The Journal of Rheumatology 2022;49 Suppl 1:13–5
doi:10.3899/jrheum.211320
First Release April 1 2022

The Journal of Rheumatology

Basic Science Session 1. Biomarkers for Psoriatic Arthritis Treatment Response and Joint Damage Progression: An Update on 2 Industry-GRAPPA Projects

James C. Waddington[1], Orla Coleman[1], Philip J. Mease[2], Vinod Chandran[3], Denis O'Sullivan[4], Oliver FitzGerald[5], and Stephen R. Pennington[5]

ABSTRACT. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has identified several priority areas for biomarker development, including biomarkers to predict at baseline which patients may progress to develop joint damage and whether a patient will respond to a specific targeted therapy. Two industry-GRAPPA projects were initiated in 2020 on these biomarker research areas: (1) the Pfizer-GRAPPA project, focused on biomarkers of treatment response to tofacitinib in the Oral Psoriatic Arthritis TriaL program; and (2) the Lilly-GRAPPA project, focused on biomarkers of damage in the ixekizumab SPIRIT-P1 randomized controlled trial. Preliminary results from these 2 projects were presented by the GRAPPA team, with both studies showing promising initial results. Data from these studies will be published when the studies have been completed. Large-scale validation studies are required and are under discussion.

Key Indexing Terms: GRAPPA, psoriasis, psoriatic arthritis

Introduction

Prof. Oliver FitzGerald introduced 2 industry-GRAPPA collaborative projects. Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis (PsO) that is usually seronegative for rheumatoid factor and affects 30% of patients with PsO.[1,2] Patients with PsA may develop progressive joint damage, with 47% developing erosions within 2 years of disease diagnosis.[3] The annual healthcare costs associated with PsA are considerable and linked to disease severity.[4] Although annual healthcare costs are difficult to quantify, it is known that failure to identify effective treatment early also adds to the clinical and economic impact of PsA, as patients often cycle through several therapies before disease is adequately controlled.

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has identified these priority areas of biomarker research: (1) the identification of biomarker(s) present at baseline in patients with PsA that may predict which patients are likely to respond to a specific therapy; and (2) the identification of biomarker(s) present at baseline in patients with PsA, which predict those likely to experience radiographic progression (damage).

A collaborative, 3-phase program was agreed upon by GRAPPA and Pfizer to focus on treatment response to tofacitinib (TOF) using serum samples obtained from patients at baseline participating in the Oral Psoriatic Arthritis TriaL (OPAL) Broaden (A3921091) and OPAL Beyond (A3921125) randomized controlled trials (RCTs).[5,6] Phase I involved a targeted evaluation of a panel of approximately 200 existing candidate

As part of the supplement series GRAPPA 2021, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

Industry-GRAPPA projects were funded by Pfizer and Eli Lilly.

[1]J.C. Waddington, MBiolSci, PhD, O. Coleman, PhD, Atturos Ltd., Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland; [2]P.J. Mease, MD, MACR, Rheumatology Research, Swedish Medical Center/Providence St. Joseph Health, Washington, and University of Washington School of Medicine, Seattle, Washington, USA; [3]V. Chandran, MBBS, MD, DM, PhD, Department of Medicine, Division of Rheumatology, University of Toronto, Toronto, and Krembil Research Institute, Toronto Western Hospital, Toronto, Ontario, Canada; [4]D. O'Sullivan, BE, GRAPPA Patient Research Partner, Our Lady's Hospice & Care Services, Rheumatic & Musculoskeletal Disease Unit, Dublin, Ireland; [5]O. FitzGerald, MD, FRCPI, FRCP, Consultant Rheumatologist and Newman Clinical Research Professor, S.R. Pennington, PhD, School of Medicine, Conway Institute for Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland.

PJM has received research grants, consultation fees, and speaker honoraria from AbbVie, Amgen, Boehringer Ingelheim, BMS, Eli Lilly, Galapagos, Gilead, GSK, Janssen, Merck, Novartis, Pfizer, Sun Pharma, and UCB. VC has received consulting fees and/or speaking fees and/or honoraria from AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, and UCB; his spouse is an employee of AstraZeneca and a former employee of Eli Lilly. OF has received research grants and/or consulting fees from AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, and UCB. JCW, OC, DO, and SRP report no conflicts of interest.

This paper does not require institutional review board approval.

Address correspondence to Prof. S.R. Pennington, School of Medicine, Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Belfield, Dublin 4, Ireland. Email: stephen.pennington@ucd.ie.

Accepted for publication December 7, 2021.

biomarkers (PAPRICA assay) using OPAL Broaden and Beyond samples (n = 1450). Phase II looked for novel serum protein biomarkers using unbiased liquid chromatography–tandem mass spectrometry (LC-MS/MS) on selected baseline samples (n = 96) in "best responders" compared with nonresponders. In phase III, an updated biomarker panel will be developed to include markers from the PAPRICA evaluation and also the new markers from discovery. These will be evaluated in the full OPAL program with an estimated 1450 samples.

