Assessing Single Joints in Arthritis Clinical Trials

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ABSTRACT. Endpoints and outcome measurements to detect changes in joint structure for the assessment of single joints are needed to enable rheumatology clinical trials of therapies targeting preservation of joint structure, especially via locally applied therapies. While the assessment of certain aspects of single joint inflammation and function is accepted in the evaluation of osteoarthritis (OA) using the WOMAC, it tends to be limited to the knee and hip. The advent of therapies that are directed toward a single joint in inflammatory arthritis, including intraarticular cytokine antagonists and gene therapeutics, requires reliable measures to assess change over time in single joints and the clinical meaningfulness of such change. Traditionally, clinical trials for inflammatory arthritis have used composite response indices such as American College of Rheumatology response or improvement in Disease Activity Score as outcomes based on multiple joint clinical measures, acute phase reactants, and functional status. However, it is not known whether these will appropriately detect changes referable to single joint intervention. This Special Interest Group was developed to bring together interested individuals to identify and evaluate outcome measurements for single joints. The knee was the initial focus, as clinical, radiographic, and functional assessments have been well developed for knee OA. A PubMed English language review was conducted before OMERACT 8, evaluating existing clinical instruments in the context of the OMERACT filter. At OMERACT 8, the group developed a research agenda to perform additional validation studies of clinical and functional indices, imaging, synovial histopathology, and soluble biomarkers. (J Rheumatology 2007;34:641–7)

Key Indexing Terms:

OUTCOME ASSESSMENT	ARTHRITIS	VALIDITY
RELIABILITY	RESPONSIVENESS	JOINT EXAMINATION

Pharmacotherapies for inflammatory arthritis have traditionally been delivered systemically, either as oral small molecules or parenteral biologics, administered to patients with multiple affected joints. Composite assessment criteria used in clinical trials of these agents [e.g., American College of Rheumatology (ACR) responder criteria, or EULAR response measured by Disease Activity Score for rheumatoid arthritis (RA) or psoriatic arthritis (PsA), or PsARC for PsA] are weighted heavily according to standardized assessment of tender and/or swollen joint counts as well as global assessments. The ability of composite measurements to assess interventions directed toward a single joint has not been studied, but it is likely that some validity and discriminative ability would be lost if utilized outside of their intended polyarticular framework.

The need for therapies that are directed toward "refracto-

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ry" inflamed joints that may fail to respond to systemically delivered therapy is being addressed by several groups, who have stimulated the need for this Special Interest Group (SIG). Further, in disorders such as gout and osteoarthritis (OA) that may be characterized by aggressive mono- or pauciarticular involvement, a similar approach may be useful. Already, intraarticular corticosteroids are commonly used in these conditions, as well as hyaluronate derivatives. Preliminary evidence has suggested that approaches such as intraarticular injections of tumor necrosis factor inhibitors[1] and other cytokine antagonists, gene transfer agents that express cytokine antagonists[2,3], growth factors or their antagonists, or other antiinflammatory approaches are feasible. However, the lack of validated assessment criteria may hinder development of these agents in the treatment of single joints.

Single joint assessments have been developed for OA of the knee and hip. Past and present efforts by OMERACT and OARSI have developed clinical trial outcomes for OA[4], with most work focusing on relief of signs and symptoms measured by the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) and its component domains (patient and physician global assessments, and patient assessment of pain), but with limited attention to changes in clinical examination (swelling/tenderness). Intraarticular delivery of hyaluronic acid derivatives has been approved for the treatment of OA; however, the requirements for approval for these "devices" have sometimes differed from the criteria for "drugs," with different standards and benchmarks used. These standards, which include the demonstration of safety and "substantial equivalence" to a previously marketed device, do not typically require the preclinical and extensive clinical testing required for investigations drugs and biologics[5]. The development of structure-modifying therapies for OA requires additional exploration of the role of advanced imaging techniques, as well as the validation of biochemical and imaging biomarkers that may reflect disease activity, changes in joint structure, and outcomes. Additional correlations between novel assessment methods and clinical assessment and functional evaluation are needed. Further, short-term measurements to provide preliminary evidence of efficacy in proof of concept and short-term clinical studies may not necessarily equate with longterm assessments of clinically relevant benefit and outcomes. The relationships between changes in single joint status and various measurements of disease state and function have largely been unexplored.

