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Proceedings of the 2020 GRAPPA Collaborative Research Network (CRN) Meeting

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ABSTRACT. At the 2020 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)-Collaborative Research Network (CRN) annual meeting, the GRAPPA-CRN group presented a pilot investigator-initiated study protocol to test electronic case report forms (eCRFs) and proposed Standardized Operating Procedures (SOPs) to evaluate biomarkers of psoriatic arthritis (PsA) associated with axial disease. The progress on 3 studies was also presented: BioDAM PsA (Biomarkers as Predictors of structural DAMage in PsA; to validate soluble biomarkers as predictors of structural damage in PsA), PreventPsA (examining the development of PsA and risk factors among patients with psoriasis and no arthritis), and PredictORPsA (Predicting Treatment respOnse in patients with eaRly PsA; in collaboration with Pfizer using samples from the Oral Psoriatic Arthritis TriaL [OPAL], to identify biomarkers of treatment response). GRAPPA-CRN funding partnerships and applications are also underway with both the Innovative Medicines Initiative (IMI) in Europe and Accelerating Medicines Partnerships (AMP) 2.0 in the USA, and the progress of these applications and associated objectives were presented.

Key Indexing Terms: GRAPPA, psoriasis, psoriatic arthritis

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The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)-Collaborative Research Network (CRN) held its fourth meeting at the GRAPPA 2020 Annual Meeting, which, due to the coronavirus disease 2019 (COVID-19; caused by SARS-CoV-2) pandemic, was held virtually. The GRAPPA-CRN meeting was organized by a committee cochaired by Professors Oliver FitzGerald and Christopher Ritchlin. Attendees included 41 rheumatologists, 16 representatives from the pharmaceutical industry, 10 dermatologists, 6 patient research partners (PRPs), 3 others including nonclinical scientists, and 2 trainee physicians.

The GRAPPA-CRN meetings in 2018 and 2019 had identified 3 unmet needs in psoriatic disease, which were subsequently proposed as 3 investigator-initiated studies (IIS): (1) BioDAM psoriatic arthritis (PsA), to prospectively validate soluble biomarkers as predictors of structural damage in PsA; (2) PreventPsA, to evaluate biomarkers of the development of PsA among patients with psoriasis and no arthritis (PsC); and (3) PredictORPsA, to identify biomarkers predicting treatment response in patients with early PsA.

Significant progress has been made over the last 12 months, and the 2020 GRAPPA-CRN meeting provided an opportunity to report back on the progress and consolidate future steps. An IIS to test electronic case report forms (eCRFs) and standardized operating procedures (SOPs) for the collection, storage, and analysis of liquid and tissue samples to be used in future GRAPPA-CRN IIS was presented. Rather than focusing on the unmet needs identified in the previous meetings, this pilot IIS explored biomarkers of PsA associated with axial disease. Progress of BioDAM PsA has resulted in partnerships with Amgen (SEAM-PsA) and Lilly (SPIRIT-P1 and -P2), in order to identify soluble protein biomarkers predictive of joint damage. These biomarkers could be validated in future studies using other GRAPPA-CRN PsA cohorts. To facilitate progress of the PreventPsA study, terms to define the transition from PsC to PsA were proposed by way of PAMPA (Preventing Arthritis in a Multi-center Psoriasis At-risk Population), and risk factors associated with this transition were presented. With respect to the progress of PredictorPsA, a partnership with Pfizer and the Oral Psoriatic Arthritis TriaL (OPAL) study is underway to evaluate, discover, and validate soluble protein biomarkers of treatment response, again to be validated within other PsA cohorts from the GRAPPA-CRN. Progress on funding applications in both Europe, through the Innovative Medicines Initiative (IMI), and in the USA, through AMP 2.0, was presented.

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Goals for the GRAPPA-CRN 2020 Annual Meeting

Prof. FitzGerald opened the CRN session with a review of the agenda from the 2019 meeting, in which 3 objectives were presented: (1) to review and seek feedback on the development of a shared database or eCRF to be used in GRAPPA-CRN studies; (2) to review and obtain feedback on agreed SOPs, which would be used to collect biosamples in any CRN study; and (3) to propose and seek feedback on an IIS to facilitate testing of both eCRFs and SOPs. The proceedings and outcomes of the 2019 GRAPPA-CRN meeting were published in 2020.[1]

Since the last meeting, GRAPPA had registered an office in the Netherlands (GRAPPA-European Union [EU]), thereby allowing GRAPPA to participate in EU-funded research programs and help EU-based educational initiatives. The 2020 GRAPPA-CRN annual meeting began with a keynote lecture from Prof. Anne Barton and was followed by an overview of project updates since the 2019 annual meeting.

