Developing a Standardized Definition for Disease "Flare" in Rheumatoid Arthritis (OMERACT 9 Special Interest Group)

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ABSTRACT ***Objective.*** Traditional outcome measures in randomized controlled trials (RCT) include well-established response criteria as well as ACR EULAR responses using Disease Activity Score 44 (DAS44)/DAS28 to assess improvement; however, a measure to assess worsening of disease has yet to be developed. This special interest group (SIG) was established to develop an evidence-based, consensus-driven standard definition of "flare" in rheumatoid arthritis (RA).

Methods. At OMERACT 8, the need for a standardized definition of RA flare was recognized; interested individuals developed a proposal to form a SIG. A literature review was performed to identify publications and abstracts with flare definitions applied in RA, JIA, and lupus RCT as well as concerning patient perspectives on disease worsening. A SIG was held at OMERACT 9 with breakout sessions for patients and investigators.

Results. The RA flare SIG was attended by about 120 participants, including 11 patients. Patients and investigators held separate breakout sessions to discuss various aspects of disease worsening. The following consensus was obtained at OMERACT 9: a working definition of flare should indicate worsening of disease activity (88%), persistence, and duration as critical elements (77%), and consideration of change or increase in therapy (74%).

Conclusion. A working definition of RA flare was developed based on these votes: flare is any worsening of disease activity that would, if persistent, in most cases lead to initiation or change of therapy; and a flare represents a cluster of symptoms of sufficient duration and intensity to require initiation, change, or increase in therapy. Using this working definition, evaluation of candidate domains will be conducted via Delphi exercise and further informed by patient focus groups. Validation of candidate definitions in appropriate RCT will be required. (J Rheumatol First Release August 15 2009; doi:10.3899/jrheum.090369)

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This special interest group (SIG) was established to develop an evidence-based, consensus-driven standard definition of "flare" in rheumatoid arthritis (RA) to describe clinically-relevant worsening in randomized controlled trials (RCT), incorporating the patient's perspective. Such a definition is needed to improve the ability to capture loss of efficacy as a part of the assessment of safety and effectiveness in RCT, longitudinal observational studies (LOS), and postmarketing studies.

Outcome measures used in most RA RCT were developed to confirm the efficacy of a therapy reported as the proportion of patients achieving a designated level of relative improvement from baseline in core set variables [e.g., American College of Rheumatology (ACR) responses], or as improvement from baseline and a lower disease activity state in absolute terms [European League Against Rheumatism (EULAR) responses using Disease Activity

Score (DAS44)/DAS28)]. These endpoints have been well validated but only for sensitivity to change in the positive (improvement) direction. Neither provides information concerning the proportion of patients who have worsened at any timepoint, or in whom initial improvement of RA is followed by worsening.

At OMERACT 8, the Drug Safety Working Group, as part of its research agenda, determined that a standardized definition of RA flare was needed for the Rheumatology Common Toxicity Criteria (RCTC) effort[1]. This need was recognized from a regulatory perspective, to more clearly and quantitatively characterize reasons for study withdrawal based on loss or lack of efficacy in RCT. In current trials, various definitions have described flares or worsening of disease, such as withdrawals due to lack of efficacy, often driven by patient's perceptions, but in the absence of standard criteria for "inadequate" or "loss of response." These are, at best, inexact measurements, and the decision to report flare as an adverse event or to withdraw a patient from the trial may be influenced by other variables. Defining disease worsening or flare in RA is likely represented by composite changes in multiple variables rather than worsening in only a single characteristic (e.g., painful or swollen joints). Such a rigorous definition for "RA flare" is of interest in comparator RCT (e.g., those sponsored by US National Institutes of Health) as well as LOS.

During discussions it became apparent that there are multiple settings in which a standardized definition of RA flare may be useful — to evaluate not only efficacy but also safety. As therapeutic choices for RA are increasing, benefit-to-risk profiles are now examined in both monotherapy and combination use. Outcomes such as sustained (drug-free) remission could utilize a definition of flare to facilitate induction/withdrawal trial designs, as utilized in juvenile idiopathic arthritis (JIA). Time to flare and number of flares have been used for regulatory approval of several products[2,3]. A formal definition could facilitate measurement of variability of disease activity over time to better understand "regression to the mean" in LOS, and impact of single joint worsening related to systemic flare[4]. Further, while minimally clinically important differences (MCID) and patient acceptable symptom states have been established for improvements in RA,[5,6] "minimally detectable," "clinically significant," and "patient-acceptable" differences for worsening or flare have not been rigorously evaluated and established[7]. The purpose of this SIG at OMERACT 9 was to initiate a process to identify domains and develop a consensus-based definition for RA disease flare that could be used for multiple purposes.

