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ORIGINAL RESEARCH

Urinary methotrexate dosage in rheumatoid arthritis, in patients treated for at least 6 months: a potential marker of adherence

Noémie Théate ,[1,2] Marion Geoffroy,[2] Lukshe Kanagaratnam,[3,4] Claire Gozalo,[5,6] Isabelle Charlot,[2] Lois Bolko,[2] Ambre Hittinger-Roux,[2] Zoubir Djerada,[5,6] Jean-Hugues Salmon[1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Noémie Théate;
ntheate@chu-reims.fr

ABSTRACT

Objectives Non-adherence to rheumatoid arthritis (RA) treatments must be identified. A methotrexate (MTX) urinary dosage (METU) was recently developed. The aim of our study was to assess adherence to MTX in RA using METU in real-life conditions and to compare it with indirect adherence measurement technics.

Methods We performed a cross-sectional study at Reims University Hospital. We included over 18-year-old patients with RA treated by MTX for more than 6 months. Patients were invited to complete demographic, clinical and psychological questionnaires and adherence measurement technics (Compliance Questionnaire of Rheumatology (CQR) and Medication Possession Ratio (MPR)). A urinary sample was collected to measure MTX and information about tolerance was evaluated through Methotrexate Intolerance Severity Score.

Results 84 patients were included, 26 using oral MTX, 58 subcutaneous (SC) MTX. Among them, 73% were female, mean age was 61.5 years, MTX mean dose was 15 mg/week and 61.9% were treated by biological DMARDs (Disease Modifying Antirheumatic Drugs). 77 patients (91.7%) were adherent to treatment according to METU, whereas MPR and CQR reported less adherence (69.5% and 61.9%, respectively). MPR and METU were not significantly different in SC MTX users (p=0.059). Non-adherent patients had a higher number of tender joints and C reactive protein value (p<0.05).

Conclusion This is the first largest study evaluating MTX adherence in patients with RA using a urinary dosage. We identified that indirect adherence measurements did not reflect real-life adherence. It would be appreciable to realise METU, in a new study, in patients with RA with unexplained response to treatment, to consider it before escalating therapeutic strategy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Therapeutic adherence is a crucial concept in patient management, and its measurement is complex. Adherence varies widely in rheumatoid arthritis (RA), ranging from 30% to 99%.

⇒ The urinary methotrexate (MTX) dosage developed in 2020 can measure adherence with very good sensitivity and specificity.

WHAT THIS STUDY ADDS

⇒ This study confirms that measuring adherence is difficult and that adherence varies according to the method used.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Urinary MTX dosage can be used in everyday practice to assess non-adherence in patients with RA.

⇒ A new study should be made using MTX urinary dosage in patients with RA with chronic unexplained high activity, frequent flares or the need to increase treatments.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that leads to significant morbidity in the absence of treatment.[1] Methotrexate (MTX) is the first-line treatment for this disease. It remains an essential tool for subsequent therapeutic line due to its impact on immunogenicity and its synergy with biologics and targeted synthetic DMARDs.[2 3] Moreover, The European Alliance of Associations for Rheumatology (EULAR) has recently defined the concept of 'difficult-to-treat RA', which takes into consideration treatment compliance and adherence before concluding that treatments are ineffective.[4 5] Indeed, therapeutic adherence is a public health concern that manifests across all chronic illnesses.[6] In RA, adherence is estimated at 70%, but in some studies, it can range from 30% to 99%.[7 8] Current therapies are becoming increasingly expensive, sometimes with a higher risk of infections,

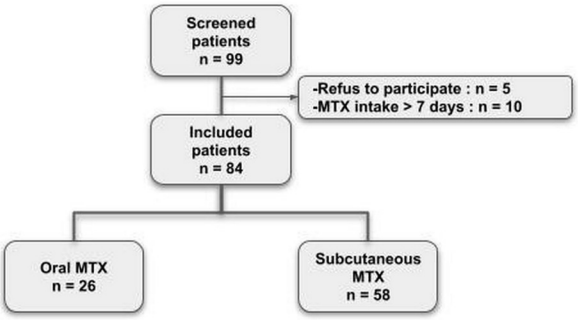

Figure 1 Flowchart. MTX, methotrexate.

