Developing a Construct to Evaluate Flares in Rheumatoid Arthritis: A Conceptual Report of the OMERACT RA Flare Definition Working Group

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ABSTRACT. Rheumatoid arthritis (RA) patients and healthcare professionals (HCP) recognize that episodic worsening disease activity, often described as a “flare,” is a common feature of RA that can contribute to impaired function and disability. However, there is no standard definition to enable measurement of its intensity and impact. The conceptual framework of the Outcome Measures in Rheumatology Clinical Trials (OMERACT) RA Flare Definition Working Group includes an anchoring statement, developed at OMERACT 9 in 2008: “flare in RA” is defined as worsening of signs and symptoms of sufficient intensity and duration to lead to change in therapy. Subsequently, domains characterizing flare have been identified by comprehensive literature review, patient focus groups, and patient/HCP Delphi exercises. This led to a consensus regarding preliminary domains and a research agenda at OMERACT 10 in May 2010. The conceptual framework of flare takes into account validated approaches to measurement in RA: (1) various disease activity indices (e.g., Disease Activity Score, Clinical Disease Activity Index, Simplified Disease Activity Index); (2) use of patient-reported outcomes (PRO); and (3) characterization of minimally clinically detectable and important differences (MCDD, MCID). The measurement of RA flare is composed of data collection assessing a range of unique domains describing key features of RA worsening at the time of patient self-report of flare, and then periodically for the duration of the flare. The components envisioned are: (1) Patient self-report using a “patient global question” with well characterized and validated anchors; (2) Patient assessment using a flare questionnaire and PRO available at the time of each self-report; (3) Physician/HCP assessment of disease activity status; and (4) Physician’s determination whether to change treatment. In randomized controlled trials and observational studies, such a conceptual approach is intended to lead to a valid measure of this outcome/response, thus expanding an understanding of the true impact of a therapy to limit disease activity. Clinically, this approach is intended to enhance patient-HCP communication. This article describes the conceptual framework being used by the OMERACT RA Flare Definition Working Group in developing a standardized method for description and measurement of “flare in RA” to guide individual patient treatment. (J Rheumatol 2011;38:1745-50; doi:10.3899/jrheum.110400)

Key Indexing Terms:
RHEUMATOID ARTHRITIS  FLARE  PATIENT PERSPECTIVE  WORSENING  DISEASE ACTIVITY  OUTCOME MEASURES

The term “flare in RA” is commonly used by both patients and clinicians to describe episodes of worsening signs and symptoms, often a temporary state, but sometimes indicating persistent deterioration from a previous state. While periodic fluctuations of disease activity are common in RA, these vary widely in their intensity, frequency, duration, and impact on the patient. There is no commonly accepted understanding of the constituents of a “flare in RA” or a standardized method...
to accurately quantify these events. Patients will often describe “good days” and “bad days,” but may have difficulty communicating the severity and impact of their “bad days” to their healthcare provider (HCP). Clinicians will often require changes in “objective measures,” such as increases in joint swelling and tenderness or worsening in laboratory values such as C-reactive protein (CRP) or/and erythrocyte sedimentation rate (ESR) in making a decision whether a patient is in a flare. These differences in perspectives between patients and clinicians may lead to erroneous assumptions of the actual aggregate state of disease activity and its impact on function and quality of life.

With the advent of more effective therapies, the need to detect, measure, and assess flare becomes more apparent. Thus, validating a definition should enhance clinical research and facilitate clinical decision-making. An accepted definition, for example, could be a study endpoint or guide medication tapering, retreatment, or changed pharmacotherapy or self-management strategies.

This article describes the conceptual framework being used by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) RA Flare Definition Working Group in developing a standardized method for description and measurement of “flare in RA,” initially in the context of randomized controlled trials (RCT) and longitudinal observational studies (LOS), and ultimately to guide individual patient treatment.

**Why Define Flare in RA?**

Flares are a common occurrence in patients with RA and likely represent an under-recognized and potentially disabling aspect of the disease experience. There are limited data to inform us on the nature and impact of flares. Whether these episodes of flare, their intensity, frequency, and/or their duration can be mitigated or modulated has not been studied, in part because we lack a fundamental understanding of many aspects of the experience of RA flare.

With the recognition of flares as an integral feature of disease for most RA patients, there is an opportunity, if not a requirement, to evaluate their impact, and to incorporate an assessment of flares into the design of RCT assessing therapeutic efficacy (Table 1).

At OMERACT 8, a decision was made to develop a standardized definition of flare in RA, recognizing that such a definition was lacking for the reporting of RA flare as an adverse event. In addition, for RCT such a definition appeared to be needed to fully define “Remission” or “Low Disease Activity,” and to characterize a relevant aspect of the benefit versus risk of potent biologic therapies. In addition, such a definition is needed to determine ability to taper therapy once remission is established, and to determine an optimally effective maintenance regimen. Potential endpoints include “time to flare” (i.e., duration of benefit), absence of flare, number of flares over a period of time, or time of readministration, as used for studies in juvenile inflammatory arthritis.

