Biomarkers of Radiographic Progression in Psoriatic Arthritis: A Report from the GRAPPA 2011 Annual Meeting

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ABSTRACT. Clinical markers of radiographic progression have been studied in patients with psoriatic arthritis (PsA), and results have clearly confirmed the progression of radiographic damage over a 2-year period. Biomarkers of radiographic progression damage (erosion and new bone formation) have also been identified as a critical research issue in these patients. At the 2011 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), members discussed development of a pivotal observational study (PsA Biodam study) to determine the validity of several soluble biomarkers in predicting structural damage in patients with PsA receiving standard therapies. Specific protocol issues discussed were the inclusion criteria, selection of candidate biomarkers, timing of sample collection, the primary radiographic outcome measure, radiographic scoring methods, possible substudies, and funding strategies. (J Rheumatol 2012;39:2189–92; doi:10.3899/jrheum.120820)

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Biomarkers of radiographic progression in patients with psoriatic arthritis (PsA) have been identified as a critical research issue that might ultimately assist in the stratification of patients requiring more aggressive therapies. While PsA is certainly associated with the development of joint damage, erosions in PsA are less prevalent [odds ratio (OR) 0.609; p < 0.001] and progress at a slower rate than in rheumatoid arthritis (RA) based on a study from the Consortium of Rheumatology Researchers of North America (CORRONA) registry[1]. Other radiographic features well described in PsA include new bone formation, particularly at juxtaarticular margins, together with bony spurs or bridging that frequently develop at entheseal sites. Bony resorptive change is also commonly seen and can be quite dramatic in some patients, appearing as the classic pencil-in-cup deformity. Indeed, in affected individuals, this phenotype, known as arthritis mutilans, can be a predominant feature leading to digital shortening, joint instability, and associated poor function. Finally, asymmetrical spinal involvement is well described in PsA at sacroiliac joints and elsewhere in the spine. Significant cervical spine disease appears to be a feature in PsA, at times even in the absence of significant spinal disease elsewhere.

Studies of patients with early PsA have clearly confirmed the progression of radiographic damage over a 2-year period of followup. At baseline, erosions, assessed by a modified Sharp score to include 30 joints in the hands and 10 in the feet, were present in 27% of patients, and this progressed to 47% at 2 years of followup[2]. The number of erosions also increased from a mean of 1.2 (range 0–19) to a mean of 3 (0–25). Other studies have confirmed radiographic progression in established disease. At the University of Toronto Psoriatic Arthritis Clinic, Toronto, Canada, where radiographs are taken every 2 years, radiographic progression in biologic-naive patients with early PsA occurred in over 40% of patients between the first and second visit, and in 66% of patients between the first and third visits (unpublished data). Among patients receiving tumor necrosis factor inhibitors (TNFi), progression was observed in 30% from visit 1 to visit 2, and 33% from visit 1 to visit 3. These data suggest that a 20% progression over a 2-year period in an inception cohort is a conservative estimation, regardless of whether patients are on treatment or not.

A recent study focused on microcomputerized tomography changes in the metacarpophalangeal joints of a small cohort of patients with PsA compared with RA[3]. Patients with PsA had the same number of bone erosions, but erosions were less severe overall (smaller in size and depth) than in patients with RA. Erosions in PsA were mostly Ω- or tubule-shaped, whereas in RA, U-shaped lesions were more typical. Erosions in PsA were also more evenly distributed,

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whereas in RA, the radial aspects of the joints were more often affected. Finally and most interestingly, osteophytes reflecting new bone formation were increased in number, extent, and size in PsA compared with RA, often affecting the entire circumference of bone, forming a crown or bony corona. These data suggest that mechanisms of bone repair may be much more active in PsA. Thus, it would be important to include measurement of new bone formation in any future study of radiographic progression.

Clinical Markers of Radiologic Outcome

Clinical markers of radiographic progression have been the subject of a number of studies, in particular those using the Toronto database resource. Multivariate analyses of predictors for both clinical and radiological damage in 625 patients demonstrated that age, time in clinic, initial erythrocyte sedimentation rate, number of tender and swollen joints at previous visit, and number of deformed joints at previous visit were related to both clinical and radiological damage[4]. The number of actively inflamed joints, particularly the number of swollen joints, was associated with progression of radiological damage. In addition, the higher the number of previously damaged joints, the higher the risk for progression of damage. In a subsequent study, increased radiological progression was noted in digits showing dactylitis versus those without dactylitis (50% vs 38%, respectively; $p < 0.0001$)[5].

Followup studies from clinical trial data have also provided more information. For example, in the ADEPT (Adalimumab Effectiveness in PsA Trial), systemic inflammation in PsA, as indicated by elevated baseline C-reactive protein (CRP), was the only strong independent predictor of radiographic progression[6].