and adherence must be assessed before considering therapeutic escalation.[1 4 9–11]

Various methods exist to measure adherence, but there are no strict recommendations on which measures to use, especially as each method has its advantages and disadvantages.[12 13] The optimal assessment method has not been determined.[13] In a recent study, a pharmacokinetic model able to describe expected patterns of urinary MTX was created, called methotrexate urinary dosage (METU).[14] This allowed us to propose a new objective test of MTX adherence, helping in routine practice to differentiate adherent and non-adherent patient, thanks to CI of described concentrations depending on MTX dosage and time post intake. METU can be used in patients with RA for tasks such as blood-level assessment of hydroxychloroquine or azathioprine, which are typically used in systemic lupus erythematosus or Crohn's disease, respectively.[15–18]

The aim of our study was to measure MTX adherence in patients with RA using METU. Additionally, we compared the results between patients treated with oral (PO) and subcutaneous (SC) MTX and compared our adherence measurement method with other validated methods. Finally, we analysed factors associated with non-adherence.

METHODS

Study design and population

We performed a single-centre cross-sectional epidemiological study in the rheumatology department of the University Hospital of Reims between 9 June 2021 and 3 January 2022. All included patients were required to be adults and receiving outpatient or inpatient care for RA meeting the ACR (American College of Rheumatology)/EULAR 2010 criteria. They had to be using MTX for more than 6 months, with or without additional therapies, and had to agree to participate in the study. Pregnant or breastfeeding women, minors and adults under legal protection were excluded.

Data collection

Urinary methotrexate measurement (METU)

A non-sterile urine sample of at least 3 mL was collected from each patient at the time of enrolment. Patients were informed of the aim of the study. There was no lag time between the information about the study and urine collection, as the urine sample was taken directly after the consultation with the referent rheumatologist proposing the study to the patient.

The pharmacology laboratory measured MTX concentrations using chromatography coupled with mass spectrometry. The analysis takes less than half a day. The analysis is now routine in the laboratory and is usually returned to the prescribing doctor within a week.

The presence of urinary MTX is detected with an analytical threshold of 1 nM. Patients were considered adherent if their urinary MTX concentration was within the CI of values observed in the previous study, according to the delay between the intake and the dose of MTX.[14] For example, the tables of distribution of attended urinary MTX values according to the time post intake (from day 0 to 7) for SC MTX doses ranging from 7.5 to 25 mg per week are available in online supplemental material (online supplemental table 1).[14]

METU is reliable, direct and non-invasive. It is not expensive and can stay 24 hours at room temperature before achieving pharmacology laboratory.[19] Sensitivity and specificity were 100% from days 1 to 6 and over 93% on day 7 for SC administration.[14] Sensitivity and specificity after day 7 were evaluated in silico using a validated model, as MTX is administered only once a week.

To explore the ability of the METU kinetic profile to identify compliance, we compared the profiles of adherent patients, with repeated doses (online supplemental sub-figures of S1A, S1B, S1C, S1D on the right), with non-adherent patients who had missed one, two, three or four doses (the patient was supposed to take his dose every week). For each dose, we compared the METU values between the two groups of patients and identified the days on which the concentration ratio (R_METU=(METU) of adherent/(METU) of non-adherent) was lowest, as evidence of loss of discriminatory ability between the two groups of patients.

For all doses and days (from 10 days to 28 days post administration), the most critical days were 11, 12, 13 and 14 (online supplemental figures S2A–S8A). The ratios on the other days were very high (>>>5), enabling us to identify adherent and non-adherent patients with sufficient sensitivity and specificity (online supplemental figures S2A–S8A).

