

FRI0034 MULTI-PROTEIN BIOMARKER PANEL INTEGRATES CRITICAL PATHOPHYSIOLOGIC MECHANISMS IN MEASUREMENT OF RA DISEASE ACTIVITY

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Background: Quantitative measurement of disease activity is needed for monitoring and tight control in RA therapy. Given the multifactorial nature of RA, assessing distinct components of disease pathogenesis in an integrated activity measure would be desirable. We thus sought a multi-marker test of RA disease activity. An initial set of ~400 serum proteins identified from a review of RA literature, biological databases, and proprietary data was reduced in progressive steps to 25 prioritized markers based on correlation to clinical measures including the DAS28 from >700 patients. Additional data from >600 patients were used to determine a reduced robust multi-protein test of RA disease activity.

Objectives: To use state of the art bioinformatic and molecular mapping approaches to analyze and refine a biologically meaningful marker set that reflects the multiplicity of pathogenetic effector mechanisms in RA.

Methods: The prioritized markers were incorporated into a mechanistic network map of RA biology. This map and the public domain literature were reviewed to identify sources and functions of the markers and their relationship to mechanisms of action of RA therapies. Ingenuity® IPA was used to identify pathways associated with the prioritized marker set and to characterize its relationship to RA disease biology and systemic impact, including cardiovascular risk.

Results: The prioritized set comprises a diversity of markers including cytokines/receptors, chemokines, growth factors, MMPs, adhesion molecules, acute phase reactants, lipoproteins and hormones. Many of these are targets of approved or proposed therapies. Unlike single markers, the combined panel captures cross-talk between innate and adaptive immunity, vascular activation, fibroblast hyperplasia, skeletal damage, and systemic acute phase and inflammatory responses. Pathway analysis reveals associations with RA-specific, cell signaling, cardiovascular, hepatic, and cancer-related pathways: (1) overlap with RA and signaling pathways reflects the immunological basis of RA; (2) overlap of cytokines and acute phase proteins with hepatic pathways reflects chronically modified hepatic activity and lipid metabolism; (3) overlap of cytokines and vascular markers with atherosclerosis pathways reflects increased cardiovascular risk; and (4) overlap of MMPs and growth factors with cancer pathways reflects stromal activation and remodeling. A subset of the markers that captures much of the biological diversity of the larger panel was used to define and then verify a disease activity test based on correlation to DAS28 and other disease activity measures from multiple clinical studies.

Conclusion: We have evolved a combinatorial, prioritized group of molecular markers of RA disease activity that simultaneously captures key features of RA including immune activation, a “metastatic” stromal signature, altered hepatic regulation, and atherosclerotic associations. These markers were used to define a test that synthesizes critical information on multiple RA-related mechanisms into a patient-specific measure of disease activity and provides for the first time an integrated, quantitative, pathogenesis-based approach to disease activity assessment.

Disclosure of Interest: S. Ramanujan Employee of: Crescendo Bioscience, M. Centola Employee of: Crescendo Bioscience, G. Cavet Employee of: Crescendo Bioscience, I. McInnes Consultant for: Crescendo Bioscience