Systematic Monitoring of Disease Activity Using an Outcome Measure Improves Outcomes in Rheumatoid Arthritis

WANRUCHADA KATCHAMART and CLAIRE BOMBARDIER

ABSTRACT. ***Objective.*** To systematically review the literature on the value of outcome measures to monitor treatment response in patients with rheumatoid arthritis (RA).

Methods. Canadian rheumatologists participating in the International 3e (evidence expertise exchange) Initiative formulated the question "Which parameters should be recommended for use in the management of RA patients to assess a clinically meaningful response in clinical practice?". Searches in 3 electronic databases, Medline, Embase, and Cochrane Central Register of Controlled Trials, yielded no relevant study addressing this question. Experts in the field proposed to extrapolate evidence from 3 randomized controlled trials of systematic monitoring or tight control strategy in the management of RA.

Results. Three studies were included in this review. The TICORA study showed that intensive management using systematic monitoring with the Disease Activity Score (DAS) aiming at least low disease activity, monthly followup, and more aggressive disease-modifying antirheumatic drug (DMARD) treatment improves outcomes with higher remission rates (65% vs 16%; $p < 0.0001$). Fransen, *et al* demonstrated that targeted therapy aimed at low disease activity (DAS28 < 3.2) led to more changes in DMARD treatment, resulting in a larger number of patients with low disease activity (31% vs 16%; $p = 0.028$). The CAMERA study showed that systematic monitoring using the objective computer decision program evaluation and monthly followup yielded a greater remission rate (50% vs 37%; $p = 0.0001$).

Conclusion. Systematic monitoring of disease activity, aiming for at least low disease activity, and frequent followup improves outcome in RA. (J Rheumatol First Release May 1 2010; doi:10.3899/jrheum.090980)

Key Indexing Terms

RHEUMATOID ARTHRITIS SYSTEMATIC MONITORING TREATMENT OUTCOME
TIGHT CONTROL STRATEGY DAILY PRACTICE SYSTEMATIC REVIEW

From the Department of Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada; Division of Rheumatology, Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; and Department of Health Policy, Management, and Evaluation, University of Toronto, and Division of Clinical Decision Making and Health Care, Toronto General Research Institute, University Health Network, Toronto, ON, Canada.

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W. Katchamart, MD, FRCP(T), Clinical Research Fellow, Department of Rheumatology, Mount Sinai Hospital, University of Toronto; Division of Rheumatology, Department of Medicine, Siriraj Hospital, Mahidol University; C. Bombardier, MD, FRCPC, Professor, Department of Rheumatology, Mount Sinai Hospital; Department of Health Policy, Management, and Evaluation, University of Toronto; and Division of Clinical Decision Making and Health Care, Toronto General Research Institute, University Health Network.

Address correspondence to Dr. W. Katchamart, Division of Rheumatology, Department of Medicine, Siriraj Hospital, 2 Prannok Road, Bangkoknoi, Bangkok, Thailand 10700; E-mail: wanda.katchamart@utoronto.ca

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Rheumatoid arthritis (RA) is a systemic inflammatory joint disease with heterogeneous manifestations and outcomes. Current management consists of early aggressive treatment to suppress inflammation in the early stage of disease before patients develop permanent deformity and functional impairment[1]. Many measures for assessing patient response to treatment have been developed, validated, and are widely used in clinical trials[2-7]. They usually consist of composite measures that require complex calculation or special training and skill, e.g., modified Sharp/van der Heijde score. These composite scores may not be practical in daily practice due to time constraints. We therefore undertook a systematic review to find evidence supporting the use of specific outcome variables in routine practice.

Our review is part of the 3e Initiative (evidence, expertise, exchange) in Rheumatology, a multinational effort aimed at promoting evidence-based medicine by formulating detailed recommendations for the use of methotrexate

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(MTX) in RA[8]. We summarize the evidence provided to the Canadian 3e expert panel for developing practice recommendations[9] to answer the following question: "Which parameters should be recommended for use in the management of RA patients to assess a clinically meaningful response in daily practice?".

MATERIALS AND METHODS

Search strategy. Our search strategy included the following 3 broad categories — Population: patients with RA; Intervention: single and composite monitoring parameters; and Setting of interest: everyday or clinical practice (for search terms details see Appendix).

