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Compliance with methotrexate treatment in patients with rheumatoid arthritis: Influence of patients' beliefs about the medicine. A prospective cohort study

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ABSTRACT

Objective: To investigate how compliance during the first year of methotrexate (MTX) treatment in rheumatoid arthritis (RA) is influenced by the patients' perception of the necessity for and concern about MTX, the patients' functional disability, and the dose of MTX.

Methods: A total of 126 RA patients, completed a questionnaire at MTX treatment start and after 9 months. The MTX compliance was measured by using the Compliance Questionnaire Rheumatology (CQR). The prevalence of having a CQR score in the bottom quartile was stratified according to age, gender, the duration of RA, MTX dose, years of school education, functional disability, use of folic acid, and co-morbidity. Crude and adjusted prevalence ratios (PR) with 95% confidence intervals (CI) were calculated by using log-binomial regression. The necessity and concern scales of the Beliefs about Medication Questionnaire (BMQ) were dichotomised into high perception of MTX necessity and low concern about MTX treatment, and the crude and adjusted PR of having a CQR score in the bottom quartile were estimated.

Results: The prevalence of having a CQR in the bottom quartile was 23%, both at baseline and after 9 months, and this finding was not associated with the MTX dose level or the patients' functional disability. Among patients with a CQR in the bottom quartile, the prevalence of having low perceptions of MTX necessity was 37.1% vs. 14.0% for patients with high perceptions of necessity (adjusted PR: 0.3 (95% CI: 0.2-0.8)). The same tendency was seen after 9 months. The prevalence of having a CQR in the bottom quartile or not was almost equally distributed among patients who had high or low concerns about treatment at baseline. After 9 months, however, the prevalence of having a CQR in the bottom quartile was 18.9% for patients who had low concerns about the MTX treatment, vs. 37.7% for patients who had higher concerns about the treatment (adjusted PR: 0.5 (95% CI: 0.2-1.3)).

Conclusion: During the first year of treatment, compliance with MTX treatment among RA patients could be explained by strong perceptions of a personal need for the treatment. Compliance did not seem to be influenced by the patients' functional impairment or the MTX dose level.

INTRODUCTION

Methotrexate (MTX) is the disease-modifying drug (DMARD) of first choice in the treatment of RA [1, 2]. Early versus late treatment of RA reduces long-term radiographic progression and functional disability [3], and compliance in the early state of the treatment is therefore important. The causes of non-compliance versus high compliance have been examined in many chronic diseases, but the findings are inconsistent [3, 4]. Recently, however, the patients' personal motivation for treatment has been shown to influence compliance [5], and compliance can be described as the balance between the patients' beliefs about the necessity of the treatment and their concerns about its side effects [6, 7]. So far, studies investigating MTX compliance have mainly been based on prescription data, and no information on personal perceptions has been presented [8-10]. In a small number of studies, RA patients' compliance with different medications has been investigated by using self-reported data [11-14], but, to the best of our knowledge, no study has specifically addressed self-reported MTX compliance. Two cross-sectional studies have described the influence of RA patients' perceptions about treatment on compliance. One British study from 2004 included 85 patients with RA [15], and it showed that holding strong beliefs about the necessity of the treatment predicted higher reported compliance with disease-modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. In another British study from 2005 of 323 RA patients, it was similarly found that concerns about side effects and potential long-term consequences of treatment were associated with DMARD non-compliance [16]. However, given the cross-sectional designs, these studies only provided weak evidence of cause and effect and further failed to capture how change in symptoms during the course of the disease may have affected compliance. Generally, RA patients experience improvement of symptoms 3-6 months after initiation of MTX treatment, and at the same time, many patients develop minor adverse events [17]. By using self-reported data in a prospective study design, we therefore aimed at examining the impact of RA patients' perception of necessity and concern about MTX on compliance during the first year of treatment, and we further aimed at describing the influence of MTX dose and functional disability.

METHODS

Study population

We conducted this study in the former County of Aarhus (approximately 650,000 inhabitants) in Denmark. The study was carried out among all RA patients (> 18 years), who began receiving MTX treatment between 1 November 2006, and 31 October 2007.

Identification of MTX users

Patients who began receiving MTX were identified through the regional Pharmaco-Epidemiological Prescription Database (PEPD). All pharmacies in Denmark have electronic accounting systems that are used to secure reimbursement from the Danish National Health Service, which reimburses a variable proportion of the cost of prescribed medicine for all Danish citizens. Data are transferred to the PEPD, which thus covers all reimbursed drugs at the level of the individual user. To be included in the study, the patients should be first-time MTX users defined as users who had not used MTX for a period of at least two years prior to the date of enrollment.