In the absence of an established flare definition, studies to date have largely used an inverse of a response measure developed and validated to measure disease improvement (e.g., increase in Disease Activity Score) or important changes in nonsteroidal antiinflammatory drugs (NSAID) or corticosteroids.

**Heterogeneous Signs and Symptoms of Flare**

The heterogeneity of signs and symptoms that may constitute a flare is recognized by patients and their clinicians; similarly, there is variation in the specific actions and interventions taken, dependent on a variety of factors such as intensity, frequency, manageability, and duration. Some exacerbations are short-lived (e.g., a “bad day”) and often managed by the patient with watchful waiting or with changes in activities, pacing, rest, or nonpharmacological interventions. Others may be of sufficient severity that patients self-manage with increased analgesics, NSAID, or short-term increase in corticosteroid dose. Finally, there are flares of sufficient intensity that patients request HCP consultation and change in treatment. Although the phenomenology of flare is well recognized by both clinicians and patients, there are no generally agreed-upon parameters to define disease flare/worsening, to characterize its severity, or to describe its onset and duration.

Within the OMERACT RA Flare Definition Working Group, qualitative research with patients, systematic literature reviews, and parallel iterative Delphi processes (healthcare providers and researchers, patient research partners) yielded a preliminary set of unique domains that characterized the flare experience. After obtaining final consensus regarding essential domains for detection and measurement of RA flare, the Working Group will identify available validated instruments that capture elements of these domains to enable PRO instrument development. It is anticipated that new additional instruments will need to be developed and validated to appropriately define and measure RA flare.

Another aspect of the use of the term “Flare” likely represents a continuum, so an anchor for flare assessment is required. The anchor must be appropriate to reflect detectable or important change in RA disease activity. An initial assumption was that a clinically relevant flare occurs when RA signs and symptoms worsen in both intensity and duration to the point that a patient requests evaluation, and to the extent that a clinician determines that a change in treatment is appropriate.
The Critical Role of the Patient Perspective in Defining Flare

PRO are increasingly recognized as a critical component of the assessment of efficacy in clinical trials and clinical practice. Thus, involvement of patients has been a key aspect of the OMERACT process, and patient research partners have played an integral role to enable understanding of the totality of the disease experience. For example, patient research partners contributed to the recognition of fatigue as an important domain to evaluate in the assessment of RA disease activity.

In our qualitative research with patients, several questions regarding the RA flare experience were identified. First, for patients, there is no consensus on the “meaning of flare” and the context(s) in which the term is used. For example, some of the domains used in describing the flare experience include pain, stiffness, fatigue, functional ability, participation in life activities, sleep, and emotional distress. While it is likely that individual patients can generally distinguish different levels of flare in terms of severity and impact, the metrics that patients use to make this determination are not yet defined. The actions of patients (e.g., self-management) in response to episodic disease worsening have also been poorly quantified, including pharmacologic and nonpharmacologic interventions.

The characteristics of a flare or the threshold at which patients decide to contact a health professional for change in management are also unknown. In turn, the perceived efficacy of different treatments to mitigate flares requires further evaluation. The influence of a patient’s prior level of disease activity and control in their perception of flare is also an important variable that requires integration into the flare concept.

To evaluate these aspects of the flare concept, investigators and patient research partners in our group have conducted qualitative research in 5 countries on 3 continents to better understand the patient’s experience of flare. Several important concepts have thus far emerged: (1) Patients use the term “flare” to refer to several distinct levels of disease experience; (2) Many patients identify a prodromal state that precedes a worse flare; (3) The duration of symptoms and persistence are important qualifiers; and (4) There is a progression from an initial uncertainty as to whether the symptoms experienced are a “normal” fluctuation, or the beginning of disease becoming more unmanageable. There is significant utilization of various strategies of self-management in response to specific symptom clusters. From the patient’s perspective, increasing utilization and ultimately the failure of self-management strategies to maintain control of RA disease activity is an important and particularly disabling aspect of flare in RA. Patients have also identified several key unique features.

