OMERACT 10 Sharp Symposium: Important Findings in Examination of Imaging Methods for Measurement of Joint Damage in Rheumatoid Arthritis

VIBEKE STRAND, SARAH R. KINGSBURY, THASIA WOODWORTH, ROBERT LANDEWÉ, MIKKEL ØSTERGAARD, CHARLES PETERFY, DÉSIRÉE van der HEIJDE, MARIA-ANTONIETTA D'AGOSTINO, WALTER MAKSYMOWYCH, PAUL P. TAK, GEORGE WELLS, and PHILIP G. CONAGHAN

ABSTRACT. The Sharp Symposium was held at the Outcome Measures in Rheumatology Clinical Trials 2010 meeting (OMERACT 10) in honor of the late John Sharp, consummate rheumatologist and researcher. The symposium focused on the status of current scoring methods in radiography, magnetic resonance imaging (MRI), and ultrasound (US) in rheumatoid arthritis (RA), as well as on the use of soluble and tissue biomarkers in RA, with the aim of updating recommendations regarding methods for enhanced detection, monitoring, and prediction of joint damage in clinical trials. (J Rheumatol 2011;38:2009–13; doi:10.3899/jrheum.110415)

Key Indexing Terms:
OMERACT RADIOGRAPHS MAGNETIC RESONANCE IMAGING
ULTRASOUND BIOMARKERS

The Sharp Symposium at the 2010 meeting of Outcome Measures in Rheumatology Clinical Trials (OMERACT 10) was organized in honor of the late John Sharp, MD, a consummate rheumatologist and researcher who contributed significantly to the assessment of bone and joint damage in rheumatoid arthritis (RA) and OMERACT efforts in this field. Dr. Sharp developed and validated a radiographic scoring system that has been widely utilized in randomized controlled trials (RCT) in RA. He had long advocated the importance of assessing both hands and feet and the reporting of "total," as well as separate "erosion" and "JSN" (joint space narrowing) scores, regardless of scoring system[1]. Dr. Sharp's later interests included radiographic assessment of repair of erosions and development of automated methods for assessing joint damage in RA[2,3].

The focus of the Sharp Symposium was to review the status of current scoring methods in radiography, magnetic resonance imaging (MRI), and ultrasound (US), and the use of soluble and tissue biomarkers for their ability to rapidly assess and predict progression of joint damage. The aim of the symposium was to update recommendations for use of methods for enhanced detection, monitoring, and prediction of joint damage in clinical trials. The importance of this effort is highlighted by the growing body of evidence that prevention and/or inhibition of joint damage preserves function, which can delay and even prevent disability and loss of work productivity.

Conventional Radiography

Dr. Sharp developed and validated a radiographic scoring system for assessing erosions on a scale of 0–5 and JSN 0–4 in individual joints in the hands, wrist, and feet that has been widely utilized in RCT in RA[4]. Two subsequent modifications, the van der Heijde-Sharp (vdH-S), which scores erosions in the joints of the feet on a scale of 0–10, and Genant-Sharp (G-S), which omits scoring of 2 carpal bones to avoid errors due to overlying shadows and placement on the

From the Division of Immunology/Rheumatology, Stanford University School of Medicine, Portola Valley, CA, USA; Section of Musculoskeletal Disease, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, UK; Leading Edge Clinical Research LLC, Stuart, FL, USA; Department of Internal Medicine/Rheumatology and Caphri School for Public Health, Maastricht University Medical Center, Maastricht, The Netherlands; Department of Rheumatology, Copenhagen University Hospital at Glostrup, Copenhagen, Denmark; Spire Sciences, LLC, San Francisco, CA, USA; Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands; Versailles-Saint Quentin En Yvelines University, Department of Rheumatology, Ambroise Paré Hospital, APHP, Boulogne-Billancourt, France; Department of Medicine, University of Alberta, Edmonton, AB, Canada; Division of Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands; and Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Canada.

