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Determinants of methotrexate adherence in rheumatoid arthritis patients

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Determinants of methotrexate adherence in rheumatoid arthritis

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Abstract**Introduction:**

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.

Methods:

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.

Results:

Of all participants 58% were fully adherent, 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 ($r=.552$, $p=0.01$).

Conclusion:

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.

Keywords

Patient compliance – medication adherence – drug therapy – anti rheumatic agents – methotrexate – rheumatoid arthritis

1 Introduction

Rheumatoid arthritis (RA) is the most prevalent inflammatory rheumatic disease causing joint pain, swelling and morning stiffness, leading to 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 a 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).

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?

2 Materials and methods

2.1 Research Field

146 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

2.2 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 one 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 2 discriminant formulas to detect intake compliance ($\leq 80\%$ and $\leq 50\%$) (6). The MARS-5 is an adherence measure developed to use in patients suffering from a variety of chronic diseases (7). It consists of 5 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, 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.

2.3 Assessment of possible determinants

We included socio-demographic 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 9 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 6 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 medication adherence. Motivation can be autonomous (internally regulated) or coerced (externally regulated). Eleven items were rated on a seven point Likert scale (1 = totally disagree, 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).

2.4 Statistical analysis

Differences between categorical data were analyzed using chi square 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 .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.

3 Results

3.1 Sampling

Figure 1 describes the process of inclusion.

Fig. 1 Inclusion and retention tree

The sample ($n=129$) consisted for 60% of women. The average age of the participants was 61 years. They had a mean disease duration of 12 years and 65% was in remission status. The MTX was taken orally by 64% of the participants. Of the total sample, 43% reported side effects of MTX treatment.

3.2 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 3 times to take their medication and was thus less than 80% adherent.

Fig. 2 Medication adherence rate for methotrexate

The MARS-5 had an acceptable internal consistency (Cronbach alpha = 0,71). The mean score was 24,2 (SD = 1,7). The CQR showed a poor internal consistency in this population (Cronbach alpha = 0,51). Following the discriminant formula of De Klerk and colleagues (6) to detect 80% taking compliance, 14,3% of the participants was less than 80% adherent. The visual analogue scale indicated a mean adherence of 94% (SD = 10,0).

3.3 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.

Table 1: Logistic regression analysis: predictors of adherence

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 .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. 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 figure 3).

Fig. 3 *Correlation visual analogue scale and electronic adherence monitoring*

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, 19) resulting in a good consistency (Cronbach alpha = 0.77). There was however no significant correlation between the results of the electronic monitoring system and the sumscore 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 ($\chi^2 (2, N = 104) = 0.09$, $p = .77$).

4 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 six 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 a 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).

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.

5 **Acknowledgements**

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6 **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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Legends

Table 1: Logistic regression analysis: predictors of adherence

Figure 1: Inclusion and retention tree

Figure 2: Medication adherence rate for methotrexate

Figure 3: Correlation visual analogue scale and electronic adherence monitoring

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Table 1 Logistic regression analysis: predictors of adherence^a

	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

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

*p<.05 ** p<.01

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Abstract

Introduction:

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.

Methods:

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 (CROCQR) 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.

Results:

Of all participants 58% were fully adherent, 75% skipped at most one dose during 16 weeks 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 ($r=.552$, $p=0.01$).

Conclusion:

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.

Keywords

Patient compliance – medication adherence – drug therapy – anti rheumatic agents – methotrexate – rheumatoid arthritis

1 Introduction

Rheumatoid arthritis (RA) is the most prevalent inflammatory rheumatic disease causing joint pain, swelling and morning stiffness, disease leading to 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. DMARDs reduce disease activity and radiological progression resulting in limited long-term functional impairment. MTX is given in a dosage of 7.5 to 30 mg per week and is taken orally or administered by subcutaneous or intramuscular injection. It can be used as monotherapy or in combination with other DMARDs (2).

