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ORIGINAL ARTICLE

Optimization of flare management in patients with rheumatoid arthritis: results of a randomized controlled trial

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Abstract

Introduction/objectives To evaluate the effect of a flare management intervention guided by non-physician providers versus usual care between rheumatology visits on flare occurrence and rheumatoid arthritis (RA) disease activity.

Methods Adult patients with established RA (per 2010 ACR criteria, $n = 150$) were randomized to the intervention arm ($n = 75$) versus usual care ($n = 75$). The Flare Assessment in Rheumatoid Arthritis (FLARE-RA) questionnaire was administered monthly during 24 months to all patients in the intervention arm to assess flare status. Telephone nurse-led counseling or an expedited visit with a rheumatology provider was offered to patients in the intervention arm who indicated they were in flare.

Results Patients in the intervention arm completed a median of 8.5 (range 1–24) questionnaires. RA flare was reported on 122 (19%) of these questionnaires; average FLARE-RA score, 4.72 on 0 (no flare) to 10 (maximum flare) scale. Patients preferred an expedited clinic visit with a rheumatology provider during 39 (32%) of flares. The majority of patients preferred to self-manage their flare (76, 62%); some patients received nursing advice on flare management over the phone (7, 6%). There were no differences in RA flare by OMERACT9 definition, DAS28-CRP, CDAI, SDAI, anti-rheumatic treatment change by rheumatology provider, or remission by CDAI between the study arms over 24-month follow-up.

Conclusions The flare management intervention did not have any major effect on flare occurrence or RA disease activity metrics over the 24-month follow-up. The majority of patients in the intervention arm preferred self-management to an expedited visit with their rheumatology provider.

Trial registration ClinicalTrials.gov Identifier: NCT02382783 (https://clinicaltrials.gov/ct2/show/NCT02382783)

Key Points
- *The flare management intervention had no effect on rheumatoid arthritis (RA) disease activity.*
- *Patients preferred self-management of their RA flares to expedited rheumatology provider visits.*

Keywords Flare · Randomized controlled trial · Rheumatoid arthritis

Introduction/objectives

Flares are inherent to the rheumatoid arthritis (RA) disease course and associated with poor clinical outcomes, including low quality of life, joint damage, comorbidity burden, and disability [1–3]. Despite the recent advances in RA disease management and overall success in management of RA disease activity, up to 30% of patients with RA experience flares on a regular basis [4], suggesting the need for systematic patient-tailored changes to optimize RA flare management. The shortage of readily available specialized care may hinder early detection and timely management of RA flares. Earlier randomized controlled studies showed benefits of nurse-led interventions for comorbidity management and cost-effectiveness of nurse-led care for control of RA disease activity [5–7]. Clinical trials testing interventions involving non-physician rheumatology providers in management of RA flares are lacking.

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In this randomized controlled study, we aimed to evaluate the effect of RA flare management intervention guided by non-physician providers versus usual care between rheumatology visits on flare occurrence and RA disease activity. We hypothesized that the intervention will reduce the rates of flares and improve RA disease activity metrics and patient satisfaction in patients with RA randomized to the intervention arm as opposed to the usual care arm.

Methods

Trial design and participants This single-center prospective randomized parallel-group two-arm phase 3 trial was conducted at Mayo Clinic, Rochester, MN and included adult (age ≥ 18 years) patients with prevalent RA based on the 2010 ACR/EULAR criteria who have been seen by a rheumatology health care provider at least two times within the last 18 months at Mayo Clinic, Rochester and are willing to return to Mayo Clinic, Rochester for their follow-up appointments. Patients with early RA (RA duration < 1 year) were excluded, as treatment is adjusted frequently to achieve initial disease control during the first year of RA and flare occurrence as well as frequency of visits with a rheumatology provider during this period may differ from the rest of RA disease course. Study flow diagram is shown (Fig. 1).

Randomization Block randomization was by a computer-generated random number algorithm prepared by a statistician with no clinical involvement in the trial using a block size of 10, which was not known to anyone other than the statistician. After the study coordinator obtained the patient's consent, she entered the patient information into RedCap for allocation consignment. The allocation was concealed until the consent was confirmed. The allocation was 1:1.

