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A survey on the medication adherence to methotrexate among rheumatoid arthritis patients treated with self-administered biologic drugs

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ABSTRACT

Objective. *Methotrexate (MTX) is the most widely used co-therapy among rheumatoid arthritis (RA) patients using biological disease-modifying anti-rheumatic drugs (bDMARDs). However, adherence to MTX treatment remains a concern with estimates of adherence ranging from 59 to 63%. The objective of this study was to assess the self-reported use and adherence to MTX among RA patients treated with self-administered bDMARDs.*

Methods. *An electronic questionnaire survey was conducted in 68 community pharmacies in Finland. To be included in the present study patients had to be at least 18 years old, be currently using a self-administered bDMARD and be diagnosed with RA. The results are presented as medians with their respective interquartile ranges (IQR) or percentages.*

Results. *Of the 158 pharmacy customers asked to participate, 135 (85%) consented to complete the questionnaire. The included respondents were predominantly female (72%) with a median age of 55 (IQR 44–65) and rheumatic activity of 3 out of 10 (IQR 2–6.5).*

The majority (91%) of the included respondents were using TNF-inhibitors and 27% of all patients were on biologic monotherapy. MTX was currently used by 45% of the respondents while 50% were past users. Of the current MTX users, 6.8% identified themselves moderately non-adherent to the treatment. MTX-related adverse events were important factors associated with non-adherence and discontinuation of the treatment.

Conclusion. *Only 45% of the respondents were currently using MTX co-therapy, but the ones who did were adherent to their treatment. Self-reported adherence may however be subject to social desirability bias and recall bias.*

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease, which is treated with anti-inflammatory and immunosuppressive medication with the aim of clinical remission (1). European guidelines suggest starting disease-modifying anti-rheumatic drug (DMARD) therapy using a synthetic DMARD (sDMARD) strategy in combination with glucocorticoids, followed by the addition of a biological DMARD (bDMARD) or another sDMARD strategy if the treatment target is not reached within 6 months (or improvement not seen at 3 months) (2). In Finland, current treatment guidelines suggest that early RA should be treated with a combination of MTX, hydroxychloroquine (HCQ), sulfasalazine (SSZ) and prednisolone to reach fast and persistent remission (1). Biologic treatment should be initiated only if remission is not reached with sDMARD combination therapy.

Combination of tumour necrosis factor (TNF)-inhibitors and MTX has been shown to be superior in efficacy in comparison to monotherapy of either, however MTX has often to be discontinued owing to intolerability (3, 4). Between 2011–2012, 21% of Finnish RA patients treated within specialised healthcare used bDMARDs of which, 60% were self-administered subcutaneous injections reimbursed by the Social Insurance Institution (5). Of the patients using the self-administered TNF-inhibitors, 59% were concomitantly using MTX while 17% were reported to be on biologic monotherapy.

Medication adherence in chronic diseases is low as estimated 50% of patients are non-adherent to their treatment (6). Among patients with RA, previous studies have yielded results on medication adherence ranging from 30% to 80%, signifying that low adherence remains a serious concern (6, 7). In a study using electronic device counting the every opening of the drug bottle, 63% of the MTX doses were taken as prescribed (7). Similarly, Grijalva *et al*. arrived at a medication possession ratio (MPR) of 59% using information on pharmacy claims (8). Medication adherence to sDMARDs has not been shown to be influenced by simultaneous use of bDMARDs (7). Adherence to anti-rheumatic medication is essential as poor adherence can lead to elevated disease activity (9).

The objective of this study was to assess the self-reported use and adher-

ence of MTX and other sDMARDs among RA patients using bDMARDs. Also, we sought to identify the most prevalent reasons for poor adherence.

Methods

The cross-sectional survey data was collected in 2014–2015 in 68 community pharmacies distributed around Finland. To be included, the pharmacy customer had to be at least 18 years old, be currently using a self-administered bDMARD (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab or tocilizumab) and be diagnosed with RA. Eligible participants were asked to fill in a self-administered electronic questionnaire, which comprised questions on patients' background information, co-medication, medication history, adherence to MTX as well as factors related to poor adherence to or the discontinuation of MTX among current and former MTX users, respectively.

The study was approved by the Ethics Committee of the South Karelia Social and Health Care District (Dnro 283/13.01.02/2014). All potential participants were provided with detailed written information about the survey. Completing the questionnaire was considered as consent to participate. The results are presented as either medians with their respective interquartile ranges (IQR) or percentages. Mann-Whitney U-test and Pearson's chi-squared test were employed to test for differences in variable distributions between two groups. Missing data was imputed using multiple imputation. The data were analysed using R software v. 3.1.1 (R Foundation for statistical computing, Vienna, Austria).

Results

Of the 158 eligible pharmacy customers asked to participate, 135 completed the survey. The included patients were predominantly female (72%) with a median age of 54 (IQR 44–65) and rheumatic activity of 3.0 on a scale of 0 to 10 (IQR 2.0–6.5). Additional information on patient characteristics is presented in Table I. The fraction of missing data varied from 0 to 15% across the variables in the dataset.

