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BRIEF REPORT

Determinants of methotrexate adherence in rheumatoid arthritis patients

Ellen De Cuyper[1] · Veronique De Gucht[3] · Stan Maes[3] · Yoleen Van Camp[4] ·
Luc S. De Clerck[1,2]

Abstract In rheumatoid arthritis (RA) patients, weekly intake of methotrexate (MTX) is the basic drug treatment. This observational study aims to investigate how many RA patients are adherent in terms of MTX intake and to identify determinants of non-adherence. Intake of MTX (orally or via injection) was recorded in 129 RA patients with an electronic monitoring system (MEMS®) during 16 weeks. In addition, two adherence questionnaires, the Medication Adherence Report Scale (MARS-5) and the Compliance-Questionnaire-Rheumatology (CQR) as well as a visual analogue scale (VAS) measuring MTX adherence, were administered to these patients. As possible determinants of adherence, data on demographics, disease and treatment characteristics, depression, illness cognitions, motivation, and social support were collected. Of all participants, 58 % were fully adherent and 75 % skipped at most one dose during 16 weeks. A better

mental health status and suffering from comorbidities had a positive effect on adherence, while living alone had a negative effect. These three predictors explained 30 % of the variance in MTX adherence. Of the three self-report medication adherence measures, the VAS correlated the highest with the results of the electronic monitoring system ($r = 0.552$, $p = 0.01$). A relatively high adherence rate was observed in RA patients treated with MTX. The determinants identified by this study could be used to screen patients at risk for non-adherence. A simple VAS scale seems to be an acceptable way for a preliminary screening of MTX adherence.

✉ Ellen De Cuyper
ellen.decuyper79@gmail.com

✉ Luc S. De Clerck
Luc.declerck@uantwerpen.be

1   Department of Immunology-Rheumatology-Allergology, Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem, Belgium

2   Faculty of Medicine and Health Sciences, Department of Immunology-Rheumatology-Allergology, University of Antwerp, Campus Drie Eiken T4.08, Universiteitsplein 1, 2610 Antwerpen, Belgium

3   Institute of Psychology, Medical and Health Psychology, Leiden University, Pieter de la Courtgebouw, room 2A05A, Wassenaarseweg 52, 2333 AK Leiden, The Netherlands

4   Faculty of Medicine and Health Sciences, Center for Research and Innovation in Care (CRIC), University of Antwerp, Campus Drie Eiken S.143, Universiteitsplein 1, 2610 Antwerpen, Belgium

Introduction

Rheumatoid arthritis (RA) is the most prevalent inflammatory rheumatic disease causing joint pain, swelling, and morning stiffness, leading to the destruction of cartilage and bone loss, potentially resulting in important disability [1]. Basic drug treatment consists of disease modifying anti-rheumatic drugs (DMARDs) of which methotrexate (MTX) is the first choice.

To achieve the disease modifying effects, medication adherence is crucial. Assessing adherence and identifying reasons for (non-) adherence is therefore important from a clinical perspective. The way medication adherence is measured may however be responsible for diversity in results [2]. Self-reported adherence mostly results in higher adherence rates than electronic monitoring, which was only used in two studies in RA patients [3, 4].

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This observational study aims to answer the following questions:

– To what extent do RA patients take their MTX as prescribed?
– Which factors indicate an increased risk of non-adherence and can thus be useful for screening purposes?
– Which self-report measure, useable in daily practice, is the most valid, compared to an electronic monitoring system?

Materials and methods

Research field

One hundred forty-six patients who visited the ambulatory rheumatology unit (outpatient/day clinic) of Antwerp University Hospital (Belgium) between September and November 2013 and who met the following inclusion criteria were invited to participate:

• Diagnosed RA according to the ACR/EULAR criteria of 2010 treatment with MTX
• Sufficient knowledge of the Dutch language
• Not suffering from severe mental disorders

Data collection

The study was approved by the ethics committee of Antwerp university hospital (B300201318114). Patients who met the inclusion criteria were asked by their rheumatologists or the rheumatology nurse to participate. An informed consent was obtained from all patients prior to the study.

