Flares in Rheumatoid Arthritis: Frequency and Management. A Report from the BRASS Registry

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ABSTRACT. ***Objective.*** To describe the frequency, duration, and management of flares as reported by patients with rheumatoid arthritis (RA).

Methods. Data were collected in a prospective observational study of patients with RA recruited from a single academic center and treated according to the rheumatologists' discretion. Every 6 months, patients reported the number and duration of RA flares and described how these were managed in terms of adding or changing medication and use of nonpharmacologic strategies.

Results. Of patients who reported flares at least once during the study, 74% reported having flares 6 months prior to study entry and 59% reported flares prior to the first 6-month visit. At subsequent visits, 54–57% reported having > 1 flare. Thirty percent of patients in remission reported flares. Flare duration lasted ≥ 2 weeks in 30%, 1–2 weeks in 13%, and < 1 week in 57%. Forty percent reported medication changes at the time of their flare; 16% changed medication and used nonpharmacologic strategies and 26% of patients reported no changes in treatment as a result of flares. Longer duration of flare was associated with changes in disease-modifying therapy.

Conclusion. Patients with RA experienced flares more often when noted to be in higher disease activity states than when in remission and reported changes in disease-modifying antirheumatic drugs or biologics more frequently when flares were of longer duration. There is a need to prospectively study symptom intensity and duration of flare in relation to disease activity and consider self-management strategies in the development of a measure of flare. (J Rheumatol First Release Dec 15 2013; doi:10.3899/jrheum.121521)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
FLARES
DISEASE-MODIFYING ANTIRHEUMATIC DRUGS
DISEASE MANAGEMENT

Patients treated for rheumatoid arthritis (RA) experience a variable disease course punctuated by periods of worsening disease activity that patients and healthcare providers refer to as "flares." In 2009 the Outcome Measures in Rheumatology Clinical Trials (OMERACT) flare group defined flare as any worsening of disease activity that would, if persistent, lead to initiation or change of therapy. According to patient descriptions, a flare represents a cluster of symptoms of sufficient duration and intensity as to require changes in therapy[1]. Flares may be sufficiently intense or persistent as to require patient-initiated measures ranging from decreased physical activity to use of ice or heat. Although the word "flare" is used frequently in the medical literature and in practice, the concept of flare is not fully understood, and there is no currently well-validated measure for flare in RA[1,2]. Recently, 2 groups have published means to identify flares in RA[3,4].

Reports from focus groups indicate that patients with RA

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experience periodic worsening of disease — even at times when the disease is thought to be under firm control[5]. This remains a hurdle in optimizing outcomes for patients living with RA, despite more optimal use of disease-modifying antirheumatic drugs (DMARD) combined with treat-to-target approaches that reduce joint damage and increase states of low disease activity and remission[6].

Data from the Brigham RA Sequential Study (BRASS) indicate that fewer than half of patients were able to sustain remission beyond 1 year[7], and radiographic progression was observed more often in patients who did not remain in sustained remission[8]. These data suggest that periodic worsening of disease occurs and raises the question as to whether flares can contribute to suboptimal outcomes in RA. Moreover, flare continues to be described by patients as "a disabling, under-appreciated, yet integral feature of the overall RA experience"[5,9]. Thus, the frequency and severity of flares along with their management need further study in RA.

The OMERACT RA Flare Definition Working Group has been conducting research since 2006 to establish standard criteria for flare in RA[1,9,10,11]. In 2010, several domains were identified as important in developing a working definition of flare. In particular, the patient perspective of flare was recognized as essential and largely unexplored. Qualitative studies revealed that patients anchored their experience of flare based on a number of self-management strategies[5]. In this article, we describe the frequency of flare and patients' experiences with flare and its management through patient self-report.

MATERIALS AND METHODS

Study design and patients. Patients from the BRASS with at least 3 years of followup reporting and at least 1 visit reporting on their experience with flare were included in this analysis[12]. BRASS is a dynamic cohort study including 1105 patients who have established RA determined either by 1987 criteria[13] (97.2%) or based on the opinion of their rheumatologist (2.8%). The BRASS study started in 2003 with the aim of evaluating outcomes of RA in a real-world setting. Questions about flare were implemented at the beginning of the study with the intent of analyzing patient self-reported flares over time as a secondary outcome measure. Given the recent publications about flare in RA, as part of a posthoc analysis plan we examined the relationship between flare frequency and the patient's most recent classification of disease activity, and the relationship between reported changes in treatment and duration of flare. Most patients were recruited for this study from 2003–2004. This particular analysis was performed in 2011–2012.