MATERIALS AND METHODS

A group of interested individuals, including 2 Fellows, one each from the European Union and United States, assembled following OMERACT 8 to begin discussions regarding approaches to define RA flare. Through a series of approximately bimonthly teleconferences and informal meetings, a preliminary framework was developed to establish and conduct a SIG at OMERACT 9.

Literature review. A comprehensive literature review was performed to identify flare definitions applied in RCT in various rheumatic diseases using Medline/PubMed for English and German publications, with no date limitations. Additional publications were identified from references within these publications, ACR and EULAR meeting abstracts, and other sources from individual investigators. Search terms included: flare, worsening, RA, JIA, systemic lupus erythematosus (SLE), MCID, disease activity, and patient perspectives. Methods sections from RCT in RA, JIA, SLE were also evaluated for flare definitions. Seventeen articles in RA were identified that contained data relevant to a flare definition; outcomes used to measure worsening of disease activity or flare were extracted[8-22,36,37]. A summary was provided to participants for review before OMERACT 9.

RESULTS

Flare in JIA and SLE. The definition for improvement in JIA [ACR Pediatric 30 criteria (Pedi30)] requires ≥ 30% improvement from baseline in ≥ 3 of 6 variables with worsening of ≥ 30% in no more than one[23] of physician global assessment, patient/parent global assessment of disease activity, active joint counts, joints with decreased range of motion, function using the Childhood Health Assessment Questionnaire (CHAQ), and acute phase reactants. In the pivotal RCT for etanercept in polyarticular JIA, a withdrawal-flare study design used disease flare as an endpoint[3]. All children initially received etanercept for 3 months, those with Pedi30 responses were randomized to blinded withdrawal (placebo) or etanercept continuation for 4 months or until flare occurred. Flare was defined as a worsening of ≥ 30% in 3 of 6 Pedi30 variables, and improvement of ≥ 30% in no more than one variable. The primary endpoint was the proportion of patients with flare in etanercept versus placebo groups from beginning to end of the double-blind withdrawal period. Similar definitions of flare have been used in registration studies of adalimumab[24] and abatacept[25] for JIA.

Using data from the etanercept RCT, a sensitivity analysis of various definitions of disease flare in JIA was conducted[2]. Candidate definitions included 20% to 50% changes in 2 to 4 core variables. The 3 best performing definitions for detecting flare were: (a) worsening in 2 of 6 variables by ≥ 40% without improvement in > 1 variable by ≥ 30%; (b) worsening in 3 variables by ≥ 30%; (c) any worsening in CHAQ; worsening in erythrocyte sedimentation rate ≥ 30%, and in active joint count ≥ 10%.

Several definitions of flare have been used in SLE RCT[26], including "major flares" defined as new or increased use of high dose corticosteroids and/or immunosuppressives, and hospitalizations or death due to SLE disease activity[27]. The British Isles Lupus Assessment Group disease activity index incorporates both definitions and gradations of flare within the instrument itself[26]. The recently reported "SELENA flare index" incorporates thresholds for change in SLEDAI, new symptoms in different organ systems, medication changes, hospitalization, and increases in physician global assessment[27,28]. A recent Delphi process to define

flare in SLE has been concluded with validation planned in upcoming RCT.

