High Degree of Nonadherence to Disease-modifying Antirheumatic Drugs in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To test medication adherence using the Compliance-Questionnaire-Rheumatology (CQR).

Methods. Invitation letter and CQR were sent to 240 patients with rheumatoid arthritis. Followup CQR was sent 3 months later. Adherence was evaluated using CQR 80% cutoff scores.

Results. Seventy-eight patients who were being treated with disease-modifying antirheumatic drugs provided full information on the CQR at both points in time. Eleven patients (14.1%) were classified as adherent based on taking compliance (TC), with only 3 patients (3.8%) adherent in regard to correct dosing (CD) [followup: 13 (16.7%) and 3 (3.8%) for TC and CD, respectively]. Nonadherence was not related to disease activity or side effects.

Conclusion. We demonstrated low adherence, suggesting differences between doctors' records and patients' practice of antirheumatic drug therapy. (J Rheumatol First Release Jan 15 2015; doi:10.3899/ jrheum.140982)

Key Indexing Terms:
ADHERENCE COMPLIANCE RHEUMATOID ARTHRITIS CQR
DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

In 1976, Sackett defined compliance as "the extent to which a person's behavior coincides with medical advice"[1]. Adherence is defined as "the extent to which a person's behavior — taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider"[2]. Following this definition, adherence incorporates aspects of shared decision making, resulting in dose-taking compliance, persistence, and correct dosing, all of which are key to the effectiveness of therapy in patients with chronic diseases such as rheumatoid arthritis (RA). In Germany, the costs of market-approved antirheumatic therapies prescribed by rheumatologists are covered by the national healthcare system. Therefore, the question of whether patients can afford antirheumatic treatment should not affect the findings presented in our study. This may contrast with studies from countries with a different type of healthcare system[3]. If there is a lack of adherence, poor treatment outcomes are more likely[4,5]. Therapeutic success is especially important in RA because it not only reduces symptoms, but also inhibits joint deformities, preventing irreversible functional damage[6]. Poor adherence can lead to a failure of treatment resulting in a need for more aggressive therapy, possibly at higher costs[7]. Some studies of adherence to drug therapy in patients with RA report adherence rates ranging from 20% to 107%[3,8]. This variability may be because of the different measurement methods used, such as pharmacy data, electronic monitoring, self-report, and physician report[8]. Electronic monitoring is considered to be the most accurate method when measuring adherence[9,10]. De Klerk, *et al* used this method to validate the Compliance-Questionnaire-Rheumatology (CQR)[10,11]. An overall weighted CQR score could predict taking compliance (TC) and correct dosing (CD) adequately. The CQR is easy to understand and cost-efficient, making it suitable for use as a screening tool[10]. In our study, we tested a German translation of the CQR at a single-center institution reflecting a real-life clinical setting. We investigated the stability of patient-reported statements in regards to TC and CD in patients treated with regular antirheumatic medication and those undergoing treatment change. In addition, we took account of patient-reported symptom severity, as well as side effects.

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MATERIALS AND METHODS

Sample description. Two-hundred forty patients with RA at our outpatient clinic (Erlangen, Germany, with a team of 12 physicians with no defined patient allocation) were invited by letter to participate in our study, and were sent copies of the questionnaires. After 2 weeks, patients were reminded about the completion of the questionnaires. Three months after the initial survey, they were sent the same set of questionnaires, to follow up on their responses. Seventy-eight of the initial 240 patients invited completed the CQR at both timepoints, of which 66 were receiving stable medication and 12 had changed their treatment between the initial questionnaire and the followup. We limited the corresponding analyses to patients receiving biologic and/or conventional disease-modifying antirheumatic drug (DMARD) therapy at the baseline. Patients receiving only infusions were not included. Ethical approval was obtained from the local medical ethics committee (Erlangen). All patients had to sign an informed consent form to participate in our study.

CQR translation and application. The original CQR was translated from English into German with the support of a certified translator. Initial forward translation followed a back translation to guarantee equivalency of content between the source language and the target language (similar to Gilworth, *et al*'s study[12]). Further details on the design of the CQR are presented elsewhere[10]. The weighted analysis of the CQR was derived from a spreadsheet provided by the authors of the original work to calculate corresponding cutoff values for TC and CD. Patients with results above a cutoff point of 80% were defined as satisfactorily adherent. Those with results below this cutoff point were defined as unsatisfactorily adherent.

