Adherence Rates and Associations with Nonadherence in Patients with Rheumatoid Arthritis Using Disease Modifying Antirheumatic Drugs

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ABSTRACT. ***Objective.*** Nonadherence in patients with rheumatoid arthritis (RA) using disease modifying antirheumatic drugs (DMARD) may result in unnecessarily high levels of disease activity and function loss. The aim of this descriptive study was to assess adherence rates with self-report measures in a large random population, and to identify potential risk factors for nonadherence.

Methods. A randomly selected sample of 228 patients with RA using DMARD was invited for a standardised interview. For each medicine, the patients were asked about adherence, consumption and perceived (side) effects. After the interview, the patients received self-report questionnaires to assess adherence [Compliance Questionnaire on Rheumatology (CQR) and the Medication Adherence Scale (MARS)], coping, beliefs about medicines, satisfaction about medicine information, and physical functioning. Subsequently, associations between adherence and demographics, clinical characteristics, and patient attitudes were examined.

Results. Depending on the instrument used, 68% (CQR) and 60% (MARS) of the patients were adherent to DMARD. Nonadherence was not associated with demographic and clinical characteristics, satisfaction about information, medication concerns, and coping styles. The disease duration, the number of perceived side-effects, and beliefs about the necessity of the medicine were weakly associated with adherence.

Conclusion. In this large study with a random RA population, 32%–40% of the patients did not adhere to their DMARD prescription. As none of the possible risk factors was strongly related to adherence, no general risk factor seems to be powerful enough as a possible screening tool or target for adherence-improving interventions. This implies that nonadherence barriers should be assessed on an individual basis. (First Release Sept 1 2009; J Rheumatol 2009;36:2164–70; doi:10.3899/jrheum.081204)

Key Indexing Terms:
PATIENT COMPLIANCE ANTIRHEUMATIC AGENTS RHEUMATOID ARTHRITIS DRUG THERAPY HEALTH KNOWLEDGE ATTITUDES PRACTICE

Disease modifying antirheumatic drugs (DMARD) reduce disease activity and radiological progression and improve longterm functional outcome in patients with rheumatoid arthritis (RA)[1]. However, patient adherence to DMARD treatment is a prerequisite for these positive effects. Adherence, or the extent to which patients take medications as prescribed, is low in chronic medical conditions: 20% to 50% of patients do not take their medications as prescribed[2-4].

Adherence levels in RA patients taking DMARD have been studied in 3 relatively small studies (N = 26–49), with reported adherence levels ranging from 58% to 82%[5-7]. Studies including both DMARD users and nonsteroidal anti-inflammatory drug (NSAID) users[8-10] reported similar adherence levels. However, the patient selection methods in those studies did not exclude selection bias. For example, patients were enrolled by verbal or written invitation without random selection or systematic inclusion. Therefore, a larger study using nonbiased patient inclusion is needed to obtain a reliable estimate of adherence levels in RA.

In order to be able to improve adherence, nonadherent individuals have to be identified[11]. The most feasible way to identify nonadherents in clinical practice is by using self-report measures. Compared to other more intrusive measures, self-report measures are characterized by low costs, minimal participant burden, ease and administrative speed, and flexibility in terms of mode of administration and

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timing of assessment. However, self-report measures of adherence are not without drawbacks, including tendency to give socially desirable answers and recall bias. Currently, there is only one validated rheumatology-specific adherence questionnaire: the Compliance Questionnaire on Rheumatology (CQR)[12,13].

Adherence questionnaires can also be used to identify variables related to nonadherence. However, although previous studies in RA identified a variety of sociodemographic, psychological (self-efficacy), and/or clinical variables related to adherence, none of these variables was consistently related in all studies[5-10]. Therefore, it has been concluded that adherence seems to be influenced by less visible and more subtle patient characteristics. For example: patients' attitudes towards or beliefs about taking medication, satisfaction with medication information, and coping[14]. To date, these patient characteristics have not been assessed in a study in relation to adherence with DMARD in RA using a systematic selected sample of RA patients.

The purpose of this descriptive study was therefore to assess the extent of nonadherence in an unbiased group of RA patients who use DMARD. Further, we tried to identify demographic, clinical (drug use, side effects, and physical functioning), and psychological (beliefs and cognitions) risk factors for nonadherence in order to identify adherent and nonadherent patients and to assess potential intervention targets.

MATERIALS AND METHODS

Participants. Patients using oral or subcutaneous DMARD who fulfilled the American College of Rheumatology criteria for RA visiting the outpatient clinic of the Sint Maartenskliniek between December 2004 and May 2005 were considered for inclusion in the study[15]. Patients were included if their next regular checkup was scheduled on either a Thursday or Friday as on these days the specialist pharmacy assistant was available. Reasons for exclusion from the study were illiteracy, life-threatening disorders, and severe mental disorders. All other patients were included, regardless of disease duration, the seriousness of the condition, recent surgery, or comorbidity.

Methods. Two weeks before the scheduled visit to the rheumatologist, patients received an invitation by mail for a medication interview with a specialist pharmacy assistant. This was accompanied by 3 questionnaires: 2 assessing adherence [CQR and the Medication Adherence Scale (MARS)] and one questionnaire assessing beliefs about medication [the Beliefs about Medicines Questionnaire (BMQ)]. If 2 or more patients had an appointment with a rheumatologist at the same moment, the patients were selected in alphabetical order for an appointment with the pharmacy assistant. The 15–20 minute interview, standardized in a written protocol, took place immediately after the patient's visit to the rheumatologist. As part of the interview, patients were informed about the nature of the study and informed consent was obtained. During the interview the patients received a set of standardized self-report questionnaires [Satisfaction about Medication Scales (SIMS), Health Assessment Questionnaire (HAQ), and the Utrecht Coping List (UCL)]. They were asked to complete the questionnaires at home and return them by mail.