Flare in rheumatoid arthritis. Several RCT in RA have recorded flare as an outcome. Definitions were quite variable, ranging from physician reported worsening to specific levels of change in core set variables. In 2 recent studies of infliximab, a definition for flare used components of the ACR response criteria. In the Infliximab RA Methotrexate Tapering trial[10] and the Safety Trial for Rheumatoid Arthritis with Remicade Therapy (START) trials of infliximab[11], RA flare was defined as ≥ 50% worsening in combined tender and swollen joint counts compared to either baseline or prior visit. An "inversed EULAR" response to define flare was used in 2 small trials and defined as an increase in DAS28 > 1.2 or an increase in DAS28 > 0.6 and a current DAS28 > 5.1[14]. Other studies have used flare definitions based on an "intention-to-treat" reported as a physician's decision to change therapy (e.g., increased methotrexate dose, increase, or initiation of steroids, intraarticular steroids) based on increased signs and symptoms[9]. A number of trials have reported flares in various contexts, with differing definitions. A comprehensive analysis of "loss of response" in patients in a clinical practice registry in the US (CORRONA) provided insight regarding potential candidate domains[29]. Domains and variables that have been incorporated into published RA flare definitions[8-22,36,37] are summarized in Table 1. A more detailed literature review of this topic is in preparation.

Patient reported worsening of disease. Patient perspectives are critical in developing minimally detectable, clinically meaningful, and patient-acceptable definitions of response; therefore, patients formally participate in the OMERACT process[30-32]. The patient perspective group recently demonstrated the importance of fatigue as a domain in RA, which led to an OMERACT consensus that fatigue assessment should be included in RCT[32,33]. Although some work has been done to examine patient-determined thresholds for improvement, there has been little research to understand patient perspectives on disease worsening or flare. A study that evaluated patient satisfaction and its relation to physician assessment of RA disease activity showed that patients detected worsening with lesser decrements of change than for improvement[7]. These results imply that a definition for "worsening" or flare from the patient perspective may represent far less of a change than the change used to define response criteria for improvement in some RCT. Similarly, in a recent SLE RCT, MCID for improvement in SF-36 scores were in the range previously reported for OA and RA; however, MCID for clinically important worsening defined a lesser degree of deterioration than change for improvement[34].

OMERACT 9 results. The OMERACT 9 SIG was attended by about 120 participants including 11 patients. After introducing the meeting's aims, patients convened in a separate breakout group to limit the influence of the discussion by clinical research investigators on their deliberations.

Table 1. Variables and domains reported in previous studies of flare in rheumatoid arthritis.

Variable	No. of Studies in which variable/domain was used	References
Tender joint count	13	8, 10, 11, 12, 13, 14, 15, 19, 20, 21, 22, 36, 37
Swollen joint count	13	8, 10, 11, 12, 13, 14, 15, 19, 20, 21, 22, 36, 37
Patient global assessment	10	8, 10, 11, 14, 15, 19, 20, 21, 22, 36
Erythrocyte sedimentation rate	10	10, 11, 13, 14, 15, 16, 19, 20, 22, 36
Patient assessment of pain	7	8, 10, 11, 12, 13, 17, 22
Disease Activity Score	7	14, 15, 18, 19, 20, 22, 36
C-reactive protein	6	10, 12, 15, 16, 20, 22
Health Assessment Questionnaire	6	10, 11, 12, 15, 20, 22
Physician global assessment	5	8, 10, 11, 21, 22
Fatigue	3	13, 17, 22
Physician assessment of pain	2	8, 22
Morning stiffness	2	13, 22
Ritchie Articular Index	2	13, 22
ARA functional class	2	8, 22
Synovitis	2	13, 22
Van der Heijde modified Sharp Score	2	15, 22
Complete blood count, liver enzymes, creatinine, radiographs	2	16, 22
Bone absorptiometry	2	16, 22
RADAI score	2	19, 22
Change in patient global assessment	1	22
Grip strength	1	22
50 foot walk time	1	22

ARA: American Rheumatology Association; RADAI: rheumatoid arthritis disease activity index.

Delegates reviewed and discussed the literature review, and then breakout groups examined and expanded lists of candidate domains to be included in a definition of RA flare, and recommended contexts for utilizing such a definition. In their breakout group, patients discussed what constituted a "flare" or disease worsening from their perspective, and tried to identify symptoms or signs that discriminate this from daily fluctuations of RA. The discussion was facilitated by a researcher/clinician (SH), using open questions and prompting further debate among the group. Ideas were noted on flip charts.

