Are the 2002 American College of Rheumatology Guidelines for the Management of Rheumatoid Arthritis Being Followed in Canada's Largest Academic Rheumatology Center?

CHRISTOPHER R. KITAMURA, GINA ROHEKAR, VIVIAN P. BYKERK, and SIMON CARETTE

ABSTRACT. ***Objective.*** To determine whether rheumatologists working in Canada's largest academic rheumatology center (University Health Network/Mount Sinai Hospital) adhere to the 2002 American College of Rheumatology (ACR) guidelines for the management of rheumatoid arthritis (RA).

Methods. Ten patients with RA seen between January 1 and December 30, 2005, were randomly selected from each rheumatologist. A standardized form was used to verify whether the following items were collected at each visit: (1) degree of joint pain, (2) duration of morning stiffness, (3) degree of fatigue, (4) number of tender/swollen joints, and (5) assessment of function. Items recommended for periodic assessment were also collected and included: (1) examination for joint damage, (2) erythrocyte sedimentation rate and/or C-reactive protein, and (3) radiographic assessment of joint damage (radiograph/magnetic resonance imaging).

Results. One hundred thirty charts and 313 total visits met inclusion criteria. No rheumatologist consistently assessed each ACR item. Of the recommended items, tender and swollen joint counts and pain were most commonly assessed (95%, 95%, and 69%, respectively). Functional assessment, morning stiffness, and fatigue were least commonly reported (48%, 46%, and 33%, respectively). Items recommended for periodic assessment were not regularly recorded. There was a trend for the recommended items to be reported more regularly for new patients, patients taking a disease modifying antirheumatic drug (DMARD), and patients for whom a DMARD was added or increased in dosage.

Conclusion. Rheumatologists follow many but not all of the recommendations included in the revised ACR guidelines. The reasons underlying the noncompliance to some of the recommendations are not fully understood. In order to improve the adoption of future clinical practice guidelines, the ACR may have to plan specific dissemination and implementation strategies and fund studies to formally assess the effect of guideline use on clinical outcomes. (First Release Oct 15 2007; J Rheumatol 2007; 34:2183–92)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
PHYSICIAN'S PRACTICE PATTERNS
PRACTICE GUIDELINES
AMERICAN COLLEGE OF RHEUMATOLOGY

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by inflammation of synovial joints as well as extraarticular features including nodulosis, lung inflammation, and small-vessel vasculitis. The disease affects about 1% of the population[1]. If left unchecked, RA can result in joint destruction, deformity, reduced functioning, disability, and sometimes death[2]. This suggests a need to recognize the disease early and closely monitor and treat its symptoms and signs in accordance with best practice guidelines.

From the Division of Rheumatology, University Health Network/Mount Sinai Hospital, Toronto, Ontario, Canada.

C.R. Kitamura, HBSc; G. Rohekar, MD, FRCPC; V.P. Bykerk, MD, FRCPC; S. Carette, MD, MPhil, FRCPC, Division of Rheumatology, University Health Network/Mount Sinai Hospital.

Address reprint requests to Dr. S. Carette, Toronto Western Hospital, University Health Network, 399 Bathurst Street, EW1-422, Toronto, Ontario M5T 2S8, Canada. E-mail: simon.carette@uhn.on.ca

Accepted for publication July 18, 2007.

The American College of Rheumatology (ACR) first developed guidelines for the management of RA and monitoring of drug therapy in 1996[3-5]. This set of guidelines was updated in 2002[6] to reflect an increase in the understanding of the disease and treatment advances, particularly the growing body of evidence reflecting the importance of early treatment[7-11]. Since then, several organizations and individuals have developed their own versions of effective management guidelines for RA[12-17].

Given the proliferation of published guidelines, it is important to understand the usage patterns of these guidelines in the clinical setting. The primary goal of our study was to understand how rheumatologists working in Canada's largest academic rheumatology center [University Health Network (UHN)/Mount Sinai Hospital (MSH)] assess their patients with RA, and whether they adhere to the 2002 ACR guidelines.

MATERIALS AND METHODS

From lists of billing codes, 10 patients with RA seen between January 1 and December 30, 2005, under the code 714 (RA) were randomly selected (using a table of random digits) and audited from each consenting rheumatologist. All charts were reviewed by the same data abstractor (CK), who first ensured that the selected patients had a confirmed diagnosis of RA. This step was necessary as the code 714 is applied to patients with RA, juvenile RA, and undifferentiated inflammatory arthritis. Charts of patients whose diagnosis was not RA were replaced until a total of 10 patients from each rheumatologist could be evaluated. A maximum of 5 visits per patient were reviewed to ensure that the reporting characteristics of a given physician were not heavily biased by an individual patient.

A standardized form (Appendix) was used to record whether or not the following items related to the assessment of disease activity were collected at each visit: (1) degree of joint pain, (2) duration of morning stiffness, (3) degree of fatigue, (4) number of tender joints, (5) number of swollen joints, and (6) assessment of function. The presence of items recommended for periodic assessment was also assessed. These items included: (1) an examination for joint damage, (2) erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP), and (3) a radiographic assessment of joint damage [radiograph or magnetic resonance imaging (MRI)]. Patient use of prednisone, disease modifying antirheumatic drugs (DMARD), and biologics was recorded at each visit.

Reports of pain, fatigue, and morning stiffness were subcategorized as being quantitative (numeric, e.g., 7/10), qualitative (e.g., "mild" and "severe"), or simply indicated as being present (without qualifiers). While the ACR guidelines indicate that function may be assessed using the Arthritis Impact Measurement Scales[18] or the Health Assessment Questionnaire[19], reference to the patients' ability to carry out activities of daily living (ADL) or the ACR functional class was also accepted. Given that the recommended periodic assessment items are not expected to be performed at each visit, the abstractor noted whether the items were reported within one year of the first 2005 visit.

Patient visits were dichotomized as being: (1) new visit versus followup visits, (2) patients taking DMARD versus not taking DMARD, and (3) patients for whom a DMARD was increased in dosage/added versus decreased in dosage/discontinued. This was done because it was hypothesized that patients might be assessed more thoroughly if they were new patients, if they were taking a DMARD, or if the physician added a new drug to the treatment regimen or increased the dosage.

Rheumatologists were approached and asked to participate on the basis that there would be no direct comparisons between participating physicians or between sites, and that the data would be presented anonymously. Results presented are in the form of frequencies and proportions. Beyond this, no further statistical analysis was performed.

