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Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)

2017 Annual Meeting
Amsterdam, the Netherlands

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Prologue: 2017 Annual Meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)

Philip S. Helliwell, Dafna D. Gladman, and Alice B. Gottlieb

ABSTRACT. The 2017 Annual Meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) was held in Amsterdam, the Netherlands, and was attended by rheumatologists, dermatologists, representatives of biopharmaceutical companies, and patients. As in previous years, GRAPPA members held a symposium for trainees to discuss their research in psoriatic disease with experts in the field. Other subjects featured during the annual meeting included a discussion of the history, clinical features, controversies, and immunogenetics of juvenile psoriatic arthritis; updates from working groups in Outcome Measures in Rheumatology and International Dermatology Outcome Measures; a discussion of the benefits and challenges of setting up a longitudinal psoriatic arthritis (PsA) database; 3 separate discussions of the effects of the microbiome on skin and joints in psoriasis and PsA; a discussion of options for assessing joints and entheses in PsA by ultrasonography and magnetic resonance imaging; an update on GRAPPA's research and educational projects; a discussion of patient centricity, including the incorporation of patient research partners (PRP) into psoriasis and PsA research and educational efforts, from GRAPPA's PRP; and a discussion of the GRAPPA-Collaborative Research Network's inaugural meeting. In this prologue, we introduce the papers that summarize that meeting. (J Rheumatol Suppl. 2018 June;94:1–3; doi:10.3899/jrheum.180129)

Key Indexing Terms:
PSORIASIS INTERNATIONAL DERMATOLOGY OUTCOME MEASURES
PSORIATIC ARTHRITIS GRAPPA OUTCOME MEASURES IN RHEUMATOLOGY

The 2017 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) was held in Amsterdam, the Netherlands. Currently, there are 933 worldwide GRAPPA members, including investigators in rheumatology and dermatology (n = 632), representatives of biopharmaceutical companies (n = 211), patient research partners (PRP; n = 25), and other members (n = 65). Reports of previous yearly meetings have been published elsewhere[1,2,3,4,5,6,7,8].

A Trainees Symposium was held prior to the annual meeting. Rheumatology and dermatology researcher-trainees from Europe, North America, and South America, who are current GRAPPA members or who were nominated by GRAPPA members, presented and discussed their studies with experts in the field. A total of 40 abstracts were submitted and ranked by a committee of reviewers. Six trainees with the highest-scored abstracts were invited to deliver oral presentations; all trainees presented posters that outlined key aspects of their research. Christopher T. Ritchlin (Rheumatologist, Rochester, New York, USA) and Wolf-Henning Boehncke (Dermatologist, Geneva, Switzerland) co-chaired the symposium in which GRAPPA members discussed the findings presented by trainees and suggested how trainees might further their current research projects[9].

In a symposium on juvenile psoriatic arthritis (JPsA), several GRAPPA members discussed the history, clinical features, controversies, and immunogenetics of this condition. Their discussion included reports of conflicting HLA associations in JPsA, with both HLA class I and II allele associations suggested. They also discussed the JPsA associ-

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As part of the supplement series GRAPPA 2017, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

Financial support to enable these meetings was provided in 2017 by AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Eli Lilly & Company, Novartis, Pfizer, and UCB. In addition, the Innovation Partners in 2017 were Mallinckrodt, LEO Pharma, and Sun Pharma.

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ations with alleles of *MEFV* and *NLRP3*, genes that cause monogenic autoinflammatory disorders. They recommended an increased collaboration between pediatric and adult physicians, and comparative research on these clinically related conditions[10].

The GRAPPA-Outcome Measures in Rheumatology (OMERACT) Psoriatic Arthritis (PsA) Core Set working group is in the process of selecting core instruments for PsA clinical trials. During the annual meeting, the first set of candidate instruments to be taken through the OMERACT Filter 2.1 instrument selection process was discussed: 66/68 swollen/tender joint count, Spondyloarthritis Consortium of Canada Enthesitis Index, patient's global assessment (GRAPPA and OMERACT formulations), Health Assessment Questionnaire–Disability Index, PsA Impact of Disease questionnaires 9 and 12, and Functional Assessment of Chronic Illness Therapy Fatigue[11].

GRAPPA members have shown great interest in developing a common GRAPPA database. To address this interest, GRAPPA included a symposium at its 2017 annual meeting to examine the concepts of registries and databases. At this symposium, examples of existing databases were reviewed, and their challenges and achievements were discussed[12].

In a symposium on the microbiome, the effects of the microbiome on the skin and joints in patients with psoriasis and PsA were discussed with particular reference to pathogenesis and treatment. It was concluded that a better understanding of microbe-host interactions could lead to novel diagnostic and therapeutic targets[13,14,15].

The International Dermatology Outcome Measures (IDEOM) psoriasis working group presented an overview of IDEOM's work to establish comprehensive psoriasis outcome measures. In addition, the working group discussed replacements for the Psoriasis Area and Severity Index (PASI) that can be used in clinical practice, including data that support the use of the physician's global assessment × body surface area measurement score as a PASI surrogate; the contribution of skin disease to composite measures of PsA; and the National Psoriasis Foundation's efforts to establish treat-to-target strategies for psoriasis care[16].

Recent work on outcome measures from the GRAPPA ultrasound and magnetic resonance imaging (MRI) working groups was summarized. The working groups discussed how recent advances in imaging, including ultrasound and MRI, allow for the accurate evaluation of the extent of inflammation and damage in the peripheral joints, spine, and entheses. The group concluded that the development and validation of outcome measures are critical steps in creating standardized evaluations of musculoskeletal inflammation and damage in psoriatic patients[17].

Members received updates on several ongoing educational and research efforts. Among them were updates on GRAPPA's continued education efforts worldwide; GRAPPA's continued research efforts, including the Biomarker Project, a collaborative research effort to identify and study biomarkers of joint damage; treatment recommendations, including recommendations and core principles related to biosimilars; efforts to update GRAPPA's Website and to create a GRAPPA smartphone application; and the Psoriasis and PsA Clinics Multicenter Advancement Network[18].

PRP held another session at the annual meeting to discuss their involvement within GRAPPA since the GRAPPA 2016 annual meeting, as well as their evolution as a group since their first formal attendance at the GRAPPA 2013 annual meeting. PRP were educated on the Core Outcome Measures for PsA Clinical Trials (COMPACT) study and participated in focus groups to evaluate the content validity and feasibility of selected patient-reported outcome measurements[19].

The GRAPPA-Collaborative Research Network (CRN) held its inaugural meeting over 2 days following the GRAPPA 2017 annual meeting. The GRAPPA-CRN aims to address gaps in the knowledge of the etiopathogenesis and management of psoriatic disease by using the large community of experienced investigators who are already collecting clinical phenotype data and biologic samples using validated techniques. The key immediate priorities to establish the CRN were discussed, and 4 CRN candidate flagship research areas were identified[20].

At the conclusion of the GRAPPA meeting, members discussed future action items in a business meeting. The next annual meeting will be held in Toronto, Canada, in July 2018.

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REFERENCES

1. Mease PJ, Gladman DD. Prologue: 2009 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). J Rheumatol 2011;38:522-5.
2. Mease PJ, Gladman DD. Prologue: 2010 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). J Rheumatol 2012;39:391-3.
3. Mease PJ, Gladman DD. Prologue: 2011 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). J Rheumatol 2012;39:2181-3.
4. Mease PJ, Boehncke WH, Gladman DD. Prologue: 2012 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). J Rheumatol 2013;40:1407-9.
5. Boehncke WH, Gladman DD. Prologue: 2013 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). J Rheumatol 2014;41:1194-6.
6. Boehncke WH, Gladman DD. Prologue: 2014 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). J Rheumatol 2015;42:1011-3.
7. Boehncke WH, Gladman DD, Helliwell PS. Prologue: 2015 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). J Rheumatol 2016;43:949-51.
8. Helliwell PS, Gladman DD, Gottlieb AB. Prologue: 2016 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). J Rheumatol 2017;44:658-60.
9. Furer V, Manasson J, Boehncke WH, Ritchlin CT. GRAPPA trainees

symposium 2017: a report from the GRAPPA 2017 annual meeting. J Rheumatol Suppl. 2018 June;94:4-10.
10. Zisman D, Stoll ML, Butbul Aviel Y, Mellins ED. Juvenile psoriatic arthritis: a report from the GRAPPA 2017 annual meeting. J Rheumatol Suppl. 2018 June;94:11-16.
11. Holland R, Tillett W, Ogdie A, Leung YY, Gladman DD, Callis Duffin K, et al. Content and face validity and feasibility of five candidate instruments for psoriatic arthritis randomized controlled trials: the PsA OMERACT Core Set Workshop at the GRAPPA 2017 annual meeting. J Rheumatol Suppl. 2018 June;94:17-25.
12. Gladman DD, Coates LC, Jadon DR, Tillett W, Mease PJ, Vis M. The benefits and challenges of setting up a longitudinal psoriatic arthritis database. J Rheumatol Suppl. 2018 June;94:26-9.
13. Thio HB. The microbiome in psoriasis and psoriatic arthritis: the skin perspective. J Rheumatol Suppl. 2018 June;94:30-1.
14. Scher JU. The microbiome in psoriasis and psoriatic arthritis: joints. J Rheumatol Suppl. 2018 June;94:32-5.
15. Gilis E, Mortier C, Venken K, Debusschere K, Vereecke L, Elewaut D. The role of the microbiome in gut and joint inflammation in psoriatic arthritis and spondyloarthritis. J Rheumatol Suppl. 2018 June;94:36-9.
16. Gottlieb A, Coates L, van Mens J, Armstrong AW, Merola JF. Report of the Skin Research Working Groups from the GRAPPA 2017 annual meeting. J Rheumatol Suppl. 2018 June;94:40-3.
17. Eder L, Aydin SZ, Kaeley GS, Maksymowych WP, Ostergaard M. Options for assessing joints and entheses in psoriatic arthritis by ultrasonography and MRI: how to move forward. J Rheumatol Suppl. 2018 June;94:44-7.
18. Callis Duffin K, FitzGerald O, Kavanaugh A, Mease PJ, Merola J, Ogdie A, et al. GRAPPA 2017 project report. J Rheumatol Suppl. 2018 June;94:48-51.
19. Goel N, O'Sullivan D, de Wit M, Lindsay CA, Bertheussen H, Latella J, et al. The patient research partner network matures: a report from the GRAPPA 2017 annual meeting. J Rheumatol Suppl. 2018 June;94:52-3.
20. Jadon DR, Chandran V, Stober C, Ogdie A, Armstrong AW, Duffin KC, et al. Proceedings of the 2017 GRAPPA Collaborative Research Network (CRN) meeting. J Rheumatol Suppl. 2018 June;94:54-61.

GRAPPA Trainees Symposium 2017: A Report from the GRAPPA 2017 Annual Meeting

Victoria Furer, Julia Manasson, Wolf-Henning Boehncke, and Christopher T. Ritchlin

ABSTRACT. At the 2017 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) in Amsterdam, the Netherlands, a trainees symposium was held. Rheumatology and dermatology trainees engaged in psoriasis or psoriatic arthritis research presented their work. This report briefly reviews 6 oral presentations and 25 posters presented at the meeting. (J Rheumatol Suppl. 2018 June;94:4-10; doi:10.3899/jrheum.180130)

Key Indexing Terms:

PSORIASIS	PSORIATIC ARTHRITIS	GRAPPA
DERMATOLOGIST	RHEUMATOLOGIST	TRAINEE

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) held this year's trainees symposium at its 2017 annual meeting in Amsterdam, the Netherlands. Following the tradition of the past 7 years, rheumatology or dermatology trainees from North America, South America, and Europe who are current GRAPPA members or who were nominated by GRAPPA members were invited to submit abstracts based on recent research in psoriatic arthritis (PsA) or psoriasis[1,2,3,4,5,6,7]. A total of 40 abstracts were submitted and ranked by a committee of reviewers. Six trainees with the highest-scored abstracts were invited to deliver oral presentations, and 25 trainees presented posters that outlined key aspects of their research. Dr. Christopher T. Ritchlin (Rochester, New York, USA) and Dr. Wolf-Henning Boehncke (Geneva, Switzerland) co-chaired the symposium in which GRAPPA members discussed the findings presented by trainees and suggested how trainees might further develop their current research projects.

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Oral Presentations

A new and simpler tool for global psoriatic arthritis assessment: simplified Composite Psoriatic Disease Activity Index (Maria Laura Acosta Felquer, Buenos Aires, Argentina)

Psoriatic arthritis (PsA) is a heterogeneous disease with involvement of multiple domains. The Composite Psoriatic Disease Activity Index (CPDAI) is a comprehensive clinical tool accounting for 5 disease domains, including peripheral joints [joint count and Health Assessment Questionnaire (HAQ)], skin [Psoriasis Area and Severity Index (PASI) and Dermatology Life Quality Index], spine [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Quality of Life], enthesitis [Leeds Enthesitis Index (LEI) and HAQ], and dactylitis (digit count and HAQ). The CPDAI tool is a complex measure to perform in daily practice. Dr. Felquer's study evaluated the performance of a simplified CPDAI (sCPDAI) based on joint count, digit count, enthesitis (LEI) assessment, skin (body surface area) assessment, and patient-reported outcomes of HAQ and BASDAI in a large PsA cohort from the Measuring Outcome in Psoriatic Arthritis database.

The study included 214 consecutive PsA patients (111 women, 52%) with a mean age of 49 ± 12 years. Seventy-six patients (35.5%) achieved minimal disease activity (MDA). Median (interquartile range) Clinical Disease Activity Index (CDAI), clinical Disease Activity in Psoriatic Arthritis (cDAPSA), CPDAI, and PASI were 7 (4–16), 10 (5–18), 3 (2–5), and 0.8 (0–3), respectively. A very good correlation was demonstrated between sCPDAI and most outcome measurements used in PsA [tender and swollen joint count, CPDAI, CDAI, cDAPSA, PASI, Psoriatic Arthritis Quality of Life, patient visual analog scale (VAS), and patient's and physician's global VAS]. Patients in MDA had significantly lower sCPDAI compared to patients not in MDA [mean (SD) 1.7 (1.4) vs 5.3 (2.8); $p < 0.0001$]. The sCPDAI area under the curve of the receiver-operating characteristic curve

for MDA was 0.87 (95% CI 0.83–0.92), with 4 as the best cutoff value to discriminate among patients not in MDA status (sensitivity: 68.42%; specificity: 87.67%; +LR: 5.55, –LR: 0.36). The study results suggest that sCPDAI performed well in a large PsA cohort, had good correlation with most PsA measurement tools, and discriminated especially well among patients in MDA versus non-MDA.

Whole spine and sacroiliac joints magnetic resonance imaging of patients with psoriatic arthritis: descriptive study of the spine and SIJ involvement in a cross-sectional large cohort (Victoria Furer, Tel Aviv, Israel)

Detection of axial disease in psoriatic arthritis (PsA) has important implications. The prevalence and distribution of spinal changes in PsA as detected by magnetic resonance imaging (MRI) is largely unknown. Dr. Furer evaluated acute and structural changes in spine and sacroiliac joints (SIJ) by whole-spine MRI performed in a consecutive clinical cohort of PsA.

The study included 96 consecutively recruited patients with PsA with a mean age of 50 ± 13 years (50 male, 52%), psoriasis/PsA duration of 19 ± 13.6 years/9 ± 8 years, Psoriasis Area and Severity Index (PASI) 3.9 ± 8.9, and Ankylosing Spondylitis Disease Activity Score with C-reactive protein 2.2 ± 1. Only 4.4% were carriers of the HLA-B27 antigen. The majority of patients (70%) reported back pain, whereas inflammatory back pain (IBP) was present in 30%. At the time of enrollment, 45% were treated with disease-modifying antirheumatic drugs and 35% with biologics. All patients underwent an MRI of the entire spine and SIJ. All MRI were evaluated by an experienced musculoskeletal radiologist blinded to the clinical data.

Active, structural, and total sacroiliitis were detected in 26%, 11.5%, and 37.5% of patients, respectively. Spinal spondyloarthritis (SpA; ≥ 3 bone marrow edema segments or ≥ 4 fatty vertebral corners) was demonstrated in 15.6% and involved the thoracic and lumbar segments, with a rare involvement of the cervical spine. Isolated spinal changes were detected in 2.1% of the cohort.

Presence of IBP by Assessment in Spondyloarthritis International Society criteria correlated with the prevalence of active sacroiliitis ($p = 0.024$) and SpA (axial/SIJ; $p = 0.003$). The extent of psoriasis severity (PASI) correlated with both SIJ and whole spine SpA changes ($p = 0.02$ for both). Sex differences or biologic therapy did not affect the prevalence of SIJ or spine involvement.

Active and structural sacroiliitis was more prevalent compared to typical spinal SpA changes in the presented cohort. In particular, there were few SpA changes in the cervical spine. The most prominent axial findings included fatty corners and syndesmophytes. IBP presence and extensive skin disease correlated with SpA axial and SIJ changes.

Treating psoriatic arthritis to target: comorbidities, nonadherence, and factors related to the public health system prevent escalation of therapy in real life (Manoela F. Ferreira, Porto Alegre-RS, Brazil)

A treat-to-target (T2T) strategy in psoriatic arthritis (PsA) results in better functional and activity measures compared to standard care. Yet the implementation of a T2T strategy in daily practice is often limited. Dr. Ferreira conducted an observational retrospective cohort study to determine the prevalence of patients achieving minimal disease activity (MDA) in a PsA clinic based at a public university hospital in Brazil and analyzed the factors that prevent the implementation of a T2T strategy.

Medical records of 74 patients with PsA (40 women, 54%) with 131 visits were reviewed from June 2016 through February 2017. The mean patient age was 57.9 ± 10.9 years, and the mean disease duration was 11.9 ± 9.5 years. Twenty-nine patients (39.2%) had current or previous use of biological therapy. MDA score data were available for 113 visits (86.2%), and MDA was achieved in 35 visits (31.0%). Twenty-five (36.2%) of the patients achieved MDA in at least 1 visit during followup. Although MDA was not achieved in 78 (69.0%) visits, optimization of therapy was done in only 33 (42.3%) of those visits. The main reasons treatment escalation was prevented were physician impression of remission (n = 24, 55.3%), physician impression of pain and global components of MDA overestimated by comorbid conditions [i.e., fibromyalgia, osteoarthritis, soft tissue disease, and PsA deformities (n = 16, 35.5%)], nonadherence to previous prescriptions (n = 8, 17.8%), delay in receiving drugs from public health insurance (n = 8, 17.8%), adverse events (n = 5, 11.1%), patient low cognitive level (n = 3, 6.7%), and patient refusal to escalate therapy (n = 2, 4.4%). When a physician-determined impression of remission was recorded, the Psoriasis Area and Severity Index (PASI) and swollen joint components of the MDA were reached in almost 90% of visits (n = 21, 87.5%).

The author concluded that rheumatologists were reluctant to escalate therapy in PsA even if patients were not in MDA if "objective" components of the MDA score, such as PASI and swollen joint count, were reached. Comorbid conditions, patient nonadherence to therapy, and factors related to the public health system influenced a tight control strategy in a real-life clinical practice.

Achieving pain visual analog scale target is the most difficult in patients with psoriatic arthritis (Flora Farkas, Dublin, Ireland)

Remission, defined by the minimal disease activity (MDA) criteria as MDA ≥ 5/7, or a more stringent definition of very low disease activity (VLDA) 7/7, is considered an appropriate therapeutic target in psoriatic arthritis (PsA). Dr. Farkas performed a study to identify which disease component targets of PsA were the most difficult to achieve.

A total of 258 patients with PsA and 431 visits were

included in the analysis. MDA ≥ 5/7 was achieved in 199 visits (46.2%). Of those in MDA ≥ 5/7, there were 147 visits (73.9%) that also achieved LDA (defined as MDA 5–6/7) and 52 (26.1%) that achieved VLDA. The percentage of visits in which patients achieved the targets of tender joint count ≤ 1/68, Psoriasis Area and Severity Index ≤ 1, or body surface area ≤ 3%, patient's global assessment activity visual analog scale (VAS) ≤ 2 cm, pain VAS ≤ 1.5 cm, and Health Assessment Questionnaire ≤ 0.5 was significantly lower in LDA compared to the VLDA group, but there were no differences for the other MDA components. Patients fulfilled the pain VAS ≤ 1.5 cm target in only 26.3% of visits where they met MDA 5/7, 61.2% with MDA 6/7, and 42.2% with LDA 5–6/7. Logistic regression analysis revealed that the pain VAS target had the strongest correlation with not achieving a VLDA state. The study identified that the remission target of pain VAS ≤ 1.5 cm was the most difficult to achieve.

GM-CSF+IFN-γ+ CD4+ and CD8+ T cell are enriched in synovial fluid of patients with psoriatic arthritis, while this subset is reduced in patient peripheral blood relative to healthy donors (Carmel Strober, Cambridge, UK)

Genetic studies have identified haplotypes containing *IL23R*, *IL12B*, *STAT3*, and *CARD9* variants that are associated with psoriasis and ankylosing spondylitis, and all function in the interleukin 23 (IL-23)/Th17 signaling pathway. In murine experimental autoimmune encephalomyelitis, IL-23 increases the pathogenicity of Th17 cells by upregulating granulocyte-macrophage colony-stimulating factor (GM-CSF) release, whereas IL-17 is not required for central nervous system inflammation. Dr. Strober investigated whether GM-CSF may be upregulated in psoriatic arthritis (PsA).

Study results revealed that in PsA synovial fluid, CD4+ T cells were significantly enriched with GM-CSF+ interferon-γ (IFN-γ)+ cells compared to peripheral blood (PB) CD4+ T cells ($p < 0.0001$). There were significantly lower proportions of GM-CSF+IFN-γ+ CD4+ and CD8+ cells in PsA patients' PB relative to healthy donors ($p < 0.05$). CD161 and IL-23R expression levels were comparable in GM-CSF+IFN-γ+ and GM-CSF+ cells, whereas CCR6 was lower for GM-CSF+IFN-γ+ cells ($p < 0.01$). GM-CSF release was higher and IFN-γ similar in patients with PsA relative to healthy donors. IL-17 release was increased ($p < 0.001$), but GM-CSF downregulated by exogenous IL-23 ($p < 0.05$). IL-23 also increased IL-17 ($p < 0.05$) and decreased GM-CSF ($p < 0.001$) using naive CD4+ cells differentiated in Th17-expanding conditions, and this was augmented by the addition of transforming growth factor-β. The study demonstrated co-expression of GM-CSF with IFN-γ in diseased joints, but not in PB of patients with PsA. The mechanism GM-CSF+IFN-γ+ upregulation in PsA joints warrants further investigation.

Interleukin 17 blockade, but not tumor necrosis factor-α inhibition, alters the gut microbiota in psoriatic arthritis (Julia Manasson, New York, New York, USA)

Dr. Manasson presented preliminary results from a study that evaluated the effects biologic therapies have on the intestinal microbiome. Subjects with psoriatic arthritis who received interleukin 17 (IL-17) inhibitors demonstrated a microbial dysbiosis compared to those who received tumor necrosis factor-α inhibitors. Similar perturbations were seen in wild-type mice exposed to anti-IL-17 antibody.

Poster Presentations

Lenno Anjos (Sao Paulo, Brazil) characterized the rates of nonalcoholic fatty liver disease (NAFLD) in psoriatic arthritis (PsA). A total of 114 adults with PsA (64 men, 56%) meeting the Classification Criteria for Psoriatic Arthritis (CASPAR) were evaluated (those with hepatitis C and significant alcohol intake were excluded). NAFLD was defined using abdominal ultrasound. The study population had a median age of 58 years and a median body mass index (BMI) of 31 kg/m^2. Of the subjects, 71% had polyarticular disease, 37% had axial disease, 16% had enthesitis, and 14% had dactylitis; 64% were found to have NAFLD, which also correlated with higher average BMI ($p < 0.001$), higher rates of dyslipidemia ($p = 0.002$), and lower rates of dactylitis ($p = 0.003$). These differences were maintained in the multivariate logistic regression. The author concluded that NAFLD is common in the PsA population and should be recognized by healthcare providers.

Sardar Bahadur (London, UK) used a novel hand radiograph scoring system to differentiate PsA from nodal osteoarthritis (NOA). The scoring system was based on interphalangeal joint, soft tissue, and bone features. The tests were based on radiographs collected from 48 subjects with PsA, 50 with NOA, and 1 with rheumatoid arthritis. Foot radiographs were also assessed. A musculoskeletal radiologist blinded to the clinical diagnoses identified 5 sets of normal hand radiographs and correctly identified the remainder of subjects using the scoring system. Rheumatology and radiology trainees correctly diagnosed 67% and 70% of radiographs, respectively. Foot radiographs showed fewer changes attributable to clinical disease. The author concluded that this novel scoring system appears to be effective at differentiating PsA from NOA and can be successfully taught to trainees and clinicians.

Peter Barnes (Portland, Oregon, USA) performed a retrospective analysis of patients with psoriasis and PsA to determine whether earlier treatment with tumor necrosis factor inhibitor (TNFi) leads to better quality-of-life outcomes. There was a statistically significant association between improvement in the Perceived Quality of Life-12 (PQoL-12) scale and timeliness of treatment, whereby a delay in treatment by 1 day resulted in a 4.4×10^{-4} change in PQoL-12 ($p = 0.007$). There were no statistically significant differences between the timing of TNFi initiation and the Routine Assessment of Patient Index Data 3, 12-Item Short

Form Health Survey, or body surface area affected by psoriasis. The author concluded that earlier initiation of TNFi had an effect on some quality-of-life measures.

Bashaar Boyce (Bath, UK) analyzed working patients from the Long-term Outcomes in PsA II UK-based multicenter prospective observational study to determine the validity of the Work Productivity and Activity Index Specific Health Problem (WPAI-SHP) in PsA. Of the 229 working patients, 177 (77.3%) had complete data available at baseline and 3-month followup. The mean age was 48 years and the median disease duration was 6 years [interquartile range (IQR) 2–12]. The mean change of presenteeism was –7.9 (SD 30.0), standard error of the mean 16.2, and standardized response mean –0.26. Among 105 patients (59.3%) who reported no change between baseline and followup, the mean change in WPAI was absenteeism 2.9 (SD 30.7), presenteeism 4 (26.5), productivity loss 7.7 (27.2), and activity impairment 1.9 (24.4). Using the health-based anchor method (mean change in score among 72 patients who reported improvement), the minimally important difference (MID) for improvement was absenteeism –6.1 (26.2), presenteeism –20.8 (28.2), productivity loss –21.7 (30.8), and activity impairment –27.2 (29.5). Using the receiver-operation characteristic curve method, the MID was presenteeism –5.0 [area under the curve (AUC) 0.75], productivity loss –11.3 (AUC 0.76), and activity impairment –25.0 (AUC 0.79). The author concluded that presenteeism and productivity loss were moderately correlated with clinical measures, while responsiveness had a small to moderate correlation among the group as a whole.

Casandra Buzatu (Bucharest, Romania) performed a cross-sectional study to estimate the prevalence of hyperuricemia and identify associated factors in patients with PsA. The study included a total of 120 patients with PsA (69 women, 57.5%), with a mean age of 54 ± 11.8 years and a mean disease duration of 7 ± 7.4 years. The median tender joint count was 2 (range 0–22), the median swollen joint count (SJC) was 0 (range 0–9), 24 (20%) had moderate/severe psoriasis, and 30 (25%) were treated with a biologic agent. Notably, 33 (27.5%) of subjects with PsA had hyperuricemia (defined as uric acid > 6.8 mg/dl), which was associated with obesity (1.86; p = 0.03), diabetes (4.95; p = 0.01), and ischemic heart disease (3.61; p = 0.05), but not skin psoriasis using multivariate analysis. The author concluded that hyperuricemia in PsA appears to correlate with metabolic syndrome rather than skin psoriasis.

Francisco Colombres (Tucuman, Argentina; poster presented by Alberto Berman) evaluated the work capacity and quality of life of patients with recent-onset PsA, defined as disease duration of less than 3 years. The study included 108 patients (57 men, 53%) who met CASPAR criteria, with a mean age of 48.4 ± 12.5 years and a mean disease duration of 17.6 ± 9.8 months. Only 4 (6.6%) were HLA-B27–positive. Disease was characterized by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of 4.81 ± 2.66, Bath Ankylosing Spondylitis Functional Index (BASFI) of 3.75 ± 2.70, Psoriatic Arthritis Quality of Life (PsAQoL) scale of 7.24 ± 6.44, Health Assessment Questionnaire (HAQ) of 0.72 ± 0.61, physician's global assessment (PGA) by visual numeric scale (VNS) of 3.76 ± 2.33, and pain assessment by VNS of 5.22 ± 2.98. The average number of work days lost because of PsA in the preceding 6 months was 8.6 ± 32.1, which was significantly associated with the presence of enthesitis, number of swollen joints, higher BASDAI and BASFI scores, higher PGA and pain assessments, and lower education level ($p < 0.0001$ for all). Five patients lost their jobs because of PsA. The linear regression model showed that lower PsAQoL significantly correlated with PGA ($p < 0.001$) and pain ($p < 0.01$). The author concluded that deterioration of work capacity was associated with disease activity variables and functional disability in this cohort of patients with early PsA.

Elena Generali (Milan, Italy) evaluated whether serum antibodies against human LL-37, a cationic protein that is overexpressed in psoriatic skin lesions, are involved in the pathogenesis of PsA. Samples from 35 patients with PsA meeting CASPAR criteria and 34 healthy controls were studied, with 32 subjects (94.1%) also having skin psoriasis and 5 (14.3%) also having axial disease. The median 28-joint Disease Activity Score (DAS28)-C-reactive protein (CRP) was 3.19 (IQR 2.78–3.94). Of the subjects, 10 (28.6%) were taking methotrexate and 9 (25.7%) were taking TNFi. Human (h) LL-37 was synthesized and levels of anti-hLL-37 IgM and IgG were determined using an ELISA developed by the research group. Anti-hLL-37 IgM antibodies were detected in 22 subjects with PsA (63%) compared to 2 (6%) controls ($p < 0.001$). From those PsA subjects who had IgM antibodies, 2 (9%) were in remission according to DAS28-CRP, compared to 5 (39%) who did not have IgM antibodies ($p = 0.036$). The author concluded that this is the first report suggesting an association of anti-hLL-37 antibodies with PsA and correlation with disease activity.

Catherine Hughes (London, UK) looked at quality of life and function in patients with PsA who were deemed to have minimal disease activity (MDA) compared to those who were not. Quality of life was assessed using the EQ-5D, and function was assessed using the HAQ–Disability Index (HAQ-DI). A total of 129 subjects with PsA were analyzed, with 83 (64%) not achieving MDA, 46 (36%) achieving MDA, and 19 (15%) achieving very low MDA (VL-MDA). The mean DAS28 scores were 3.88 ± 1.25 for non-MDA subjects, 1.86 ± 0.54 for MDA subjects, and 1.6 ± 0.46 for VL-MDA subjects. Of the patients who achieved MDA, 20% had an EQ-5D of 1 (which indicated perfect health), and 39% had a HAQ-DI of 0. The author concluded that disease state is an important factor for predicting quality-of-life outcomes.

Natsumi Ikumi (Dublin, Ireland) compared the different composite measures of MDA in patients with PsA, including

Disease Activity in Psoriatic Arthritis (DAPSA), clinical DAPSA (cDAPSA), Composite Psoriatic Disease Activity Index (CPDAI), and MDA. Cutoff points for remission were DAPSA ≤ 4, cDAPSA ≤ 4, CPDAI ≤ 2, and MDA 7/7. Quality of life was assessed by the PsAQoL. A total of 258 patients with PsA who met CASPAR criteria and 435 visits were evaluated. The average number of patient visits that achieved remission were 68 according to DAPSA, 122 according to cDAPSA, 144 according to CPDAI, and 52 according to MDA 52. Interestingly, pain visual analog scale (VAS) and patient's global assessment questionnaires had higher values in those achieving CPDAI remission compared to the other composite measures ($p < 0.01$). There were no significant differences in PsAQoL in any of the measures. DAPSA and cDAPSA correlated strongly with MDA (Pearson coefficient $r = 0.7$ for both pairings). CPDAI did not correlate with DAPSA and weakly correlated with cDAPSA ($r = 0.14$) and MDA ($r = 0.2$). The author concluded that MDA was the most stringent and CPDAI the least stringent remission measures. However, none of the measures predicted PsAQoL.