While the assessment of therapeutic response has been developed for clinical trials of OA (primarily for the knee only), these methods of single joint assessment may not be valid in RA or other forms of inflammatory arthritis. The established Minimal Clinical Importance Difference (MCID) for OA assessments are also likely to differ in inflammatory arthritis. The responsiveness of these OA measurements in response to therapeutic intervention in inflammatory disease is unknown, and whether outcomes such as OMERACT-OARSI responses in OA are applicable to inflammatory diseases also has not been explored.

Objectives of the Special Interest Group

The primary objective of this SIG was to develop a core set of domains to assess therapeutic responses in single joints. An initial focus of this SIG was to determine whether clinical and functional assessments of the knee joint used in OA studies can be used for inflammatory arthritis, or if new assessments will be required. This SIG was intended to cover in more depth the specific areas of interest regarding single joint assessment that will be integrated with other OMERACT groups. The longterm goals of the group also complement the early assessment of the joint Superworkshop by examining single joints in this framework, and to ultimately determine applicability across a range of disease states and other joints, and longer term outcomes. The participation of OMERACT members from other groups including OA, ultrasound, magnetic resonance imaging (MRI), and histopathology/synovitis will be helpful in guiding the discussions and directions of this SIG to take advantage of the collective experience and previously conducted evaluations.

Longterm objectives. The longterm objectives of this SIG were:

1. To establish key domains needed for single joint assessment;
2. To review currently used assessments of single joints and determine if these have been validated in inflammatory arthritis as well as OA, specifically in the setting of therapeutic delivery of agents designed to act on single joints;
3. To determine which domains have validated assessment instruments;
4. To evaluate the need for developing instruments to assess other joints for which methods may not currently exist;
5. To develop a research plan to ensure all such measures fulfill the requirements of the OMERACT filter.

The short-term focus of the group was the knee joint, with an initial evaluation of clinical and functional assessments of this joint in RA and OA, which will serve as a model for later expansion to other joints and disease states.

Methods

A group of interested individuals was assembled in the Spring of 2005, under the co-chairmanship of C. Bingham and P. Mease. Monthly teleconferences were held over the year to discuss the preliminary goals of the SIG and to develop a preliminary agenda. A fellow (J. Giles) was chosen to participate in the SIG. The Chairs of the SIG met with members of the OMERACT Executive Board and the other representatives of the Superworkshop at EULAR 2005 in Vienna. In line with the ongoing work of the surrogate measures ("Superworkshop") group, the decision was made to focus first on the knee joint in RA.

Pre-conference literature reviews were conducted to evalu-

ate the performance characteristics (using the OMERACT filter) of the clinical examination, patient-derived functional assessments, and imaging modalities in OA and RA of the knee. A summary of the results of the literature review was presented, the details of which are to follow in a separate publication. Integration of the Single Joint SIG within the context of the larger Superworkshop on Surrogate Measures was also discussed. Additional participants (e.g., physiotherapy, orthopedics, outcome researchers) will be sought through the course of review of existing data to expand the SIG to reflect these important domains of inquiry.

Clinical examination. A comprehensive literature review evaluated clinical domains of inquiry for the assessment of the knee in arthritis clinical trials. A search was conducted in PubMed for English language publications using individual or linked search terms including osteoarthritis, rheumatoid arthritis, knee, examination, assessment, validity, reliability, responsiveness, change, outcome, and the individual components of the knee examination from 1966 to 2005. Additional pertinent references were identified from the bibliographies of these sources and included for review. Data were synthesized for the individual components of the clinical knee examination in OA and RA regarding validity (truth), reliability/responsiveness to change (discrimination), and feasibility.

Table 1. Characteristics of published evaluations of clinical knee examination in OA and RA.