Assessing Validity of a Flare Definition

As introduced earlier, selecting a proper anchor to reflect the “truth” of a flare measure will depend on several likely overlapping features, including a patient self-report of flare that will need to be developed, together with clinical variables (e.g., swollen and tender joints and laboratory parameters) to evaluate both construct and content validity. In initial data-mining exercises in LOS and RCT, we are evaluating whether worsening in patient and physician global assessments of disease can be used as a surrogate for an episodic increase in disease activity that a patient describes as a flare, or if a physician decision to increase or change therapy can be used in initial assessment of a more directed or comprehensive flare tool. It is important to recognize that while measures such as Disease Activity Score 28 or Clinical Disease Activity Index or inverse response criteria (European League Against Rheumatism response and American College of Rheumatology response) may capture disease worsening, they may not be sufficiently sensitive to detect a potentially disabling flare or to accurately measure flare, considering the hetero-

<table>
<thead>
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<th>Table 1. Settings for use of a rheumatoid arthritis flare measure.</th>
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<td><strong>Clinical Trials</strong></td>
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<tr>
<td>Detecting adequacy of dose/ regimen for duration of therapeutic effect — driving to remission (“tight control”)</td>
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<tr>
<td>Aiding dose/ regimen optimization — titration and tapering while maintaining remission</td>
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<tr>
<td>Assessing effect of concomitant medications to control oscillating symptoms/signs</td>
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<td>Assessing and reporting of episodic disease-worsening as an adverse event</td>
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<td>Determining remission as absence of disease flare among other measures</td>
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<td><strong>Clinical Practice</strong></td>
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<td>Facilitating MD-patient communication when considering change in therapy for intermittent disease-worsening</td>
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<td>Determining need to change treatment</td>
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<td>Assessing patient-specific interventions to control episodic worsening</td>
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<td>Enabling assessments to apply “tight control” strategies on an individual patient basis</td>
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<td>Assessing episodic disease-worsening</td>
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<td>Limiting effect of and disability associated with periodic disease-worsening (e.g., time lost from work)</td>
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Is Remission Also Defined by the Absence of Flares?
A final concept to introduce is that flare is a real and consequen-
tial part of disease. Often unpredictable and at times dis-
abling, these episodes are very real. The current goal, to treat
RA to attain a low disease activity state or remission, fails to
take into account the potential of ongoing flares to represent
the persistence of disease activity, which is not reflected in our
current outcome measurements as goals of therapy. Estab-
lishing a framework to assess flare will permit further explo-
ration of the criterion validity of remission based on current
outcome measures against a new standard. Integration of
measures such as the RA Impact of Disease (RAID) question-
naire and concepts such as the patient acceptable symptom
state are also critical to evaluate in relationship to the assess-
ment of flare as applied to low disease activity states.

Next Steps
This hypothesized conceptual framework to evaluate RA flare
will serve as the basis for a process to develop an outcome
measure that will quantify this complex RA disease experi-
ence. Our preliminary anchoring definition, based on wors-
ening disease activity that leads to an assessment for a change
in therapy, will allow data-mining to be conducted in retro-
spective datasets, as well as in prospective studies that will
actually measure intensity and the influence of flare for the
RA patient. A particular RCT context in which the compo-
nents of a preliminary flare measure can be incorporated
includes studies of patients aimed at achieving remission
based on current validated disease measures. These remis-
sion studies could incorporate a flare assessment to determine
the occurrence, intensity, duration, and frequency of flares.

Alternatively, or additionally, studies could seek to deter-
mine the optimal maintenance dosing regimen, and the ability
to achieve drug-free remission, including algorithms for
blinded dose reduction, tapering, or elimination; these studies
would include the number of patients who successfully reduce
therapy without flare, experience increasing time to flare, or
experience a number of flares (this may include both intensi-
ity and duration).

The current conceptual model will be refined as such addi-
tional data are integrated into defining the concept of RA
flare. The consistent, continued involvement of experienced
and knowledgeable patient research partners enables reality-
based testing of the criterion validity of our work, including
its relevance across varying cultures.

Conclusion
A “flare in RA” is a multilayered and complex feature of this
chronic, often disabling disease. It is an integral feature of the
RA disease process that has hitherto been poorly described or
measured. There is an immediate need to develop methods to
accurately capture and measure flares and to facilitate the
design of RCT incorporating flare as an outcome. Importantly,
the quantification of flares and a means to assess their severi-
ty and impact will serve to enhance clinical care for patients with RA. Patients’ descriptors of their RA flares include more than joint symptoms or traditionally measured elements of the endpoint core sets used in RCT, LOS, and clinical practice. Some features may be even more important to patients than these standard clinical variables in terms of their effects on function and participation in usual activities. Through qualitative and quantitative research, multiple stakeholders including patient research partners have worked together in the OMERACT RA Flare Definition Working Group to conceptualize the flare experience in a manner that encompasses constitutional, physical, functional, psychological, and time-oriented elements. The work of our group will help to improve both clinical trials and clinical care through an expansion of the vocabulary to enhance patient-healthcare provider communication of a potentially disabling aspect of RA.

ACKNOWLEDGMENT
We are grateful for the participation of patients and health professional participants in focus groups and Delphi exercises.

APPENDIX

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