V. Strand, MD, Division of Immunology/Rheumatology, Stanford University School of Medicine; S.R. Kingsbury, PhD, Section of Musculoskeletal Disease, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit 2; T. Woodworth, MD, Leading Edge Clinical Research LLC; R. Landewé, MD, PhD, Department of Internal Medicine/Rheumatology & Caphri School for Public Health, Maastricht University Medical Center; M. Østergaard, MD, PhD, DMSc, Department of Rheumatology, Copenhagen University Hospital at Glostrup; C. Peterfy, MD, PhD, Spire Sciences; D. van der Heijde, MD, PhD, Department of Rheumatology, Leiden University Medical Center; M-A. D'Agostino, MD, Versailles-Saint Quentin En Yvelines University, Department of Rheumatology, Ambroise Paré Hospital, APHP; W. Maksymowych, MB, CHB, FRCPC, Department of Medicine, University of Alberta;, P.P. Tak, MD, PhD, Division of Clinical Immunology and Rheumatology, Academic Medical Center/University of Amsterdam; G. Wells, MSc, PhD, Department of Epidemiology and Community Medicine, University of Ottawa; P.G. Conaghan, MBBVS, FRACP, Section of Musculoskeletal Disease, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit.

Address correspondence to Dr. Strand; E-mail: vstrand@stanford.edu

radiographic plate, have been developed[5,6]. Overall, in the hand, the modified Sharp method scores: 17 locations for erosions and 18 for JSN; vdH-S: 16 for erosions and 15 for JSN; and G-S: 14 for erosions and 13 for JSN. All methods have been validated and accepted by the US Food and Drug Administration and European Medicines Agency.

Radiographic datasets with images of hands and feet from 6 RCT in RA in early[2] and later disease[4] were examined. The goal was to determine which joints demonstrated the most damage at baseline and which showed the most progression over 6 and/or 12 months, investigating the possibility of simplifying the scoring system. Erosions and JSN were assessed separately for their involvement at baseline and change, to determine whether there were differences in distribution of joint involvement in early versus later disease, as well as the pattern of progression.

In hopes of developing a more abbreviated and uniform scoring system, the following questions were asked.
Which joints in hand and wrist should be scored by:

- Frequency of involvement
- Reliability of scoring
- Reader competency
- Image quality, recognizing the problem of projectional superimposition.

The goal of an abbreviated system would be to eliminate joints infrequently involved or difficult to read.

Drs. Philip Conaghan, Sarah Kingsbury, and Vibeke Strand reviewed established RA datasets that included DE019, a 52-week study of adalimumab in RA patients with inadequate response to methotrexate (MTX-IR) and mean disease duration = 11.0 ± 9.2 yrs, scored by 2 readers using the modified Sharp method[7]. They also reviewed datasets from the study Abatacept in Inadequate responders to Methotrexate (AIM, mean disease duration = 8.5 ± 7.3 yrs)[8], scored by 2 readers using G-S; as well as the Rheumatoid Arthritis Prevention of structural Damage (RAPID) studies 1 and 2 (certolizumab)[9,10], previously analyzed by Drs. Desirée van der Heijde and Robert Landewé using the vdH-S method. Data showing frequency of joint involvement (erosion and JSN, baseline, and change at 12 mo scores) from the DE019 and AIM datasets are presented in Tables 1 and 2. Drs. Landewé and van der Heijde reviewed 4 datasets scored by vdH-S from the Combination of Methotrexate and Etanercept (COMET) trial in early disease[11], as well as the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) study[12] and RAPID 1 and 2 trials in later disease[9,10]. Their detailed analyses are the subject of a separate publication in this section[13].

These analyses demonstrated remarkable similarity in distribution of radiographic involvement as well as which joints showed progression, and they revealed that the entire spectrum of joints were involved by both erosions and JSN, independent of disease duration and previous treatment. Regardless of early or later disease, assessments of feet as well as hand/carpal joints were equally important. Recognizable patterns were similar regardless of scoring system employed: Erosions in early disease showed involvement of metatarsophalangeal (MTP) joints (5, 1) and metacarpophalangeal joints (MCP); and JSN in early disease showed involvement of wrist, MCP (2, 3), and MTP.

No consistent pattern emerged for joints that could be excluded. This is particularly important, as the "signal" for change, in other words progression of joint damage, is much lower now than 10 years ago and even more skewed. It was thus concluded that it does not appear worthwhile to proceed with developing a more abbreviated scoring system.

Based on the question, "Do the data inform us such that work towards more abbreviated scoring systems should be initiated?", voting was Yes 37%, No 46%, and Don't Know 16%. Thus, it does not appear prudent to pursue further research to attenuate the number of joints evaluated in radiographic scoring.

