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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10.1136/lupus-2019-lsm.185

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

REFERENCES

1. Wallace, D. *et.al*. DOI:10.1136/annrheumdis-2018-eular.1918
2. Hoffman,W. *et.al*. ArthritisRheumatol.2017;**69**:643–654.

186 NRF2 REGULATION OF THE INTERFERON SIGNATURE IN LUPUS MACROPHAGES

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10.1136/lupus-2019-lsm.186

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