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SHORT REPORT

Effectiveness of electronic drug monitoring feedback to increase adherence in patients with RA initiating a biological DMARD: a randomised clinical trial

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ABSTRACT

Objective Medication non-adherence in rheumatoid arthritis (RA) is associated with disease flares, increased disability and increased costs. This study assessed the effectiveness of electronic monitoring feedback (EMF) on medication adherence in patients with RA starting with or switching to a new biological disease-modifying antirheumatic drug (bDMARD).

Methods In this randomised controlled trial, bDMARD starters were assigned to the intervention or control group and followed for 1 year. The intervention group received a needle container with a Medication Event Monitoring System (MEMS) cap registering patient's adherence to injections. Scores were calculated every 3 months with MEMS and motivational interviewing feedback was given. The control group received usual care. Effectiveness of EMF on adherence was measured with the medication possession ratio (MPR).

Results 104 consecutive intervention patients were included and 102 controls. MPR was 0.95 (SD: 0.10) and 0.90 (0.16) after 12 months (B: 0.036, 95% CI: 0.001 to 0.007, p=0.045). bDMARD-naive patients receiving EMF achieved low disease activity (LDA) sooner compared with the control group, adjusted for baseline DAS (HR: 1.68, 95% CI: 1.00 to 2.81, p=0.050). Side effects and DAS28 were similar.

Conclusion EMF increased adherence for patients with RA starting with or switching to a bDMARD. Especially bDMARD-naive patients achieved LDA sooner compared with the control group, which holds promise for the future.

Key messages

What is already known about this subject?
► Medication non-adherence occurs frequently in patients with rheumatoid arthritis (RA) and decreases treatment outcomes. Effective interventions to improve adherence are absent.

What does this study add?
► Electronic monitoring feedback (EMF) improves medication adherence in patients with RA starting with or switching to a new biological disease-modifying antirheumatic drugs, as measured with the medication possession ratio.

How might this impact on clinical practice or further developments?
► EMF might be applied in usual care to improve medication adherence. In order to have maximum clinical effect, it is advisable for future research to focus on the most suitable subgroup of patients with RA.

INTRODUCTION

Effectiveness of pharmacotherapy can be limited by inadequate medication adherence, defined as the degree to which the person's behaviour corresponds with the agreed recommendations from a healthcare provider.[1] In rheumatoid arthritis (RA), it is estimated that 4%–37% of the patients are non-adherent to medication, depending on the duration of disease and/or study, method of measurement and medication.[2–8] Non-adherence is associated with disease flares, radiological damage and increased disability and increased costs.[9 10] Therefore, increasing medication adherence is essential for both patients and society.

In a systematic review, electronic monitoring feedback (EMF) as an intervention to improve adherence showed promising results. However, the included studies had several limitations, such as inadequate sample sizes, too short follow-up and not specific for RA.[8 11] To address these limitations, we developed a study based on EMF to encourage dialogue between patients and healthcare professionals regarding concerns about

medication, practical barriers and necessity of regular medication intake.

The primary objective was to examine the effectiveness of the electronic drug monitoring adherence feedback on medication adherence, in standard care for patients with RA starting with or switching to a new biological disease-modifying antirheumatic drug (bDMARD).

The secondary objectives of this study were to study the effect of the intervention on time to low disease activity (DAS28 ESR 2.6–3.2) and remission (DAS28 ESR <2.6), proportion of patients with low disease activity/remission and proportion of switching patients to another bDMARD, side effects and mean disease activity after 1 year.

METHODS

In this open randomised clinical trial, consecutive adult patients with a clinical diagnosis of RA (2010 ACR classification criteria) were included in Reade, Amsterdam, The Netherlands, between December 2015 and July 2019 (protocol in online supplemental file 2). Patients starting with or switching to a (new) subcutaneously administered bDMARD were invited. Patients were randomly assigned 1:1 to the experimental or control condition using a computer-generated randomisation list (blocks of 8). This study was conducted regarding the ethical principles for medical research as stated in the Declaration of Helsinki and reported according to the CONSORT guidelines. The Medical Ethics Committee of Reade and Slotervaart approved this study. Patients and public were involved in the design of a prior study, which was the basis for this study.[12]

Interventions

Patients in the intervention group received a special needle disposal container which was equipped with a Medication Event Monitoring System cap (MEMS and MEMS Adherence Software, AARDEX Group).[13]

Adherence was read out every 3 months and motivational interviewing (MIT)-based feedback was given by pharmacists and pharmacy technicians. In case of valid medical reasons (eg, infections or surgery) to miss one or several doses, a non-monitored period was added in the digital MEMS platform. If non-adherence was measured, possible barriers to medication intake were counselled. Communication about non-adherence was facilitated with a communication (semi structured) model developed by Linn *et al* (online supplemental material).[14]

Pharmacists and pharmacy technicians received a communication training by Linn based on the practical and perceptual barriers typology.[14] Pharmacists gave feedback regularly on the communication of the pharmacy technicians, assuring correct EMF.

Patients in the control group received standard care.