Magnetic Resonance Imaging

As with conventional radiography, data in early and established RA cohorts were examined for the bone areas most frequently showing damage and change over time, as well as for features — synovitis and osteitis — that have been demonstrated to be associated with joint damage. The RA MRI Scoring System (RAMRIS), a semiquantitative scoring system developed for erosion, synovitis, and osteitis assessment by the OMERACT MRI in Inflammatory Arthritis task force, was utilized for characterization of joint damage and sensitivity to change. Joints with narrowing were also identified in each image. Analyses performed by Dr. Charles Peterfy are presented in more detail in this section[14].

As a result, data from 4 RCT were available, 2 using 1.5 T MRI and 2 using 0.2 T MRI, with a total of 522 patients, each with 3 to 4 visits, a total of 1347 patient-visits with the same imaging quality control methods using the same readers. Special care was taken to protect contributor confidentiality.

Patterns of joint damage were comparable to those seen with radiography. Erosion prevalence was much higher on MRI, but the pattern was similar to that on radiographs, with slight decreases in involvement from proximal to distal and radial to ulnar. Patterns of erosions were similar across datasets and whether in early or later disease. There is a close correlation between MRI bone edema and post-surgery histologic assessment of osteitis; and bone edema by MRI is the strongest predictor of subsequent radiographic progression in early RA[15,16,17]. Thus MRI offers the ability to assess synovitis and osteitis, likely modifiable earlier in disease, thus offering the ability to prevent progression to erosive disease. Although more expensive per patient, MRI methods are potentially better suited to centralized reading and quality control, and the enhanced sensitivity of 3D scanning can potentially enable improved precision and sensitivity to change with smaller sample sizes and therefore lower total cost than required for radiographic studies.

Dr. Mikkel Ostergaard presented analyses of erosion distribution and progression based on MRI datasets from 258 RA patients (126 with early RA < 6 months), for whom 223, including all of the early RA patients, had 1-year followup. All patients had MRI (1.5, 0.6, or 0.2 T) of one wrist, and 86 had MCP joint images. Results are presented in more detail in this section[18]. Although wrist bones most frequently showed erosions at baseline, as well as progression, no bones were without erosion in at least some patients. Nevertheless, these analyses suggested that bone involvement patterns might be considered for some MRI protocols.

Dr. Conaghan, in conjunction with Dr. Mike Bowes (Imorphics Ltd.), presented a small MRI study of RA patients demonstrating the feasibility and high reproducibility of fully automated quantitative joint pathology evaluation for synovitis and erosions, using modern 3D image analysis techniques based on statistical shape modeling. Such technologies may contribute to more rapid and accurate assessment of MRI datasets with improved responsiveness over current "gold standard" semiquantitative scoring methods.

Conclusions from the analyses of radiographic and MRI datasets revealed similar and recognizable patterns of structural damage:

- Erosions
- (Early) involvement of MTP and MCP
- Continued progression in those joints
- JSN / osteitis / synovitis
- (Early) involvement of wrist, MCP, and MTP
- Continued progression in those joints

Overall, MRI datasets indicated earlier evidence of but no differences in the distribution or type of bone and joint damage.

Based on the question, "Should we continue to optimize semiquantitative scoring for MRI?", voting was Yes 61%, No 24%, Don't know 15%; and "Should we put quantitative scoring by MRI through the OMERACT filter?", voting was Yes 89%, No 5%, Don't Know 6%.

Thus OMERACT 10 participants agreed that further research was desirable to optimize semiquantitative scoring, and were especially enthusiastic to apply the OMERACT filter to quantitative methods.

Ultrasound

A detailed overview of the status of US in assessing joint involvement in RA was presented by Dr. Maria-Antonietta D'Agostino and is the subject of a subsequent publication in this section[19]. A systematic literature review documented that many studies have demonstrated ultrasonographic examination of joints in RA to be more sensitive than physical examination for detection of synovitis. As a result of work by the OMERACT-EULAR US Group, there is now consensus on scoring synovitis at the individual joint level, as well as methods to characterize erosions. However, there is still no consensus regarding scoring synovitis at the patient level for RCT. The OMERACT global synovitis score (GLOSS) will require further research to determine the most reliable method for assessing inflammation at the joint level.

Based on the question, "Do you support development of the OMERACT Ultrasound GLOSS?", voting was Yes 73%, No 8%, and Don't Know 18%. There was consensus among OMERACT 10 participants to pursue this research.