Identification of RA patients

Data about MTX use from the PEPD were linked to the National Patient Registry (NPR). The NPR includes data on all somatic hospital admissions for inpatients since 1977 and for outpatients since 1995, including information on discharge diagnoses, hospital department and dates of admission and discharge. Patients admitted to privately practicing rheumatologists are not included in the NPR. Since 1994, discharge diagnoses in the NPR have been classified according to the International Classification of Diseases, 10th revision [18]. We used the following codes for RA: M05.3, M05.9, M05.8, M06.0 and M06.9.

Procedure

All patients were invited to participate in the study by letter, and after 3-5 days they were contacted by phone to obtain informed consent. All patients who were willing to participate in the study then completed a questionnaire at baseline and after 9 months.

Compliance

Compliance was assessed by using the Compliance Questionnaire Rheumatology (CQR), which is a 19-item questionnaire that has been tested and validated with electronic monitoring in patients with rheumatic diseases [19]. Each item presents a statement, which is related to compliance, and the patients are asked to respond to these items on a 4-point Likert scale ranging from 1 (do not agree at all) to 4 (agree very much). The total score is a continuous variable ranging from 0 (complete non-compliance) to 100 (perfect compliance).

Beliefs about medication

The validated Beliefs About Medication Questionnaire (BMQ) section for evaluating patients' specific beliefs about necessity of and concern about drug treatment [20] was used to assess the patients' perception of MTX. Each item in the BMQ is rated on a 5-point Likert scale. The specific necessity scale contains 5 items which are used to assess the patients' beliefs about the necessity of the prescribed drug for controlling the disease (score range: 5-25). The specific concerns scale contains 5 items which are used to assess the patients' concerns in relation to potential adverse effects or long-term consequences of the treatment (score range: 5-25).

Functional disability

Functional disability was assessed by using the Health Assessment Questionnaire (HAQ) [21]. The HAQ is a validated measure of disability which includes 20 specific functions that are grouped into 8 categories: dressing and grooming, arising, eating, walking, personal hygiene, reaching, gripping and other activities. HAQ scores range from 0 (no difficulty) to 3 (unable to do).

Duration of RA and present MTX dose

We retrieved information on the RA disease duration from the NPR. The duration is defined as the time between the date of the first RA diagnosis recorded in the NPR and the date of the present MTX treatment start. As the PEPD does not include data regarding daily dosage at the single patient level, information on MTX dosage (defined as the last dose of MTX prescribed before the date of each questionnaire) was retrieved from the medical records.

Concurrent medication and co-morbidity

In order to take side effects into account, we asked the respondents to self-report the use of folic acid.

We also asked the patients to self-report co-morbidity by asking "*Please state if you have or have had any of the following conditions*": 1) myocardial infarction, congestive heart failure, peripheral vascular disease or cerebrovascular disease, 2) chronic pulmonary disease, 3) diabetes, 4) cancer, 5) ulcer disease and mild liver disease, and 6) depression or schizophrenia. These statements were recorded into a dichotomous co-morbidity variable (co-morbidity: yes/no).

Demographics

Demographic variables included age, gender and educational level. Age and gender were derived from the CPR number, which is an individual 10-digit number assigned to all Danish citizens at birth. Age was recorded at the date of the MTX treatment start. Patients were asked to self-report their educational level.

Statistical methods

We estimated the prevalence of having a CQR score in the bottom quartile, and the prevalence was stratified according to age (< 55, >55), gender, the duration of RA (< 5 years, > 5 years), MTX dose (< 12.5 mg, 12.5-17.5 mg, > 17.5 mg), concurrent use of folic acid (yes/no), years of school education (< 10 years, > 10 years), functional disability (HAQ) (< 0.75, 0.75-1.75, > 1.75), use of folic acid (yes/no) and co-morbidity (yes/no). Furthermore, crude and adjusted prevalence ratios (PR) with 95% confidence intervals (CI) for having a CQR in the bottom quartile were estimated by using log-binomial regression.