Outcome

The primary outcome measure was the difference in the medication possession ratio (MPR) in the feedback group compared with usual care after 12 months MPR is the ratio of the number of days with 'coverage' of bDMARDs in a defined period, divided by the total number of days in that period (≥80% is adherent). We corrected for temporal discontinuation because of contra-indications and for syringe defects and returns.

Secondary outcome measures were the Compliance Questionnaire in Rheumatology (CQR) at 12 months, DAS28, proportion of switchers, time to at least LDA and remission and side effects. We used the discriminant CQR Z_k score.[15] This cutting score for taking compliance was used, since it was validated with the MPR. Three or less 'missings' were imputed according to Zwikker *et al*.[16]

Patient's DAS28-ESR was assessed approximately every 3 months, by a physician or a nurse. Time to LDA and remission were calculated, from 3 (±1 month) months onwards, corresponding to the first moment of feedback in the intervention group. Total number of patients in remission or LDA was noted, as well as the use of comedication (other DMARD's, corticosteroids). We obtained documented side effects.

Sample size

The target sample size was computed using Stata to provide 80% power to detect a 18% difference in adherence between an expected 83% adherence rate in the intervention group after 1 year versus 65% in the usual care arm, using a significance level of 0.05.[7 17] The required sample size would be 206 (103 patients per arm), taking into account a 10% non-inclusion and/or loss to follow-up.

Statistical methods

Descriptive statistics were used for demographic data, using means (±SD), medians (IQR) or percentages, based on intention-to-treat.

Linear regression analysis was used to evaluate differences in MPR (dependent) between intervention and control patients (primary outcome). Logistic regression analyses were used for proportions of adherent patients and other binary outcomes. Differences in DAS28 scores (dependent) over time between intervention and control patients were analysed with linear mixed-model analysis. To analyse whether there is a difference in time to achievement of low disease activity and/or time to the next bDMARD, cox proportional hazards analysis was used to generate HRs and a 95% CI. Between-group differences were visualised by Kaplan-Meier time-to-event curves. In all (regression) analyses possible confounders (ie, independent variables baseline DAS28-ESR, age, gender, disease duration and bDMARD use before) were selected with a forward procedure (final selection criterion >10% change in effect estimate).

Table 1 Baseline characteristics

	Baseline	
	Feedback (n=104)	Control (n=102)
Female gender, (%)	73 (70)	74 (73)
Age, years (SD)	53.5 (12.1)	51.2 (13.6)
BMI, kg/m^2 (SD)	26.1 (5.9)	25.9 (4.8)
Ethnicity, Caucasian (%)	90 (87)	85 (83)
Disease duration (years, SD)	6.3 (7.07)	5.7 (5.85)
DAS28-ESR, (SD)	4.0 (1.4)	3.8 (1.5)
DAS28-ESR, (%)		
▶ Remission (<2.6)	16 (15.2)	21 (20.6)
▶ Low (≥2.6 and <3.2)	12 (11.4)	8 (7.8)
▶ Moderate (≥3.2 and ≤5.1)	42 (40.0)	41 (40.2)
▶ High (>5.1)	27 (25.7)	22 (21.6)
HAQ (SD)	1.13 (0.7)	0.98 (0.6)
Concomitant medications, (%)		
▶ Methotrexate	64 (61)	56 (55)
▶ Prednisolone or triamcinolone	36 (35)	41 (40)
▶ Other csDMARD(s)	30 (29)	39 (38)
▶ Triamcinolone acetonide injection (intramuscular) (%)	4 (3.8)	3 (2.9)

Number of patients and means are presented, unless otherwise stated.
BMI, body mass index; csDMARD, conventional disease modifying antirheumatic drug; DAS28, Disease Activity Score for 28 joints; ESR, Erythrocyte sedimentation rate.

RESULTS

A total of 206 consecutive patients were included (table 1). Most patients started with etanercept or adalimumab. In both groups, 76% of the patients started a first bDMARD.

Table 2 displays the most important findings. Patients in the intervention group had higher adherence levels as measured by MPR, but proportions of adherent patients did not differ. Mean DAS28-ESR was 2.90 (SD: 1.5) and 2.79 (1.3) at month 3 for interventions and controls, respectively, 2.71 (1.4) and 2.71 (1.3) at month 6, 2.50 (1.5) and 2.48 (1.3) at month 9 and 2.58 (1.3) and 2.74 (1.6) at month 12 (no differences at all time points). Overall, the intervention did not result in improvement of disease activity (0.504, p=0.260, 95% CI: −0.38 to 1.39).

Adverse effects (AEs) such as injection side reactions and respiratory complaints were reported by 49 (47%) intervention patients and 58 (57%) controls (χ^2: 2.154, p=0.142). No serious AEs were reported. In total, 42% ceased their bDMARD, because of side effects, loss of effect or other reasons (similar for both groups). The proportion of switchers to another bDMARD was alike.