Patient breakout group. Eleven patients with inflammatory arthritis (mainly RA) reported "flare" as a wide range of physical, emotional, and cognitive symptoms. Pain was recognized as a critical factor in defining a flare, and might be global, or related to multiple or single joints (a single untreated joint could potentially lead to a generalized flare). Traditional signs of inflammation such as joint swelling or stiffness were reported, but there were many reports of night and day sweats associated with a developing flare, and one patient reported irritated, red eyes (with blurred vision). Fatigue, loss of function and stamina were reported by many patients. These symptoms were seen as key components, with concomitant reduction in mobility, including difficulty waking up and getting out of bed. Global symptoms of flare included a general feeling of being ill, pallor, weight loss, flu-like symptoms, tremor, weakness, and sensitivity to noise and light. Mood changes were reported, including irritability, intolerance, tearfulness, anxiety, feeling down, with a desire to withdraw from social situations ("no-people days"). Sleep disturbance by pain or for no discernible reasons, with reduced sleep quality and quantity and a need to sleep during the day were also reported. Cognitive disruptions such as an inability to concentrate, find words, make decisions, and process thoughts were also reported. Patients reported that family members sometimes noticed various signs of an impending flare, even before the patient was aware of them.

From the perspectives of these patients pain was considered as an essential component of "flare." Joint swelling and stiffness, however, were not deemed essential although they might contribute to a flare. Patients appear to experience a flare as a cluster of symptoms, which vary between patients and within an individual on different occasions. Early signs of flare, such as fatigue and/or night/daytime sweats, may suggest a prodrome. Early symptoms are addressed by patients using self-management strategies such as medication increase, and pacing and planning activities. In distinguishing between expected fluctuations in disease pattern versus a flare, patients take multiple issues into account: lack of obvious cause of the onset of symptoms, symptom intensity and persistence, response to self-management, frequency of symptom clusters, and loss of good days between episodes. The patient group suggested that a flare occurs when a cluster of symptoms are intense, persist, and cannot be managed by usual self-management strategies, thus leading to a decision to seek help. This might be as early as 2 or as long as 7 days, but intensity and non-response to self-management are more important than symptom duration.

These experienced patients suggested that the duration that a patient had lived with disease influenced their perception of a flare as they could better place worsening within the context of disease variability. For example, in early disease, a single joint worsening may be considered a flare whereas in later disease this may be understood as disease fluctuation. Patients reflected that experience came with longer disease duration, which meant that they became more likely to use self-management strategies before deciding a period of worsening was a flare. Because of the possibility of improvement using self-management strategies, patients indicated that both persistence and intensity of symptoms were critical components.

Investigator breakout groups. An important finding from the investigator groups was that to discuss "flare," a working "definition" of the term was required. Some participants raised concern that the term "flare" was not necessarily translatable or used in all languages. Each breakout group recognized that persistence of symptoms was an important and necessary component to classify disease worsening as a flare. There was also significant discussion in some groups as to whether a flare of disease represented a change from a prior point in time, or in addition, a certain level of disease activity was required (e.g., a state).

In terms of specific domains and variables, each group indicated that joint counts (swelling and tenderness) were critical to include in an overall definition. Other core set components, including patient and physician reported global assessments of disease activity and patient reported pain, and acute phase reactants were also recognized as important. Among these patient global assessment was ranked highly. All groups included fatigue as an important domain to capture in a flare definition. There was some discussion about, but variable acceptance of, use of negative changes in composite measures such as ACR, EULAR, Clinical Disease Activity Index, Simplified Disease Activity Index, and Routine Assessment of Patient Index Data (RAPID) responses as well as inclusion of imaging such as magnetic resonance imaging and ultrasound. In some groups the need for the addition or increase in medications was considered important to capture. Others encouraged inclusion of an instrument to measure patient and physician-reported flare as a domain.

Reports and voting. Summaries of patient and investigator groups were presented to the reassembled audience, followed by voting. A clear consensus of 95% was obtained asserting that there was a need to study and develop a formal definition for RA flare or worsening of disease, and agreement that there were multiple contexts in which such a def-

inition could be useful. There was consensus for use in RCT (85%) as well as for LOS (89%); a majority agreed as to its use in clinical practice (69%). Despite the origination of this SIG to develop a definition for flare to facilitate adverse-event reporting, less than 50% of the SIG participants thought this was needed. However, in the context of adverse-event capture, the majority of participants agreed that a grading system for flare, as used in SLE, would be helpful. After discussion, it was also agreed that the first area in which a flare definition should be established would be for RCT, with followup or parallel work in the context of an adverse or undesirable event.