GRAPPA and Lilly devised a collaborative 2-phase program to focus on the identification of biomarkers which might predict radiographic progression (damage) using baseline serum samples from the SPIRIT-P1 (Clinical Trials.gov: NCT01695239) ixekizumab (IXE) trial.[7] Phase I looked for novel serum protein biomarkers using unbiased LC-MS/MS on baseline samples (n = 83) selected on the basis of having progressed radiographically during the course of the trial vs those who showed no evidence of progression. In phase II, a targeted evaluation of the PAPRICA assay in 473 SPIRIT-P1 serum samples derived from 84 patient participants with PsA was undertaken.

Approaches to protein biomarker discovery

Prof. Stephen Pennington described how, in both projects, 2 different MS-based proteomics approaches were employed to discover and evaluate candidate serum protein biomarkers: (1) unbiased discovery of novel candidate biomarker proteins; and (2) the targeted measurement of identified biomarker candidates.

In the unbiased approach, the 14 most abundant serum proteins, which constitute over 95% of total serum proteins, were removed from trial participant samples by an efficient and highly selective affinity-depletion approach. The resulting "depleted samples" were subjected to protein digestion using trypsin. Prior to unbiased discovery (using LC-MS/MS), the extent of abundant protein removal was evaluated by targeted protein measurement using triple quadrupole (QQQ) MS and an assay that measures high- as well as low-to-moderate–abundance serum proteins. This step established the extent of high-abundance protein depletion in each participant sample and the reproducibility of the depletion process. Having established the effectiveness of the depletion, the samples were subjected to LC-MS/MS using high-resolution MS platforms and a data-dependent acquisition strategy. The resulting data were analyzed using a pipeline of relevant MS software packages to reveal qualitative and quantitative differences in the peptides/proteins present in the samples.

In the targeted measurement approach, a panel of just over 200 candidate biomarker proteins was analyzed. This PAPRICA panel comprises optimized multiple reaction monitoring (MRM) methods to measure > 400 peptides using high-sensitivity QQQ MS. The PAPRICA panel of candidate biomarker proteins was assembled from a series of studies in rheumatoid arthritis, PsA, and juvenile idiopathic arthritis, and some of the proteins present in the panel may have relevance to the evaluation studies undertaken here. In each study, relevant quality control samples and methods were included.

Update on the Pfizer-GRAPPA project: Biomarkers of treatment response

Dr. James Waddington introduced the collaborative project with Pfizer aiming to identify and assess protein biomarkers that may predict response to TOF in patients with PsA. Participant samples from Pfizer-sponsored phase III trials of TOF in PsA (OPAL Broaden and OPAL Beyond) were used in this project.

In phase I of the project, all OPAL serum samples were evaluated using the PAPRICA panel. Data were acquired over a 6-month period with robust quality control measures in place. Univariate and multivariate analyses were performed, and candidate peptides representing several proteins were identified as potential biomarkers for predicting treatment response.

In phase II of the study, 96 baseline samples representing strong responders and nonresponders were analyzed by unbiased LC-MS/MS. Seven reference serum samples were depleted and digested alongside the baseline samples to monitor depletion reproducibility. Additional reference serum samples (crude/undepleted) were digested to monitor digestion efficiency. LC-MS/MS spectral data was analyzed using PEAKS Studio Xpro (v.10.6 build 20201015; Bioinformatics Solutions Inc.) and the resulting peptide peak areas identified 66 peptides representing 39 proteins as novel candidate biomarkers.

Phase III of the study is currently underway and targeted MS methods are being developed to incorporate peptides representing proteins identified in phase I and phase II. After analytical validation of the MRM assay, this set of candidate biomarkers will be measured in OPAL clinical trial samples and used to evaluate the random forest models for predicting treatment response from phase I and phase II, as well as the development of additional models using the different sample subsets in the OPAL samples.

Update on the Lilly-GRAPPA project: Biomarkers of radiographic damage

Dr. Orla Coleman provided an update on a project undertaken in collaboration with Lilly focusing on identifying protein biomarkers of radiographic progression (damage) in PsA. In order to evaluate protein biomarkers of joint damage, this study utilized serum samples obtained as part of the SPIRIT-P1 study of IXE, which focused on the treatment of biologic-naïve patients with active PsA.[7] In phase I, a total of 473 serum samples from 84 patients recruited to the SPIRIT-P1 trial were obtained. Of these 84 patients, 28 developed evidence of joint damage on follow-up radiographs (progressors) and 56 did not show any evidence of joint damage on follow-up radiographs (nonprogressors). Joint damage progression was defined as a minimum score change of +0.5 from baseline to 24 and/or 52 weeks using the modified total Sharp score (mTSS). Nonprogression of joint damage was diagnosed if there was an mTSS change of < 0.5 from baseline to weeks 24 and/or 52.