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. Adherence is the degree to which patients take prescribed medication in accordance with the recommendations by the health care provider \(3\). Suboptimal adherence leads to progression of the disease, impaired quality of life, avoidable health care cost because of complications, additional examinations, consultations and hospitalization and ultimately even to mortality \(4\). These problems grow with an increasing non-adherence to prescribed medication \(5\).](#)

[Failure in RA patients to take their medication as prescribed is considered to be a significant problem in the literature. Adherence percentages vary from 30 to 100 depending on the study \(6\). The way medication adherence is measured may however be responsible for this a diversity in results \(72\). In most studies adherence is measured by means of an interview or a questionnaire. In only two studies electronic monitoring devices were used \(8\), \(9\). Self-reported adherence mostly results in higher adherence rates than electronic monitoring, which was only used in two studies in RA patients \(8\), \(93, 4\). \(3\). In addition, differences in study population may influence adherence rates \(10\).](#)

[Various factors may affect the development and maintenance of medication adherence \(11\). According to the existing literature \(12\) possible determinants of non-adherence are socioeconomic factors \(age, gender, education, social-economic status, living situation\), health care system factors \(patient-provider relationship, lack of reimbursement\), condition-related factors \(disease activity, pain, stiffness, quality of life\), therapy-related factors \(type of medication, drug load, side effects\) and patient-related factors \(patient knowledge, stress, illness and treatment cognitions and beliefs including pros and cons of medication intake and perceived social support\).](#)

[In view of interventions aiming at improving adherence, it is important to identify characteristics of patients who are the least adherent. In order to screen patients from this perspective, knowledge of determinants that can have a detrimental impact on medication adherence is a prerequisite.](#)

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?

2 Materials and methods

2.1 Research Field

[This observational study in RA patients treated with MTX was carried out at the ambulatory rheumatology unit of the Antwerp university hospital, Belgium. Patients of three rheumatologists and a rheumatologist in training were recruited for this study.](#)

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Patient selection

146 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 (13)
- treatment with MTX
- sufficient knowledge of the Dutch language
- not suffering from severe mental disorders

2.2 Data-collection

The study ~~was~~ has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and approved from by the ethics committee of Antwerp university hospital for this study was obtained (B300201318114). The medical records of all scheduled patients were screened on disease and treatment characteristics. Patients who met the inclusion criteria were asked by the their rheumatologists or the rheumatology nurse to participate. An informed consent was obtained from all the study participants after receiving information patients prior to about the study. After signing the informed consent participants were instructed on the use of the electronic medication container. If the patients had questions during the trial, a nurse was reachable by phone.

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 (72). ~~Even though this indirect monitoring system is not a foolproof method to measure the intake behavior, it is currently considered to be the best choice for research on adherence since it provides detailed, accurate and objective data over an extended period of time (7).~~

MTX is taken once a week via tablets or administered via injection. Patients taking the tablets, were asked to fill the container with their own medication. For intramuscular injection, the needles were placed in the container. Whenever patients accidentally opened the MEMS[®] box, they were to note time, date and reason.

After 16 weeks of registering, the MEMS[®] data were downloaded. A web-based application, the medAmigo[®] portal of the MWV Healthcare group was used to download and store data.

A patient was considered fully adherent if over a period of one 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. The MEMS[®] data from patients who participated less than 12 weeks, were not used. Four patients with measurements in between 13 and 16 weeks, received the average of the weeks for which data were available for the missing weeks.

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In addition to the electronic monitoring, adherence was also measured by means of three adherence self-report measures described below. The Compliance Questionnaire Rheumatology (CQR) (14), (15), the Medication Adherence Report Scale (MARS-5) (16) and a visual analogue scale were used.

The CQR (14), (15), (6) is the only self-report adherence measure that was specifically developed for rheumatic diseases. It consists of 19 statements concerning medication intake in which the patient indicates to what extent (s)he agrees on a 4 point Likert scale, (1= don't agree at all, 2= don't agree, 3= agree, 4= agree very much). The multivariate weighed model of De Klerk and colleagues proposes 2 discriminant formulas to detect intake compliance ($\leq 80\%$ and $\leq 50\%$) (6), (5).