Final plenary presentation. In the final OMERACT 9 plenary session several questions were posed for voting. As in the breakout groups, there was some disagreement whether flare represented a change from an earlier state or an absolute disease activity state. Consensus was obtained that a working definition of flare should indicate a worsening of disease activity (88%); only 49% felt that flare represented an absolute disease state and 20% "did not know." There was consensus that a working definition of RA flare should include persistence and duration as critical elements (77%), and should include change or increase in therapy in the definition (74%).

To facilitate the research agenda, a working definition of RA flare was developed based on these votes and presented: A flare occurs with any worsening of disease activity that would, if persistent, in most cases lead to initiation or change of therapy; and a flare represents a cluster of symptoms of sufficient duration and intensity to require initiation, change or increase in therapy.

DISCUSSION

It was agreed that a standardized data-driven, consensus-based definition for RA flare was needed for use in multiple clinical research contexts. Methods used to develop definitions in other diseases, including JIA and SLE, are informative. In contrast to the methodology used in other diseases, participation of patients at OMERACT 9 introduced important new perspectives to our overall understanding of flare.

First, patients provided useful insight, causing investigator groups to acknowledge that the term "flare" was not a universally understood concept and that patients sometimes successfully self-manage some forms of "worsening" disease. Thus any working definition of flare may need to include disease worsening of a duration and severity that cannot be self-managed. In contrast to investigators, who sought concrete and standardized domains for a definition, patients engage in significant self-management strategies, including pacing and/or changing self-medication, and thus exclusion of these strategies from RCT or LOS may lead to confusion of results. If patients engage in some self-management activities in an RCT (e.g., self-adjusting steroid or NSAID dose) they may be withdrawn for protocol deviation or, alternatively, patients may not report these activities to physicians or investigators. Further research is needed to assess the implications of these findings and to establish ways to consistently capture these data as they are likely to influence interpretation of treatment failure criteria.

Second, the patient group raised issues about the characteristics of flare that need in-depth and systematic exploration using rigorous qualitative research methods. Informal discussions suggest that patients may detect early signs of a flare (fatigue, irritability, sweats) and that they use clusters of unremitting and unmanageable symptoms to define their flares. While patients indicated that pain was always present during a flare, they did not necessarily include synovitis. This is in contrast to features defined in investigator breakout groups, where synovitis was deemed essential and possibly the only requirement. It is possible that patients and physicians are simply prioritizing different signs of inflammation (e.g., pain versus synovitis), or describing different events. Therefore, the potential for controversy needs to be recognized and managed to assure consensus is ultimately achieved and face validity is obtained.

One issue arose that was of particular importance. While there was disagreement between patients and investigators on some domains, fatigue was recognized by all as a critical within a flare definition. However, tools to more accurately capture all features of this important domain need to be validated. They must be able to reflect systemic manifestations of RA, as this has been recognized as an important element for detecting improvement in disease. A research agenda is provided to better address these areas of disparity, in order to gain consensus.

As domains are identified to be included within an RA flare core set, it will be important to also link the domains typical and relevant for flares identified by different perspectives (literature, patients, and experts) to the International Classification of Functioning Disability and Health (ICF), a universal model and classification to describe human functioning. The ICF Core set for RA[35] can also be examined to determine if other areas that have not been discussed may be relevant to evaluate within the RA flare definition.

There are some limitations of the findings from this first OMERACT SIG on "RA flare." First, the group of individuals assembled may have required more time and context in preparation for the SIG, and may have benefited from further discussions, in order to provide fully informed and deliberate input regarding their opinions and voting. In the context of the limited time for presentations there was a possibility that important areas may not have been thoroughly captured and presented. While information from patients was extremely important, it should be recognized that this group of patients may not be fully representative of patients with RA in general, especially concerning: disease duration, range of disease severity, and experience in communicating

in focus groups. These issues will be addressed through a Delphi process that will be informed by results of patient focus group protocols and data mining of Phase III RCT data.