Keynote Lecture

The keynote lecture, "Predicting Treatment Response: Lessons from Rheumatoid Arthritis" from Prof. Barton, provided insights into the challenges faced when undertaking multicenter studies to address treatment responses and precision medicine in rheumatoid arthritis (RA). Half a million patients in the UK have RA, with a cost to the NHS of £560 million/year. There is significant patient morbidity, as 28% are estimated to stop working within 2 years of diagnosis. "Precision medicine" was defined as "a concept where we start with our patient group and use a defined statistical algorithm to stratify patients to the correct treatment." MAximizing Therapeutic Utility for Rheumatoid Arthritis was a national program involving several research centers: the Medical Research Council, Versus Arthritis, and 9 industry partners. The program comprised 2 workstreams: (1) synovial tissue sampling and pathobiology from dedicated randomized controlled trials (RCTs), and (2) large-scale blood-based screening from observational studies.

Prof. Barton provided an overview of the challenges encountered by precision medicine in identifying predictors of response, in particular: (1) suitable outcome measures, (2) patient adherence to medications as a confounder, (3) immunogenicity status as a confounder, and (4) the merits of tissue versus peripheral blood sampling and analysis.

The Disease Activity Score in 28 joints (DAS28) is the standard outcome measure for RA in many parts of the world. However, Prof. Barton had previously shown that tender joint counts (TJCs) and visual analog scale (VAS) scores correlate with psychological factors more than swollen joint counts (SJCs) or erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP),[2] and went on to demonstrate that the heritability of SJCs and ESR/CRP was greater than that of the TJC or VAS.[3] Further, the DAS28 poorly correlated with ultrasound-based synovitis scores, whereas a reweighted DAS28, using just SJC28 and CRP, was a better predictor of both ultrasound synovitis and erosions.[4] Even with a more objectively assessed outcome measure, other factors can confound the identification of robust biomarkers of treatment responses. For example, drug levels of

adalimumab (ADA) at 3 and 6 months correlate with treatment response at 12 months, but drug levels were influenced by BMI, antidrug antibody levels, and medication adherence.[5] Even when such factors are accounted for in the analysis, the best tissue for biomarker sampling remains a subject of debate.

Peripheral blood would provide the easiest source for biosampling, but it is argued that the tissues that are the target of pathology may be more informative. For example, the Pathobiology of Early Arthritis Cohort (PEAC), led by Prof. Costantino Pitzalis at Queen Mary University of London, sampled synovial biopsies from patients with early inflammatory arthritis who have then been followed prospectively. They reported a baseline lymphomyeloid pathotype, which correlates with seropositivity, high disease activity, and radiographic progression at 12 months, when compared to a pauciimmune fibroid or diffuse myeloid subtype.[6] Work is ongoing with respect to correlating the pathotype with treatment response.

In summarizing the data thus far, Prof. Barton identified the importance of carefully considering factors (challenges 1–4 listed above) when designing precision medicine studies moving forward in PsA trials. Following the presentation, there was an interesting discussion around patient behavioral endophenotypes, whether they could be modified, and whether strategies could be taken to improve patient adherence, including motivational interviewing. Further, adjustment for ADA drug levels and the use of the modified 2-component DAS28 score were identified as factors that could optimize current analysis approaches. Prof. Philip Mease described how there had been similar findings in patients with PsA in Denmark,[7] with patients experiencing high levels of widespread nonarthritic pain failing to achieve minimal disease activity. This has led to the inclusion of a questionnaire on central pain sensitization in the Corrona registry. Prof. Ritchlin supported the use of machine-learning approaches in order to integrate synovial biopsy pathotypes with RNA sequencing in the PEAC cohort,[6] which has been employed by other research groups.[8]

Update on the Pilot Project/Investigator-initiated Study

Prof. FitzGerald presented an update on an IIS proposed by the GRAPPA-CRN, which would be a multicenter pilot study to validate eCRFs and SOPs, and Janssen expressed interest in supporting this pilot study. Rather than the pilot being one of the studies resulting from the 3 unmet needs, Janssen was keen to support a study on axial PsA. The proposed objectives would be to identify candidate biomarkers associated with the presence of axial involvement in PsA. The study would be a multicenter pilot study designed to obtain high-quality clinical data (eCRFs) and associated biosamples (liquid and tissue) utilizing validated SOPs, which would assist in identifying biomarkers associated with the presence of axial involvement in PsA. Five GRAPPA-CRN centers with an established record of clinical research, biosample collection, and storage would be selected. Eight patients with PsA would be recruited per center, with a total of 40 patients: 20 with axial involvement and 20 without axial involvement.