Statistical analysis. After a descriptive analysis of the demographic background of our sample group, we evaluated drug adherence among our patients using the CQR 80% cutoff scores for TC and CD proposed by de Klerk, *et al*[10]. In a subsequent step, we investigated the reproducibility of TC and CD using either the Bravais-Pearson (r) or Spearman correlation (r_s) in 2 subgroups: patients with RA receiving stable antirheumatic therapy (r) and those undergoing a change of therapy (r_s). Further, we investigated whether symptom severity and side effects were related to drug adherence. Therefore, we related the 80% cutoffs for TC and CD from the CQR to the acceptable symptom status determined by the Rheumatoid Arthritis Impact of Disease questionnaire (RAID)[13,14] and the presence of side effects of current antirheumatic therapy with the help of chi-square tests. All inferential analyses were 2-tailed and performed using IBM SPSS version 21 (IBM SPSS Inc.). P values ≤ 0.05 were considered statistically significant.

RESULTS

Background cohort information on demographic variables and disease-related characteristics is shown in Table 1, whereby the overall mean Disease Activity Score at 28 joints was 3.1 ± 1.6 with an average disease duration of 14.4 ± 11.1 years. Of the 118 patients who returned the baseline questionnaire, most frequently omitted items were 13, 14, and 18 at both timepoints (see Appendix 1 and Appendix 2 for item wording and German CQR). The 95% CI of average unweighted CQR scores did not suggest any differences between patients receiving stable therapy and those undergoing treatment change at any timepoint:

Baseline: 95% CI_{stable} = 70.1–75.6 vs
95% CI_{change} = 66.6–83.4

Followup 2: 95% CI_{stable} = 69.5–74.8 vs
95% CI_{change} = 67.0–83.6

As in the original work, the weighted 80% cutoff points were –0.58 for TC and 0.35 for CD, which corresponded to 80% compliance on either score[10]. At baseline, 11 patients (14.1%) were classified as adherent based only on TC and 3 patients (3.8%) were categorized as adherent regarding CD. At followup, 13 patients (16.7%) achieved a result above the cutoff for TC and 3 for CD (3.8%).

A correlational analysis of weighted scores for TC ($r = 0.34$, $p = 0.006$) and CD ($r = 0.36$, $p = 0.003$) showed limited reproducibility in the stable treatment subgroup with only 11.6% and 13.0% of shared variance between baseline and followup. This finding was confirmed when comparing TC and CD regarding values below and above cutoff between baseline and followup [$chi\text{-}square_{TC}(1) = 0.79$, $p = 0.40$; $chi\text{-}square_{CD}(1) = 0.15$, $p = 1.00$], suggesting independence of cutoff values. Extending the analysis to individual CQR items returned low to good correlations ranging from $r = 0.18$–0.81 ($p \leq 0.14$) with 6 items showing correlations exceeding $r = 0.50$ ($p \leq 0.001$). Thus, the interaction of items included in the weighting procedure may have a decreasing effect on the weighted scores of the CQR. For the subgroup of participants undergoing a change in antirheumatic treatment, results for TC and CD obtained from the Spearman correlation analysis were smaller compared with the stable therapy subgroup ($r_{s,TC} = -0.05$, $p = 0.88$; $r_{s,CD} = 0.26$, $p = 0.42$) with 8 items exceeding $r_s = 0.50$ ($p \leq 0.09$). Corresponding chi-square tests could not be calculated because no patient among those changing therapy was above the 80% CD or TC cutoff at baseline.

For patients receiving stable therapy, the RAID acceptable status (i.e., total RAID score of 2 and below)[13] was independent of CQR-weighted score cutoff values for 80% TC [$chi\text{-}square_{baseline}(1) = 1.04$, $p = 0.46$; $chi\text{-}square_{followup}(1) = 1.42$, $p = 0.32$] and 80% CD [$chi\text{-}square_{baseline}(1) = 0.02$, $p = 1.00$; $chi\text{-}square_{followup}(1) = 1.27$, $p = 0.55$] at any of the 2 timepoints in a chi-square analysis using exact p value calculation with Fisher's exact test adjustment when necessary. The presence of side effects also appeared to be independent of the weighted cutoffs, again suggesting no relationship between side effects and TC [$chi\text{-}square_{baseline}(1) = 2.85$, $p = 0.15$; $chi\text{-}square_{followup}(1) = 1.75$, $p = 0.31$] or with CD [$chi\text{-}square_{baseline}(1) = 1.25$, $p = 0.55$; $chi\text{-}square_{followup}(1) = 1.54$, $p = 0.55$]. This was a surprising finding. Effect sizes confirmed this finding for both TC and CD ($V \leq 0.21$). For patients undergoing treatment change, respective chi-square tests could only be calculated for the 80% TC cutoff at baseline in correspondence with side effects. This test did not suggest any relation of TC to the occurrence of side effects [$chi\text{-}square(1) = 2.18$, $p = 0.33$]. The other tests were not feasible because patients were either not above the cutoff values or not acquiring the RAID acceptable status.