	Cibere[6]	Theiler[7]	Jones[8]	Bellamy[9]	Hart[10]	Cushnaghan[11]	Claessens[12]	Altman[13]	Marks[14]	Hauzeur[15]	Karim[16]	Kraus[17]	Ike[18]
Multicomponenet assessment†	✔	✔	✔	✔	✔	✔	✔	✔	✔				
Single component assessment†										✔	✔	✔	✔
Evaluated in OA	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔	✔
Evaluated in RA									✔	✔	✔		✔
Examination componenets assessed													
Bony swelling													
Qualitative				✔	✔	✔	✔	✔					
Semiquantitative	✔								✔				
Effusion													
Qualitative	✔	✔	✔				✔		✔		✔		
Semiquantitative								✔	✔	✔			
Syovitis/soft tissue swelling		✔	✔		✔	✔	✔		✔				
Circumference		✔							✔				
Tenderness/pain													
Qualitative													
Global			✔		✔		✔						
Location-specific	✔		✔			✔		✔					
Pain on movement	✔				✔		✔						
Quantitative		✔											
Range of motion	✔			✔		✔		✔	✔				
Alignment													
Qualitative*	✔							✔					
Quantitative*												✔	
Active crepitus													
Global qualitative	✔				✔			✔					
Location-specific	✔		✔			✔							✔
Warmth	✔	✔	✔			✔		✔	✔				
Erythema								✔					
Instability													
Mediolateral	✔	✔				✔		✔	✔				
Anteroposterior	✔	✔				✔		✔	✔				
Domains Assessed													
Validity (diagnostic)		✔			✔		✔	✔		✔	✔	✔	✔
Reliability													
Intraobserver			✔			✔			✔	✔		✔	
Interobserver	✔	✔		✔	✔	✔			✔	✔			
Standardization used	✔			✔									
Responsiveness to change													
Feasibility													

† Denotes number of examination components studied in the publication. * i.e., normal/varus/valgus. ** Assessed with goniometer.

Thirteen studies of oral therapies, physical therapy, surgical interventions, and intraarticular therapy that evaluated at least one quantitative, semiquantitative, or qualitatively assessed component of the clinical knee examination were first reviewed (Table 1), including bony enlargement, effusion, synovitis, tenderness, range of motion, and alignment[6-18]. The sensitivities and specificities of each measurement were tabulated and compared to other variables regarding responsiveness to change, reliability, feasibility, and whether assessed in clinical trials in RA or other inflammatory arthritis. Data were synthesized for individual components of the clinical knee examination in OA and RA regarding validity (truth), reliability, responsiveness to change (discrimination), and feasibility. In general, the reported methods for clinical evaluation of the knee joint in arthritis have been validated only for diagnostic validity and primarily in the context of OA. Intraobserver reliability is generally good, particularly for experienced examiners[8,11,14,15,17]. Interobserver reliability is best for quantitative assessments, and standardization/training improved interobserver reliability for some but not all qualitative or semiquantitative assessments[6,9]. We found no data available on responsiveness to change in response to therapeutic intervention.

Patient-derived assessments of joint function. We also reviewed the literature focusing on the most commonly used knee-specific and generic patient-derived assessments used in OA and RA of the knee. The instruments included WOMAC, the Knee Injury and Osteoarthritis Outcome Score (KOOS), Rheumatoid Arthritis Outcome Score (RAOS), Lequesne Index, SF-36, and the Stanford Health Assessment Questionnaire (HAQ) (Table 2). Individual features of each questionnaire were tabulated, and data regarding validity, reliability, and responsiveness to change in RA compared to OA are summarized. Few studies have evaluated the performance of patient-derived assessments developed for knee OA[19-29] in the context of inflammatory arthritis[27,28,30]. The RAOS for inflammatory arthritis is a modification of the KOOS for OA and includes all WOMAC domains, but responsiveness to change over time with pharmacologic intervention is not known[31]. While several studies have utilized active functional assessments in OA including walk time, stair climbing, and distance traveled, these have not been widely used in RA or other inflammatory arthritides[32,33].