Funding would be provided by Janssen through an IIS grant mechanism, a grant submitted through GRAPPA or by a named US-based principal investigator, and a subcontract with other participating sites. The IIS is to be submitted shortly, following some delays resulting from the COVID-19 pandemic. Considerations for participating site selection include a track record of successful research studies; experience in PsA/PsC clinical assessment tools; expertise in synovial and skin biopsy techniques; expertise in liquid (serum, DNA, peripheral blood mononuclear cells, synovial fluid mononuclear cells) and tissue processing and storage; and no local regulatory issues with sending data or transporting samples to the University Health Network in Toronto, Canada.

Update on Biomarkers as Predictors of structural DAMage in PsA (BioDAM PsA) Study

Dr. Vinod Chandran provided an update on BioDAM PsA, a prospective validation of soluble biomarkers as predictors of structural damage in PsA. Baseline erosions can be observed in an estimated 27% of patients with early PsA, which increases to an estimated 47% two years following diagnosis.[9,10,11] Joint erosions reflect damage and are associated with more severe disease, as measured by worse functional status, higher economic effect of disease, and mortality. Identifying biomarkers of joint damage might therefore help to stratify risk groups and facilitate personalized medicine. There is evidence that synthetic disease-modifying antirheumatic drugs (DMARDs) are ineffective at preventing damage progression, while in observational studies, tumor necrosis factor inhibitors (TNFi)—but not methotrexate (MTX)—reduce damage progression.[12,13]

The GRAPPA-CRN has partnered with Amgen's SEAM-PsA study, a phase III multicenter, double-blind RCT of 851 subjects randomized to etanercept (ETN) and MTX combination therapy, ETN monotherapy, or MTX monotherapy.[14] The primary endpoint of the SEAM-PsA study was the American College of Rheumatology 20% (ACR20) response at 24 weeks. The hypothesis of the BioDAM PsA study was that biomarkers will predict peripheral radiographic damage in PsA. The objectives of the study were to determine the independent predictive validity of several candidate biomarkers in predicting structural damage in PsA patients receiving the 3 regimens detailed above. Radiographs were done at 24 and 48 weeks, and blood samples were collected at baseline, 8, 24, and 48 weeks, with associated clinical indices. A panel of candidate protein biomarkers will be tested on the serum samples using optimized multiple reaction–monitoring (MRM) assays developed at the University College Dublin. An agreement between Amgen and the GRAPPA-CRN for funding and material transfer was nearing completion at the time of submission.

Prof. Stephen Pennington provided an update on the progress of the BioDAM PsA study utilizing samples from the Lilly SPIRIT-P1 and -P2 RCTs. SPIRIT-P1 compared the efficacy and safety of placebo (n = 106), ADA (n = 101), or ixekizumab at 80 mg every 2 weeks (IXEQ2W; n = 103) or 80 mg every 4 weeks (IXEQ4W; n = 107), with the primary objective being to assess the superiority of IXEQ2W or IXEQ4W vs placebo, as measured by the proportion of patients achieving ACR20 at 24

weeks.[15] SPIRIT-P2 compared the long-term efficacy and safety in patients with an inadequate response to TNFi (n = 363) to placebo, IXEQ2W, or IXEQ4W.[16] The objective of this component of the BioDAM PsA project is to identify biomarkers that predict joint damage, thereby guiding the stratification of therapeutic benefit vs adverse effect. The project is divided into 2 parts: Discovery and Evaluation. Discovery will use baseline samples from SPIRIT-P1 (n = 83), then compare progressors (n = 28) where the modified total Sharp/van der Heijde score (mTSS) exceeds the smallest detectable change at Week 24 and/or 52, compared to nonprogressors (n = 55; no change in mTSS up to Week 52). Evaluation involves the evaluation of a panel of 200 existing candidate biomarkers—the PAPRICA assay—using SPIRIT-P1 and -P2 samples (n = 473). Both Discovery and Evaluation have begun, and the hope is that there will be subsequent validation using separate cohorts from GRAPPA-CRN members and pharmaceutical partners.