BRASS patients receive usual care from their rheumatologists at the Brigham and Women's Hospital in Boston[12]. Participants were required to speak English, be at least 18 years of age, and have a diagnosis of RA as per the 1987 American College of Rheumatology criteria[13] or in the opinion of a rheumatologist. All patients signed an informed consent form that was obtained according to the Declaration of Helsinki and approved by the Partners Institutional Review Board at Brigham and Women's Hospital.

Patients were asked to complete a set of questions every 6 months including questions about flares of their RA that they had experienced in the preceding 6 months (Figure 1A). Patients reported past and current medication use. In each 6-month questionnaire, patients were asked "During the PAST 6 MONTHS, have you had a flare in your rheumatoid arthritis?" If a patient answered yes, the patient was queried about flare frequency, resolution, and how he/she treated the most recent flare in regards to use of medications or nonpharmacologic treatments such as modification of activity, splints/braces, heat/ice, and physical therapy, or no treatment. At the baseline visit, data were collected on age, sex, ethnicity, disease duration, rheumatoid factor, anticyclic citrullinated peptide antibody status, function (Health Assessment Questionnaire), C-reactive protein (CRP) levels, Disease Activity Status (DAS28)-CRP, and medication use for all patients who answered the flare questionnaire. Patients were seen annually by their rheumatologists to assess disease activity status and CRP levels. Patients' flare data reported just prior to their physician's visit were related to disease activity calculated at that visit.

Statistical analyses. The proportion of patients reporting a flare in the 6 months prior to each visit was calculated at each 6-month followup visit. The proportion of flares lasting greater than 2 weeks, 1–2 weeks, 4–6 days, and 3 or fewer days was calculated for those reporting flares. The management strategy described by each patient regarding his/her flare was tabulated and described. We used descriptive statistics including the mean and SD to summarize continuous data, and frequency tables, graphs, and pie charts to summarize categorical data. Pearson's chi-squared tests and Student's t tests were performed to compare the frequency of flare to the reporting month, frequency of flare to disease activity (DAS28-CRP) and disease activity status, and flare duration to use of medications. For this analysis, severe disease activity was defined as a DAS28-CRP of > 5.1, moderate disease activity as DAS28-CRP of 3.2–5.1, low disease activity as a DAS28-CRP of 2.6– < 3.2, and remission as a DAS28-CRP of < 2.6. All analyses were conducted in SAS v 9.2 (SAS Institute).

RESULTS

Of 1105 patients with RA, 744 had at least 3 years of followup. Of those, 738 reported that a flare had occurred at least once and were included for this analysis. Of the 4621 questionnaires completed by 738 patients in 3 years of followup, 55 had questionnaires missing and 6 were missing flare data only. These were omitted from the analysis. We included anyone with at least 3 years of followup who reported on flares at any timepoint. Baseline characteristics of the flare study population are shown in Table 1; 692 patients reported on flares at baseline and 736 patients reported on flares more than once during the course of observation. During this study, 47% never achieved remission, 19% achieved remission once, 17% twice, and only 12% were noted to be in remission at each visit over the 3 years.

Flare frequency and disease activity. Patients frequently reported experiencing flares over the course of observation. At baseline, 74% of 692 patients reported having flares in the 6 months prior to study entry, which was the greatest number of flare reports for any 6-month period throughout the study. Over the first 6 months following study entry, 59% reported flares. During the remainder of the study period, 54–57% of patients reported flares at each 6-month followup. A decrease in flare frequency from baseline through followup was statistically significant ($p < 0.001$ by chi-square). By 36 months, 99% of patients had reported a flare in 1 of the preceding 6-month periods prior to a followup visit.