It is important to note that while many of the domains assessed with these instruments are common to most joints (i.e., pain, function), the items within the domain will vary depending on the joint or joint group of interest. This will present some difficulty in comparison in trials in which the single joint of interest may vary across subjects. Additional research will be needed to determine if it is possible to establish a basic instrument of joint function that retains the core items required to assess the domain, while at the same time retaining its performance characteristics across various joints or joint groups.

Imaging. Results of a literature review comparing imaging modalities in the assessment of OA and RA of the knee were presented (Tables 3 and 4 summarize the findings for RA). In general, performance characteristics of both MRI and ultrasound for validity, reliability, and responsiveness to change have been superior to clinical examination or plain radiography for the assessment of inflammation (synovitis or effusion) in OA and RA of the knee[34,35]. Unlike clinical examination

Table 2. Characteristics and evaluation of commonly used knee-specific and generic patient-derived assessment instruments in OA and RA of the knee.

	WOMAC	Lequesne ISK	KOOS	RAOS	SF-36	HAQ
Knee-specific instrument	✔	✔	✔	✔		
Generic instrument					✔	✔
Domains						
Pain	✔	✔	✔	✔	✔	✔
Stiffness/symptoms	✔		✔	✔		
General function	✔	✔	✔	✔	✔	✔
Activities of daily living	✔	✔	✔	✔	✔	✔
Leisure activities			✔	✔	✔	
Quality of life			✔	✔	✔	
Evaluation in knee OA						
		Lequesne[21]			Brazier[26]	
Validity	Bellamy[19]	Faucher[22]	Roos[25]	—	Ware[27]	Bruce[29]
Reliability	Bellamy[19]	Faucher[22]	Roos[24]	—	—	—
	Bellamy[19]	Faucher[22]			Brazier[26]	
Responsiveness to change	Angst[20]	Theiler[23]	Roos[24]	—	Keller[28]	Bruce[29]
Evaluation in knee RA						
Validity	Wolfe[30]	—	—	Bremander[31]	Ware[27]	—
Reliability	—	—	—	Bremander[31]	—	—
Responsiveness to change	—	—	—	Bremander[31]	Keller[28]	—

Table 3. Summary of literature for magnetic resonance imaging in evaluating RA knees.

Evaluation	Gd	DCMRI
Synovial hypertrophy		
Validity	+++	+++
Reliability	++	++
Sensitivity to change	++	++
Erosions		
Validity	?	
Reliability	?/+	
Sensitivity to change	?	
Bone edema		
Validity	?	
Reliability	?	
Sensitivity to change	?	

"+ or ?" refer to the relative quantity of literature on a given area. Gd: gadolinium MRI; DCMRI: dynamic contrast-enhanced MRI.

Table 4. Summary of literature for ultrasonography in evaluating RA knees.

Evaluation	GS	PD
Synovial hypertrophy, effusions		
Validity	++	+
Reliability	+	?
Sensitivity to change	+	+
Erosions		
Validity	?	
Reliability	?	
Sensitivity to change	?	

"+ or ?" refer to the relative quantity of literature on a given area. GS: grey-scale ultrasonography; PD: power Doppler ultrasonography.

and plain radiography, relevant pathologic structures (i.e., synovial hypertrophy in RA) can be directly visualized with MRI and ultrasound. For the assessment of articular damage, MRI has distinct advantages over ultrasound, plain radiography, and the clinical examination in both knee RA and OA because it can tomographically assess cartilage and bone[36]. Although rapidly expanding, little work outside the hand/wrist and knee has been conducted for MRI in the context of RA. Feasibility issues for MRI include expense and patient tolerability, while operator training and experience may limit multicenter applications utilizing ultrasound.

Synovial histology and biomarkers. It is recognized that the integration of synovial histology/biomarkers will provide important comparisons with observed changes in imaging and serum biomarkers. Representatives from this SIG participated in discussions with the synovial histopathology and soluble biomarkers group at OMERACT 8 in further developing a research agenda to cross-validate various modalities in the assessment of the single joint.