RESULTS

Seventeen rheumatologists hold a full-time academic appointment at UHN/MSH. Of these, 4 were excluded as they saw fewer than 10 patients with RA in 2005. The remaining 13 rheumatologists agreed to participate. One hundred sixty-six patient charts were reviewed to acquire the 130 charts (10 per physician) specified in the protocol. Three hundred thirteen visits were assessed. The number of patient visits for each rheumatologist ranged from 15 to 30 (mean 24.1). There were 15 new patient visits and 298 followup visits. Patients were taking DMARD in 249 visits (79.5%). DMARD were increased or added on 61 visits and the dosage decreased or the medication discontinued in 35 visits.

The overall reporting frequencies are shown in Table 1. The reporting frequencies of each ACR-recommended assessment item are presented as a group aggregate (Figure 1) and for each physician (Figures 2-10). Reporting frequencies for each physician were not dichotomized due to the limited number of visits for each physician.

No rheumatologist consistently assessed each of the ACR items. Of the items recommended for assessment at each visit, tender and swollen joint counts were the most commonly assessed items. All participating physicians conducted tender and swollen joint assessments at least 80% of the time (mean reporting frequency 95%, range 81%–100%). Pain was the second most commonly reported item. All rheumatologists reported a measure of pain at least 50% of the time (mean reporting frequency 69%, range 50%–92%). Functional assessment (mean reporting frequency 48%, range 8%–89%) and morning stiffness (mean reporting frequency 46%, range 7%–90%) were reported less than 50% of the time for the group. Fatigue was the least commonly reported item (mean reporting frequency 33%, range 5%–90%), with only 3 participating physicians reporting this item more than 50% of the time.

Items recommended for periodic assessment were not assessed as frequently during the 2005 visits. An examination for joint damage was reported in 54% of the patients (range 12%–95%) and acute-phase reactant (ESR or CRP) assessments were done in 48% of the patients (range 12%–95%). Radiological assessments were far less common, as they were performed in only 10% of the patients (range 0–24%). Given that the ACR recommends the documentation of these items only periodically, when we extended the period of observation to the year preceding the first 2005 visit, we noted better compliance to the guidelines, with the examination for joint damage, hematology, and radiological assessments being performed in 75%, 85%, and 39% of patient visits, respectively.

There was an overall trend for the ACR guideline items to be reported more frequently for new patient visits than for followup visits. The same trends held for patients taking a DMARD versus those not taking a DMARD, and for patients for whom a DMARD was added or increased in dosage versus patient visits when a DMARD was decreased or discontinued (Table 1).

DISCUSSION

Overall, rheumatologists at UHN/MSH, the largest academic rheumatology center in Canada, do not fully and consistently adopt the 2002 ACR guidelines for the assessment of their patients with RA in clinical practice. Nevertheless, the group adhered well to the ACR's recommendations for regular assessments of tender joints, swollen joints, and pain. It is not surprising that active joint assessments were conducted a large proportion of the time, given that the number of active joints serves as one of the best prognostic indicators of the course of the disease[20], including future joint damage[21] and functional impairment[22,23]. Moreover, swollen joint count has proven to be among the best predictors of physicians' decisions to

Table 1. Overall reporting frequency of ACR assessment items.

	Total, n = 313	New Patient, n = 15	Followup Patient, n = 298	Taking DMARD, n = 249	Not Taking DMARD, n = 64	Increased/Add DMARD, n = 61	Decrease/Discontinue DMARD, n = 35
Routine assessment %							
Pain	69	100	67	69	69	72	63
Morning stiffness	46	67	45	48	36	59	43
Fatigue/energy	33	60	32	37	20	38	29
Function assessment	48	100	46	46	56	44	43
Tender joint count	95	100	95	96	92	97	97
Swollen joint count	95	100	95	96	92	97	97
Periodic assessment, %							
Physical examination for joint damage	54	93	52	52	63	54	37
Hematology (ESR/CRP)	48	40	48	51	34	54	51
Radiology (x-rays/MRI)	10	27	9	8	17	18	3

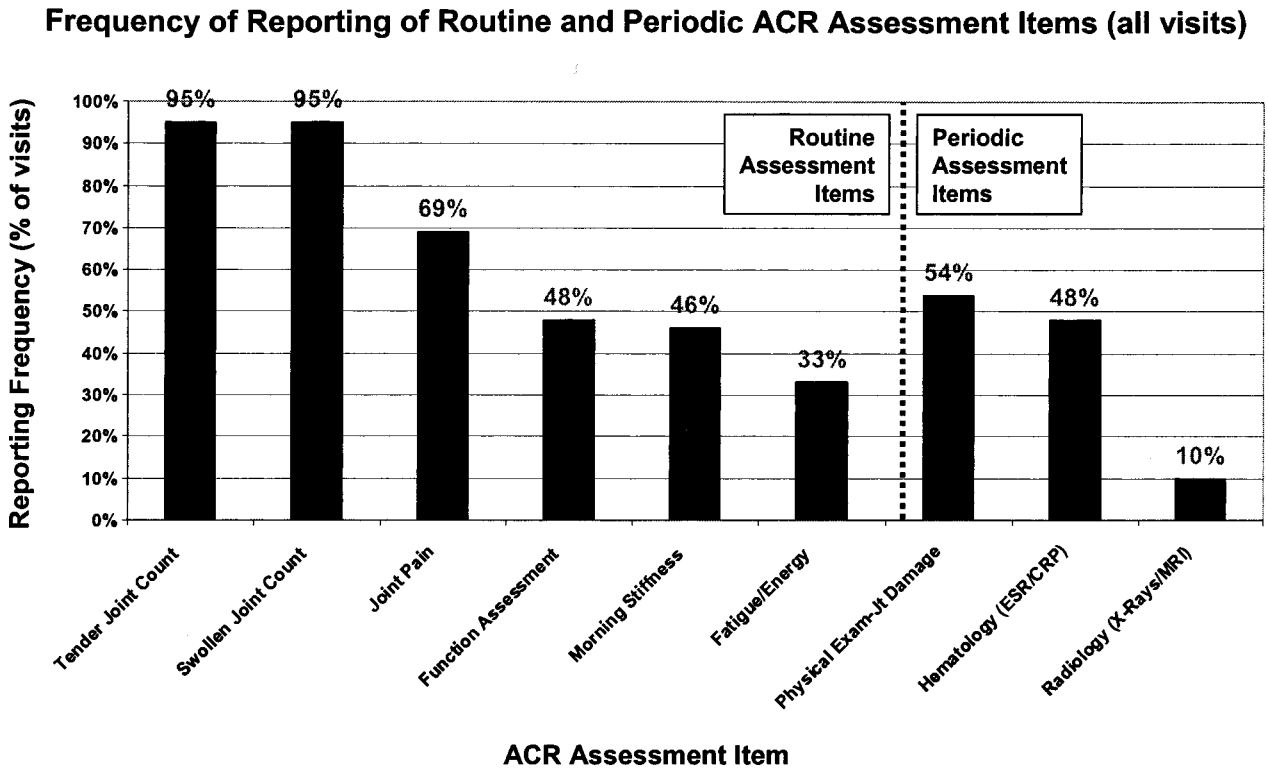

Figure 1. Overall reporting frequency of ACR assessment items.