The occurrence of the patients' perception of MTX necessity and concern according to the two CQR levels was examined and followed by construction of box-and-whisker plots. We dichotomised the BMQ necessity and the BMQ concern summary score into high perception of MTX necessity (yes/no) and low concern about MTX treatment (yes/no) by using the median point. We then examined the prevalence of having a CQR score in the bottom quartile according to the level of these two variables, and we used log-binomial

regression to compute crude and adjusted PR with 95% CIs with adjustment for gender, age, functional disability, disease duration, co-morbidity, MTX dose, and use of folic acid. To examine whether the participants who completed the study differed from those who dropped out, we compared median baseline CQR scores and median baseline BMQ scores in completers versus dropouts by using Mann-Whitney U tests for comparison of continuous variables and Fisher's exact test for comparison of categorical variables.

RESULTS

A total of 126 RA patients filled in a new prescription of MTX in the former County of Aarhus between 1 November 2006 and 31 October 2007. Among these, 8 patients missed the invitation and 15 patients declined to participate, leaving 103 patients in the study (Figure 1). Twelve patients did not respond to the first questionnaire, which made 91 patients available for baseline analysis. A total of 33 patients was lost to follow-up (32%) and the response rate to the 9-month questionnaire was 68%. 12 patients (11.6%) stopped the MTX treatment between the dates of the two questionnaires (6 of these because of side effects). Six patients at baseline and 5 patients at 9 months were excluded because they did not complete all 19 items in the CQR, leaving 85 (83%) and 65 (63%) patients for analysis at baseline and follow-up, respectively.

Baseline characteristics

At baseline, the median age was 63 years (interquartile range (IQR): 32-80), and 64% were women. At the date of the MTX treatment start, 63% of the patients were rheumatoid factor IgM-positive, and 60% had erosive changes. The median disease duration was 6.3 years (IQR: 0-27). The average MTX dose at baseline was 13.8 mg/week (95% CI: 12.5-15.1), after which it increased to 15.5 mg/week (95% CI: 14.1-17.1) at 9 months ($p < 0.02$). The average HAQ score at baseline was 0.9 (95% CI: 0.7-1.1), after which it declined to 0.5 (95% CI: 0.4-0.6) at 9 months ($p < 0.00$). The median time in MTX treatment before study entrance was 126 days (IQR: 60-239).

MTX compliance

The overall median CQR score at baseline was 70.1 (IQR: 36.8-93.0) compared with 70.6 (IQR: 42.1-91.2) at 9 months. Table 1 shows the descriptive data for patients with and

without a CQR score in the bottom quartile, at baseline and after 9 months. The prevalence of having a CQR score in the bottom quartile was 23%, both at baseline and after 9 months.

The prevalence of a CQR score in the bottom quartile was lower for men than for women, both at baseline (17.2% vs. 25.0% (adjusted PR: 0.8 (95% CI: 0.3-2.0)) and after 9 months (13.6% vs. 29.3% (adjusted PR: 0.3 (95% CI: 0.1;1.3)). At baseline, the prevalence of a CQR score in the bottom quartile was 32.3% for patients < 55 years compared with 15.9% for patients > 55 years (adjusted PR: 0.5 (95% CI: 0.2-1.1)). After 9 months, no significant differences were found between the age groups. Patients treated with MTX doses < 12.5 mg/week at baseline had a prevalence of CQR in the bottom quartile of 31.0% compared with 19.4% among patients treated with 12.5-17.5 mg/week (adjusted PR: 0.7 (95% CI: 0.3;1.7)). After 9 months, no differences between high and low MTX doses were found. Patients treated with folic acid had a prevalence of having CQR scores in the bottom quartile of 6.7% compared with 27.9% among non-users (adjusted PR: 0.3 (95% CI: 0.0;2.7)). The same trend was seen after 9 months. Among patients with more than 10 years of school education, the prevalence of having a CQR score in the bottom quartile at baseline was 29.5% compared with 17.5% for patients, who had less than 10 years of school education (adjusted PR: 1.5 (95% CI: 0.5-4.1)). This tendency was less pronounced after 9 months (30.3% vs. 22.6%, adjusted PR: 1.0 (95% CI: 0.3;2.8)).

Perception about the necessity of MTX treatment and concern about potential side effects

Figure 2 shows the compliance distribution indicated by the CQR score according to the levels of the patients' perceptions about high MTX necessity (yes/no) and low MTX concern (yes/no) at baseline and after 9 months.

