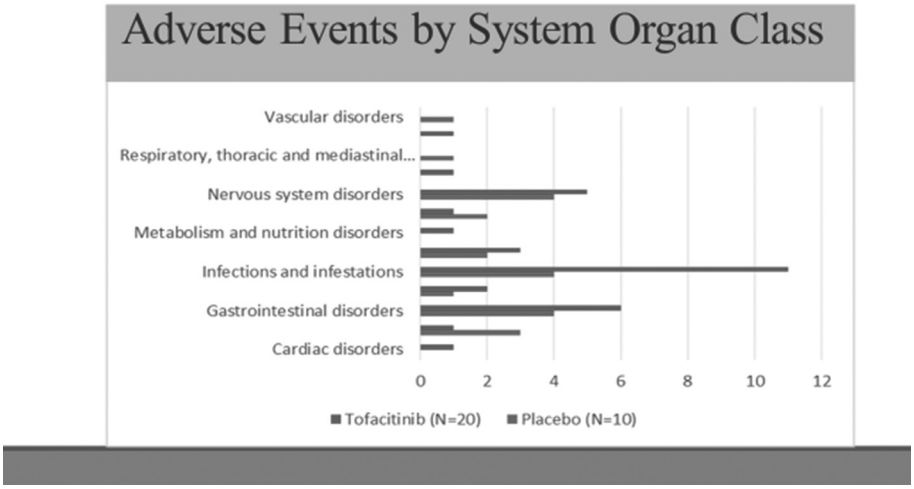


**Abstract 183 Figure 1** Adverse Events by Organ System. Adverse Events in Subjects on Tofacitinib vs Placebo

**Results** Tofacitinib was well tolerated with no worsening of SLE disease activity, and no severe AEs, opportunistic infections or liver function abnormalities. A total of 43 AEs (mostly mild respiratory infections) occurred in the treated group compared to 28 AEs in placebo. There was a significant increase in HDL-C and HDL particle size in tofacitinib-treated patients at day 56 (p=0.006) accompanied by significant improvements in plasma protein lecithin: cholesterol acyltransferase (LCAT) concentration. There were also trends for improvements in vascular stiffness in the tofacitinib-treated group. The Interferon response genes (type I IFN), the levels of low- density granulocytes (LDGs) and neutrophil extracellular trap (NET remnants) significantly decreased in the tofacitinib treated group who were STAT 4 risk allele positive but not in the placebo group at day 56, accompanied by significant changes in pSTAT phosphorylation of different immune cells. Levels of activation and checkpoint markers CD103, CXCR3, ICOS, and PD-1 were significantly decreased on multiple T cell subsets, in tofacitinib treated individuals that lack the STAT4 risk allele.

**Conclusions** In a short-term trial, tofacitinib was well tolerated in SLE subjects with mild-moderate disease activity. Use of tofacitinib resulted in improvements in lipoprotein profile and HDL function and decreases in the type I IFN and aberrant neutrophil responses characteristic of SLE. Long-term studies are needed to determine the efficacy of tofacitinib in the various manifestations of SLE.

**Funding Source(s):** Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health and in part by Pfizer Inc.

Adverse Events in Subjects on Tofacitinib vs Placebo

## 184 PATIENT PERCEPTION OF SLE BURDEN: THE ROLE OF DISEASE ACTIVITY, COMORBIDITIES AND TREATMENT

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**Background** Physician-based assessment of SLE activity and damage may not be able to capture the real disease impact on patients life. Objective of our study was to investigate the role of disease activity, comorbidities and treatment in determining patient perception of SLE burden.

**Methods** This is a cross-sectional study that enrolls patients with a diagnosis of SLE (ACR 1997 criteria). For each patient, demographics, comorbidities, treatment, clinical and laboratory data were collected. Disease activity was evaluated with the SELENA-SLEDAI score and organ damage with the SLICC/DI. The Lupus Impact Tracker (LIT) questionnaire was used to assess SLE impact. The Spearman test has been used for linear correlation between continuous data.

**Results** We included 195 adult SLE patients (97,4% Caucasian, 94,4% female, mean age 44,212,8 years, median disease duration 13 years).

Median SLEDAI at enrollment was 2 (IQR 0–4) and median SLICC/DI was 0 (IQR 0–2). 9,8% of patients had a concomitant fibromyalgia. The most frequent active disease manifestations at baseline were hematological (27/195), articular and cutaneous (24/195 both); 13 patients had active renal involvement. 52,8% of the cohort was on steroid therapy with a mean daily dose of 2,84,9 mg of methylprednisolone. 46,15% was on immunosuppressive treatment and 77,95% on hydroxychloroquine (HCQ). The median LIT score was 20 (IQR 7,5–37,5).

Among the LIT items, those with the highest score, suggestive of a severe disease impact, were: anxiety, fatigue and pain. We found no significant correlation between SLEDAI and the score of each LIT item.

We found that active articular and cutaneous manifestations, but not renal involvement, influence patient subjective perception of SLE impact. In the multivariate analysis, active arthritis shows a significant correlation with LIT items relative to: pain (p=0,02), daily activities and future planning (p<0,01), irrespective of comorbidities. Fibromyalgia resulted associated with a higher score for the item of fatigue (p<0,01).

Finally, we found that also ongoing therapy can contribute to determine SLE burden. In the multivariate analysis, we found a significant correlation between steroid therapy and higher scores for the items of family responsibilities, future planning, discomfort due to physical appearance and drug side effects (p<0,01), irrespective of disease activity.