change treatment[24]. A measure of pain was also reported with a high degree of consistency, presumably because pain is an immediate and pressing concern for the patient and has a great effect on the patient's quality of life. It is also likely a major driving force towards treatment-seeking[25]. It therefore follows that pain would be a critical concern that must be addressed by the rheumatologist.

Participating physicians did not regularly assess morning stiffness, fatigue, and function. It is surprising that an assessment of function was not commonly documented, given that maintenance of function is among the ultimate goals in the management of RA. The lower reporting frequencies of fatigue and morning stiffness are perhaps justifiable, given that these outcomes are generally reflections of disease severity, as opposed to the causes of impairment, and are predicted by other clinical outcomes such as pain[26].

Given that an examination and medical imaging for assessing joint damage are only recommended for periodic assessment, the reporting frequencies of these items by rheumatologists in our study meet the guidelines. This might reflect the abundance of evidence suggesting that the presence of joint damage is an excellent predictor of disease progression[27],

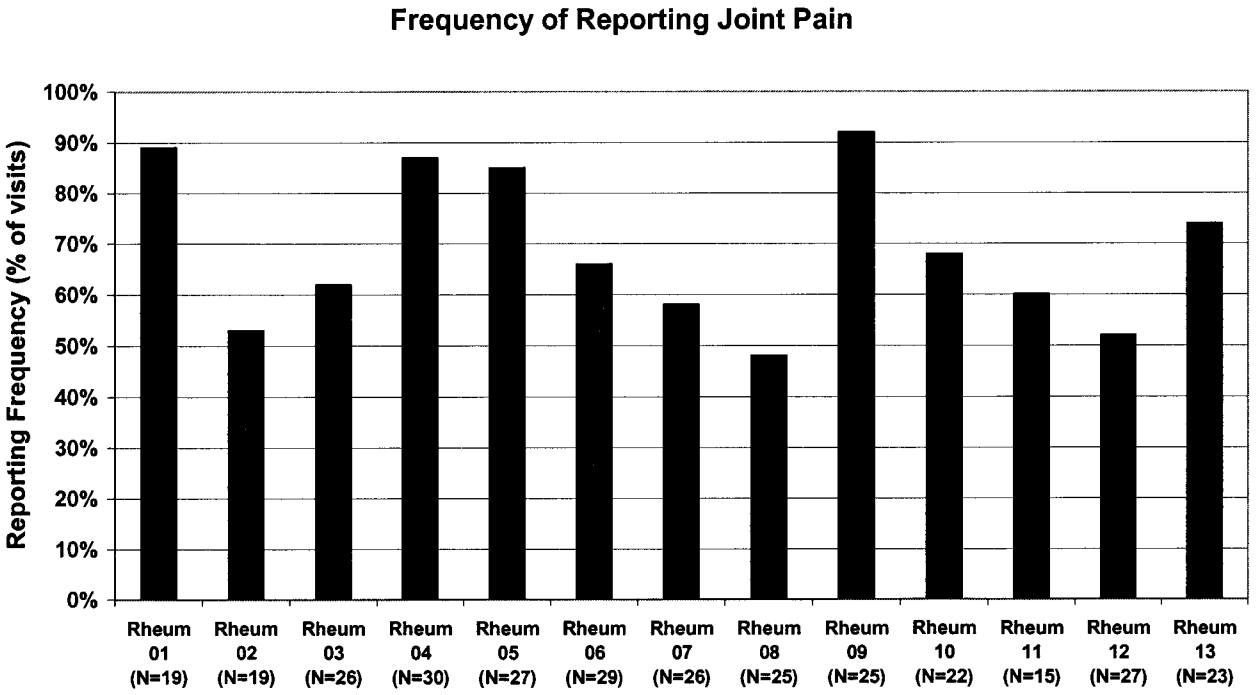

Figure 2. Individual reporting frequency of joint pain.