Anna Keszegpal (Leeds, UK) used a novel modified tape-stripping method to identify disease subtypes of psoriatic skin and predict treatment response. CuDerm adhesive tapes were used to remove the epidermis. Proteins were subsequently isolated and analyzed to quantify cytokines and chemokines. An example of this approach was presented in the context of a severely ill 38-year-old female patient who was hospitalized for generalized pustular psoriasis. Ten tapes were obtained from her lesional skin before and 5 days after the initiation of systemic therapy with prednisone, infliximab, and acitretin. Before therapy there were high levels of interleukin (IL)-1β (3.34 pg/μg compared to an average of 0.58 pg/μg in plaque psoriasis) and IL-8 (104.67 pg/μg compared to an average of 17.44 pg/μg in plaque psoriasis). These levels dramatically decreased with therapy. Other inflammatory markers, including S100A8/A9, CCL20, and GRO-α, were also elevated, but did not change with therapy. IL-18 expression actually increased post-therapy. The author concluded that tape stripping appears to be a promising diagnostic method to analyze epidermal inflammation with the potential to identify molecular disease subgroups and choose individualized therapy.

Fabiana B. Oliveira (Porto Alegre-RS, Brazil) reported on 4 years of multidisciplinary management of patients with psoriasis and PsA in an outpatient clinic by dermatology-rheumatology teams. The study evaluated 84 patients (46 women, 54.76%) with a mean age of 53.42 ± 12.18 years. A total of 162 consults were performed (52.2% were first-time consults). The most common reason for an appointment in the clinic was joint symptoms (n = 57, 67.9%). PsA was newly diagnosed in 19 (22.6%) and confirmed in 21 patients (25%), while 31 (36.6%) were diagnosed with other rheumatic diseases. The preexisting diagnoses were modified in 18 patients (21.4%) and treatments changed in 49 (53.3%). The author concluded that a multidisciplinary approach with collaborative dermatology-rheumatology teams improves the diagnosis and management of psoriatic disease.

Perez-Alamino Rodolfo (Tucuman, Argentina) analyzed the prevalence of subclinical atherosclerosis in psoriatic disease in an Argentinian cohort. The study included 32 psoriasis subjects, 33 PsA subjects meeting CASPAR criteria, and 42 healthy controls. The psoriatic subjects (30 women, 46%) had a mean age of 53.2 ± 14.9 years. The mean disease duration in patients with psoriasis was 17.8 ± 13.6 years versus 5.47 ± 3.6 years in PsA. The psoriatic disease subjects had an average BMI of 32.8 ± 6.4, average glucose of 101.9 ± 25.3 mg/dl, average Psoriasis Area and Severity Index (PASI) of 13.1 ± 8.1, and average DAS28 of 3.2 ± 0.8. Fifty-six subjects (86.1%) were taking disease-modifying antirheumatic drugs (DMARD) and 22 (33.8%) were taking biologic agents. Psoriatic patients had, on average, greater mean carotid artery intima-media thickness (IMT) compared to healthy controls (0.68 ± 0.24 mm psoriatic disease vs 0.49 ± 0.16 mm healthy; $p = 0.003$). No significant differences were found between psoriasis and PsA subjects. Atherosclerotic plaques were found in 9 (14%) subjects with psoriatic disease, which was similar to healthy controls. IMT values did not correlate with various measures of disease activity. The author concluded that subjects with psoriatic disease had a higher prevalence of macrovascular disease compared to healthy controls.

Ari Polachek (Toronto, Canada) used a questionnaire-based approach to analyze the effect of PsA on fertility and pregnancy outcomes. Subjects who were diagnosed with PsA before at least 1 pregnancy were compared to healthy controls. A total of 74 PsA and 74 healthy control subjects were studied. There were no significant differences in age, ethnicity, marital status, level of education, number of pregnancies, and number of children between the 2 groups. There were no statistically significant differences in fertility between PsA and control subjects, including diagnosis of infertility [30% PsA vs 22% control; p = not significant (ns)], failure to conceive in 1 year (25% PsA vs 15% control; p = ns), and use of fertility medications (5% PsA vs 1% control; p = ns). The pregnancy outcomes were also similar in both groups, including live births (76% PsA vs 76% control; p = ns), vaginal delivery (48% PsA vs 51% control; p = ns), gestational age (38.5 weeks PsA vs 38.3 weeks control; p = ns), birth weight (3.4 kg PsA vs 3.4 kg control; p = ns), rate of maternal and fetal complications, and the duration and rate of breastfeeding. Notably, 58% of cases reported favorable PsA disease activity (defined as no activity or improvement in disease) during pregnancy, though 50% subsequently had worsening disease activity within the first postpartum year. Similarly, 49% had favorable psoriasis disease activity during pregnancy, with 29% reporting worsening activity within the first postpartum year. The

author concluded that patients with PsA have similar fertility and pregnancy outcomes compared to healthy controls.

Reason Wilken (Sacramento, California, USA) characterized the glycosylation profiles (serum glycome and cell-surface glycome) of psoriasis and healthy subjects using a mass spectrometry–based multiple reaction monitoring method. The study analyzed 25 patients with psoriasis and 25 age- and sex-matched healthy controls, and 61 unique serum glycoproteins were identified that were differentially expressed in patients with psoriasis. Of these, 12 glycoconjugates could be used to distinguish disease state, and 34 glycoconjugates were differentially expressed following therapy with adalimumab, several of which were modifiers of lipoproteins. In addition, 20 glycoconjugates were found to correlate with psoriasis severity as measured by the PASI. The author concluded that glycans are likely contributors to the pathogenesis of psoriasis and may serve as biomarkers for presence of disease.

Alper Sari (Ankara, Turkey) characterized the clinical features, disease activity, and treatment choices for patients with PsA in a nationwide Turkish PsA registry (PsArt), comparing early-onset and late-onset PsA. The early-onset PsA group (< 60 yrs of age at diagnosis) included 911 subjects, whereas the late-onset PsA group (≥ 60 yrs of age at diagnosis) included 88 subjects. The mean age was 67.6 ± 5.3 years in the late-onset group compared to 44.9 ± 11.4 in the early-onset group. Mean disease duration was 2.7 ± 3.2 years in the late-onset group compared to 6.0 ± 7.0 years in the early-onset group ($p < 0.001$). Axial involvement was less frequent in the late-onset group (22.7% late vs 36.3% early; $p = 0.01$), though the median BASFI score was higher (34 late vs 20 early; $p = 0.007$). Patients with late-onset disease appeared to have higher disease activity as demonstrated by mean tender joint count (3 late vs 2 early; $p = 0.004$), mean SJC (1 late vs 0 early; $p = 0.04$), PGA (40 late vs 30 early; $p = 0.04$), pain VAS (50 late vs 40 early; $p = 0.03$), and erythrocyte sedimentation rate (29 mm/h late vs 20 mm/h early; $p = 0.001$). However, TNFi use was significantly lower in the late-onset group (15.7% late vs 34.7% early; $p = 0.001$). The author concluded that there were clinical differences between late-onset and early-onset PsA. Even though patients with late-onset PsA appeared to have more active disease, biologic therapies were less frequently used, which could be due to clinician concern for safety in the face of other comorbidities.

Danielle Tartar (Sacramento, California, USA) performed Hi-D multicolor fluorescence activated cell sorting (FACS) analysis at the single-cell level to characterize T cells in patients with PsA compared to age- and sex-matched healthy controls. PB mononuclear cells (PBMC) and synovial fluid mononuclear cells (SFMC) were collected from 10 patients with PsA and 15 healthy controls. rIL-23 induced activated IL-17+ T cells were generated and FACS was performed to identify activated memory effector CD11a+CD45RO+IL-17+ T cells. Analysis demonstrated that IL-23 increased the percentage of IL-17+ CD3+ T cells in the PBMC and SFMC populations in both patients with PsA and healthy controls, yet levels of IL-17+ CD3+ T cells were higher in patients with PsA compared to controls ($p < 0.001$). Patients with PsA demonstrated the following T cell phenotypes: αβ T cells (CD3+αβTCR+), γδ T cells (CD3+γδTCR+), mucosal associated invariant T (MAIT) cells (CD3+Vα7.2TCR+ CD161high), and natural killer T cells (CD1d/PBS-57 tetramer+CD3+). The dominant phenotype was αβ T cells (81.4 ± 2.8% in PBMC, 79.2 ± 0.9% in SFMC). MAIT cells were enriched in SFMC (3.3 ± 0.7%) compared to PBMC (1.2 ± 0.1%) cell populations and were predominantly CD8+. The author concluded that pathologic CD11a+CD45RO+IL-17+ T cells in PsA were composed of cells from both the innate and acquired immune system, which were dominated by the conventional Th17 αβ T cells.

Cagri Unal (Istanbul, Turkey) investigated the occurrence of neuropathic pain in PsA and how it associates with disease activity, sleep, fatigue, and quality of life. The study included 40 patients with PsA (27 women, 67.5%) who met CASPAR criteria, with a mean age of 50 ± 9.8 years and a mean disease duration of 99.7 ± 97.7 months. Mean DAS28 was 2.8 ± 1.2. The PainDETECT tool was used to identify neuropathic pain. Ambiguous neuropathic pain was identified in 4 (10%) subjects, and 12 (30%) had a PainDETECT score > 18. PsAQoL and the Pittsburgh Sleep Quality Index (PSQI) were significantly higher in patients with neuropathic pain compared to those without ($p < 0.05$). Further, PainDETECT correlated with several functional variables, including the PsAQoL (Spearman correlation $\varrho = 0.66$, $p = 0.0001$), PSQI ($\rho = 0.40$, $p = 0.01$), and Multidimensional Assessment of Fatigue (MAF; $\rho = 0.39$, $p = 0.01$). In addition, neuropathic pain became more likely with increasing age ($\rho = 0.40$, $p = 0.01$). The author concluded that a substantial number of patients with PsA have neuropathic pain, which appears to correlate with worse quality of life and sleep disturbances.

Firat Ulutatar (Istanbul, Turkey) analyzed how fibromyalgia (FM) affects PsA disease activity and functional status. A total of 40 patients with PsA (27 women, 67.5%) who met CASPAR criteria were enrolled in the study, with a mean age of 50 ± 9.8 years. Of the patients, 29 (72.5%) fulfilled 2010 American College of Rheumatology criteria for FM. Patients with FM had higher mean Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), PSQI, MAF, and PsAQoL ($p < 0.001$). Further, Fibromyalgia Impact Questionnaire (FIQ) scores correlated with MASES (Spearman correlation $\rho = 0.44$, $p = 0.01$), MAF ($\varrho = 0.47$, $p = 0.01$), and PsAQoL ($\rho = 0.50$, $p = 0.005$). There was no significant correlation between FIQ and DAS28. The author concluded that FM in patients with PsA is associated with poor quality of life, sleep disturbance, and fatigue.

Leonieke J.J. van Mens (Amsterdam, the Netherlands) conducted a cross-sectional study to assess the current clinical practice of defining residual disease and the subsequent

treatment decisions made in PsA. Among 142 patients with PsA, two-thirds (90/142) had residual disease activity, with half of these patients having moderate to high disease activity according to the Clinical Disease Activity Index. Of the patients, 74% with residual disease activity were being treated with either DMARD monotherapy or a first TNFi. In 23% of patients with residual disease, treatment adjustment was initiated. Treatment changes were considered less frequent in those taking a second TNFi. No differences were seen in disease activity and demographics between those with or without a treatment adjustment. Judgment by the physician and/or patient rather than objective hurdles to treatment intensification drove the decisions not to modify therapy. The author concluded that a majority of patients with residual disease had no treatment adjustment, which was not explained by comorbidity profiles or lack of treatment options.

Kim Wervers (Rotterdam, the Netherlands) described the effect of specific manifestations of PsA on health-related quality of life (HRQOL) in newly diagnosed patients. Data were collected at the time of PsA diagnosis on 399 patients (200 male, 50%), with a mean age of 50.2 ± 13.8 years from the Dutch South-West Psoriatic Arthritis Registry. HRQOL was assessed by 8 domains of the Medical Outcomes Study Short Form-36 (SF-36) questionnaire. The majority of patients (n = 317) first presented with peripheral arthritis, whereas other subtypes of disease were infrequent at initial presentation, including enthesitis (n = 34), axial disease (n = 9), and dactylitis (n = 39). Mean scores of SF-36 domains were lower than the Dutch reference population and similar across arthritis subtypes. Overall, the dactylitis subtype had higher SF-36 scores, and the enthesitis subtype had lower scores. Stratifying arthritis subtypes for the presence of enthesitis HRQOL decreased substantially for all groups with enthesitis across all domains. Severity of psoriasis and presence of dactylitis did not lead to significantly different SF-36 values compared to those who were not affected. Patients with chronic back pain had lower SF-36 scores, and no differences were found between those fulfilling Assessment of Spondyloarthritis international Society criteria for inflammatory back pain compared to those who did not. The author concluded that this study demonstrated a diminished HRQOL in PsA at the time of diagnosis compared to the Dutch reference population. The presence of enthesitis affected HRQOL more than the severity of joint involvement.

WanLi Zhou (Toronto, Ontario, Canada) examined the association between occupational-related mechanical factors and the severity of radiographic peripheral and axial joint damage in patients with longstanding PsA. A total of 307 patients with PsA (41.4% women) with a disease duration ≥ 10 years and an occupational history of paid occupations since age 18 were assessed for occupational-related mechanical exposures and physical activities. The mean age was 56.6 ± 11.3 years, and the mean disease duration was 21 ± 9.2 years. The mean duration in the workforce was 28.1 ± 12.5 years. At the time of the study, 42.2% of the patients were working. Multivariable regression analysis showed that prolonged exposure to repetitive hand movements ($\beta = 29.5$, $p = 0.007$) and occupations that required a higher level of finger dexterity ($\beta = 5.4$, $p = 0.005$) were associated with higher peripheral radiographic joint damage scores [by modified Steinbrocker Score (mSS)]. A borderline association was found between prolonged sitting time and lower mSS ($\beta = -11.9$, $p = 0.085$). With regard to axial damage, a borderline association was found between occupations that involved prolonged walking/running ($\beta = 4.4$, $p = 0.04$) and those that required a higher level of static strength ($\beta = 0.6$, $p = 0.052$) and higher modified Stokes Ankylosing Spondylitis Spine Scores. The author concluded that a high level of occupation-related mechanical stress was associated with increased radiographic peripheral joint damage. This finding supports the potential role of microtrauma in the pathogenesis of PsA.

The following abstracts were presented at the conference, but are not published here because of confidentiality of the work in progress. Mariana Araujo Barbosa (Rio de Janeiro, Brazil) presented the clinical investigation of fissured tongue in psoriatic patients. Claudia Camargo (Rio de Janeiro, Brazil) introduced the investigation of an immunogenetic association between geographic tongue and psoriasis through frequencies of *HLA* and *KIR* genes in a mixed population. Daiane Matana (Rio de Janeiro, Brazil) evaluated bone mineral density in patients with PsA. Pedro Secchin (Rio de Janeiro, Brazil) compared the histological Trozak's score before and after phototherapy in treatment of psoriasis.

GRAPPA members were enthusiastic in their appreciation of the trainees' work and encouraged them to continue their research. The next GRAPPA Trainees Symposium will be held in July 2018 in Toronto, Canada.

REFERENCES

1. Coates LC, Ritchlin CT. GRAPPA Trainees Symposium 2009: a report from the GRAPPA 2009 annual meeting. J Rheumatol 2011;38:526-9.
2. Ritchlin CT. GRAPPA Trainees Symposium 2010: a report from the GRAPPA 2010 annual meeting. J Rheumatol 2012;39:394-7.
3. Ash Z, Ritchlin CT. GRAPPA Trainees Symposium 2011: a report from the GRAPPA 2011 annual meeting. J Rheumatol 2012;39:2184-8.
4. Garg N, Touma Z, Ritchlin CT. GRAPPA Trainees Symposium 2012: a report from the GRAPPA 2012 annual meeting. J Rheumatol 2013;40:1413-8.
5. Szentpetery A, Johnson MA, Ritchlin CT. GRAPPA Trainees Symposium 2013: a report from the GRAPPA 2013 annual meeting. J Rheumatol 2014;41:1200-5.
6. Eder L, Tillett W, Ritchlin CT. GRAPPA Trainees Symposium 2014: a report from the GRAPPA 2014 Annual Meeting. J Rheumatol 2015;42:1016-20.
7. Milliken M, Generali E, Marin J, Ritchlin CT. GRAPPA Trainees Symposium 2015: a report from the GRAPPA 2015 annual meeting. J Rheumatol 2016;43:952-8.

Juvenile Psoriatic Arthritis: A Report from the GRAPPA 2017 Annual Meeting

Devy Zisman, Matthew L. Stoll, Yonatan Butbul Aviel, and Elizabeth D. Mellins

ABSTRACT. Juvenile psoriatic arthritis (JPsA), a subtype of juvenile idiopathic arthritis (JIA), constitutes 5% of JIA. The literature is inconsistent regarding features of JPsA, and physicians debate whether it is a distinct entity within JIA. A biphasic age of onset distribution has been noted. Early-onset disease is characterized by female predominance, small joint involvement, dactylitis, and positive antinuclear antibodies. Late-onset JPsA resembles adult-onset psoriatic arthritis (PsA), with male predominance, psoriasis, enthesitis, and axial disease. Recent studies report improved outcomes, likely due to the widespread use of traditional and biologic disease-modifying antirheumatic drugs. Conflicting HLA associations have been reported in JPsA, but notably both HLA class I and II allele associations are suggested. Similar to PsA cohorts, subjects with JPsA have a lower frequency of a protective interleukin 23R allele than controls or other JIA subtypes. Data in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) patient registry suggest the aggressive characteristics of JPsA: 24.6% of children have joint damage 4.6 years after symptom onset. Pediatric and adult PsA classification criteria define different JPsA cohorts within the registry and support a previous suggestion that the International League of Associations for Rheumatology criteria for JPsA may be overly stringent. Increased collaboration between pediatric and adult physicians and comparative research on these clinically related conditions are warranted. (J Rheumatol Suppl. 2018 June;94:11–16; doi:10.3899/jrheum.180131)

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History of JPsA

Juvenile psoriatic arthritis (JPsA) is one of 7 subtypes of juvenile idiopathic arthritis (JIA) and constitutes about 5% of JIA[1]. In 1962, Ansell and Bywaters published the first description of psoriasis in the context of a child with arthritis as part of a case series of what was then called Still disease (now JIA)[2]. In 1976, Lambert, *et al* published the first case series of JPsA in a retrospective evaluation of 43 children[3]. An important observation from this study is that arthritis can precede the development of psoriasis by as many as 15 years. These observations were echoed in a case series of 60 children published by Shore and Ansell in 1982, in which the authors also noted features present early in the disease that predicted the subsequent development of arthritis, including nail pits, an asymmetrical arthritis, and a family history of psoriasis[4]. The authors called for the development of criteria that would permit JPsA diagnosis without frank psoriasis. This call was answered by Southwood, *et al*, who proposed a JPsA definition that required arthritis plus either frank psoriasis or at least 2 minor criteria consisting of nail pits, dactylitis, a psoriatic-like rash, or a family history of psoriasis in a first- or second-degree relative[5]. These criteria, dubbed the Vancouver criteria, were validated in 1996[6]. At the time, under both the American College of Rheumatology and European League Against Rheumatology definitions, the juvenile arthritis umbrella was limited to categories currently referred to as oligoarticular, polyarticular, and systemic; psoriatic arthritis (PsA) and spondyloarthritis (SpA) were considered separate diseases[7]. This changed in 1997 when Petty, *et al* convened the International League of Associations for Rheumatology (ILAR) to generate a set of JIA criteria that included the psoriatic and SpA forms and that generated mutually exclusive categories. The first set of criteria was published in 1998[8], with a second and final version published

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As part of the supplement series GRAPPA 2017, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

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in 2004[9]. The current diagnostic criteria are summarized in Table 1, although it has been suggested that the ILAR criteria are overly stringent and result in missed JPsA diagnoses[10].

Clinical Features of JPsA

Clinically, JPsA is a heterogeneous condition that is generally an asymmetrical arthritis, which frequently extends from oligo- to polyarticular[6,11]. Both small and large joint involvement are present in the majority of patients[5,12,13], with axial disease seen in up to 25%[4] and dactylitis in 15–50%[4,5,12]. Extraarticular features are common. The initial descriptions required psoriasis as an entry criterion, which by definition caused it to be present in 100% of cases[3,4]. Descriptions published since the Vancouver criteria show psoriasis to be present in 25–60% of cases, with the remainder of cases diagnosed on the basis of minor criteria[5,12,13]. As noted above, psoriasis develops after the onset of arthritis in about 50% of cases[13], underscoring the value of the minor criteria in the diagnosis of this disorder. Additional extraarticular features include nail pits in 50–80% of cases[6,14], uveitis in 8–15%[3,5,6,14], and inflammatory bowel disease (IBD) in at most 1%[15]. Notably, most descriptions of uveitis in children with JPsA are consistent with the chronic uveitis characteristic of oligo- and polyarticular JIA, rather than the acute anterior uveitis associated with HLA-B27+ SpA[5,6,12]. Laboratory findings are generally unremarkable, although the antinuclear antibody (ANA) test may be positive in at least 50% of cases[5,6,16]. Radiographic studies can reveal a variety of abnormalities, including erosive disease, joint space narrowing, and sacroiliitis[3,11,17]. JPsA's outcome has improved considerably over the years following the introduction and widespread use of modern therapeutics. Initial studies revealed functional class III or IV outcomes in nearly one-third of patients[6,11], while more recently published descriptions have shown remission in over 50% of subjects[16,18,19]. There is very little treatment data specifically geared toward JPsA. The German BIKER registry included 127 children with JPsA who were treated with etanercept. This registry reported response rates and a safety profile similar to other JIA categories[20].

Table 1. Diagnostic criteria for juvenile psoriatic arthritis.

Inclusion criteria
Arthritis and psoriasis; OR
Arthritis plus at least 2 of the following:
Nail pits or onycholysis
Dactylitis
Psoriasis in a first-degree relative
Exclusion criteria
Arthritis in an HLA-B27–positive male beginning after the sixth birthday
AS, ERA, sacroiliitis with IBD, reactive arthritis or acute anterior uveitis, or a history of 1 of these disorders in a first-degree relative
The presence of IgM RF on at least 2 occasions at least 3 months apart
The presence of systemic JIA in a patient
Arthritis fulfilling ≥ JIA categories

Criteria are adapted from Petty, *et al*[9]. AS: ankylosing spondylitis; ERA: enthesitis-related arthritis; IBD: inflammatory bowel disease; IgM: immunoglobulin M; RF: rheumatoid factor; JIA: juvenile idiopathic arthritis.

Disagreements about JPsA

JPsA has provided pediatric rheumatologists with debate topics for many years. The 2 main topics on which there is no consensus are (1) Does JPsA constitute a homogeneous group of patients? and (2) Does JPsA exist as a distinct entity within JIA?

Does JPsA constitute a homogeneous group of patients? Many old and recent studies have shown a biphasic age of onset distribution in children with JPsA[3,5,15,16], directing the clinical manifestations. Children with early-onset disease tend to have similar features compared to other children with early-onset JIA, including increased predominance in females, positive ANA, and chronic uveitis; whereas children with onset older in life tend to have features suggestive of SpA, including axial disease, enthesitis, and less small joint disease[15,16,21]. Somewhat unexpectedly, dactylitis appears to be largely associated with early-onset disease, despite its association with adult PsA, as well[13,15].

Butbul Aviel, *et al* also showed that JPsA is a heterogeneous condition based upon clinical phenotype. Butbul Aviel, *et al* retrospectively evaluated 122 patients with JPsA, dividing their cohort into 4 main groups according to clinical manifestations that were comparable to the JIA definition suggested by the ILAR criteria: (1) oligoarticular (55%); (2) rheumatoid factor (RF)–negative polyarticular (29%); (3) RF-positive polyarticular (3%); (4) enthesitis-related arthritis (ERA; 13%). Of the 65 patients with oligoarticular onset, 32% eventually developed polyarticular disease[22]. The study found differences in the course, as well as the outcome, of the disease between the groups. The ERA group tended to be older and to have sacroiliac and hip involvement, whereas the polyarticular group had involvement of small joints of the hand, as well as wrist involvement. They also found that the patients in the polyarticular group had the worst outcomes because they took longer to achieve remission and were more likely to have contractures[22]. Therefore, JPsA is clearly a heterogeneous disorder, resembling in part the heterogeneity that has long been identified in its adult counterpart[23].

Does JPsA exist as a distinct entity within JIA? Another disputed issue is whether JPsA exists as a distinct entity within JIA. Only a few studies have addressed these uncertainties. Most of the studies have focused on comparing clinical data between groups, but later, new genetics data were published. Stoll, *et al* compared patients with JPsA and JIA with oligoarticular onset in the first 6 months and found that the JPsA group were older, more likely to have involvement of small joints and wrists, and more likely to extend to a polyarticular course[24]. Even when the comparison

was limited to children with age of onset under 5 years, similar clinical differences in joint distribution were observed. These data corroborated the study by Huemer, *et al*, which showed increased small joint and wrist disease among patients with oligoarticular JPsA as compared to oligoarticular JIA[12]. They were also corroborated by Ravelli, *et al*, whose findings showed that even ANA+ patients with JPsA tended to be older at disease presentation than the rest of their ANA+ JIA counterparts[25].

Contradictory data have been published. Butbul Aviel, *et al* used a case control study to compare 53 children with JPsA to 53 children with JIA: 32 with oligoarticular and 21 with polyarticular onset. Patients were matched by sex, age, date of diagnosis, and articular-onset pattern. There were no differences between the groups in the percentage of patients in the oligoarticular groups who extended to a polyarticular course or in the type of joint involvement. There were limited data on outcome, which suggests that time to first inactive disease with or without treatment was similar in both groups[26]. Therefore, it remains unclear whether there are clinical differences between oligoarticular/polyarticular JIA and oligoarticular/polyarticular JPsA.

Late-onset JPsA, however, appears to be substantially different from ERA. Compared to their counterparts with ERA, children with JPsA are less likely to carry the HLA-B27 marker[15,27], less likely to have sacroiliitis[15,27], less likely to have hip involvement[16,27], and as noted above more likely to have chronic, rather than acute, uveitis. Additionally, psoriatic features such as psoriasis and dactylitis were protective against the development of sacroiliitis[19,28], whereas hip involvement was a risk factor[28]. Therefore, JPsA is a heterogeneous condition in which children with early-onset are generally similar to children with early-onset JIA, yet children with late-onset disease are clearly distinct from their counterparts with ERA, but do resemble early-onset PsA.

We have likely gleaned as much information as we can from clinical studies. The next step is to use genetics to better delineate the differences between JIA and JPsA, as well as to define correspondences with adult inflammatory arthritides[29].

Immunogenetics of JPsA

Analysis of JPsA genetics has the potential to provide clues to the basis of the earlier onset of this disease compared to PsA and to suggest immune mechanisms in JPsA. There are several strategies for identifying JPsA genetic risk factors: testing for associations with HLA alleles, testing candidate genes identified by PsA genome-wide association studies (GWAS), and testing genes that cause monogenic disorders with phenotypic overlap with JPsA.

The first study of HLA association with JPsA, published by Ansell, *et al* in 1993[30] compared a cohort of 70 children diagnosed with JPsA to 310 controls, all from the United Kingdom. Of the 69 subjects with JPsA, 47 had a strong family history of psoriasis. A statistically significant association with HLA-B27 was observed. In a UK study that examined HLA class II associations across ILAR JIA subtypes, 37 patients with JPsA were analyzed[31]. The DRB1*01/DQA1*0101/DQB1*0501 haplotype conferred risk with an OR of 3.8 (95% CI 1.7–9.8). The most recent study by Hinks, *et al* used dense single-nucleotide polymorphism (SNP) typing of the HLA region to study 5043 JIA cases, 112 JPsA cases, and 14,390 controls[29]. No JPsA associations reached genome-wide significance ($p < 5 \times 10^{-8}$), but the following associations were observed: DRB1*08 ($p = 0.0003$); DQA1*0401 ($p = 0.0001$); DQB*1*0402 ($p = 0.0008$); HLA-B27 ($p = 0.003$); and HLA-C*0602 ($p = 0.008$). Age-stratified analysis was not reported. These results could reflect 2 subtypes of JPsA or independent genetic associations. Interestingly, the class I associations overlap with PsA associations, and the B27 and C*0602 alleles are associated with different phenotypes in PsA subjects[32]. Overall, to date, HLA association studies in JPsA found varied results, but do suggest both HLA class I and class II associations. Notably, a study of HLA associations in JIA from Murray, *et al* showed that having more HLA risk alleles predisposed the earlier onset of JIA[33].

Several mechanisms underlying HLA-B27 associations with rheumatic diseases have been hypothesized. The earliest hypothesis pertained to the ability of HLA alleles to present arthritogenic peptides[34]. However, additional hypotheses have emerged in recent years. One model emphasizes the propensity of HLA-B27 to misfold, causing endoplasmic reticulum stress; another emphasizes the recognition of B27 dimers by KIR3DL2 receptors on CD4+ Th17 cells[35]. For the associated DQ alleles, impaired interactions with accessory molecules that regulate peptide loading of HLA class II molecules have been observed and hypothesized to be a basis for presentation of cryptic epitopes of self-proteins, which break immune tolerance[36]. However, specific, mechanistic contributions of associated HLA class I or class II alleles to JPsA pathogenesis, in particular, have not yet been identified.

Using the approach of testing genetic associations observed for PsA, Hinks, *et al* studied 1244 JIA cases, 93 JPsA cases, and 5200 controls. The study found a negative association between JPsA and an SNP linked to the minor, protective allele of interleukin 23R (IL-23R), the IL-23 receptor gene[37]. This association was not observed in JIA overall or in other ILAR JIA subtypes. Testing the role of IL-23 in JPsA using pharmacologic blockade of the pathway has not been done to date, and further investigation is warranted.

The approach of testing genes that cause monogenic disorders with some phenotypic overlap with JPsA was used by Day, *et al*[38]. Genes causing hereditary periodic fever syndromes were tested in 950 UK white JIA cases, including 67 JPsA cases and 728 controls. The genes tested were *MEFV*

(familial Mediterranean fever), *NLRP3* (cryopyrin-associated periodic syndrome), *NOD2* (Blau syndrome), and *PSTPIP1* [pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome]. After correction for multiple testing, 2 SNP were significantly associated with JPsA: rs224204 in *MEFV* (pyrin), corrected p = 0.025, and rs3806265 in *NLRP3* (inflammasome component), corrected p = 0.04. These findings raise the possibility of an autoinflammatory basis to JPsA, although these associations have not been reported in PsA GWAS studies or in other JPsA cohorts to date. Another strategy worth considering is DNA sequencing of "JPsA" patients with severe phenotypes; this approach may reveal new monogenic diseases in which the causative gene affects pathways involved in JPsA pathogenesis.

Overall, work to date on JPsA biology, using genetic or other approaches, has been limited by the relative rarity of JPsA and the heterogeneity of JPsA. Collaborative efforts, leveraging the pediatric rheumatology research networks already established in many parts of the world, are needed to make progress in understanding the immunogenetics and immunopathogenesis of JPsA.

Lessons from a Large Database of Children with JPsA

The CARRA legacy registry contains disease-specific cohorts as defined by treating physicians from over 100 sites in the United States and Canada and collected data on 9450 children with pediatric rheumatic diseases between May 2010 and December 2013. Data from this cohort were retrospectively analyzed in light of the current understanding of PsA reflected in the pediatric and adult rheumatology literature[15].