The MARS-5 is an adherence measure developed to use in patients suffering from a variety of chronic diseases including asthma, COPD, cardiovascular diseases, diabetes, inflammatory bowel disease, depression and bipolar disorder (7), (7), (17). It The basic questionnaire consists of 5 statements with regard to aspects of non-adherent behaviors, that are generic across treatments. Patients indicate to what extent each statement applies to them on a 5 point Likert scale (1 = always, 2 = often, 3 = sometimes, 4 = rarely, 5 = never). By summing up the answers, a score in between 5 and 25 is obtained. A higher score indicates higher self-reported adherence.

A visual analogue scale ranging from "in 0 % of the cases" to "in 100% of the cases" was used to ask asking patients to what extent they took the MTX exactly as prescribed. Patients gave a mark on a 10 cm line resulting in a score in between 0 and 100. The answer between "in 0 % of the cases" and "in 100% of the cases" was given by a mark along a line of 10 cm. The location of this mark was measured and resulted in a score in between 0 and 100. VAS scales have already been used for assessing adherence in hypertension and HIV (18).

2.3 Assessment of possible determinants

While many factors are thought to be associated with adherence to pharmaceutical treatment for RA patients, a recent systematic review (19) showed that some demographic factors and disease characteristics, general cognitions as well as the belief that medication is necessary, DMARD use prior to the use of anti-TNF, provision of adequate information and satisfactory contact with the health care provider show at least some relationship with adherence to pharmaceutical treatment in RA patients. We included socio-demographic characteristics, condition related factors and cognitions as potential determinants of medication adherence based on the evidence resulting from a systematic review (8), (9). Predictors, which is congruent with this review. In addition, we added therapy related factors as there is also other evidence for their potential importance (9), (20). 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 as they were lacking in the systematic review by Pasma and colleagues, while there is some evidence for a possible association with adherence (10, 11), (21), (22), (23).

Potential determinants of adherence were assessed by means of medical files and questionnaires. 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, ~~affected by present disease activity, and~~ acquired damage to the joints, assessed by the ~~Health Assessment Questionnaire~~ (HAQ) ~~(12)(24)~~ and comorbidities. To assess somatic symptoms, the validated Patient Health Questionnaire 15 (PHQ-15) was used ~~(1325)~~.

~~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 ~~(1426)~~.

Depression was assessed using the 9 items of the validated Patient Health Questionnaire 9 (PHQ-9) ~~(1527)~~.

Anxiety was measured by means of the anxiety subscale of the validated ~~Dutch version of the~~ Brief Symptom Inventory, consisting of 6 items ~~(1628)~~.

Therapy related factors measured were: disease duration, the dosage of MTX, the mode of patient follow up ~~(ambulatory or in the day clinic if intravenous biologic treatment was required)~~, the number of doctor visits during the last 6 months, ~~and~~ the number of prescribed pills per day ~~and~~ ~~In addition,~~ possible side effects ~~were explored by means of an open question.~~

Patient related characteristics ~~measured were illness cognitions, social support and patient motivation. Illness cognitions are the thoughts, beliefs, expectations and ideas that a person has about his or her illness and health. These cognitions determine how someone deals with health problems (11).~~ The IPQ-K, the Dutch shortened version of the Illness Perception Questionnaire was used ~~to measure illness cognitions for this purpose.~~ ~~(1729)~~. 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 ~~(1830)~~.

The motivation to take MTX ~~as prescribed~~ was assessed by means of ~~two sub-scales from~~ the Treatment Self-Regulation Questionnaire (TSRQ), adapted to measure medication adherence. Motivation can be autonomous (internally regulated) or coerced (externally regulated). ~~A person is more autonomously motivated to take medication, when (s)he is personally convinced that taking medication is important. When the medication is rather taken to please the doctor or partner or because one would otherwise be ashamed or feel guilty, the patient is considered to be externally controlled.~~ Eleven items were rated on a seven point Likert scale (1 = totally disagree, 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 ~~(1934)~~.