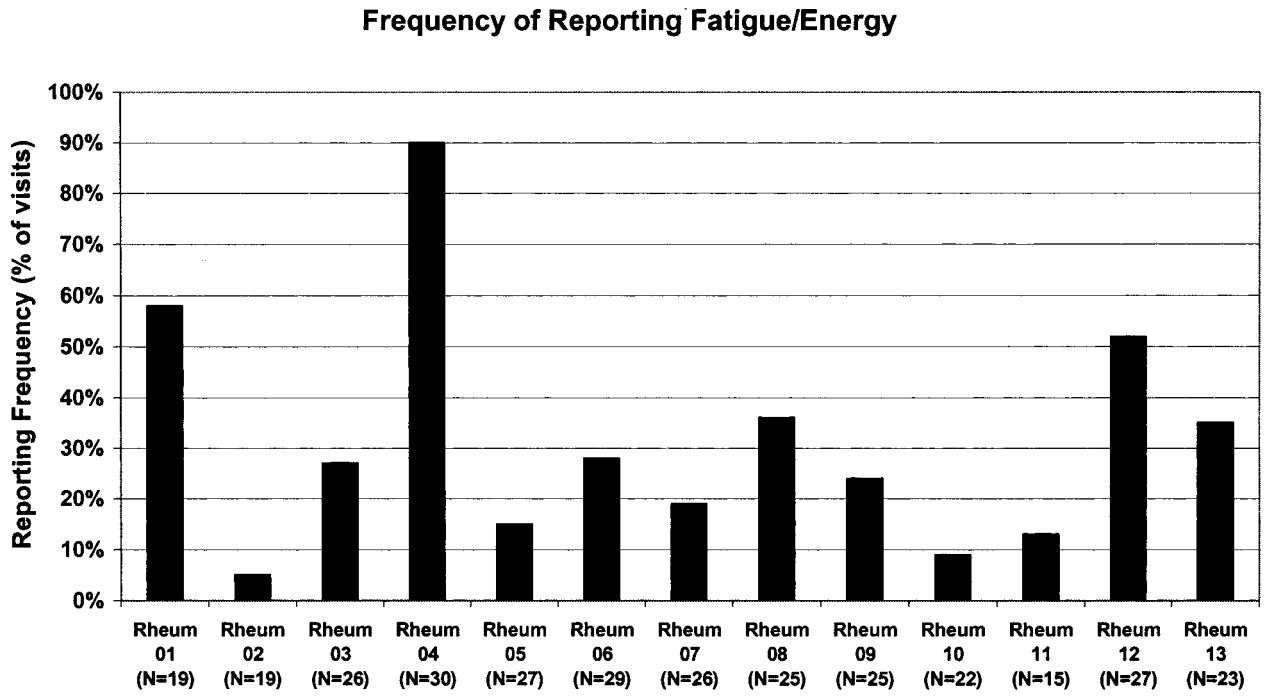

Figure 3. Individual reporting frequency of fatigue.

future impairment[28,29], and present and future function[30]. Similarly, acute-phase reactants (ESR or CRP), while recommended for periodic assessment, were ordered quite regularly by the participating rheumatologists. This, too, likely reflects the large and growing body of evidence suggesting the prognostic capabilities of laboratory markers, such as the ESR and CRP[31,32]. While not formally a component of the 2002 ACR guidelines, a large body of evidence also implicates the utility of the rheumatoid factor (RF)[33] and, more recently, antibodies to citrullinated peptides (anti-CCP)[34-36] as valuable prognostic indicators for joint damage and patient outcomes. It is expected that the role of these markers will be better

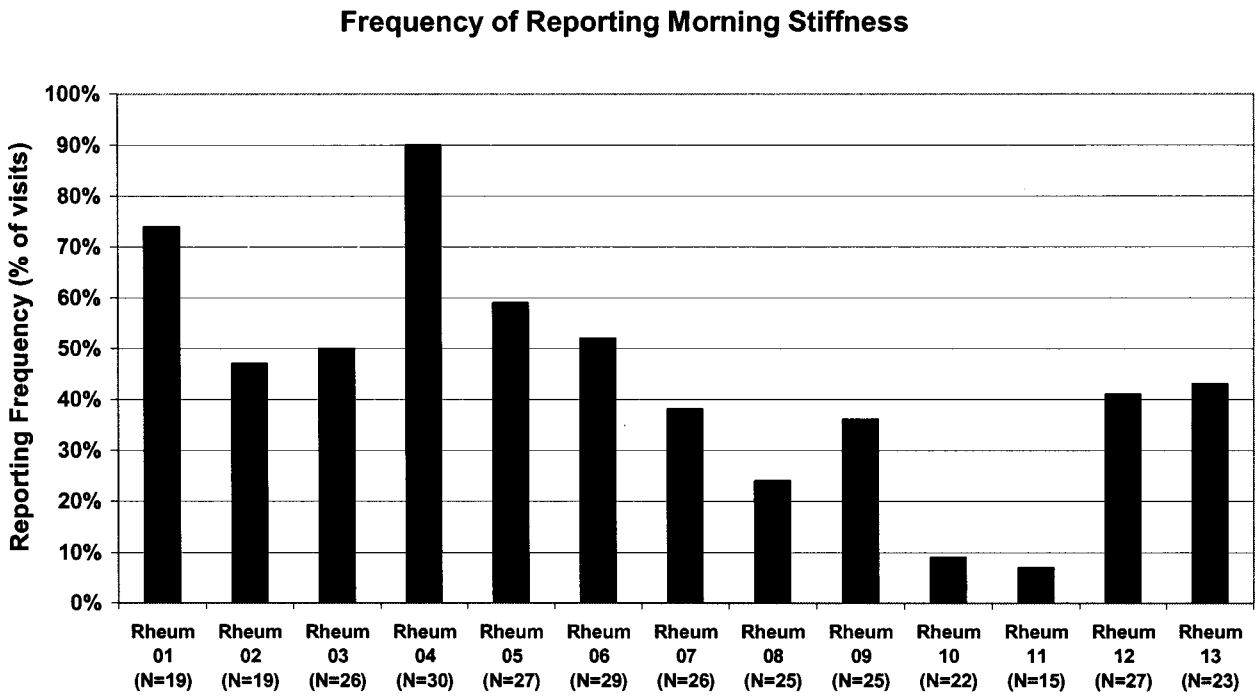

Figure 4. Individual reporting frequency of morning stiffness.