The JPsA cohort of 361 children (4.9%) in this registry is in line with published data on the prevalence of this JIA subtype[5,39,40]. The majority were white (93.9%) and non-Hispanic (91.7%), with a female predominance (62%). Average age at symptom onset was 8.34 ± 4.57 years, with a delay of 1.04 ± 1.46 years from the first symptom to the first pediatric rheumatology appointment. The most common musculoskeletal manifestation was polyarthritis (55.3%), followed by oligoarthritis (44.7%), enthesitis (32.7%), dactylitis (29.7%), and sacroiliitis (16.7%). Dermatologic manifestations included rash in 66.8% and nail pitting in 37.5%, lower prevalence than those reported for PsA[41]. A possible explanation is that, in contrast to adult PsA, the articular manifestations precede skin manifestations in JPsA[5,16], and disease-modifying antirheumatic drugs (DMARD) may obscure their appearance. The prevalence of ANA (46.2%) and RF (4.7%) positivity in the cohort is in the range reported in other JPsA studies[4,5,16,22] and in studies of adult PsA[42]. Radiographic evidence of joint damage in 24.6% of the patients, an average of 4.6 years from the time of symptom onset, despite treatment with conventional and biologic DMARD (52.9%) is similar to the Southwood, *et al* findings in 1989[5] before the use of biological therapies. These data were confirmed in a report describing radiographic damage in patients with PsA that underscores the potential of psoriatic joint disease, in general, to cause joint damage[43] and the importance of early diagnosis and therapy.

Similar to PsA, the JPsA cohort exhibited asymptomatic axial involvement and no correlation between the presence of HLA-B27 and radiographic findings of sacroiliitis or the presence of clinical sacroiliitis[4,44]. At enrollment, half of the patients were treated with glucocorticosteroids (52.1%) and biological DMARD (52.9%), consisting mainly of antitumor necrosis factor-α agents. Conventional DMARD, the most common being methotrexate, were prescribed to 81.4% of the cohort[14].

The objective improvement in the clinical variables, including arthritis, psoriasis, nail pitting, dactylitis, and enthesitis, was not accompanied by improvement in scores on health-related questionnaires, highlighting JPsA's potential, as in PsA[45], to cause disability beyond the objective measurable variables.

The biphasic age of onset observed in the CARRA cohort, in line with previous JPsA studies[4,16], may suggest an interesting phenotype of disease presentation according to the age of symptom onset, probably influenced by genetic factors[46]. JPsA manifested in early childhood, predominantly as a disease of females with peripheral arthritis, followed by presentation of late-onset JPsA and early-onset PsA in males with SpA features, and a later presentation with a tendency to peripheral arthritis.

The recent conception of PsA in adults, in the spectrum of SpA including enthesitis and inflammatory back pain, is the main difference between the adult classification criteria for PsA (CASPAR criteria)[47] and the ILAR classification criteria[9] for JIA (Table 2). This concept was partially implemented by pediatric rheumatologists in the CARRA registry. In the JPsA cohort, 105 children who did not fulfill the ILAR criteria, but who were diagnosed by their treating physicians, exhibited fewer typical manifestations, such as dactylitis, nail pitting, and psoriasis. On the other hand, 52 additional patients who fulfilled CASPAR criteria for PsA but who were not classified in that way by their pediatric rheumatologists were identified in the entire JIA cohort. Those patients had less psoriasis but more features of SpA, such as enthesitis, inflammatory back pain, IBD, and uveitis. The evidence of asymptomatic enthesitis in patients with JPsA is additional support for this concept[48].

Awareness of these differences in classification is important to ensure that young adults with JPsA are successfully transferred from pediatric to adult care and that their evaluation and treatment are directed by an appropriate diagnosis, particularly as we learn more about the pathogenesis of JPsA.

To overcome the gaps, increased collaboration between pediatric and adult dermatologists and rheumatologists is needed, such as establishing a study group in the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

Table 2. Comparison between ILAR criteria for JPsA and CASPAR criteria for PsA.

Variables	ILAR Criteria[9]	CASPAR Criteria[47]
Rheumatic manifestations		
Arthritis	X	X
Enthesitis	Favors diagnosis of ERA	X
Axial spine	Favors diagnosis of ERA	X
Dactylitis	X	X
Skin manifestations		
Psoriasis	X	X
History of psoriasis		X
Family history	X first-degree relatives only	X first- or second-degree relatives
Nail involvement	X	X
Laboratory results		
RF positivity	Exclusion if 2 tests positive 3 mos apart	Exclusion
Radiologic manifestations		+
Genetics (*HLA-B27*)	Exclusion in male, if arthritis started after the age of 6	A patient must have inflammatory articular
Requirements	Arthritis 6 weeks duration and psoriasis or at least 2 of dactylitis, nail involvement, history of psoriasis	disease (joint, spine, or entheseal) with 3 points from the 5 categories:skin, nail, RF test, dactylitis, radiographic
Exclusions	Arthritis in an HLA-B27–positive male beginning after the sixth birthday. AS, ERA, sacroiliitis with IBD, Reiter syndrome or acute anterior uveitis, or a history of 1 of these disorders in a first-degree relative: (1) the presence of IgM RF on at least 2 occasions at least 3 mos apart; (2) the presence of systemic JIA in the patient.	None
Sensitivity		91.4%
Specificity		98.7%

ILAR: International League of Associations for Rheumatology; PsA: psoriatic arthritis; JPsA: juvenile PsA; CASPAR: ClASsification for Psoriatic ARthritis criteria; ERA: enthesitis-related arthritis; RF: rheumatoid factor; AS: ankylosing spondylitis; IBD: inflammatory bowel disease; IgM: immunoglobulin M; JIA: juvenile idiopathic arthritis.

(GRAPPA) organization. This study group may initiate validation of the CASPAR criteria across the age spectrum to reflect the current knowledge.

Patient Transition

Increased collaboration between pediatric and adult physicians is crucial to the successful transition of young adults with JPsA from pediatric to adult care. Beyond the discussion of clinical aspects, studies on the immunogenicity and pathogenesis of the psoriatic disease in the whole age spectrum may provide the biological knowledge needed to improve diagnosis and therapy.

REFERENCES

1. Beukelman T, Kimura Y, Ilowite NT, Mieszkalski K, Natter MD, Burrell G, et al. The new Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry: design, rationale, and characteristics of patients enrolled in the first 12 months. Pediatr Rheumatol Online J 2017;15:30.
2. Ansell BM, Bywaters EG. Diagnosis of "probable" Still's disease and its outcome. Ann Rheum Dis 1962;21:253-62.
3. Lambert JR, Ansell BM, Stephenson E, Wright V. Psoriatic arthritis in childhood. Clin Rheum Dis 1976;2:339-52.
4. Shore A, Ansell BM. Juvenile psoriatic arthritis—an analysis of 60 cases. J Pediatr 1982;100:529-35.
5. Southwood TR, Petty RE, Malleson PN, Delgado EA, Hunt DW, Wood B, et al. Psoriatic arthritis in children. Arthritis Rheum 1989;32:1007-13.
6. Roberton DM, Cabral DA, Malleson PN, Petty RE. Juvenile psoriatic arthritis: followup and evaluation of diagnostic criteria. J Rheumatol 1996;23:166-70.
7. Southwood TR, Woo P. Juvenile chronic arthritis. Baillieres Clin Rheumatol 1995;9:331-53.
8. Petty RE, Southwood TR, Baum J, Bhettay E, Glass DN, Manners P, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol 1998;25:1991-4.
9. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al; International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.
10. Stoll ML, Lio P, Sundel RP, Nigrovic PA. Comparison of Vancouver and International League of Associations for rheumatology classification criteria for juvenile psoriatic arthritis. Arthritis Rheum 2008;59:51-8.
11. Wesolowska H. Clinical course of psoriatic arthropathy in children. Mater Med Pol 1985;17:185-7.
12. Huemer C, Malleson PN, Cabral DA, Huemer M, Falger J, Zidek T, et al. Patterns of joint involvement at onset differentiate oligoarticular juvenile psoriatic arthritis from pauciarticular juvenile rheumatoid arthritis. J Rheumatol 2002;29:1531-5.
13. Stoll ML, Nigrovic PA. Subpopulations within juvenile psoriatic arthritis: a review of the literature. Clin Dev Immunol 2006; 13:377-80.
14. Sills EM. Psoriatic arthritis in childhood. Johns Hopkins Med J 1980;146:49-53.
15. Zisman D, Gladman DD, Stoll ML, Strand V, Lavi I, Hsu JJ, et al; CARRA Legacy Registry Investigators. The Juvenile Psoriatic Arthritis Cohort in the CARRA Registry: clinical characteristics,

classification, and outcomes. J Rheumatol 2017;44:342-51.
16. Stoll ML, Zurakowski D, Nigrovic LE, Nichols DP, Sundel RP, Nigrovic PA. Patients with juvenile psoriatic arthritis comprise two distinct populations. Arthritis Rheum 2006;54:3564-72.
17. Hamilton ML, Gladman DD, Shore A, Laxer RM, Silverman ED. Juvenile psoriatic arthritis and HLA antigens. Ann Rheum Dis 1990;49:694-7.
18. Flatø B, Lien G, Smerdel-Ramoya A, Vinje O. Juvenile psoriatic arthritis: longterm outcome and differentiation from other subtypes of juvenile idiopathic arthritis. J Rheumatol 2009;36:642-50.
19. Ekelund M, Aalto K, Fasth A, Herlin T, Nielsen S, Nordal E, et al; Nordic Study Group of Pediatric Rheumatology (NoSPeR). Psoriasis and associated variables in classification and outcome of juvenile idiopathic arthritis - an eight-year follow-up study. Pediatr Rheumatol Online J 2017;15:13.
20. Windschall D, Muller T, Becker I, Horneff G. Safety and efficacy of etanercept in children with the JIA categories extended oligoarthritis, enthesitis-related arthritis and psoriasis arthritis. Clin Rheumatol 2015;34:61-9.
21. Stoll ML, Punaro M. Psoriatic juvenile idiopathic arthritis: a tale of two subgroups. Curr Opin Rheumatol 2011;23:437-43.
22. Butbul Aviel Y, Tyrrell P, Schneider R, Dhillon S, Feldman BM, Laxer R, et al. Juvenile Psoriatic Arthritis (JPsA): juvenile arthritis with psoriasis? Pediatr Rheumatol Online J 2013;11:11.
23. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973;3:55-78.
24. Stoll ML, Nigrovic PA, Gotte AC, Punaro M. Clinical comparison of early-onset psoriatic and non-psoriatic oligoarticular juvenile idiopathic arthritis. Clin Exp Rheumatol 2011;29:582-8.
25. Ravelli A, Varnier GC, Oliveira S, Castell E, Arguedas O, Magnani A, et al. Antinuclear antibody-positive patients should be grouped as a separate category in the classification of juvenile idiopathic arthritis. Arthritis Rheum 2011;63:267-75.
26. Butbul YA, Tyrrell PN, Schneider R, Dhillon S, Feldman BM, Laxer RM, et al. Comparison of patients with juvenile psoriatic arthritis and nonpsoriatic juvenile idiopathic arthritis: how different are they? J Rheumatol 2009;36:2033-41.
27. Burgos-Vargas R, Vázquez-Mellado J. The early clinical recognition of juvenile-onset ankylosing spondylitis and its differentiation from juvenile rheumatoid arthritis. Arthritis Rheum 1995;38:835-44.
28. Stoll ML, Bhore R, Dempsey-Robertson M, Punaro M. Spondyloarthritis in a pediatric population: risk factors for sacroiliitis. J Rheumatol 2010;37:2402-8.
29. Hinks A, Bowes J, Cobb J, Ainsworth HC, Marion MC, Comeau ME, et al. Fine-mapping the MHC locus in juvenile idiopathic arthritis (JIA) reveals genetic heterogeneity corresponding to distinct adult inflammatory arthritic diseases. Ann Rheum Dis 2017;76:765-72.
30. Ansell B, Beeson M, Hall P, Bedford P, Woo P. HLA and juvenile psoriatic arthritis. Br J Rheumatol 1993;32:836-7.
31. Thomson W, Barrett JH, Donn R, Pepper L, Kennedy LJ, Ollier WE, et al; British Paediatric Rheumatology Study Group. Juvenile idiopathic arthritis classified by the ILAR criteria: HLA associations in UK patients. Rheumatology 2002;41:1183-9.
32. Winchester R, Giles J, Jadon D, Haroon M, McHugh N, FitzGerald O. Implications of the diversity of class I HLA associations in psoriatic arthritis. Clin Immunol 2016;172:29-33.
33. Murray KJ, Moroldo MB, Donnelly P, Prahalad S, Passo MH, Giannini EH, et al. Age-specific effects of juvenile rheumatoid arthritis-associated HLA alleles. Arthritis Rheum 1999;42:1843-53.
34. Benjamin R, Parham P. Guilt by association: HLA-B27 and ankylosing spondylitis. Immunol Today 1990;11:137-42.
35. Powis SJ, Colbert RA. Editorial: HLA-B27: the story continues to unfold. Arthritis Rheumatol 2016;68:1057-9.
36. Busch R, De Riva A, Hadjinicolaou AV, Jiang W, Hou T, Mellins ED. On the perils of poor editing: regulation of peptide loading by HLA-DQ and H2-A molecules associated with celiac disease and type 1 diabetes. Expert Rev Mol Med 2012;14:e15.
37. Hinks A, Martin P, Flynn E, Eyre S, Packham J; Childhood Arthritis Prospective Study-CAPS; BSPAR Study Group, et al. Subtype specific genetic associations for juvenile idiopathic arthritis: ERAP1 with the enthesitis related arthritis subtype and IL23R with juvenile psoriatic arthritis. Arthritis Res Ther 2011;13:R12.
38. Day TG, Ramanan AV, Hinks A, Lamb R, Packham J, Wise C, et al. Autoinflammatory genes and susceptibility to psoriatic juvenile idiopathic arthritis. Arthritis Rheum 2008;58:2142-6.
39. Berntson L, Fasth A, Andersson-Gare B, Kristinsson J, Lahdenne P, Marhaug G, et al; Nordic Study Group. Construct validity of ILAR and EULAR criteria in juvenile idiopathic arthritis: a population based incidence study from the Nordic countries. International League of Associations for Rheumatology. European League Against Rheumatism. J Rheumatol 2001;28:2737-43.
40. Hafner R, Michels H. Psoriatic arthritis in children. Curr Opin Rheumatol 1996;8:467-72.
41. Duarte GV, Faillace C, Freire de Carvalho J. Psoriatic arthritis. Best Pract Res Clin Rheumatol 2012;26:147-56.
42. Silvy F, Bertin D, Bardin N, Auger I, Guzian MC, Mattei JP, et al. Antinuclear antibodies in patients with psoriatic arthritis treated or not with biologics. PLoS One 2015;10:e0134218.
43. 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.
44. Williamson L, Dockerty JL, Dalbeth N, McNally E, Ostlere S, Wordsworth BP. Clinical assessment of sacroiliitis and HLA-B27 are poor predictors of sacroiliitis diagnosed by magnetic resonance imaging in psoriatic arthritis. Rheumatology 2004;43:85-8.
45. Taylor WJ. Impact of psoriatic arthritis on the patient: through the lens of the WHO International Classification of Functioning, Health, and Disability. Curr Rheumatol Rep 2012;14:369-74.
46. Queiro R, Tejón P, Coto P, Alonso S, Alperi M, Sarasqueta C, et al. Clinical differences between men and women with psoriatic arthritis: relevance of the analysis of genes and polymorphisms in the major histocompatibility complex region and of the age at onset of psoriasis. Clin Dev Immunol 2013;2013:482691.
47. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665-73.
48. Tuttle KS, Vargas SO, Callahan MJ, Bae DS, Nigrovic PA. Enthesitis as a component of dactylitis in psoriatic juvenile idiopathic arthritis: histology of an established clinical entity. Pediatr Rheumatol Online J 2015;13:7.

Content and Face Validity and Feasibility of 5 Candidate Instruments for Psoriatic Arthritis Randomized Controlled Trials: The PsA OMERACT Core Set Workshop at the GRAPPA 2017 Annual Meeting

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ABSTRACT. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)–Outcome Measures in Rheumatology (OMERACT) Psoriatic Arthritis (PsA) Core Set working group is in the process of selecting core instruments for PsA clinical trials. During a 2-h workshop and breakout group discussions at the GRAPPA 2017 annual meeting in Amsterdam, the Netherlands, participants discussed the first set of candidate instruments to be taken through the OMERACT Filter 2.1 instrument selection process: 66/68 swollen/tender joint count (66/68JC), Spondyloarthritis Consortium of Canada (SPARCC) enthesitis index, patient's global assessment (GRAPPA and OMERACT formulations), Health Assessment Questionnaire–Disability Index (HAQ-DI), Psoriatic Arthritis Impact of Disease (PsAID) questionnaires 9 and 12, and Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue. Based on the assessment of domain match (content and face validity) and feasibility according to the OMERACT instrument selection criteria, the working group recommends continuing with appraisal of construct validity and discrimination for 66/68JC, SPARCC, PsAID 9 and 12, HAQ-DI, and FACIT-Fatigue. In addition, it recommends repeating the OMERACT Filter 2.1 process for patient global instruments because of insufficient votes. Additional sets of candidate instruments for the PsA core instrument set will be evaluated in a similar process. (J Rheumatol Suppl. 2018 June;94:17–25; doi:10.3899/jrheum.180142)

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Psoriatic arthritis (PsA) randomized controlled trials (RCT) measure many outcomes to assess the safety and efficacy of interventions on multiple disease-specific manifestations[1]. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), in collaboration with Outcome Measures in Rheumatology (OMERACT), developed the first core set of domains to be measured in PsA RCT in 2006[2] to standardize the measurement of outcomes across PsA RCT. The PsA core domain set was updated to reflect both patient and physician priorities for PsA domains and to fulfill OMERACT Filter 2.0 criteria for domain selection[3,4,5]. OMERACT endorsed the updated PsA core domain set in 2016[6]. The updated PsA core domain set includes musculoskeletal (MSK) disease activity, skin disease activity, pain, patient's global assessment (PtGA), physical function, health-related quality of life, fatigue, and systemic inflammation.

The GRAPPA-OMERACT PsA working group is currently developing a PsA core instrument set to guide the selection of outcome measures for PsA RCT. The Core Outcome Measures for Psoriatic Arthritis Clinical Trials (COMPACT) study will guide this process and comprises several international work streams[7] with 2 key aims: to identify candidate instruments to measure the PsA core domain set, and to retain instruments that meet OMERACT Filter 2.1 standards (which rely on evidence-based appraisal of candidate instruments using criteria for content validity, feasibility, construct validity, and discrimination)[8]. Candidate instruments are being identified and their measurement properties appraised in systematic literature reviews by members of the working group[9] and additional evidence on construct validity and discrimination is being obtained from RCT and longterm observational studies (LOS). This evidence will be synthesized and a decision reached as to whether each instrument passes the Filter 2.1 for use in the target trials/research.

OMERACT Filter 2.1 Process Applied to PsA Core Instrument Selection

A comprehensive list of instruments used in PsA RCT and LOS was drafted in May 2017 based on systematic literature reviews and expanded upon with input from the working group (Supplementary Table 1, available with the online version of this article). The working group began the OMERACT instrument selection process with all participants at the GRAPPA 2017 annual scientific meeting with the aim of obtaining feedback on the OMERACT process and the content validity and feasibility of preselected instruments. Prior to the GRAPPA 2017 annual meeting, steering group members (n = 13) discussed the instruments, and a steering group survey was conducted to select 1 candidate instrument for each core domain (except pain, which is the focus of the Pain OMERACT working group; and skin disease activity, which is the focus of International Dermatology Outcome Measures).

At the GRAPPA core instrument set workshop, the working group began the first 2 steps of the instrument selection process. Six breakout groups discussed the following domain-instrument pairs: (1) MSK disease activity arthritis: 66/68 swollen/tender joint count (SJC/TJC)[10]; (2) MSK disease activity enthesitis: Spondyloarthritis Consortium of Canada (SPARCC) Enthesitis Index[11]; (3) PtGA: OMERACT[5] and GRAPPA[12] patient's global assessment visual analog scales; (4) physical function: Health Assessment Questionnaire—Disability Index (HAQ-DI)[13]; (5) health-related quality of life (HRQOL): Psoriatic Arthritis Impact of Disease questionnaires 9 and 12 (PsAID9, PsAID12)[14]; and (6) fatigue: Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue[15].

Four questions must be answered to ascertain whether an instrument has passed the OMERACT Filter 2.1. The assessment of face and content validity addresses the first question: Is the instrument a good match with the target domain? Participants [rheumatologists, dermatologists, patient research partners (PRP), industry representatives, rheumatology trainees] were asked for their opinions about whether there was sufficient overlap between the content of the domain intended to be measured and the information gathered by the instrument[7]. To illustrate domain content, the working group used domain definitions developed for the nominal group technique consensus meeting conducted as part of the PsA core domain set update[4]. These definitions, where relevant, were supplemented with patient quotes from international focus groups that described the domains from

the patient perspective[4]. Materials for use during the breakout groups included printouts of the instrument with instructions and an explanation of method of data collection and scoring, the domain to be measured, and additional domain content information such as patient descriptions so participants could compare and discuss domain content with instrument content (see Appendices 1, 2, and 3). In collaboration with PRP, the working group developed a booklet for PRP that contains OMERACT process information, domain definitions, and the instruments with details on their use and scoring. This booklet was distributed to PRP (n = 12) 2 weeks prior to the meeting to optimize PRP participation in the meeting. Twelve PRP participated in 2 OMERACT Webinars conducted and organized by Dr. Maarten de Wit, an expert in participatory research, prior to the annual meeting to familiarize PRP with the instrument appraisal and selection process. Further, in a 4-h premeeting workshop, PRP were introduced to the OMERACT instrument selection process and instrument psychometric property appraisal. PRP then assessed 4 instruments using the OMERACT scoring system.

GRAPPA Meeting PsA Core Instrument Set Workshop

The PsA Core Instrument Set Workshop was structured into an introductory plenary session (20 min), followed by 6 breakout group discussions (60 min), and ending with a plenary session that reported initial results from the breakout groups (30 min). At the introductory session, Drs. Ana-Maria Orbai, Alexis Ogdie, Katy Leung, and William Tillett presented the COMPACT study and the OMERACT Filter 2.1 process. They also demonstrated the use of the OMERACT domain match (encompassing content and face validity) and the feasibility questionnaires for the patient-reported outcomes, such as the PsAID instrument. Working group members (1 moderator and 1 rapporteur) then facilitated 6 breakout groups that each focused on 1 PsA domain and 1 corresponding instrument. Meeting participants, including patients (with 2 PRP per group), clinicians, trialists, methodologists, and payers were spread evenly among the groups. PRP helped facilitate discussion and voting during the breakout sessions.

In each breakout group, facilitators introduced the domain definition and its corresponding instrument. Participants were then asked to review and discuss the preselected instrument and individually appraise the instrument by completing paper-based OMERACT questionnaires that examine domain match and feasibility. These anonymous questionnaires were collected at the end, and votes for each aspect of domain match and feasibility were centralized by instrument. At the conclusion of each breakout group, a global vote was taken from participants (through show of hands) on whether the assigned instrument met the requirements for domain match and feasibility using the OMERACT traffic-light scoring system for a final assessment (quantity, consistency, and performance on that property) of the available evidence for each measurement property (green: instrument meets requirements to proceed with collecting evidence for additional measurement properties; amber: there is concern, caution, or weakness, but the instrument is good enough to go forward; red: should not proceed, does not meet content validity and/or feasibility standards)[5]. Traditionally, OMERACT consensus is defined as more than 70% agreement within a group. The working group also examined majority agreement, defined as more than 50% agreement within a group. These levels of agreement then determined the strength of the evidence for the overall conclusion on domain match and feasibility based on these votes [evidence for domain match and feasibility being stronger (green level) if consensus vs majority (amber level) agreement was achieved].

Workshop outcome. There were 145 participants across all breakout groups. Anonymized votes on content validity and feasibility are summarized across groups and instruments in Table 1 and Table 2, respectively. There was a breakout group discussion on PtGA; however, only 2 participants completed the anonymized questionnaires in this group (data not reported because of this small number).

Domain match. More than 70% of participants in the respective breakout groups endorsed the PsA instrument 66/68 SJC/TJC as a good match with the target domain of MSK disease activity arthritis, the FACIT-Fatigue as a good match with Fatigue, and the PsAID12 as a good match with HRQOL. More than 50% of participants voted for SPARCC as a good match with MSK disease activity enthesitis and PsAID9 as a good match with HRQOL. There were concerns about the redundancy of items for PsAID9 and FACIT-Fatigue, where no majority vote was achieved (all options < 50% agreement). In addition, the working group noticed a significant spread of opinions regarding instrument redundancy in all groups. There were also concerns over the adequacy of content ["Have all important elements been included (consider breadth and depth needed)?"] for SPARCC, HAQ-DI, and PsAID9. The voting results suggest that a better description of elements and technique for the 66/68 SJC/TJC may be helpful. There was consensus (> 70% voted yes) that response options were adequate for the SPARCC, PsAID9, PsAID12, and FACIT-Fatigue, and majority agreement (> 50% voted yes) for the 66/68 SJC/TJC and HAQ-DI. There was consensus (> 70% voted yes) that scoring was adequate for the 66/68 SJC/TJC and SPARCC, and majority agreement (> 50% voted yes) for the HAQ-DI. The vote was "uncertain" for adequacy of scoring (41–46% voted yes, 38–50% voted uncertain) for the PsAID9, PsAID12, and FACIT-Fatigue (Table 1).

Feasibility. There was consensus (> 70% voted yes) that the 66/68 SJC/TJC, HAQ-DI, and FACIT-Fatigue were easy to understand and majority agreement (> 50% voted yes) for both the PsAID9 and PsAID12. There was no consensus for SPARCC (note missing votes). Time to complete, method of

Table 1. GRAPPA meeting participants' ratings for OMERACT domain match questionnaires for each PsA instrument.

Participant Ratings for OMERACT Content and Face Validity Items (% votes)	66/68 SJC/TJC, n = 22	SPARCC, n = 17	HAQ-DI, n = 9	PsAID9, n = 22	PsAID12, n = 24	FACIT-Fatigue, n = 22
Domain match						
Yes	20 (***91***)	10 (**59**)	4 (44)	12 (**55**)	17 (***71***)	16 (***73***)
Uncertain	2 (9)	4 (24)	5 (**56**)	7 (32)	6 (25)	4 (18)
No	0	2 (12)	0	2 (9)	1 (4)	0
Missing	0	1 (6)	0	1 (5)	0	2 (9)
Not redundant						
Yes	13 (**59**)	9 (**53**)	5 (**56**)	9 (41)	8 (33)	6 (27)
Uncertain	7 (32)	4 (24)	4 (44)	3 (14)	2 (8)	7 (32)
No	2 (9)	3 (18)	0	9 (41)	12 (**50**)	8 (36)
Missing	0	1 (6)	0	1 (5)	2 (8)	1 (5)
Adequacy of content						
Yes	16 (**73**)	8 (47)	0	10 (45)	15 (**63**)	12 (**55**)
Uncertain	0	4 (24)	5 (**56**)	3 (14)	5 (21)	6 (27)
No	6 (27)	5 (29)	2 (22)	9 (41)	3 (13)	2 (9)
Missing	0	0	2 (22)	0	1 (4)	2 (9)
Adequacy of phrasing						
Yes	n/a	n/a	9 (***100***)	15 (**68**)	14 (**58**)	13 (**59**)
Uncertain	n/a	n/a	0	2 (9)	2 (8)	2 (9)
No	n/a	n/a	0	4 (18)	7 (29)	5 (23)
Missing	n/a	n/a	0	0	1 (4)	2 (9)
Elements described						
Yes	9 (41)	9 (**53**)	n/a	n/a	n/a	n/a
Uncertain	3 (14)	4 (24)	n/a	n/a	n/a	n/a
No	0	0	n/a	n/a	n/a	n/a
Missing	10 (45)	2 (12)	n/a	n/a	n/a	n/a
Adequacy of response options						
Yes	14 (**64**)	13 (***76***)	5 (**55**)	19 (***86***)	20 (***83***)	20 (***91***)
Uncertain	7 (32)	3 (18)	2 (22)	3 (14)	2 (8)	0
No	0	1 (6)	2 (22)	0	0	1 (5)
Missing	1 (5)	0	0	0	2 (8)	1 (5)
Adequacy of scoring						
Yes	18 (***82***)	13 (***76***)	6 (**67**)	10 (45)	11 (46)	9 (41)
Uncertain	4 (18)	3 (18)	1 (11)	11 (**50**)	9 (38)	10 (45)
No	0	1 (6)	2 (22)	1 (5)	1 (4)	2 (9)
Missing	0	0	0	0	3 (13)	1 (5)

Bold and italic indicate consensus (≥ 70%); bold only indicates majority agreement (≥ 50% but < 70%). GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; OMERACT: Outcome Measures in Rheumatology; PsA: psoriatic arthritis; SJC/TJC: swollen/tender joint count; SPARCC: Spondyloarthritis Consortium of Canada; HAQ-DI: Health Assessment Questionnaire–Disability Index; PsAID: Psoriatic Arthritis Impact of Disease; FACIT: Functional Assessment of Chronic Illness Therapy; n/a: not applicable.

administration, and equipment needs were found adequate (by 64–100% in each group) for all 6 instruments considered. The majority voted that cost, copyright, and availability in languages needed were feasible for 66/68 SJC/TJC, SPARCC, HAQ-DI, PsAID9, and PsAID12. Participants felt they needed more information on these aspects for FACIT-Fatigue.

A facilitated discussion was held of content/face validity and feasibility while addressing the OMERACT criteria. Important considerations from breakout group discussions are summarized for each instrument in Table 3. A show of hands vote that was taken at the end of the breakout group discussions is summarized in Table 4.

OMERACT process. Participants reported that the domain matching process was complex and that contextual/confounding factors (Table 3 shows examples) play an important role when instrument to domain match is assessed. Although some contextual/confounding factors are accounted for in clinical trials, it is important to carefully consider these at the stage of clinical trial design for each study population, intervention, and outcome of interest. Domain definitions and patient quotes, where applicable, were found generally helpful. In addition, for instruments in which technique was important (66/68 SJC/TJC), there was a suggestion to use demonstrational videos in addition to or instead of printed materials. When voting for domain match and feasibility,

Table 2. GRAPPA meeting participants' ratings for OMERACT feasibility questionnaires for each PsA instrument.

Participant Ratings for OMERACT Feasibility Items (% votes)	66/68 SJC/TJC, n = 22	SPARCC, n = 17	HAQ-DI, n = 9	PsAID9, n = 21	PsAID12, n = 24	FACIT-Fatigue, n = 22
Easy to understand						
Yes	19 (***86***)	7 (41)	7 (***78***)	12 (**57**)	14 (**58**)	17 (***77***)
Uncertain	1 (5)	2 (12)	2 (22)	6 (29)	3 (13)	2 (9)
No	0	0	0	3 (14)	5 (21)	2 (9)
Missing	2 (9)	8 (47)	0	0	2 (8)	1 (5)
Time to complete reasonable						
Yes	14 (**64**)	15 (***88***)	8 (***89***)	18 (***86***)	18 (***75***)	18 (***82***)
Uncertain	7 (32)	2 (12)	0	3 (14)	3 (13)	3 (14)
No	0	0	1 (11)	0	1 (4)	0
Missing	1 (5)	0	0	0	2 (8)	1 (5)
Method of administration feasible						
Yes	19 (***86***)	17 (***100***)	7 (***78***)	19 (***90***)	21 (***88***)	20 (***91***)
Uncertain	1 (5)	0	1 (11)	1 (5)	1 (4)	1 (5)
No	0	0	1 (11)	0	0	0
Missing	2 (9)	0	0	1 (5)	2 (8)	1 (5)
Costs feasible						
Yes	20 (***91***)	15 (***88***)	9 (***100***)	16 (***76***)	16 (**67**)	5 (23)
Uncertain	1 (5)	2 (12)	0	5 (24)	6 (25)	16 (***73***)
No	0	0	0	0	0	0
Missing	1 (5)	0	0	0	2 (8)	1 (5)
Copyright issues feasible						
Yes	13 (**59**)	10 (**59**)	7 (***78***)	15 (***71***)	14 (**58**)	7 (32)
Uncertain	3 (14)	1 (6)	1 (11)	4 (19)	6 (25)	14 (64)
No	3 (14)	3 (18)	1 (11)	2 (10)	2 (8)	0
Missing	3 (14)	3 (18)	0	0	2 (8)	1 (5)
Equipment needs feasible						
Yes	16 (***73***)	13 (***76***)	9 (***100***)	18 (***86***)	19 (***79***)	14 (**64**)
Uncertain	3 (14)	2 (12)	0	3 (14)	3 (13)	5 (23)
No	1 (5)	2 (12)	0	0	0	2 (9)
Missing	2 (9)	0	0	0	2 (8)	1 (5)
Availability in language/culture needed						
Yes	17 (***77***)	9 (**53**)	8 (***89***)	16 (***76***)	17 (***71***)	9 (41)
Uncertain	1 (5)	3 (18)	1 (11)	3 (14)	3 (13)	11 (50)
No	0	1 (6)	0	1 (5)	1 (4)	0
Missing	4 (18)	4 (24)	0	1 (5)	3 (13)	2 (9)

Bold and italic indicate consensus (≥ 70%); bold only indicates majority agreement (≥ 50% but < 70%). GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; OMERACT: Outcome Measures in Rheumatology; PsA: psoriatic arthritis; SJC/TJC: swollen/tender joint count; SPARCC: Spondyloarthritis Consortium of Canada; HAQ-DI: Health Assessment Questionnaire–Disability Index; PsAID: Psoriatic Arthritis Impact of Disease; FACIT: Functional Assessment of Chronic Illness Therapy.

participants asked whether the appraisal process would be best performed for each instrument individually versus examining multiple instruments concomitantly and comparatively that measure the same domain. Participants found the group discussion process essential in evaluating candidate instruments.

