Automated text message enhanced monitoring versus routine monitoring in early rheumatoid arthritis: a randomized trial

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Abstract

Objective: Frequent monitoring of early rheumatoid arthritis (RA) patients is required for achieving good outcomes. We studied the influence of text message (SMS) enhanced monitoring on early RA outcomes.

Methods: We randomized 166 early, disease-modifying antirheumatic drug naive RA patients to SMS-enhanced follow-up or routine care. All patients attended visits at 0, 3, and 6 months, and a follow-up visit at 12 months. Treatment was at the physicians' discretion. The intervention included 13 SMSs during weeks 0–24 with questions concerning medication problems (yes/no) and disease activity (patient global assessment [PGA], scale 0–10). If response SMSs indicated medication problems or PGA exceeded predefined thresholds the patients were contacted. Primary outcome was 6-month Boolean remission (no swollen or tender joints, normal CRP). Quality of life (QOL, Short Form 36) and 28-joint disease activity scores (DAS28) were assessed.

Results: Six and 12-month follow-up data were available for 162 and 157 patients. In the intervention group, 47% (38/82) of the patients reported medication problems and 49% (40/82) of the patients reported SMS-PGAs above the alarm limit. Remission rates in the intervention and control groups were 51% and 42% at 6 months (p=0.34); and 57% and 43% at 12 months (p=0.17). The respective DAS28 scores were 1.92±1.12 and 2.22±1.11 at 6 months (p=0.09); and 1.79±0.91 and 2.08±1.22 at 12 months (p=0.28). No differences in QOL were observed.

Conclusion: The study failed the primary outcome despite a trend favoring the intervention group. This may be explained by the notably high overall remission rates.

Key words: Early rheumatoid arthritis, Clinical trials, DMARD, Mobile Health, Mobile phone use, Telemedicine, Remission

Significance and innovations

- Automated text message monitoring is a feasible tool for remote assessment of disease activity and medication use in early RA.
- Patients find text message monitoring easy to use, and would recommend it to other RA patients.
- In this study, remote monitoring did not influence early RA outcomes.

Achieving good outcomes in the treatment of early rheumatoid arthritis (RA) requires frequent monitoring and treatment targeted towards clinical remission. Current international recommendations suggest clinical assessments in active disease every one to three months (1). Some patients might benefit from even more frequent contacts with the rheumatology clinic. Implementation of the international guidelines may be challenging particularly in less affluent settings, possibly translating into worse outcomes. Therefore, barriers to more intensive monitoring should be overcome.

Poor medication adherence is another challenge in the treatment of early RA. Adherence to disease modifying anti-rheumatic drugs (DMARDs) is on average 66% (2), but decreases over time (2, 3). In early RA, non-adherence has been associated with worse outcomes during the first six months (3). However, improving medication adherence can be challenging (4, 5).

Patient reported outcomes (PROs) have been shown to distinguish poor treatment responses as successfully as clinical activity scores (6). Use of PROs allows assessment at short intervals without a physician office visit. Thus, PROs could be used for early recognition of patients who do not achieve low disease activity enabling prompt medication adjustment. Additionally, more frequent contacts may increase patient confidence and promote medication adherence.

We have recently developed a simple and inexpensive automated monitoring system for RA patients based on text messages (SMS). This monitoring

system aims at supporting successful initiation of DMARDs and improving drug adherence during the crucial first 6 months after the diagnosis of RA.

In the current study, we assessed the effectiveness of 6-month SMS-enhanced follow-up compared to routine follow-up in early RA.

Patients and methods

Study design and selection of patients

We conducted an open, randomized trial comparing text message enhanced monitoring to routine monitoring of early RA. The study has been registered at ClinicalTrials.gov (NCT02424877). We recruited 166 patients from six Finnish rheumatology centers from August 2013 through July 2015, and ceased randomization after reaching the minimum predefined sample size due to slow recruitment. The patients were DMARD naïve and fulfilled American College of Rheumatology/European League Against Rheumatism 2010 RA classification criteria. In addition, the participants were required to own a mobile phone and had to be able to send and receive text messages.