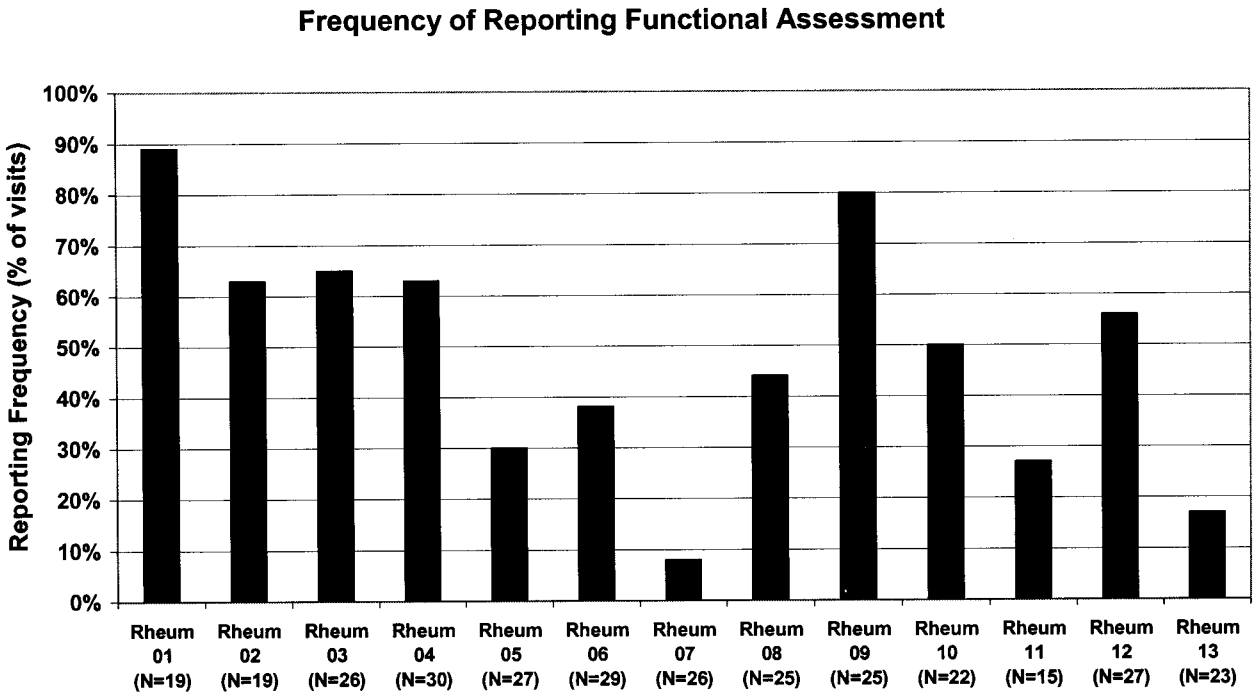

Figure 5. Individual reporting frequency of function.

defined in upcoming years and possibly recommended for assessment in future revisions of the ACR guidelines.

Participating rheumatologists were not asked why they did not strictly adhere to the ACR guidelines. Nonadherence could reflect a lack of familiarity with the guidelines due to poor dissemination or it could stem from disagreement with the guideline recommendations as they currently exist. There is a growing body of literature suggesting that rheumatologists differ greatly in the assessment criteria they deem important in the treatment and monitoring of patients with RA[37].

Other than publishing the initial guidelines and the revision in *Arthritis and Rheumatism*, the ACR did not use other spe-

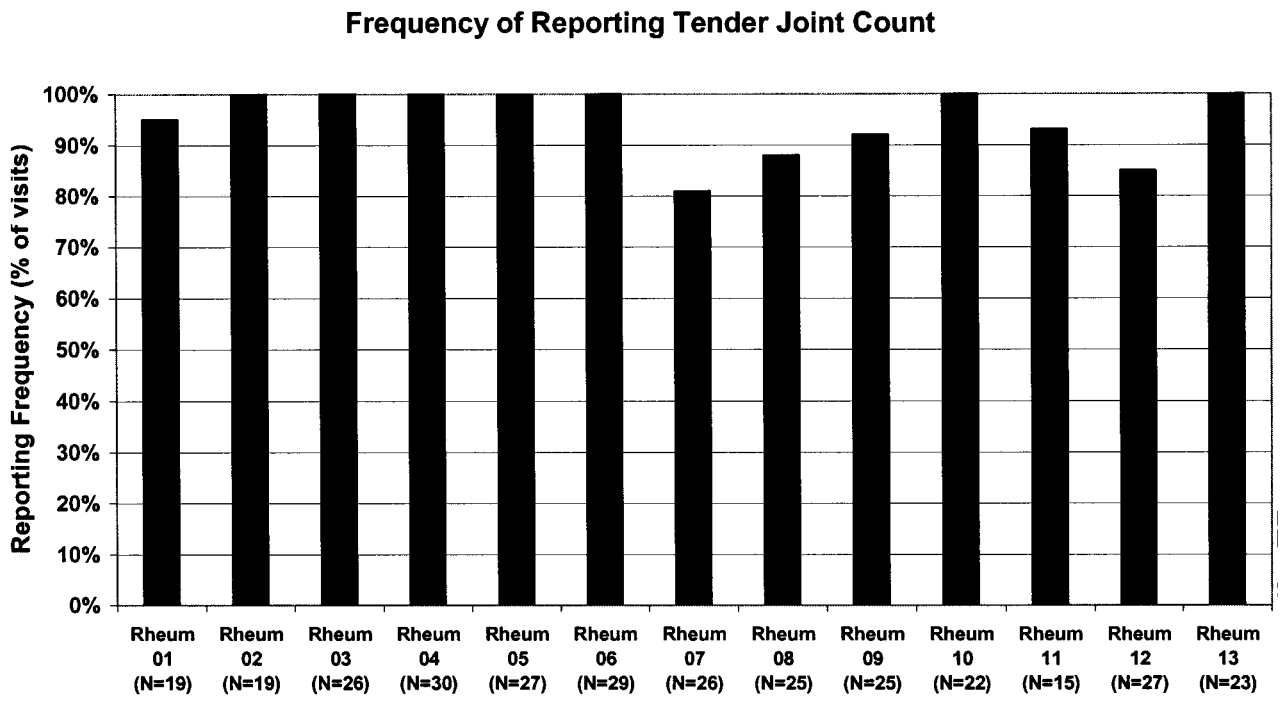

Figure 6. Individual reporting frequency of tender joint count.