Intervention Based on the results of the monthly over-the-phone patient report of the flare status to the non-physician providers, patients in the intervention arm who were in flare were offered an expedited appointment with a rheumatology provider or over-the-phone counseling on flare management from a nurse. Details of the intervention are described below.

Flare occurrence in the intervention arm was assessed monthly during 24 months using the Flare Assessment in Rheumatoid Arthritis (FLARE-RA) questionnaire [8]. The self-administered FLARE-RA questionnaire was devised and validated to improve the detection of current and recent flares in RA, taking into account both patient and provider perspectives [8, 9]. The questionnaire includes 11 questions examining 11 domains identified as being associated with RA flare by patients and physicians: joint swelling, joint pain, morning stiffness, analgesic intake, fatigue, decrease in daily activities, need for help, withdrawal from social activities, night awakening, depression, and irritability. Each domain was graded by a patient on a numerical rating scale from 0 (completely untrue) to 10 (absolutely true). The overall score for the questionnaire ranges from 0 (no flare) to 10 (maximum flare) as the mean of the scores for the 11 items.

The results of the FLARE-RA questionnaire and patient's response to the question "Are you currently in a flare of your RA?" were recorded by a study coordinator on a monthly basis. Telephone nurse-led counseling and/or a visit with an available rheumatology provider, i.e., rheumatology staff physician, nurse practitioner (NP), physician assistant (PA), or rheumatology fellow supervised by a rheumatology staff physician within 7 days of detection of flare, was offered to patients in the intervention arm who indicated they were in flare. Rheumatology providers participating in the study were asked to provide their opinion on whether their patient was having a flare at each clinic visit. Patients' and providers' opinions on flare status were based on each person's own understanding of RA flare. None of the participants was primed by a definition of a flare in RA or any additional information about RA flares.

Patients in the *usual care arm* received standard rheumatology ambulatory care by their rheumatology providers at Mayo Clinic (50%—physician providers, 50%—non-physician providers) and were seen for routine follow-up on average every 6 months. They had access to patient messaging and could call their provider's office with questions on their management. However, unlike the intervention arm, there was no pre-specified protocol for flare management such as flare-dedicated nursing counseling and/or an option of expedited rheumatology appointment.

Blinding Due to the nature of the intervention, blinding for the intervention itself was not possible. However, the hypothesis of the study was not disclosed to patients, providers, and study coordinator.

The following working definition of flare developed by the OMERACT 9 Special Interest Group was used to ascertain flares based on provider assessments recorded in the medical records and compare flare occurrence between the study arms: "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" [10]. Patients in both study arms completed satisfaction surveys at baseline, 12 months, and 24 months.

The following demographic and clinical data were extracted by the study coordinator from patient's medical records:

a. Baseline characteristics: age, sex, education status, RA disease duration
b. At baseline and each clinic visit: swollen (SJC28) and tender joint counts out of 28 joints (TJC28), pain on visual analogue scale (VAS), patients global assessment of