We randomized the patients 1:1 in blocks of four in each study center to text message enhanced follow-up (intervention) or to routine follow-up (control). The six-month intervention consisted of 13 text messages at 1–2 week intervals during weeks 0–24. All patients were scheduled visits at 0, 3, and 6 months, after which the intervention ended. A follow-up visit after the intervention was scheduled at 12 months. Clinical assessments included a 46 swollen and tender joint count, patient's global assessment of RA disease activity within the previous three days [PGA, 100 mm Visual Analogue Scale (VAS)], patient's assessment of pain (VAS), patient's confidence in the treatment (VAS), physician's global assessment (VAS), and the Health Assessment Questionnaire (HAQ). Radiographs of the hands and feet were

taken at baseline. Health-related quality of life was assessed using Short Form 36 (SF-36) questionnaire at 0, 6, and 12 months (7). Visits were scheduled at similar intervals as in routine clinical practice following treat-to-target guidelines and national recommendations (8, 9). Treatment was not prespecified and was administered at the physician's discretion following the Finnish Current Care guidelines (9). The protocol was approved by the ethics committee of South Karelia Central Hospital (400/13.02.02/2013) and the study was conducted according to the Declaration of Helsinki. We obtained written informed consent from all patients.

Showing any need for Re-Assessment (SandRA) software

The monitoring system used in the intervention group was an automated cloud-based software aiming at (1) improving medication adherence and (2) early identification of patients responding poorly to treatment. Questions in the text messages concerned medication use and possible adverse effects at weeks 1 (“Have you started the prescribed medication?”), 2, 4, 8, 16, and 20 (“Have you had problems with your medication?”), and requested patient’s assessment of disease activity at weeks 0, 6, 10, 12, 18, 22, and 24 (“What is the severity of your RA symptoms on a scale from 0 to 10, where 0 corresponds to no symptoms and 10 to as severe symptoms as you can imagine?”). Answers were given as a single letter (Y/N), or as a whole number (0–10). We used a simplified version of a PGA using whole numbers, which has been validated previously (10). The software included a cut-off limit of 4, 4, 3, and 2 for PGA at 6, 10, 18 and 22-week time points. Very low cut-off limits were chosen in order to detect possible problems early and to improve

odds of reaching early strict remission. These limits were set based on data from two earlier Finnish early RA treatment strategy studies, in which patients with PGAs above the cut-off limit had a low likelihood of achieving 6-month remission (11, 12).

If patients' responses suggested medication problems or insufficient reduction in disease activity, the system notified the treating clinic and sent the patient the following text message: "Your nurse will call you within 2 working days". The nurse called the patient, discussed the problem in hand, and consulted a physician if needed, as in routine clinical practice. If the problem could not be solved over the phone, the patient was called in for a visit before a scheduled appointment. If no problems were detected, the system responded: "Have a nice day".

Participating rheumatology nurses received a short training of approximately 60 minutes in the use of the cloud-based SMS-monitoring system. The patients in the intervention group were given written and 30-minute oral instructions on performing the SMS-monitoring. The patients were also able to practice its use during 0 and 3-month office visits. The patients in the control group did not receive text messages; in case of problems they left a callback request to their rheumatology nurse. After the intervention, the patients were asked to complete a short feedback questionnaire (see supplementary file) concerning the SMS-monitoring. The nurses' actions were not documented in detail; only the number of additional nurses' and physicians' contacts was documented.

Outcomes

As primary outcome, we assessed strict Boolean remissions, defined as no tender or swollen joints (46 joint count) and normal CRP, at 6 months. Secondary outcomes were 1) quality of life (SF-36) at 6 months, 2) Boolean remissions at 12 months, 3) patient confidence to the treatment (VAS) assessed at clinic visits at 0, 3, and 6 months, and 4) use of health care resources during the 6-month intervention defined as the number of visits (physician or nurse office visits) and contacts (telephone contacts with physician or nurse) to the treating rheumatology clinic.

Statistical methods

We calculated the sample size based on remissions at 6 and 12 months in the combined patient cohorts from two earlier Finnish RA trials (11, 12). We estimated that, with a power of 85% and at a significance level of 0.05, detecting a 25% difference in remission rates (30% versus 55%) between the groups would require 80 to 100 patients per group with an estimated dropout rate of 10%.

We analyzed the outcome measures by intention-to-treat. Statistical comparisons between the groups were performed by t-test, Chi-square test, or Fisher test when appropriate. Repeated measures were analyzed using generalizing estimating equations (GEE) models with appropriate distribution and link function or analysis of covariance. In the case of violation of the assumptions (e.g. non-normality), a bootstrap-type method (10 000 replications) was used for estimating standard error. The normality of

variables was evaluated using the Shapiro-Wilk W test. In multivariable models, age, sex, years of education, and when appropriate, baseline disease activity, were used as covariates. Stata 14.1, StataCorp LP (College Station, TX, USA) statistical package was used for the analyses.