Over the course of the study, 467 patients reported 882

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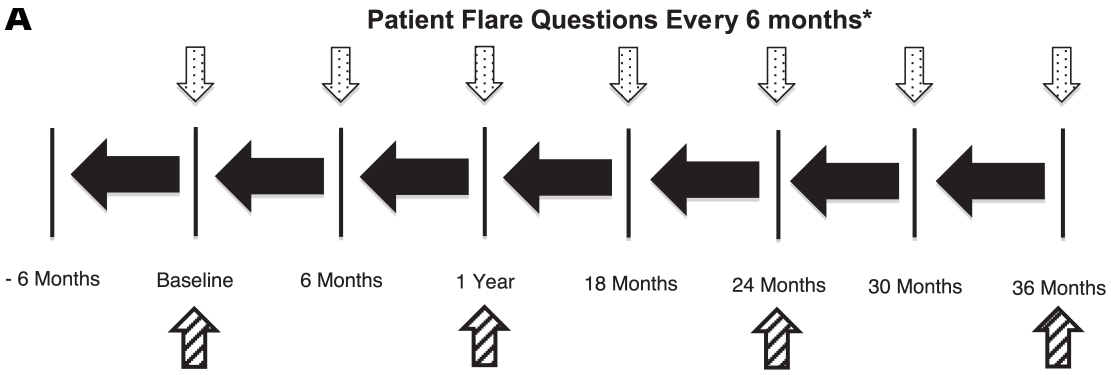

Physician Domains Measured at Baseline and Yearly**

B

	Flare Questions Asked at Each Study Visit	Possible Answers				
1	During the PAST 6 months have had a flare of your rheumatoid arthritis?	Yes	No	--	--	--
2	If yes, how many flares have you had during the PAST 6 MONTHS?	1	2-3	4-5	>5	--
3	How did you treat your flares? (Check all that apply)	New medication (please specify)	Increased medication dose (please specify)	Other treatment (please specify)	No treatment	--
4	How long did your flare last?	Less than 1 day	1-3 days	4-6 days	1-2 weeks	More than 2 weeks
5	Has your arthritis returned to your pre-flare status?	Yes	No	--	--	--

*Patients answered flare questions at their annual visits or by a mailed questionnaire at 6 months between the annual visits; **Disease activity was measured annually.

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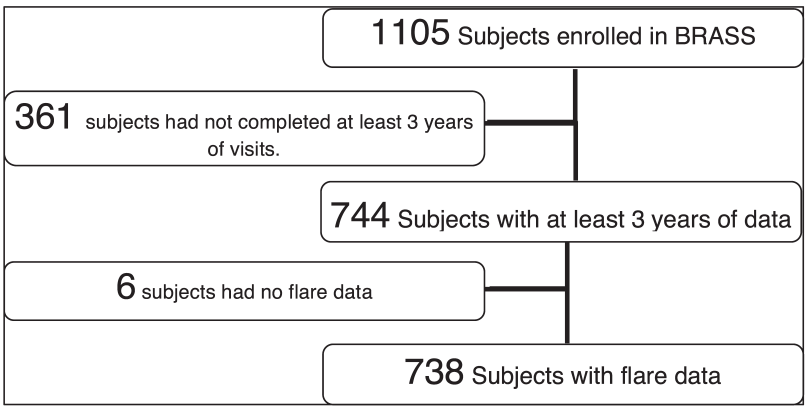

Figure 1. Assessment of patient self-reports of flare. A. Patient flare questions were measured at baseline and annually. B. Questions asked at each study visit about flares. Patients answered flare questions at their annual visits or by a mailed questionnaire at 6 months between the annual visits. Disease activity was measured annually. C. Flow diagram showing study patients who answered the flare questions from the BRASS cohort.

Table 1. Baseline characteristics of patients at study entry (n = 738). All data are presented as mean (SD) except where noted.

Characteristic	
Female, % (n)	83.7 (618)
Age, yrs	56.3 (12.9)
Ethnicity (white), % (n)	93.3 (683)
Disease duration (yrs since diagnosis)	14.1 (11.9)
Early RA patients (disease duration < 2 yrs), % (n)	13.0 (96)
RF-positive, % (n)	64.1 (446)
CCP-positive, % (n)	67.0 (485)
Anti-CCP or RF-positive, % (n)	73.0 (539)
DAS28-CRP	4.0 (1.6)
MD-HAQ physical function (range 0–3)	0.62 (0.52)
C-reactive protein*	9.2 (18.7)
Physician global assessment, 0–100	34.0 (21.8)
Patient global assessment, 0–100	30.9 (24.5)
Tender joint count (28)	8.6 (8.0)
Swollen joint count (28)	7.9 (7.4)
NSAID, % (n)	61.7 (455)
Narcotic analgesics, % (n)	11.3 (83)
MTX, % (n)	48.2 (356)
Biologic therapies, % (n)	38.2 (282)
Prednisone, % (n)	31.8 (235)
HCQ, % (n)	16.9 (125)
SSZ, % (n)	6.0 (44)
Leflunomide, % (n)	10.2 (75)

* The C-reactive protein (CRP) is reported as a high-sensitivity CRP in mg/dl: the concentration of CRP was determined using an immunoturbidimetric assay on the Roche P Modular system (Roche Diagnostics), using reagents and calibrators from DiaSorin. NSAID: nonsteroidal antiinflammatory drugs; MTX: methotrexate; HCQ: hydroxychloroquine; SSZ: sulfasalazine; MD-HAQ: physicians' Health Assessment Questionnaire; DAS28-CRP: 28-joint Disease Activity Score using CRP; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide; RA: rheumatoid arthritis.