DISCUSSION

PsA is a rheumatologic disease manifesting with arthritis, enthesitis, dactylitis, axial arthritis, and skin and nail psoriasis. There is significant variability among individuals with PsA in their combination of clinical manifestations, response to treatment, prognosis, and reported life effect, which makes the comprehensive assessment of this disease especially important in both RCT and LOS. Disease heterogeneity and timeline for availability of instruments for disease-specific manifestations (e.g., dactylitis, enthesitis) has resulted in the use of a multitude of instruments and a relative lack of standardization across RCT and LOS. The updated PsA core domain set has now defined which core domains should be assessed routinely in RCT, and the GRAPPA-OMERACT PsA working group is developing a core instrument set to measure these domains.

At the GRAPPA 2017 annual meeting, the working group completed the first 2 steps of the OMERACT instrument selection process (domain match and feasibility) for 5 candidate instruments, and 145 GRAPPA members participated in a workshop and breakout group discussions. GRAPPA participants selected the first set of candidate instruments to undergo the OMERACT Filter 2.1 construct

Table 3. Important arguments for and against for each instrument as discussed by participants in breakout groups.

Breakout Group	Instrument	Pros	Cons
MSK disease activity — Arthritis	66/68 SJC/TJC	Standard of measurement of active joints in clinical trials	Potential for TJC to be confounded by comorbidities including osteoarthritis and fibromyalgia. Lack of clarity of definition. Time to perform.
MSK disease activity — Enthesitis	SPARCC	Relates well to pain at the entheses. Feasible and quick to perform.	May not reflect purely inflammatory pathology and may measure other disease aspects (tender joints, overlying psoriasis). Tenderness may reflect pain from other etiologies (fibromyalgia). Developed using imaging data; selected points may not be clinically tender sites. May be difficult/less exact in overweight patients.
Patient global	GRAPPA patient global	Assesses patient global over the preceding week. Defines "arthritis" and "skin disease" separately.	
	OMERACT patient global		Assesses patient global only at a single timepoint.
Physical function	HAQ-DI	Feasible—easy to administer Widely used PROM	May not be disease-specific and could be influenced by comorbidities. Questions may not be relevant to all patients. Not all aspects of physical function included (e.g., high-intensity physical activity). Could be complemented by performance-based physical function assessment.
Health-related quality of life/life effect	PsAID9 and PsAID12	Strong face and content validity from being developed through a robust, multinational mixed methods study with extensive patient involvement. Feasible, although could be improved with electronic version.	Questionnaire wording may confuse some patients, particularly the use of the term *psoriatic arthritis* when referencing skin disease. Does not include all aspects of domain, for example sexual function. May not be relevant for all cultures.
Fatigue	FACIT-Fatigue	Questions worded both ways (positive and negative) may increase responder attention and improve precision	Alternating positively and negatively worded questions can be confusing to respondents. Redundancy, with some questions identical except the term used to describe fatigue. Seems long, and scoring is complex. May not translate well in languages where there is only one word for fatigue. Interpretation of each question may be different across languages.

MSK: musculoskeletal; SJC/TJC: swollen/tender joint count; SPARCC: Spondyloarthritis Consortium of Canada; GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; OMERACT: Outcome Measures in Rheumatology; HAQ-DI: Health Assessment Questionnaire–Disability Index; PROM: patient-reported outcome measures; PsAID: Psoriatic Arthritis Impact of Disease; FACIT: Functional Assessment of Chronic Illness Therapy.

validity and discrimination appraisal: 66/68 SJC/TJC, SPARCC, PsAID9, PsAID12, HAQ-DI, and FACIT-Fatigue instruments. The limitations of this process were that only a limited number of instruments could be discussed within the time constraints, and only GRAPPA members who were present at the 2017 annual meeting could participate. Completion of anonymous domain match and feasibility questionnaires was limited for PtGA (n = 2), and the process will have to be repeated with the inclusion of more participants for these instruments. Importantly, following the workshop at the GRAPPA 2017 annual meeting, GRAPPA members will participate in the assessment and rating of additional PsA measurement instruments. Based on evidence from systematic literature reviews and RCT, a multistep consensus process with relevant participants reviewing the evidence will follow with the objective of selecting the

Table 4. Outcome of voting on domain match and feasibility for candidate outcome measurement instruments.

	Number Voting	Domain Match			Feasibility		
		Green	Amber	Red	Green	Amber	Red
MSK disease activity (arthritis)							
66/68 joint count	26	23	3	0	24	0	0
MSK disease activity (enthesitis)							
SPARCC enthesitis index	23	9	14	0	20	3	0
Physical function							
HAQ-DI	17	1	14	0	8	7	0
Health-related quality of life							
PsAID12	25	4	19	2	2	20	3
PsAID9	25	17	8	0	15	10	0
Fatigue							
FACIT fatigue scale	25	12	11	1	15	8	2

MSK: musculoskeletal; SPARCC: Spondyloarthritis Consortium of Canada; HAQ-DI: Health Assessment Questionnaire–Disability Index; PsAID: Psoriatic Arthritis Impact of Disease; FACIT: Functional Assessment of Chronic Illness Therapy.

optimal instruments to be included in the core instrument set for PsA clinical trials.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665-73.
2. Gladman DD, Mease PJ, Strand V, Healy P, Helliwell PS, Fitzgerald O, et al. Consensus on a core set of domains for psoriatic arthritis. J Rheumatol 2007;34:1167-70.
3. Tillett W, Eder L, Goel N, De Wit M, Gladman DD, FitzGerald O, et al. Enhanced patient involvement and the need to revise the core set — report from the Psoriatic Arthritis Working Group at OMERACT 2014. J Rheumatol 2015;42:2198-203.
4. Orbai AM, de Wit M, Mease PJ, Callis Duffin K, Elmamoun M, Tillett W, et al. Updating the Psoriatic Arthritis (PsA) Core Domain Set: a report from the PsA Workshop at OMERACT 2016. J Rheumatol 2017;44:1522-8.
5. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epidemiol 2014;67:745-53.
6. Orbai AM, de Wit M, Mease P, Shea JA, Gossec L, Leung YY, et al. International patient and physician consensus on a psoriatic arthritis core outcome set for clinical trials. Ann Rheum Dis 2017;76:673-80.
7. Tillett W, Orbai AM, Ogdie A, Leung YY, Strand V, Gladman DD, et al. GRAPPA-OMERACT initiative to standardise outcomes in psoriatic arthritis clinical trials and longitudinal observational studies. Ann Rheum Dis 2017 Jul 26 (E-pub ahead of print).
8. Boers M, Kirwan JR, Tugwell P, Beaton D, Bingham CO III, Conaghan PG, et al. The OMERACT Handbook. [Internet. Accessed February 8, 2018.] Available from: www.omeract.org/resources
9. Hojgaard P, Klokker L, Orbai AM, Holmsted K, Bartels EM, Leung YY, et al. A systematic review of measurement properties of patient reported outcome measures in psoriatic arthritis: A GRAPPA-OMERACT initiative. Semin Arthritis Rheum 2017 Sep 9 (E-pub ahead of print).
10. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum 1993;36:729-40.
11. Maksymowych WP, Mallon C, Morrow S, Shojania K, Olszynski WP, Wong RL, et al. Development and validation of the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index. Ann Rheum Dis 2009;68:948-53.
12. Cauli A, Gladman DD, Mathieu A, Olivieri I, Porru G, Tak PP, et al. Patient global assessment in psoriatic arthritis: a multicenter GRAPPA and OMERACT study. J Rheumatol 2011;38:898-903.
13. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. J Rheumatol 1982;9:789-93.
14. Gossec L, de Wit M, Kiltz U, Braun J, Kalyoncu U, Scrivo R, et al. A patient-derived and patient-reported outcome measure for assessing psoriatic arthritis: elaboration and preliminary validation of the Psoriatic Arthritis Impact of Disease (PsAID) questionnaire, a 13-country EULAR initiative. Ann Rheum Dis 2014;73:1012-9.
15. Cella D, Lai JS, Chang CH, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer 2002;94:528-38.

APPENDIX 1. Patient quotes from international focus groups describing their experience of fatigue and psoriatic arthritis.

Definition: Experiencing fatigue, tiredness, lack of energy, feeling worn out or exhausted.

Fatigue

- *During the day I feel like sleeping, in the morning, and if I allow myself to and don't have anything to do, I go to sleep, but the tiredness is as though I'd been working hard. At times I cry because I want to do things, I'm used to doing my housework. I do it, but it's not like it was before. It wears me out a lot. I get tired. (Brazil)*
- *There are two sorts of fatigue, the physical fatigue originating from the pain and then you have the mental and emotional fatigue. For instance, the people around you, like your friends and family, they know it but do not fully understand it. You always have to pretend to be cheerful. (France)*
- *When I'm having a flare or when I'm just generally not doing better, not under control or need an adjustment in my medicine the fatigue is a lot worse, and I can just tell a difference. I just feel more tired or I don't sleep as well and when I don't sleep as well I will ache the next day too, just like my joints that have activity will hurt more, I just will always feel tired, and I could come home from work and go right to bed. That's not like me, I'm a very active person. (USA)*
- *I think everyone is suffering from fatigue, from whether or not there is understanding and you can't do some things. That I find myself very difficult and if you're used to wanting everything and doing everything you want, you never look exactly for how far you can go. And then you go too far. So you always have regrets afterwards and you think, oh I will pay better attention next time. But you don't do that, you just keep going on. Because if I would not do that then I would feel very weird in life. So you just keep going on. I think everyone actually does that with such a disease. (Netherlands)*

APPENDIX 2. FACIT fatigue tool and scoring guidelines.

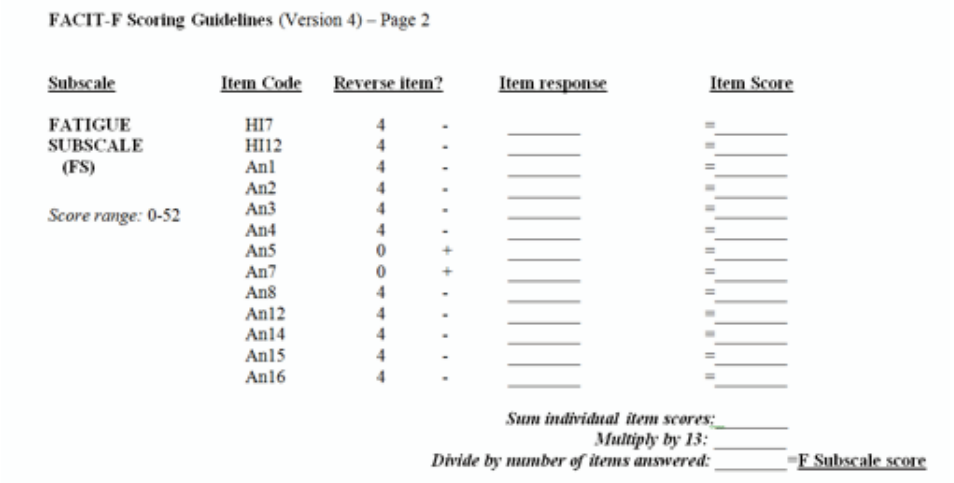
Domain: Fatigue

Definition: Experiencing fatigue, tiredness, lack of energy, feeling worn out or exhausted

Tool: FACIT-Fatigue, PROMIS Short Form v1.0 - Fatigue 13a (FACIT-Fatigue)

How the tool is used: This is a patient-reported outcome. The patient completes the questionnaire. Item response values in the short form are logged as below under Item response and the operation is performed (the item response is subtracted from 4, except for items An5 and An7, the item response is kept as is). Item scores are calculated as below and added together to obtain the raw score. This is then multiplied by 13 and then divided by the total number of answered item (see scoring table below). The score range is 0-52. Higher scores mean less fatigue.

Scoring[1]



FACIT-F Scoring Guidelines (Version 4) – Page 2

Subscale	Item Code	Reverse item?		Item response	Item Score
FATIGUE SUBSCALE (FS)	HI7	4	-	_____	=_____
	HI12	4	-	_____	=_____
	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
Score range: 0-52	An3	4	-	_____	=_____
	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 13: _____
Divide by number of items answered: _____ =F Subscale score

Important: the FACIT-Fatigue can now also be scored as a PROMIS instrument using T scores referenced to US population norms (see PROMIS Fatigue 7a).

PsA: psoriatic arthritis; FACIT: Functional Assessment of Chronic Illness Therapy; PROMIS: Patient Reported Outcomes Measurement Information System; FS: fatigue subscale.

1. Cella D, Lai JS, Chang CH, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer 2002;94:528-38. Available from: www.FACIT.org (scoring available upon registration).

APPENDIX 3. FACIT Fatigue Scale (Version 4).

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Somewhat	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

The Benefits and Challenges of Setting Up a Longitudinal Psoriatic Arthritis Database

Dafna D. Gladman, Laura C. Coates, Deepak R. Jadon, William Tillett, Philip J. Mease, and Marijn Vis

ABSTRACT. The members of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) have shown great interest in developing a common GRAPPA database. To address this interest, GRAPPA included a symposium at its 2017 annual meeting to examine the concepts of registries and databases. At this symposium, examples of existing databases were reviewed, and their challenges and achievements were discussed. (J Rheumatol Suppl. 2018 June;94:26–9; doi:10.3899/jrheum.180132)

Key Indexing Terms:
DATABASES PSORIASIS PSORIATIC ARTHRITIS REGISTRIES PROGNOSIS GRAPPA

Psoriatic arthritis (PsA) is a complex condition characterized by a variety of clinical manifestations and disease courses. As with other similar conditions, the best way to understand the course of disease and patient prognosis is through observational cohort studies. These studies depend on the prospective collection of data on a large number of patients followed according to standard protocols[1]. At the GRAPPA 2017 annual meeting in Amsterdam, the Netherlands, examples of existing databases were reviewed and their challenges and achievements were discussed.

Dr. Dafna D. Gladman (Toronto, Ontario, Canada) discussed the differences between registries and cohorts. She stated that there are several types of registries, including administrative registries, registries for clinical trials, registries for genetic studies, registries for biologics, and registries for longitudinal observational studies.

Administrative registries are set up for administrative purposes to record patients with individual diagnoses and usually do not include detailed information about individual patients or their disease course. Some contain information on medications, hospitalizations, and healthcare use. Moreover, the validity of the diagnosis is often unproven. Registries for clinical trials record patients with the disease in question and include only the minimum information necessary to determine whether a patient is eligible for a clinical trial. Registries for genetic studies include patients with a particular disease (and usually also healthy controls) and minimal disease process information, but detailed genetic analyses information. Registries for biologics usually include only the minimum information necessary to determine therapy response and any particularly adverse events that relate to the therapy. Registries for longitudinal observational studies usually include more detailed information and are generally considered databases as opposed to registries (Table 1). Compared to clinical trials, longitudinal databases include all patients, record all drugs, provide longterm observation with a large sample, have inclusive information, and record all possible outcomes. Thus, databases allow the prospective collection of data from a large number of patients and use standardized protocols, including clinical, laboratory, imaging, and genetic data. These data are collected over a long observation period, which allows for varied presentations and courses to be analyzed. In addition, databases require computer tracking of all information. This allows for the description of disease course and longterm medication complications, the understanding of pathogenesis, and the study of associations between disease course and drug therapy. In addition, this provides insight into disease progression and allows researchers to plan for future trials.

To gain the most benefit from databases and to be able to

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As part of the supplement series GRAPPA 2017, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

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Table 1. Information collected in different registry types.

Type of Registry	Information Collected
Administrative	Demographic
Clinical trials	Demographic plus some clinical information, especially drugs
Genetic studies	Proband and family information including enough details to define a phenotype, together with genetic information
Biologic registries	Demographic, clinical, and therapeutic information to determine response and adverse events
Cohort database	As much detail as possible to follow disease progression and identify new features

replicate or increase the power of specific observations, it is important that similar registries have the same information collected in a similar way. Thus, clinical and laboratory assessment should be confirmed to be similar and the consistency of variables must be assured. The actual platform need not be the same as long as harmonization between items is confirmed. Whatever database platform is used, it must allow for the easy transfer of data to a statistical system for data analysis.

It is important to avoid selection bias and demonstrate internal and external validity. Methods of observation and measurement must be clearly defined, and complete followup should be attempted to avoid information bias. It is also important to consider confounding factors such as time and intervention, although these may be overcome by design and analysis.

Dr. Gladman provided an example of the database from the University of Toronto Psoriatic Arthritis Program. The Toronto cohort currently includes 1450 patients and has been operating since 1978. Patients are assessed at 6- to 12-month intervals according to a standard protocol[2]. The reliability of joint assessment has been proven through a number of studies[3,4], and the radiographic method has also been proven to be reliable[5]. In addition, patients lost to followup and those followed regularly had similar disease characteristics at presentation[6].

Dr. Gladman highlighted the challenges of setting up a computer database, including quality assurance, data entry costs, issues with exporting data for statistical analysis, and the large number of staff required to maintain a database. Even with these challenges, the database provided the substrate for many investigations.

Current and Proposed PsA Cohorts

Dr. Marijn Vis (Rotterdam, the Netherlands) discussed the Dutch cohort of PsA, which is composed of 40 rheumatologists from 11 hospitals in the southwest of the Netherlands. The Dutch cohort's mission is to improve care for patients with PsA through education, research, and standardization. To set up their database, the Dutch cohort involved rheumatologists and patients with unmet needs who set up a clinical and science committee. Members contributing to the cohort own their own data. If possible, laboratory results, medication, and other data are taken directly from the hospital data warehouse, with patient questionnaires completed online. These data are all imported into 1 database. Data warehouses are used to store data from the hospitals' electronic patient files, and data collection is currently semiautomatic. To date, there are over 500 patients included in this database. In addition to the scientific use of data, the data will also be used, together with the automatic data import, to create a support tool for clinical care. The aim is to develop a decision-support system to assist physicians in using the appropriate treatment for the right patient based on the information collected in the database.

Drs. Laura C. Coates (Oxford, UK), William Tillett (Bath, UK), and Deepak R. Jadon (Cambridge, UK) presented a collaboration from the United Kingdom that will establish a cohort with embedded trials using a new methodology. This cohort will recruit patients from Oxford, Bath, and Cambridge starting in 2018. The Trials within Cohorts (TWiCs) or cohort multiple randomized controlled trial design will be used and was first published in 2010. This method recruits a central cohort having "treatment as usual" with regular observations and then adds pragmatic trials of alternative therapies. Eligible patients for trials are identified in the cohort and randomized to the offer of an intervention or to remain as controls in the cohort.

This design is particularly useful for open-label efficiency comparisons of therapeutic interventions with "treatment as usual" as the comparator. It is ideal for chronic conditions and where expensive desirable treatments are being tested. It allows robust generalizability from studies to routine healthcare, avoids attrition and disappointment bias from controls in open-label studies because patients only receive information relevant to their care, aids recruitment to trials, allows routine collection of longterm outcomes, and increases efficiency with multiple trials within 1 cohort[7].

In collaboration, members of the group are establishing a cohort of patients with early PsA who will all receive step-up treatment guided by a treat-to-target (T2T) approach. This will form the central cohort and will collect outcome data on a real-world feasible T2T model. At present, 2 interventional trials are planned: the first in mild PsA with low disease effect in which patients will not be prescribed the usual disease-modifying therapy, and the second in moderate-severe PsA in which patients will be offered more aggressive therapy.

A number of TWiCs studies are currently running across Europe with the majority in the oncology field. The UK cohort study will be the first in rheumatology and also one of the first TWiCs studies testing investigational medicinal products. This has required appropriate liaison with regulators during protocol development. There are chal-

lenges, including ethical and good clinical practice issues with consent, and that data collection must balance the robustness necessary for clinical trials and feasibility for regular clinic visits. Many people are unfamiliar with the TWiCs concept, which has made it important to connect and educate university staff, charity and industry funders, clinical trials units, and ethics and medicines regulatory authorities.

In Oxford, the cohort will be new and has been established specifically as a TWiCs study. In Cambridge, the cohort is new. In Bath, the cohort is preexisting. Discussions among the 3 centers have aligned outcomes and timepoints for data collection to allow this collaboration.

Dr. Jadon is harmonizing a group of 750 PsA cases, historically looked after by 10 consultants at the Addenbrooke's Hospital, into a single cohort looked after in a dedicated PsA service that started in 2015. Using the EPIC platform, clinical data are collected to an electronic patient record system. In late 2017, electronic tablets will be used to collect patient-reported outcome measures (PROM) in the clinic waiting area and from home. The cohort includes both inception patients and prospective, established PsA patients. The program includes a consultant, research fellow, resident, research nurse, and PsA specialist nurse. The program takes direct referrals from general practitioners, dermatologists, gastroenterologists, ophthalmologists, and internal referrals. All patients undergo a series of PROM according to a protocol, examination indices, imaging, and laboratory tests. Patients have the opportunity for education and counseling about their condition, as well as management by the PsA specialist nurse and doctors. They also have the opportunity to attend 6 monthly patient and family education evenings hosted by Dr. Jadon.

In keeping with GRAPPA recommendations for the management of PsA[8], multispecialty working has been a tenet of providing a holistic PsA service. In 2016, a monthly dermatology-PsA multidisciplinary team (MDT) meeting, 2 monthly inflammatory bowel disease (IBD)-spondyloarthritis (SpA) MDT meetings, and 2 monthly hepatology-PsA MDT meetings were established. These MDT meetings are attended by consultants, trainees, fellows, and specialist nurses. Complex patients, diagnostic conundrums, and treatment escalation are discussed, with a view to ensuring more harmonized care of the many facets of psoriatic disease. The MDT have also forged screening initiatives for PsA in patients with psoriasis and for SpA in patients with IBD. The challenges of setting up this PsA service have included optimizing patient flow between the MDT, information technology that enables direct referrals to the PsA clinic, funding and implementing the electronic data collection initiative using tablets, funding dedicated PsA staff and job planning, and convincing commissioners and funders of the clinical and economic virtues such a service provides to both patients and the hospital.

Dr. Tillett (Bath, UK) presented a historical perspective on the Bath PsA cohort and the opportunities and challenges of integrating a new TWiCs cohort into an established cohort database. The Bath PsA cohort was set up in 1989 by Professor Neil McHugh to answer questions about the PsA disease pathogenesis, clinical manifestations, prognostic indicators, the natural course of disease, and the real-world effect of treatment. The cohort is a secondary-care cohort primarily serving the local community (95%) with 5% of participants coming as tertiary referrals from farther afield in the United Kingdom. Therefore, the cohort broadly represents patients with PsA in the United Kingdom. Patients are recruited to the cohort with any disease duration, including both new and established diagnoses (thus, it is not purely an inception cohort). In addition to a baseline set of data, clinical, patient-reported, and radiographic data are collected at routine clinical reviews (every 3 mos for patients with active disease and every 6 mos for those with more stable disease). Additional cross-sectional and longitudinal substudies have been undertaken to answer specific questions over the last 28 years. Patients and clinicians have historically collected data on paper, and these data are then scanned into a database where they are monitored and validated by a database team.

Ensuring that the cohort fulfills the most up-to-date PsA classification criteria has been an important consideration over time. Initially, entry to the cohort was based on physician diagnosis, then the application of Moll and Wright criteria, and finally retrospectively applying ClASsification for Psoriatic ARthritis (CASPAR) criteria[9]. Several milestones have necessitated changes to the data collected such as the introduction of biologic therapies, the need for more clinical and mediation data collection and development, and changes to the Outcome Measures in Rheumatology (OMERACT) core set of domains as measures in randomized controlled studies and longitudinal observational studies[10,11].

The decision to set up a new TWiCs subcohort in Bath coincided with a recognition of the importance of moving to electronic data collection and integration with other clinical systems to widen the routinely collected research data. It became clear after discussions involving the Oxford, Cambridge, and Bath cohorts that having a single data collection platform across sites would not be achievable with the different organizations' funding priorities and existing contract commitments. The solution was to avoid real-time data upload and instead upload study data from existing systems at set timepoints during the study. A decision was made to harmonize datasets based on the OMERACT core set using the best-validated and most feasible measures. Feasibility of data collection was a significant consideration because each site has different clinic structures and staff resources. A dataset that could be achieved at each site was negotiated.

Prior to the open discussion about cohorts, Dr. Philip J. Mease (Seattle, Washington, USA) discussed the Corrona

registry, a consortium of over 100 investigative centers in the United States that began as a registry for rheumatoid arthritis (RA) and PsA, but more recently added patients with SpA[12]. The RA registry currently tracks over 44,000 patients. The PsA/SpA registry has enrolled more than 2500 patients and collects detailed information on clinical disease manifestations, including enthesitis, dactylitis, spine and skin disease, comorbidities, and treatment efficacy and safety. This registry identifies only imaging data as done in practice, and for PsA/SpA has no biobanking component at this time. Examples of publications from this registry are referenced[13,14,15].

During the discussion, GRAPPA members were interested in the difficulties of setting up the cohorts, the financial considerations, as well as the feasibility of collecting detailed information on all patients.

GRAPPA members have expressed interest in developing a GRAPPA database, a concept that was further discussed during the research meeting that followed the 2017 GRAPPA annual meeting.

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REFERENCES

1. Gladman DD, Farewell VT. Longitudinal cohort studies. J Rheumatol Suppl. 2005 Jan;72:30-2.
2. Gladman DD, Shuckett R, Russell ML, Thorne JC, Schachter RK. Psoriatic arthritis (PSA)—an analysis of 220 patients. Q J Med 1987;62:127-41.
3. Gladman DD, Farewell V, Buskila D, Goodman R, Hamilton L, Langevitz P, et al. Reliability of measurements of active and damaged joints in psoriatic arthritis. J Rheumatol 1990;17:62-4.
4. Gladman DD, Cook RJ, Schentag C, Feletar M, Inman RI, Hitchon C, et al. The clinical assessment of patients with psoriatic arthritis: results of a reliability study of the spondyloarthritis research consortium of Canada. J Rheumatol 2004;31:1126-31.
5. Rahman P, Gladman DD, Cook RJ, Zhou Y, Young G, Salonen D. Radiological assessment in psoriatic arthritis. Br J Rheumatol 1998;37:760-5.
6. Brubacher B, Gladman DD, Buskila D, Langevitz P, Farewell VT. Followup in psoriatic arthritis: relationship to disease characteristics. J Rheumatol 1992;19:917-20.
7. Relton C, Torgerson D, O'Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. BMJ 2010;340:c1066.
8. Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Laura Acosta-Felquer M, Armstrong AW, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 treatment recommendations for psoriatic arthritis. Arthritis Rheumatol 2016;68:1060-71.
9. Tillett W, Costa L, Jadon D, Wallis D, Cavill C, McHugh J, et al. The ClASsification for Psoriatic ARthritis (CASPAR) criteria—a retrospective feasibility, sensitivity, and specificity study. J Rheumatol 2012;39:154-6.
10. Gladman DD, Mease PJ, Strand V, Healy P, Helliwell PS, Fitzgerald O, et al. Consensus on a core set of domains for psoriatic arthritis. J Rheumatol 2007;34:1167-70.
11. Orbai AM, de Wit M, Mease P, Shea JA, Gossec L, Leung YY, et al. International patient and physician consensus on a psoriatic arthritis core outcome set for clinical trials. Ann Rheum Dis 2017;76:673-80.
12. Kremer JM. The Corrona US registry of rheumatic and autoimmune diseases. Clin Exp Rheumatol 2016;34 Suppl 101:S96-9.
13. Mease PJ, Karki C, Palmer JB, Etzel CJ, Kavanaugh A, Ritchlin CT, et al. Clinical characteristics, disease activity, and patient-reported outcomes in psoriatic arthritis patients with dactylitis or enthesitis: results from the Corrona Psoriatic Arthritis/Spondyloarthritis Registry. Arthritis Care Res 2017;69:1692-9.
14. Mease PJ, Karki C, Palmer JB, Etzel CJ, Kavanaugh A, Ritchlin CT, et al. Clinical and patient-reported outcomes in patients with psoriatic arthritis (PsA) by body surface area affected by psoriasis: results from the Corrona PsA/Spondyloarthritis Registry. J Rheumatol 2017;44:1151-8.
15. Harrold LR, Stolshek BS, Rebello S, Collier DH, Mutebi A, Wade SW, et al. Impact of prior biologic use on persistence of treatment in patients with psoriatic arthritis enrolled in the US Corrona registry. Clin Rheumatol 2017;36:895-901.

The Microbiome in Psoriasis and Psoriatic Arthritis: The Skin Perspective

Hok Bing Thio

ABSTRACT. Psoriasis is a chronic, inflammatory immune-mediated skin disease that affects about 2% of the world's population. In 20% of patients with psoriasis, the characteristic skin lesions are accompanied by psoriatic arthritis (PsA). Psoriasis arises in genetically predisposed individuals who have a dysregulated immune response to various environmental factors. The human body is home to many microbial species, and both the skin and the gut microbiome influence the development and function of immune tissue development and function. Studies on the cutaneous microbiome show a trend toward an increased relative abundance of *Streptococcus* and a decreased level of *Propionibacterium* in patients with psoriasis compared to healthy controls. In the gut microbiome, the ratio of *Firmicutes* and *Bacteroidetes* was perturbed in psoriatic individuals compared to healthy controls. *Actinobacteria* was relatively underrepresented in patients with psoriasis compared to healthy individuals. A decrease in skin microbiome flora diversity seems to be a sign that a patient with psoriasis is at elevated risk for developing arthritis. Modulating the skin microbiota for therapeutic reasons can be achieved by antimicrobial (antibiotic) therapy, the application of prebiotics or probiotics, or the transplantation of an entire healthy microbial population. (J Rheumatol Suppl. 2018 June;94:30–1; doi:10.3899/jrheum.180133)

Key Indexing Terms:
PSORIASIS PSORIATIC ARTHRITIS MICROBIOME SKIN GRAPPA

Psoriasis is an inflammatory, immune-mediated skin disease that affects about 2% of the world's population. In 20% of patients with psoriasis, red, scaling skin lesions are accompanied by psoriatic arthritis (PsA). The skin harbors a wide range of different cell populations, including keratinocytes, macrophages, dendritic cells, innate lymphocytes, and different T cell populations that belong to or perform functions of the innate and adaptive immune system. Psoriasis arises in genetically predisposed individuals who have a dysregulated immune response to various environmental factors. Similar to the gastrointestinal (GI) tract, the skin is a dynamic living interface between an individual and the exogenous environment. Studies have identified an array of genetic, epigenetic, and immunological factors that are involved in the disease pathogenesis of psoriasis and PsA. The human body is home to multiple microbial species (bacteria, fungi, parasites, and viruses), and the genetic materials of all these microorganisms form the microbiome. The microbiome was not generally recognized to exist until the late 1990s. Both the skin and the gut microbiome influence the development and function of immune tissue.