For these critical days, using ROC (Receiver Operating Characteristic) curves, we analysed the discriminatory abilities of METU. For all doses and critical days,[11–14] the AUCs (Area Under the Curve) of the ROC curves were greater than 90%. Sensitivity and specificity were above 80%. As indicated by the ratios (>>>5), the AUC of the ROC curve, sensitivities and specificities for other days are all greater than 90%, whatever the dose (online supplemental figures S2–S8).

Conventional adherence measurement methods

The Compliance Questionnaire of Rheumatology (CQR) is a validated self-administered questionnaire for patients

Table 1 Characteristics of the population at inclusion (n=84)

Characteristics	Values
Age (years)	61.5 (49.5:71)
Female sex	62 (73.8)
Ethnicity	
Caucasian	81 (96.4)
African	1 (1.2)
Maghrebian	2 (2.4)
BMI (kg/m^2)	26.1 (22.7:30.1)
Number of treatments per day	3 (1:5)
Number of tablets per day	3 (1:5)
Comorbidities (Charlson Score)	3 (2:5)
Immunopositivity (CCP and/or RF)	63 (75)
Disease duration (months)	130.5 (41:202.5)
Duration of MTX treatment (months)	94.5 (27:164)
MTX dose (mg/week)	15 (11.2:20)
MTX administration mode	
PO	26 (30.9)
SC	58 (69.1)
Biologic therapy at inclusion	52 (61.9)
Usual follow-up	
Outpatient consultation	51 (60.7)
Day hospitalisation	33 (39.3)
RA activity at inclusion	
Remission	47 (55.9)
Low	10 (11.9)
Moderate	22 (26.2)
High	5 (5.9)
DAS28-CRP at inclusion	2.38 (1.75:3.72)
CRP (mg/L)	4 (1:8.4)
Albumin (g/L)*	41.1 (39.3:44)
MCV (fL)	94 (91:96)

Qualitative variables are expressed as frequency (%), and quantitative variables are expressed as median (Q1:Q3). RA activity was determined based on the DAS-CRP value at inclusion.
*10 missing data.
BMI, body mass index; CCP, Cyclic Citrullinated Peptides; CRP, C reactive protein; DAS28, Disease Activity Score-28; MCV, mean corpuscular volume; MTX, methotrexate; PO, oral; RA, rheumatoid arthritis; RF, Rheumatoid Factor; SC, subcutaneous.

with inflammatory rheumatic diseases, consisting of 19 questions.[20] Scores ranged from 0 to 100, with scores above 80/100 indicating good adherence.

The Medication Possession Ratio (MPR) represents the medication possession rate. An MPR greater than 80% is considered good adherence in the literature.[21] We obtained the amount of MTX dispensed by the patient's regular pharmacy over a retrospective 6-month period starting from the date of inclusion, 6-month being the usual time between two consultations.

Data related to adherence

Clinical and demographic data collected included gender, age, weight, height, body mass index, ethnicity, educational level, socioprofessional category, marital status, disease duration, duration of MTX treatment, dose, and the administration method, associated therapy, use of external assistance for medication administration or injection, and the number of treatments and tablets prescribe to the patient.

Comorbidities were assessed using the Charlson Comorbidity Index predicting 1-year and 10-year mortality.[22] Regarding the disease, we collected the number of swollen and/or tender joints, the visual analogue scale for disease activity and the immunopositivity of RA (CCP -Cyclic Citrullinated Peptides- and/or RF -Rheumatoid Factor-). On the biological side, we gathered data on creatinine, albumin, C reactive protein (CRP), mean corpuscular volume and eGFR (Estimated Glomerular Filtration Rate) levels. Using this information, we determined RA activity at enrolment using Disease Activity Score-28 (DAS28)-CRP.