6-month periods with 1 flare, 470 patients reported 1005 6-month periods with 2–3 flares, 217 patients reported 323 6-month periods with 4–5 flares, and 230 patients reported 456 6-month periods with > 5 flares.

Most patients (65%) reported their flare(s) had resolved by the time of their study visits. Disease activity (measured with DAS28-CRP) and flare frequency were strongly related (chi-square p = 0.0003), indicating the relationship between the 2 categories is not independent (Figure 2). Patients in remission reported fewer flares compared to patients measured to be in higher disease activity states at their baseline and annual followup visits. Patients in remission formed the largest proportion reporting 1 flare and the smallest proportion reporting 6 or more flares in the previous 6 months. This subgroup represented 29% of patients reporting 1 flare, 24% of patients reporting 2–3 flares, 20% of patients reporting 4–5 flares, and 16% of patients reporting 6 or more flares in the previous 6 months. Conversely, patients with the highest disease activity formed the smallest proportion of patients reporting only 1 flare and the largest proportion of patients reporting 6 or more flares in the previous 6 months. This subgroup represented 19% of patients reporting 1 flare, 21% of patients reporting 2–3 flares, 24% of patients reporting 4–5 flares, and 31% of patients reporting 6 or more flares in the preceding 6 months.

Patient self-reported treatment approaches to flare. Patients reported a range of treatment strategies for coping with flares (Figure 3). Most (40%) managed their flares with medication, either by increasing the dose of a previously prescribed medication or by obtaining a new medication prescription from their physicians. Some (27%) reported no treatment for their flares; 18% used nonpharmacologic therapy, and 16% combined medication changes with nonpharmacologic therapies.

Of those patients who took a new medication to treat their episode of flare, most (20%) reported that they started prednisone. Others started medications including biologic therapies (17%), nonbiologic DMARD (15%), or nonsteroidal antiinflammatory drugs (NSAID; 13%). Some started multiple new medications (13%). Narcotics and injections were the least frequently used new medications, with 4% and 2% reporting the use of them, respectively.

Among patients who increased the dose of a previously prescribed medication, most (33%) increased prednisone along with additional medications. NSAID were the most frequently increased medication (20%) followed by nonbiologic DMARD (18%) and other pain medications (9%). Narcotics and biologics were infrequently increased in 6% and 5% of patients, respectively. Only 2% reported increasing other medications.

Of all patients experiencing flares, 18% reported using nonpharmacologic therapy not involving medication as their primary means of management, including resting, applying heat or cold, attending physical therapy, and/or using a splint or brace (Figure 3).

Medication use and flare duration. Over the course of the study, 30% of patients reported flares lasting at least 2 weeks, 14% reported flares that lasted 1–2 weeks, and 57% reported flares lasting 6 days or fewer. Medication use for flare management varied depending on the duration of flare ($p < 0.0001$; Figure 4). Most patients reported that short flares (< 2 weeks) were managed with prednisone and NSAID. Few patients reported using narcotics. The use of biologics and nonbiologic DMARD was reported more often for flares lasting 2 weeks or longer.

DISCUSSION

To date, to our knowledge, there have been no studies of patients with RA from typical practice followed longitudinally that assessed either the frequency of patient-reported flare over time or patients' experience with management of their flares. In addition to confirming that patients with RA frequently report flares during the course of their disease, we have shown that patients reported flares regardless of their disease activity state, with flares reported more often