The microbiome has been implicated as a potential trigger for immune dysregulation, which promotes systemic inflammation[1]. Microbial profiling has revealed the presence of highly diverse commensal communities along distinct topographical skin sites. While a healthy skin microbiome functions to protect its host, an increased or decreased skin microbiome bacterial composition (called dysbiosis) leads to skin inflammation and disease. Assuming a skin surface of 2 m^2 and maximum microbial (bacterial) cell densities of about 10^6 per cm^2, the skin of healthy adults can be estimated to be colonized by a maximum of 10^{10} microorganisms in total. However, bacteria are distributed very unevenly across the different niches of the human skin. Cell numbers range from about 10^2 per cm^2 (fingertips, back) to 10^6 per cm^2 (forehead, axilla). Together, *Firmicutes*, *Actinobacteria*, *Bacteroidetes*, and *Proteobacteria* form the largest microbial populations that inhabit the skin. Human skin microbiota is heterogeneous because of the existence of several microhabitats that are characterized by the predominance of a specific bacteria: sebaceous sites with *Propionibacterium spp*, moist sites (such as axilla and inguinal crease) with *Staphylococcus* and *Corynebacterium spp*, and dry sites with gram-negative microorganisms. While it was long believed that microbial life on healthy skin was restricted to epidermis, hair follicles, and sebaceous and sweat glands, various analyses suggest that viable microbes are also found in deeper skin layers, i.e., the dermis and underlying fat tissue. In humans, the microbial

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variation is higher among different microhabitat skin sites of the same individual than among skin sites from the same microhabitat of different individuals.

Although the psoriatic microbiome field is relatively new, initial studies on the cutaneous microbial compositions of subjects with psoriasis and PsA in both psoriatic lesions and unaffected skin reveal interesting differences in microbiome composition[2,3]. Studies on the cutaneous microbiome show a trend toward an increased relative abundance of *Streptococcus* and a decreased level of *Propionibacterium* in patients with psoriasis compared to healthy controls. In the gut microbiome, the ratio of *Firmicutes* and *Bacteroidetes* has been shown to be perturbed in individuals with psoriatic disease compared to healthy controls[2]. *Actinobacteria* has also been shown to be relatively underrepresented in patients with psoriasis compared to healthy individuals[2]. *Staphylococcus* and *Corynebacterium* have been the predominant bacteria in all samples. It seems that a decrease in skin microbiome flora diversity could be an initial sign that a patient with psoriasis is at an elevated risk for developing PsA[4].

Given the interindividual variation in the composition of the (skin) microbiota of healthy subjects, it is challenging to define a standard "healthy" skin; however, it is generally believed that a healthy skin microbiota is characterized by a high diversity of commensal or even beneficial (symbiotic) bacteria. In contrast, disease (in our case psoriasis) is thought to be associated with a dysbalanced microbiota (dysbiosis) characterized by a loss of microbial diversity and an increase in absolute numbers and relative abundance of pathogenic bacteria.

Next to the role of specific gut bacteria, the human fungal and yeast microbial community (mycobiome) has been appreciated as important for health[5]. The majority of a human host's interactions with yeast and fungi take place in the intestines and skin. Recent studies identified hundreds of different types of fungi in oral and colonic microbiota. Most fungi are resident to skin, genital, and GI mucosa without causing disease.

An interesting report in this field is that the baker's yeast, *Saccharomyces cerevisiae*, a highly abundant fungus in the human gut, has been found to be decreased in the gut of patients with psoriasis, but appears to be restored upon oral immunomodulatory therapy with dimethylfumarate[6]. *S. cerevisiae* is generally classified as a yeast with beneficial immunomodulatory properties. In psoriasis, there are many therapeutic options, including topical treatment, ultraviolet therapy, conventional systemic therapy such as dimethylfumarate and cyclosporin, and biologic therapy. The effects of these therapies on the GI and cutaneous microbiome and mycobiome still need to be elucidated.

Different factors, such as the environment, host genetic variation, lifestyle, and hygiene may cause shifts in the microbiota of the skin. These shifts in microbiota structure and composition could establish a dysbiotic state that, if not recovered, could result in a dermatologic immune dysregulation state such as psoriasis. The accessibility of skin coupled with the longitudinal stability of skin microbiota allow clinical studies to investigate alterations at different stages of disease states in psoriasis. In addition, rapid and high throughput DNA sequencing platforms and data integration can shed light on the individualized skin microbiome for personalized skin care and therapeutics. Further, patients with psoriasis have a higher prevalence of associated comorbid diseases, including cardiometabolic dysfunction, depression, and metabolic syndrome. Whether the gut and skin microbiota are involved in this comorbidity association is unclear.

Manipulating the skin microbiota for therapeutic reasons can be achieved by antimicrobial (antibiotic) therapy, the application of prebiotics or probiotics, or the transplantation of an entire microbial population to diseased skin. While antibiotics aim to eliminate specific (pathogenic) microorganisms, the main purpose of applying probiotics or transplanting microbiota is to increase selected, beneficial microorganisms.

Microbiome research is currently very popular. Many associations with health and disease outcomes are being investigated, including associations with psoriasis and PsA, and several types of microbiota-related interventions are being developed.

REFERENCES

1. Egert M, Simmering R, Riedel CU. The association of the skin microbiota with health, immunity, and disease. Clin Pharmacol Ther 2017 Apr 5 (E-pub ahead of print).
2. Yan D, Issa N, Afifi L, Jeon C, Chang HW, Liao W. The role of the skin and gut microbiome in psoriatic disease. Curr Dermatol Rep 2017;6:94-103.
3. Tett A, Pasolli E, Farina S, Truong DT, Asnicar F, Zolfo M, et al. Unexplored diversity and strain-level structure of the skin microbiome associated with psoriasis. NPJ Biofilms Microbiomes 2017;3:14.
4. Langan EA, Griffiths CEM, Solbach W, Knobloch JK, Zillikens D, Thaci D. The role of the microbiome in psoriasis: moving from disease description to treatment prediction? Br J Dermatol 2017 Oct 26 (E-pub ahead of print).
5. Nakajima S, Harrison O, Linehan JL, Belkaid Y. Candida albicans colonization exacerbates skin inflammation in a murine model of psoriasis. J Immunol 2017;198 Suppl:149-16.
6. Eppinga H, Thio HB, Schreurs MWJ, Blakaj B, Tahitu RI, Konstantinov SR, et al. Depletion of Saccharomyces cerevisiae in psoriasis patients, restored by Dimethylfumarate therapy (DMF). PLoS One 2017;12:e0176955.

The Microbiome in Psoriasis and Psoriatic Arthritis: Joints

Jose U. Scher

ABSTRACT. The microbiome is a known and established immunomodulator of many inflammatory disorders, including psoriasis and psoriatic arthritis. Microbes co-evolved with their human hosts and provide them with nutritional, metabolic, and immunologic support. An accumulating body of evidence has revealed that psoriatic diseases are characterized by a state of intestinal dysbiosis, which has been linked to a decrease in beneficial commensals and fatty acids. This has been shown in both animal models and human samples, and multiple studies have addressed the physiological and potentially pathogenic role of intestinal and cutaneous microbes in human health and disease. In this review, we discuss state-of-the-art literature in the field of the microbiome in psoriatic diseases that was presented during the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2017 annual meeting, with a special emphasis on synovio-entheseal inflammation. A better understanding of these microbe-host interactions can lead to novel diagnostic and therapeutic targets. (J Rheumatol Suppl. 2018 June;94:32–5; doi:10.3899/jrheum.180134)

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MICROBIOME JOINTS SPONDYLOARTHRITIS

For millennia, microbes have co-evolved with their human hosts, populating most mucosal sites. These microorganisms are fundamental to their host's physiology and help maintain immune and metabolic homeostasis. An accumulating body of literature has established the mechanisms that underlie the crosstalk between the microbiome-mucosal interface and the downstream host immune response. However, the precise molecular signaling that directs this microbial influence in disease pathogenesis is emerging and continues to be a central research area in the fields of inflammation, oncology, and autoimmunity.

Joshua Lederberg defined and described the microbiome as "the ecological communities of commensal, symbiotic, and pathogenic microorganisms (including their genes) that literally share our body space"[1]. While adults carry 2–3 pounds of bacteria at any given moment, the genes within the human microbiome astoundingly outnumber the host's genetic contribution 100-fold[2]. These populations, with niche-specific characteristics, inhabit the upper and lower respiratory tract, skin, upper gastrointestinal tract, and female genital tract. However, the largest proportion of human microorganisms resides in the lower gastrointestinal tract, which is home to hundreds of bacterial, viral, and fungal species that form a complex and dynamic ecosystem[3].

The microbial colonization of the gut begins at birth with vaginal- or cutaneous-derived bacteria, depending on delivery mode[4]. These populations vary significantly, and the intestine's final composition depends on many factors, including host genetics, milk and food types, maternal microbiota, and exposure to antibiotics and other insults[5].

After the first year of life (when solid food is introduced), the human microbiome begins to maintain its overall structure over time and becomes robust and resilient[2,6]. However, when this equilibrium is perturbed, a dysbiotic process can serve as a triggering factor for the initiation and perpetuation of many inflammatory arthritides, including rheumatoid arthritis (RA), spondyloarthritis (SpA), and psoriatic arthritis (PsA)[7]. This process has been studied and validated over the last 2 decades in animal models of these disorders, where specific perturbations in the microbiome's composition can result in downstream inflammatory events at mucosal surfaces, ultimately leading to systemic disease in susceptible hosts[5]. Multiple cells residing in the intestinal lamina propria appear to be important in translating dysbiosis into local and distal proinflammatory programs, including

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dendritic cells, Th17 cells, plasma cells, innate lymphoid cells, γ-δ T cells, and several others[8]. Several mechanisms have been proposed through which microbiome community perturbations may direct the immune response, including altered epithelial and mucosal permeability, loss of immune tolerance to components of commensals, and trafficking of effector immune cells into the synovium.

Intestinal Microbiome in PsA and SpA: From Models to Humans

The clinical and biological connection between SpA, PsA, and gut inflammation is well established. As a group, SpA-spectrum diseases share a genetic predisposition (i.e., HLA-B27); effector immune cells in their pathogenesis (Th17 cells and other type-17 cells); and clinical manifestations around peripheral and axial arthritis, psoriasis, and intestinal inflammation. The reason certain specific phenotypes are expressed in particular individuals at the expense of other phenotypes has remained one of the leading enigmas in the field. What is more certain is the well-established connection between the development of synovio-entheseal inflammation and psoriasis in the context of clinical (and subclinical) gut inflammation (and vice versa). This is best exemplified by the so-called "enteroarthropathies," in which intestinal infectious agents trigger distal disease.

This is indeed the case in reactive arthritis (ReA), where bacterial gut pathogens cause joint inflammation in genetically predisposed patients[9]. Moreover, about 20% of patients with ReA go on to develop ankylosing spondylitis (AS). A similar pattern of gut-joint axis pathology is evidenced in Whipple disease and jejunoileal bypass arthritis[10,11]. Intriguingly, over 50% of patients with SpA and PsA have subclinical gut inflammation, supporting the involvement of mucosal inflammation in the pathogenesis of these diseases[12,13].

Similarly, there is an intimate and reciprocal connection between gut and joint inflammation in inflammatory bowel disease (IBD), in which peripheral arthritis occurs in up to 25% of patients[14]. Spine involvement, particularly asymptomatic sacroiliitis, is even more frequent, with fully manifested AS developing in up to 1 in 10 patients with IBD.

Animal models of SpA and PsA (i.e., HLA-B27 transgenic rats and SKG mice) do not develop SpA-like disease when raised under germ-free conditions (cages voided of microorganisms). It is only when exposed to specific members of the enteric community that these animals develop the phenotype (peripheral arthritis, SpA, psoriasiform skin disease, and Crohn-like ileitis), supporting the hypothesis that gut microbiota is indeed necessary for the initiation of disease[15,16]. However, the mechanism by which this occurs is still a matter of intense research. Certainly, the role of Type-17 cells and the interleukin (IL)-23/IL-17 axis appears to play a central role[17,18,19] because these cells are essential in the initiation and maintenance of gut inflammation in IBD[20]. Similarly, the high expression of IL-17 can be found in the synovial fluids of SpA, while increased circulating Th17 cells have also been reported[21].

To date, there have been few comprehensive studies of intestinal inflammation characterization in humans with SpA spectrum disease and PsA. Classic work by Mielants, *et al* initially found an increased intestinal permeability in patients with RA, SpA, and IBD[22]. More recent, Ciccia, *et al* found that more than half of patients with PsA have subclinical gut inflammation and increased levels of Th17 as well as Th9 cells[23]. Similarly, only a handful of studies have characterized the link between PsA and the microbiome. Two studies have assessed the cutaneous microbiota composition in patients with psoriasis, with somehow divergent findings. However, both Gao, *et al* and Fahlén, *et al* found that psoriatic plaques have a significantly lower abundance of *Propionibacterium spp*.[24,25]. This is of interest because PsA develops in up to one-third of patients with psoriasis, making the skin microbiome a potential biomarker (and target) for the development of synovio-entheseal inflammation.

Our group described the intestinal microbiome in both patients with psoriasis and PsA compared to healthy controls and found that, while both psoriasis and PsA groups showed decreased abundance of the *Coprococcus* genus compared to healthy controls, the PsA group was further characterized by significantly lower levels of the *Akkermansia* and *Ruminococcus* genera. This suggests a continuum in the loss of diversity that may potentially correlate with the natural history of disease[26]. Curiously, studies in IBD also implicate these genera, with a decreased abundance of *Ruminococcus* and *Akkermansia* in both ulcerative colitis and Crohn disease[27]. Further, we found that this intestinal dysbiosis in patients with PsA correlates with decreased levels of medium-chain fatty acids (MCFA) in the intestinal luminal content, which are known to be beneficial for the maintenance of gut epithelial health[28]. These may also represent potentially modifiable biological factors in the progression from psoriasis to PsA[26]. Although this is still a nascent field, recent work on human SpA[29], IBD-arthritis[30], and ReA[31] points toward a common gut dysbiotic process that underlies these inflammatory arthritides.

Strategies to Restore Intestinal Homeostasis

There are multiple potential ways to alter the intestinal microbial community in an attempt to restore gut health and downstream immune responses in psoriatic disease. The strategies range from dietary habit changes to modifying the bioactive molecules that are produced by bacterial strains. Although there is some evidence for a potential clinical benefit of weight loss in psoriasis and PsA[32,33], the data remain nonexistent for microbial ecosystem therapeutics through fecal microbiota transplant. This is not the case in IBD, where many studies have shown significant positive results in the treatment of colitis[34,35,36], supporting an

argument that these interventions could at least theoretically be applied to the treatment of psoriatic disease.

The involvement of the microbiome in humans has been studied for several decades and is familiar to the rheumatology community. The advent of large, parallel sequencing technologies and dramatic advances in the understanding of mucosal immunology have provided a more precise knowledge of the microbe-host cross-talk in physiology and inflammatory disease. How and why microorganisms and their components influence immune homeostasis and the downstream activation of proinflammatory events in autoimmunity is a matter of intense research. Similarly, the application of this basic knowledge in the clinical setting and as potential therapeutic targets is offering new opportunities for the treatment and prevention of psoriatic disease and related conditions.

REFERENCES

1. Lederberg J. Infectious history. Science 2000;288:287-93.
2. Ley RE, Lozupone CA, Hamady M, Knight R, Gordon JI. Worlds within worlds: evolution of the vertebrate gut microbiota. Nat Rev Microbiol 2008;6:776-88.
3. Human Microbiome Jumpstart Reference Strains Consortium, Nelson KE, Weinstock GM, Highlander SK, Worley KC, Creasy HH, Wortman JR, et al. A catalog of reference genomes from the human microbiome. Science 2010;328:994-9.
4. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A 2010;107:11971-5.
5. Yeoh N, Burton JP, Suppiah P, Reid G, Stebbings S. The role of the microbiome in rheumatic diseases. Curr Rheumatol Rep 2013;15:314.
6. Koenig JE, Spor A, Scalfone N, Fricker AD, Stombaugh J, Knight R, et al. Succession of microbial consortia in the developing infant gut microbiome. Proc Natl Acad Sci U S A 2011;108 Suppl 1:4578-85.
7. Scher JU, Littman DR, Abramson SB. Microbiome in inflammatory arthritis and human rheumatic diseases. Arthritis Rheumatol 2016;68:35-45.
8. Honda K, Littman DR. The microbiome in infectious disease and inflammation. Annu Rev Immunol 2012;30:759-95.
9. Carter JD, Hudson AP. Reactive arthritis: clinical aspects and medical management. Rheum Dis Clin North Am 2009;35:21-44.
10. Moos V, Schneider T. Changing paradigms in Whipple's disease and infection with Tropheryma whipplei. Eur J Clin Microbiol Infect Dis 2011;30:1151-8.
11. Ross CB, Scott HW, Pincus T. Jejunoileal bypass arthritis. Baillieres Clin Rheumatol 1989;3:339-55.
12. Mielants H, Veys EM, De Vos M, Cuvelier C, Goemaere S, De Clercq L, et al. The evolution of spondyloarthropathies in relation to gut histology. I. Clinical aspects. J Rheumatol 1995;22:2266-72.
13. Manasson J, Scher JU. Spondyloarthritis and the microbiome: new insights from an ancient hypothesis. Curr Rheumatol Rep 2015;17:10.
14. Arvikar SL, Fisher MC. Inflammatory bowel disease associated arthropathy. Curr Rev Musculoskelet Med 2011;4:123-31.
15. Rath HC, Herfarth HH, Ikeda JS, Grenther WB, Hamm TE Jr, Balish E, et al. Normal luminal bacteria, especially Bacteroides species, mediate chronic colitis, gastritis, and arthritis in HLA-B27/human beta2 microglobulin transgenic rats. J Clin Invest 1996;98:945-53.
16. Hammer RE, Maika SD, Richardson JA, Tang JP, Taurog JD. Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human beta 2m: an animal model of HLA-B27-associated human disorders. Cell 1990;63:1099-112.
17. Yoshitomi H, Sakaguchi N, Kobayashi K, Brown GD, Tagami T, Sakihama T, et al. A role for fungal {beta}-glucans and their receptor Dectin-1 in the induction of autoimmune arthritis in genetically susceptible mice. J Exp Med 2005;201:949-60.
18. Benham H, Rehaume LM, Hasnain SZ, Velasco J, Baillet AC, Ruutu M, et al. Interleukin-23 mediates the intestinal response to microbial β-1,3-glucan and the development of spondyloarthritis pathology in SKG mice. Arthritis Rheumatol 2014;66:1755-67.
19. Rehaume LM, Mondot S, Aguirre de Carcer D, Velasco J, Benham H, Hasnain SZ, et al. ZAP-70 genotype disrupts the relationship between microbiota and host, leading to spondyloarthritis and ileitis in SKG mice. Arthritis Rheumatol 2014;66:2780-92.
20. Seiderer J, Elben I, Diegelmann J, Glas J, Stallhofer J, Tillack C, et al. Role of the novel Th17 cytokine IL-17F in inflammatory bowel disease (IBD): upregulated colonic IL-17F expression in active Crohn's disease and analysis of the IL17F p.His161Arg polymorphism in IBD. Inflamm Bowel Dis 2008;14:437-45.
21. Appel H, Maier R, Wu P, Scheer R, Hempfing A, Kayser R, et al. Analysis of IL-17(+) cells in facet joints of patients with spondyloarthritis suggests that the innate immune pathway might be of greater relevance than the Th17-mediated adaptive immune response. Arthritis Res Ther 2011;13:R95.
22. Mielants H, Veys EM, De Vos M, Cuvelier C. Increased intestinal permeability in ankylosing spondylitis. Gut 1992;33:1150.
23. Ciccia F, Guggino G, Ferrante A, Raimondo S, Bignone R, Rodolico V, et al. Interleukin-9 overexpression and Th9 polarization characterize the inflamed gut, the synovial tissue, and the peripheral blood of patients with psoriatic arthritis. Arthritis Rheumatol 2016;68:1922-31.
24. Gao Z, Tseng CH, Strober BE, Pei Z, Blaser MJ. Substantial alterations of the cutaneous bacterial biota in psoriatic lesions. PLoS One 2008;3:e2719.
25. Fahlén A, Engstrand L, Baker BS, Powles A, Fry L. Comparison of bacterial microbiota in skin biopsies from normal and psoriatic skin. Arch Dermatol Res 2012;304:15-22.
26. Scher JU, Ubeda C, Artacho A, Attur M, Isaac S, Reddy SM, et al. Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease. Arthritis Rheumatol 2015;67:128-39.
27. Png CW, Linden SK, Gilshenan KS, Zoetendal EG, McSweeney CS, Sly LI, et al. Mucolytic bacteria with increased prevalence in IBD mucosa augment in vitro utilization of mucin by other bacteria. Am J Gastroenterol 2010;105:2420-8.
28. Anbazhagan AN, Priyamvada S, Gujral T, Bhattacharyya S, Alrefai WA, Dudeja PK, et al. A novel anti-inflammatory role of GPR120 in intestinal epithelial cells. Am J Physiol Cell Physiol 2016;310:C612-21.
29. Tito RY, Cypers H, Joossens M, Varkas G, Van Praet L, Glorieus E, et al. Brief report: dialister as a microbial marker of disease activity in spondyloarthritis. Arthritis Rheumatol 2017;69:114-21.
30. Viladomiu M, Kivolowitz C, Abdulhamid A, Dogan B, Victorio D, Castellanos JG, et al. IgA-coated E. coli enriched in Crohn's disease spondyloarthritis promote TH17-dependent inflammation. Sci Transl Med 2017;9(376).
31. Manasson J, Shen N, Garcia Ferrer HR, Ubeda C, Iraheta I, Heguy A, et al. Gut microbiota perturbations in reactive arthritis and post-infectious spondyloarthritis. Arthritis Rheumatol 2018;70:242-54.
32. Eder L, Thavaneswaran A, Chandran V, Cook RJ, Gladman DD. Obesity is associated with a lower probability of achieving sustained minimal disease activity state among patients with psoriatic arthritis. Ann Rheum Dis 2015;74:813-7.

33. di Minno MN, Peluso R, Iervolino S, Lupoli R, Russolillo A, Scarpa R, et al. Obesity and the prediction of minimal disease activity: a prospective study in psoriatic arthritis. Arthritis Care Res 2013;65:141-7.
34. Borody TJ, Warren EF, Leis S, Surace R, Ashman O. Treatment of ulcerative colitis using fecal bacteriotherapy. J Clin Gastroenterol 2003;37:42-7.
35. Kelly CR, Khoruts A, Staley C, Sadowsky MJ, Abd M, Alani M, et al. Effect of fecal microbiota transplantation on recurrence in multiply recurrent Clostridium difficile infection: a randomized trial. Ann Intern Med 2016;165:609-16.
36. Moayyedi P, Surette MG, Kim PT, Libertucci J, Wolfe M, Onischi C, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. Gastroenterology 2015;149:102-9.e6.

The Role of the Microbiome in Gut and Joint Inflammation in Psoriatic Arthritis and Spondyloarthritis

Elisabeth Gilis, Céline Mortier, Koen Venken, Karlijn Debusschere, Lars Vereecke, and Dirk Elewaut

ABSTRACT. Spondyloarthritis (SpA) encompasses a group of diseases characterized by an inflammatory arthritis involving both joints and entheses. However, extraarticular symptoms constitute a large element of the pathology and should not be underestimated. Microscopic gut inflammation is observed in 50% of patients with SpA and has been linked to disease activity, underscoring the effect of gut inflammation in SpA. In this review, we discuss the influence of gut microbiota on SpA pathogenesis. A change in microbiota composition has been linked to the development of various inflammatory arthritides, and dysbiosis is a potential factor in the pathogenesis of multiple inflammatory diseases. In this context, several groups have reported the modulatory effects of gut microbiota-derived metabolites on the effect of immune cells. The gut mucosa is populated by several types of regulatory T cells, but also some specialized unconventional innate-like T cells. These cells are predominantly found at mucosal and epithelial barrier sites, where they serve an essential role in modulating host-microbial interplay. Apart from the close association between the composition of the microbiota and inflammatory diseases, the therapeutic value of dysbiosis needs further investigation, and the identification of a causal inflammatory pathway between gut dysbiosis and musculoskeletal inflammation could revolutionize the therapeutic approach in SpA. (J Rheumatol Suppl. 2018 June; 94:36–9; doi:10.3899/jrheum.180135)

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The Gut: Gateway to Joint Inflammation in Spondyloarthritis

Spondyloarthritis (SpA) consists of a group of chronic inflammatory diseases that primarily affect the musculoskeletal system and share common clinical features, genetic susceptibility, and pathophysiological mechanisms[1]. These diseases include axial spondyloarthritis, including ankylosing spondylitis (AS), psoriatic arthritis (PsA), some juvenile forms, reactive arthritis, and inflammatory bowel disease (IBD)-associated arthritis. SpA affects up to 1% of Western society[2], and its prominent clinical features include inflammatory stiffness, swelling, and/or loss of function of the axial skeleton (spine and sacroiliac joints) and/or peripheral joints, which may lead to irreversible structural and functional impairments and decreased quality of life[1]. Patients with SpA frequently develop extraarticular manifestations such as acute anterior uveitis, psoriasis, and IBD.

Over the past 3 decades, our group has played a leading role in the examination of gut-joint disease in patients with SpA. We found that about 50% of SpA patients without gastrointestinal symptoms demonstrate microscopic signs of intestinal inflammation. Overall, 6.5% of these patients with SpA evolved to Crohn disease in 5 years' time, but this fraction reached 20% of patients in the subset with chronic microscopic gut inflammation[3,4]. Interestingly, the presence of microscopic gut inflammation was also linked to early disease onset, high disease activity, and the presence of bone marrow edema in sacroiliac joints[5,6]. This finding underscores the potential effect of gut inflammation on the extent

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of disease in patients with SpA. Conversely, patients with IBD commonly develop joint inflammation with features of SpA[1]. The mechanism by which gut inflammation affects joint disease has been a longstanding area of research, but is still not well understood. Particularly, it is far from clear how gut microbiota influence SpA pathogenesis.

The human gut harbors a tremendously diverse microbial community, including the microbiota that modulate many physiological processes during homeostasis. The contribution of gut microbiota to the development of gut and joint disease is apparent from multiple experimental animal models, including HLA-B27 transgenic rats[7] and SKG mice[8]. These models mimic gut and joint involvement in human SpA. Interestingly, these models do not develop SpA-like symptoms under germ-free conditions.

The microbiota, however, have been linked to the development of both chronic gut inflammation[9] and arthritic pathologies[10,11] when its composition is disturbed in animal models.

Dysbiosis, a change in microbial diversity and community composition, has gained much attention as a potential causal or contributing agent to many chronic inflammatory diseases, including IBD and SpA. Important immune- and barrier-modulating functions of the intestinal microbiota are attributed to the fermentation of dietary fibers into short-chain fatty acids (acetate, propionate, and butyrate). In Crohn disease, butyrate-producing bacteria, such as members of the cluster IV and XIVa *Clostridia*, which are known to steer regulatory T cell (Treg) functionality and to help maintain barrier integrity, are underrepresented[9]. Beyond butyrate, other metabolites, and antigens associated with *Clostridium* cluster IV and XIVa have gut barrier-protective effects. There is also evidence that gut microbiota-derived metabolites may modulate immunity by affecting innate-like T cell functions.

Data have shown a reduction of *Faecalibacterium prausnitzii*, which belongs to the cluster IV *Clostridia*, in stool samples of patients of SpA[12]. Moreover, we observed a significant correlation between the abundance of the genus *Dialister* in ileal and colon biopsies and the Ankylosing Spondylitis Disease Activity Score, a validated measure of disease activity that is widely used in axial SpA[13]. Other researchers have also found associations between the mucus-degrading *Ruminococcus gnavus* and Bath Ankylosing Spondylitis Disease Activity Index in AS stool samples[14,15].

Collectively, microbial alterations are associated with clinical readouts of inflammation, which suggests the possibility of a connection between dysbiosis and disease status, although it is not firmly established.

Microbial-responsive T Cells in the Intestine: Regulators of Gut and Joint Inflammation?

Genome-wide association studies in both SpA and IBD have revealed polymorphisms in signaling pathways implicated in disease development, such as the interleukin 23 (IL-23) pathway[1]. This was strikingly shown in the SKG model, which carries a ZAP70 mutation, altering T cell receptor (TCR) signaling that depends on the IL-23/IL-17 pathway for development of gut and joint pathology[16,17]. These mice only show SpA-like disease (enthesitis and ileitis) when injected with β1,3-glucan, a microbial component[16], but not when kept in germ-free conditions[8]. Further, tumor necrosis factor (TNF), a proinflammatory cytokine, is one of the most important cytokines involved in SpA and IBD pathogenesis, as proven by the success of anti-TNF therapy in both diseases[18] and the development of Crohn-like ileitis, sacroiliitis, and enthesitis in a TNF-overexpressing mouse model ($TNF^{\Delta ARE/+}$)[19]. Recently, it was shown that germ-free $TNF^{\Delta ARE/+}$ mice do not develop Crohn-like ileitis. $TNF^{\Delta ARE/+}$-associated dysbiosis is actively contributing to ileitis development, but its effect on enthesitis and arthritis is currently unknown[20]. Thus, aberrations in both pathways might result in an altered immune response to mucosal bacteria and their products, leading to disease initiation and progression.

The gut immune system harbors a number of regulatory cells, of which the CD4+CD25+FOXP3+ Tregs are the most studied population. Tregs are very important in maintaining peripheral tolerance and preventing exaggerated immune responses to physiologic environmental entities[21]. Next to Tregs, the gut mucosa is populated by several highly specialized, unconventional T cells with potent immune-modulatory properties that can also respond to gut microbiota either directly or indirectly. Innate-like T cells, such as invariant natural killer T cells (iNKT), mucosal-associated invariant T (MAIT) cells[22], and γ-δ T cells[21], are predominantly found at mucosal and epithelial barrier sites where they serve an essential role in modulating host-microbial interplay. These cells can release a broad spectrum of Th1-related cytokines (e.g., interferon-γ and TNF), Th2 (e.g., IL-4 and IL-10), or Th17 (e.g., IL-17 and IL-22) upon TCR activation, but also upon TCR-independent stimulation and act as a "bridge" between innate and adaptive immune responses. iNKT and MAIT cells both express a semi-invariant TCR that shows antigen restriction toward nonpolymorphic MHC-like molecules (CD1d and MR1, respectively) and that respond to microbial-derived products[22]. iNKT cells recognize bacterial-derived glycolipid molecules, whereas MAIT cells can be activated by vitamin B2 (riboflavin) metabolites, which are endproducts of bacterial and yeast biosynthetic pathways. These innate-like immune cells display plasticity; they can be skewed from an immune-protective role toward a predominant proinflammatory IL-17 profile in response to uncontrolled IL-23 signaling events[23]. The alteration in cellular phenotype could be mediated either directly or indirectly by chronic inflammation, by an aberrant Treg crosstalk, or by altered

microbial-derived signals. There is some evidence from mouse studies that innate-like T cells are functionally skewed with altered features compared to steady state[19,24]. However, whether these processes also occur in humans and whether there are regional differences according to the site of inflammation remains to be determined.

Is the Intestinal Microbiota a Potential Target for SpA?

Dysbiosis in inflammatory diseases such as SpA is poorly understood. The plasticity of the dysbiosis will determine whether correcting dysbiosis has therapeutic applications. In this context, 2 distinct hypotheses have been proposed to explain the relationship between microbiota and disease association[25]. The first involves a unidirectional model in which dysbiosis occurs early in life (e.g., influenced by early-life antibiotic exposure, delivery mode, breastfeeding, etc.) with subsequent alterations in the mucosal immune system development. This leads to a permanent alteration in microbiota composition and immune polarization in adult life. Such a scenario has been described in mice lacking lymphotoxin αβ, which affects the formation of gut-associated lymphoid tissue in the neonatal period and leads to the colonization and expansion of segmented filamentous bacteria that ultimately drive IL-17–mediated autoimmunity[26]. The second model suggests a more reversible balance between microbiota composition, gene susceptibility, and immune activation that is compatible with the therapeutic application of microbiota as a target.