A discovery proteomic approach was used to look for baseline serum proteins differentially expressed at baseline in patients whose joint damage progressed compared to those whose did not progress. Discovery proteomic analysis of the baseline serum samples involved depletion of the 14 high-abundance

serum proteins, sample concentration, and enzymatic digestion prior to liquid chromatography, coupled with an unbiased discovery MS (LC-MS/MS). In total, 21,940 peptides corresponding to 588 proteins were identified across the depleted baseline serum samples. Quantitative data analysis identified 92 peptides corresponding to 62 proteins with an ANOVA P value < 0.01 and a 20% minimum change in abundance levels between progressors and nonprogressors. Random forest machine learning analysis of the identified peptides provided a 15-peptide signature, which predicts joint damage progression at baseline with an area under the curve (AUC) of 0.76 (95% CI 0.56–0.97) in a test subset of samples. Future work will verify the differential abundance levels of these novel protein candidates and validate their use as potential biomarkers of joint damage progression by testing them in a separate and larger cohort of baseline PsA serum samples.

Additionally, in phase II, a targeted proteomics approach for quantitative analysis of the PAPRICA multiplexed protein assay in all serum samples was undertaken. The samples were divided across 6 preparation plates intermingled with reference serum samples. Samples were digested, supplemented with quality control heavy isotope–labeled peptides and analyzed using MRM-based targeted MS over a 6-week period. Random forest machine learning analysis of the 416 PAPRICA assay peptides provided a 15-peptide signature, which predicts joint damage progression at baseline with an AUC of 0.84 (95% CI 0.71–0.97) in a test subset of samples. Ongoing work to integrate baseline clinical variables such as the number of bone erosions, mTSS, and C-reactive protein levels with the targeted PAPRICA peptide data is in progress to try to improve the prediction of joint damage progression at baseline.

Discussion

These preliminary results for both industry-GRAPPA studies are encouraging but projects have not yet been completed, and validation is required in separate, large, well-characterized cohorts. To date, the development of biomarkers, which may have clinical utility in the diagnosis and management of PsA, have struggled to make progress due to the relatively small datasets available at individual centers, the considerable heterogeneity of disease presentation and progression, and the failure to validate findings in large datasets. Whereas exciting recent work has highlighted biomarkers of potential interest in PsA, there is an urgent need for studies that include sufficiently large cohorts of patients.

Advancing from biomarker identification to validation and ultimately to use in the routine clinical setting presents significant challenges. However, we suggest that this is most likely to be achieved successfully if future studies are undertaken using collaborative multigroup, multicohort approaches and multianalyte investigations incorporating relevant quality controls focused on the development of new diagnostic tools.

In relation to treatment response, it is unclear whether any identified biomarker(s) of response will be specific for a particular drug or class (eg, tumor necrosis factor inhibitors), or whether there will be biomarkers that identify patients who appear not to respond to multiple agents with different mechanisms of action. Whichever way it works, we suspect that by using such biomarker panels, the physician will learn the probability of a patient responding to a particular treatment approach. This would be hugely beneficial when trying to select the most appropriate treatment from among the choices currently available.

The ability of biomarkers to predict joint damage in the context of optimal disease management will help guide the development of recommendations for biomarker testing in PsA so that joint damage is prevented, and long-term outcomes improved. In relation to joint damage prediction, there are several challenges to consider, including the slow rate of progression in many patients with PsA and the small number of progressors in most of the more recent RCTs. It is quite likely that a large observational cohort rather than an RCT dataset will be required for validation. Such a cohort would need to have a detailed clinical database and sequential radiographs available, as well as at least baseline collection of serum from each subject. As such an existing cohort is difficult to identify, it may well be necessary and timely for GRAPPA to reconsider establishing its own longitudinal, observational, multicenter cohort.

This summary of ongoing industry-GRAPPA protein biomarker studies suggests that there remains an important opportunity to continue to develop protein biomarkers that might have clinical utility in the management of patients with PsA. We look forward to working further with our industry partners to complete the current projects and to explore with them, and others, the necessary steps involved in bringing these potential biomarkers to routine clinical practice.

REFERENCES

1. Chandran V, Cook RJ, Edwin J, et al. Soluble biomarkers differentiate patients with psoriatic arthritis from those with psoriasis without arthritis. Rheumatology 2010;49:1399-405.
2. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973;3:55-78.
3. Kane D, Stafford L, Bresnihan B, FitzGerald O. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. Rheumatology 2003;42:1460-8.
4. Poole CD, Lebmeier M, Ara R, Rafia R, Currie CJ. Estimation of health care costs as a function of disease severity in people with psoriatic arthritis in the UK. Rheumatology 2010;49:1949-56.
5. Gladman D, Rigby W, Azevedo VF, et al. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. N Engl J Med 2017;377:1525-36.
6. Mease P, Hall S, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. N Engl J Med 2017; 377:1537-50.
7. Mease PJ, van der Heijde D, Ritchlin CT, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis 2017;76:79-87.