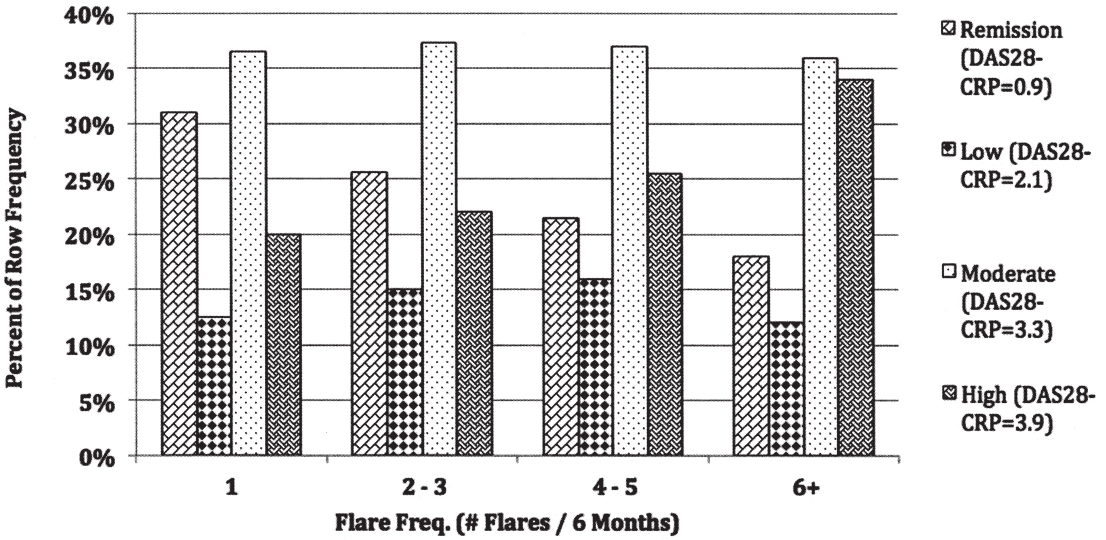

Figure 2. Flares are reported more often in patients with higher disease activity; however, even patients in remission report they have had flares. A chi-squared test examining the relationship between disease activity (measured with 28-joint Disease Activity Score-C-reactive protein) and flare frequency was statistically significant ($p = 0.0003$), indicating that the relationship between the 2 categories is not independent.