2.4 Statistical analysis

Differences between categorical data were analyzed using chi square 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 .01 or lower with MTX adherence in univariate analyses, until the best statistically significant model was found ($p < 0.05$). Correlations

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between the different measures of adherence were calculated with Pearson’s correlations. The statistical analyses were performed with SPSS 21.0.

3 Results

3.1 Sampling

Between September and November, 140 patients were enrolled in the study. Figure 1 describes the process of inclusion. Records of 1140 patient were screened. Of these, 152 patients were diagnosed with RA and treated with MTX. Six patients didn’t meet all inclusion criteria. Of the remaining 146 patients who were invited to participate, 140 signed the informed consent, but 11 patients did not participate long enough or lost the MEMS[®] container, resulting in data from 129 patients who could be used for the analyses.

Fig. 1 Inclusion and retention tree

3.2 Patients characteristics

The sample (n=129) consisted for 60% of women. The average age of the participants was 61 years. They had a mean disease duration of 12 years and 65% was in remission status. The MTX was taken orally by 64% of the participants. Of the total sample, 43% reported side effects of MTX treatment. Table 1 describes the study population. The mode of administration of methotrexate may be of importance for patient’s adherence. The groups did not differ in socio-demographic and patient related characteristics. Patients receiving injections had however a poorer disease condition. They also had a higher disease activity, a worse functional and physical health status and a longer disease duration. They also differed in therapy related characteristics since they got a higher dose of MTX. In addition, patients receiving injections think their rheumatic disease will last longer than patients who take MTX tablets.

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Table 1 Description of the study population

n=129

		Administration mode		p
		Oral n=82	Injection n=47	
Socio-demographic characteristics				
Age, years		60.63 ±13.92	61.98 ±13.90	0.598
Female patients (%)		59.8	63.8	0.648
Living situation (%)	living alone	15.9	17.0	0.863
Occupational status (%)	retired	17.1	21.7	0.788
	working	36.6	32.6	
	not working	46.6	45.7	
Condition-related characteristics				
Disease activity (DAS28)		1.94 ±0.85	2.47 ±1.21	0.011
Functional health status (HAQ-DI)		0.58 ±0.61	0.95 ±0.74	0.005
# comorbidities		0.78 ±0.86	0.79 ±0.88	0.966
Physical health status (SF36)		40.70 ±11.13	36.99 ±8.79	0.039
Mental health status (SF36)		51.78 ±11.33	50.97 ±13.40	0.731
Somatic symptoms		19.99 ±4.02	21.10 ±3.86	0.151
Depression		4.78 ±5.03	4.96 ±4.80	0.845
Anxiety		1.38 ±0.53	1.42 ±0.72	0.690
Duration RA (years)		11.00 ±9.19	15.45 ±12.15	0.033
Therapy-related characteristics				
Dosage MTX (mg)		11.89 ±4.23	13.73 ±3.90	0.013
Follow up (%)	ambulatory	68.3	57.4	0.216
	day clinic	31.7	68.3	
# e-visit last 6 months	GP	3.37 ±3.84	4.63 ±5.30	0.123
	specialist	1.76 ±1.71	2.37 ±1.70	0.054
Total number of prescribed pills / day		2.73 ±2.77	3.51 ±3.51	0.556
Side effects of MTX (%)		40.2	45.7	0.552
Patient-related characteristic				
Illness cognitions (0-10)				
Consequences		4.06 ±2.81	4.74 ±2.52	0.170
Timeline		9.01 ±2.64	9.70 ±0.95	0.035
Personal control		5.65 ±3.22	5.62 ±3.11	0.957
Treatment control		8.17 ±2.18	8.07 ±2.15	0.789
Identity		4.41 ±2.70	4.50 ±2.61	0.862
Concern		5.37 ±3.14	6.28 ±3.01	0.110
Illness-comprehensibility		6.71 ±3.10	5.68 ±2.92	0.068
Emotional consequences		3.77 ±3.29	4.36 ±3.27	0.324
Social support (1-27) ^a		18.12 ±6.76	19.55 ±6.14	0.234
Motivation (6-6) ^b		1.56 ±1.50	1.79 ±1.75	0.419
Values are the mean ±SD unless otherwise indicated				
^a Cronbach's α= 0.852 ^b Cronbach's α= 0.823				

Values are the mean ±SD unless otherwise indicated

^a Cronbachs α= 0.853 ^b Cronbachs α= 0.833

3.3.3.2 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 3 times to take their medication and was thus less than 80% adherent.