In the context of PsA and SpA, there is evidence for both unidirectional and multidirectional models. For example, breastfeeding was reported to protect against the development of AS[27], which could be an indirect link with its effect on microbiota composition. In addition, HLA-B27 may lead to changes in gut microbiota composition[28]. In psoriasis, a differential relationship exists between microbiota and disease in adult versus neonatal life[29]. In human PsA, profound changes in microbiota have been described[30]. Whether similar shifts in microbiota occur in all different forms of SpA is not clear[31]. Further, whether the gut is the only involved barrier site is equally unclear in view of data on lung microbiota[31] and other rheumatic diseases such as rheumatoid arthritis[32,33].

The contribution of dysbiosis to inflammatory disease opens perspectives for the development of novel therapies aimed at restoring homeostatic microbial ecological communities. The concept of ecosystem restoration follows the idea that a dysregulated microbiota can be restored by the transfer of specific microbial consortia or even full microbial ecosystems [fecal microbiota transplantation (FMT)] from a healthy donor to a diseased individual. FMT is highly effective in restoring microbial complexity as a treatment for recurrent *Clostridium difficile* infections in humans[34] and for the restoration of rumen function in ruminants[35]. The success of ecosystem restoration in several diseases may be a key to better understanding the precise effect of microbial changes on SpA disease initiation and progression, especially in analyzing the potential use of microbial supplementation as a therapeutic choice for patients with SpA.

Collectively, the data highlight that much more needs to be understood about the complex interrelation between genetics, environment, and inflammation, including regional and time-dependent effects. Further, the role of microbiota in educating and altering the functionality of local immune cells and its role in the development of SpA needs further research.

REFERENCES

1. Van Praet L, Jacques P, Van den Bosch F, Elewaut D. The transition of acute to chronic bowel inflammation in spondyloarthritis. Nat Rev Rheumatol 2012;8:288-95.
2. Hootman JM, Helmick CG. Projections of US prevalence of arthritis and associated activity limitations. Arthritis Rheum 2006;54:226-9.
3. Mielants H, Veys EM, Cuvelier C, De Vos M, Goemaere S, De Clercq L, et al. The evolution of spondyloarthropathies in relation to gut histology. III. Relation between gut and joint. J Rheumatol 1995;22:2279-84.
4. De Vos M, Mielants H, Cuvelier C, Elewaut A, Veys E. Long-term evolution of gut inflammation in patients with spondyloarthropathy. Gastroenterology 1996;110:1696-703.
5. Van Praet L, Van den Bosch FE, Jacques P, Carron P, Jans L, Colman R, et al. Microscopic gut inflammation in axial spondyloarthritis: a multiparametric predictive model. Ann Rheum Dis 2013;72:414-7.
6. Van Praet L, Jans L, Carron P, Jacques P, Glorieus E, Colman R, et al. Degree of bone marrow oedema in sacroiliac joints of patients with axial spondyloarthritis is linked to gut inflammation and male sex: results from the GIANT cohort. Ann Rheum Dis 2014; 73:1186-9.
7. Taurog JD, Richardson JA, Croft JT, Simmons WA, Zhou M, Fernandez-Sueiro JL, et al. The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats. J Exp Med 1994;180:2359-64.
8. Ruutu M, Thomas G, Steck R, Degli-Esposti MA, Zinkernagel MS, Alexander K, et al. β-glucan triggers spondylarthritis and Crohn's disease-like ileitis in SKG mice. Arthritis Rheum 2012;64:2211-22.
9. Atarashi K, Tanoue T, Shima T, Imaoka A, Kuwahara T, Momose Y, et al. Induction of colonic regulatory T cells by indigenous Clostridium species. Science 2011;331:337-41.
10. Lin P, Bach M, Asquith M, Lee AY, Akileswaran L, Stauffer P, et al. HLA-B27 and human β2-microglobulin affect the gut microbiota of transgenic rats. PLoS One 2014;9:e105684.
11. Hoentjen F, Welling GW, Harmsen HJ, Zhang X, Snart J, Tannock GW, et al. Reduction of colitis by prebiotics in HLA-B27 transgenic rats is associated with microflora changes and immunomodulation. Inflamm Bowel Dis 2005;11:977-85.
12. Stoll ML, Kumar R, Morrow CD, Lefkowitz EJ, Cui X, Genin A, et al. Altered microbiota associated with abnormal humoral immune responses to commensal organisms in enthesitis-related arthritis. Arthritis Res Ther 2014;16:486.
13. Tito RY, Cypers H, Joossens M, Varkas G, Van Praet L, Glorieus E, et al. Brief report: dialister as a microbial marker of disease activity in spondyloarthritis. Arthritis Rheumatol 2017;69:114-21.
14. Vereecke L, Elewaut D. Spondyloarthropathies: Ruminococcus on the horizon in arthritic disease. Nat Rev Rheumatol 2017;13:574-6.
15. Breban M, Tap J, Leboime A, Said-Nahal R, Langella P, Chiocchia G, et al. Faecal microbiota study reveals specific dysbiosis in spondyloarthritis. Ann Rheum Dis 2017;76:1614-22.

16. Benham H, Rehaume LM, Hasnain SZ, Velasco J, Baillet AC, Ruutu M, et al. Interleukin-23 mediates the intestinal response to microbial β-1,3-glucan and the development of spondyloarthritis pathology in SKG mice. Arthritis Rheumatol 2014;66:1755-67.
17. Rehaume LM, Mondot S, Aguirre de Carcer D, Velasco J, Benham H, Hasnain SZ, et al. ZAP-70 genotype disrupts the relationship between microbiota and host, leading to spondyloarthritis and ileitis in SKG mice. Arthritis Rheumatol 2014;66:2780-92.
18. De Wilde K, Debusschere K, Beeckman S, Jacques P, Elewaut D. Integrating the pathogenesis of spondyloarthritis: gut and joint united? Curr Opin Rheumatol 2015;27:189-96.
19. Jacques P, Venken K, Van Beneden K, Hammad H, Seeuws S, Drennan MB, et al. Invariant natural killer T cells are natural regulators of murine spondylarthritis. Arthritis Rheum 2010; 62:988-99.
20. Schaubeck M, Clavel T, Calasan J, Lagkouvardos I, Haange SB, Jehmlich N, et al. Dysbiotic gut microbiota causes transmissible Crohn's disease-like ileitis independent of failure in antimicrobial defence. Gut 2016;65:225-37.
21. Honda K, Littman DR. The microbiome in infectious disease and inflammation. Annu Rev Immunol 2012;30:759-95.
22. Salio M, Silk JD, Jones EY, Cerundolo V. Biology of CD1- and MR1-restricted T cells. Annu Rev Immunol 2014;32:323-66.
23. Eken A, Singh AK, Oukka M. Interleukin 23 in Crohn's disease. Inflamm Bowel Dis 2014;20:587-95.
24. Kenna TJ, Davidson SI, Duan R, Bradbury LA, McFarlane J, Smith M, et al. Enrichment of circulating interleukin-17-secreting interleukin-23 receptor-positive gamma/delta T cells in patients with active ankylosing spondylitis. Arthritis Rheum 2012;64:1420-9.
25. Van de Wiele T, Van Praet JT, Marzorati M, Drennan MB, Elewaut D. How the microbiota shapes rheumatic diseases. Nat Rev Rheumatol 2016;12:398-411.
26. Van Praet JT, Donovan E, Vanassche I, Drennan MB, Windels F, Dendooven A, et al. Commensal microbiota influence systemic autoimmune responses. EMBO J 2015;34:466-74.
27. Montoya J, Matta NB, Suchon P, Guzian MC, Lambert NC, Mattei JP, et al. Patients with ankylosing spondylitis have been breast fed less often than healthy controls: a case-control retrospective study. Ann Rheum Dis 2016;75:879-82.
28. Asquith M, Davin S, Stauffer P, Michell C, Janowitz C, Lin P, et al. Intestinal metabolites are profoundly altered in the context of HLA-B27 expression and functionally modulate disease in a rat model of spondyloarthritis. Arthritis Rheumatol 2017;69:1984-95.
29. Zanvit P, Konkel JE, Jiao X, Kasagi S, Zhang D, Wu R, et al. Antibiotics in neonatal life increase murine susceptibility to experimental psoriasis. Nat Commun 2015;6:8424.
30. Scher JU, Ubeda C, Artacho A, Attur M, Isaac S, Reddy SM, et al. Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease. Arthritis Rheumatol 2015; 67:128-39.
31. Manasson J, Shen N, Garcia Ferrer HR, Ubeda C, Iraheta I, Heguy A, et al. Gut microbiota perturbations in reactive arthritis and post-infectious spondyloarthritis. Arthritis Rheumatol 2018; 70:242-54.
32. Scher JU, Joshua V, Artacho A, Abdollahi-Roodsaz S, Ockinger J, Kullberg S, et al. The lung microbiota in early rheumatoid arthritis and autoimmunity. Microbiome 2016;4:60.
33. Thio HB. The microbiome in psoriasis and psoriatic arthritis: the skin perspective. J Rheumatol Suppl. 2018 June;94:30-1.
34. Khoruts A, Dicksved J, Jansson JK, Sadowsky MJ. Changes in the composition of the human fecal microbiome after bacteriotherapy for recurrent Clostridium difficile-associated diarrhea. J Clin Gastroenterol 2010;44:354-60.
35. DePeters EJ, George LW. Rumen transfaunation. Immunol Lett 2014;162:69-76.

Report of the Skin Research Working Groups from the GRAPPA 2017 Annual Meeting

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ABSTRACT. At the 2017 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), the International Dermatology Outcome Measures (IDEOM) psoriasis working group presented an overview of its cutaneous domain of psoriatic arthritis (PsA) projects. First, the group presented an overview of IDEOM's work to establish psoriasis outcome measures that satisfy the needs of all those involved. Second, the group discussed replacements for the Psoriasis Area and Severity Index (PASI) that can be used in clinical practice, including data that support the use of the physician's global assessment × body surface area measurement score as a PASI surrogate. Third, the group discussed the contribution of skin disease to composite measures of PsA. Last, the group summarized the National Psoriasis Foundation's efforts to establish treat-to-target strategies for psoriasis care. (J Rheumatol Suppl. 2018 June;94:40–3; doi:10.3899/jrheum.180137)

Key Indexing Terms:
PSORIATIC ARTHRITIS PSORIASIS GRAPPA
IDEOM PSORIASIS OUTCOMES MINIMAL DISEASE ACTIVITY

International Dermatology Outcomes Measures Group

The International Dermatology Outcome Measures (IDEOM) group is a nonprofit organization whose mission is to establish patient-centered measurements to enhance research and treatment for those with dermatologic disease[1,2,3,4,5]. From the onset in 2013, IDEOM's efforts have included perspectives of patients, health economists, payers, physicians, and regulatory agencies. The dermatology division of the US Food and Drug Administration has also been involved in these efforts and regularly attends IDEOM's annual meetings. IDEOM's goal is to establish validated and standardized outcome measures that satisfy all needs and that can be applied to clinical research and practice.

At the 2017 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) annual meeting in Amsterdam, the Netherlands, selected deliverables to date were discussed[5]. The domains for psoriasis clinical trials were presented. These had been selected by a process akin to that used by Outcome Measures in Rheumatology for rheumatologic outcomes. The core domains were skin manifestations [primary: body surface area (BSA)/erythema/induration/scale], location of skin lesions (palmar-plantar and scalp psoriasis), investigator's global assessment, psoriasis and psoriatic arthritis (PsA) symptoms, patient's global assessment, treatment satisfaction, and health-related quality of life. Important, but not required, were the skin manifestations of nail, inverse, genital, guttate psoriasis, and secondary symptoms. The research agenda included PsA signs (because it was felt that dermatologists would not be able to or desire to assess these), economic consequences, work productivity and participation, and cardiovascular disease. In collaboration with the Hidradentis Suppurativa Core Outcomes Set International Collaboration (HISTORIC), an international consortium of hidradenitis suppurativa (HS) healthcare providers and patients, HS clinical trial domains that were selected through an iterative Delphi process were briefly mentioned, because HS has been associated with seronegative spondyloarthopathies[6].

Because PsA symptoms and psoriasis treatment satis-

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As part of the supplement series GRAPPA 2017, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

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faction were selected to be in the core set of domains to be measured in all psoriasis clinical trials, and because these domains have not routinely been studied in psoriasis clinical trials, 2 working groups were formed to select or develop outcome measures for these domains[3]. Results from these 2 working groups are anticipated by the next annual GRAPPA meeting in 2018.

IDEOM is proceeding to develop psoriasis outcome measures that are useful for clinical practice. The need is urgent because, at least in the United States, payers are making judgments on physicians and making access decisions that do not have disease clearance as a major criterion. Additionally, treat-to-target (T2T) strategies and registries for clinical practice require practical and brief outcome measures that are compatible with major electronic medical record systems. In the United States, payers want universally accepted, published outcome measures that are useful in clinical practice and mandated to be performed by published guidelines that are issued by major professional societies. They want clinically meaningful outcome measures, i.e., it is not enough to be better than placebo. Outcomes should justify the cost given the benefit and risk aspects of a given drug. They would like outcomes that measure how the overall cost of care decreases by treatment intervention and how work productivity increases by treatment intervention. Outcomes should be applied universally in clinical practice to reduce variability in practice and make costs more predictable. Last, they would like to see a measure that looks like a diagnostic test (e.g., HbA1c or blood pressure measurement) so that a solid connection can be made between the clinical outcome and a therapeutic decision[7].

Summarizing IDEOM's ongoing motivation, drug regulatory agency approval and publications are only the beginning. The true finish line is when patients get to the right doctors and treatments, and their disease has minimal to no effect on their quality of life.

PGA×BSA as a PASI Proxy

There is an unmet need for practical psoriasis outcome measures. While the Psoriasis Area and Severity Index (PASI) has been a gold standard assessment, it is not practical in the clinical setting and involves complex nonlinear scoring. In addition, its absolute values are poorly understood by clinicians and patients, and there is poor sensitivity to change with poor discrimination at lower score ranges. The product of the physician's global assessment (PGA) and body surface area measurement (BSA %) represents a highly feasible measure that identifies both the severity and extent of psoriasis, has demonstrated sensitivity to change, correlates with PASI, and has the potential for use both in the clinical trials' setting, as well as the clinical practice setting[8,9]. Further, the PGA×BSA measure can be easily understood by providers, patients, regulators, and payers. It has multiple potential uses beyond clinical documentation, including Physician Quality Reporting System use, registry use, and prior authorization documentation. In addition to the PGA×BSA product, each number individually offers a quick glance into the characteristics of the disease from the perspective of plaque severity, as well as area of involvement.

The clinical response and correlation with a minimal disease activity (MDA) target was reported at the 2017 GRAPPA annual meeting based upon data analysis from the Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) phase III trials of apremilast in psoriasis[9,10]. In the ESTEEM data, subjects had moderate to severe plaque psoriasis with PASI ≥ 12, BSA ≥ 10%, static PGA (sPGA) ≥ 3. Primary endpoints were measured at Week 16 with a maintenance phase to Week 32 and a week 32–52 randomized withdrawal phase. A 5-point PGA was used, and other relevant outcomes including Dermatology Life Quality Index (DLQI), BSA, and PASI were collected. Specific baseline demographics and other results are outside the scope of this report and will be reported separately in a future publication[9]. A few highlights of the data presented included PGA×BSA scores as they correlated with PASI response categories at Week 16, as well as correlation with a proposed MDA criterion definition of PASI90 + DLQI = 0 or 1. The percent of patients achieving response at Week 16 by PASI or PGA×BSA in 2 ESTEEM trials (ESTEEM1 and 2) were presented and demonstrated best correlation of > PASI 90 with PGA×BSA scores of 0 to 1 and 0 to 1.5[9,10].

One current limitation is that several versions of the sPGA/Investigator's Global Assessment of psoriasis exist. IDEOM is actively addressing this gap with a planned consensus project to drive the use of a single sPGA in clinical trials and practice.

PGA×BSA has been shown to be a feasible measure that is sensitive to change in disease severity in apremilast-treated patients with moderate to severe psoriasis. Also, PGA×BSA bands can aid measurement and interpretation of meaningful clinical response, including MDA in patients with psoriasis. Ongoing work includes looking at PsA data in a population of low PASI baseline subjects to compare with PASI outcome data. The potential for a PGA×BSA cutoff as a potential T2T goal with validation in a real-world clinical trial is also being considered[10].

Composite Scores for PsA: The Role of Cutaneous Disease in Composite PsA Measures

There is increasing interest in treating to an objective target in PsA as discussed in the European League Against Rheumatism treatment recommendations[11] and the National Psoriasis Foundation (NPF) published guidance on T2T in PsA and psoriasis[12]. The new T2T recommendations for spondyloarthritis state that either the Disease Activity in PsA (DAPSA) remission/low disease activity, or very low disease

activity (VLDA)/MDA criteria are recommended[13]. DAPSA focuses on articular disease incorporating joint counts, patient assessment of pain and disease activity, and C-reactive protein[14]. VLDA/MDA are composite measures that incorporate more PsA domains with 7 different cutpoints: tender joint count ≤ 1; swollen joint count ≤ 1; PASI ≤ 1; patient's pain visual analog scale (VAS) ≤ 15 mm; patient's global VAS ≤ 20 mm; Health Assessment Questionnaire ≤ 0.5; and tender entheseal points ≤ 1[15]. To be in VLDA, patients must meet all 7 cutpoints, while to achieve MDA, patients must meet 5 of 7 cutpoints[16].

DAPSA does not include a measure of skin disease. VLDA requires a PASI of ≤ 1; MDA only requires that 5 cutpoints be met, with only 1 cutpoint measuring psoriasis. Thus it is possible for a patient to meet MDA, but have psoriasis activity. Therefore, different modifications of MDA have been tested that mandate joint counts, skin criteria, or both. Data were presented from 2 posthoc analyses that investigated these criteria. The first analysis was from the Psoriasis Randomized Etanercept Study in Subjects with PsA, a large randomized controlled trial in patients with severe psoriasis (mean baseline PASI 20) and PsA[17,18]. The second analysis was from a clinical cohort of 250 patients[19,20]. These studies showed good control of disease activity with all definitions, but highlighted potential issues, particularly with psoriasis. In VLDA or MDA with skin mandated, the PASI needed to be ≤ 1 so that skin control was assured. However, in MDA without skin mandated, residual skin disease could be present despite meeting 5 cutpoints, which is particularly common in cohorts with severe skin disease. In DAPSA, because skin disease is not measured at all, residual skin disease could be present to a significant extent. Even in the clinic, with more modest skin disease (baseline median PASI 0.3), people meeting DAPSA remission with a PASI ≥ 2 had a significantly poorer quality of life.

Reassuringly, the T2T recommendations state that "validated measures of musculoskeletal disease activity and assessment of cutaneous […] manifestations should be used in clinical practice to define the target and to guide treatment decisions"[13]. If physicians are aiming for a target of VLDA, then skin would be assessed and treatment escalated in cases with active psoriasis. Caution should be exercised when using MDA, and domains with residual disease activity including skin should be addressed even if the minimum 5 domain cutpoints are met. If rheumatologists use a peripheral joint-focused measure such as DAPSA, it is imperative that additional measures of other important domains in PsA (e.g., skin and enthesitis) be assessed within a target of treatment.

US Treatment Targets for Patients with Psoriasis

At the GRAPPA 2017 annual meeting, Dr. April W. Armstrong (Los Angeles, California, USA) discussed a pivotal effort to establish treatment targets for patients with psoriasis in the United States[12]. This effort, which was organized by the NPF, was the first to establish treatment goals for those with plaque psoriasis. NPF is a US-based nonprofit organization whose mission is to drive efforts to cure psoriatic disease and improve the lives of those affected.

There is a critical need in the United States to establish treatment goals for patients with psoriasis. NPF used a rigorous process to arrive at consensus for treatment goals. The NPF process consisted of literature review, elicitation of patient input in the creation of the Delphi survey, and a multiround Delphi consensus-building procedure involving experts in providing psoriasis care. The key principles of the Delphi consensus-building process are anonymity and transparency. In this process, the anonymity of individual responses prevents a participant's authority, personality, and reputation from dominating others. This also minimizes "bandwagon effect" and fosters self-critique.

The consensus-building process results showed that the most preferred instrument to assess treatment goals was the BSA, and 3 months was the most preferred time for evaluating patient response after starting new therapies. Two levels of response, acceptable response and target response, were defined at 3 months after treatment initiation. Acceptable response was either BSA 3% or less or BSA improvement 75% or more from baseline. The target response was BSA 1% or less. During the maintenance period, the target response should be BSA 1% or less at every 6-month evaluation interval.

The NPF treatment target publication explicitly states that the treatment targets are to be used to increase access to therapies and never to limit treatment options[12]. The treatment targets provide the start point from which clinicians and patients can evaluate their current regimen and determine whether changes are necessary to achieve treatment goals. Specifically, the treatment targets encourage clinicians and patients to monitor disease progression and evaluate patient treatment response.

Discussion at the 2017 GRAPPA annual meeting centered on the clinical application of these treatment targets and what would be recommended if treatment targets are not met. If treatment goals are not met, providers and patients have an opportunity to reevaluate the patient's disease state, comorbidities, and current treatments. Any therapeutic decision making would need to be based on a patient's comorbidities, which is part of a thorough benefit-risk assessment. Ways to help patients achieve treatment targets include, but are not limited to, current therapy dose escalation, combination therapy, or switching the primary treatment. It is also important to ensure that the primary therapy has had enough time to achieve its optimal therapeutic effect before changing treatments.

REFERENCES

1. Gottlieb AB, Armstrong AW. Psoriasis outcome measures: a report from the GRAPPA 2012 annual meeting. J Rheumatol 2013;40:1428-33.

2. Gottlieb AB. IDEOM: International Dermatology Outcomes Measures: a call to action. Psoriasis Forum 2013;19:107-9.
3. Elman SA, Merola JF, Armstrong AW, Duffin KC, Latella J, Garg A, et al. The International Dermatology Outcome Measures (IDEOM) Initiative: a review and update. J Drugs Dermatol 2017;16:119-24.
4. Gottlieb AB, Levin AA, Armstrong AW, Abernethy A, Duffin KC, Bhushan R, et al. The International Dermatology Outcome Measures Group: formation of patient-centered outcome measures in dermatology. J Am Acad Dermatol 2015;72:345-8.
5. Perez-Chada LM, Singh S, Callis-Duffin K, Garg A, Gottlieb AB, Latella J, et al. International Dermatology Outcome Measures (IDEOM) Group 2016 New York Meeting: Meeting Summary and Data from the Psoriasis Working Group. J Drugs Dermatol 2017;16:770-7.
6. Thorlacius L, Ingram JR, Garg A, Villumsen B, Esmann S, Kirby JS, et al. Protocol for the development of a core domain set for hidradenitis suppurativa trial outcomes. BMJ Open 2017;7:e014733.
7. Greb JE, Merola J, Garg A, Latella J, Howard L, Acharya N, et al. The Psoriatic Disease Payer Advisory Panel. J Drugs Dermatol 2016;15:641-4.
8. Walsh JA, McFadden M, Woodcock J, Clegg DO, Helliwell P, Dommasch E, et al. Product of the Physician Global Assessment and body surface area: a simple static measure of psoriasis severity in a longitudinal cohort. J Am Acad Dermatol 2013;69:931-7.
9. Duffin KC, Papp KA, Bagel J, Levi E, Chen R, Gottlieb AB. Evaluation of the physician global assessment and body surface area composite tool for assessing psoriasis response to apremilast therapy: results from ESTEEM 1 and ESTEEM 2. J Drugs Dermatol 2017;16:147-53.
10. Gottlieb AB, Merola JF, Chen R, Levi E, Duffin KC. Assessing clinical response and defining minimal disease activity in plaque psoriasis with the Physician Global Assessment and body surface area (PGA × BSA) composite tool: An analysis of apremilast phase 3 ESTEEM data. J Am Acad Dermatol 2017;77:1178-80.
11. Gossec L, Smolen JS, Ramiro S, de Wit M, Cutolo M, Dougados M, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis 2016;75:499-510.
12. Armstrong AW, Siegel MP, Bagel J, Boh EE, Buell M, Cooper KD, et al. From the Medical Board of the National Psoriasis Foundation: treatment targets for plaque psoriasis. J Am Acad Dermatol 2017;76:290-8.
13. Smolen JS, Schols M, Braun J, Dougados M, FitzGerald O, Gladman DD, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis 2018;77:3-17.
14. Schoels M, Aletaha D, Funovits J, Kavanaugh A, Baker D, Smolen JS. Application of the DAREA/DAPSA score for assessment of disease activity in psoriatic arthritis. Ann Rheum Dis 2010; 69:1441-7.
15. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. Ann Rheum Dis 2010;69:48-53.
16. Coates LC, Helliwell PS. Defining low disease activity states in psoriatic arthritis using novel composite disease instruments. J Rheumatol 2016;43:371-5.
17. Sterry W, Ortonne JP, Kirkham B, Brocq O, Robertson D, Pedersen RD, et al. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. BMJ 2010;340:c147.
18. Coates LC, Aikman L, Szumski A, Chhabra A. Comparison of different remission targets in patients with psoriatic arthritis and evaluation of their prognostic value. SAT0441 poster presentation. Ann Rheum Dis 2017;76:939.
19. van Mens LJJ, Turina MC, van de Sande MGH, Nurmohamed MT, van Kuijk AWR, Baeten DLP. Residual disease activity in psoriatic arthritis: discordance between the rheumatologist's opinion and minimal disease activity measurement. Rheumatology 2018; 57:283-90.
20. van Mens LJJ, van de Sande MGH, van Kuijk AWR, Baeten D, Coates LC. Ideal target for psoriatic arthritis? Comparison of remission and low disease activity states in a real-life cohort. Ann Rheum Dis 2018;77:251-7.

Options for Assessing Joints and Entheses in Psoriatic Arthritis by Ultrasonography and Magnetic Resonance Imaging: How to Move Forward

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ABSTRACT. Psoriatic arthritis (PsA) is a heterogeneous disease with various manifestations of musculoskeletal inflammation. Recent advances in imaging, including ultrasound (US) and magnetic resonance imaging (MRI), allow for the accurate evaluation of the extent of inflammation and damage in the peripheral joints, spine, and entheses. The development and validation of outcome measures are critical steps in creating standardized evaluations of musculoskeletal inflammation and damage in psoriatic patients. At the 2017 meeting of the Group for Research and Assessment of Psoriasis and PsA (GRAPPA), recent work on outcome measures from the GRAPPA US and MRI working groups was summarized. The GRAPPA US group has been developing and validating a sonographic enthesitis scoring system in PsA. The GRAPPA MRI group focuses on the evaluation of whole-body MRI for the assessment of musculoskeletal inflammation in the joints and entheses in patients with PsA. (J Rheumatol Suppl. 2018 June;94:44–7; doi:10.3899/jrheum.180140)

Key Indexing Terms:
PSORIASIS PSORIATIC ARTHRITIS JOINTS
GRAPPA ULTRASOUND MAGNETIC RESONANCE IMAGING

Psoriatic arthritis (PsA) is a heterogeneous disease with various manifestations of musculoskeletal inflammation. Advances in imaging, including ultrasound (US) and magnetic resonance imaging (MRI), have allowed for the accurate evaluation of the extent of inflammation and damage in the peripheral joints, spine, and entheses. The development and validation of outcome measures is a critical step in allowing for a standardized evaluation of musculoskeletal inflammation and damage in psoriatic patients. The following is a summary of recent outcome measure work from the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) US and MRI working groups as presented at the GRAPPA 2017 annual meeting in Amsterdam, the Netherlands.

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As part of the supplement series GRAPPA 2017, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

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US Working Group: Assessment of Sonographic Enthesitis in PsA

Enthesitis assessment is recommended in every patient with PsA[1]. However, the accuracy of clinical examination of enthesitis is limited because it relies primarily on subjective findings of tenderness over entheseal sites. US imaging can show entheses in high fidelity, thus improving the accuracy of enthesitis diagnoses in patients with PsA[2].

In 2014, the Outcome Measures in Rheumatology (OMERACT) US special interest group reached a consensus regarding the sonographic elementary lesions defining spondyloarthritis (SpA)-related enthesitis[3]. This was an important first step toward ensuring a high degree of consistency across studies. However, while this group defined the concept of enthesitis at the level of the enthesis, it did not address how to score the degree or severity of enthesitis activity at the global patient level.

Numerous studies have used US to evaluate enthesitis at the global patient level in PsA to study aspects of the disease, such as early diagnosis and improved care[4]. Although several global sonographic enthesitis scoring systems have been developed, many studies used variations of these methods or other nonvalidated scoring systems. This lack of standardization has limited the ability to compare results across studies. In addition, very few studies controlled for important

confounding factors in PsA, such as obesity. Therefore, the GRAPPA US working group concentrated on the sonographic assessment of enthesitis in PsA as its initial project.

Systematic literature review of sonographic enthesitis scores. The first step in this process included a systematic literature review (SLR) to evaluate the current evidence and knowledge gaps in scoring systems of enthesitis in PsA[5]. The search strategy was constructed to find original publications containing terms related to US, enthesitis, SpA, or PsA. Data extraction focused on the enthesitis scoring system properties used in each study and followed each OMERACT filter component: reliability, feasibility, discriminative validity, responsiveness, and construct validity as they related to clinical enthesitis assessment, inflammation biomarkers, and enthesitis imaging by other modalities. The SLR included a total of 51 of 310 identified manuscripts. Only 1 scoring system was developed and validated in patients with PsA. Only 18 (35%) of the studies included patients with PsA, while the rest focused on axial SpA. Construct validity of enthesitis scores was assessed using biomarkers, clinical examination, and imaging (MRI and radiographs) in only 1 (2%), 11 (21.5%), and 0 studies in patients with PsA, respectively. Responsiveness was assessed in 7 studies, none of which included patients with PsA. Only 2 (4%) studies assessed discriminative validity in PsA, and only 1 study evaluated the effect of body mass index and age on sonographic enthesitis. Overall, the results of the SLR highlight existing gaps in knowledge regarding the validity of existing enthesitis sonographic scoring systems in PsA.

Preliminary enthesitis score in PsA. Because of these notable limitations, the GRAPPA US working group set a goal to develop and validate a novel enthesitis sonographic score for PsA through a combined data-driven and expert-opinion driven approach. It then included a pilot study to collect preliminary data regarding the performance of various sonographic entheseal lesions and sites in distinguishing between PsA and healthy controls that will inform the development of a novel sonographic enthesitis score for PsA. In this pilot study, a total of 100 age- and sex-matched individuals (50 PsA and 50 controls) were evaluated[6]. Eleven entheseal sites were scanned bilaterally according to a standardized protocol. Because the OMERACT definition for elementary lesions for enthesitis does not include a scoring system, each elementary lesion was scored 1 point for its presence. A series of regression models was used to find the optimal combination of entheseal sites and elementary lesions that distinguished PsA from controls. The optimal model included 5 elementary lesions (enthesophytes, Doppler signal, erosions, thickness, and structural changes) and 6 entheseal sites (proximal and distal patellar ligament attachments, Achilles tendon, plantar fascia, lateral epicondyle, and supraspinatus). The area under the receiver-operation characteristic curve for this model was 0.93 (95% CI 0.88–0.98). This study identified potential elementary lesions and entheseal sites that could distinguish PsA and controls with high accuracy. This information will contribute to the development of a new sonographic enthesitis scoring system in patients with PsA. The GRAPPA US group aims to further develop and validate the new scoring system using an independent cohort of patients with PsA and controls, as well as to evaluate the scoring system's discriminative ability and responsiveness.

MRI Working Group

PsA is a heterogeneous disease that involves both peripheral and axial joints and entheses. MRI is the only imaging modality that allows assessment of all inflammatory components [synovitis, tenosynovitis, osteitis, enthesitis, periarticular inflammation, and bone marrow edema (BME)], as well as structural damage (bone erosion and bone proliferation) in the peripheral joints and entheses of patients with PsA. Further, MRI can also assess inflammation and damage in the joints and entheses of the axial skeleton, i.e., the spine, sacroiliac joints, and anterior chest wall.

