Disclosure of Interests: None declared
DOI: 10.1136/annrheumdis-2019-eular.8617

WEDNESDAY, 12 JUNE 2019

18:15:00 – 19:45:00

Personalised medicine in rheumatic disease

SP0034 RA-MAP. PATIENT STRATIFICATION IN RA

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Background: When we assess rheumatoid arthritis in the clinic we quantify inflammation. Apart from measuring auto-antibodies we do not assess the immune system.

Objectives: The MRC/ABPI RA-MAP study was an academia-industry consortium designed to characterise the immune dysregulation that presents clinically as RA¹. Key questions were:

- o Are there baseline immune markers of prognosis/therapeutic response?
- o What is the molecular signature of the disease state (is there an immune correlate of inflammation)?
- o Can 'RA' be defined in terms of immune dysregulation and are there distinct subtypes?

Methods: RA-MAP was a systems immunology analysis of 275 patients with seropositive, treatment-naïve early RA (the TACERA cohort). Patients were assessed at baseline and every 3 months for up to 18 months. At each visit, clinical samples were collected for transcriptomic (blood), proteomic (blood) and metabolomic (blood and urine) analyses. Peripheral blood mononuclear cells were characterised by flow cytometry. Clinical and demographic information was collected at each visit. Primary analyses addressed the key questions by seeking associations between immune parameters and disease activity or disease state.

Results: Latent class analysis of clinical data revealed three main disease trajectories². Transcriptomic and systems approaches highlighted at least two subtypes of seropositive RA. Proteomic analyses also supported multiple RA subtypes. Metabolomic analyses revealed prognostic baseline signatures. Flow cytometry revealed a reduction in peripheral blood mononuclear cell complexity as disease became less active. Combinatorial analyses of different datasets is currently underway.

Conclusion: RA-MAP has provided important insights into the immunological and molecular heterogeneity of RA. Our findings require replication and validation, and some analyses are ongoing. RA is the consequence of dysregulated immunity characterized by distinct molecular 'endotypes'.

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- [1] Cope AP, et al. The RA-MAP Consortium: a working model for academia-industry collaboration. *Nat Rev Rheumatol* 2018;14:53-60. doi: 10.1038/nrrheum.2017.200
- [2] Tom BDM, et al. Novel methodology to discern predictors of remission and patterns of disease activity over time using rheumatoid arthritis clinical trials data. *RMD Open* 2018;4:e000721. doi:10.1136/rmdopen-2018-000721

Disclosure of Interests: John Isaacs Grant/research support from: Pfizer, Grant/research support from: Pfizer, Consultant for: Abbvie, Pfizer, Roche, Galvani, Merck, Gilead, Eli Lilly, Amgen, Janssen, Celltrion, NAPP, Consultant for: Abbvie, Pfizer, Roche, Galvani, Merck, Gilead, Eli Lilly, Amgen, Janssen, Celltrion, NAPP, Speakers bureau: Abbvie, Pfizer, Eli Lilly, Speakers bureau: Abbvie, Pfizer, Eli Lilly

DOI: 10.1136/annrheumdis-2019-eular.8506

SP0035 PRECISION MEDICINE IN PSA

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Background: Biological DMARDs targeting particular molecules relevant to pathological processes have revolutionized the treatment of rheumatoid arthritis (RA) and clinical remission is now realistic targets. However, several issues to be addressed still remain. First, less than half of patients who are treated with methotrexate and biological DMARDs achieved remission defined by stringent composite measures. Second, from multiple biological DMARDs, how to select the most appropriate treatment in each patient remain unclear. Third, how to expand the treatment strategies learned from RA to other rheumatic and/or systemic autoimmune diseases are still under investigations.

Objectives: Psoriatic arthritis (PsA) is a typical complication of psoriasis that causes irreversible destruction and dysfunction of joints and/or the spine and

appropriate and timely intervention is prerequisite to inhibit progress in the damages. Various cytokines including IL-12, IL-23, IL-17 and TNF play important roles in the pathogenesis of PsA. Therefore, biological DMARDs targeting these key effector cytokines are currently available and actually effective in supporting the resolution of enthesitis and subsequent arthritis as well as damages of spine/joint in PsA.