Update on PreventPsA: Evaluating Biomarkers of the Development of PsA among Patients With Psoriasis (PsC)

Dr. Alexis Ogdie described a theoretical transition of PsC to PsA. Initially, there is a preclinical phase influenced by environmental and genetic factors, followed by a subclinical silent inflammatory phase that could correlate with musculoskeletal (MSK) findings demonstrable by imaging. Finally, there is a prodromal phase in which there is arthralgia and fatigue, followed by classifiable PsA, evident on imaging and identified by clinical synovitis, enthesitis, dactylitis, and presence/absence of axial disease.[17] PAMPA, a study group within the Psoriasis and Psoriatic Arthritis Clinics Multicenter Advancement Network (PPACMAN), implemented 3 rounds of a Delphi survey to define several terms for the transition from PsC to PsA, which were presented. Term 1, "increased risk for PsA," was defined as any individual with PsC and ≥ 1 risk factor(s) for progression to PsA, with 9 risk factors being identified. Term 2, "psoriasis with asymptomatic synovio-entheseal imaging abnormalities," was defined as any individual with PsC with imaging evidence of synovio-entheseal abnormalities that is not associated with clinical signs or symptoms. Proposed imaging modalities were summarized, including magnetic resonance imaging and ultrasound signs. Term 3, "psoriasis with MSK symptoms not explained by another diagnosis," was defined as any individual with psoriasis and heel pain, stiffness, and/or arthralgias not explained by another diagnosis.[18]

Several risk factors for the transition from PsC to PsA were presented and summarized in a review by Scher, *et al*,[17] with psoriasis severity and obesity identified as risk factors. Dr. Ogdie's group has previously evaluated obesity in the presence of severe, moderate, or mild psoriasis and PsA development. They found that psoriasis severity and obesity are additive risk factors, in that the risk of developing PsA is increased by a relative risk (RR) of 1.45 (95% CI 0.75–2.82) when severe psoriasis is present, while in the presence of obesity, the RR increased to 3.90 (95% CI 2.22–6.85).[19] Use of a time-varying exposure of biologics in PsC was found to reduce the risk of developing PsA, documented by a fully adjusted HR of 0.65 (95% CI 0.64–0.65).[20] However, those receiving biologic therapy are very different to those who are not. When data were examined comparing the time of commencing biologic therapy vs the time commencing oral therapy or phototherapy, the time to PsA was actually shorter in the biologic group using an unadjusted model (HR 1.52, 95% C.I. 1.45–1.61) or a model using propensity scoring (HR 1.50, 95% CI 1.42–1.58). An explanation might be that biologic therapy is commenced due to a suspicion of PsA. In summary, moving forward with PreventPsA will require (1) defining the stages of transition from PsC to PsA, (2) identifying factors associated with this transition and whether they are singular or additive, and (3) intervention to alter the course of these transitions.

Update on PredictORPsA (Predicting Treatment RespOnse in patients with EaRly PsA): Identifying Biomarkers

Prof. Mease identified cancer therapy paradigms, in which genetic, cellular, and soluble biomarkers are increasingly being used to select and predict treatment responses, as a model to apply in PsA. In PsA, early effective treatment can more rapidly and reliably result in remission, prevent irreversible joint damage, improve function and quality of life, reduce adverse event profiles, and ultimately reduce healthcare costs. Treatment with conventional synthetic DMARDs or biologics is often not durable and a delay in effective treatment might reduce clinical benefits. A number of soluble biomarkers have predicted treatment response to TNFi, including a decrease in baseline matrix metalloproteinase-3 predicting TNFi efficacy; increased cartilage oligomeric matrix protein predicting TNFi response;[21] elevated CRP predicting infliximab (IFX) response;[22] and elevated adiponectin and factor VII predicting golimumab response.[23] Polymorphisms in a number of genes have also been associated with treatment response in PsA, including *TNF* −308/*FCGR2A* with ETN, and *TNFR1*/*TRAIL-R1* with IFX response.[24] A precision medicine approach has been reported using flow cytometric analysis of peripheral T cell subsets, stratified ustekinumab to a Th1-predominant patient group; secukinumab to Th17-predominant patients; secukinumab to Th1/Th17-high patients; and TNFi to Th1/Th17-low patients.[25] This revealed improved outcomes in patients that were stratified compared to those receiving standard treatment, as determined using the Simplified Disease Activity Index, DAS28, and Psoriasis Area and Severity Index.