Majority (91%) of the included patients were using TNF-inhibitors as abatacept and tocilizumab were used by 6.7% and 2.2%, respectively. MTX, HCQ and SSZ were the most commonly used sDMARDs with percentages of 45%, 27% and 21%, respectively. Additional information on medication use is presented in Table II.

Twenty-seven per cent of the RA patients were currently on biologic monotherapy. The patients on biologic monotherapy had started their first biologic therapy earlier as compared to those using concomitant sDMARDs (6.5 *vs*. 4.0 years, p=0.03).

In addition to the patients currently using MTX, another 50% identified themselves as former MTX users. Six patients of out 135 claimed they had never been prescribed MTX while no one admitted having declined to commence MTX treatment against their doctor's orders. Of the former MTX users, 12% reported having made the decision to discontinue the drug themselves without their doctor's consent while another 35% had made so after consulting their doctor. In the majority of cases, however, the decision to discontinue the treatment had been made by the doctor.

Of the patients currently using MTX, only 6.8% identified themselves moderately non-adherent to the treatment while another 5.1% and 22% reported seldom or very seldom ignoring to take the their medication, respectively (Fig. 1). The results were similar for the past users of MTX.

While 67% of the concurrent MTX users reported undergoing a surgical operation as a reason for temporary non-adherence, only 10% of the past users mentioned it as a reason for treatment discontinuation. Either experiencing an adverse event or being worried about adverse events were important factors affecting the medication adherence or leading to treatment discontinuation among current and past MTX users, respectively.

The majority of the patients ever exposed to MTX had received information regarding the drug treatment from their doctor (90%), nurse (77%) or pharmacist (60%).

Table I. Patient characteristics.

Variable	Median (IQR) / n (%)
Age*	55 (44–65)
Women	97 (72%)
Time from diagnosis*	15 (9.0–25)
Rheumatic activity**	3.0 (2.0–6.5)
Time from first biologic treatment onset*	4.0 (2.0–8.0)
Education	
Primary (0–9 years)	26 (19%)
Secondary (10–12 years)	50 (36%)
Higher (>12 Years)	59 (45%)

*years, **scale of 0–10.

Table II. Current and previous medication use.

Variable	Median (IQR) / n (%)
Methotrexate	61 (45%)
Hydroxychloroquine	36 (27%)
Sulfasalazine	29 (21%)
Leflunomide	22 (16%)
IMGold	3 (2.2%)
Cyclosporine	4 (3.0%)
No sDMARDs	36 (27%)
Etanercept	60 (44%)
Adalimumab	24 (18%)
Golimumab	20 (15%)
CertolizumabPegol	17 (13%)
Abatacept	9 (6.7%)
Tocilizumab	3 (2.2%)
Number of sDMARDs	1.0 (0–2.0)
Number Of Other Medications	3.0 (1.5–4.5)
Previous sDMARDs	121 (90%)
Previous Biologics	64 (47%)

sDMARD: synthetic disease-modifying antirheumatic drug.

Discussion

Current treatment guidelines emphasize the importance of MTX as co-therapy during the use of bDMARDs (2). Also, the dose of MTX should be sufficiently high (10). However, monotherapy with tocilizumab seems to be more effective in comparison to monotherapy with TNF-inhibitors, which is important in case co-therapy with MTX or other sDMARDs is not possible (11, 12). Recent observational studies found that 17-34% of MTX users discontinued the treatment, which was due to adverse events in 23-78% of the cases (4, 13). Similarly, 77% previous MTX users in our survey reported having experienced an MTX-related adverse event. The fraction of