Patient beliefs about medications and their illness were assessed using the Belief about Medicines Questionnaire (BMQ).[23 24] MTX tolerance was evaluated using the Methotrexate Intolerance Severity Score (MISS), where a score≥6 indicates intolerance to the treatment.[25]

Statistical analysis

Quantitative variables were presented as medians with IQRs, while qualitative variables were presented as frequencies and percentages. The primary objective of the study was analysed based on the percentage of adherent patients and its 95% CI (using binomial distribution). The agreement between different adherence measurement tools was assessed using the kappa coefficient. A McNemar test was conducted to compare the percentage of adherence between different tools. For the comparison of patients treated with PO or SC MTX, univariate analysis was performed using the χ^2 test or Fisher's exact test according to their validity condition. Concerning factors associated with non-adherence, univariate analysis using the χ^2 test, Fisher's exact test, Student's t-test or Mann-Whitney test were conducted. P values less than 0.05 were considered significant. CIs were calculated at 95%. Statistical analysis was performed using SAS software V.9.4, R software V.4.1.2 (The R Foundation for Statistical Computing, http://www.r-project.org) and a non-linear mixed effects modelling approach within the Monolix software (V.2021R1; Lixoft, Antony, France, http://lixoft.com/).

Legal aspects and data handling

All patients received PO information from their referring rheumatologist about the study's purpose and procedures. Written information was provided along with a

Table 2 Comparison of different adherence measurement methods

Adherence measurement method	PO+SC (n=84)			SC (n=58)			PO (n=26)		
	Effective	Percentage (CI)	P value	Effective	Percentage (CI)	P value	Effective	Percentage (CI)	P value
METU	77	91.7 (83.6 to 96.6)	Reference	53	91.4 (81.0 to 97.1)	Reference	24	92.3 (74.9 to 99.1)	Reference
MPR*	57	69.5 (58.4 to 79.2l)	<0.05	45	77.6 (64.7 to 87.5)	0.059	12	50 (29.1 to 70.9)	<0.05
CQR	52	61.9 (50.7 to 72.3)	<0.05	37	63.8 (50.1 to 76.0)	<0.05	15	57.7 (36.9 to 76.6)	<0.05

*Two missing data (one pharmacy refusal and one patient refusal).
CQR, Compliance Questionnaire-Rheumatology; METU, methotrexate urinary dosage; MPR, medication possession ratio; PO, oral; SC, subcutaneous.

non-opposition form. For each patient included in the study, a unique identifier was assigned, and collected data were anonymised. All data were recorded in an observation notebook and transcribed into electronic format for interpretation and analysis.

RESULTS

Population

The study was proposed to 99 patients. Five refused to participate. 10 reported having taken their MTX treatment more than 7 days ago. Descriptive analyses were conducted on a total of 84 patients, with 26 in the PO group and 58 in the SC group (figure 1). The characteristics of the 84 patients at baseline are detailed in table 1.

The study population consisted of patients with a median age of 61.5 years, with 73.8% being female (n=62). Most patients had immunopositive RA, with 55.9% of patients in remission according to the DAS28-CRP at baseline. The median dose of MTX used was 15 mg/week (IQR: 11.2–20), most commonly in combination with a biologic therapy.

Adherence according to METU

According to METU, 91.7% (CI: 83.6% to 96.6%) of patients were defined as adherent. There was no statistically significant difference between patients treated orally (PO) or subcutaneously (SC), with 92.3% of adherent patients in the PO population (CI: 74.9 to 99.1; p=1) and 91.4% in the SC population (CI: 81.0 to 97.1; p=1) (table 2).

Comparison of different adherence measurement methods

Subsequently, we compared various adherence measurement methods (table 2). There was no statistically significant difference between the use of METU or MPR to quantify adherence in patients treated with SC MTX (p=0.059).

Factors associated with non-adherence

We then compared adherent and non-adherent patients according to METU (table 3). Non-adherent patients had a higher number of swollen joints and higher CRP levels at baseline (p=0.011 and p=0.048, respectively). They also had a higher number of flares within 6 months prior to the study and a higher DAS28-CRP 6 months prior to inclusion. The BMQ-Concerns Score tended to be higher in non-adherent patients (p=0.068). There were no statistically significant differences in terms of gender, age, follow-up location or disease duration. The median MISS was 0 (0–1), with the most common side effects being nausea and fatigue.