DISCUSSION

Our study reports on the use of a German version of the

Table 1. Demographic background of participants at baseline completing CQR at both timepoints.

Characteristics	Participants Completing CQR Twice, Total	Participants Taking Stable Antirheumatic Therapy Completing CQR Twice, Subgroup	Participants Undergoing Treatment Change and Completing CQR Twice, Subgroup
Patients, n	78	66	12
Sex, male/female (female %)	18/60 (76.9)	15/51 (77.3)	3/9 (75.0)
Age, yrs, mean ± SD	58.9 ± 11.9	58.9 ± 11.7	59.1 ± 13.7
Conventional DMARD therapies, n	56	47	9
MTX	41	34	7
SSZ	5	4	1
LEF	8	8	—
HCQ	1	—	1
AZA	1	1	—
Biologic DMARD, %	69.2	71.2	58.3
Glucocorticoids, %	51.3	47.0	75.0

CQR: Compliance-Questionnaire-Rheumatology; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; SSZ: sulfasalazine; LEF: leflunomide; HCQ: hydroxychloroquine; AZA: azathioprine.

CQR that demonstrates a high frequency of nonadherence in a single-center sample of patients with RA receiving DMARD. Nonadherence was shown in 83%–86% of patients with respect to TC and therefore raises serious questions about current patient-physician interaction. Our results confirm previous findings from Waimann, *et al* of a nonadherence of 80% — even though healthcare systems in the United States and Germany are not directly comparable[3]. Because nonadherence rates in other countries are comparable to the ones in our sample, our results do not seem to be caused by a factor that is specific to 1 country (i.e., Germany).

Our study prompts several points for consideration. First, because this questionnaire deals with a delicate topic, the total response rate (n = 118) was 49.2%, which may be lower than in projects dealing with different patient-reported outcomes [e.g., pain questionnaires with > 70% returns (unpublished data)]. Because the number of responders was low in this case, it would be interesting to see what the results would have been if more patients had responded. Given the relatively high proportion of patients classified as nonadherent in our study, one could hypothesize that nonadherence may have been even more prevalent if more patients had participated. Second, the issue of a social desirability bias with an eagerness to please must be kept in mind and accounted for in the future[15]. However, answering items in a socially desirable manner (i.e., pretending to be more compliant) ought not to have been a problem in our study considering the high rates of nonadherence in our sample. This is especially surprising because patients being treated in a hospital rheumatology department are likely to have a more severe course of the disease compared with patients being treated by a resident rheumatologist. Third, because symptom state was not related to cutoff scores and the influence of side effects on adherence was questionable, our data do not support the contribution of disease status to medication adherence that has been shown by others[3]. Finally, baseline values for TC, as well as CD, were clearly not related to followup values (whereas single items in the CQR partially revealed better reproducibility). The poor reproducibility in both subgroups could be attributable to multiple factors, such as the number of different medications[16], patient-related reasons[16], self-efficacy[8], patient–healthcare provider relationship[8], social support[8], or patient beliefs about medication.

All these factors could also relate to reasons for not following the instructions of the clinicians. However, because self-reporting measures such as the CQR are derived directly from the patients, they may have potential for investigating critical factors that contribute to nonadherence (e.g., personal attitudes or beliefs) that electronic means cannot measure. This may also be an advantage for longterm evaluations of adherence in a clinical setting or a trial because it provides an opportunity to respond instantly to conspicuous results. In the future, the German CQR will need to be compared against an external validation criterion (e.g., medical event monitoring) in larger samples. At the same time, measures are required to address this significant degree of nonadherence.