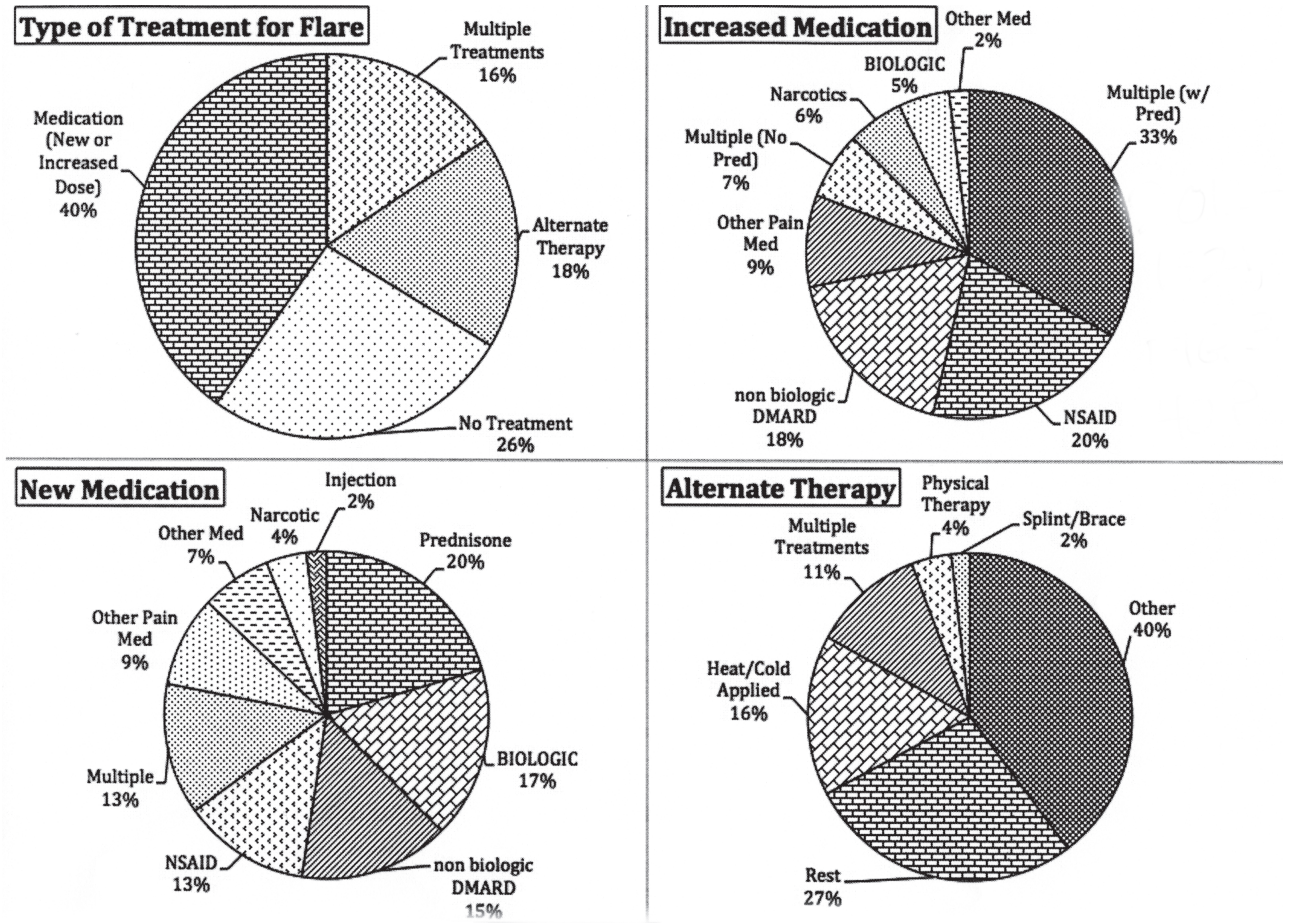

Figure 3. Patients reported a range of treatment strategies for coping with flares. While medication was the most frequently reported self-management approach, a similar proportion of patients used alternate therapies such as resting and physical therapy, and some used no strategy at all. The range of coping strategies reported by patients illustrates the extent to which flare and coping with flare are accepted as integral features of rheumatoid arthritis. DMARD: disease-modifying antirheumatic drug; NSAID: nonsteroidal antiinflammatory drug.