DISCUSSION

According to METU method, adherence rate was 91.7%. METU was not correlated with the indirect measurement methods studied (CQR and MPR). Factors associated with non-adherence were more swollen joints and a higher CRP value at inclusion in non-adherent patients.

This is the first study to evaluate METU in current practice. METU is an innovative, simple, direct and non-invasive technique.[14] This technique can be developed in all healthcare establishments and for several diseases. The practitioner can have confidence in the results before discussing adhesion with their patients.

Studies evaluating adherence in patients with RA are common and the percentage of adherent patients varies widely, depending on the assessment method.[8] The lack of gold standard for adherence measurement concerning MTX makes the comparison difficult. Our adherence rate is similar to 95% (n=138) found in the only study using direct measurement in current practice (by plasma assay).[26] However, blood sampling appears to be more invasive, technical and time-consuming than urinalysis. Conversely, our rate is higher than those in the literature using indirect methods.[27 28] This difference may be explained by the evaluation method and the safety profile of MTX. Indeed, only 9.5% of patients were intolerant, compared with 30 to 40% in most studies.[29 30] Therefore, the conclusions of our study cannot stand for all patients with RA and a new adherence study using METU 3–6 months after starting MTX should be made.

In line with the literature, these different methods were not correlated with each other.[8] This can be related to

Table 3 Comparison of adherent and non-adherent patients according to METU

Factors related to adherence	Adherent (n=77)		Non-adherent (n=7)		P value
	N (%)	Median (Q1:Q3)	N (%)	Median (Q1:Q3)	
Age (years)		61 (49:70)		72 (54:76)	0.384
Female sex	56 (72.7)		6 (85.7)		0.670
Education level	0.313				
Primary	11 (14.3)		2 (28.6)		
Secondary	38 (49.3)		4 (57.1)		
Higher education	28 (36.4)		1 (14.3)		
Usual follow-up	0.425				
Outpatient consultation	48 (62.3)		3 (42.9)		
Day hospitalisation	29 (37.7)		4 (57.1)		
BMI (kg/m^2)		26.2 (22.9:30.8)		23.2 (18.0:27.7)	0.072
Number of treatments per day		3 (1:5)		4 (1:12)	0.500
Number of tablets per day		3 (1:5)		2 (2:16)	0.609
Pill organiser use	31 (40.3)		4 (57.1)		0.443
Comorbidities (Charlson)		3 (2:5)		4 (3:6)	0.172
Disease duration (months)		135 (39:204)		105 (72:186)	0.859
Duration of MTX treatment (months)		95 (27:165)		86 (9:104)	0.524
MTX dose (mg/week)		15 (12,5:20)		15 (10:20)	0.675
External assistance for treatments	0.099				
None	60 (77.9)		3 (42.9)		
Family support	8 (10.4)		2 (28.6)		
Nurse or pharmacy	9 (11.7)		2 (28.6)		
Biologic therapy at inclusion	47 (55.9)		5 (71.4)		0.704
Number of flares within 6 months		0 (0:2)		2 (0:6)	0.36
DAS28-CRP 6 months prior to inclusion*		2.53 (1.83:3.48)		4.93 (2.67:6.27)	0.04
DAS28-CRP at inclusion		2.32 (1.75:3.31)		3.99 (2.08:5.51)	0.126
Tender joint count		0 (0:2)		3 (0:9)	0.274
Swollen joint count		0 (0:2)		3 (2:6)	< 0,05
CRP (mg/L)		4.0 (1.0:8.0)		8.6 (4.9:11.9)	< 0,05
Albumin (g/L)		41.0 (39.1:44.0)		41.3 (39.7:42.0)	0.544
MCV (fl)		94.0 (91.0:96.0)		95.5 (90.2:96.2)	0.846
Tolerance (MISS)		0 (0:1)		0 (0:0)	0.448
BMQ					
BMQ-Necessity		18 (17:20)		19 (17:22)	0.330
BMQ-Concerns		17 (15:20)		21 (19:22)	0.068
BMQ-General		18 (14:22)		21 (19:24)	0.144