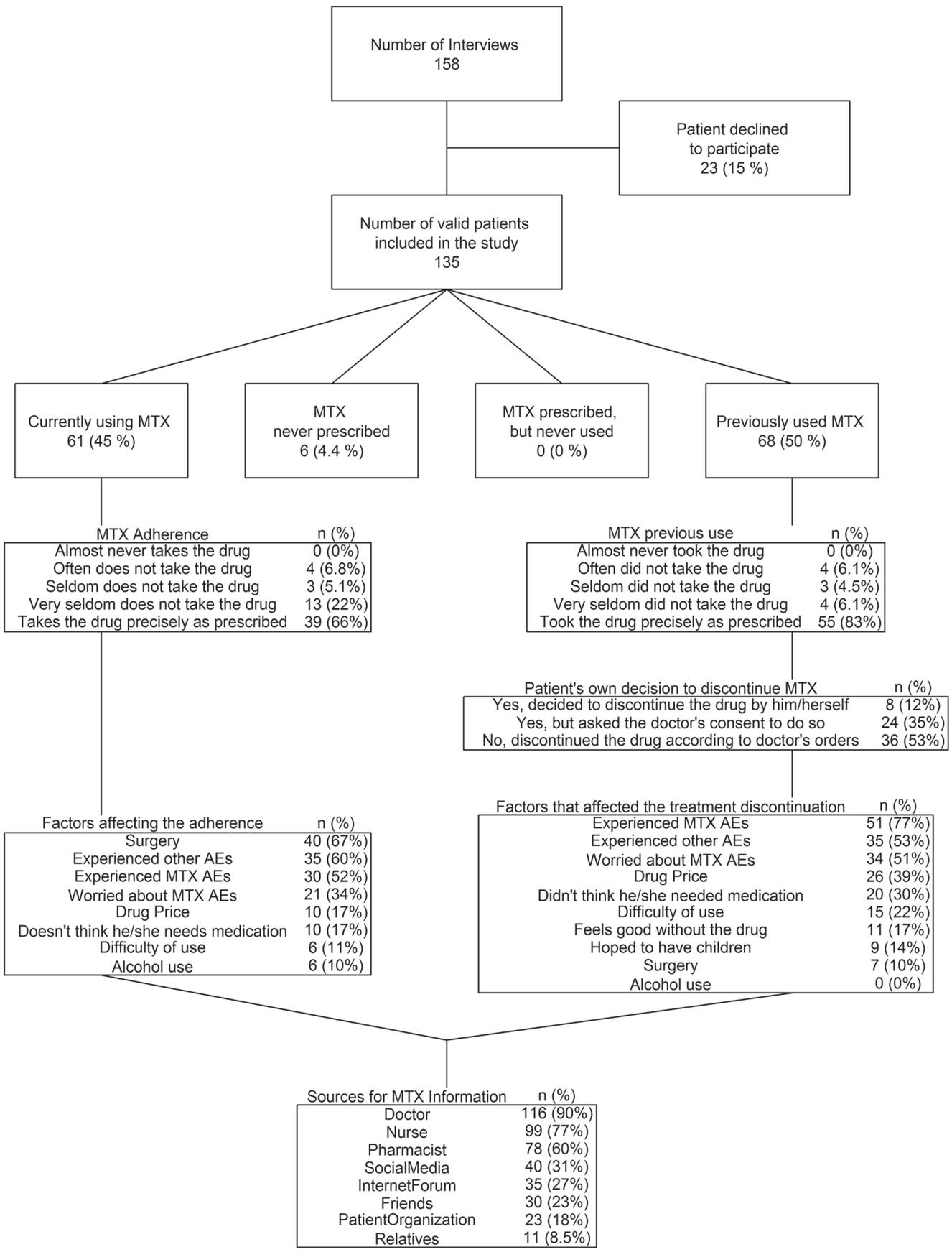

Fig. 1. Flowchart on patient selection, adherence and sources for medical information (MTX: Methotrexate; AE: Adverse events).

patients on self-reported bDMARD monotherapy (27%) in our study was higher than the figures based on a previous cross-sectional study using physician-reported data where 17% of the patients were reported by the treating physician to be on monotherapy (5). More accurate fraction of monotherapy patients would be available from the prescription claims data base. Only one patient on biologic monotherapy was using tocilizumab, reflecting the brief time it has been available as self-injectable injections. Patients on biologic monotherapy have started their biologic medication earlier compared to concomitant sDMARD users despite the time from diagnosis was similar between the groups.

In a survey by van den Bemt *et al*., 99% of the patients identified themselves as adherent based on a structured interview conducted by a pharmacist while the results from the same patients obtained using Compliance Questionnaire on Rheumatology (CQR) and Medication Adherence Report Scale (MARS) instruments showed adherence ratings of 67% and 60%, respectively (14). The latter figures are close to the results obtained from studies using pharmacy claims or pill bottle counters as a data source (7, 8). In the light of these previous findings, it is plausible that the self-reported results of our study may be overestimating the true medication adherence of the patients using MTX. In addition, the non-adherent patients seldom visit pharmacies.

Self-reported adherence may be a subject to social desirability bias, which means that the survey respondents are inclined to give answers, which they believe are viewed favourably by the researchers. Additionally, recall bias may be affecting the results as the survey featured questions regarding the participants' past. Also, the questions employed in our survey could not be used to quantify the exact degree of adherence. The small number of study respondents precludes any analysis of factors associated with drug adherence. Finally, the cross-sectional design means that no causal conclusions can be made based on our study.

Despite the seemingly excellent medication adherence, considerations should be given to how to deal with non-adherent patients. Previous research has concluded that simply making the rheumatologist aware of the patients' non-adherence does not improve adherence (15). Additional research is needed to find better ways to both identify the non-adherent patients and to address the causes behind it.

In our study aimed to assess the self-reported use and adherence to MTX among RA patients treated with self-administered bDMARDs, we found that only 45% of survey participants were currently using concomitant MTX and biologic monotherapy may be more common than previously thought, especially among patients with prolonged biologic treatment. The self-reported medication adherence to MTX among current MTX-users was found to be good. Experiencing an MTX-related adverse event or being worried about them does have an effect on most patients' medication adherence.

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