Methods: We have compared efficacies of biological DMARDs in PsA patients who were treated according to 2015 EULAR recommendations and whose biological DMARDs were strategically selected based on peripheral blood lymphocyte phenotyping using 8-colour flow cytometry with specific focus on helper T cell subsets.

Results: Patients with PsA were divided to 4 groups by the dominance of Th1- and Th17-phenotypes and biological DMARDs were stratified in each subgroup: an anti-p40 antibody to the activated Th1 cell-predominant patients, anti-IL-17 antibodies to the activated Th17 cell-predominant, IL-17 inhibitors or TNF inhibitors to the Th1/Th17-high, and TNF inhibitors to the Th1/Th17-low patients. Significant improvement of simplified disease activity index (SDAI) and psoriasis area and severity index by both the standard treatment and the strategic selection of biological DMARDs after the 6-month treatments. It is noteworthy SDAI values were improved in the vast majority of patients in the strategic treatment group, whereas the values were sustained in some patients despite standard biological DMARDs.

Conclusion: Although accumulation of evidence and development of new markers are expected, the obtained results indicate potential for precision medicine via the strategic selection of different biological DMARDs for PsA based on the phenotypic differences in peripheral helper T cells.

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- [1] Miyagawa I, Nakayamada S, Nakano K, Kubo S, Iwata S, Miyazaki Y, Yoshikawa M, Yoshinari H, Tanaka Y. Precision medicine using different biological DMARDs based on characteristic phenotypes of peripheral T helper cells in psoriatic arthritis. *Rheumatology* (2019) 58: 336-344.
- [2] Tanaka Y. Psoriatic arthritis in Japan: difference in clinical features and approach to precision medicine. *Clin Exp Rheumatol* (2016) 34, 49-52.

Disclosure of Interests: Yoshiya Tanaka Grant/research support from: Abbvie, Astellas, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, MSD, Ono, Taisho-Toyama, Takeda, Speakers bureau: Abbvie, Asahi-kasei, Astellas, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eli Lilly, Eisai, Glaxo-SmithKline, Janssen, Mitsubishi-Tanabe, Novartis, Pfizer Japan Inc, Sanofi, Takeda, UCB, YL Biologics

DOI: 10.1136/annrheumdis-2019-eular.8599

SP0036 MASTERPLANS – TAILORING SLE FOR THERAPY

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Background: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease which is highly heterogeneous in its clinical manifestations and also in its response to specific therapies. Across a number of trials of novel agents, overall response rates are approximately 40-60% and in the past almost 60 years only one drug (belimumab) has been licensed for use in SLE. Current therapy is therefore based on a 'trial and error' approach frequently involving glucocorticoid co-therapy. Delayed and poor control of inflammation results in organ damage, cardiovascular disease and glucocorticoid toxicity. We established a consortium of academia and industry partners (MAXimizing SLE Therapeutic Potential by Application of Novel and Stratified approaches (MASTERPLANS) with the aim of identifying key endotypes associated with response and low disease activity on particular therapies.

Objectives: Our consortium is addressing the hypothesis that strata exist within SLE populations that will enable more targeted use of existing and novel therapeutic agents and improve response rates. Specifically, B-cell related biomarkers including dynamics and function predict responses to mycophenolate mofetil (MMF) and B-cell targeted biologics and interferon signature/pathway dynamics identifies patients with poorer responses to these agents.

Methods: Our approach will firstly be to re-analyse data already available from large studies and trials to identify key predictive factors of response. Also, using data from a large UK cohort, the BiLAg-Biologics Register, we will assess clinical factors and biomarkers that predict response and low disease activity. Combining results from these studies with that gained from previous studies will enhance our ability to identify endotypes of response.

Conclusion: Identifying biomarkers of response will allow better selection of therapy for individual patients. Using the right drug at the right time will improve control of inflammation for patients with SLE and contribute to improving long-term outcomes.

Disclosure of Interests: Ian N. Bruce Grant/research support from: Genzyme Sanofi, GlaxoSmithKline, Consultant for: AstraZeneca, Eli Lilly, GlaxoSmithKline,