Qualitative variables are expressed as frequency (%), and quantitative variables are expressed as median (Q1:Q3).
*Available data for 6/7 non-adherents patients and 76/77 adherents patients.
BMI, body mass index; BMQ, Beliefs about Medicine Questionnaire; CRP, C reactive protein; DAS28, Disease Activity Score-28; MCV, mean corpuscular volume; METU, methotrexate urinary dosage; MISS, methotrexate intolerance score system; MTX, methotrexate.

several points. First, the temporality of the measurement methods is different. METU has a 7-day setback, which is equivalent to one dose, while CQR and MPR evaluate adherence over months. METU reflects short-term adhesion, does not consider the dynamic process of adhesion, which varies over time. Second, MPR, CQR and METU have different limitations. MTX adherence may be overestimated by METU due to a white coat effect.[31] MPR can overestimate adherence, and it does not reflect treatment intake but delivery. It is time-consuming, making it difficult to use in common practice.[12] Most studies use self-administered questionnaires as CQR.[20 32]

However, a recent systematic review of the literature concluded that, to date, there is no simple, reliable and valid questionnaire for assessing medication adherence.[33] Some argue that Medication Event Monitoring Systems are gold standards, but because of the bias due to the patient knowing he is monitored, the possible tampering of data, and its cost, it cannot be used in clinical practice.[20]

The limitations of the study include the monocentric recruitment in a tertiary centre, where adherence is reputed to be higher due to frequent intervention in therapeutic education.[34] Moreover, the low number of non-adherent patients resulting in a lack of power to study the factors associated with non-adherence.

More swollen joints and a higher CRP value at inclusion were associated with non-adherence. Factors associated with non-adherence to treatment are largely evaluated in the current literature, but studies are discordant.[34] In our study, there was also a trend toward higher BMQ-Concerns in non-adherent patients, consistent with other studies.[35 36] In contrast to previous study, age, sex, duration and dose of MTX were not associated with non-adherence.[37 38] The need of an external aid for medication preparation or injection's realisation was not associated with adherence. These data have not been studied in previous studies.

In summary, there is no gold standard for measuring compliance, and it is important to have a direct method. METU has a real potential for finding non-adherent patients. However, monitoring MTX adherence in all patients with RA treated by MTX might be bothering for patients, and more costly than useful. Therefore, METU might be restricted to patients with a chronic unexplained high activity of RA or frequent flares, or the need to increase treatments. It would be appreciable to monitor MTX adherence in a better selected population. In addition, future research can focus on other diseases using MTX or level of urinary concentration to assess efficacity.

Author affiliations
[1]Rhumatologie, Université de Reims Champagne-Ardenne, Reims, France
[2]Rhumatologie, Centre Hospitalier Universitaire de Reims, Reims, France
[3]UR 3797 VieFra, Université de Reims Champagne-Ardenne, Reims, France
[4]Unité d'Aide Méthodologique, Centre Hospitalier Universitaire de Reims, Reims, France
[5]UR 3801 PPF, Université de Reims Champagne-Ardenne, Reims, France
[6]Pharmacologie-Toxicologie, Pôle de Biologie Territoriale, Centre Hospitalier Universitaire de Reims, Reims, France

Contributors NT, MG, LK, ZD and JHS contributed to the conception and design of the study. MG, IC, LB, AH-R and JHS furnished patients. NT collected the samples. CG and ZD contributed to the analysis of the samples. LK contributed to the analysis. NT, MG, JHS, AH-R and LB revised it critically for important intellectual content. NT is responsible for the overall content as guarantor.

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ORCID iD
Noémie Théate http://orcid.org/0009-0003-6674-3536

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