Unfortunately, the widespread and variable PsA disease manifestations have challenged the development of MRI outcome measures that identify the disease activity in all patients with PsA because conventional MRI methods have allowed only for the assessment of a selected area, e.g., a hand, knee, or entheseal region. However, recent technical developments have made MRI of the entire body in 1 imaging session (whole-body MRI; WB-MRI) possible. The following is a discussion of conventional and new MRI techniques and a proposal for an MRI approach that may bring crucial new knowledge regarding the optimal use of MRI as an outcome measure for monitoring disease activity and damage in PsA.

Approaches to MRI assessment of 1 or few joints. Semiquantitative scoring systems for synovitis, BME, and/or erosions in peripheral PsA have been described, but most of these have only been used in a few patients. The international MRI in arthritis group of OMERACT has developed the Psoriatic Arthritis Magnetic Resonance Imaging MRI Score (PsAMRIS) for evaluation of inflammatory (synovitis, tenosynovitis, periarticular inflammation, osteitis) and destructive (bone erosion, new bone formation) changes in PsA hands and feet[7]. PsAMRIS is the only validated assessment system available in PsA and has a documented good intra- and interreader reliability for status and change scores of all variables. In addition, the inflammatory variables have also demonstrated good sensitivity to change and discrimination[7,8,9]. The OMERACT PsAMRIS is currently the method of choice for MRI assessment of patients with PsA in clinical trials.

Quantitative methods. Quantitative methods previously applied in PsA include quantification of contrast enhancement by dynamic contrast-enhanced MRI[10]. Further, different methods of quantification of synovitis, BME, and

bone erosions have been described in other inflammatory arthritides[8,11] and in osteoarthritis (OA) of the knee and hip[12,13,14,15,16]. The latter, the Knee and Hip Inflammation Magnetic Resonance Imaging Scoring Systems (KIMRISS and HIMRISS, respectively), are planned to be applied in the proposed development plan and will, therefore, be described further.

KIMRISS and HIMRISS focus on the assessment of active lesions in the hip and knee, specifically, bone marrow lesions (BML) and synovitis effusion[12,13,14,15,16]. Although originally validated in OA, these scoring methods can, in principle, be applied to the objective assessment of hip and knee inflammation in other inflammatory joint disorders such as PsA. The principal innovation of these imaging scoring tools lies in their application of electronic overlays on a Web-based interface to facilitate rapid touch- or click-based binary scoring of BML in many small regions of bone on fluid-sensitive (intermediate-weighted fat-saturated or short-tau inversion recovery) sequences (see www.carearthritis.com, "Osteoarthritis Imaging" under Imaging Portal). The presence or absence of BML is scored on a dichotomous basis on consecutive slices through the joint rather than according to the percent volume of a bone region that contains BML.

In KIMRISS, BML is scored using specific overlays for the femur, tibia, and patella on consecutive sagittal slices through the knee joint. KIMRISS has been shown to have very good reliability for status and change scores in a patient sample (n = 80) from the Osteoarthritis Initiative observational cohort that was assessed over a year[15,16]. Responsiveness to change and correlation with Western Ontario and McMaster Universities Osteoarthritis Index scores for knee pain were also demonstrable in a pilot evaluation of adalimumab over 12 weeks in patients with inflammatory knee OA[16].

In HIMRISS, BML is scored using a single overlay positioned over the femoral head and extending into the acetabulum on consecutive coronal slices through the hip joint[13]. HIMRISS has been shown to have very good to excellent reliability for status and change scores, especially in the femoral head, in an observational study of 40 patients where scans were obtained 8 weeks before and after steroid injection into the hip joint[13]. Standardized calibration modules based on a Web-based interface and real-time iterative feedback referenced to expert reader scores for individual bone regions have been developed and validated for each method to facilitate the attainment of prespecified acceptable targets for reliability[14,15].

Approaches to MRI assessment of many joints (WB-MRI). WB-MRI is a relatively new technique that allows for the assessment of the entire body in 1 examination in less than an hour. WB-MRI can potentially provide a global assessment of the inflammatory status of a patient with arthritis[17,18,19,20]. This may improve the utility of MRI in ankylosing spondylitis, rheumatoid arthritis, and particularly PsA, which presents with varying patterns of arthritis, enthesitis, spondylitis, and/or dactylitis. The OMERACT MRI in arthritis group has taken the first steps toward standardizing WB-MRI image acquisition and assessment, as well as an OMERACT scoring system[19]. After an SLR, the MRI working group decided to primarily focus on inflammation in peripheral joints and entheses. It then developed MRI definitions for these pathologies, selected anatomical locations for assessment, agreed on a core set of MRI sequences and imaging planes for the different regions, and proposed a preliminary semiquantitative scoring system. In addition, it was decided to test and further develop the system in ongoing iterative multireader exercises[19]. A Web-based case report form with line drawings has been developed to facilitate correct registration of bone and soft tissue inflammation in all peripheral joints and entheses.

How to move forward. The GRAPPA MRI working group proposes to perform a longitudinal, multicenter, and preferably randomized treatment study of patients with active PsA, which will build on WB-MRI assessment of peripheral and axial joints and entheses according to the OMERACT recommendations. This study would also incorporate assessments of hands and feet according to PsAMRIS and knees and hips according to KIMRISS/HIMRISS. This approach will allow both the objective assessment of the therapeutic effect of the tested drug by validated MRI methods as well as simultaneously generate MRI data that will provide crucial information about the relative performance of different MRI approaches and their best combinations regarding assessment of patients with PsA in clinical trials and practice.

The varying pattern of involvement of axial and peripheral joints and entheses challenges the use of MRI and US in PsA clinical trials and observational studies. US is an accessible and cost-effective modality for enthesitis assessment; however, the development and validation of clinical outcome measures for enthesitis evaluation is an unmet need. WB-MRI allows for the evaluation of the various features of musculoskeletal inflammation in PsA and is extremely promising for the objective assessment of inflammation in PsA. The technical and methodological development and validation of different WB-MRI assessment methods, in combination with more detailed assessments of selected areas, such as hips and knees, are highly relevant.

REFERENCES

1. Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Laura Acosta-Felquer M, Armstrong AW, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 treatment recommendations for psoriatic arthritis. Arthritis Rheumatol 2016;68:1060-71.
2. D'Agostino MA. Ultrasound imaging in spondyloarthropathies. Best Pract Res Clin Rheumatol 2010;24:693-700.
3. Terslev L, Naredo E, Iagnocco A, Balint PV, Wakefield RJ, Aegerter P, et al; Outcome Measures in Rheumatology Ultrasound Task Force. Defining enthesitis in spondyloarthritis by ultrasound: results of a Delphi process and of a reliability reading exercise. Arthritis Care Res 2014;66:741-8.

4. Zabotti A, Bandinelli F, Batticciotto A, Scire CA, Iagnocco A, Sakellariou G; Musculoskeletal Ultrasound Study Group of the Italian Society of Rheumatology. Musculoskeletal ultrasonography for psoriatic arthritis and psoriasis patients: a systematic literature review. Rheumatology 2017;56:1518-32.
5. Elalouf O, Bakirci S, Touma Z, Anderson M, Kaeley G, Aydin S, et al. Psoriatic arthritis sonographic enthesitis scores — systematic review of the literature [abstract]. Arthritis Rheumatol 2017;69 Suppl 10:254.
6. Tom S, Zhong Y, Cook R, Aydin S, Kaeley G, Eder L. Development of an ultrasonographic enthesitis score for psoriatic arthritis patients [abstract]. Arthritis Rheumatol 2017;69 Suppl 10:1874.
7. Ostergaard M, McQueen F, Wiell C, Bird P, Bøyesen P, Ejbjerg B, et al. The OMERACT psoriatic arthritis magnetic resonance imaging scoring system (PsAMRIS): definitions of key pathologies, suggested MRI sequences, and preliminary scoring system for PsA Hands. J Rheumatol 2009;36:1816-24.
8. Bøyesen P, McQueen FM, Gandjbakhch F, Lillegraven S, Coates L, Wiell C, et al. The OMERACT Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) is reliable and sensitive to change: results from an OMERACT workshop. J Rheumatol 2011;38:2034-8.
9. Glinatsi D, Bird P, Gandjbakhch F, Mease PJ, Bøyesen P, Peterfy CG, et al. Validation of the OMERACT Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) for the hand and foot in a randomized placebo-controlled trial. J Rheumatol 2015;42:2473-9.
10. Cimmino MA, Parodi M, Innocenti S, Succio G, Banderali S, Silvestri E, et al. Dynamic magnetic resonance of the wrist in psoriatic arthritis reveals imaging patterns similar to those of rheumatoid arthritis. Arthritis Res Ther 2005;7:R725-31.
11. Ostergaard M. Magnetic resonance imaging in rheumatoid arthritis. Quantitative methods for assessment of the inflammatory process in peripheral joints. Dan Med Bull 1999;46:313-44.
12. Maksymowych WP, Cibere J, Loeuille D, Weber U, Zubler V, Roemer FW, et al. Preliminary validation of 2 magnetic resonance image scoring systems for osteoarthritis of the hip according to the OMERACT filter. J Rheumatol 2014;41:370-8.
13. Maksymowych WP, Pitts M, Budak MJ, Gracey D, Lambert RG, McDougall D, et al. Development and preliminary validation of a digital overlay-based learning module for semiquantitative evaluation of magnetic resonance imaging lesions in osteoarthritis of the hip. J Rheumatol 2016;43:232-8.
14. Jaremko JL, Azmat O, Lambert RGW, Bird P, Haugen IK, Jans L, et al. Validation of a knowledge transfer tool according to the OMERACT filter: does web-based real-time iterative calibration enhance the evaluation of bone marrow lesions in hip osteoarthritis? J Rheumatol 2017;44:1713-7.
15. Jaremko JL, Azmat O, Lambert RG, Bird P, Haugen IK, Jans L, et al. Validation of a knowledge transfer tool for the knee inflammation MRI scoring system for bone marrow lesions according to the OMERACT filter: data from the Osteoarthritis Initiative. J Rheumatol 2017;44:1718-22.
16. Jaremko JL, Jeffery D, Buller M, Wichuk S, McDougall D, Lambert RG, et al. Preliminary validation of the Knee Inflammation MRI Scoring System (KIMRISS) for grading bone marrow lesions in osteoarthritis of the knee: data from the Osteoarthritis Initiative. RMD Open 2017;3:e000355.
17. Weckbach S, Schewe S, Michaely HJ, Steffinger D, Reiser MF, Glaser C. Whole-body MR imaging in psoriatic arthritis: additional value for therapeutic decision making. Eur J Radiol 2011;77:149-55.
18. Poggenborg RP, Pedersen SJ, Eshed I, Sørensen IJ, Møller JM, Madsen OR, et al. Head-to-toe whole-body MRI in psoriatic arthritis, axial spondyloarthritis and healthy subjects: first steps towards global inflammation and damage scores of peripheral and axial joints. Rheumatology 2015;54:1039-49.
19. Østergaard M, Eshed I, Althoff CE, Poggenborg RP, Diekhoff T, Krabbe S, et al. Whole-body magnetic resonance imaging in inflammatory arthritis: systematic literature review and first steps toward standardization and an OMERACT Scoring System. J Rheumatol 2017;44:1699-705.
20. Krabbe S, Ostergaard M, Eshed I, Sorensen I, Jensen B, Moller J, et al. Whole-body magnetic resonance imaging in axial spondyloarthritis: reduction of sacroiliac, spinal, and entheseal inflammation in a placebo-controlled trial of adalimumab. J Rheumatol 2018 (In press).

GRAPPA 2017 Project Report

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ABSTRACT. At the 2017 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), members received updates on several ongoing educational and research efforts. Among them were updates on GRAPPA's continued education efforts; GRAPPA's continued research efforts, including the Biomarker Project, a collaborative research effort to identify and study biomarkers of joint damage; treatment recommendations, including recommendations and core principles related to biosimilars; efforts to update GRAPPA's Website and to create a GRAPPA smartphone application (app); and the Psoriasis and Psoriatic Arthritis Clinics Multicenter Advancement Network. (J Rheumatol Suppl. 2018 June;94:48–51; doi:10.3899/jrheum.180139)

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PSORIASIS PSORIATIC ARTHRITIS EDUCATION RESEARCH GRAPPA PPACMAN

Members of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) continue to pursue core objectives of GRAPPA's mission, specifically providing education, identifying research assessment tools, and pursuing research in disease pathophysiology. At the 2017 annual GRAPPA meeting, members received updates on GRAPPA's continued education efforts; GRAPPA's continued research efforts, including the Biomarker Project, a collaborative research effort to identify and study biomarkers of joint damage; treatment recommendations, including recommendations and core principles related to biosimilars; efforts to update GRAPPA's Website and to create a GRAPPA smartphone application (app); and the Psoriasis and Psoriatic Arthritis Clinics Multicenter Advancement Network (PPACMAN).

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Educational Committee

A core objective of GRAPPA's mission is education. GRAPPA members around the world provide psoriasis and psoriatic arthritis (PsA) education to many people, including other healthcare professionals (physicians, nurses, physician assistants, medical students, residents, and fellows), patients and their families, and those otherwise involved in the care of patients with psoriasis and PsA (people working in healthcare agencies, payor groups, and pharmaceutical company employees). This education is provided in many forms, including live lectures, hands-on patient workshops, Webcasts and audioconferences, online reading material and slides, articles for publication in medical journals, textbook chapters, and brochures for patient-service leagues.

Because of GRAPPA's global reach, education occurs in many languages, sometimes aided by simultaneous translators, and with appropriate cultural sensitivity. Although much of this activity is conducted by GRAPPA alone, GRAPPA performs many of these efforts in collaboration with other organizations such as the National Psoriasis Foundation (NPF), the International Federation of Psoriasis Associations, the Arthritis Foundation, the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), the Pan American League Against Rheumatism, the Asian Pacific League Against Rheumatism, the Assessment of Spondyloarthritis international Society (ASAS), and the Spondyloarthritis Assessment and Treatment Network (SPARTAN).

In 2016 and 2017, an ongoing collaboration between GRAPPA and SPARTAN yielded a number of half- and full-day continuing medical education symposia on PsA, psoriasis, and spondyloarthritis in New York, Cleveland, New Orleans, Dallas, Boston, Denver, and Salt Lake City. In addition, GRAPPA has continued to collaborate with ASAS to conduct a well-attended symposium at the ACR meeting, which took place in Washington, D.C., in 2016 and San Diego in 2017. In each of these settings, junior and regionally derived faculty teach alongside senior GRAPPA faculty members. These symposia are supported by unrestricted educational grants from pharmaceutical sponsors, including Abbvie, Janssen, Celgene, Amgen, and Mallinckrodt. European symposia have been conducted in cities such as Leeds, London, Milan, Stockholm, Paris, Rome, and Utrecht. Symposia have also been conducted in other countries, including Japan, Korea, China, and Brazil, with sponsorship that has included Abbvie, Janssen, and UCB.

To aid with lectures, GRAPPA has developed an educational slide library for speakers to use that is updated as new information about disease or treatment emerges. In addition, GRAPPA members have developed online videos that teach students, residents, fellows, and clinical trial investigators how to properly examine skin, nails, joints, spine, and entheses.

Plans for future GRAPPA educational activities include updating GRAPPA's physical examination Web-based teaching modules, developing additional online education modules, developing GRAPPA smartphone apps, educating dermatology residents and rheumatology fellows on psoriasis and PsA as part of their training in academic centers, and continuing to educate healthcare providers and patients about PsA in underresourced parts of the world. The GRAPPA education committee is co-chaired by Philip J. Mease, MD (Seattle, Washington, USA), and Amit Garg, MD (Lake Success, New York, USA).

Biomarker Project

At the GRAPPA 2017 annual meeting in Amsterdam, the Netherlands, Dr. Oliver FitzGerald (Dublin, Ireland) provided an update on the proposed PsA Biomarkers of Damage project and reported that significant progress has been made in negotiations with industry partners. Amgen, which is conducting the Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects with Psoriatic Arthritis (SEAM) study (NCT02376790), has been collecting appropriate imaging and bio-samples and has agreed in principle to share these samples with GRAPPA. A contract between Amgen and GRAPPA is under negotiation and should be finalized in the near future. Because it will be important to be able to validate any biomarker findings in independent cohorts, discussions are also under way with both Pfizer and Lilly. These discussions include but are not limited to the tofacitinib and ixekizumab studies, respectively, but also determining biomarkers of treatment response and biomarkers of disease activity.

Dr. FitzGerald highlighted 3 recent studies that demonstrate continued progress in biomarker development. The first study demonstrated how baseline levels of serum CXCL10 (which recruits inflammatory cells to sites of inflammation) have been shown to be increased in patients with psoriasis who converted to PsA as compared to those who did not convert[1]. Interestingly, levels appear to fall again following conversion to PsA. While validation is required, these data suggest that CXCL10 levels may be useful as a way to monitor patients with psoriasis for the development of PsA. The second study identified a panel of serum proteins that clearly separates early PsA from rheumatoid arthritis (RA) with an area under the curve (AUC) of 0.9 (unpublished). Validation work is ongoing with biomarker panel testing by Multiple Reaction Monitoring being undertaken in a number of disease cohorts. The third study, conducted by Siebert, *et al*[2], reported on panels of urine peptides that were each specific for disease cohorts that included PsA, RA, osteoarthritis, inflammatory bowel disease (as an inflammatory control group), and normal controls. The AUC were all > 0.9 when comparing each individual disease with the other groupings combined. These results suggest that multibiomarker panels may offer promise as diagnostic tests for rheumatic diseases including PsA.

Research Committee

The Research Committee, under the leadership of Drs. Christopher T. Ritchlin (Rochester, New York, USA) and April W. Armstrong (Los Angeles, California, USA), released a request for applications from trainees and junior investigators for pilot projects in psoriasis and PsA. In 2017, GRAPPA received 23 applications and funded 5 proposals at $25,000 each. These proposals were awarded to: (1) C. Magee (Ireland), Biomarkers of progression to PsA; (2) L. Eder (Canada), Psoriasis to PsA transition; (3) M. van Mechelen (Belgium), Role of biomechanical stress and psoriasis in PsA; (4) J. Manasson (USA), Effect of biologics on gut microbiome and PsA; and (5) H.J. Weng (Taiwan), Neural pruritus mechanisms in psoriasis. The Research Committee sent a new request for applications in February 2018 with additional information and details provided at that time.

After considerable discussion within the steering committee and relevant committees involved, it was decided to merge the Biomarkers and Research Committees. The biomarker efforts have greatly expanded and dovetail well with the Research Committee's activities. Drs. FitzGerald, Ritchlin, and Armstrong will co-chair the committee and will oversee the development of the GRAPPA Collaborative Research Network and Biorepository. This work is well under way[3].

Additional changes to the Research Committee were also discussed and agreed upon. GRAPPA will establish both a Trainees Symposium Sub-Committee to help plan, organize,

and supervise the Trainees Symposium, as well as a Research Grant Review Committee to oversee GRAPPA's grant evaluation program. Several GRAPPA members have expressed interest in joining these committees, and members were formally invited to join by January 2018.

Treatment Recommendations Update

The ACR and NPF are collaborating to develop treatment guidelines for the management of PsA. The guideline development process differs from that used by GRAPPA and EULAR in the use of the Grades of Recommendation, Assessment, Development, and Evaluation methodology. The process began in September 2016 with a meeting held to determine the scope of the guidelines. The draft treatment guideline was presented at the ACR meeting in November 2017 in San Diego, California, USA.

When the 2015 GRAPPA treatment recommendations update was published[4], it was clear that the brisk pace of relevant developments in therapies for psoriasis and PsA would make it necessary to provide periodic treatment recommendation updates covering key emerging topics prior to the next complete revision. Biosimilars, now in broad use across the globe, were one of the initial key topics[5]. A multidisciplinary, international group of GRAPPA members, including patient research partners, discussed the topic. The group agreed upon the following core principles:

1. Biosimilars must be approved through a robust regulatory review; "biomimics" or "intended copies" are not biosimilars, which should be clearly understood.
2. Periodic reevaluation of biosimilar products post-approval is important to ensure ongoing quality.
3. Extrapolation to psoriasis or PsA, even when no studies are conducted in psoriasis or PsA, is acceptable; ideally, additional studies specifically in psoriasis and PsA should be conducted after approval.
4. Patients and physicians need to be involved in decisions about switching therapies.
5. Pharmacovigilance is crucial, and naming conventions need to allow for the tracking of specific agents and batches.
6. Multiple switches of biosimilars should be studied in a rigorous fashion.
7. Savings realized from the use of biosimilars should be utilized to improve access to these biologic agents for a larger number of patients.
8. Immunogenicity is a concern that should be monitored on an ongoing basis.

In addition to the recommendations developed by consensus, a research agenda will address additional relevant issues in the publication and recommend future research.

Website and Smartphone App Development

In 2015, the GRAPPA Website underwent renovation and rebranding and was relaunched in 2016. In September 2016, GRAPPA successfully bid its first competitive funding program with the Independent Grant for Learning and Change program run by Pfizer. The funding was used to establish an online learning portal that addresses recently published GRAPPA Treatment Recommendations. The grant was submitted as a collaboration between a committee of GRAPPA members and Guideline Central. GRAPPA had previously partnered with Guideline Central to design and produce a quick reference guide about GRAPPA treatment recommendations. The technical expertise that GRAPPA's prior partnership with Guideline Central provided aided in the development of this online GRAPPA Treatment Recommendation learning portal.

The online portal went live on September 1, 2017, and is available to all, regardless of GRAPPA membership. All GRAPPA members were sent a link on launch, and the Website is available from the GRAPPA educational page. The portal includes 4 modules that discuss overarching treatment principles, optimal treatment choices, new therapies, and comorbidities in PsA. Each module has a slide presentation with an audio narration covering key points from treatment recommendations and beyond. Participants can complete pre- and post-presentations test questions to test their knowledge and can compare their scores with other participants. Interactive case studies are also included that illustrate the material discussed in each module.

In 2017, GRAPPA began to develop a smartphone app to aid physicians in clinical practice. The app will include information on GRAPPA and PsA; a module to calculate the Psoriasis Area and Severity Index and body surface area; a module that allows patients to complete the PsA Impact of Disease (PsAID) questionnaire and that calculates and presents its results to the physician and patient; and a module to assess treat-to-target goals in PsA that calculates very low disease activity and minimal disease activity. The app will not record any data internally to avoid any data protection issues. It will be free to download and available in both Android and Apple formats.

Initially, the PsAID questionnaire module will be available in 11 languages: English, French, German, Spanish, Portuguese, Italian, Arabic, traditional Chinese, simple Chinese, Japanese, and Russian. If demand exists, additional languages could be added in future versions. GRAPPA will track the number of downloads of the app by country. This information will help to prioritize which new languages should be added in possible future versions of the PsAID module.

The app is now available in English, and additional languages will become available through 2018. It will be promoted through GRAPPA educational activities to ensure that physicians worldwide are aware of this resource.

The Psoriasis and Psoriatic Arthritis Clinics Multicenter Advancement Network (PPACMAN)

Dermatologists and rheumatologists each play a key role in

the management of PsA. Diagnosis and treatment decisions for the patient with psoriatic disease can be complex. The relative severity of skin and musculoskeletal manifestations, as well as a host of potential drug interactions and potential comorbid, co-prevalent conditions, further complicate PsA treatment decision making.

Combined clinic models present a unique multidisciplinary care delivery model for patients with psoriatic disease. Patients benefit from these models through increased education and support for the many aspects of their disease, a "one-stop shopping" model, access to a wider array of therapies, combined discussions with their dermatologist and rheumatologist, and a quicker transition to appropriate systemic therapy, including disease-modifying antirheumatic drugs and biologics. Clinicians benefit from these models through increased collegiality, cross-disciplinary education, and increased work satisfaction. Rheumatology trainees benefit from these models through their increased awareness of the differential diagnosis of presenting skin disorders and comfort in the use of topical agents; dermatology trainees benefit from an increased awareness of the rheumatology evaluation and examination. These elements were previously reported in the *PPACMAN Survey of Benefits and Challenges to Combined Rheumatology-Dermatology Clinics* publication in 2017[6].

PPACMAN is a nonprofit corporation whose mission is to encourage psoriatic disease combined clinics and centers in both academic and community settings. The combined sites are meant to advance a multilevel approach for psoriatic patients, increase disease awareness, and accelerate disease management. PPACMAN does this through educational, administrative, and research activities. It seeks to improve education about the importance of PsA screening, the early identification of PsA, and the value of collaborative care for patients with psoriatic disease. It also supports the formation of combined multidisciplinary clinic models and regional dermatologist-rheumatologist partnerships. PPACMAN provides opportunities for trainees and practicing dermatologists and rheumatologists to travel to sites within the North American network to observe a combined clinic model. PPACMAN is also developing a core curriculum in the management and collaborative care of psoriatic patients.

PPACMAN's research goals include the evaluation of multisite PsA screening processes, multidisciplinary shared note templates for data collection across network sites, the effectiveness of these novel care delivery models (i.e., defining ideal care outcomes), and comorbidity identification. In the future, PPACMAN would like to offer small pilot grants to investigators who are actively developing lines of research that address collaborative care models in psoriatic diseases.

This paper summarizes GRAPPA's recent work on a number of projects. These projects are part of GRAPPA's core roles: to address educational and unmet research needs, to create opportunities for networking within the psoriatic community, and to optimize patient care through collaborative care networks and treatment recommendations. These projects are ongoing and should continue to add value in the years to come.

REFERENCES

1. Abji F, Pollock RA, Liang K, Chandran V, Gladman DD. Brief report: CXCL10 is a possible biomarker for the development of psoriatic arthritis among patients with psoriasis. Arthritis Rheumatol 2016;68:2911-6.
2. Siebert S, Porter D, Paterson C, Hampson R, Gaya D, Latosinska A, et al. Urinary proteomics can define distinct diagnostic inflammatory arthritis subgroups. Sci Rep 2017;7:40473.
3. Jadon DR, Chandran V, Stober C, Ogdie A, Armstrong AW, Duffin KC, et al. Proceedings of the 2017 GRAPPA Collaborative Research Network (CRN) meeting. J Rheumatol Suppl. 2018 June; 94:54-61.
4. Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Laura Acosta-Felquer M, Armstrong AW, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 treatment recommendations for psoriatic arthritis. Arthritis Rheumatol 2016;68:1060-71.
5. Kay J, Schoels MM, Dorner T, Emery P, Kvien TK, Smolen JS, et al; Task Force on the Use of Biosimilars to Treat Rheumatological Diseases. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. Ann Rheum Dis 2018;77:165-74.
6. Okhovat JP, Ogdie A, Reddy SM, Rosen CF, Scher JU, Merola JF. Psoriasis and Psoriatic Arthritis Clinics Multicenter Advancement Network Consortium (PPACMAN) survey: benefits and challenges of combined rheumatology-dermatology clinics. J Rheumatol 2017;44:693-4.

The Patient Research Partner Network Matures: A Report from the GRAPPA 2017 Annual Meeting

Niti Goel, Denis O'Sullivan, Maarten de Wit, Chris A. Lindsay, Heidi Bertheussen, John Latella, Jeffrey Chau, Roland MacDonald, Suzanne Grieb, Ingrid Steinkoenig, and Willemina Campbell

ABSTRACT. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has reached the third of 5 stages of organizational maturity regarding incorporating patient research partners (PRP) into psoriatic arthritis (PsA) and psoriasis research and educational efforts. Herein, we report the involvement of PRP at the GRAPPA 2017 annual meeting and plans for future PRP engagement. (J Rheumatol Suppl. 2018 June;94:52–3; doi:10.3899/jrheum.180138)

Key Indexing Terms:
PSORIATIC ARTHRITIS PATIENT RESEARCH PARTNERS PATIENT CENTRICITY
GRAPPA PSORIASIS ORGANIZATIONAL MATURITY

Over the last 5 years, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has made substantial progress to incorporate patient input into the group's work. As a result, the GRAPPA patient research partner (PRP) network has evolved in parallel. Herein, the PRP network's involvement since the GRAPPA 2016 annual meeting and their evolution as a group since their first formal attendance at the GRAPPA 2013 annual meeting are summarized.

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As part of the supplement series GRAPPA 2017, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

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PRP Involvement at the GRAPPA 2017 Annual Meeting

Premeeting. Twelve PRP who attended the GRAPPA 2017 annual meeting were educated on the Core Outcome Measures for Psoriatic Arthritis Clinical Trials (COMPACT) study. They then participated in focus groups to evaluate the content validity and feasibility of selected patient-reported outcome measurements. The summary of this premeeting is planned to be presented separately. Generally, such collaboration between patients and researchers should improve researcher understanding of the effect of psoriatic arthritis (PsA) on patients and patient priorities regarding outcomes. Subsequently, the PRP, including 1 who attended by Skype, and the PRP Executive Liaison met to evaluate an initial draft of the PRP Policies and Procedures document.

During the GRAPPA 2017 meeting, PRP were present at all sessions. They participated in breakout groups that built upon the premeeting work to evaluate instrument content validity and feasibility. During the GRAPPA project update session, PRP shared how their membership has progressed (Table 1). From 2013 through 2017, 16 PRP had attended at least 1 meeting, and 3 PRP had consecutively attended all 5 annual meetings since 2013.

PRP Involvement in GRAPPA Activities

Since the GRAPPA 2016 annual meeting, PRP have continued to be involved in multiple projects, including several activities related to the Outcome Measures in Rheumatology-GRAPPA update of the PsA core set, the COMPACT study, the composite measures consensus meeting, the PsA treatment guidelines slide deck, the GRAPPA mobile device application, the GRAPPA research proposals review, and the GRAPPA Collaborative Research Network. In addition, PRP are planning how best to disseminate the PRP-generated booklet, *A Patient's Guide to Treatments for Psoriatic Arthritis*.

Reflecting upon the PRP premeeting work, PRP shared

Table 1. Evolution of PRP attendance at annual GRAPPA meetings from 2013 to 2017.

Characteristic	2013	2014	2015	2016	2017
PRP attending, n (first-time attendees, n)	7 (6)	8 (3)	8 (0)	11 (4)	12 (2)
Males, n (%)	3 (43)	4 (50)	4 (50)	5 (45)	6 (50)
Racial/ethnic composition, n (%)					
Asian	1 (14)	1 (13)	1 (13)	2 (18)	2 (17)
White	6 (86)	7 (87)	7 (87)	8 (73)	9 (75)
Latin American	—	—	—	1 (9)	1 (8)
Geographical representation, n (%)					
Asia	—	—	—	1 (9)	1 (8)
Europe	4 (50)	3 (38)	3 (38)	3 (27)	4 (33)
North America	4 (50)	5 (62)	5 (62)	6 (55)	6 (50)
South America	—	—	—	1 (9)	1 (8)

PRP: patient research partners; GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis.

with the general GRAPPA membership that the PRP network is creating a governance document to dovetail with the current GRAPPA bylaws, and that they plan to create a PRP handbook to provide additional details. Further, the GRAPPA Executive Committee assigned an Executive Liaison to facilitate the PRP network.

These latter activities highlight how the GRAPPA PRP network may be operating close to the third level of organizational maturity, the "Defined" maturity level, in the Capability Maturity Model Integration (CMMI) model (Table 2)[1,2]. This model, originally used to define best practices related to software development, has been expanded to help organizations improve their processes at all levels from services to people.

The GRAPPA PRP network has not undergone any formal process improvement procedures and may not be the type of organization intended to undergo a CMMI assessment. However, as the PRP network continues to develop, achieving a state similar to those described in levels 4 and 5 of the CMMI model might signal that PRP themselves start to lead the investigation of their own questions related to psoriatic disease as considered at the GRAPPA 2016 annual meeting[3].

PRP are actively defining their participation within the GRAPPA community. As their role evolves within the organization, the benefits realized from their contributions to GRAPPA initiatives will hopefully be recognized and grow. The PRP appreciate their involvement in GRAPPA and anticipate a future where incorporating patient input into research and educational endeavors is routine.