Preliminary application of clinical and functional assessments in a clinical trial of single joints

Prior to the conference, based largely on the results of the literature reviews (discussed above) showing limited published data for the performance characteristics of clinical and functional assessments of the knee in inflammatory arthritis, a small pilot study was initiated within a human Phase IA trial of a novel intraarticular gene transfer agent by members of the SIG affiliated with the Phase IA trial. The goal of the pilot study was to examine the responsiveness to change of 2 clinical examination findings, joint tenderness and swelling, each semiquantitatively graded on a zero to 3 scale (none, mild, moderate, severe/large; at the discretion of the examiner). This study included patients with RA, psoriatic arthritis, or ankylosing spondylitis with peripheral joint involvement[3]. Semiquantitative, graded clinical assessments of joint tenderness and swelling were performed at baseline and at each study visit out to 24 weeks after delivery of the experimental agent. Within the context of this small trial, neither serial assessments of joint tenderness, nor swelling, nor the combination were adequate measures to definitively distinguish active therapy from placebo. This may be because the study was not adequately powered for efficacy, the measures have not been validated or the nature of the particular measurement scales used, or the therapy was not effective. Efficacy and safety outcomes of the study and the results of the pilot substudy will be reported in separate publications. Further investigations using these clinical examination measures, a patient-derived functional assessment, and a radiographic assessment have been incorporated into the next Phase I/II trial to assess which of these measures individually or in combination should be developed and validated to detect a therapeutic effect.

Discussion points from OMERACT 8

The work performed by the SIG thus far highlights the limited information available to guide selection of appropriate domains for single joint assessment in inflammatory arthritis. Even for the knee, a large and accessible joint for which the most information is available, validation of the clinical examination and its sensitivity to change over time, and for functional indices and their sensitivity to change over time, are poorly studied in inflammatory arthritis. Recent data presented at ACR 2005[37] suggest that clinical examination for swelling in inflammatory arthritis is poorly correlated with the more sensitive imaging modalities of ultrasound and MRI in detecting synovitis, confirming the importance of additional correlative studies.

OMERACT 8 group interaction prompted consensus on key issues concerning further direction for research initiatives. The group felt that a focus on inflammatory arthritis was vital for a number of scientific and practical reasons:

1. The potential that a true therapeutic effect will be detected is greater in interventional trials of inflammatory arthritis compared to OA. The ability to discern a therapeutic effect

will allow greater certainty in the determination of performance characteristics for assessment measures.
2. A focus on inflammatory arthritis will provide integration into other studies that are under way.

Research agenda

Several research opportunities were proposed to allow further evaluation of key domains for assessing therapeutic response in single joints:

1. A clinical trial integrating clinical examination, functional assessments, imaging, histopathology, and soluble biomarkers with intraarticular corticosteroids in patients with active RA of the knee.
2. Continuing to investigate responsiveness to change of clinical and patient-derived functional assessments in a Phase II trial of a novel intraarticularly delivered gene-transfer cytokine antagonist (discussed above). Various assessments will be investigated in this study, including interobserver variability in tenderness and swelling scores and correlation between tenderness and swelling assessments with subjective patient responses on the RAOS questionnaire, with a feasibility study to determine if the number of items can be reduced. Because the study involves joints outside the knee, a comparison of the knee-specific assessments to other joints will be performed. The correlation between MRI findings, clinical assessments of swelling and tenderness, and patient-derived functional assessments will be determined in a subset of patients.
3. Opportunities to mine existing longitudinal clinical trials data to compare the performance characterisitics of therapeutic responses in single joints within the context of aggregate measures using multiple joint assessments will be further explored.

Outstanding issues

Despite the extensive research agenda proposed at the SIG meeting, several questions originally posed by the SIG will require additional further study, as follows.

Can we use the method ultimately derived for knee assessment to inform investigations of other joints, for which there may be fewer existing assessment instruments?

How do clinically measurable changes in a single joint translate into functional improvement that is meaningful to the individual patient and feasible to demonstrate and describe in a large cohort of patients? For example, improvement of a single metacarpophalangeal joint may be highly significant for a pianist in a study, but this significance may be diluted by the aggregate experience in which such improvement may not be as important.