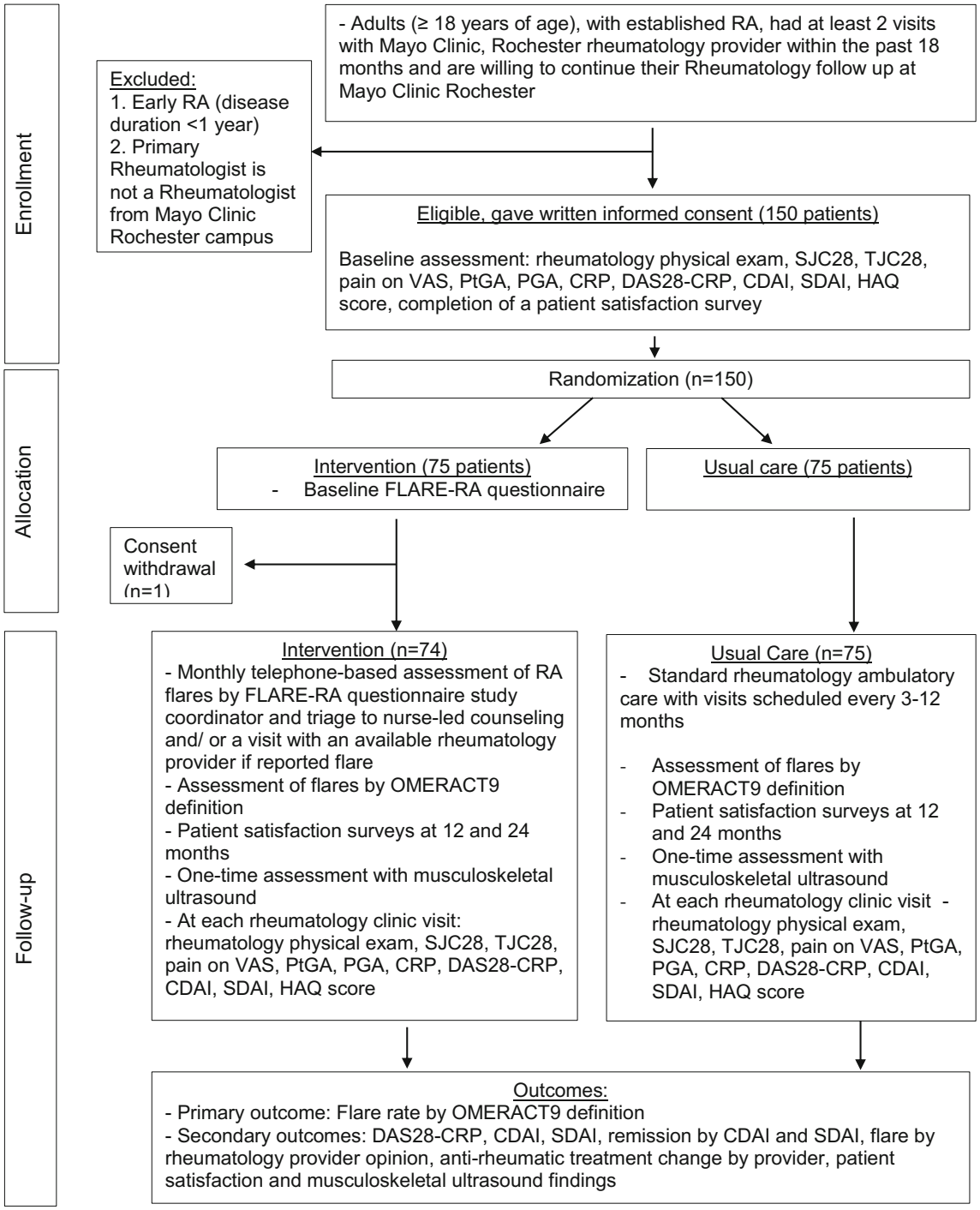

Fig. 1 Study flow diagram. RA, rheumatoid arthritis; SJC28, swollen joint counts out of 28 joints; TJC28, tender joint counts out of 28 joints; VAS, visual analogue scale; PtGA, patients' global assessment of disease activity by VAS; PGA, provider global assessment by VAS; CRP, C-reactive protein; DAS28-CRP, Disease Activity Score with 28-joint count and CRP; CDAI, Clinical Disease Activity Index; SDAI, Simplified Disease Activity Index; HAQ, Health Assessment Questionnaire score; FLARE-RA, Flare Assessment in Rheumatoid Arthritis questionnaire; OMERACT, Outcome Measures in Rheumatology initiative

disease activity by VAS (PtGA), provider global assessment by VAS (PGA), C-reactive protein (CRP), Disease Activity Score with 28-joint count and CRP (DAS28-CRP), Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), Health Assessment Questionnaire (HAQ) score, medications including synthetic and biologic disease-modifying anti-rheumatic drugs (DMARDs), systemic and injectable glucocorticoids, change in medications. Remission defined as CDAI < 2.8 or SDAI < 3.3.

A standardized musculoskeletal ultrasound with power Doppler (PD) was performed at one time-point by experienced rheumatology providers certified in musculoskeletal ultrasound for patients in both study arms to assess the activity of synovial inflammation in the joints of wrists, hands, and feet. The results were reported using a validated scale, 0–27 for gray scale (GS) synovitis; 0–39 for synovitis on PD; 0–7 for GS tenosynovitis; 0–21 for tenosynovitis per PD assessment [11, 12]. This information was then utilized to define concordance between the patient and physician flare opinion with respect to active synovitis/tenosynovitis as detected on ultrasonography.