Fig. 2 Medication adherence rate for methotrexate

With regard to the self-report measures of adherence, the MARS-5 had an acceptable internal consistency in this population (Cronbach alpha = 0,71). The mean score was 24,2 (SD = 1,7). The CQR showed a poor internal consistency in this population (Cronbach alpha = 0,51). Following the discriminant formula of De Klerk and colleagues (615) to detect 80% taking compliance, 14,3% of the participants was less than 80% adherent. The visual analogue scale indicated a mean adherence of 94% (SD = 10,0).

3.4.3.3 Factors associated with adherence to MTX

Table 12 lists reports on the predictors for adherence to MTX. A criterion of 100% adherence was used to construct the dependent variable.

Table 2 Logistic regression analysis: predictors of adherence ^a					
	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

^a Being adherent is defined as taking 100% of the prescribed doses. 0= non-adherent; 1= adherent
*p<.05 ** p<.01

Table 1 Logistic regression analysis: predictors of adherence

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 .01 level were considered to be entered in the logistic regression analysis: living alone, suffering from comorbidities, mental health status, depression and, the illness cognitions identity and perceived emotional consequences. All these variables were entered in the logistic regression analysis with the exception of depression because of high multicollinearity with mental health status (r = 0.75). 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.

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~~The~~ These 3 predictors explained 30% of the variance in adherence (see table 2).

3.5 Association between electronic monitoring and self-report measures of adherence

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 ~~in comparison to the electronic monitoring system~~ (see figure 3).

Fig. 3 Correlation visual analogue scale and electronic adherence monitoring

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 ~~to use this scale for comparison purposes, the internal consistency of the scale was increased by deleting items. After omitting~~ 8 questions out of 19 ~~were deleted~~ (items 4, 5, 8, 9, 11, 12, 16, 19) ~~resulting in~~ a good consistency ~~was reached~~ (Cronbach alpha = 0,77). There was ~~however however~~ no significant correlation between the results of the electronic monitoring system and the sumscore of the remaining items. In addition, no association was found between the discriminant formula of De Klerk and colleagues (~~156~~) to detect 80% taking compliance and the results of the 80% adherence level measured with the electronic monitoring system. (χ^2 (2, N = 104) = 0.09, $p = .77$)

4 Discussion

~~Of all rheumatoid arthritis patients 58% were fully adherent in taking MTX during 16 weeks, registered with electronic monitoring devices. Living alone was negatively associated with adherence while suffering from at least one other active disease, and a better mental health status had a positive influence on medication intake. Of the three self-report medication adherence measures, the VAS correlated the highest with the results of the electronic monitoring system.~~

~~Two studies specifically studied adherence with MTX. In A large one study including 1668 patients, on MTX adherence showed that only 64% of the participants took at least 80% of the prescribed dose (3220). In another American study in 455 patients, this was 81% (33). Adherence was measured by means of pharmacy data which was considered to be similar to electronic measurement (3). In the present study, a much higher adherence was found: 92% of the patients took at least 80% of the prescribed dose. In a Dutch study assessing adherence for different drug regimens in three rheumatic diseases, full adherence for methotrexate was found in a small sample of patients (94). It should be noted that in the present study the definition of adherence was not very strict. A participant who took the medication one or a few days late was still considered to be fully adherent, which is clinically justified. The is high adherence rate in our study may also be due to a selection bias: possibly, patients who were less adherent did not want to participate or did not complete the medication registration. As this concerns however only 17 patients out of 146, there must also be other reasons for the high adherence rate. The fact that Belgian patients in the Belgian social security system patients only contribute for a very small part to health care costs may also have played a role. There is at least some evidence that high contribution of the patients with regard to cost of the treatment is associated to lower adherence (198). In~~