Assessment of adherence

Adherence was measured using the Medication Event Monitoring System (MEMS®, MWV Healthcare). The intake behavior is quantified by the use of a medication container of which the cap includes a chip that registers the moment of opening [2]. A patient was considered fully adherent if over a period of 1 week the MEMS® container was opened once or more in accordance with the prescription. For each of the 16 consecutive weeks, every patient was given a score of 1 (opened) or 0 (not opened). The average of these 16 measurements, multiplied by 100, resulted in a score of medication adherence.

Adherence was also measured by means of three self-report measures. The CQR [5, 6] consists of 19 statements concerning medication intake in which the patient indicates

to what extent (s) he agrees on a 4-point Likert scale. The multivariate weighed model of De Klerk and colleagues proposes two discriminant formulas to detect intake compliance (≤80 and ≤50 %) [6]. The MARS-5 is an adherence measure developed to use in patients suffering from a variety of chronic diseases [7]. It consists of five statements with regard to aspects of non-adherent behaviors. Patients indicate to what extent each statement applies to them on a 5-point Likert scale (1 = always, 2 = often, 3 = sometimes, 4 = rarely, and 5 = never). By summing up the answers, a score in between 5 and 25 is obtained. A visual analogue scale ranging from "in 0 % of the cases" to "in 100 % of the cases" was used to ask patients to what extent they took the MTX as prescribed. Patients gave a mark on a 10 cm line resulting in a score in between 0 and 100.

Assessment of possible determinants

We included sociodemographic characteristics, condition-related factors, and cognitions as potential determinants of medication adherence based on the evidence resulting from a systematic review [8]. In addition, we added therapy-related factors as there is also evidence for their importance [9]. Next, determinants such as quality of life, depression and anxiety, and patient-related characteristics such as social support and motivation were added based on more recent publications [10, 11].

Socio-demographic characteristics such as age, gender, living situation, and occupational status were collected by means of a structured questionnaire.

Condition-related factors retrieved from the medical file were disease activity of RA assessed by means of the Disease Activity Score 28 (DAS28) (remission status < 2,6) [1], daily functional limitations, and acquired damage to the joints, assessed by the HAQ [12] and comorbidities. To assess somatic symptoms, the validated Patient Health Questionnaire 15 (PHQ-15) was used [13]. The Short Form 36 (SF36), a validated generic instrument that measures quality of life, provided information on the patient's physical and mental health status [14]. Depression was assessed using the nine items of the validated Patient Health Questionnaire 9 (PHQ-9) [15]. Anxiety was measured by means of the anxiety subscale of the validated Dutch version of the Brief Symptom Inventory, consisting of six items [16].

Therapy-related factors measured were disease duration, the dosage of MTX, the mode of patient follow up, the number of doctor visits during the last 6 months, the number of prescribed pills per day, and possible side effects.

Patient-related characteristics: The IPQ-K, the Dutch shortened version of the Illness Perception Questionnaire, was used to measure illness cognitions [17]. Eight statements were scored on a scale from 0 to 10. Social support was measured by means of a questionnaire concerning social support

with the disease in general and more specific in relation to the medication intake [18]. The motivation to take MTX was assessed by means of the Treatment Self-Regulation Questionnaire (TSRQ), adapted to measure the medication adherence. Motivation can be autonomous (internally regulated) or coerced (externally regulated). Eleven items were rated on a 7-point Likert scale (1 = totally disagree and 7 = totally agree). A subscore for autonomous and for coerced motivation was compiled by calculating the average score of the corresponding items. By subtracting the score for coerced regulation from the score for autonomous regulation, a combined score was calculated [19].

Statistical analysis

Differences between categorical data were analyzed using chi-squared analysis, between continuous data with t tests. A logistic regression analysis with as dependent variable being fully adherent or not was carried out by a stepwise input of independent variables that showed a significant relationship of 0.01 or lower with MTX adherence in univariate analyses, until the best statistically significant model was found ($p < 0.05$). Correlations between the different measures of adherence were calculated with Pearson's correlations. The statistical analyses were performed with SPSS 21.0.

Results

Sampling

Figure 1 describes the process of inclusion.