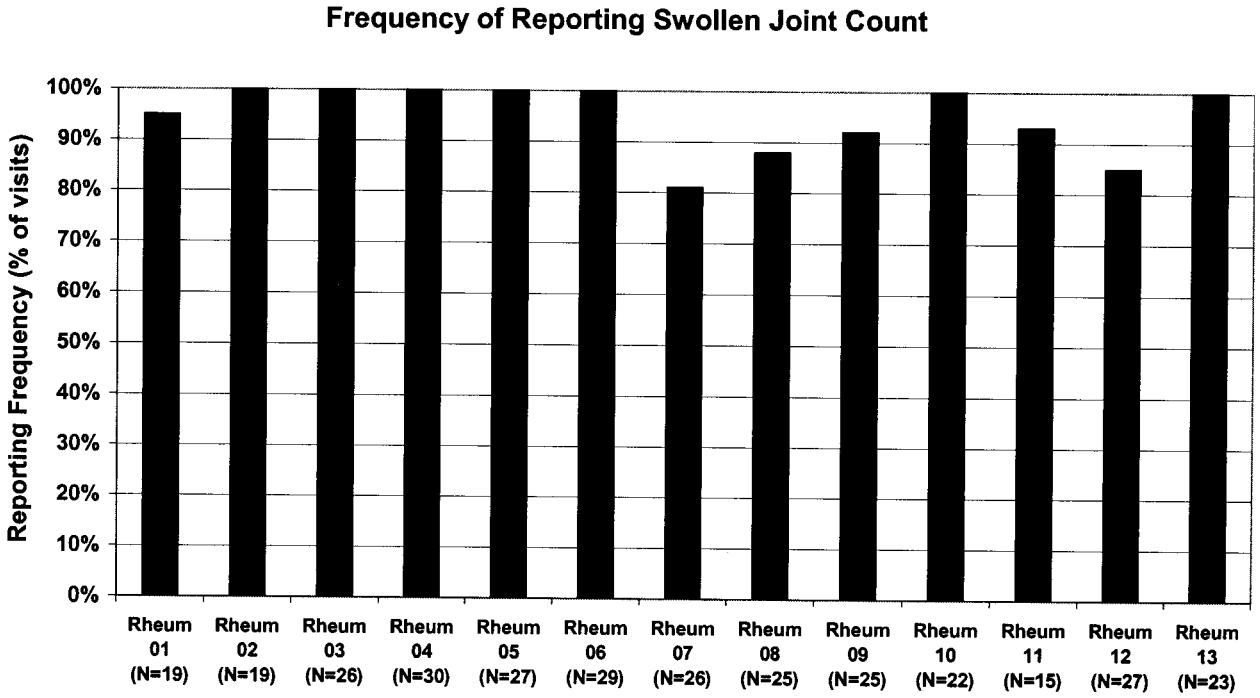

Figure 7. Individual reporting frequency of swollen joint count.

cific dissemination and implementation strategies, nor did it assess the efficiency of guideline use on patient outcomes. The Health Technology Assessment Programme in the UK undertook a systematic review of the effectiveness and costs of different guideline dissemination and implementation strategies from a range of medical disciplines[38]. From the 235 studies reviewed, we observed that most commonly used interventions, including reminders, educational materials,

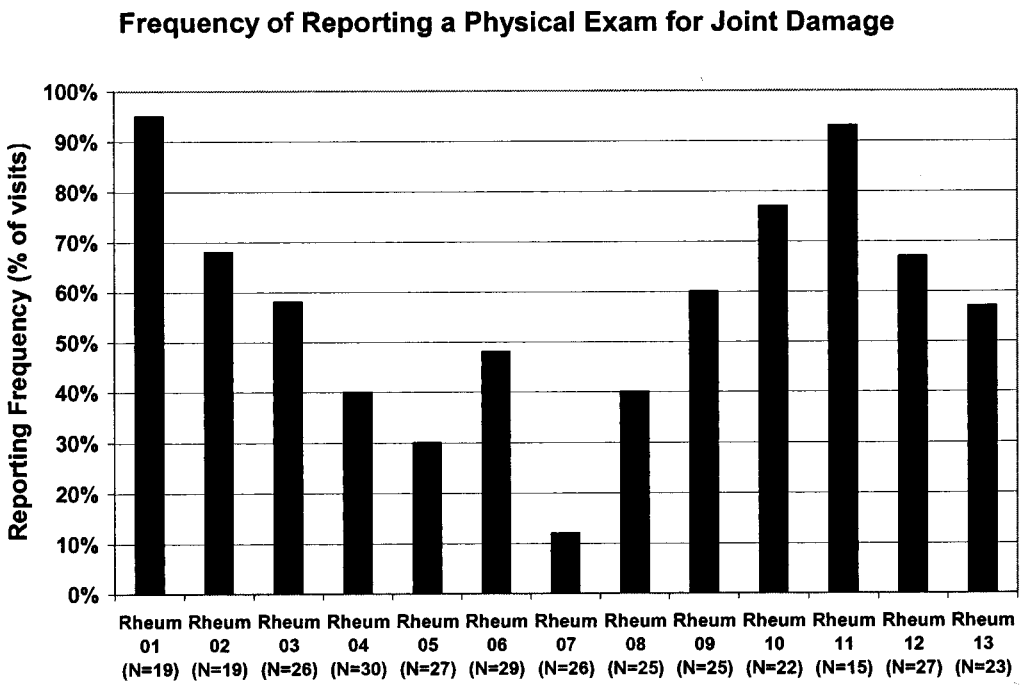

Figure 8. Individual frequency of conducting an examination to assess joint damage.

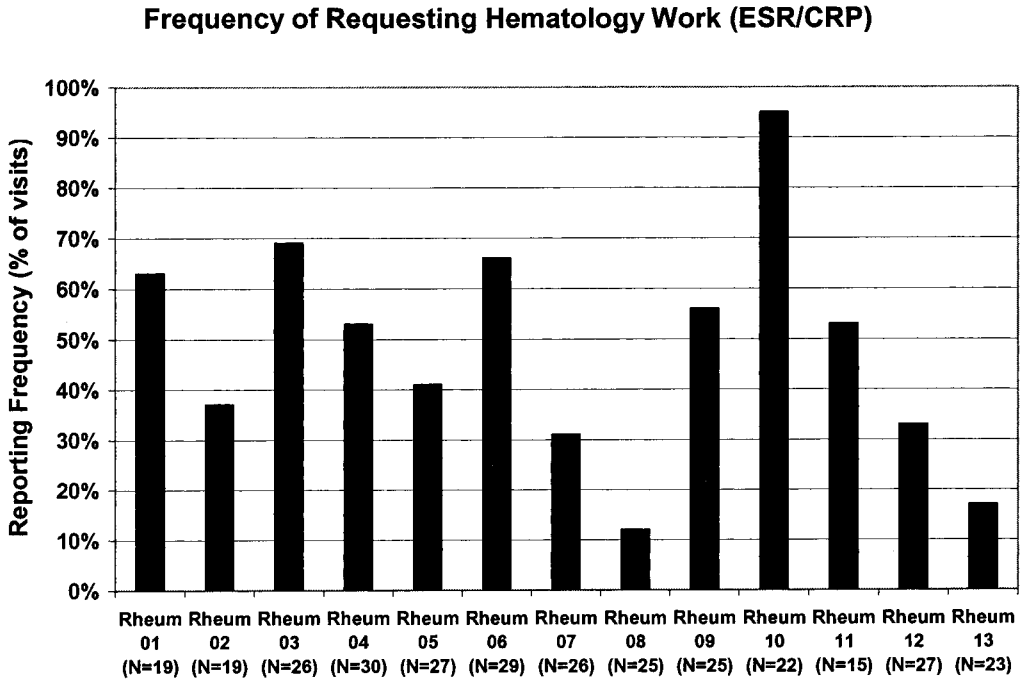

Figure 9. Individual frequency of requesting acute-phase reactants (ESR and/or CRP).

audit and feedback, and patient-directed interventions, when used alone or as part of multifaceted dissemination strategies, in general, resulted in modest to moderate improvements in care. However, there was considerable variation in the observed effects both within and across interventions. Only 29% of studies reported any economic data on costs of guideline dissemination and implementation strategies. The authors concluded that current evidence is insufficient to determine which strategy is most efficient in different circumstances.