Outcomes: primary outcome of the study Flare rate by OMERACT 9 definition in intervention arm vs usual care arm by provider assessment as documented in the medical records.

Secondary outcomes: RA disease activity metrics including DAS28-CRP, CDAI, SDAI, remission by CDAI and SDAI, flare by rheumatology provider opinion, anti-rheumatic treatment change by provider, patient satisfaction, and musculoskeletal ultrasound findings.

The study was approved by the Institutional Review Board of Mayo Clinic and was registered at the ClinicalTrials.gov Identifier: NCT02382783 (https://clinicaltrials.gov/ct2/show/NCT02382783). All patients included in the study signed a written informed consent for participation in this study. In this manuscript, we followed the CONSORT 2010 statement and checklist for reporting parallel group randomized trials [13].

Statistical methods

Descriptive statistics (means, percentages, etc.) were used to summarize the data for the two study arms. Changes in disease activity measures over time between the arms were compared using generalized linear models with random subject effects including inverse probability weights (IPW) based on propensity scoring to adjust for baseline imbalances that occurred despite the randomization. Propensity scores were obtained from a logistic regression model of treatment arm including sex, SJC, DAS28-CRP, CDAI, confidence in RA flare detection, and desire for additional information and guidance on RA flare management. These models make use of all available data without requiring any imputation of missing data.

In all cases, two-tailed tests were used. Test statistics with $p < 0.05$ were considered statistically significant. Analyses comparing the arms of the study used the originally assigned groups (intervention arm vs usual care arm), which is consistent with the intention-to-treat (ITT) approach. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and R 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Power and sample size calculation A sample-size of $N = 150$ subjects randomized into 2 groups of 75 subjects in each was considered appropriate for a repeated measures analysis (e.g., paired t test) to provide statistical power (two-tailed, alpha = 0.05) of 80% to detect a difference of 0.33 SD in any disease activity measure.

Results

Participant flow and recruitment A total of 150 patients with RA were randomized to intervention ($n = 75$) versus usual care ($n = 75$) between 03/11/2015 and 08/16/2016. One patient from the intervention arm withdrew from the study. Length of enrollment was similar in the intervention arm: mean (SD), 20.03 (7.03) months and usual care arm: mean (SD), 21.31 (5.16) months.

Baseline data Baseline patient characteristics are shown in Table 1. Patients were similar in their age, sex, education level, and majority of RA disease characteristics. Despite randomization, patients in the intervention arm had lower SJC28 and HAQ score than those in the usual care arm. The groups were balanced after IPW with no significant differences.

All patients in the intervention arm completed the baseline FLARE-RA questionnaire. However, the compliance with filling out the FLARE-RA questionnaire during the follow-up was suboptimal: the number of patients who completed the questionnaires at 6, 12, 18, and 24 months was 37, 27, 13, and 23, respectively. Patients in the intervention arm completed a median of 8.5 (range 1–24) questionnaires. RA flare was reported on 122 (19%) of these questionnaires, with an average FLARE-RA score of 4.72. Patients agreed to have an expedited visit with a rheumatology provider during 39 (32%) of these flares. Of the 39 visits, 34% saw a physician, 45% saw a PA, and 21% saw an NP. In the vast majority of cases of reported flares, patients were seen on the same day (34, 86%) or within 1 day of reported flare (3, 8%), and rarely within 2 days (1, 3%) or 6 days of reported flare (1, 3%). Most patients preferred to self-manage their flare (76, 62%) and some chose to receive nursing advice on management of their RA flare over the phone (7, 6%). Overall, there were 47 unique patients who had at least 1 RA flare; among them, 28 patients saw a rheumatology provider at some point during the follow-up. The number of patients' visits to their rheumatology provider was similar between the arms: mean (SD) of 4.41 (1.84) in the intervention arm and 4.65 (1.70) in the usual care arm. No harmful or unintended effects were observed in the study.