Among patients with a CQR score in the bottom quartile, the prevalence of having low perceptions of MTX necessity was 37.1% vs. 14.0% for patients with high perceptions of necessity (adjusted PR: 0.3 (95% CI: 0.2-0.8)). The same trend was seen after 9 months. The prevalence of having a CQR score in the bottom quartile or not was almost equally distributed among patients, who had high or low concerns about the treatment at baseline. However, after 9 months, the prevalence of having a CQR score in the bottom quartile was 18.9% for patients who had low concerns about the MTX treatment, vs. 37.7% for patients

who had higher concerns about the treatment (adjusted PR: 0.5 (95% CI: 0.2-1.3)) (Table 2).

Dropouts

Completers and dropouts did not differ substantially in terms of gender, age, disease duration, or in the proportion of patients being rheumatoid factor IgM-positive (data not shown). However, at baseline, the CQR score among dropouts was lower (median CQR: 68.4 (IQR: 36.8-89.5)) than the CQR score among completers (median CQR: 71.9 (IQR: 38.6-94.7)). Completers also held stronger beliefs in the necessity of MTX treatment compared with dropouts (median BMQ, necessity: 17 (IQR: 12-24) vs. 15 (IQR: 6-21)), and the completers were less concerned about MTX side effects and potential long-term consequences of the drug (median BMQ, concern: 16 (IQR: 9-23) vs. 17 (IQR: 11-21)).

DISCUSSION

In this prospective study among RA patients newly started on MTX treatment, self-reported compliance could be explained by strong perceptions of a personal need for the treatment. Concern about the MTX treatment seemed to play a minor role in comparison to compliance. During the first year of treatment, compliance was not influenced by functional impairment and MTX dose level.

The compliance found in the present study was lower than the reported compliance of 80-90% found in the few additional studies, where MTX compliance among RA patients has been examined [8, 10, 22]. In three of these studies, prescription-based data were used to assess compliance, and in one study, electronic pill count was used [23]. However, compliance results based on different methods might not measure the same concepts [24, 25]. Hence, self-reported compliance directly reflects the patients' motivation and their ability to take the drug, while compliance based on pharmacy claims data indirectly reflects compliance by measuring the availability of medication [26]. Thus, caution is necessary when comparing compliance results obtained by different methods [24].

The overall finding of compliance being closely associated with RA patients' strong beliefs in the necessity of MTX treatment is consistent with previous findings from cross-sectional

studies [15, 16], and it is probably conditioned by the patients' experience that in order to get symptom relief in RA, treatment is, indeed, necessary. We have previously examined MTX compliance by using prescription-based data and found that high compliance rates were associated with high levels of C-reactive protein, a marker of disease activity [27]. In the present study based on self-reported data, we used functional impairment indicated by the HAQ to assess disease activity, and we found that compliance was unrelated to functional capacity. However, the HAQ measures both disease activity and the level of joint damage, but only disease activity is responsive to treatment. Therefore, less improvement in the HAQ is expected in treatment in late RA [28]. The present study population consisted of incident MTX users, among whom many were prevalent RA patients, and this could have influenced our inability to find an association between the HAQ score and compliance.

In the present study, compliance behaviour was found to be different in early versus late RA with a higher prevalence of self-reported low compliance among patients with a disease duration of more than 5 years. This is consistent with our findings in a previous study based on MTX prescription data [27]. In an American meta-analysis among 1,435 RA patients, it was found that the strongest predictor of overall response to DMARD treatment was the disease duration. Hence, patients with a disease duration of less than one year had a response rate of 53% compared with 35% among patients with more than 10 years of disease duration [29]. This indicates that compliance behaviour changes with the duration of RA and that some RA patients probably skip doses from time to time when they experience less severe symptoms in more stable disease phases.

In MTX treatment, a dose-response relation exists [30], but higher MTX doses are also more prone to result in side effects [31]. During our study period, we found an increase in the median MTX dose of only 1.7 mg/week. We therefore find it less likely that side effects due to an increased dose would cause compliance changes in our study.

We found an association between the use of folic acid and increased compliance. According to guideline recommendations, folic acid supplementation should be given routinely to MTX patients in order to prevent side effects [32]. In our study, however, only

20% of our respondents reported a use of folic acid, and thus the use of folic acid may have been underreported. Such misclassification would, however, have made us underestimate the difference in compliance between folic acid users and non-users. Compliance to drug therapy may be associated with an overall healthier behaviour [33], i.e. patients are seldom compliant to only one drug [34]. Consequently, the finding of an association between increased compliance among folic acid users may reflect the fact that compliant users of folic acid are also compliant users of MTX.