The importance of evaluating the effectiveness of clinical

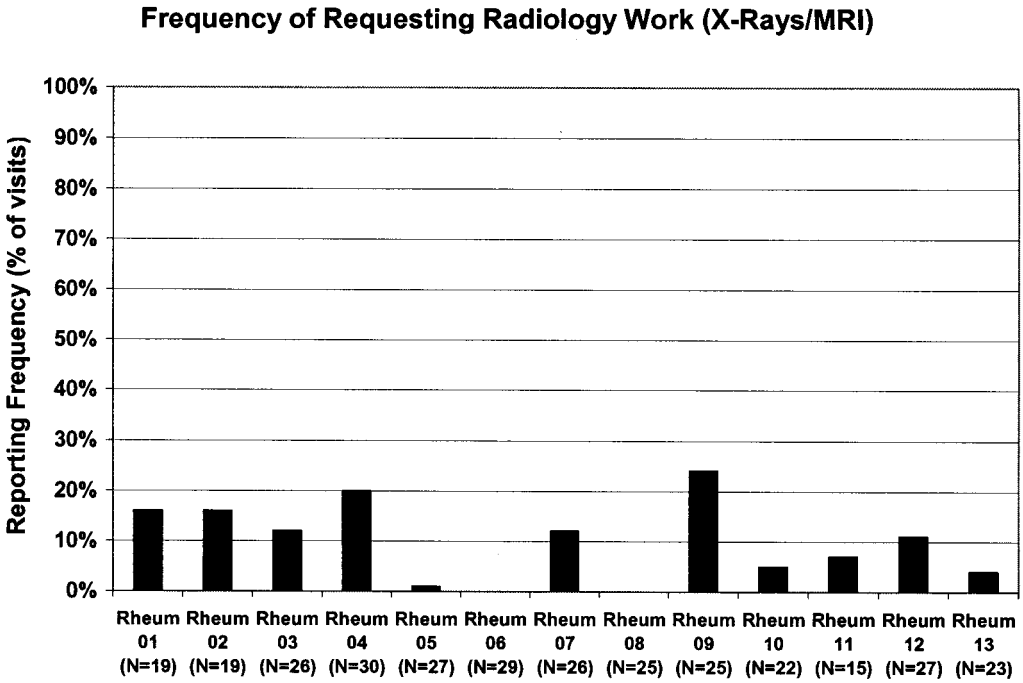

Figure 10. Individual frequency of requesting radiology work (radiograph or MRI).

APPENDIX

RA confirmed: YES NO

Rheumatologist code: ____

MRN: ____

Date of patient visit: ____

NP F/U

Routine Assessment

Degree of joint pain (VAS):	Y	N
Duration of morning stiffness:	Y	N
Duration of fatigue:	Y	N
Tender joint count:	Y	N
Swollen joint count:	Y	N
Functional assessment:	Y	N

Periodic Assessment

Physical exam for damage:	Y	N	If N, last:	<6m	6-12m	>12 m	U
X-Rays:	Y	N	If N, last:	<6m	6-12m	>12 m	U
ESR and/or CRP:	Y	N	If N, last:	<6m	6-12m	>12 m	U

Treatment

Patient on DMARD Y N Specify: HCQ MTX SSZ ARA ETA INF HUM KIN GOLD PRED

Changes in DMARD Y N Specify: Increase Decrease Add D/C

Comments:

Evaluator:

practice guidelines on a continuing basis was emphasized in a recent Cochrane Collaboration systematic review that compared integrated clinical pathways (ICP) for stroke care with standard medical care[39]. Stroke care pathways were developed based on best evidence from the literature to improve patient outcomes. The Cochrane reviewers found no significant difference in stroke survival and discharge destination between ICP and control groups. While patients managed in the ICP were less likely to be readmitted [odds ratio (OR) 0.51, 95% confidence interval (CI) 0.03 to 0.39] and less likely to suffer a urinary tract infection (OR 0.51, 95% CI 0.34–0.79), they were more dependent at discharge ($p = 0.04$), and their satisfaction and quality of life were significantly lower than in the control groups ($p = 0.02$ and $p < 0.0005$, respectively). The authors concluded that there was insufficient supporting evidence to justify the routine implementation of care pathways for acute stroke management or stroke rehabilitation.

Strengths of our study include the moderately robust sample size (in terms of both the number of participating physicians and the number of patient visits) and the context of the chart audit in a clinical rather than a research setting. Physicians were free to adopt any strategy they chose, and were not bound to strict management protocols or treatment regimens.

It should be noted, however, that for the purposes of our study, a failure to document an ACR assessment item in the patient's chart was taken to mean that the item was not evaluated. It is possible that an unremarkable inquiry or assessment was not documented, but nonetheless still evaluated.

Rheumatologists practicing in Canada's largest rheumatology academic center tend to follow most, but not all, of the recommendations included in the revised ACR guidelines for the clinical assessment of patients with RA. The reasons underlying the noncompliance to some of the recommendations are not fully understood. In order to improve the adoption of future clinical practice guidelines, the ACR may have to plan specific dissemination and implementation strategies and fund studies to formally assess the influence of guideline use on clinical outcomes.

