Background Treatment with ustekinumab (UST), an anti-IL-12/23, p40-neutralizing monoclonal antibody, improved global and organ-specific measures of disease activity in a randomized, placebo (PBO)-controlled trial of patients with active SLE (NCT02349061).1 Type I interferon (IFN-I) and type II IFN (IFN-gamma) are elevated in a subset of SLE patients. Although targeting IFN-I (anifrolumab) has demonstrated inconsistent efficacy and a preliminary study with anti-IFN-gamma mAb (AMG811) failed to establish benefit,2 3 we sought to determine if UST affects either pathway and if those effects correlated with a positive SRI-4 response at wk24.

Methods A phase-2, PBO-controlled study enrolled 102 adults with seropositive SLE (SLICC criteria) and active disease (baseline SLEDAI score 6 and 1 BILAG A and/or 2 BILAG B scores) despite standard-of-care therapy.1 Gene expression analysis using a 21 gene IFN-I gene signature (IGS)4 or IFN-gamma signature5 was performed by microarray analysis using whole blood PAXgene RNA samples. Serum IFN-gamma and IFN- levels were assessed using MSD (IFN-gamma) and Quanterix (IFN-).

Results Serum IFN-gamma and IFN- and the IGS were elevated at baseline in SLE compared to healthy controls (p<0.0001). IGS was increased in approximately 67% of the SLE patients at baseline. No decrease was observed with IFN-protein or IGS levels after treatment with either UST or PBO. Whereas the proportion of patients achieving an SRI-4 response at wk24 was numerically greater in the IGS low population (81.8% UST vs. 54.5% PBO) versus IGS high (48.6% UST vs. 20% PBO), the magnitude of the treatment effect (UST vs. PBO) was similar in both subsets (IGS low effect size=27.3% vs. IGS high effect size=28.6%). Despite similar baseline levels, UST-treated patients achieving an SRI-4 response at wk24 exhibited a significant decrease in IFN-gamma protein versus non-responders (p<0.05) at 4 and 8 wks and IFN-gamma gene signature at 4 wks (p<0.0001) and 24 wks (p<0.05) post-dosing.

Conclusions In this SLE trial population which had significant upregulation of IFN-I at baseline, clinical response to UST was not associated with IFN-I reduction. In contrast, a significant decrease in IFN-gamma protein and gene signature was associated with UST response. These findings suggest that a broad population of SLE patients may respond to UST regardless of baseline IFN-I status. Moreover, UST may have affected TH1 responses in SLE since IFN-gamma levels decreased following treatment.

Funding Source(s): Janssen Research and Development, LLC supported this study.

REFERENCES