Table 1 Baseline patient characteristics

	Intervention (*N* = 75)	Usual care (N = 75)	*p* value
Age	60.0 (12.1)	62.3 (12.5)	0.198
Sex	49 (65%)	58 (77%)	0.104
Education level			0.66
- Primary and secondary education	18 (24%)	17 (24%)	
- Undergraduate education	41 (55%)	44 (60%)	
- Post-graduate studies	16 (21%)	12 (16%)	
Swollen joint count, 28 joints	1.1 (2.7)	2.4 (4.5)	0.003
Tender joint count, 28 joints	2.5 (4.8)	3.5 (6.8)	0.432
Health Assessment Questionnaire (HAQ) Score	0.6 (0.6)	0.9 (0.6)	0.005
Pain, 100 mm VAS	33.6 (27.3)	42.8 (27.6)	0.059
Patient global assessment of disease activity, 100 VAS	31.4 (27.0)	35.5 (25.6)	0.353
Physician global assessment, 100 mm VAS	16.6 (22.2)	20.0 (26.6)	0.446
CRP	7.1 (10.8)	6.1 (5.6)	0.869
DAS28CRP	2.6 (1.2)	2.9 (1.3)	0.188
CDAI	8.6 (10.5)	12.0 (14.7)	0.090
SDAI	15.3 (16.8)	17.4 (15.6)	0.156

CRP, C-reactive protein; *CDAI*, Clinical Disease Activity Index; *SDAI*, Simplified Disease Activity Index; *VAS*, visual analogue scale

Outcomes: flare rates and RA activity metrics

There were no differences in RA flare rate by OMERACT 9 definition, DAS28-CRP, CDAI, or SDAI between the intervention arm and usual care arm over 24 months of follow-up (Fig. 2). Similarly, no difference was detected in flare rate by rheumatology provider opinion, probability of anti-rheumatic treatment change by rheumatology provider, or remission by CDAI or by SDAI between the arms of the study. In the majority of cases, patient and provider opinion on presence or absence of RA flare was concordant: 159, (79%); they disagreed in 41 (21%) of cases.

Patient satisfaction survey results

The baseline satisfaction survey was completed by all patients. The majority of patients in the intervention arm (62, 83%) and in usual care arm (56, 77%) were satisfied with the management of their RA flares at baseline. Many of the patients randomized to the intervention arm (37, 49%) and to the usual care arm (45, 62%, $p = 0.06$) expressed interest in additional information and guidance on management of flares. About a quarter of patients in the intervention arm (19, 25%) and in usual care arm (18, 24%) felt that rheumatology appointments are not provided in a reasonable time frame. The majority of patients in the intervention arm (38, 51%) and in the usual care arm (44, 60%, $p = 0.32$) expressed interest in expedited appointments with their rheumatology provider if in RA flare.

Forty-six (63%) of patients randomized to the intervention arm and 57 (76%) of patients in the usual care arm completed the 12-month follow-up survey. Essentially, all patients in the intervention arm (44, 96%) and in usual care arm (55, 97%) were satisfied with the management of their RA flares at 12-month follow-up. Only 7 (16%) of patients in the intervention arm and 18 (32%, $p = 0.25$) of patients in the usual care arm felt that rheumatology appointments are not provided in a reasonable time frame.

Thirty-three (45%) of patients randomized to the intervention arm and 48 (64%) of patients in the usual care arm completed their 24-month follow-up survey. The level of patient satisfaction with RA flare management was very high: 31 (97%) in the intervention arm and 44 (98%, $p = 0.48$) in the usual care arm. At their 24-month follow-up survey, only 2 (6%) of patients in the intervention arm and 9 (19%, $p = 0.41$) of patients in the usual care arm felt that rheumatology appointments are not provided in a reasonable time frame. At the end of the study, a higher proportion of patients in the intervention arm (14, 44%) versus the usual care arm (10, 21%, $p = 0.04$) reported positive effect of participation in the study on the management of RA flares.