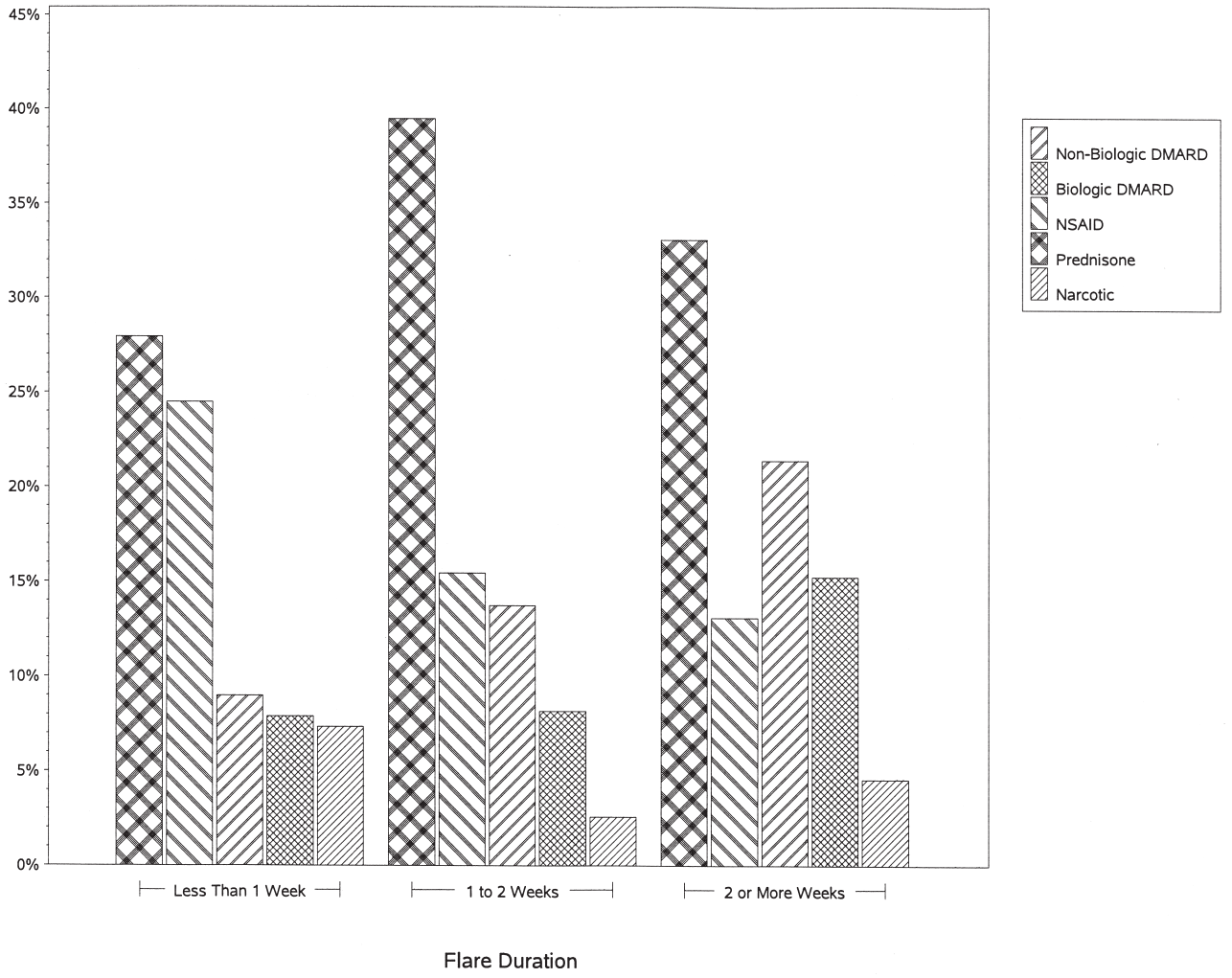

Figure 4. Medication use varied with flare duration. Of 57% of patients whose flare lasted < 1 week, more patients used prednisone and nonsteroidal antiinflammatory drug (NSAID), whereas in the 30% of patients with flares ≥ 2 weeks, more patients used disease-modifying antirheumatic drugs (DMARD) and biologic therapies. The kinds of medication used for flare management varied depending on the duration of flare ($p \leq 0.0001$ based on a chi-square test).

when patients were noted to be in a high disease activity state but also occurring often when patients were noted to be in remission. We also observed that medication changes varied according to the length of a flare.

Although it is not unexpected that patients report flares more often when disease activity is moderate or high, the observation that patients noted to be in a low disease activity state or remission also experienced frequent flares suggests that some patients are not maintaining remission or low disease activity between visits. This may have implications on function or risk for joint damage over time. In another study of 85 patients with RA in remission or low disease activity, those who experienced disease relapses, defined as an increasing need for treatment or worsening of the DAS, were also noted to have more radiographic progression than those who did not have flares[14].

For patients who do not reach targets of low disease activity or remission, these findings support the need to step up efforts to enable patients to achieve and maintain these targets as part of "protocolized" care involving patient-specific targeted treatment strategies. Barriers as to why targets are not met may in part relate to disease flares.

This is the first study, to our knowledge, to demonstrate that the duration of flare influences changes in disease management and that patients will often use strategies on their own initiative to manage flares ("self-management"). Patients' reported changes in medication and other alternative strategies involved increases in prednisone, NSAID, and analgesics most commonly when flares were of shorter duration, whereas patients were likely to seek care more often if flares lasted longer than a week, as reflected by the initiation or increases in nonbiologic DMARD and biologic therapies. The effect of frequent flares and these management strategies on longterm function or joint damage remains to be determined.

It is unclear whether patient self-management can be

more effectively harnessed as part of a guided treatment strategy using a standard definition and measure of flare, and we suggest this be tested formally in clinical trials[9,15]. Hewlett, *et al*[5] has reported that patients used the term "flare" to convey multiple situations, ranging from increased symptoms within normal variation to unprovoked, increased symptoms that are unmanageable, persistent, and lead to seeking help. Several studies highlight that there are a range of symptoms that patients describe when discussing flare, including difficulties with pain, fatigue, stiffness, joint swelling, and coping[2,3,5,11]. A single question about disease flare may reflect a complex event and a flare questionnaire may need to enquire about several domains[3]. In Hewlett's study, patients reported that when symptoms were intense, patients increased self-management of symptoms, with strategies that included resting, pacing, applying heat or cold, and in some cases escalating medications without seeking medical advice. Only after self-management strategies had failed was the flare considered unmanageable and medical advice sought. Based on these qualitative data and on our observations, it is possible that our patients initiated changes in treatment, be it nonpharmacologic strategies that could be considered self-management or changes in medication that may or may not have been initiated with the advice of the patients' treating physicians. Results from our study indicate that patient-reported flares occurred with varying duration, the diversity of which is reflected in the range of medication changes and treatment strategies observed. The increased use of DMARD and biologics in prolonged flares may have reflected, as proposed by Hewlett, the longer period of intensifying symptoms that lead to seeking of professional help[5].