Research agenda. An initial research agenda has been developed based on discussions at OMERACT 9 that will evaluate various aspects of a flare definition, initially concentrating on RA RCT:

(1) To understand the patient's perspective of flare in order to evaluate additional domains that may be required for inclusion through qualitative research in larger groups of multinational (USA, Canada, EU, Australia) RA patients representing the spectrum of disease duration and severity and other important ethno-demographic and cultural variables. Recognizing the increasing participation of RCT subjects from other areas, further expansion to Asia and Latin America will be desirable. (2) To explicitly characterize fatigue measures that may sensitively detect the onset of flare. (3) To examine the performance of suggested flare core set domains and measurements to detect clinically relevant worsening of disease in available RCT and LOS datasets. Receiver-operator curve characteristics of definitions in relation to other clinical variables will be evaluated. (4) To develop consensus on core domains for a definition of RA flare for use in RCT through a structured Delphi process with SIG participants and experienced clinical trialists.

In conclusion, development of a standardized definition of "RA flare" is needed for several settings including RCT, LOS, and clinical care, and may be different in different scenarios. In this SIG, we characterized a working definition of RA flare that captures worsening of disease over time, that is of a significant level to necessitate an intervention, and that recognizes a clustering of symptoms and signs dependent on both patient and investigator perspectives. The next required steps in developing an RA flare core set will depend on additional input from patients as well as exploration and validation of candidate definitions in appropriate RCT data sets.

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REFERENCES

1. Woodworth T, Furst DE, Alten R, et al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v.2.0. J Rheumatol 2007;34:1401-14.
2. Brunner HI, Lovell DJ, Finck BK, Giannini EH. Preliminary definition of disease flare in juvenile rheumatoid arthritis. J Rheumatol 2002;29:1058-64.
3. Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med 2000;342:763-9.
4. Giles JT, Mease P, Boers M, et al. Assessing single joints in arthritis clinical trials. J Rheumatol 2007;34:641-7.
5. Wells G, Boers M, Shea B, et al. MCID/Low Disease Activity State Workshop: low disease activity state in rheumatoid arthritis. J Rheumatol 2003;30:1110-1.
6. Wells G, Anderson J, Boers M, et al. MCID/Low Disease Activity State Workshop: summary, recommendations, and research agenda. J Rheumatol 2003;30:1115-8.
7. Leeb BF, Sautner J, Leeb BA, Fassl C, Rintelen B. Lack of agreement between patients' and physicians' perspectives of rheumatoid arthritis disease activity changes. Scand J Rheumatol 2006;35:441-6.
8. Kremer JM, Rynes RI, Bartholomew LE. Severe flare of rheumatoid arthritis after discontinuation of long-term methotrexate therapy. Double-blind study. Am J Med 1987;82:781-6.
9. Yazici Y, Erkan D, Kulman I, Belostocki K, Harrison MJ. Decreased flares of rheumatoid arthritis during the first year of etanercept treatment: further evidence of clinical effectiveness in the "real world". Ann Rheum Dis 2002;61:638-40.
10. Fleischmann RM, Cohen SB, Moreland LW, et al. Methotrexate dosage reduction in patients with rheumatoid arthritis beginning therapy with infliximab: the Infliximab Rheumatoid Arthritis Methotrexate Tapering (iRAMT) trial. Curr Med Res Opin 2005;21:1181-90.
11. Rahman MU, Strusberg I, Geusens P, et al. Double-blinded infliximab dose escalation in patients with rheumatoid arthritis. Ann Rheum Dis 2007;66:1233-8.
12. Barrett JH, Brennan P, Fiddler M, Silman A. Breast-feeding and postpartum relapse in women with rheumatoid and inflammatory arthritis. Arthritis Rheum 2000;43:1010-5.
13. Ten Wolde S, Breedveld FC, Hermans J, et al. Randomised placebo-controlled study of stopping second-line drugs in rheumatoid arthritis. Lancet 1996;347:347-52.
14. Van den Bemt BJ, den Broeder AA, Snijders GF, et al. Sustained effect after lowering high dose infliximab in patients with rheumatoid arthritis: a prospective dose titration study. Ann Rheum Dis 2008;67:1697-701.
15. van der Bijl AE, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Infliximab and methotrexate as induction therapy in patients with early rheumatoid arthritis. Arthritis Rheum 2007;56:2129-34.
16. Maravic M, Berge C, Daures JP, Boissier MC. Practices for managing a flare of long-standing rheumatoid arthritis: survey among French rheumatologists. Clin Exp Rheumatol 2005;23:36-42.
17. Carr A, Hewlett S, Hughes R, et al. Rheumatology outcomes: the patient's perspective. J Rheumatol 2003;30:880-3.
18. Fransen J, Hauselmann H, Michel BA, Caravatti M, Stucki G. Responsiveness of the self-assessed rheumatoid arthritis disease activity index to a flare of disease activity. Arthritis Rheum 2001;44:53-60.
19. Den Broeder AA, Creemers MC, van Gestel AM, van Riel PL. Dose titration using the Disease Activity Score (DAS28) in rheumatoid arthritis patients treated with anti-TNF-alpha. Rheumatology 2002;41:638-42.
20. de Man YA, Hazes JM, van de Geijn FE, Krommenhoek C, Dolhain RJ. Measuring disease activity and functionality during pregnancy in patients with rheumatoid arthritis. Arthritis Rheum 2007;57:716-22.
21. Caldwell JR, Furst DE, Smith AL, et al. Flare during drug