We performed a search of electronic bibliographic databases including Medline (1950 to October 2007), Embase (1980 to 2007, Week 43), and the Cochrane Central Register of Controlled Trials (CCRT; 4th Quarter 2007). We also searched the abstracts of the annual scientific meetings of the American College of Rheumatology and the European League Against Rheumatism from 2005 to 2007. We identified 175, 295, and 12 citations, respectively, in Medline, Embase, and CCRT, and none from the abstracts of meetings. One reviewer (WK) screened the titles and abstracts of the retrieved citations using the following 3 inclusion criteria: (1) Patients with RA ≥ 18 yrs old; (2) randomized controlled trials (RCT) comparing between (a) use of an outcome measure versus no specific outcome measure used to monitor the response to the treatment, or (b) use of 2 different outcome measures; and (3) data reported on any outcomes listed above. After applying our inclusion criteria, we could not identify relevant studies directly addressing our clinical question. The bibliographic team asked experts in the field (the Steering Committee of Canadian 3e Initiative) whether they recalled or recognized studies that may indirectly address this question. After discussions, it was decided to extrapolate the evidence from 3 studies investigating "tight control strategy" versus "usual or routine care strategy" in patients with RA.

Data abstraction, quality assessment, and data synthesis. One reviewer (WK) abstracted the data and assessed the quality of included studies using the van Tulder's scale[10]. This scale comprises 11 questions assessing the adequacy of randomization, blinding procedure (patient, care provider, and outcome assessor), and concealed treatment allocation; similarity of important baseline characteristics, co-intervention, and timing of the outcome assessment; adequacy of compliance; report of withdrawals; and use of intention-to-treat analysis. Data abstraction and quality assessment were performed without masking trial identifiers. Each item is rated as "yes," "no," or "do not know." The study characteristics and their results were descriptively summarized.

RESULTS

The experts identified 3 RCT: the Tight Control for Rheumatoid Arthritis (TICORA) study[11]; Fransen, *et al*[12]; and the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) study[13]. These 3 studies investigated the efficacy of a "tight control strategy" using intensive treatment and standardized monitoring versus "usual or routine care strategy" in patients with RA.

Study quality. Quality assessment for each study is summarized in Table 1. The TICORA study was a well conducted RCT, but patients, care givers, and outcome assessors were not blinded. Several co-interventions in the intensive care group might have led to better outcomes including more frequent followup and an aggressive treatment protocol. Fransen's study was generally of high quality. Due to the nature of the intervention, patient and care provider blinding could not be performed in all studies; but in Fransen's study outcome assessor blinding was used to reduce detection and performance bias. The CAMERA study was well conducted but had a high dropout rate in both arms (23% vs 39%). The 3 most common causes of dropout in this study were adverse events from MTX and cyclosporine (CSA) and lack of efficacy. Additionally, blinding of outcome assessors was not performed, and the intensive group was followed up more frequently than the conventional care group.

Table 1. Study quality assessment.

Quality Assessment	TICORA[11]	Fransen[12]	CAMERA[13]
Method of randomization adequate	Y	Y	Y
Patient blinded	N	N	N
Care providers blinded	N	N	N
Outcome assessors blinded	N	Y	N
Treatment allocation concealed	Y	Y	Y
Groups similar at baseline regarding the most important prognostic factors	Y	Y	Y
Cointerventions avoided or similar	N	Y	N
Timing of outcome assessment in both groups comparable	Y	Y	Y
Compliance acceptable in all groups	Y	Y	N
Dropout rate described and acceptable	Y	Y	N*
Intention to treat analysis used	Y	Y	Y

* High dropout rate. Y: yes; N: no.

TICORA[11]. The characteristics of the 3 studies are summarized in Table 2. The TICORA study was a single-blind RCT in 2 teaching hospitals in the UK. One hundred eleven RA patients receiving nonbiologic DMARD were randomly assigned to intensive care or routine care. In the intensive care group, patients were monitored monthly, and treatment was adjusted according to a well defined protocol. If the DAS was more than 2.4 (moderate disease activity), a step-up strategy was used starting with sulfazalazine (SSZ), followed by triple therapy of SSZ + MTX + hydroxychloroquine (HCQ), followed by MTX + CSA, and then leflunomide (LEF) and intramuscular gold, respectively; intraarticular steroid was also allowed at the monthly visit. In the routine care group, patients were evaluated every 3 months without formal use of a composite measure of disease activity, and treatment regimens were left to the rheumatologist's discretion. After 18-month followup, patients in the intensive group had a significantly better mean DAS response (–3.5 vs –1.9; $p < 0.0001$), and a higher percentage of DAS good response (82% vs 44%; $p < 0.0001$) and DAS remission (65% vs 16%; $p < 0.0001$); they were also more likely to be prescribed DMARD combinations compared to the routine group (67% vs 11%). The numbers of dropouts and patients lost to followup were not significantly different between the 2 groups (1 vs 2 in intensive vs routine care, respectively). Functional status, quality of life, radiographic outcomes, and costs were more favorable in the intensive

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Table 2. Study characteristics.