Biomarkers of Radiologic Outcome

Mullan, et al examined collagen-related markers in a cohort of inflammatory arthritis patients, including both RA and PsA[7]. After treatment with TNFi therapy, regression analyses showed that 1-month changes in $Col2-3/4C_{long\ mono}$, $Col2-3/4C_{short}$, or C-propeptide levels of this molecule were independently associated with, and correctly predicted, radiographic outcome in 88% of the patients. No significant difference was observed between RA and PsA patients. These collagen biomarkers may therefore be valuable early indicators of short-term biologic treatment efficacy in clinical trials and in individual patients with inflammatory erosive arthritis.

The question of bone remodelling, osteoclastogenesis, and bone erosion in PsA has been the subject of a number of articles. In one study, Anandarajah, et al examined the frequency of osteoclast precursors (OCP) in patients treated with etanercept. A decrease in OCP was observed after 3 and 6 months of therapy but there was no correlation with bone marrow edema volume on MRI scanning[8]. In a report by Dalbeth, et al, patients with PsA had higher circulating concentrations of Dickkopf-related protein and macrophage colony-stimulating factor (M-CSF) compared to psoriasis patients and controls[9]. Levels of M-CSF and receptor activator of nuclear factor kappa-B ligand (RANKL) also correlated with erosion, joint space narrowing, and osteolysis scores. Finally, in a study of PsA and RA patients by Ng and colleagues, bone biomarkers were measured at baseline, 1 month, 1 year, and 3 years after commencing treatment with a TNFi[10]. An increase in bone alkaline phosphatase was seen in PsA, both at baseline and following treatment. Other markers of bone formation were also increased, although not significantly. These observations are consistent with the observation that PsA patients, in contrast to RA, frequently show both erosive destruction changes and features of new bone formation.

PsA Biodam Study

Members of GRAPPA and OMERACT (Outcome Measures in Rheumatology) have identified the need to conduct a study of biomarkers of radiographic progression/damage (erosion and new bone formation) in PsA. A similar study in RA commenced recruitment in 2011 and a study in ankylosing spondylitis is planned.

The primary objective of this pivotal observational study would be to determine the independent predictive validity of several soluble biomarkers in predicting structural damage in patients with PsA receiving standard disease-modifying antirheumatic drug (DMARD) and TNFi therapy. Secondary objectives would include establishing which modifiable clinical and laboratory variables used in routine practice individually or in combination have the strongest and most consistent association with change in radiographic damage. Investigators hope to establish the additional predictive value of high-priority soluble biomarkers to the optimum risk prediction model developed from modifiable clinical and laboratory variables assessed in routine care of patients who exhibit radiographic progress while receiving DMARD therapy or TNFi therapy, or irrespective of the type of treatment. In developing this protocol, a number of issues have been discussed in depth: inclusion criteria, selection of candidate biomarkers, timing of collection of biologic specimens, the primary radiographic outcome measure, how radiographs should be scored, and suggested substudies.

Inclusion Criteria

A primary issue regarding inclusion criteria has been to determine if the study should have an inception PsA cohort, or a cohort enriched for the presence of joint damage, or should be a study of all-comers with PsA. It was agreed that the central question in this study is how to identify early those patients who will develop erosive disease so that more targeted treatment can prevent such damage. Thus, although we know that presence of erosion at baseline will predict

further erosion, to include only patients with joint damage will not allow us to answer this question. If we elect to focus on an inception cohort, one concern is that about 50% of patients will not develop erosions within a 2-year period of followup. Further, the rate of progression of erosive change is small in those who do erode (estimated mean, 1 new erosion/year). Evidence presented earlier from the Toronto database suggests that a conservative estimate of 20% of patients in an inception cohort would develop radiographic progression over a 2-year period.

Assisting in this discussion was Dr. Richard Cook (University of Waterloo, Waterloo, Canada), who has conducted power calculations based on the assumption of 20% progression and a weak correlation between a known marker (CRP) and a novel biomarker. With 1000 subjects, an OR of 1.261 with 80% power can be detected, but with 600 subjects, only larger effects (OR 1.351) of the novel biomarker can be detected when controlling for CRP. Thus, while a study of 600 patients would provide useful data, a larger study of 1000 patients should maximize the chance of a candidate biomarker or group of biomarkers identifying a significant change in radiographic progression.

GRAPPA members further discussed the definition of an inception cohort, particularly regarding duration of disease, type of patient recruited, and what medications might be permitted. It was agreed that duration of disease should be < 2 years since diagnosis; patients would be identified using the ClASsification for Psoriatic ARthritis (CASPAR) and those with only spinal or only entheseal disease should be excluded; and patients could be on a DMARD as long as they are naïve to biologic therapies.

Imaging Outcome Measure
While many members argued in favor of including magnetic resonance imaging (MRI) as the primary imaging tool, the difficulty is that minimal, if any, data on MRI are available as a radiographic outcome measure in PsA. Therefore, members agreed that the primary imaging outcome measure would be progression of erosive change on plain radiographs. In order to gather as much data as possible from this cohort and to build information for the future, members also agreed that MRI of the predominantly involved hand or foot at baseline and at 2 years would be a valuable secondary outcome measure in selected centers. Members agreed that radiographs of hands and feet at baseline and at 1 and 2 years were sufficient in PsA. This frequency of radiographic examination is different from that planned in the RA Biodam study (every 6 months), but members believed that the slower radiographic assessments at 6-month intervals may not be informative given the slower rate of progression in PsA.