Prof. Pennington presented results from a proof-of-concept pilot study for PredictORPsA that evaluated the discovery and confirmation of a protein biomarker panel (using MRM) with the potential to predict response to biologic therapy in PsA.[26] This has paved the way for the identification of candidate serum protein biomarkers that have the potential to discriminate subsets of patients who are responders or nonresponders to treatment. The next objective is to use samples from the OPAL phase III study (in collaboration with Pfizer) and a statistical analysis that will include multivariate analysis combining clinical and protein biomarkers to improve predictors of response. This project, taking place over 24 months, has 3 parts: (1) evaluation of 200 existing candidate biomarkers using the PAPRICA assay (n = 1450); (2) discovery of novel serum protein biomarkers

using baseline samples (n = 96) and unbiased liquid chromatography-mass spectrometry (MS)/MS; and (3) development of an updated biomarker panel to include markers from PAPRICA and new markers of discovery, to be further investigated with OPAL samples.

Update on Innovative Medicines Initiative (IMI) Application

IMI is a combined EU and industry partnership providing substantial research support. In January 2020, IMI announced a call for proposals, addressing "early diagnosis, prediction of radiographic outcomes and development of rational, personalized treatment strategies to improve long-term outcomes in PsA."[27] The aim is to characterize the natural history of PsA from psoriasis as "early" PsA to "full-fledged" PsA. This would be achieved by discovering new biomarkers and endotypes, constructed on genetic, epigenetic, transcriptomic, proteomic, and/or clinical markers, as well as by incorporating artificial intelligence and machine learning. The topic aims to achieve 4 objectives: (1) to enable rheumatologists, dermatologists, and general practitioners to make an early diagnosis of PsA in patients with PsC and other rheumatic diseases; (2) to identify early patients at risk of progression to PsA in order to enable earlier interventions and possibly prevent the development of PsA; (3) to identify factors associated with disease progression in PsA patients, including early prediction of bone and/or joint damage, leading to the development of more targeted treatment strategies; and (4) to develop rational and personalized treatment strategies with optimized outcomes in patients with PsA and reduce the disease burden. The consortium entitled Health Initiatives in Psoriasis and PsOriatic arthritis ConsoRTium European States (HIPPOCRATES) included GRAPPA-EU as a partner, with this partnership helping to support PRP involvement and the participation of other GRAPPA sites. If successful, the project will be launched in the second quarter of 2021.

Update on Accelerated Medicines Partnership (AMP) Psoriatic Disease Spectrum

In order to incorporate PsD into the AMP 2.0 endeavor, Prof. Ritchlin, Dr. Jose Scher, Dr. Stacie Bell, and Dr. Wilson Liao met with key stakeholders (the Foundation for the National Institutes of Health [FNIH], pharmaceutical partners, Sage Bionetworks). The working group joined the AMP autoimmunity working group and have attended several meetings with AMP and FNIH leaders to discuss strategic goals and a collaboration with the National Psoriasis Foundation (NPF). AMP RA/systemic lupus erythematosus 1.0 has been a successful endeavor, and there are already strong dermatology-rheumatology networks in place in the USA, including the NPF, GRAPPA, PPACMAN, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the Arthritis Foundation. AMP 2.0 has defined a number of aims, including: (1) to define the role of different cell states, cell types, and pathways within affected tissues, between and within different autoimmune diseases; (2) to identify the mechanisms of cell interactions that mediate tissue damage, using spatial data at the transcriptional, proteomic, and metabolic level; (3) to identify the serological and tissue changes that occur prior to and during the earliest stages of disease; and (4) to apply these technologies to define the mechanisms of disease progression in patients with multiple treatment failures. The proposed AMP 2.0 structure will have the following: (1) disease-focused teams; (2) shared functional network teams comprising a technology group, a molecular analysis group, and a systems biology group; and (3) shared network components consisting of a tissue and biospecimen repository, clinical data management, and data dissemination. The AMP psoriatic disease key scientific objectives will address the following: (1) cellular and molecular pathways of disease and treatment response in PsC; (2) interaction between skin and synovial cellular and molecular pathways in disease biology, as well as treatment response in PsA; (3) determinants of PsC to PsA transition; and (4) informing the novel trial designs. Dr. Scher also presented AMP 2.0 key performance indicators, with a key component being training and opportunities for the next generation of physicians and scientists. The working plan for AMP 2.0 is to be presented to the executive committee and funding is likely to come from several sources, including industry partners.