withdrawal as a method to support efficacy in rheumatoid arthritis: amiprilose hydrochloride as an example in a double blind, randomised study. J Rheumatol 1998;25:30-5.
22. Aletaha D, Stamm T, Smolen J. [Measuring disease activity for rheumatoid arthritis]. Z Rheumatol 2006;65:93-6, 98-102.
23. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997;40:1202-9.
24. Ruperto N, Lovell DJ, Goodman S, et al. Long-term efficacy and safety of adalimumab in children with juvenile rheumatoid arthritis (JRA): Data over two years of treatment in a phase III Study [abstract]. Ann Rheum Dis 2007;66 Suppl II:THU0195.
25. Ruperto N, Lovell DJ, Quartier P, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet 2008;372:348-50.
26. Gordon C, Sutcliffe N, Skan J, Stoll T, Isenberg DA. Definition and treatment of lupus flares measured by the BILAG index. Rheumatology 2003;42:1372-9.
27. Petri M, Buyon J, Kim M. Classification and definition of major flares in SLE clinical trials. Lupus 1999;8:685-91.
28. Petri M, Kim MY, Kalunian KC, et al. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med 2005;353:2550-8.
29. Furst D, Chang H, Ranganath V, et al. Defining change in disease activity parameters associated with loss of response over time in RA patients [abstract]. Arthritis Rheum 2007;56 Suppl:S709.
30. Kirwan J, Heiberg T, Hewlett S, et al. Outcomes from the Patient Perspective Workshop at OMERACT 6. J Rheumatol 2003;30:868-72.
31. Kirwan JR, Ahlmen M, de Wit M, et al. Progress since OMERACT 6 on including patient perspective in rheumatoid arthritis outcome assessment. J Rheumatol 2005;32:2246-9.
32. Kirwan JR, Hewlett S. Patient perspective: reasons and methods for measuring fatigue in rheumatoid arthritis. J Rheumatol 2007;34:1171-3.
33. Kirwan JR, Minnock P, Adebajo A, et al. Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. J Rheumatol 2007;34:1174-7.
34. Strand V, Crawford B. Improvement in health-related quality of life in patients with systemic lupus erythematosus following sustained reductions in anti-dsDNA antibodies. Expert Rev Pharmacoeconomics Outcomes Res 2005;5:317-26.
35. Stucki G, Cieza A, Geyh S, et al. ICF core sets for rheumatoid arthritis. J Rehabil Med 2004;44 Suppl:87-93.
36. Smolen JS, Keystone EC, Emery P, Breedveld FC, Betteridge N, Burmester GR, et al. Consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 2007;44:143-50. Epub 2006 Oct 26
37. Gotzsche PC, Hansen M, Stoltenberg M, Svendsen A, Beier J, Faarvang KL, et al. Randomized, placebo controlled trial of withdrawal of slow-acting antirheumatic drugs and of observer bias in rheumatoid arthritis. Scand J Rheumatol 1996;25:194-9.