Overall, participants expressed a high interest in better understanding the clinical relevance of changes in structural damage in RA, assessed by all 3 imaging techniques. Based on the question, "Do we want to explore the clinical relevance of change by x-ray?", voting was Yes 80%, No 14%, Don't know 5%. And "Do we want to explore the clinical relevance of change by MRI?", voting was Yes 88%, No 8%, Don't Know 5%. And "Do we want to explore the clinical relevance of change by US?", voting was Yes 83%, No 11%, and Don't Know 6%.

Biomarkers

Attention turned to whether soluble or/and tissue biomarkers could be utilized to more sensitively detect and monitor the occurrence of joint damage, perhaps even before it is visible by imaging methods. In addition, there was interest in determining whether biomarkers could be used to select therapy for individual patients.

Soluble biomarkers. There are limited data on the relationship between abnormalities detected by imaging methods and soluble biomarkers.

The OMERACT Soluble Biomarker working group, led by Walter Maksymowych, established a plan, working with statistician George Wells, to conduct a prospective study with 2 aims: (1) to assess whether change in one or more biomarkers could reflect/predict change in a joint damage endpoint at the group level as an endpoint for RCT and cohort studies, or/and at the individual patient level as a tool for monitoring in clinical practice; and (2) to assess whether changes in particular biomarkers reflect or predict change in a joint damage endpoint independently of known predictors such as baseline damage scores, rheumatoid factor and/or anti-cyclic citrullinated peptide antibody positivity, shared epitope, C-reactive protein/erythrocyte sedimentation rate, or Disease Activity Score, regardless of treatment.

Participants were asked to consider the design and sample size assumptions, together with statistical methodology appropriate for such a study.

Tissue biomarkers. Since RA primarily involves the synovial tissue, markers detected by examination of synovial biopsies represent a logical opportunity to assess changes in pathobiology that could indicate improvement with treatment and the possibility to inhibit/prevent joint damage. This area has been further stimulated by technical advances, such as the advent of new methods to obtain synovial tissue specimens from both actively inflamed and clinically quiescent joints[20]. Dr. Paul

Tak presented data showing that, in small studies, synovial immunohistochemistry predicts treatment responses on the group level by decreases in synovial sublining macrophages across different mechanisms of action. This approach may be used to screen for proof of principle in small, high density of data clinical trials during early drug development. In addition, the decrease in synovial plasma cells predicts clinical response to rituximab treatment, supporting the importance of autoantibodies in the pathogenesis of RA. Patients with lymphocyte aggregates and high levels of tumor necrosis factor (TNF) in the synovium are more likely to respond well to infliximab, although positive and negative predictive values are too low to recommend this approach in the context of personalized healthcare. The OMERACT Synovial Tissue group described a recently initiated research program, termed the Synoviomics Project, which aims to identify diagnostic and prognostic factors based on synovial tissue analysis in very early disease.

Based on the general question, "Should the methodology of power calculations in longitudinal observational databases be a topic for OMERACT 11?", voting was Yes 53%, No 33%, Don't Know 14%. And, "Is this methodology applicable to OMERACT activities other than biomarkers?", voting was Yes 49%, No 19%, Don't Know 32%.

There was modest agreement to pursue these methodologies, but participants were unclear about the applicability of them to other settings.

Conclusions

Overall, updates regarding each of the imaging modalities in RA were presented, as well as the potential utility of soluble and tissue biomarkers to identify and predict joint damage. Dr. Sharp's important and longterm commitment to defining and further improving methods for assessing joint damage in RA was reaffirmed. The gold standard of radiographic damage assessment using the Sharp scoring method was confirmed, as well as agreement between existing modified Sharp scores, i.e., the vdH-S and G-S. Based on the distribution of joint damage in both early and later disease and those joints most likely to demonstrate progression, in both radiographic and MRI studies, an abbreviated scoring system will lead to loss of information, and thus not result in improved sensitivity and/or specificity.

There is a range of promising soluble and synovial tissue biomarkers that may enhance the timeliness and sensitivity of measurement of joint inflammation and damage. They will require additional research to determine whether they meet the OMERACT filter and to validate them for use in both clinical research and clinical practice.

ACKNOWLEDGMENT

The authors acknowledge the following sponsors for generously providing results from their imaging databases for analyses: Abbott, Amgen, BMS, Centocor, Genentech, Sanofi-Aventis, Roche, UCB, and Wyeth/Pfizer.