Summary

The GRAPPA-CRN has made significant progress over the past 4 years, and success has been realized due to relationships forged within GRAPPA between rheumatologists, dermatologists, our industry partners, and importantly, our PRPs. Such relationships have placed us in a competitive position where the ability to obtain funding to pursue unmet needs has been and will continue to be realized. The collaborations already in place within the network, such as involvement in AMP 1.0, have resulted in there being a framework in place to accelerate progression based upon lessons learned. At the 2020 virtual meeting, Prof. Barton also presented important considerations when performing precision medicine studies in another inflammatory disease: RA. The outcome of the GRAPPA-CRN to date is that there are a number of projects either in development or already underway: Industry-partnered projects with Lilly and Pfizer have commenced, a GRAPPA-CRN IIS application on axial involvement in PsA is under consideration, and the EU-based IMI and USA-based AMP 2.0 psoriatic disease–focused projects addressing the key unmet needs originally proposed within the GRAPPA-CRN framework are moving forward.

Future Directions

GRAPPA-CRN pilot project/IIS. The proposal for the IIS has been submitted to Janssen and is currently awaiting feedback. The next step will be to finalize the eCRF platform and minimal dataset to be collected, and to ensure that the SOPs for collection and storage of biosamples are agreed upon.

BioDAM PsA. Soluble protein biomarkers predictive of joint damage are currently being evaluated in Dublin using samples from the Lilly (SPIRIT-P1 and -P2) studies. The examination of biosamples from Amgen (SEAM-PsA study) should be underway following the finalization of contracts. Having

identified biomarkers of damage, the next step will be to validate the biomarker panels using other GRAPPA PsA cohorts.

PreventPsA. PAMPA has identified terminology to define the transition of PsC to PsA and, along with PPACMAN, are interested in validating risk factors for the transition and whether they are modifiable with intervention. A large prospective study in patients with PsC will be necessary to address this unmet need, so AMP 2.0 in particular will focus on this endeavor.

PredictORPsA. The OPAL study from Pfizer and the evaluation of protein biomarkers to improve predictors of response is underway. Grant applications to IMI and AMP 2.0 with GRAPPA as a partner are in progress. Lessons learned from AMP 1.0, in terms of collaborative networks and the use of validated SOPs, as well as the outcome of the IIS above, will provide a framework for the next steps.