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APPENDIX 1. English wording of the 3 most omitted CQR-items, including corresponding omission rates in patients with RA receiving DMARD.

- Item 13: "If I don't take my antirheumatic medicines regularly, the inflammation returns."
  Missing values (questioning 1): 9 (7.6%)
  Missing values (questioning 2): 25 (21.2%)
- Item 14: "If I don't take my antirheumatic medicines, my body warns me."
  Missing values (questioning 1): 7 (5.9%)
  Missing values (questioning 2): 24 (20.3%)
- Item 18: "If I don't take my antirheumatic medicines, I have more complaints."
  Missing values (questioning 1): 9 (7.6%)
  Missing values (questioning 2): 24 (20.3%)

Annotation: Omission rates refer to the 118 patients who returned the baseline questionnaire package, at least completing some of the CQR items. Numbers and percentages for second questioning are also higher because of patients completing the first, but not the second, questionnaire package. CQR: Compliance-Questionnaire-Rheumatology; RA: rheumatoid arthritis; DMARD: disease-modifying antirheumatic drug.

APPENDIX 2. Compliance Questionnaire Rheumatology (CQR) — German version. Nachstehend finden Sie verschiedene Aussagen von Patienten mit rheumatischen Erkrankungen. Bitte geben Sie jeweils an, inwieweit Sie den einzelnen Aussagen zustimmen und **kreuzen Sie die Aussage an**, die Ihre Meinung am besten widerspiegelt.

	Ich stimme überhaupt nicht zu	Ich stimme nicht zu	Ich stimme zu	Ich stimme vollkommen zu
1. Wenn mir mein Rheumatologe Medikamente verordnet, dann nehme ich sie auch ein.	☐	☐	☐	☐
2. Ich nehme die mir verordneten Antirheumatika ein, weil ich dadurch weniger Probleme habe.	☐	☐	☐	☐
3. Ich würde es unter keinen Umständen wagen meine Antirheumatika nicht einzunehmen.	☐	☐	☐	☐
4. Würde ich gute Erfahrungen mit alternativen Heilmethoden machen, würde ich diese gegenüber den verordneten Medikamenten meines Rheumatologen bevorzugen.	☐	☐	☐	☐
5. Meine Medikamente befinden sich immer am gleichen Ort, somit vergesse ich ihre Einnahme nicht.	☐	☐	☐	☐
6. Ich nehme meine Medikamente ein, da ich meinem Rheumatologen voll und ganz vertraue.	☐	☐	☐	☐
7. Ich nehme meine Antirheumatika in erster Linie deshalb ein, damit ich weiterhin das tun kann, was ich tun möchte.	☐	☐	☐	☐
8. Ich bin kein Freund von Medikamenten. Wenn es auch ohne Medikamente geht, verzichte ich auf sie.	☐	☐	☐	☐
9. Im Urlaub passiert es mir manchmal, dass ich meine Medikamente nicht einnehme.	☐	☐	☐	☐
10. Natürlich nehme ich meine Antirheumatika ein, weshalb sollte ich sonst einen Rheumatologen aufsuchen?	☐	☐	☐	☐
11. Ich erwarte von meinen Antirheumatika keine Wunder.	☐	☐	☐	☐
12. Wenn ich meine Medikamente nicht mehr sehen kann, denke ich mir möglicherweise „weg damit, was soll's".	☐	☐	☐	☐
13. Bei unregelmäßiger Einnahme meiner Antirheumatika kehren die Entzündungserscheinungen zurück.	☐	☐	☐	☐
14. Mein Körper sendet Warnsignale, wenn ich meine Antirheumatika nicht einnehme.	☐	☐	☐	☐
15. Meine Gesundheit steht über allem und wenn ich Medikamente einnehmen muss, um gesund zu bleiben, dann tue ich das auch.	☐	☐	☐	☐
16. Ich verwende für meine Medikamente eine Dosierhilfe.	☐	☐	☐	☐
17. Ich halte mich an das, was mein Arzt sagt.	☐	☐	☐	☐
18. Wenn ich meine Antirheumatika nicht einnehme, leide ich unter stärkeren Beschwerden.	☐	☐	☐	☐
19. Ab und zu passiert es, dass ich über das Wochenende wegfahre und meine Medikamente nicht einnehme.	☐	☐	☐	☐

Adapted and translated from de Klerk, *et al*. J Rheumatol 2003;30:2469-75; with permission.