How do short-term changes in single joints correlate with longterm outcomes such as joint survival?

Can studies from physical therapy, orthopedic, crystalline arthritis literature help to further define the research agenda?

Additional interested individuals were identified at OMERACT 8 to participate in the ongoing activities of the Single Joint SIG. Working subgroups were established to address specific research tasks and to develop more formal working groups.

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REFERENCES

1. Conti F, Priori R, Chimenti MS, et al. Successful treatment with intraarticular infliximab for resistant knee monarthritis in a patient with spondylarthropathy: a role for scintigraphy with ^{99m}Tc-infliximab. Arthritis Rheum 2005;52:1224-6.
2. Evans CH, Robbins PD, Ghivizzani SC, et al. Gene transfer to human joints: progress toward a gene therapy of arthritis. Proc Natl Acad Sci USA 2005;102:8698-703.
3. Mease P, Hobbs K, Kivitz A, Wei N, Anklesaria P, Heald A. Clinical studies of intra-articular administration of a recombinant adeno-associated vector containing a TNF-α antagonist gene in inflammatory arthritis. Ann Rheum Dis 2006;65 Suppl 2:77.
4. Pham T, van der Heijde D, Lassere M, et al. Outcome variables for osteoarthritis clinical trials: The OMERACT-OARSI set of responder criteria. J Rheumatol 2003;30:1648-54.
5. US Food and Drug Administration Center for Devices and Radiologic Health. Device Advice: Clinical studies. FDA Document §860.7. 2002. Available from: http://www.fda.gov/cdrh/devadvice/pma/clinical_studies.html#determination. Accessed Dec 8, 2006.
6. Cibere J, Bellamy N, Thorne A, et al. Reliability of the knee examination in osteoarthritis: effect of standardization. Arthritis Rheum 2004;50:458-68.
7. Theiler R, Stucki G, Schutz R, et al. Parametric and non-parametric measures in the assessment of knee and hip osteoarthritis: interobserver reliability and correlation with radiology. Osteoarthritis Cartilage 1996;4:35-42.
8. Jones A, Hopkinson N, Pattrick M, Berman P, Doherty M. Evaluation of a method for clinically assessing osteoarthritis of the knee. Ann Rheum Dis 1992;51:243-5.
9. Bellamy N, Carette S, Ford PM, et al. Osteoarthritis antirheumatic drug trials. I. Effects of standardization procedures on observer dependent outcome measures. J Rheumatol 1992;19:436-43.
10. Hart DJ, Spector TD, Brown P, Wilson P, Doyle DV, Silman AJ. Clinical signs of early osteoarthritis: reproducibility and relation to x-ray changes in 541 women in the general population. Ann Rheum Dis 1991;50:467-70.
11. Cushnaghan J, Cooper C, Dieppe P, Kirwan J, McAlindon T, McCrae F. Clinical assessment of osteoarthritis of the knee. Ann Rheum Dis 1990;49:768-70.
12. Claessens AA, Schouten JS, van den Ouweland FA, Valkenburg HA. Do clinical findings associate with radiographic osteoarthritis of the knee? Ann Rheum Dis 1990;49:771-4.
13. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039-49.
14. Marks JS, Palmer MK, Burke MJ, Smith P. Observer variation in examination of knee joints. Ann Rheum Dis 1978;37:376-7.
15. Hauzeur JP, Mathy L, De Maertelaer V. Comparison between clinical evaluation and ultrasonography in detecting hydrarthrosis of the knee.