The sample ($n = 129$) consisted for 60 % of women. The average age of the participants was 61 years. They had mean disease duration of 12 years and 65 % was in remission status.
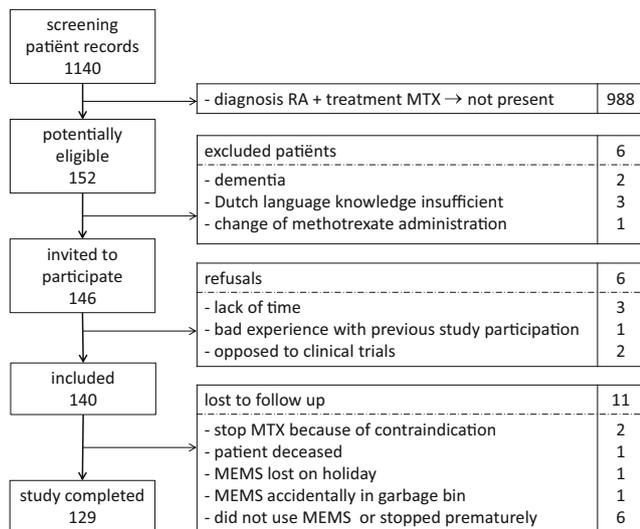

Fig. 1 Inclusion and retention tree

The MTX was taken orally by 64 % of the participants. Of the total sample, 43 % reported side effects of the MTX treatment.

Adherence with regard to methotrexate

Figure 2 gives a description of the number of doses of MTX missed over a period of 16 weeks. More than half of the participants (58 %) took faithfully each week the MTX. A quarter skipped the medication for at least 2 weeks, corresponding to less than 90 % adherence. Only 9 % failed more than three times to take their medication and was thus less than 80 % adherent.

The MARS-5 had an acceptable internal consistency (Cronbach's alpha = 0.71). The mean score was 24.2 (SD = 1.7). The CQR showed a poor internal consistency in this population (Cronbach's alpha = 0.51). Following the discriminant formula of De Klerk and colleagues [6] to detect 80 % taking compliance, 14.3 % of the participants were less than 80 % adherent. The visual analogue scale indicated a mean adherence of 94 % (SD = 10.0).

Factors associated with adherence to MTX

Table 1 reports on the predictors for adherence to MTX. A criterion of 100 % adherence was used to construct the dependent variable.

The following determinants were dichotomized: living situation (living alone, yes/no) and comorbidities (yes/no). Only independent variables that showed a significant univariate relationship with the dependent variable at a 0.01 level were entered in the logistic regression analysis: living alone, suffering from comorbidities, mental health status, and the illness cognitions identity and perceived emotional consequences.
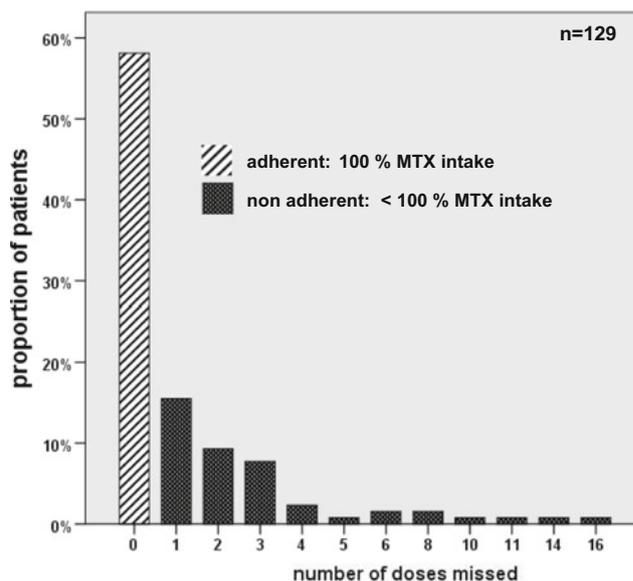

Fig. 2 Medication adherence rate for methotrexate

Table 1 Logistic regression analysis: predictors of adherence

	B	S.E.	Wald	OR	95 % CI
Socio-demographic characteristics					
Living alone	−1.550	0.600	6.668**	0.212	0.065–0.688
Condition related characteristics					
Comorbidities	1.481	0.444	11.149**	4.398	1.844–10.493
Mental health status (SF36)	0.049	0.023	4.623*	1.050	1.004–1.098
Illness cognitions					
Identity	−0.113	0.096	1.386	0.893	0.739–1.078
Emotional consequences	−0.140	0.086	0.025	0.987	0.833–1.168

Being adherent is defined as taking 100 % of the prescribed doses. 0 = non-adherent and 1 = adherent

$*p < 0.05$; $**p < 0.01$

Suffering from comorbidities and a better mental health status had a positive influence on medication adherence. Living alone was negatively associated with adherence to MTX.