Results

A total of 84 patients were allocated to the intervention group, and 82 patients to the control group. Follow-up data at 6 months were available for 162 patients (**Figure 1**), and respectively, for 157 patients at 12 months. Patients' baseline characteristics are shown in **Table 1**. Despite randomization, patients in the intervention group were somewhat younger (p=0.021) and more educated (p=0.026). The patients' baseline characteristics did not differ significantly between the six study centers.

Patient reviews (n=80) of the system were positive. All patients (100%) would have recommended SMS-monitoring for other RA patients, 94% found the monitoring messages technically easy to answer, and >80% felt secure and satisfied with their treatment. However, 25% of the patients found the self-assessment of disease activity using PGA somewhat difficult or difficult.

Boolean remission rates at 6 months were 51% (95% CI 40–62%) and 42% (95% CI 32–53%) in the intervention and control groups (p=0.34). These rates were 57% (95% CI 45–68%) and 43% (95% CI 32-55%) at 12 months (p=0.17, **Figure 2**). Similar DAS28 levels were achieved in both groups during the first 6 months, 2.18 (95% CI 1.86–2.56) in the intervention group, and 2.21 in the control group (95% CI 1.86–2.51; p=0.18, **Figure 2**). The corresponding DAS28 levels were 1.79 ± 0.91 and 2.08 ± 1.22 at 12 months (p=0.28).

Quality of life at 6 months improved in both treatment groups. After adjustment for age, sex, and years of education, only improvement in SF-36 dimension of physical function was greater in the intervention group than in the control group (p=0.042). Changes in physical (p=0.076) and mental summary components (p=0.81) did not differ between the randomization groups (supplementary **Figure S1**). We did not detect significant between-group differences in patient confidence to the treatment (p=0.73).

In most cases, a combination of conventional synthetic DMARDs (csDMARDs) was initiated for all patients at the baseline visit (**Table 2**). During the first six months, 89% of the patients used a combination of 2–3 conventional synthetic DMARDs. 96% of these patients were prescribed methotrexate, and 94% oral low-dose glucocorticoids (**Table 2**). Number of intra-articular glucocorticoid injections (mean ± SD) was 2.5 ± 2.7 in the intervention, and 3.0 ± 3.9 in the control group, respectively (p=0.33). Only 3 patients required biologic DMARDs during the intervention. Adverse events, reported by 60% of the patients, were balanced between the randomization groups (**Table 3**).

During the intervention, the use of health care resources increased in the intervention group. The number of nurse's telephone contacts was 3.32 ± 2.93 in the intervention and 2.0 ± 2.55 in the control group (p=0.008). No differences were observed for other contact or visit types. The number of unscheduled nurse's visits was 0.56 ± 0.80 in the intervention group and 0.56

± 0.65 in the control group (p=0.56). In the intervention and control groups, the number of unscheduled physician's visits was 0.13 ± 0.44 and 0.11 ± 0.39 (p=0.86), and the number of physician's telephone contacts was 0.56 ± 0.93 and 0.46 ± 0.75 (p=0.65), respectively.

Of the patients in the intervention group, 49% (40/82) reported PGAs above the predefined alarm limits (**Figure 3**). Mean PGAs given in the intervention group at weeks 0, 6, 10, 12, 18, 22, and 24 were 5.3, 3.1, 2.5, 2.1, 1.9, 1.8, and 1.6 (**Figure 3**). Of the PGAs, 22% were above the alarm limit at week 6, and respectively 16%, 17% and 25% at weeks 10, 18, and 22 (**Figure 3**). Medication problems were reported by 38/81 patients, and 4/81 reported not initiating the prescribed medication.

Discussion

In this study, we compared the impact of SMS-enhanced follow-up versus routine follow-up on early RA outcomes during the initial six months. The number of Boolean remissions at 6 and 12 months was higher in the intervention group than in the control group, but despite 9% and 14% between-group differences at these time points statistical significance was not reached. Overall, achieved remission rates were remarkably high; the mean DAS28 and its upper 95% CIs were below the DAS28 remission limit (DAS28<2.6) at 6 and 12 months in both groups.