We consider the use of prospectively collected data to be one of the strengths of our study. In contrast with previous cross-sectional studies in the field [15, 16], this enabled us to be more specific about how compliance behaviour is built up during the first year of treatment in relation to different clinical factors. Furthermore, the present study complements previous knowledge in the field as it contains information on compliance behavior that cannot be obtained from registers [35].

One of the most important limitations of the present study is that we were unable to keep patients in the study when they stopped the MTX treatment. When we compared study completers with dropouts, we found a tendency among dropouts towards lower compliance and lower beliefs in the necessity of MTX. As a result, we might have studied "healthy users" and, consequently, we may have excluded patients who discontinued the MTX treatment for various reasons, including side effects or inefficiency, and among whom compliance is likely to be different from the compliance of the patients who continued the treatment. Thus, overall compliance was most likely overestimated in the present study. Hence, in conclusion, our main finding of an association between the patients' strong perceptions about the necessity of MTX treatment and compliance is considered valid, but it may not be generalisable beyond the continuous MTX users.

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CQR baseline in the bottom quartile

CQR in the bottom quartile

Table 1 Compliance to Methotrexate, indicated by the Compliance Questionnaire Rheumatology (CQR): observed scores, prevalence ratios (PR) including 95% confidence intervals (CI) of CQR in the bottom quartile, stratified by gender, age, disease duration, MTX dose, use of folic acid, functional disability and school education

	CQR baseline in the bottom quartile				CQR in the bottom quartile	
	Yes (%)	No (%)	PR (95% CI)		Yes (%)	No (%)
			Crude	Adjusted [#]		
Total	20 (23.5)	65 (76.5)			15 (23.1)	50 (76.9)
Gender						
Female	13 (25.0)	39 (75.0)	1 (ref)	1 (ref)	13 (31.7)	28 (68.3)
Male	5 (17.2)	24 (82.8)	0.7 (0.2;1.7)	0.8(0.3;2.0)	3 (13.6)	19 (86.4)
Age						
< 55 years	10 (32.3)	21 (67.7)	1 (ref)	1 (ref)	7 (28.0)	18 (72.0)
> 55 years	8 (15.9)	40 (84.1)	0.5 (0.2;1.1)	0.6(0.2;1.6)	9 (25.0)	27 (75.0)
Disease duration						
< 5 years	6(16.7)	30 (83.3)	1 (ref)	1 (ref)	6 (20.7)	23 (79.3)
> 5 years	13 (28.9)	32 (71.1)	1.7 (0.7;4.1)	1.5 (0.5;4.7)	10 (31.3)	22 (68.7)
MTX dose						
< 12.5 mg/week	9 (31.0)	20 (69.0)	1 (ref)	1 (ref)	6 (33.3)	12 (66.7)
12.5-17.5 mg/week	7 (19.4)	29 (80.6)	0.6 (0.2;1.5)	0.7(0.3;1.7)	1 (5.9)	6 (44.1)
> 17.5 mg/week	3 (16.7)	15 (83.3)	0.5(0.2; 1.7)	0.6(0.1;2.4)	8 (33.3)	6 (26.7)
Folic Acid						
No	19 (27.9)	49(72.69)	1 (ref)	1 (ref)	15 (28.3)	38 (71.7)
Yes	1 (6.7)	14 (93.3)	0.2 (0.0;1.6)	0.3(0.0;2.7)	2 (18.2)	9 (81.8)
Functional disability ¹						
< 0.75	10 (25.6)	29 (74.4)	1 (ref)	1 (ref)	12 (26.1)	34 (73.9)
0.75-1.75	0 (0.0)	13 (100.0)	-	-	2 (40.0)	3 (60.0)
> 1.75	10 (30.3)	23 (69.7)	1.2 (0.5;2.5)	1.4 (0.6; 3.1)	3 (21.4)	11 (78.6)
Co-morbidity						
No	3 (18.8)	13 (81.3)	1 (ref)	1 (ref)	3 (21.4)	11 (78.6)
Yes	17 (24.6)	52 (75.4)	1.3(0.4;3.9)	1.1 (0.4;3.3)	14 (27.5)	37 (72.5)
School education						
< 10 years	7 (17.5)	33 (82.5)	1 (ref)	1 (ref)	7 (22.6)	24 (77.4)
> 10 years	13 (29.5)	31 (70.5)	1.7 (0.7;3.8)	1.5 (0.5;4.1)	10 (30.3)	23 (69.7)

