

(TGF β)-response genes correlate with the mRSS and may provide a means to more quickly assess drug efficacy for skin fibrosis in early phase trials. For example, TGF β signature genes, cartilage oligomeric protein (COMP), and thrombospondin (THS1) showed decreased expression in most SSc patients after treatment with fresolimumab (GC1008), a first-in-class pan-neutralizing anti-TGF β human antibody.

In the first part of a Phase 2, open-label study, 7 early SSc patients were administered 2 doses of fresolimumab (1 mg/kg) at Week 0 and Week 4. Skin biopsies taken on the first day prior to treatment and at 3, 7, and 24 weeks after treatment were analyzed for gene expression by reverse transcription polymerase chain reaction, microarray, and nanostring. Seven weeks after treatment, there was a significant ($p < 0.05$) decline in the primary study outcome of expression of THS1 and COMP. The relative mRNA expression of COMP and THS1 correlated with mRSS ($R^2 = 0.44$ and 0.58 , respectively, for baseline skin biopsies) and with each other ($R^2 = 0.73$), suggesting these mRNAs are coregulated. Microarray data also indicate decreased expression of TGF β signature genes, which was confirmed by nanostring data.

In general, fresolimumab was tolerated with 1 severe adverse event of severe bleeding from a patient with known gastric antral vascular ectasia. There were no malignant or premalignant lesions, or apparent aggravation of interstitial lung disease.

Skin biomarkers are sensitive measures of skin disease, offering operator-blinded assessment of mRSS. Unlike mRSS, which changes slowly, the mRNA biomarker can be assessed after a short period; thus, drug efficacy for skin fibrosis in early phase clinical trials maybe assessed more quickly.

The results of this trial showed that using skin mRNA expression biomarkers for measuring therapeutic-induced changes in SSc implicates TGF β in SSc pathogenesis.

Inefficacy of Hydroxychloroquine in Primary Sjögren's Syndrome: Results of the JOQUER Trial

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The Hydroxychloroquine Versus Placebo in Primary Sjögren's Syndrome [JOQUER; NCT00632866] trial found no significant difference in the evolution of systemic disease activity, dryness, symptoms, and quality of life (QoL) in

patients treated with hydroxychloroquine (HCQ) when compared with placebo. The findings were presented by Jacques-Eric Gottenberg, MD, Strasbourg, University Hospital, Strasbourg, France, in a late-breaking clinical trial.

HCQ is frequently prescribed for patients with primary Sjögren's syndrome (pSS), notably for arthralgias, synovitis, or purpura but also only for dryness and fatigue; however, except for a small crossover trial ($n = 19$), no controlled trial has evaluated HCQ versus placebo [Gottenberg JE. ACR 2012 Abstract 19]. JOQUER was a multicenter, randomized, double-blind, placebo-controlled trial in patients with pSS. To participate, patients were required to fulfill the American-European Consensus Group criteria for the diagnosis of pSS. Patients previously treated with HCQ and those with severe systemic manifestations were not eligible for the study. Eligible participants ($n = 120$) were randomly assigned to receive HCQ 400 mg QD or placebo, and were followed up for 24 weeks. The primary endpoint was a $\geq 30\%$ improvement in the values of 2 out of 3 of the patients' visual analog scale scores evaluating dryness, pain, and fatigue between Weeks 0 and 24. Secondary endpoints were the evolution of the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI), EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), dryness (Schirmer's test and unstimulated salivary flow), serum gammaglobulin levels, and QoL and symptom questionnaires.

Baseline characteristics were similar between the 2 groups: mean age was 56 years, median disease duration was 5 years, anti-SSA/SSB positivity was 55.1%, and median ESSDAI and ESSPRI were 2.3 and 6.2, respectively. At Week 24, 19.2% of placebo- and 19.6% of HCQ-treated patients had a favorable overall response (OR, 1.07; 95% CI, 0.4 to 2.9; $p = 0.9$; Figure 1). No significant difference was observed in the evolution of systemic disease activity, ocular or oral dryness, symptoms, and QoL. No significant difference was observed in patients with anti-SSA/SSB autoantibodies, systemic involvement, or high immunoglobulin (Ig) G levels at enrollment. A significant decrease in IgM levels (from 1.3 g/L to 1.1 g/L) with HCQ versus no difference with placebo was noted ($p = 0.01$). Nearly all evaluated patients in the HCQ group had detectable blood levels of HCQ at 6 months. Tolerance of HCQ was comparable to placebo.

As antimalarial drugs inhibit activation of endosomal toll-like receptors and interferon (IFN) [Kuznik A et al. *J Immunol* 2011], analyses are ongoing to determine whether HCQ could have a therapeutic interest in some patients with an IFN signature.