How Should Radiographs Be Scored?
Members agreed that a modified Sharp measure to include the distal interphalangeal joints should be used to score erosive change. Scoring new bone formation was likely to be a greater challenge, with the Psoriatic Arthritis Ratingen Score (PARS) providing the only published data[11]. Many felt that the PARS was not yet adequately validated and its use might prove complex. With a successful PsA BioDam study, it is possible that a new measure of bone formation changes might be developed and tested in this cohort.

Suggested Substudies
In addition to the MRI substudy mentioned above, members discussed other substudies and selected sites that should be strongly considered, including a synovial biopsy study linked to the Pathobiology of Early Arthritis Cohort (PEAC) being undertaken by Prof. Costantino Pitzalis and colleagues. Other centers may wish to develop an ultrasound substudy, which, like MRI, is likely to provide useful data. Members agreed that the funding structure for these substudies should be separate from the funding of the primary study.

Measuring Candidate Biomarkers
Members agreed that initial funding estimates should include the cost of measuring likely candidate biomarkers (e.g., CRP, matrix metalloproteinase-3, bone turnover markers, RANKL, osteoprotegerin, and serum biomarkers of type 2 collagen degradation and synthesis) at an early stage in the project. Once the clinical and radiographic data have been collected, comparison with these candidate biomarkers can be made without delay, providing early data for publication. The second phase of the project can then focus on whether other biomarkers, including novel ones either singly or in combination, perform better than those currently available. Finally, members discussed the timing of the biomarker collection and agreed that samples should be collected at baseline and at 3, 6, 12, 18, and 24 months.

Conclusion
In the development of the PsA Biodam study, there was general agreement regarding study design. During the drafting of a more detailed study protocol, the key challenge will be identification of funding support. However, given the success of other GRAPPA-related projects, e.g., the development of the CASPAR criteria and the GRAPPA Composite Exercise Project, as well as the success of the RA Biodam study that is currently recruiting patients, members are confident that adequate funding for the PsA Biodam study will be secured.

REFERENCES
1. Reddy SM, Anandarajah AP, Fisher MC, Mease PJ, Greenberg JD, Kremer JM, et al. Comparative analysis of disease activity measures, use of biologic agents, body mass index, radiographic features, and bone density in psoriatic arthritis and rheumatoid arthritis patients followed in a large US disease registry.

J Rheumatol 2010;37:2566-72.

2. 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.

3. Finzel S, Englbrecht M, Engelke K, Stach C, Schett G. A comparative study of periarticular bone lesions in rheumatoid arthritis and psoriatic arthritis. Ann Rheum Dis 2011;70:122-7.

4. Bond SJ, Farewell VT, Schentag CT, Gladman DD. Predictors for radiological damage in psoriatic arthritis: Results from a single centre. Ann Rheum Dis 2007;66:370-6.

5. Brockbank JE, Stein M, Schentag CT, Gladman DD. Dactylitis in psoriatic arthritis: A marker for disease severity? Ann Rheum Dis 2005;64:188-90.

6. Gladman DD, Mease PJ, Choy EH, Ritchlin CT, Perdok RJ, Sasso EH. Risk factors for radiographic progression in psoriatic arthritis: Subanalysis of the randomized controlled trial ADEPT. Arthritis Res Ther 2010;12:R113.

7. Mullan RH, Matthews C, Bresnihan B, FitzGerald O, King L, Poole AR, et al. Early changes in serum type II collagen biomarkers predict radiographic progression at one year in inflammatory arthritis patients after biologic therapy. Arthritis Rheum 2007; 56:2919-28.

8. Anandarajah AP, Schwarz EM, Totterman S, Monu J, Feng CY, Shao T, et al. The effect of etanercept on osteoclast precursor frequency and enhancing bone marrow oedema in patients with psoriatic arthritis. Ann Rheum Dis 2008;67:296-301.

9. Dalbeth N, Pool B, Smith T, Callon KE, Lobo M, Taylor WJ, et al. Circulating mediators of bone remodeling in psoriatic arthritis: Implications for disordered osteoclastogenesis and bone erosion. Arthritis Res Ther 2010;12:R164.

10. Ng CT, Gibbs A, Murray B, Brady JJ, Bresnihan B, Veale DJ, et al. Bone biomarkers and bone density measurements in patients with inflammatory arthritis prior to and following anti-TNF therapy [abstract]. Arthritis Rheum 2008;58 Suppl:S587.

11. Wassenberg S, Fischer-Kahle V, Herborn G, Rau R. A method to score radiographic change in psoriatic arthritis. Z Rheumatol 2001;60:156-66.