, transcription factors and genes involved in the immune response, histone acetylation, and immune related signaling pathways, and determined differences in expression. B cells isolated from 15 female African American lupus patients and 8 age and race matched healthy controls were used for the analysis. In an effort to further understand the molecular mechanisms behind ER function, we examined the transcriptional effects of ER on the inflammatory response. Transient transfections of full length ER (66 kDa) and a shortened isoform ER46 (lacking the AF-1 activation domain and similar to the truncated ER functional knockout) were initially performed in the human breast cancer cell line MDA-MB-231, which lacks ER.

**Results** RNA-seq analysis indicates that 64% of ER associated target genes were differentially expressed between the two groups. The majority of these genes were upregulated in lupus patients compared to controls. Genes with increased expression included TLRs, NFB related transcription factors and IL-1. Preliminary results from the transfection experiments indicate that both ER isoforms reduce mRNA expression of the inflammatory cytokines IL-6 and IL-1 twenty-four hours after stimulation with a TLR4 agonist. A decrease in cytokine expression was observed when the short isoform ER46 was overexpressed in relation to ER66. Additional transfections will be carried out in immune relevant cells such as B cells, monocytes, macrophages or dendritic cells.

**Conclusions** These results support a role for ER in the pathogenesis of SLE via regulation of inflammatory mediators. Future goals include utilizing high throughput sequencing technology to examine the transcriptional impact of ER in monocytes of African American pediatric lupus patients.

**Funding Source(s):** None

## 181 ASSOCIATED FACTORS TO THE PRESENCE OF SERIOUS INFECTIONS IN A LARGE COHORT OF JUVENILE-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS

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**Background** Serious infections are included as one of the main causes of mortality in juvenile-onset systemic lupus erythematosus (jSLE) patients (Torrente-Segarra et al1) and a predictor of poor prognosis in SLE. We aimed to assess the incidence of serious infection and investigate the associated factors and clinical impact in a large jSLE retrospective cohort.

**Methods** All patients in the Spanish Rheumatology Society Lupus Registry (RELESSER) who meet 4 ACR-97 SLE criteria with disease onset before the age of 18 (jSLE) (Rúa-Figueroa et al2), were retrospectively investigated for serious infections (defined as either the need for hospitalization with parenteral antibiotherapy for a potentially fatal infection or death caused by the infection). Patients with and without infections were compared in terms of jSLE severity, damage, comorbidities, and demographic characteristics. A multivariable Cox regression model was built to calculate hazard ratios (HRs) for the first infection.

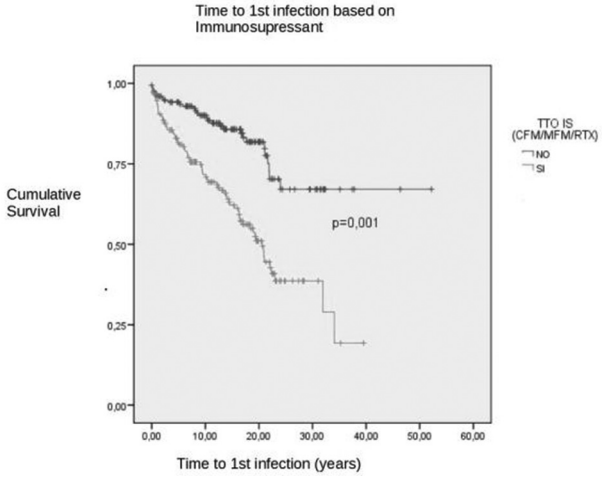
**Results** A total of 353 jSLE patients were included: 88.7% female, median age at diagnosis: 14.3 years (SD 2.9), and mean disease duration: 16.0 years (SD 9.3). A total of 104 (29.5%) patients suffered 1 serious infection (1: 55.8%; 2–5: 38.4%, and 6 infections: 5.8%). Sociodemographic data is shown in table 1.

Total serious infections recorded in these patients numbered 205. The incidence rate was 3.7 (95%CI: 3.24.2) infections per 100 patient years.

In the bivariate analysis we found association between serious infections and smoking (p=0.018), lupus nephritis (p<0.001), kidney transplantation (p=0.017), corticosteroids use (p=0.02), higher corticosteroids dosage (p<0.001), immunosupressants use (p<0.001)- azathioprine, mycophenolate, cychlophosphamide and rituximab, hospitalization due to jSLE flare (p<0.001), higher SLEDAI score (p=0.026), higher KATZ score (p<0.001) and higher CHARLSON score (p=0.02).

Serious infection localization and causal agent are described in table 1, being respiratory and bacterial infections the most frequent, respectively.

In the logistic regression analysis the use of cyclophosphamide, mycophenolate and rituximab and SLICC score showed association to serious infection (OR 2,55 [1,44–4,52], OR 1,4 [1,17–1,66], respectively; p<0.001). In the Cox regression




**Abstract 181 Figure 1** Time to 1st infection based on immunosupressant treatment