ACKNOWLEDGMENT

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REFERENCES

1. What is Capability Maturity Model Integration (CMMI)? [Internet. Accessed February 14, 2018.] Available from: cmmiinstitute.com/capability-maturity-model-integration
2. CMMI Product. CMMI for Service, Version 1.3, CMMI-SVC V.1.3 CMU/SEI-2010-TR034, Technical Report, Software Engineering Institute, 2010.
3. Goel N, O'Sullivan D, Steinkoenig I, James J, Lindsay CA, Coates LC, et al. Tackling patient centricity: a report from the GRAPPA 2016 Annual Meeting. J Rheumatol 2017;44:703-5.

Table 2. Capability Maturity Model Integration organization maturity levels.

Level	Description
1: Initial	Processes unpredictable, poorly controlled, and reactive
2: Managed	Processes characterized for projects and often reactive
3: Defined	Processes characterized for the organization and proactive (projects tailor their processes from organization's standards)
4: Quantitatively managed	Processes measured and controlled
5: Optimizing	Focus on process improvement

Proceedings of the 2017 GRAPPA Collaborative Research Network Meeting

Deepak R. Jadon, Vinod Chandran, Carmel Stober, Alexis Ogdie, April W. Armstrong, Kristina Callis Duffin, Dafna D. Gladman, Philip S. Helliwell, Denis O'Sullivan, Maarten de Wit, Oliver FitzGerald, and Christopher T. Ritchlin

ABSTRACT. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) Collaborative Research Network (CRN) is an endeavor that aims to address gaps in the knowledge of the etiopathogenesis and management of psoriatic disease by best using the large community of experienced investigators who are already collecting rich clinical phenotype data and biologic samples using validated techniques. Exemplar rheumatology and dermatology projects will inform strategies to implement the CRN, while input and funding from government organizations, charities, and industry will shape the CRN. The key immediate priorities to establish the CRN are discussed herein and include (1) strategies for building infrastructure to collect and store biosamples and associated clinical data, (2) best practices for sample collection and storage, (3) approaches to engage the GRAPPA community of investigators and industry to collaborate most effectively on shared priorities, and (4) agreement on a funding strategy. The following 4 CRN candidate flagship research areas were identified: (1) predictors of treatment response in psoriatic arthritis (PsA) and cutaneous psoriasis (PsC) to permit personalized and stratified medicine approaches; (2) predictors of structural damage and disease severity, linking with the existing PsA BioDAM project; (3) predictors of PsC progressing to PsA to enable earlier intervention and possibly halt progression to PsA; and (4) comorbidity prevalence and effect on clinical outcomes in psoriatic disease. The collaboration and momentum provided by a GRAPPA-CRN will offer more than the sum of its individual contributing centers. A CRN will permit high-quality research that can more effectively address questions pertinent to patients, clinicians, scientists, industry, and governments. (J Rheumatol Suppl. 2018 June;94:54–61; doi:10.3899/jrheum.180141)

Key Indexing Terms:
PSORIATIC ARTHRITIS PSORIASIS BIOMARKERS
RESEARCH IMAGING OUTCOME MEASURES

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) Collaborative Research Network (CRN) held its inaugural meeting over 2 days following the GRAPPA 2017 annual meeting in Amsterdam, the Netherlands. The CRN meeting was organized by a committee co-chaired by Professors Oliver FitzGerald and Christopher T. Ritchlin. The meeting was attended by 30 rheumatologists, 4 dermatologists, 11 leads from the pharma-

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ceutical industry, 6 patient research partners (PRP), and 2 nonmedical scientists.

Several motivating factors converged to catalyze the establishment of a GRAPPA CRN. Foremost are major gaps in our knowledge of the etiopathogenesis of psoriatic disease, coupled with the emergence of a large community of experienced investigators already collecting rich clinical phenotype data and biologic samples using validated standardized operating procedures (SOP). Another factor is the successes of previous and existing research efforts in this and related areas, e.g., the psoriatic arthritis (PsA) BioDAM project, rheumatoid arthritis (RA) BioDAM project, and the International Psoriasis and Arthritis Research Team (IPART). There also appears to be a willingness and building momentum from national organizations such as the Innovative Medicines Initiative (IMI), US National Institutes for Health (NIH), and the Accelerating Medicines Partnership (AMP)[1] to support such collaborations or serve as models for data collection and analysis. GRAPPA has a growing membership of over 400 rheumatologists and dermatologists. GRAPPA's community of young investigators and trainees is a precious resource, as evidenced by the Trainee Symposium at the GRAPPA 2017 annual meeting, in which 40 high-quality abstracts were submitted, translating to 6 oral and 23 poster presentations. Further, GRAPPA received 23 research grant applications in 2017, and 5 grants were awarded.

Over the last year, the GRAPPA Research and Biomarkers Committee has generated momentum for the CRN and spearheaded this meeting with the following key objectives: (1) to decide on an overall strategy for building infrastructure to collect and store biosamples and associated clinical data; (2) to determine best practices for sample collection and storage; (3) to identify approaches to engage the GRAPPA community of investigators to participate with the CRN; (4) to understand how to optimize collaborative opportunities between the CRN and industry partners; and (5) to agree on a feasible strategy to fund the CRN.

Some key questions and challenges in setting up the CRN were also identified by the committee for further examination at this meeting. The first was whether samples should be stored centrally at sampling centers, or a mixed-model approach should be used, with some samples stored at local sites and others in a central repository. The CRN must identify and address barriers to biosamples and data crossing international borders. A strategy is required to optimally engage investigators to contribute samples and research proposals, and industry partners on shared research priorities and financial support. The overarching challenge, but ultimately the reward, is how best to make the CRN's sum greater than its individual parts.

Gaps and Emerging Opportunities in PsA

The NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) reported their 2017 "Roundtable on Gaps and Emerging Opportunities in Psoriatic Arthritis"[2]. Several priority areas were identified. A better understanding is needed of the pathogenesis of PsA, including genetic, epigenetic, and environmental factors, as well as the differences and similarities between PsA and related conditions. Advancement of translational research through better-resourced research and using PsA as a model for understanding preclinical autoimmunity was stated as a priority. Clinical research and new therapies research is needed to permit personalized treatment approaches for PsA, to identify biomarkers to facilitate diagnosis and treatment, and to better address comorbidities. NIAMS also called for better engagement of patients in clinical research and trials, while also attracting and retaining clinical researchers.

AMP

The AMP, particularly its "Autoimmune Diseases of Rheumatoid Arthritis and Lupus Network"[3], was cited as an example of how multiple sites across the United States can be set up and co-funded through the NIH and industry. As well as co-funding, industry partners are actively participating and guiding the network's scientific direction. Peripheral blood mononuclear cells (PBMC) and tissues (synovial, skin, and renal tissue) are being collected and analyzed using sophisticated techniques such as single-cell RNA sequencing, CyTOF (mass cytometry), and laser capture microdissection. Centralized storage and SOP have been an integral component of the network. The network has benefited from a $41.6 million fund over 5 years, with $20.9 million from the NIH, $20.7 million from industry, and $0.3 million from nonprofit organizations.

IPART

The IPART initiative was described by Professor Dafna D. Gladman. Funded by the Canadian Institutes of Health Research until 2012, and subsequently by unrestricted grants from industry, its objectives have been to form a database of well-characterized cases (clinically, radiologically, and laboratory) to identify susceptibility factors for PsA among psoriasis-only (PsC) cases and risk factors for disease severity. A shared Internet-based database and rigorous multicenter clinical skills training underpins the effort. The model of a multicenter clinical trial was used to attain ethical approval at the different centers. Each contributing center keeps ownership of its entered data and is able to view its data. Potential collaborative studies are presented at the IPART annual meeting, and with agreement, sites release specific datasets. Only centers contributing data for a specific paper are included in the authorship. Several challenges for IPART were identified, including recruitment to yearly blood sampling, high attrition among younger patients, and the need for a research assistant supervised by the database manager to ensure complete data. Because maintenance costs have amounted to $0.5 million/year (administrator, database

manager, research assistants, sampling equipment), it is recommended that these are included in project grants.

RA BioDAM

Professor Walter Maksymowych gave an overview of the RA BioDAM project. This project was set up using the "clinical trial" model (rather than the "registry" model) and uses the biorepository platform with linked clinical data. Its objective was to determine a serum-soluble biomarker that would predict prognosis, making imaging and other laboratory tests unnecessary. This 2-year prospective observational cohort recruited 576 RA cases between 2011 and 2017 from 10 countries (Canada, Denmark, France, Germany, Ireland, Israel, Italy, the Netherlands, Norway, and the United States), with a mean followup period of 21 months. Patients were assessed and sampled for both serum and urine every 3 months. All centers signed a contract similar to contracts used in randomized control trials (RCT) to deliver outcomes pursuant to the protocol. The initiative was funded by an unrestricted grant from AbbVie. The key challenges for the RA BioDam project included the acquisition of fasting samples; case attrition of 25% over 2 years; imaging not always anonymized; imaging not submitted in a timely manner or in the correct format; linking radiographs to the electronic case report forms (eCRF); insufficient serum or urine volumes; and escalating costs, especially for laboratory consumables, salaries, and couriers.

The key recommendations for the CRN committee were to run the CRN similar to an RCT; implement an eCRF-based integration of imaging, biosample record, and shipment date; strictly adhere to validated SOP; courier samples in batches only with complete eCRF; notify customs officials in advance; incorporate a proactive platform for highly responsive quality assurance and query platform for radiography and biosamples; and incorporate realistic recruitment timelines to permit the accurate estimation of study costs.

Perspectives from Industry

Professor Paul-Peter Tak represented GlaxoSmithKline to give an industry perspective on the CRN. Several key advantages to a CRN approach were reinforced, such as a large well-characterized longitudinal cohort providing better-powered studies, collaboration of expertise using various platforms, and the integrated development of research methods.

It was recommended that the CRN consider and devise strategies to address financial obligations; overlap with other bioresource initiatives, contracts, confidentiality, and intellectual property (IP) rights; definitions of obligations and responsibilities; resourcing, timelines, and longterm sustainability; sample governance; and maintaining the engagement of contributing centers. Samples likely to be of interest to industry would be blood and synovial tissue both before and after an intervention, with associated clinical data on response versus nonresponse. The right culture should be created from the outset, with a clear and agreed vision, open exchange of expectations, and acknowledgment of geographical and functional differences or priorities. Through strong leadership and clearly apportioned responsibilities, the CRN should aim to develop a robust and accountable governance structure that includes public and private partners. An important component of governance would be the life cycle of a sample: sourcing, use, storage, further use (ownership or custodian), transport, and disposal. Choosing government or public partners, in addition to private partners, would provide more stable funding and permit studies with longer timelines. Examples of public partners to consider included IMI, NIH, AMP, and from the United Kingdom the Medical Research Council (MRC), National Institute for Health Research (NIHR), Wellcome Trust, Francis-Crick Institute, Altius Institute, and the European Bioinformatics Institute. To allow for better experimental design, the full dataset being held centrally without local researcher access was advocated. The differences in ethics, consent, and data privacy across international borders was re-emphasized. It was recommended that the CRN register with the "BioBank Directory" to attract potential users and contributors. The early dissemination of emerging study results to patients and healthcare professionals is good clinical practice, but would also motivate existing sites to recruit, new sites to join, and attract new funders.

Roundtable Discussions

Fueled by the experience of these initial sessions, a roundtable discussion was undertaken to identify further areas for debate. Specific pertinent research questions are needed as the basis for funding applications. There was an appetite to maximize collaboration between existing cohorts and apply for funding to enable new smaller centers to join. Siting hubs in geographic regions, e.g., European, North American, South American, Asian, African, and pan-Pacific, might help with the ethics and regulations associated with transferring biosamples across borders. Centers storing their own samples initially, and only later developing a central biorepository, may also help. However, this must be balanced against the ability to reproduce laboratory techniques based on validated SOP from academic centers, which might advocate a centralized processing approach for certain types of samples from the outset. Given the expense, space, and associated infrastructure required by the centralized storage of biosamples, it is essential to have generous financial planning and the justification of storage duration. Given the logistical challenges experienced by IPART and RA BioDAM, strong consideration should be given to employing a contract research organization to perform logistics for the CRN, as is done for large late-phase multinational commercial trials.

Consideration should be given to developing an electronic consent form, to enable easier tracking and ensure disposal

of data/biosamples if required. Patients withdrawing from the CRN should be given the choice to either have existing data/biosamples destroyed or continue to be used. Such a multinational effort must also accommodate the varying literacy levels and languages used by patients in the multiple centers. Given that the legal framework for GRAPPA currently resides in Seattle (USA), further investigation is needed to determine the effect of a multinational CRN on applying for grants from other geographic areas and on indemnity. Involvement of international lawyers is now therefore needed, at CRN inception, albeit aiming to keep the legal framework as simple as possible. During this inception phase, a longterm strategy for continuous active involvement of PRP is essential. Involvement of PRP at steering committee and subcommittee meetings, to write newsletters for patients, to annually present information to other patients, to review grants from inception, and to contribute to lay writing will add great value to the CRN.

Priority Areas in Psoriatic Disease Research

Drs. Vinod Chandran and April W. Armstrong identified key areas for PsA and PsC research, respectively (Table 1). They stated that identifying a flagship project that is pertinent to both PsA and PsC and that best uses the existing strengths of GRAPPA members is critical. Similarly, reporting data from the CRN in a clinically meaningful way and using innovative analytic approaches will strengthen this endeavor. The need for systematic timepoints for the biosampling of both lone and combined biomarkers was emphasized. The Vectra-DA project to identify biomarkers that predict disease activity and joint damage in RA (multibiomarker disease activity) was cited as a good example of academic and industry collaboration[4].

Table 1. Possible flagship research studies for the CRN.

1) Clinical, blood, and/or imaging biomarkers of:
(i) arthritis/skin activity (subclinical, clinical, or response to treatment)
(ii) structural damage and disease severity
(iii) global inflammatory burden
(iv) response to treatment
(v) adverse events
(vi) development of PsA phenotypes (e.g., PsA mutilans or psoriatic spondyloarthritis)
2) Modifying outcomes from comorbid diseases (e.g., through smoking cessation, weight-reduction strategies, diet, lifestyle, statins, metformin, and antihypertensives)
3) Health-related quality-of-life markers
4) Predictors of PsC progressing to PsA
5) Predictors of patients with a family history, but currently no personal history, of PsC or PsA, developing psoriatic disease
6) Development of a diagnostic kit for PsC and PsA
7) Molecular classification of psoriatic disease

CRN: collaborative research network; PsA: psoriatic arthritis; PsC: cutaneous psoriasis.

Operational Structure

Dr. Chandran debated several designs that the CRN could use (Table 2) and how each of these designs would influence the CRN's operational structure. Based on the PsA BioDAM project, it is estimated that the cost per patient would be CAN$4800 to collect clinical, blood, and imaging data [including magnetic resonance imaging (MRI)], with additional costs for bioinformatics support. Financial and academic compensation of sites for their contribution must therefore be finely mapped. The potential for reducing costs for some technologies must be balanced against inflation related to salaries, courier services, and some consumables. Converting the CRN's priority research areas into discrete work packages may help achieve this granularity of detail and aid logistical planning. Given that some other medical specialties are at more advanced stages of biomarker research and multinational collaboration (oncology, public health, cardiology, and nephrology), there may be value in liaising with such specialties.

A CRN committee structure was proposed and is detailed in Figure 1. The CRN structure could be centralized, with a few key sites directing work packages (as is done for multinational RCT); or federated, with semiautonomous decentralized sites that each send a proportion of their samples to the CRN (Figure 2).

Funding Avenues and Requirements

Professor Gladman, Professor Philip J. Mease, Jackie Anderson (representing Abbvie), and Lara Fallon (repre-

Table 2. Possible CRN designs.

Design	Observational vs interventional
	Registry vs RCT
	Cross-sectional vs longitudinal
	Inception vs cohort
	Personalized medicine
Participants	Eligibility criteria for cases
	Inclusion of control subjects, especially important for laboratory and imaging biomarkers
Sites	Number
	Geographical representation
	Targeting special populations who
	– have been underresearched to date
	– present with extreme phenotypes
	Closed vs open to new sites after commencement
	Recruitment cap for each site to improve external validity
	Biosamples contribution
	– mandatory for all sites vs some contributing clinical data only
Data management	Effective IT solutions that are robust over time
	NGS-type storage of extremely large datasets
	Different systems for genomic vs imaging data
	Data dictionary, to ensure consistency of terminology, especially for clinical terms

CRN: collaborative research network; RCT: randomized controlled trials; IT: information technology; NGS: next-generation sequencing.

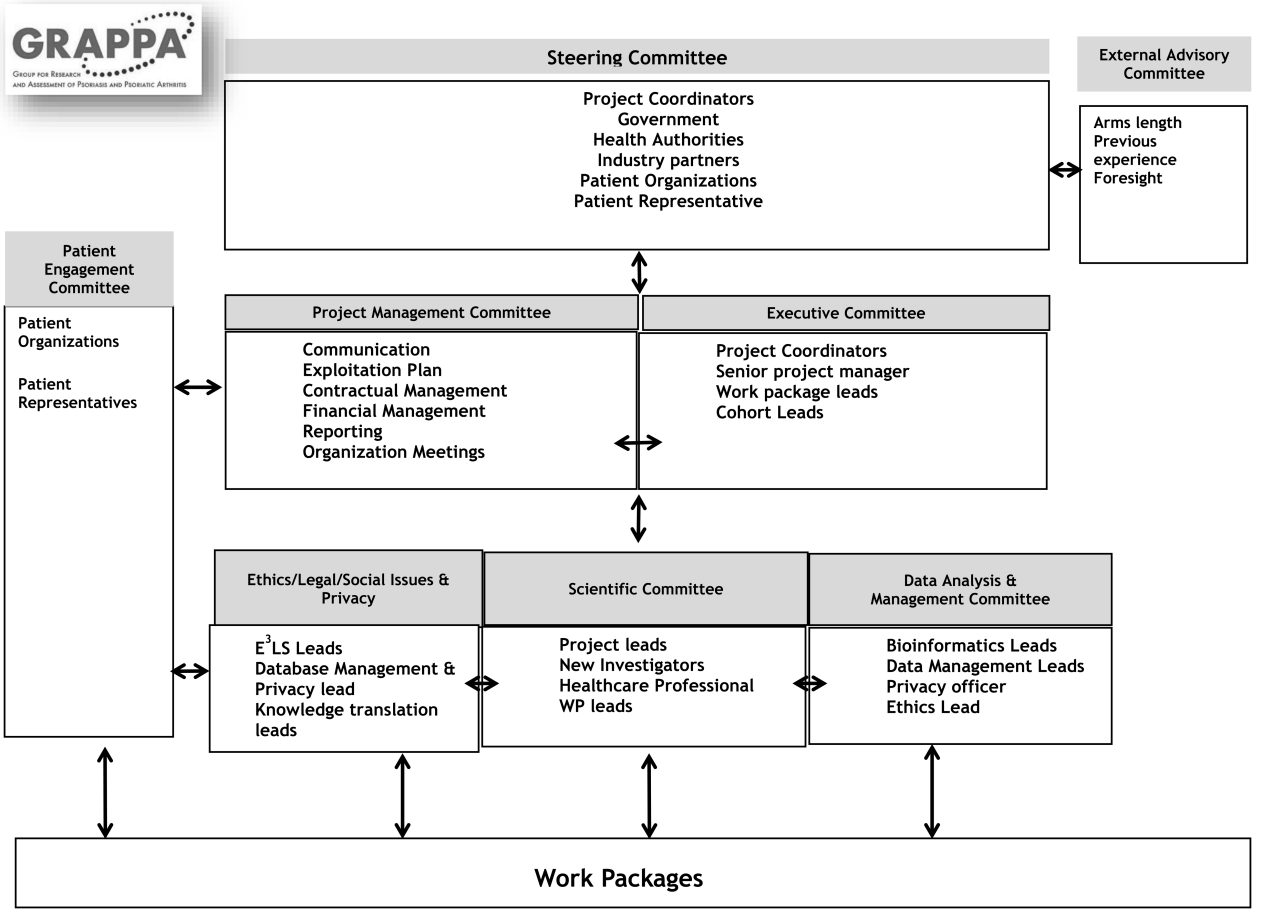

Figure 1. Possible committee structure for the Collaborative Research Network. E^3LS: Ethical, Environmental, Economic, Legal, Social Aspects; WP: work package.

senting Pfizer) participated in a panel discussion to identify potential funding avenues and related considerations. Several candidates to approach for funding were proposed, including the Foundation of NIH, which offers individual grants and requests for applications (RFA) and whose feedback on the PsA-BioDAM project was positive ("good structure, but would benefit from utilizing clinical data from existing RCTs and incorporating more imaging to help reduce the number of candidate blood biomarkers"); NIH through individual grants and RFA; European Union and UK agencies (IMI, NIHR, MRC, Wellcome); foundations, such as the Gates Foundation; local agencies, such as Arthritis Society and Arthritis Research UK; and private donors. The use of existing infrastructure should also be examined (e.g., Newfoundland genetics database supported by IBM).

Industry funding could take place through collaboration, investigator-initiated research grants, other grants, and requests for data and products. The former 2 options might best align with the current CRN remit. An example of requests for data and products is AbbVie's "Open Innovation Portal"[5], which enables researchers to access AbbVie's pipeline products at various stages of development. Industry are optimally positioned and have the experience to contribute expertise in running multinational RCT, writing SOP for biosampling, and applying for and implementing ethical approvals and material transfer agreements (MTA) across international borders. Industry's criteria to fund and collaborate with the CRN would likely be determined by a project's scientific fit with a company's strategy and pipeline products. Additional factors may include applicant experience (centers and individuals), scientific rigor, project focus, robustness of project management, and the likelihood of success. A "private-public partnership" may be appealing to some companies, with active at-inception involvement in study design and database creation.

GRAPPA may prefer to have multiple, rather than single, industry partners. This might, however, affect IP agreements. Further, the funder's legal role and position will determine IP ownership. One solution might be for GRAPPA to own the IP, and if funded by multiple industry partners, existing partners would have the first option to commercialize the IP with GRAPPA. This approach would entail further consider-

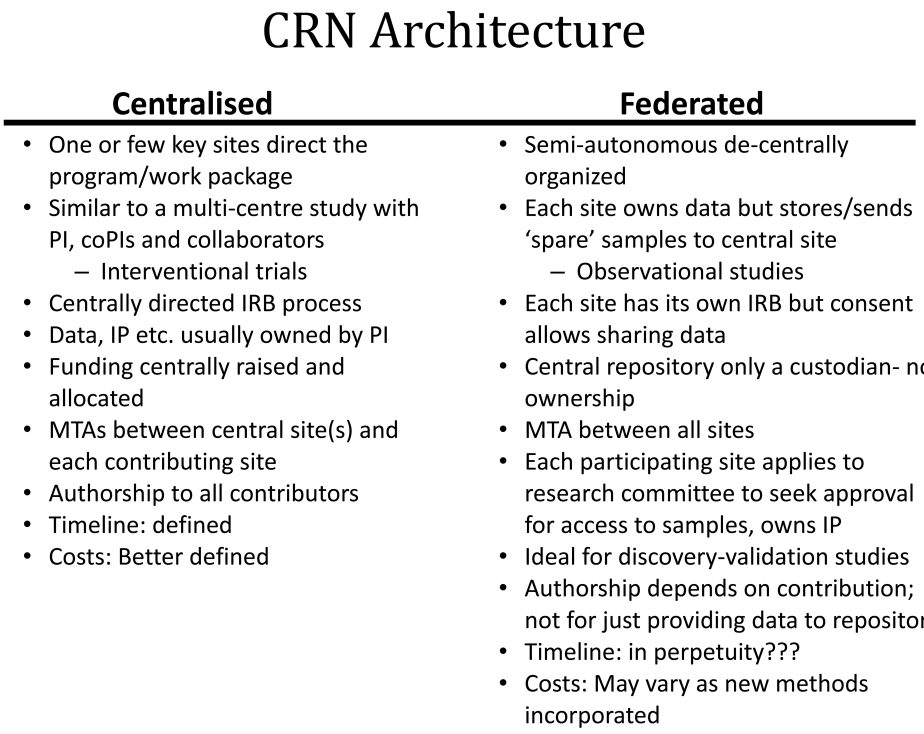

Figure 2. Possible architecture of the CRN: centralized versus federated. CRN: Collaborative Research Network; PI: principal investigator; IP: intellectual property; MTA: material transfer agreements; IRB: institutional review board.

ation regarding whether the CRN should be an "organization" or a "business," which is partly determined by the CRN's main remit.

GRAPPA Member Survey

Dr. Deepak R. Jadon and Dr. Carmel Stober reported the results of 2 surveys relating to the proposed CRN. The first survey disseminated to all 400 GRAPPA members in September 2016 was completed by 99 members, with 61 centers across 25 countries (and Hong Kong) wishing to join and contribute to the CRN (Table 3). In keeping with the proportional representation in GRAPPA, respondents included rheumatologists (81%) and dermatologists (19%).

Of centers wishing to participate, the following associated items were already being collected as part of existing research studies and could be contributed to the CRN: biosamples (53/99, 53%; including serum 41, DNA 31, RNA 18, skin 14, PBMC 10, synovial fluid 10, synovium 7, urine 9, and stool 2), clinical data (80/99, 81%; including clinical phenotype 67, demographics 67, patient-reported outcome measures 36, clinical examination indices 23, comorbidity 50), imaging (55/99, 56%; including plain radiographs 46, MRI 26, ultrasound 17, and high-resolution peripheral quantitative computed tomography 1); and biosample processing SOP for sharing (36%). The majority of respondents wanted to be both contributors and requestors of the CRN (70%), while 23% wished to be contributors only.

A second survey was performed in June 2017 of the 61 respondents wishing to join the CRN to establish what resources centers already have in place, what biosamples and analyses are already being performed, to gather information on financing, scope project proposals, and identify already established SOP. There were 31 respondents, with a similar geographical distribution to the first survey. Ninety-seven percent of centers were willing to adopt harmonized SOP for biosample and data collection, and 94% of centers have personnel in place to facilitate collection. A total of 55% of centers currently get consent from all patients attending clinic for future research studies, and 42% currently get consent from some but not all patients. A majority (81%) of centers preferred ethical approval to be sought centrally by the CRN; although 61% already had ethical approval for local collection and 77% had ethical approval to send anonymized biosamples to other centers. Biosamples from other countries were already transferred or received by 45% of centers, with 23% of centers stating some restrictions in MTA across international borders and an average time of 3 months to set up an MTA. There was a majority preference for data to be entered into a shared database (67%), with 42% of centers preferring paper and 45% eCRF. A requirement for external funding for clinical and biosample collection was stated by 55% of centers, as per the routes described earlier in this paper. The preference for biosample processing and storage was as follows: process biosamples locally and store locally

Table 3. Countries (including Hong Kong) with centers wishing to participate and contribute to the Collaborative Research Network.

Country	No. Centers
North America	
USA	19
Canada	4
Europe	
UK	9
Germany	3
Ireland	2
Spain	2
Turkey	2
the Netherlands	1
Belgium	1
Croatia	1
Iceland	1
Italy	1
South America	
Brazil	5
Argentina	4
Colombia	2
Peru	1
Venezuela	1
Middle East	
Israel	3
Bahrain	1
Asia	
Japan	1
Hong Kong	1
Singapore	1
Taiwan	1
China	1
Africa	
South Africa	2
Australia	2

(15/32; 47%); process centrally and store centrally (12/32; 38%); and process locally and store centrally (5/32; 16%).

GRAPPA members had immense enthusiasm for the CRN. The community would prefer centralized ethics, samples to be locally processed and locally stored as part of a "virtual biorepository," and a centralized clinical database. The majority of centers are currently collecting serum and DNA. The collection of RNA could be promoted through the use of a simple system such as the PAXgene Blood RNA tube.

Electronic Clinical Data Collection

Dr. Alexis Ogdie led a discussion on electronic data collection options for the CRN. A balance must be struck between comprehensive data that would address research requiring well-characterized cohorts versus feasibility, so that data collection and entry are not too onerous for centers. The research question being addressed is an important determinant of the complexity of data required and may therefore be best stratified into "core" and "extended" datasets. It would be sensible to incorporate some extra margin to permit unplanned analyses. Data should ideally be organized into tables: patient demographics, phenotype, visit information, samples collected, examination findings, diagnoses, comorbidities, social history, medications, etc., and with patient-reported outcomes for each domain. It will be important to standardize terminology for medications, dosing, and durations. It should be emphasized that "standardized data elements" does not mean standardized data collection or definitions. There can be much disparity between electronic medical records systems. Attention must be given to license fees and copyright issues relating to some clinical indices and patient-reported outcome measures. The storage of data both centrally and locally will improve clinical governance by ensuring integrity. Based upon all of these factors, it was recommended that the CRN collect data into a centralized database.

Authorship

Given the number of potential contributors to the CRN, Dr. Philip S. Helliwell led discussions on how authorship of publications relating to the CRN could be approached. There is certainly a need for an *a priori* publication policy, including a process for resolving disputes and appeals. The International Committee of Medical Journal Editors guidelines for publishing manuscripts[6] or the AMP Group Authorship Guidelines are models that could be implemented. The steering committee of the CRN or of a particular work package could agree on first and senior author roles. Other authors not to be overlooked include PRP, statisticians, sponsors, and clinical, laboratory, and imaging data collectors. Thresholds for clinical case contribution to the CRN may need to be set to attain authorship roles. A data sharing agreement would add value to the CRN's operation.

Discussion

The Classification of Psoriatic Arthritis[7] initiative is an exemplar of how 32 centers worldwide can collaborate to achieve great results through GRAPPA. Four candidate flagship research areas for the CRN include (1) predictors of treatment response in PsA and PsC, thereby permitting personalized and stratified medicine approaches; (2) predictors of structural damage and disease severity, linking with the existing PsA BioDAM project; (3) predictors of PsC progressing to PsA, thereby enabling earlier intervention and possibly even halting progression to PsA; and (4) comorbidity prevalence and effect on clinical outcomes in psoriatic disease.

A hybrid model with a centralized eCRF and harmonized SOP across sites based on rigorous validation appears to be the best approach going forward. Investigators must be

engaged through the collection of high-quality data that increases the likelihood of securing funding, opportunities to fund projects using samples from their sites, and nurturing other collaboration opportunities. PRP should be involved at every stage of the CRN's development. It may be sensible to further develop and refine existing projects such as the PsA BioDAM, into which much expertise and time has already been invested. The IPART and RA BioDAM projects will inform the CRN's centralized eCRF, biosample collection, and operational logistics. Validated SOP must be harmonized across centers, with training programs developed for both faculty and trainees to aid their correct implementation, scientific rigor, and reproducibility. A team of methodologists, biostatisticians, and "big data" scientists must be assembled to develop and implement novel analytic approaches for the CRN. While partnership with industry is fundamental, more stable longterm funding through national and government-related agencies should be sought as a priority.

The collaboration and momentum provided by a GRAPPA-CRN will offer more than the sum of its individual contributing centers. A CRN will permit high-quality research that can more effectively address questions pertinent to patients, clinicians, scientists, industry, and governments.

REFERENCES

1. National Institutes of Health. Accelerating Medicines Partnership (AMP). Overview. [Internet. Accessed February 14, 2018.] Available from: www.nih.gov/research-training/accelerating-medicines-partnership-amp
2. National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Roundtable on gaps and emerging opportunities in psoriatic arthritis. [Internet. Accessed February 26, 2018.] Available from: www.niams.nih.gov/about/meetings-events/roundtables/forum-gaps-psoriatic
3. National Institutes of Health. Accelerating Medicines Partnership (AMP). Autoimmune diseases of rheumatoid arthritis and lupus. [Internet. Accessed February 14, 2018.] Available from: www.nih.gov/research-training/accelerating-medicines-partnership-amp/autoimmune-diseases-rheumatoid-arthritis-lupus
4. Segurado OG, Sasso EH. Vectra DA for the objective measurement of disease activity in patients with rheumatoid arthritis. Clin Exp Rheumatol 2014;32 Suppl 85:S-29-34.
5. Abbvie Open Innovation Portal 2017 [Internet. Accessed February 14, 2018.] Available from: www.openinnovation.abbvie.com
6. ICMJE. International Committee of Medical Journal Editors Guidelines for Publishing Manuscripts. [Internet. Accessed February 14, 2018.] Available from: www.icmje.org
7. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665-73.