Musculoskeletal ultrasound results

A total of 95 patients were evaluated with musculoskeletal ultrasound at some point in their study. There were no statistically significant correlations between the FLARE-RA score and ultrasound findings. There were no statistically significant differences in the ultrasound findings in patients who were in a

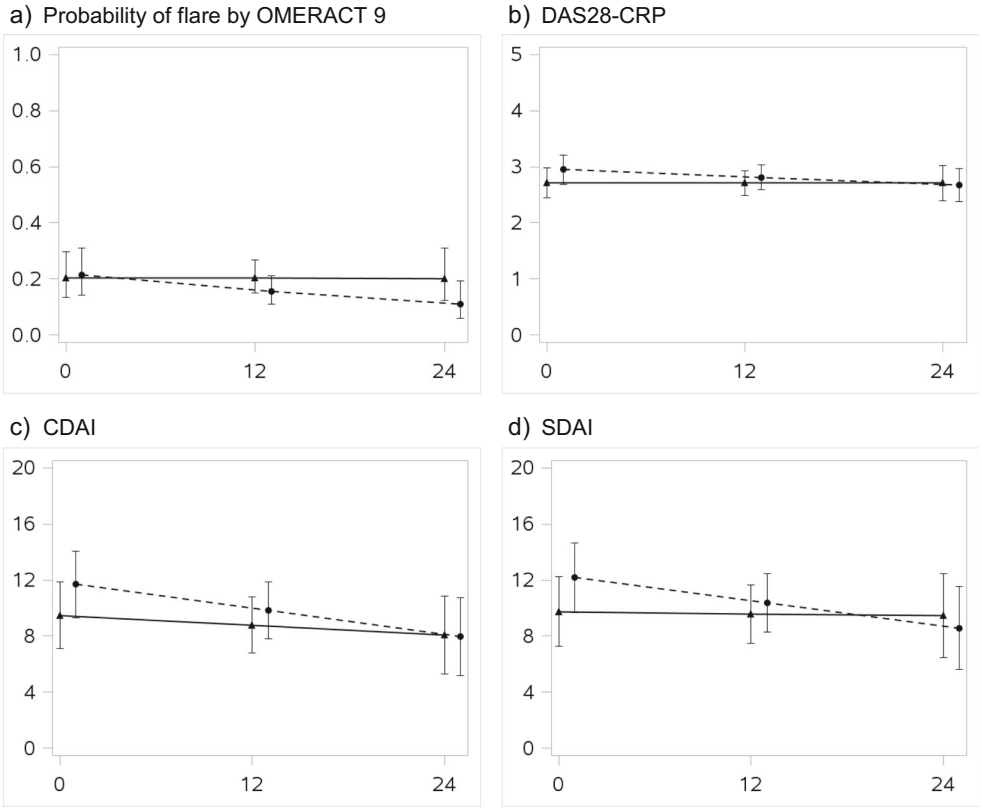

Fig. 2 Estimates for rheumatoid arthritis flare rates by OMERACT 9 definition and rheumatoid arthritis disease activity metrics in the intervention arm and usual care arm at 0, 12 months, and 24 months of follow-up. Dashed lines represent standard of care arm, solid lines represent intervention arm. CRP, C-reactive protein; CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score with 28-joint count and CRP; SDAI, Simplified Disease Activity Index

flare of their RA per physician assessment versus those who were not.

When ultrasound findings were compared in patients who responded "Yes" to the question "Are you currently in a flare of your RA?" at the time of their ultrasound assessment ($n = 7$) with those who responded "No" to this question ($n = 24$), GS tenosynovitis was more frequently observed in patients who thought they were in a flare: mean (SD) 0.4 (0.53) than in patients who felt they were not in a flare of their RA: mean (SD) 0.0 (0.0), $p < 0.01$. Somewhat more patients who reported being in a flare had tenosynovitis by PD compared with those who reported no flare: mean (SD) 0.1 (0.38) vs 0.0 (0.0), $p = 0.06$. There were no statistically significant differences in synovitis by GS ($p = 0.21$) or by PD ($p = 0.22$) between patients who reported to be in RA flare vs not in RA flare. TJC28 was marginally higher in patients reporting a flare vs no flare ($p = 0.06$) while SJC28 were similar regardless of reported flare ($p = 0.14$).

Discussion

This is the first randomized controlled study evaluating the effect of a patient-oriented flare management intervention guided by non-physician providers versus usual care between rheumatology visits on flare occurrence, RA disease activity, and patient satisfaction. Contrary to the study hypothesis, the intervention did not have any statistically significant effect on RA flare occurrence or RA disease activity metrics.