REFERENCES

1. Waxman R, Stober C, Jadon DR, Orbai AM, Chandran V, Ogdie A, et al. Proceedings of the 2019 GRAPPA Collaborative Research Network Meeting. J Rheumatol Suppl 2020;96:25-30.
2. Cordingley L, Prajapati R, Plant D, Maskell D, Morgan C, Ali FR, et al. Impact of psychological factors on subjective disease activity assessments in patients with severe rheumatoid arthritis. Arthritis Care Res 2014;66:861-8.
3. Massey J, Plant D, Hyrich K, Morgan AW, Wilson AG, Spiliopoulou A, et al. Genome-wide association study of response to tumour necrosis factor inhibitor therapy in rheumatoid arthritis. Pharmacogenomics J 2018;18:657-64.
4. Hensor EMA, McKeigue P, Ling SF, Colombo M, Barrett JH, Nam JL, et al. Validity of a two-component imaging-derived disease activity score for improved assessment of synovitis in early rheumatoid arthritis. Rheumatology 2019;58:1400-9.
5. Jani M, Chinoy H, Warren RB, Griffiths CE, Plant D, Fu B, et al. Clinical utility of random anti-tumor necrosis factor drug-level testing and measurement of antidrug antibodies on the long-term treatment response in rheumatoid arthritis. Arthritis Rheumatol 2015;67:2011-9.
6. Humby F, Lewis M, Ramamoorthi N, Hackney JA, Barnes MR, Bombardieri M, et al. Synovial cellular and molecular signatures stratify clinical response to csDMARD therapy and predict radiographic progression in early rheumatoid arthritis patients. Ann Rheum Dis 2019;78:761-72.
7. Højgaard P, Ellegaard K, Nielsen SM, Christensen R, Guldberg-Møller J, Ballegaard C, et al. Pain mechanisms and ultrasonic inflammatory activity as prognostic factors in patients with psoriatic arthritis: a prospective cohort study. Arthritis Care Res 2019;71:798-810.
8. Orange DE, Agius P, DiCarlo EF, Robine N, Geiger H, Szymonifka J, et al. Identification of three rheumatoid arthritis disease subtypes by machine learning integration of synovial histologic features and RNA sequencing data. Arthritis Rheumatol 2018;70:690-701.
9. Ali Y, Tom BD, Schentag CT, Farewell VT, Gladman DD. Improved survival in psoriatic arthritis with calendar time. Arthritis Rheum 2007;56:2708-14.
10. Kane D, Stafford L, Bresnihan B, FitzGerald O. A classification study of clinical subsets in an inception cohort of early psoriatic peripheral arthritis—'DIP or not DIP revisited'. Rheumatology 2003;42:1469-76.
11. 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.
12. Chao R, Kavanaugh A. Psoriatic arthritis: newer and older therapies. Curr Rheumatol Rep 2019;21:75.
13. Eder L, Thavaneswaran A, Chandran V, Gladman DD. Tumour necrosis factor alpha blockers are more effective than methotrexate in the inhibition of radiographic joint damage progression among patients with psoriatic arthritis. Ann Rheum Dis 2014;73:1007-11.
14. Mease PJ, Gladman DD, Collier DH, Ritchlin CT, Helliwell PS, Liu L, et al. Etanercept and methotrexate as monotherapy or in combination for psoriatic arthritis: primary results from a randomized, controlled phase III trial. Arthritis Rheumatol 2019;71:1112-24.
15. Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, 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.
16. Genovese MC, Combe B, Kremer JM, Tsai TF, Behrens F, Adams DH, et al. Safety and efficacy of ixekizumab in patients with PsA and previous inadequate response to TNF inhibitors: week 52 results from SPIRIT-P2. Rheumatology 2018;57:2001-11.
17. Scher JU, Ogdie A, Merola JF, Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. Nat Rev Rheumatol 2019;15(3):153-66.
18. Perez-Chada L, Chandran V, Rosen CF, Ritchlin C, Eder L, Mease P, et al. ACR Convergence 2020 abstract supplement: a Delphi consensus study to standardize terminology for the pre-clinical phase of psoriatic arthritis [abstract]. Arthritis Rheumatol 2020;72 Suppl 10.
19. Ogdie A, Shin D, Choi H, Ritchlin CT, Merola JF, Scher JU, et al. Objective measures of psoriasis severity and the risk for PsA: results from the incidence health outcomes and psoriasis events prospective cohort study. Ann Rheum Dis 2019;78 Suppl 2:922.
20. Ogdie A, Löve TJ, Takeshita J, Gelfand JM, Scher JU, Choi H, et al. Impact of biologic therapy on the incidence of PsA among patients with psoriasis [abstract]. Ann Rheum Dis 2020;79 Suppl 1:769.
21. Chandran V, Shen H, Pollock RA, Pellett FJ, Carty A, Cook RJ, et al. Soluble biomarkers associated with response to treatment with tumor necrosis factor inhibitors in psoriatic arthritis. J Rheumatol 2013;40:866-71.
22. Gratacós J, Casado E, Real J, Torre-Alonso JC. Prediction of major clinical response (ACR50) to infliximab in psoriatic arthritis refractory to methotrexate. Ann Rheum Dis 2007;66:493-7.
23. Wagner CL, Visvanathan S, Elashoff M, McInnes IB, Mease PJ, Krueger GG, et al. Markers of inflammation and bone remodelling associated with improvement in clinical response measures in psoriatic arthritis patients treated with golimumab. Ann Rheum Dis 2013;72:83-8.
24. Jani M, Barton A, Ho P. Pharmacogenetics of treatment response in psoriatic arthritis. Curr Rheumatol Rep 2015;17:44.
25. Miyagawa I, Nakayamada S, Nakano K, Kubo S, Iwata S, Miyazaki Y, et al. Precision medicine using different biological DMARDs based on characteristic phenotypes of peripheral T helper cells in psoriatic arthritis. Rheumatology 2019;58:336-44.
26. Ademowo OS, Hernandez B, Collins E, Rooney C, Fearon U, van Kuijk AW, et al. Discovery and confirmation of a protein biomarker panel with potential to predict response to biological therapy in psoriatic arthritis. Ann Rheum Dis 2016;75:234-41.
27. European Commission. Funding & tender opportunities. [Internet. Accessed January 25, 2021.] Available from: ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/imi2-2020-20-01