REFERENCES

1. Harris ED Jr. Rheumatoid arthritis: pathophysiology and implications for therapy. N Engl J Med 1990;322:1277–89.
2. Hochberg MC. Adult and juvenile rheumatoid arthritis: current epidemiologic concepts. Epidemiol Rev 1981;3:27–44.
3. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for the initial evaluation of the adult patient with acute musculoskeletal symptoms. Arthritis Rheum 1996;39:1–8.
4. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for the management of rheumatoid arthritis. Arthritis Rheum 1996;39:713–22.
5. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for monitoring drug therapy in rheumatoid arthritis. Arthritis Rheum 1996;39:723–31.
6. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis 2002 update. Arthritis Rheum 2002;46:328-46.
7. Van der Heijde DM, van Riel PL, Nuver-Zwart IH, Gribnau FW, van de Putte LB. Effects of hydroxychloroquine and sulfasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989;1:1036–8.
8. Van der Heide A, Jacobs JW, Bijlsma JW, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs: a randomized, controlled trial. Ann Intern Med 1996;124:699–707.
9. Tsakonas E, Fitzgerald AA, Fitzcharles MA, et al. Consequences of delayed therapy with second-line agents in rheumatoid arthritis: a 3-year follow-up on the Hydroxychloroquine in Early Rheumatoid Arthritis (HERA) study. J Rheumatol 2000;27:623–9.
10. Van Jaarsveld CH, Jacobs JW, van der Veen MJ, et al, on behalf of the Rheumatic Research Foundation, Utrecht, The Netherlands. Aggressive treatment in early rheumatoid arthritis: a randomised controlled trial. Ann Rheum Dis 2000;59:468–77.
11. Albers JM, Paimela L, Kurki P, et al. Treatment strategy, disease activity, and outcome in four cohorts of patients with early rheumatoid arthritis. Ann Rheum Dis 2001;60:453–8.
12. Browning M. Rheumatoid arthritis: a primary care approach. J Am Acad Nurse Pract 2001;13:399-408.
13. Breedveld FC, Kalden JR. Appropriate and effective management of rheumatoid arthritis. Ann Rheum Dis 2004;63:627-33.
14. Pham T, Gossec L, Fautrel B, Combe B, Flipo RM. Physical examination and laboratory tests in the management of patients with rheumatoid arthritis: development of recommendations for clinical practice based on published evidence and expert opinion. Joint Bone Spine 2005;72:222-8.
15. Gossec L, Fautrel B, Pham T, Combe B, Flipo RM. Structural evaluation in the management of patients with rheumatoid arthritis: development of recommendations for clinical practice based on published evidence and expert opinion. Joint Bone Spine 2005;72:229-34.
16. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007;66:34-45.
17. Luqmani R, Hennell S, Estrach C, Birrell F, Bosworth A. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of rheumatoid arthritis (the first two years). Rheumatology Oxford 2006;45:1167-9.
18. Meenan RF, Gertman PM, Mason JH. Measuring health status in arthritis: the Arthritis Impact Measurement Scales. Arthritis Rheum 1980;23:146–52.
19. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
20. Ansell BM. Prognosis in juvenile arthritis. Adv Exp Med Biol 1999;455:27-33.
21. Luukkainen R, Sokka T, Kautiainen H, Hannonen P, Laasonen L. Prognosis of 5-year radiographic erosions of the wrist according to early, late, and persistent wrist swelling or tenderness in patients with early rheumatoid arthritis. J Rheumatol 2007;34:50-3.
22. Gerber LH, Furst G, Yarboro C, el-Gabalawy H. Number of active joints, not diagnosis, is the primary determinant of function and performance in early synovitis. Clin Exp Rheumatol 2003;21 Suppl 31:S65-70.
23. Bandeira M, Falcone A, Pistorio A, Ruperto N, Magni-Manzoni S. Weighting improves the information provided by joint counts on the severity of arthritis and its impact on patients' well-being in juvenile idiopathic arthritis. Rheumatology Oxford 2006;45:343-7. Epub 2005 Oct 18.

24. Soubrier M, Zerkak D, Gossec L, Ayral X, Roux C. Which variables best predict change in rheumatoid arthritis therapy in daily clinical practice? J Rheumatol 2006;33:1243-6. Epub 2006 Apr 15.
25. Kothe R, Kohlmann T, Klink T, Ruther W, Klinger R. Impact of low back pain on functional limitations, depressed mood and quality of life in patients with rheumatoid arthritis. Pain 2007;127:103-8. Epub 2006 Sep 18.
26. Pollard LC, Choy EH, Gonzalez J, Khoshaba B, Scott DL. Fatigue in rheumatoid arthritis reflects pain, not disease activity. Rheumatology Oxford 2006;45:885-9. Epub 2006 Jan 31.
27. Paulus HE, Oh M, Sharp JT, Gold RH, Wong WK, Park GS. Classifying structural joint damage in rheumatoid arthritis as progressive or nonprogressive using a composite definition of joint radiographic change: a preliminary proposal. Arthritis Rheum 2004;50:1083-96.
28. Gasson J, Gandy SJ, Hutton CW, Jacoby RK, Summers IR. Magnetic resonance imaging of rheumatoid arthritis in metacarpophalangeal joints. Skeletal Radiol 2000;29:324-34.
29. Zatarain E, Strand V. Monitoring disease activity of rheumatoid arthritis in clinical practice: contributions from clinical trials. Nat Clin Pract Rheumatol 2006;2:611-8.
30. Oen K, Reed M, Malleson PN, Cabral DA, Petty RE. Radiologic outcome and its relationship to functional disability in juvenile rheumatoid arthritis. J Rheumatol 2003;30:832-40.
31. Lindqvist E, Eberhardt K, Bendtzen K, Heinegard D, Saxne T. Prognostic laboratory markers of joint damage in rheumatoid arthritis. Ann Rheum Dis 2005;64:196-201. Epub 2004 Sep 30.
32. Plant MJ, Williams AL, O'Sullivan MM, Lewis PA, Coles EC. Relationship between time-integrated C-reactive protein levels and radiologic progression in patients with rheumatoid arthritis. Arthritis Rheum 2000;43:1473-7.
33. Shin YS, Choi JH, Nahm DH, Park HS, Cho JH. Rheumatoid factor is a marker of disease severity in Korean rheumatoid arthritis. Yonsei Med J 2005;46:464-70.
34. Forslind K, Ahlmen M, Eberhardt K, Hafstrom I, Svensson B. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). Ann Rheum Dis 2004;63:1090-5.
35. Berglin E, Johansson T, Sundin U, Jidell E, Wadell G. Radiological outcome in rheumatoid arthritis is predicted by presence of antibodies against cyclic citrullinated peptide before and at disease onset, and by IgA-RF at disease onset. Ann Rheum Dis 2006;65:453-8. Epub 2005 Sep 21.
36. del Val del Amo N, Ibanez Bosch R, Fito Manteca C, Gutierrez Polo R, Loza Cortina E. Anti-cyclic citrullinated peptide antibody in rheumatoid arthritis: relation with disease aggressiveness. Clin Exp Rheumatol 2006;24:281-6.
37. Aletaha D, Ward MM. Duration of rheumatoid arthritis influences the degree of functional improvement in clinical trials. Ann Rheum Dis 2006;65:227-33. Epub 2005 Jun 23.
38. Grimshaw JM, Thomas RE, MacLennan G, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. Health Technol Assess 2004;8:iii-iv, 1-72.
39. Kwan J, Sandercock P. In-hospital care pathways for stroke. Cochrane Database Syst Rev 2004 Oct 18;4:CD002924.