**Conclusions** Disease activity, fibromyalgia and ongoing therapy all contribute to determine SLE burden. In particular, arthritis and skin disease have a great impact on patient daily living. Moreover, steroid therapy negatively influences patient perception of the disease.

**Funding Source(s):** Founding: INTEGRATE project (European Commission, 3rd Health Program, Proposal ID 769736)

## 185 BARICITINIB-ASSOCIATED CHANGES IN TYPE I INTERFERON GENE SIGNATURE DURING A 24-WEEK PHASE 2 CLINICAL SLE TRIAL

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**Background** In the phase 2 study JAHH (NCT02708095), treatment with baricitinib, an oral selective Janus kinase 1/2 inhibitor approved for the treatment of rheumatoid arthritis, resulted in significant improvements in patients with active SLE receiving standard background therapy compared with placebo.[1] Expression of type I-associated interferon (IFN) responsive genes (IRGs) is elevated in patients with SLE.[2] We developed a robust quantitative assay to measure changes in the IFN signature, and examined the relationship between the IFN signature and measures of clinical outcome.

**Methods** 314 patients were randomized 1:1:1 to receive placebo, baricitinib 2- or 4 mg once daily for 24 weeks in study JAHH. Total RNA isolated from whole blood was analyzed using a multiplex assay panel of 6 IRGs at baseline, and Weeks 2, 12, and 24. The assay was developed and optimized using RNA samples from 1760 patients with SLE enrolled in phase 3 trials of tabalumab (an anti-B cell activating factor monoclonal antibody),(2) along with healthy controls. The IFN signature assay produced a bimodal distribution.

**Results** 70% of patients had an elevated IFN signature at baseline. Baricitinib significantly reduced the IFN signature by Week 24 compared with placebo (2 mg:−20%, 4 mg:−24%, p0.05), with decreases observed as early as Week 2. In patients who had a high IFN signature at baseline, baricitinib 4 mg significantly reduced the IFN signature at Weeks 12 (-24%) and 24 (-23%) compared with placebo (p0.01); decreases were also observed at Weeks 12 and 24 with baricitinib 2 mg, but the difference from placebo was not statistically significant. Baricitinib 4 mg treatment resulted in significant clinical improvement in the resolution of arthritis or rash determined by the SLEDAI-2K.[1] However, the effect of baricitinib on IFN signature reduction (change from baseline and absolute baseline value) did not correlate with SLEDAI-2K-defined clinical improvement at Week 12 or 24.

**Conclusions** A dose-dependent decrease in the IFN signature was observed in baricitinib-treated patients with SLE. Baricitinib treatment resulted in clinical improvement across various measures of SLE disease activity.[1] Response was observed with baricitinib regardless of the change in the IFN gene signature. These data suggest that the clinical improvement observed in baricitinib-treated patients with SLE may be the result of baricitinib-mediated effects on multiple cytokine pathways that may include, but are not limited to, IFN signaling. Ongoing studies using gene arrays are now surveying global immune pathways to better characterize the mechanism of action of baricitinib in SLE.

**Funding Source(s):** Eli Lilly and Company

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## 186 NRF2 REGULATION OF THE INTERFERON SIGNATURE IN LUPUS MACROPHAGES

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**Background** Peripheral blood cells from two-thirds of adult lupus patients exhibit a gene expression program (interferon signature) attributed to the over-production of interferon (IFN) and other type I IFNs (IFN-I). IFN-I may be involved in the pathogenesis of lupus. Although plasmacytoid dendritic cells produce large amounts of IFN-I, our studies in an experimental lupus model suggest that macrophages and/or monocytes may play an important role in generating the interferon signature. This study sought to define how macrophages influence the interferon signature.

**Methods** Proinflammatory and anti-inflammatory (pro-resolving) macrophages were isolated from mice with pristane-induced lupus and were analyzed by RNA-sequencing (RNA-Seq) and quantitative PCR (qPCR). Protein expression in macrophage subsets was evaluated by flow cytometry. The role of nuclear factor erythroid 2 like 2 (Nrf2) activators was examined *in vivo*

**Results** Transcriptional profiling (RNA-Seq) of CD11b+Ly6G- peritoneal macrophages from mice with experimental lupus unexpectedly indicated a strong interferon signature in proinflammatory (Ly6ChiCD138-), but not anti-inflammatory (Ly6C-CD138+), macrophages exposed to the same IFN-I concentrations. Along with higher IFN-I regulated gene expression, proinflammatory macrophages expressed lower levels of genes regulated by nuclear factor erythroid 2 like 2 (Nrf2) than anti-inflammatory macrophages. Transcript levels of IFN receptor 1 chain (Ifnar1), IFNAR surface staining, and mitochondrial superoxide all were higher in proinflammatory macrophages. Administration of the Nrf2 activator CDDO-Im to lupus mice decreased IFNAR expression, blocked IFN-driven Stat1 phosphorylation, and reduced IFN-regulated gene expression. Thus, the interferon signature in murine lupus critically depends on Nrf2-regulated changes in IFNAR expression in macrophages. Human peripheral blood mononuclear cells exhibited a similar pattern: high IFNAR expression in classical monocytes and lower levels in non-classical monocytes. The data suggest that anti-inflammatory macrophages/monocytes are insensitive to IFN signaling, potentially serving a role in the resolution of inflammation.

**Conclusions** These studies reveal that the relative abundance of different monocyte/macrophage subsets (proinflammatory