The association between electronic monitoring and self-report measures of adherence proved to be different.

The scores on the visual analogue scale for adherence correlated moderately with the results of the electronic adherence monitoring ($r = 0.552$, $p < 0.001$) although the VAS score seems to overestimate adherence (see Fig. 3).

The correlation between the MARS-5 questionnaire and the electronic monitoring system was weaker ($r = 0.356$, $p < 0.001$). As the internal consistency of the CQR was too low, 8 questions out of 19 were deleted (items 4, 5, 8, 9, 11, 12, 16, and 19) resulting in a good consistency (Cronbach's alpha = 0.77). There was however no significant correlation between the results of the electronic monitoring system and the sum score of the remaining items. In addition, no association was found between the discriminant formula of De Klerk

and colleagues [6] to detect 80 % taking compliance and the results of the 80 % adherence level measured with the electronic monitoring system (X^2 (2, N = 104) = 0.09, $p = 0.77$).

Discussion

A large study on MTX adherence showed that only 64 % of the participants took at least 80 % of the prescribed dose [20]. In the present study, 92 % of the patients took at least 80 % of the prescribed dose. In a Dutch study, full adherence for methotrexate was found in a small sample of patients [4]. The high adherence rate in our study may be due to a selection bias: possibly, patients who were less adherent did not want to participate or did not complete the medication registration. This concerns, however, only 17 patients out of 146. The fact that Belgian patients only contribute for a very small part to health care costs may also have played a role [8]. In addition, in the Belgian context, RA patients usually see their specialist every 6 months or even more frequently. This close follow may also have increased the adherence rate. Another issue is that this study collected data in only one health care center. A larger, multicenter study might have resulted in lower adherence rates. In addition, a large number of the participants had long disease duration and most patients were in remission. Finally, extending the MEMS measurement period might also increase the validity of the results.

With respect to predictors of adherence, the negative relationship between living alone and adherence indicates that social support has an impact on medication intake. This is consistent with previous findings [21]. The positive influence of comorbidity on adherence is also in accordance with other studies [22, 23]. Finally, a better mental health status was also associated to medication adherence in at least one other study [11].

Fig. 3 Correlation visual analogue scale and electronic adherence monitoring

Adherence scores based on a visual analogue scale showed a higher correlation with results from electronic monitoring than the data obtained with two other self-report measures.
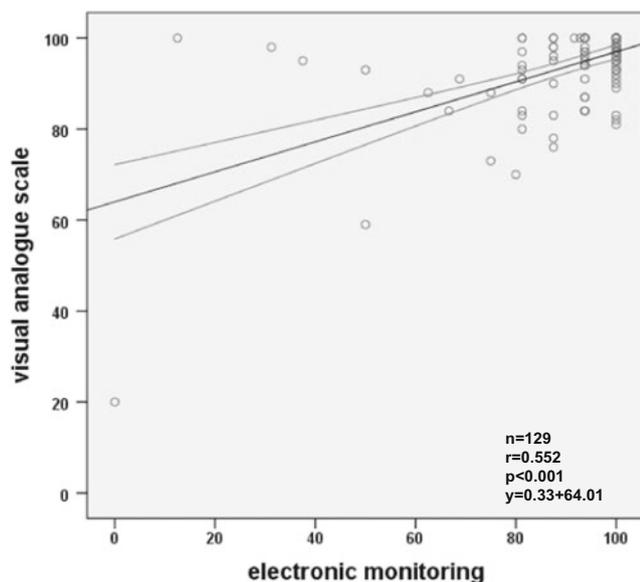
As a consequence, a VAS scale may be used in daily practice for a quick screening of medication adherence in patients. A weaker correlation was found between the MARS-5 and the electronic monitoring which is consistent with the results of an earlier study [2]. Finally, the sum score of the CQR did not show a significant association with the results of the electronic monitoring. The CQR may be more appropriate to identify determinants of treatment adherence.

Compliance with ethical standards

Conflict of interest None of the authors have a financial relationship with MSD nor other relationships or activities that could appear to have influenced the submitted work. The authors have full control of all primary data and agree to allow the journal to review their data if requested.

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