J Rheumatol 1999;26:2681-3.
16. Karim Z, Wakefield RJ, Quinn M, et al. Validation and reproducibility of ultrasonography in the detection of synovitis in the knee: a comparison with arthroscopy and clinical examination. Arthritis Rheum 2004;50:387-94.
17. Kraus VB, Vail TP, Worrell T, McDaniel G. A comparative assessment of alignment angle of the knee by radiographic and physical examination methods. Arthritis Rheum 2005;52:1730-5.
18. Ike R, O'Rourke KS. Compartment-directed physical examination of the knee can predict articular cartilage abnormalities disclosed by needle arthroscopy. Arthritis Rheum 1995;38:917-25.
19. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833-40.
20. Angst F, Ewert T, Lehmann S, Aeschlimann A, Stucki G. The factor subdimensions of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) help to specify hip and knee osteoarthritis. A prospective evaluation and validation study. J Rheumatol 2005;32:1324-30.
21. Lequesne MG, Mery C, Samson M, Gerard P. Indexes of severity for osteoarthritis of the hip and knee. Validation — value in comparison with other assessment tests. Scand J Rheumatol Suppl 1987;65:85-9.
22. Faucher M, Poiraudeau S, Lefevre-Colau MM, Rannou F, Fermanian J, Revel M. Algo-functional assessment of knee osteoarthritis: comparison of the test-retest reliability and construct validity of the WOMAC and Lequesne indexes. Osteoarthritis Cartilage 2002; 10:602-10.
23. Theiler R, Sangha O, Schaeren S, et al. Superior responsiveness of the pain and function sections of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) as compared to the Lequesne-Algofunctional Index in patients with osteoarthritis of the lower extremities. Osteoarthritis Cartilage 1999;7:515-9.
24. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS) — development of a self-administered outcome measure. J Orthop Sports Phys Ther 1998;28:88-96.
25. Roos EM, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS) — validation and comparison to the WOMAC in total knee replacement. Health Qual Life Outcomes 2003;1:17.
26. Brazier JE, Harper R, Munro J, Walters SJ, Snaith ML. Generic and condition-specific outcome measures for people with osteoarthritis of the knee. Rheumatology Oxford 1999;38:870-7.
27. Ware JE Jr, Keller SD, Hatoum HT, Kong SX. The SF-36 Arthritis-Specific Health Index (ASHI): I. Development and cross-validation of scoring algorithms. Med Care 1999;37 Suppl:MS40-50.
28. Keller SD, Ware JE Jr, Hatoum HT, Kong SX. The SF-36 Arthritis-Specific Health Index (ASHI): II. Tests of validity in four clinical trials. Med Care 1999;37 Suppl:MS51-60.
29. Bruce B, Fries J. Longitudinal comparison of the Health Assessment Questionnaire (HAQ) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Arthritis Rheum 2004;51:730-7.
30. Wolfe F, Kong SX. Rasch analysis of the Western Ontario McMaster questionnaire (WOMAC) in 2205 patients with osteoarthritis, rheumatoid arthritis, and fibromyalgia. Ann Rheum Dis 1999; 58:563-8.
31. Bremander AB, Petersson IF, Roos EM. Validation of the Rheumatoid and Arthritis Outcome Score (RAOS) for the lower extremity. Health Qual Life Outcomes 2003;1:55.
32. Walker DJ, Heslop PS, Kay LJ, Chandler C. Spontaneous ambulatory activity as a quantifiable outcome measure for osteoarthritis of the knee. Br J Rheumatol 1998;37:969-71.
33. Stratford PW, Kennedy D, Pagura SM, Gollish JD. The relationship between self-report and performance-related measures: questioning the content validity of timed tests. Arthritis Rheum 2003;49:535-40.
34. Ostergaard M, Wiell C. Ultrasonography in rheumatoid arthritis: a very promising method still needing more validation. Curr Opin Rheumatol 2004;16:223-30.
35. D'Agostino MA, Conaghan P, Le Bars M, et al. EULAR report on the use of ultrasonography in painful knee osteoarthritis. Part 1: prevalence of inflammation in osteoarthritis. Ann Rheum Dis 2005;64:1703-9.
36. Conaghan P. Is MRI useful in osteoarthritis? Best Pract Res Clin Rheumatol 2006;20:57-68.
37. Brown AK, Quinn MA, Karim Z, Conaghan PG, Wakefield RJ, Hensor EMA. Magnetic resonance imaging and ultrasonography may improve the accuracy of RA clinical remission assessment by identifying a high frequency of sub-clinical remission [abstract]. Arthritis Rheum 2005;52 Suppl:S722.