The reasons for the lack of difference in flare rate and RA activity between the arms of the study could include poor adherence of patients in the intervention arm to completing the questionnaires and/or patient preference to self-manage their flares rather than being seen by a rheumatology provider, even on expedited basis.

These findings have important implications as they align with the concept of minimally disruptive medicine (MDM), which suggests patients may choose to disregard their care for chronic illness because the burden of work that is required to accomplish this care exceeds patients' capacity to perform this work [14]. Despite the initial patients' willingness to be seen on a short-term basis if they are in a flare of RA, as recorded on the baseline patient satisfaction survey, most patients ultimately chose not to accept an expedited appointment with a rheumatology health care provider for management of their RA flares during the study.

Another important implication from this study is that in real world practice, the majority of RA flares may not come to provider attention and hence not benefit provider decision-making regarding management of RA. A prior study has shown that fluctuations in disease activity in RA had an independent effect on radiologic progression such that patients with low RA disease activity and significant fluctuations in their DAS28 score may have similar rates of radiologic

progression as those with persistently high RA disease activity [15]. Thus, clinicians should consider the possibility of undetected flares in their patients. FLARE-RA questionnaire may be helpful in detecting flares that occur between visits.

Patients who reported flare of their RA were more likely to have tenosynovitis on ultrasound examination in the absence of statistically significant differences in their joint counts. Although this observation is based on small number of patients, it suggests that patients may be able to recognize worsening of their RA disease early, even if they do not identify the nature of the symptom. This finding may also explain in part limitations of routine disease activity assessments (i.e., standard joint counts) in assessing patients with symptoms of possible disease flares. In this study, similar to earlier studies from the OMERACT group [16], there was good agreement between patients and provider opinion regarding flare status.

Higher satisfaction rates with nurse-led care as compared with MD-led care in RA were reported in previous studies [5, 17]. In this study, the vast majority of patients in both arms throughout the follow-up were satisfied with the management of flares by their providers. It is possible that adherence to the intervention might have been higher if patients were less satisfied with their flare management according to usual care.

Strengths of this study include the randomized controlled design with a 24-month follow-up. Patients, providers, and study coordinator were blinded to the hypothesis under study.

Limitations of the study include the fact that the baseline characteristics were not balanced despite randomization. The use of IPW accounted for this circumstance and facilitated balance in baseline characteristics between the groups. Poor adherence to completion of the FLARE-RA questionnaire is another potential weakness. However, only one patient from the intervention group completely discontinued his participation in the study. Importantly, patients in the intervention arm were more likely to report positive effects of participation in the study at the end of follow-up as compared with the usual care arm, suggesting positive patient perception about the intervention. The factors which influence patient and provider acceptance, adherence, and outcome of this type of intervention were not specifically examined and may differ in various rheumatology care settings. Self-limited flares of RA that did not require initiation or change in treatment were not accounted for by the OMERACT 9 definition. However, this limitation would apply to both, intervention and usual care arm, and thus unlikely to bias comparison in flare rates between the study arms.

Generalizability Patient-oriented flare management intervention used in the study can be applied to ambulatory rheumatology practices that have nursing staff available for over-the-phone communication. Implementation success and impact of the intervention on RA flare management may be expected to vary among the rheumatology practices depending on existing standard of care and patients' characteristics (i.e., socio-demographic status, access to care, insurance coverage, level of RA disease activity, satisfaction with existing rheumatology care).

In summary, the flare management intervention guided by non-physician providers had no major effect on RA flare rates and RA disease activity metrics over the 24-month follow-up. Patients in the intervention arm largely expressed a preference for self-management of RA flares as opposed to expedited visits with their rheumatology provider. Patients in the intervention arm were more likely to report positive effects of participation in the study on the management of RA flares than patients in the usual care arm. More studies are needed to further understand patient preferences for optimal RA flare management and to design interventions to meaningfully address these preferences.

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Compliance with ethical standards

The study was approved by the Institutional Review Board of Mayo Clinic and was registered at the ClinicalTrials.gov Identifier: NCT02382783 (https://clinicaltrials.gov/ct2/show/NCT02382783). All patients included in the study signed a written informed consent for participation in this study.

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Disclaimer Funders reviewed the protocol for the study but had no role in study conduct or interpretation of the results.

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