Study	Trial Duration	Intervention	Sample Size	Frequency of Followup	Treatment	Outcome
TICORA[11], UK	18 mo	Intensive care (DAS < 2.4)	55	Monthly	Specific protocol	Mean fall in DAS
		Routine care (physician's discretion)	55	Every 3 mo	No protocol	
Fransen[12], Netherlands	24 wks	Intensive care (DAS 28 < 3.2)	205	Wks 0, 4, 12, 24	No protocol	DAS28
		Usual care (physician's discretion)	179			
CAMERA[13], Netherlands	2 yrs	Intensive care (computer decision program)	151	Monthly	Specific protocol	Remission rate
		Conventional care (physician's discretion)	148	Every 3 mo		

DAS: Disease Activity Score.

group than in the routine group. This study demonstrated that intensive management of RA using systematic monitoring with DAS aiming at low disease activity, frequent followup, and more aggressive DMARD treatment improved outcomes at no additional cost.

Fransen, et al[12]. This study was a multicenter, 24-week, cluster RCT of systematic monitoring using DAS28 (DAS group) versus usual care (UC group) in 384 RA patients in The Netherlands. Patients in both groups were assessed at week 0, 4, 12, and 24. In the DAS group, DAS28 was used to guide treatment. The DMARD treatment was adjusted aiming at DAS28 ≤ 3.2 (low disease activity). In the UC group, there was no systematic monitoring of disease activity. No specific treatment protocol was provided in either group. Treatments consisted of nonbiologic DMARD, mostly MTX, SSZ, and prednisolone. At 24 weeks, the DAS group had a significantly higher proportion of patients with low disease activity as compared to the UC group (31% vs 16%; p = 0.028). Patients in the DAS group received more aggressive treatment, including more frequent changes in the drug regimens and higher doses of MTX, SSZ, and steroid. Adverse events were not significantly different between the 2 groups. It was concluded that in daily practice, systematic monitoring of disease activity using DAS28 in RA might lead to more changes in the DMARD treatments, resulting in a larger number of patients with low disease activity.

CAMERA[13]. The CAMERA study was a 2-year multicenter trial of intensive strategy versus conventional strategy using MTX in 299 RA patients in The Netherlands. Patients in both groups received the same treatment protocol, comprising MTX 7.5 to 30 mg/wk and CSA 0.5–2.5 mg/day for MTX inadequate responders. Patients in the intensive group were assessed monthly using a computer program for guiding treatment change. The program calculated the following change criteria — less than 50% improvement in the number of the swollen joint count and less than 50% improvement for 2 out of 3 variables: tender joint count, erythrocyte sedimentation rate (ESR), and patient global assessment of general well-being (PGA). In the conventional group, patients were assessed only every 3 months, and treatment changes were at the rheumatologist's discretion. More patients in the intensive group achieved at least one period of remission during 2 years of followup as compared to the conventional group (50% vs 37%; p = 0.03). Also, all clinical variables and radiographic outcomes were significantly better. The high doses of MTX and CSA were more frequently used in the intensive group than in the conventional group, without significantly increased adverse events. This study demonstrated that systematic monitoring using an objective computer decision program combined with more frequent followup improves outcomes in RA.

DISCUSSION

The objective of our study was to systematically review the literature on the value of outcome measures to monitor response to treatment in RA patients in daily practice; however, performing the systematic review to answer this clinical question was not straightforward. The major limitation of this systematic review was that there was no evidence directly addressing our question. Although the results of these 3 studies support the use of an outcome measure to follow up on clinical response, this conclusion is confounded by other factors such as frequency of clinical assessment and treatment protocol. In the TICORA and CAMERA studies, more frequent followup was provided in the intensive care group. Frequent followup provided physicians the opportunity to frequently adjust treatments to achieve their

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targets. This led to more aggressive treatment regimens, including a higher dose or more effective DMARD or DMARD combinations. Additionally, the treatment regimen is also a confounder in the TICORA study, where the choice of DMARD and treatment algorithm were provided only to the intensive group. Therefore, patients in the intensive group were treated with aggressive regimens following the protocol while the UC group might receive less effective DMARD and regimens due to the variation in clinical practice rather than nonsystemic monitoring and less frequent followup. This variation of drug choice and regimens was controlled in the CAMERA study. Systematic monitoring using Disease Activity Score, therefore, is only one component of the tight control strategy. Conversely, in Fransen, *et al*'s study, patients in both groups had the same followup schedules, and the treatment protocol was not provided. This means that patients in both groups had an equal chance of receiving a similar treatment algorithm based on the physician's discretion; hence, the benefit was the direct result of standardized monitoring using DAS28. However, this study also only partly answered our question. We can conclude only that systematic monitoring using the DAS28 improves RA outcomes as compared to routine care using physician's discretion.