The fact that vast majority of patients in both groups attained DAS28 remission may have rendered achieving significant between-group differences difficult. Furthermore, the randomization was ceased soon after reaching the minimum sample size, due to slow recruitment and a dropout rate that was lower than expected. If the randomization had continued to a sample size of 200, the trend in remission rates might have reached statistical significance. The high remission rate is likely attributable to the Finnish model of treating RA with a combination of 2-3 csDMARDs, low-dose oral prednisolone, and intra-articular GCs (9). Additionally, study centers have made efforts to optimize their rheumatology service; four out of six centers use routinely a structured, electronic monitoring tool for clinical data collection and all aim at delivering prompt, multidisciplinary care to their patients. Early RA patients in Finland are routinely scheduled visits at 0, 3, and 6 months in day-to-day clinical practice, as in the current study. Comparable outcomes have been

reported from a Finnish early RA cohort, where three out of four patients achieved a less stringent remission, DAS28 three-variable remission, at one year (13). The study design followed closely routine rheumatology clinical practice in Finland. However, the additional attention in the form of SMSs may have improved the remission rate in the intervention group. The number of additional visits in the intervention group remained very low, and was unlikely to influence the study outcome. The care of early RA is highly optimized and therefore difficult to improve. Patients groups whose care is less optimized might benefit more from similar interventions.

SMS-enhanced monitoring increased the use of health care resources. When the text messages indicated problems, the nurse contacted the patient, which increased the number of nurse's telephone contacts. The initiation of the SMS-monitoring required also patient education. In contrast to our hypothesis, the nurses' increased workload did not translate into significantly improved clinical outcomes, and did not reduce the number of contacts or visits in the intervention group. The nurses required only 60 minutes of training to use the cloud-based SMS-monitoring system. In addition to receiving a 30-minute training, the patients in the intervention group required only 1.3 additional 20-minute phone calls from a nurse compared to the control group, without any notable differences in physicians' or nurses' visits. Although the SandRA monitoring software is not currently commercially available, and its exact price is therefore unclear, the added burden resulting from SMS-monitoring in early RA seems to be modest.

Most patients were very satisfied with the text message based monitoring system. The patients felt that they were in good care and that the monitoring increased the safety of the treatment. Nevertheless, no differences were observed in reported adverse events or in quality of life. The latter improved in intervention and control groups and between-group differences remained negligible.

We chose to use PGA for assessment of disease activity due to its simplicity, as a more complex questionnaire requiring a smartphone may not have been accessible to all RA patients and may not have been as feasible to use. Nevertheless, one fourth of the patients in the intervention group found remote self-assessment of disease activity using PGA difficult despite spoken and written instructions. Previous studies have shown that PGA is a reliable measure on a group-level, as it is sensitive to change, and has a good test-retest reliability (14-16). However, on individual level factors like pain can influence PGA significantly (6).

New technologies are used increasingly in healthcare. In some chronic diseases, like diabetes and heart failure, remote monitoring improves treatment outcomes compared to conventional monitoring (17-19). To date, most remote monitoring studies on RA have focused on self-management (20, 21), and only a handful of studies have utilized remote disease activity assessments. Compared to our study, three previous remote disease activity assessment studies have used different, significantly more complex approaches. Nishiguchi el al. demonstrated in a cross-sectional study of 65

patients that a smartphone application can be used for measuring RA disease activity (22). In this study, patients gave a disease activity assessment using modified HAQ, self-assessed tender and swollen joint counts, and self-measured their gait using an accelerometer. The patients were also assessed by a rheumatologist. Using these measures, Nishiguchi et al. developed a model for predicting DAS28 levels. Later, the same model was tested in nine RA patients, who assessed their disease activity daily for three months using a smartphone (23). In this study, self-assessed disease activity had a good correlation to DAS28 at monthly clinic visits when patient's DAS28 was low or moderate. In a third study, Espinoza et. al. used a very different approach and showed that handgrip strength was negatively correlated with disease activity using a smartphone-connected dynamometer (24). These studies tested the feasibility and accuracy of different remote disease activity assessments, but did not test the influence of remote disease activity assessments to RA outcomes.

To our knowledge, the current study is the first to assess the influence of text message enhanced medication and disease activity assessments to treatment outcomes in RA. One previous study has evaluated the influence of web-based intensive monitoring to RA outcomes (25). Salaffi et al. randomized 41 early RA patients to intensive monitoring, including online assessments, additional visits and treatment advice, or to usual care. Compared to usual care, intensive monitoring improved outcomes like remission and physical function. In contrast to Salaffi et al., our intervention was aimed solely at

detecting medication problems or insufficient reduction in disease activity, and treatment intensifications were entirely at the treating physician's discretion.