¹ Health Assessment Questionnaire (HAQ) # Adjustment factors: gender, age, functional disability, use of folic acid, disease duration, MTX dose, school education

				PR (95% CI)			
		Yes (%)	No (%)	Crude	Adjusted [#]	Yes (%)	No (%)
High perceptions of MTX necessity							
No		13 (37.1)	22 (62.8)	1(ref)	1(ref)	12 (50.0)	9 (50.0)
Yes		7 (14.0)	43 (86.0)	0.4 (0.2; 0.8)	0.3 (0.1; 0.8)	5 (12.2)	36 (87.8)
Low concern about MTX treatment							
No		9 (21.4)	33 (78.6)	1(ref)	1(ref)	7 (18.9)	30 (81.1)
Yes		11 (25.6)	32 (74.6)	0.8 (0.4;1.8)	0.7 (0.3;1.8)	10 (35.7)	18 (64.3)

Table 2 Compliance to methotrexate, indicated by the Compliance Questionnaire Rheumatology (CQR): observed scores and ratios (PR), including 95% confidence intervals (CI) of CQR in the bottom quartile, stratified by perceptions of MTX necessity. Reference group * Adjustment factors: gender, age, functional disability, disease duration, co-morbidity, MTX dose, and use of folic acid

Figure 1

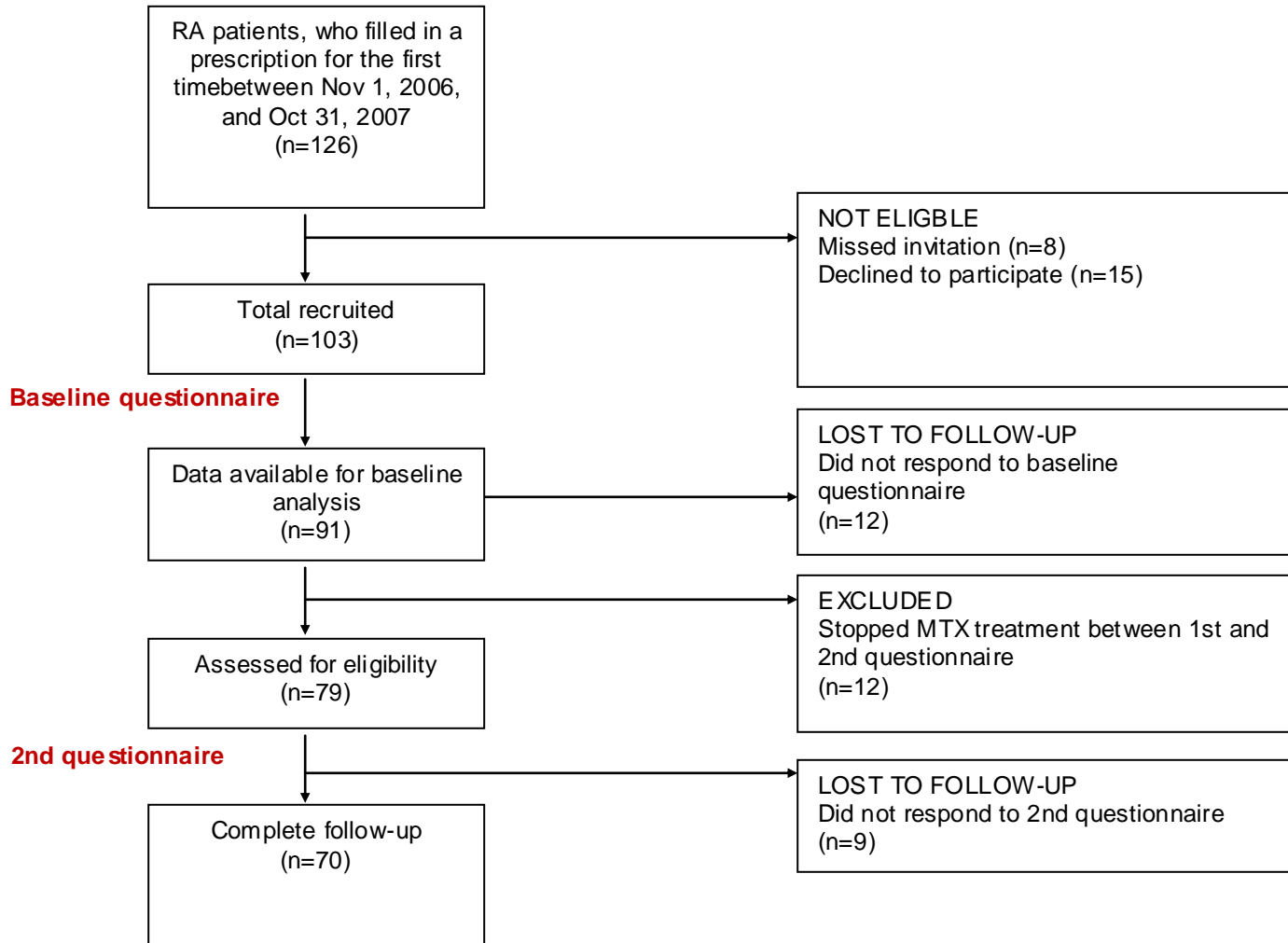
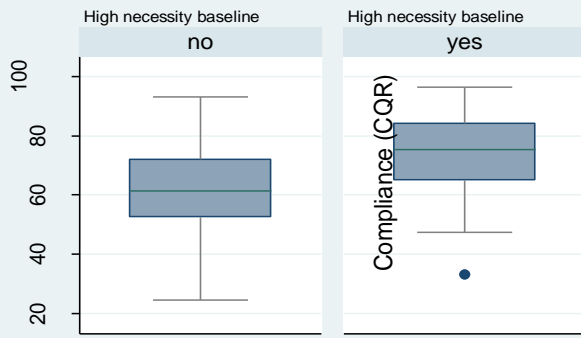
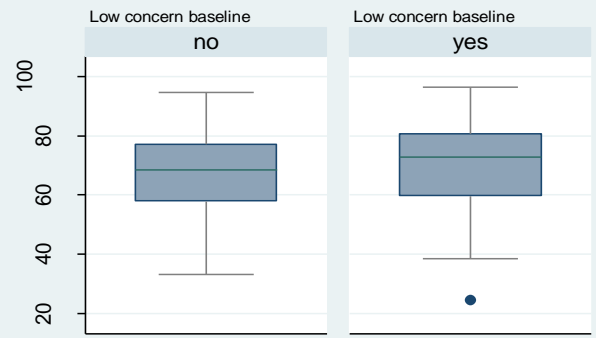