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addition, in the Belgian context, RA patients usually see their specialist every six months or even more frequently. when patients are treated at a day clinic with IV biologicals. In this sample, this was 38% of the participants. This close follow may also have increased the up could also have played a role in the observed adherence rate. Another issue potential reason for the high adherence rates is that this study collected data in only one health care center. A larger, multicenter study with a larger number of patients might have resulted in lower adherence rates. The sample is indeed composed of all RA patients of only one outpatient clinic. In addition, a large number of the participants had a long disease duration and most patients were in remission. This could also explain the difference in adherence with other RA populations. Finally, extending the MEMS measurement period was performed in this study over 16 weeks only. Extending the measurement period might also increase the validity of the results.

Some studies state that about three quarters of patients experience side effects of MTX use (34). In this study, it was only 42%, possibly because an open question was used to assess side effects in this study rather than presenting patients an extensive list of possible side effects which may be more suggestive.

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 (35,21). The positive influence of comorbidity on adherence is also in accordance with other studies (36), (37,22, 23). Suffering from other diseases most probably has as a consequence that treatment becomes more complex, which is known to have a negative influence adherence. Finally a better mental health status was also associated to medication adherence. A similar relationship was also found in at least one other study two other studies (22,11) (38). The possible explanation for this relationship is that experiencing higher levels of distress decreases attention as well as perceived control over the illness, leading to a poorer medication adherence.

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, although overestimating adherence, 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 ($r=0.356$, $p<0.001$). This which is consistent with with the results of an earlier study (27). 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.

ies that compared the MARS-5 with an electronic monitoring system. In a study with patients suffering from diabetes type 2, the correlation between adherence to oral glucose lowering medication assessed with MARS-5 and electronic monitoring was even lower ($r=0.270$) (7). Cohen et al (39) compared the results of a 10 item version of this measure to asses adherence of asthmatic adults with inhaled corticosteroids with the results of electronic monitoring, resulting in a somewhat higher correlation ($r=0.420$).

The internal consistency of the CQR in this population of RA patients treated with MTX was too low to use the full scale (Cronbach alpha=0.51). The authors of the scale found a higher internal consistency in a population of RA, polymyalgia rheumatic and gout patients (Cronbach alpha=0.71) (14). In the report of their validation study in comparison with electronic monitoring no Cronbach alpha was mentioned (15). Salt et al investigated

three medication-adherence scales in patients with RA and found the CQR to have an acceptable internal consistency (Cronbach alpha = 0.77) (17). Yet, this study collected data on all arthritis medication taken, not only on MTX use. After removing 8 items from the scale, an acceptable Cronbach alpha was obtained, but the sum score of the remaining items did not show a significant association with the results of the electronic monitoring. Another problem with this questionnaire in our study was a high number of missing values (35 out of 140). The questionnaire may be more appropriate to identify determinants of treatment adherence rather than the medication-adherence rate.

In summary, using an electronic monitoring system, this study found a high adherence to prescribed MTX in RA patients. Suffering from comorbidities and a better mental health status affect medication adherence positively. Patients living alone are less likely to take their medication correctly. These determinants may help to detect patients at risk in daily practice. Moreover, although overestimating adherence, asking patients by means of a visual analogue scale whether they correctly take their medication, seems not only to be a quick but also a more valid screening device for medication adherence than some more extensive self-report questionnaires.

5 Acknowledgements

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6 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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8 Legends

Table 1: Description of the study population

Table 12: Logistic regression analysis: predictors of adherence

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Figure 1: Inclusion and retention tree

Figure 2: Medication adherence rate for methotrexate

Figure 3: Correlation visual analogue scale and electronic adherence monitoring

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