The range of nonpharmacologic strategies reported by patients also suggests that flare is accepted as an integral feature of RA, and patients may be accustomed to managing these flares themselves, a practice that may represent a form of coping with the worsening of their disease. From the patient perspective, coping is an expected aspect of disease-worsening[11]. While medication was the most frequently reported management approach, patients also used nonpharmacologic strategies such as resting and physical therapy just as often, and some used no strategy at all. Because patients try to improve health status on their own, there are opportunities to better educate patients as to what self-management strategies are appropriate, when they should be implemented, and when patients should contact their physicians to help optimize their disease control. This could facilitate a better treat-to-target approach by engaging patients to seek help to manage more intense flares, even by simple methods such as joint injection and short courses of oral or parenteral steroid, as were administered in treat-to-target studies such as TICORA[16] and the DREAM study[17].

Our study had some limitations. We did not attempt to frame the term "flare" in a standard definition, because there is yet no agreed-upon composite definition of flare. The aim of the analysis was to determine the frequency of flare as patients understand it, and therefore the term was left open to interpretation. This approach likely yielded a broad range of flare experiences. Of 744 patients who completed 3 years of followup, only 6 subjects did not provide any data on flare. Although we recognize that this cumulative incidence of flare is high, it may be real, because we did not train or prespecify for patients what constituted a flare. In our study, 65% of our patients reported that their flares had resolved by the time of their visits for the study.

Our study was subject to recall bias. Patients were asked to recall flares over a 6-month period prior to each study assessment; thus, patients may only have recalled flares of higher severity and burden. Also, patients may only have been able to recall worsening of RA over a short period, such as 3 months[3]. Thus our results may reflect an underestimate of flares of lower intensity. However, there could also have been overreporting of flares due to other symptoms, such as viral infections and non-RA sources of pain. We also observed that more flares occurred in patients who had been noted to be in higher disease activity. In BRASS, patients had a long RA disease duration and there was no strict treat-to-target protocol in place; thus more patients than might be expected, based on treat-to-target studies, were in moderate or even high disease activity. As might be anticipated, more patients reported flares when they were in higher disease activity states. However, even patients noted to be in remission or in a low disease activity state frequently reported flares. This was also observed in another study of flare in which 93 patients with RA who were deemed to be in remission had a flare defined as the need to increase therapy. In that study, 26% of patients in remission experienced flare over a 1-year period[18], which is comparable to the proportion (30%) of patients in remission reporting flares in our study.

Our study design limited the ability to answer many outstanding questions about flare in RA. Data on objective measures such as CRP or DAS28 at the actual time of reported flares were not concurrently collected at all timepoints, limiting the ability to understand the relationship between patient-reported flare and objective composite measures of disease activity. Despite being unable to frequently link disease activity to flare reports, examination of flares reported prior to measurement of disease activity indicates that flare management is related to flare duration, with longer flares being associated with changes in DMARD and biologics. Also, given the infrequent measure of disease activity in this study, we cannot answer whether patients in sustained remission had fewer flares, and a prospective study linking flare more closely to frequent disease activity measurement is needed. Nonetheless, this is the first large study to sequentially

query patients about episodes of flares of RA and how they are managed in a clinical practice setting.

We were unable to provide data on how often patients consulted physicians to adjust medications such as prednisone or NSAID, or whether they adjusted these on their own. We hypothesize that patients will self-manage flare, but this needs validation in future studies. We also could not determine whether patients who flare more often are less adherent to their medications, or to what degree they are self-managing their medications during the course of their disease. However, our data support the need to better understand the patient perspective of flare in RA when disease worsens, given these insights from patient-reported flare management strategies and medication use.

We could not address the role of adherence, drug withdrawal, and other sources of pain in relation to patient-reported flares. In a separate analysis of pain in the BRASS study, it was noted that clinically significant pain continued in a substantial proportion of BRASS patients even though they were in DAS28 remission. Domains such as patient global assessment, disability, fatigue, sleep problems, and self-efficacy were associated with pain severity both at baseline and 1 year in that study[19]. These findings highlight the need to understand the composite of symptoms patients experience between visits, in the way of periodic worsening or flare of their diseases and their effect on quality of life, overall function, and morbidity in RA. Studies need to explore the effect of flare on function, quality of life, comorbidities, and risk for radiographic damage to determine whether flare prevention is important as a treatment strategy in RA.

These data provide an important perspective on the work of OMERACT and other groups studying flare. There is a need to prospectively study symptom intensity and duration of flare in relation to disease activity and consider self-management strategies in the development of a measure of flare.

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