Our study population consisted of adult early RA patients capable of using a simple mobile phone, making our results generalizable to most RA patients. In Finland, 99% of the population used a mobile phone in 2017 (26), which reduces the possibility of selection bias in our study. However, worldwide mobile phone penetration is significantly lower, and would likely influence patient selection in less resourced settings. The aim of the intervention was detection of treatment-related problems. SMS-based system was chosen because at the time of the initiation of the study, all patients did not have a smartphone or daily access to internet.

We conclude that despite a favorable trend, text message enhanced monitoring does not significantly improve remission rates in intensively treated early RA. However, this type of monitoring may be beneficial in less resourced settings. Future studies are required for assessing whether this simple and feasible monitoring method, which patients find easy to use, provides additional value.

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Table 1. Baseline characteristics of the patients.

	Control N=80	Intervention N=82
Demographics		
Female, n (%)	56 (70%)	58 (71%)
Age years, mean ± SD	59 ± 14	54 ± 13[¶]
RF and/or anti-CCP positive, n	69 (86%)	70 (85%)
Years of education, mean ± SD	11.3 ± 3.5	12.6 ± 3.6[§]
Body Mass Index, mean ± SD	27.5 ± 5.1	26.7 ± 5.2
Measures of disease activity		
DAS28, mean ± SD	4.4 ± 1.3	4.1 ± 3.8
Erythrocyte sedimentation rate (mm/h), mean ± SD	28 ± 18	24 ± 22
Serum C-reactive protein (mg/l), mean ± SD	20 ± 22	16 ± 22
Number of swollen joints, mean ± SD	6.5 ± 5.4	6.4 ± 5.1
Number of tender joints, mean ± SD	9.0 ± 7.4	7.7 ± 7.0
Patient's global assessment (VAS), mean ± SD	46 ± 28	45 ± 28
Physician's global assessment (VAS), mean ± SD	41 ± 19	37 ± 20
Physical function (HAQ), mean ± SD	1.0 ± 0.7	0.9 ± 0.6
Radiography		
Erosions in hand or foot radiographs, n (%)	14 (18%)	17 (21%)

CCP, cyclic citrullinated protein antibodies; DAS, disease activity score; HAQ, health assessment questionnaire; RF, Rheumatoid factor; VAS, visual analogue scale; [¶]p=0.021; [§]p=0.026

Table 2. Use of conventional synthetic DMARDs during the 6-month intervention.

	Control N=80	Intervention N=82	P-value
csDMARD treatment, n (%)			
MTX, peroral	51 (64%)	56 (68%)	0.54
MTX, subcutaneous	25 (31%)	23 (28%)	0.66
Low-dose oral GCs	76 (95%)	77 (94%)	0.71
Hydroxychloroquine	68 (85%)	76 (93%)	0.12
Sulfasalazine	47 (59%)	56 (68%)	0.21
Leflunomide	0 (0%)	1 (1%)	0.34
Treatment strategy, n (%)			
Monotherapy	10 (13%)	6 (7%)	0.27
Combination therapy	68 (87%)	76 (93%)	0.12
Two csDMARDs	28 (36%)	30 (37%)	
Three csDMARDs	40 (51%)	46 (56%)	

csDMARD, conventional synthetic disease-modifying antirheumatic drug; GC, glucocorticoid; MTX, methotrexate

Table 3. Adverse events during the 6-month intervention.

	Control N=80		Intervention N=82		P-value
Any adverse event, n (%)	46	(57)	51	(62)	0.54
Respiratory	2	(2)	5	(6)	0.44
Gastrointestinal	29	(36)	35	(43)	0.40
Mucocutaneous	10	(12)	9	(11)	0.76
Urogenital	2	(2)	1	(1)	0.62
Central nervous system	3	(4)	4	(5)	0.72
Elevated liver enzymes	5	(6)	5	(6)	0.97
Cardiovascular	2	(2)	2	(2)	0.98
Psychological	2	(5)	5	(6)	0.44
Other	12	(15)	11	(13)	0.77
Serious adverse events (SAEs), n (%)					
Gastrointestinal	0	(0)	1	(1)	0.98
Cardiovascular	1	(1)	0	(0)	0.98

Figure legends

Figure 1. Flow of the study.

Figure 2. Boolean remission rates and 28-joint Disease Activity Score (DAS28) during the follow-up in the intervention and control groups.

Figure 3. Change in text message patient global assessments (PGAs) given as a whole number (NRS, numeric rating scale) from 0 to 10 and alarms (red flags) due to insufficient reduction in disease activity during the intervention. The dashed line represents predefined PGA alarm thresholds. Clinic visits were scheduled for weeks 0, 12, and 24.