

THU0066 STEPWISE DISCOVERY OF DISEASE ACTIVITY BIOMARKERS IN RHEUMATOID ARTHRITIS

Y. Shen¹, N. Knowlton², M. Turner², C. Sutton¹, D. Smith¹, D. Chernoff¹, L. Hesterberg¹, J. Carulli³, N. A. Shadick⁴, M. E. Weinblatt⁴, G. Cavet¹, M. Centola^{2,*}

¹Crescendo Bioscience, S. San Francisco, CA, ²OMRF, Oklahoma City, OK, ³Biogen Idec, Cambridge, MA, ⁴Brigham & Women's Hospital, Boston, MA, United States

Background: Tight control is defined as a therapeutic strategy using frequent disease assessment and therapeutic changes to achieve a specific, quantitative objective. Studies such as TICORA, CAMERA and FinRACO suggest tight control focused on disease activity goals in rheumatoid arthritis improves patient outcomes; ACR and EULAR also recommend regular disease activity assessment. Precise, quantitative assays which capture the complex and heterogeneous biology of RA across the population have the potential to complement symptom-focused approaches and further improve outcomes.

Objectives: Our goal was to identify robust biomarkers of RA disease activity using a rigorous, stepwise approach which includes a comprehensive survey of relevant biological pathways in numerous clinical cohorts.

Methods: Candidate serum protein biomarkers were selected from an extensive screen of literature, databases, and experimental data. Quantitative assays for 121 proteins measurable in serum from RA patients were performed in a series of studies involving >700 patients from 3 separate cohorts. Associations between candidate biomarker levels and disease activity were assessed using univariate analysis and markers were also assessed for their relative contribution to multivariate models of disease activity. Marker sets were reduced through serial studies. The top biomarker candidates were analytically optimized for sensitivity, specificity, and dynamic range in the RA population.

Results: The original 121 proteins were narrowed down to 25 top candidates in successive studies. These 25 proteins were consistently correlated with disease activity across multiple studies and represent a diverse set of biological pathways implicated in RA pathogenesis. Statistical models with 6-11 protein biomarkers outperformed any individual biomarker, including CRP, at estimating disease activity. Models achieved average accuracy >70% for assigning patients into low and high disease activity categories, and average correlations of 0.6 with DAS28CRP in 100 iterations of cross validation. Models developed in one cohort performed similarly in independent cohorts. Models were also able to track disease activity over time (correlation of change in biomarkers with change in DAS28 was ~0.6). Assays for the top 25 markers were optimized, resulting in CVs from 2-8%, and are currently being assessed in an independent set of patients in order to train a final algorithm of RA disease activity.

Conclusion: Serum protein biomarkers contain information pertaining to RA disease activity. A combination of markers captures a rich set of biological pathways in order to comprehensively assess disease activity across the spectrum of RA. A stepwise approach, assessing biomarkers serially in multiple large patient cohorts, increases the likelihood of success in identifying robust marker panels which may prove useful in the assessment of biological disease activity in RA.

Disclosure of Interest: Y. Shen Employee of: Crescendo Bioscience, N. Knowlton Consultant for: Crescendo Bioscience, M. Turner Consultant for: Crescendo Bioscience, C. Sutton Employee of: Crescendo Bioscience, D. Smith Employee of: Crescendo Bioscience, D. Chernoff Consultant for: Crescendo Bioscience, L. Hesterberg Employee of: Crescendo Bioscience, J. Carulli Employee of: Biogen Idec, N. Shadick Grant / Research Support from: Crescendo Bioscience, Biogen Idec, M. Weinblatt Grant / Research Support from: Crescendo Bioscience, Biogen Idec, G. Cavet Employee of: Crescendo Bioscience, M. Centola Grant / Research Support from: Crescendo Bioscience, Consultant for: Crescendo Bioscience