Further, the results of these studies were subject to "incorporation bias" because the outcome measures used (DAS, DAS28, or combined clinical variable threshold) to evaluate clinical response at the end of the trial were the same measures used to monitor and determine treatments in the intensive group during followup. This may have resulted in overestimation of clinical responses in the intensive group, as compared to the routine care group.

Nonetheless, the results from these 3 studies support the benefit of systemic monitoring using an outcome measure (DAS, DAS28, and computer decision program) to guide treatments. Disease activity thresholds could be used in several ways to determine treatment: to prescribe more aggressive treatments when patients have evidence of active disease and/or to reduce or stop treatments when patients achieve the goal of very low disease activity or remission. Many outcome measures have been proposed and used to assess clinical response in clinical trials, for example, DAS, DAS28, SDAI (Simplified Disease Activity Index), and CDAI (Clinical Disease Activity Index); however, to date, we have no evidence comparing benefits of different outcome measures, e.g., DAS versus SDAI, or benefits of a single outcome measure versus a composite outcome measure, e.g., number of swollen joints versus CDAI, for monitoring RA disease activity, especially in daily practice.

Another limitation was the lack of an appropriate search strategy. We used many strategies to identify the relevant studies. Some strategies were too broad and included a large number of irrelevant citations. This search strategy was developed using the PICO method (Patient/Population — Intervention — Comparison — Outcome), which was developed for evidence-based practice searching[14]. From the citations retrieved by this comprehensive search strategy, we found that there was no study directly addressing this clinical question. When the comprehensive search strategy for RCT in a systematic review is performed to identify the relevant citations, the main sources are the electronic databases, conference proceedings, and reference lists of relevant articles[15]; however, when the evidence from the main sources was not available, experts are the best source to rely on.

APPENDIX. Search strategy.

	Search Term
1	exp arthritis, rheumatoid/
2	(felty$ adj2 syndrome).tw.
3	(caplan$ adj2 syndrome).tw.
4	rheumatoid nodule.tw.
5	(sjogren$ adj2 syndrome).tw.
6	(sicca adj2 syndrome).tw.
7	still$ disease.tw.
8	bechterew$ disease.tw.
9	(arthritis adj2 rheumat$).tw.
10	(swollen adj2 joint$).mp.
11	(tender adj2 joint$).mp.
12	((patient$ or physician$) adj2 global assessment$).mp.
13	functional status.mp.
14	health assessment question$.mp.
15	haq.mp.
16	erythrocyte sedimentation rate$.mp.
17	esr.mp.
18	c reactive protein$.mp.
19	acr 20.mp.
20	acr20.mp.
21	acr 50.mp.
22	acr50.mp.
23	acr 70.mp.
24	acr70.mp.
25	american college of rheumatology 20.mp.
26	american college of rheumatology 50.mp.
27	american college of rheumatology 70.mp.
28	disease activity score$.mp.
29	das.tw.
30	eular response$.mp.
31	radiographic score$.mp.
32	sharp$ score$.mp.
33	vdh.mp.
34	larsen$ score$.mp.
35	simple disease activit$.mp.
36	sdai.mp.
37	Clinical disease activit$.mp.
38	cdai.mp.
39	Rheumatoid Arthritis Disease Activity Index.mp.
40	radai.mp.
41	rapid assessment of disease activity in rheumatology.mp.
42	radar.mp.
43	Treatment Outcome/
44	animals/
45	humans/
46	(clinical adj2 practice$).mp.
47	(everyday adj2 practice$).mp.

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Our systematic review identified the gap in evidence for clinical practice. "Which parameters should be recommended for use in the management of RA patients to assess a clinically meaningful response in clinical practice?" is an important and relevant question in daily practice that needs to be answered; however, conducting clinical trials to answer this clinical question is complex. Blinding patient and care provider is not possible in the strategy trial although blinding of the outcome assessor is a strategy to reduce detection bias. Confounding factors that may influence the outcomes have to be controlled; these include the frequency of followup and the treatment regimen and algorithm. Additionally, to avoid incorporation bias, the outcome measure used to determine outcomes at the end of the trial should not be the same as the one used to monitor clinical response and determine treatments during the followup period.

Nonetheless, from the indirect evidence available, we conclude that in daily practice, systematic monitoring of disease activity, a tight control strategy aiming for at least low disease activity, and frequent followup improve outcomes in patients with RA.

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