The median time to achieve LDA (after 3 months or the first feedback) was 4.34 months in the intervention group versus 4.14 months in the control group. The median time to achieve remission was 6.57 months in the intervention group versus 6.44 months in the control group. In the final multivariable model for time to LDA (adjusted for baseline DAS28-ESR), HR was 1.29 (p=0.26, 95% CI: 0.83 to 2.01). For time to remission (adjusted for baseline DAS28-ESR, gender and BMI), HR was 1.21 (p=0.45, 95% CI: 0.74 to 1.96).

In the biological-naive subgroup, the HR adjusted for baseline DAS28-ESR was 1.68 for time to LDA for the intervention group compared with the control group (p=0.050, 95% CI: 1.00 to 2.81, figure 1). HR for time to remission was 1.52, adjusted for gender and baseline DAS28-ESR (p=0.141, 95% CI: 0.87 to 2.65, online supplemental figure S2). For switchers the dissimilarities were not statistically different.

DISCUSSION

We found a favourable effect of electronic drug monitoring adherence feedback on MPR. Furthermore, bDMARD-naive patients in the intervention group achieved LDA slightly sooner compared with controls. No effect was found on proportion of adherent patients based on CQR, proportion of patients ceasing their

Table 2 Adherence and disease activity outcomes at 12 months

	Intervention	Control	Crude effect estimate (p, 95% CI)	Corrected effect estimate (p, 95% CI)
Primary outcome				
MPR (SD)	0.95 (0.10)	0.90 (0.16)	B: 0.051 (0.009, 0.088 to −0.013)	B: 0.036 (0.045, 0.001 to 0.071)*
Proportion adherent, MPR ≥0.8	92	85	OR 1.63 (0.121, 1.22 to 3.35)	OR 1.83 (0.319, 1.14 to 5.10)*
Secondary outcomes				
Proportion adherent, CQR Z_k score	67	75	OR: 2.01 (0.373, 1.37 to 4.67)	NA
Proportion LDA	75	80	OR: 2.05 (0.352, 1.43 to 4.22)	NA
Proportion remission	56	68	OR: 1.83 (0.101, 1.39 to 3.01)	NA

*Means and (SD) or proportions are displayed. We corrected for baseline DAS28.
CQR, Compliance Questionnaire in Rheumatology; LDA, Low disease activity; MPR, medication possession ratio.
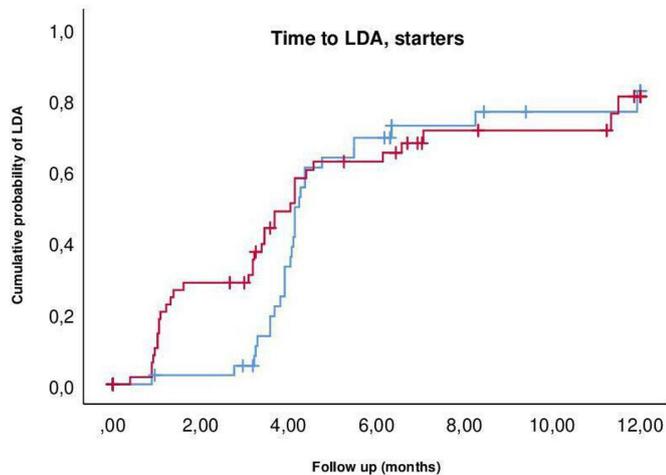
Figure 1 Kaplan-Meier plot of the cumulative probability of achieving at least LDA for biological-naive patients in the intervention (red) and control group (blue). Each step in the curve represents at least LDA, defined as DAS28-ESR <3.2. ⌐ control, ⌐ intervention, + control-censored, + intervention-censored.

bDMARD, number of patients reporting side effects, use of co-medication and mean disease activity after 1 year.

An overview of systematic reviews of adherence in patients with RA underscores that non-adherence is complex and a golden standard is non-existent.[18] Educational or behavioural interventions, of which multicomponent, tailored and motivational strategies, show the best results. In our study, we confirmed the effect of these strategies by EMF.

Our intervention EMF comprises, among others, MIT, a strategy that has been proven to improve adherence.[11] This might have affected adherence most, although this cannot formally be attributed to one particular aspect of EMF.

Adherence in these patients with RA was relatively high, as measured with MPR and MEMS (only intervention group, online supplemental figure S3), compared with other methods and other chronic diseases.[11] This might be partially due to the Hawthorn effect, although that this was not expected in the control group.[16] Furthermore, our high adherence rates correspond with other studies, since we have also corrected for periods of infections and other legitimate reasons for temporarily discontinuation.[3 18]

Although van Heuckelum *et al* in their review suggested a favourable effect of EMF on clinical outcomes in some studies we did not find this. This might be due to selection bias, adequate usual care according to the treat to target paradigm and a too small sample size to detect the limited difference in adherence rates between groups. However, we did see a small effect on time to LDA for bDMARD-naive patients, making this group a target for further research.

EMF increased adherence for patients with RA starting with or switching to a bDMARD. Especially bDMARD-naive patients benefitted most, since they achieved LDA

slightly sooner compared with the control group, which holds promise for the future.

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