REFERENCES

1. Strand V, Sharp J. Radiographic data from recent randomized controlled trials in rheumatoid arthritis: What have we learned? Arthritis Rheum 2003;48:21-34.
2. van der Heijde D, Landewe R, Sharp JT. Repair in rheumatoid arthritis, current status. Report of a workshop at OMERACT 8. J Rheumatol 2007;34:884-8.
3. Sharp JT, Angwin J, Boers M, Duryea J, Finckh A, Hall JR, et al. Multiple computer-based methods of measuring JSW can discriminate between treatment arms in the COBRA Trial — update of an ongoing OMERACT project. J Rheumatol 2009;36:1825-8.
4. Sharp JT, Lidsky MD, Collins LC, Moreland J. Methods of scoring the progression of radiologic changes in rheumatoid arthritis: correlation of radiologic, clinical and laboratory abnormalities. Arthritis Rheum 1971;14:706-20.
5. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27:261-3.
6. Genant GK, Jiang Y, Peterfy C, Lu Y, Reidei Y, Countryman P. Assessment of rheumatoid arthritis using a modified scoring method on digitized and original radiographs. Arthritis Rheum 1998;40:1583-90.
7. Jamal S, Patra K, Keystone EC. Adalimumab response in patients with early versus established rheumatoid arthritis: DE019 randomized controlled trial subanalysis. Clin Rheumatol 2009;28:413-9.
8. Genant HK, Peterfy CG, Westhovens R, Becker JC, Aranda R, Vratsanos G, et al. Abatacept inhibits progression of structural damage in rheumatoid arthritis: results from the long-term extension of the AIM trial. Ann Rheum Dis 2008;67:1084-9.
9. Keystone E, Heijde D, Mason D Jr, Landewe R, Vollenhoven RV, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 2008;58:3319-29.
10. Smolen J, Landewe RB, Mease P, Brzezicki J, Mason D, Luijtens K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis 2009;68:797-804.
11. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363:675-81.
12. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2008;372:375-82.
13. Landewé RBM, Strand V, Conaghan PG, van der Heijde DM. Damage and progression on radiographs in individual joints: data from pivotal randomized controlled trials. J Rheumatol 2011;38:2018-22.
14. Peterfy CG, Countryman P, Gabriele A, Shaw T, Anisfeld A, Tsuji W, et al. MRI in RA clinical trials: Emerging patterns based on recent experience. J Rheumatol 2011;38:2023-31.
15. McQueen FM. A vital clue to deciphering bone pathology: MRI bone oedema in rheumatoid arthritis and osteoarthritis. Ann Rheum Dis 2007;66:1549-52.
16. Jimenez-Boj E, Nöbauer-Huhmann I, Hanslik-Schnabel B, Dorotka R, Wanivenhaus AH, Kainberger F, et al. Bone erosions and bone marrow edema as defined by magnetic resonance imaging reflects true bone marrow inflammation in rheumatoid arthritis. Arthritis Rheum 2007;56:1118-24.
17. Hetland ML, Ejbjerg B, Hørslev-Petersen K, Jacobsen S,

Vestergaard A, Jurik AG, et al. MRI bone oedema is the strongest predictor of subsequent radiographic progression in early rheumatoid arthritis. Results from a 2-year randomised controlled trial (CIMESTRA). Ann Rheum Dis 2009;68:384-90.
18. Ostergaard M, Dohn UM, Duer-Jensen A, Hetland ML, Herslev-Petersen K, Stengaard-Petersen K, et al. Patterns of MRI bone erosion in rheumatoid arthritis — which bones are most frequently involved and show the most change? J Rheumatol 2011;38:2014-7.
19. Mandl P, Naredo E, Wakefield RJ, Conaghan PG, D'Agostino MA. A systematic literature review analysis of ultrasound joint count and scoring systems to assess synovitis in rheumatoid arthritis, according to the OMERACT filter. J Rheumatol 2011;38:2055-62.
20. van de Sande MG, Gerlag DM, Lodde BM, van Baarsen LG, Alivernini S, Codullo V, et al. Evaluating antirheumatic treatments using synovial biopsy: a recommendation for standardisation to be used in clinical trials. Ann Rheum Dis 2011;70:423-7.