Title: Identification of immune phenotypes associated with impaired patient-reported outcomes in established and undifferentiated autoimmune connective tissue disease and At Risk individuals

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Background: Autoimmune Connective tissue diseases (AI-CTDs) impact on quality of life, but this varies markedly between patients. AI-CTDs are a heterogeneous group of conditions including distinct entities such as SLE and primary Sjogren's syndrome, as well as large groups of individuals with preclinical or undifferentiated forms of these diseases. The latter group is particularly difficult to classify and treat. They may exhibit similar impact on quality of life to patients with established disease, but it can be more difficult to determine to what extent impairment in undifferentiated AI-CTD is due to autoimmunity rather than other causes. Type I interferon (IFN-I) has a central role in the pathogenesis and activity of all autoimmune connective tissue disease (AI-CTD). It is the most promising means to stratify AI-CTD. However, IFNs are a complex system including Type I and Type II interferons. We have shown that this can be better characterised by a 2-score gene expression system (IFN Score A and IFN Score B) rather than a simple interferon signature.

Objective: To determine the relationship between interferon status and patient-reported outcomes in CTD, UCTD and patients At-Risk of CTD

Methods: We performed a cross-sectional study in established CTD (standard classification criteria), undifferentiated CTD (ANA positive with symptoms > 12 months but not meeting any classification criteria set, UCTD) and At-Risk individuals (new presentation with ANA and symptoms <12 months). We measured symptom VAS, SF-36, EQ-5D-%L, Work Productivity and Activity Impairment Questionnaire for a Specific Health Problem (WPAI:SHP), ICEpop CAPability measure for Adults (ICECAP-A) and FACIT-Fatigue as well as IFN Scores A and B

Results: 279 patients were recruited. Of these, 127 patients had established AI-CTD, 42 UCTD and 110 At-Risk of CTD. Established AI-CTDs were: SLE (61.4%), pSS (16.5%), EGPA (6.3%), IM (5.5%), MCTD (4.7%, SSc (4.7%) and APLS (0.8%).

Approx. 1 in 5 patients failed to complete the PROM assessments in full. Overall, there were no consistent differences in the various PROMs between disease subgroups. Association between IFN Scores and PROMs varied widely among diagnoses of CTDs. Notably, the strongest and most consistent correlations were found in patients with UCTD. In the UCTD group, there were moderate correlations between IFN Score A and SF-36 Energy function ($r=0.353$, $p=0.034$), SF-36 emotional well-being ($r=0.394$, $p=0.017$), SF-36 social functioning ($r=0.337$, $p=0.044$), ICECAP ($r=0.370$, $p=0.044$) and EQ-VAS ($r=0.363$, $p=0.035$). Moderate correlation was found between both IFN scores and SF-36 General health and well-being (IFN Score A: $r=0.397$, $p=0.015$; IFN Score B $r=0.399$, $p=0.014$).

In the At-Risk group, we found only weak correlations between IFN Score B and WPAI:SH % activity impairment ($r=0.269$, $p=0.035$) and EQ-5D-5L self-care scores ($p=0.044$). Whereas in the established CTD group, the correlation of IFN Score A with VAS Arthritis ($r=-0.330$, $p=0.028$) was negative

Numeric FACIT-Fatigue scores are inversely representative of the level of fatigue. Predictors of worse FACIT-Fatigue scores (i.e. lower scores) were female gender (-5.790, $p=0.017$), fibromyalgia (-10.873, $p<0.001$), smoker (-5.602, $p=0.021$) and active disease (-6.996, $p<0.001$). Older age (0.132, $p=0.022$) and high IFN Score A (1.598, $p=0.014$) were associated with better FACIT-Fatigue (higher scores).

Conclusion: These data reveal a complex relationship between IFN status and patient-reported outcomes. In established disease there were both positive and negative associations. In UCTD there was a more consistent association between greater interferon activity and impairment of quality of life and capability. These data indicate a distinct immune phenotype underlying more impactful presentations of UCTD. It may therefore be possible to improve quality of life in UCTD by identifying these immune subtypes and treating with appropriate immune modulation.