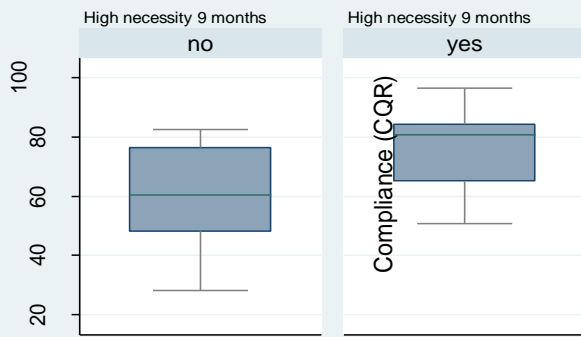
Figure 2 Patients' compliance to methotrexate (MTX) which is indicated by the Compliance Questionnaire Rheumatology (CQR) distributed on the patients' high perceptions of MTX necessity (yes/no) and low perceptions of MTX concern (yes/no). The compliance study was carried out among rheumatoid arthritis (RA) patients just after start of MTX treatment and after 9 months in the former County of Aarhus, Denmark. The cross marks the median, and the box marks the top and bottom quartiles. Observations outside this range are plotted individually.



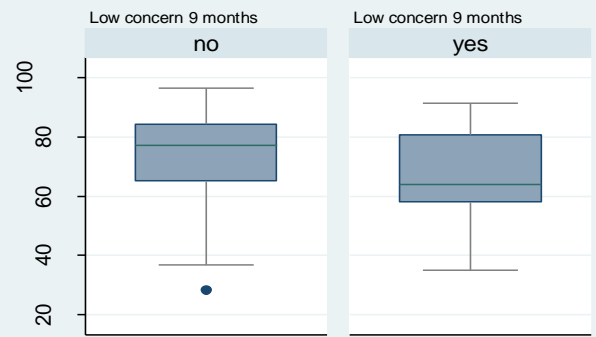
Graphs by high_ness_gA



Graphs by low_conc_gA



Graphs by high_ness_gC



Graphs by low_conc_gC