Demographics and clinical characteristics. Each interview started with an assessment of demographic variables: age, sex, marital status, education, and smoking. During this interview, for each individual medicine, inquiries were made in a structured order to check how the medication was taken. Whether the patient attributed certain (side) effects to a specific medicine was determined with the question, "Do you experience side effects? And if yes, then which?".

Self-reported adherence. Adherence was assessed with 3 self-report measures: (1) Compliance Questionnaire on Rheumatology (CQR), (2) the Medication Adherence Report Scale (MARS), and (3) during an interview-based self-report. As the CQR does not measure adherence directly, but relies partly on behavioral items, the use of the CQR could lead to a falsely increased correlation between specific cognitions and adherence measured. Therefore, the CQR was combined with the MARS. The CQR has been validated in patients with inflammatory rheumatic diseases against a Medication Event Monitoring System (MEMS device)[13]. The 19 item CQR compared well with electronic monitoring over 6 months with a sensitivity of 98%, specificity of 67%, and an estimated kappa of 0.78 to detect nonadherence[13]. Responses to the CQR items multiplied by weighting scores were compared with the cutoff score for 80% adherence. Cronbach's alpha of the CQR in this study was 0.72. The MARS questionnaire was developed to measure adherence for a wide range of medication regimens. The scale consists of 5 nonadherence behaviors that are mainly intentional and are rated for frequency on a 5 point scale[16]. Among patients with asthma, diabetes, and hypertension the MARS proved internally reliable with Cronbach alpha ranging from 0.67 to 0.90 (R. Horne, personal communication, 2007). The MARS measures adherence in a continuous scale, rather than as a dichotomous division between adherent/nonadherent categories. However, in a study with renal transplant recipients a MARS score ≤ 23 was regarded as nonadherent[17]. In this study, adherence was also defined as a MARS total score > 23. Cronbach's alpha of the MARS in this study was 0.78. For the interview-based self-report, there was a direct question during the patient interview: "Do you sometimes decide to skip a dose or do you sometimes forget a dose?" (responses 1 = never, 2 = once a month, 3 = 3 times a month, 4 = once a week, 5 = several times a week, and 6 = I never take this medicine). In our study, one missed dosage a week was defined as the cutoff score for nonadherence.

Beliefs about medicines. Patient beliefs about medicines were assessed using the BMQ, which has been validated for use in patients with somatic chronic illnesses[18]. The BMQ measures patient beliefs about the necessity of a prescribed medication to control their illness, and their concerns about the potential adverse consequences of taking the medication. Beliefs about necessity and concerns are both measured with 5 items rated on a 5 point Likert scale. The total scores of the Necessity and Concerns scales range from 5 to 25, higher scores indicating stronger beliefs. Among general medical patients the subscales have reported Cronbach's alpha of 0.86 for the Necessity scale to 0.51 for the Concerns scale. We found Cronbach's alpha of 0.81 (Necessity scale) and 0.66 (Concern scale).

Satisfaction about Medicine Information. The SIMS consist of 18 items that measure patient evaluation of information received about the different aspects of their medicines. For each item, participants can indicate whether the amount of information they have received is "too much," "about right," "too little," "none received," or "none needed." The SIMS items can be summarized under 2 topic headings or subscales: the action and use of medicines and the potential problems of medication. For the total satisfaction score, the percentage of patients satisfied with information is assessed by calculating the percentage of patients who rated scores of "about right" or "none needed" as satisfied. The complete SIMS showed a good internal reliability with Cronbach's alpha ranging from 0.81 (assessed in a sample of insulin-treated diabetes patients) to 0.91 (cardiac rehabilitation)[16]. Cronbach's alpha of the SIMS in this study was 0.87.

Coping. The UCL[19] was used to measure styles of coping with stress. The UCL consists of 7 subscales, with 47 items, representing different general stress-coping styles. The different styles are: active problem solving, palliative reaction, avoidance, seeking social support, passive reaction, expression of emotions, and comforting cognitions. In several Dutch populations (elderly people, patients with chronic conditions, and a sample of the Dutch

population), the UCL has been found to have satisfactory psychometric properties[19], with Cronbach's alpha ranging from 0.64 to 0.82.

Cronbach's alpha of the UCL in this study ranged from 0.61 (comforting cognitions) to 0.85 (active problem solving).

Physical functioning. Physical functioning was measured using the validated Dutch version of the HAQ[20]. This self-administered questionnaire consists of 8 categories, each of which has at least 2 component questions. The average of these scores represents a physical functioning score. The HAQ has been found to have good criterion validity (correlations between questionnaire or interview scores and task performance 0.71–0.95) as well as test–retest reliability (correlations 0.87–0.99).

Ethical approval for our study was obtained from the Ethics Committee Nijmegen-Arnhem (METC).

Data analysis. Descriptive statistics are provided using mean (± SD) or median (25th-75th percentile) values depending on parametric distribution of measured variables. Potential demographic, disease, and psychological variables were screened using univariate tests of the group difference (adherent versus nonadherent according to the dichotomized CQR) and the continuous CQR scores, at a lenient level of significance without correction for multiple testing (alpha = 0.05). This screening procedure was repeated with the MARS. We used Mantel-Haenszel chi-square tests to evaluate differences in proportions. Two-tailed Student t tests were used to evaluate differences in means.

While univariate analysis yielded much useful information regarding the relationship between individual variables and adherence, it did not supply any insight into how a number of variables might jointly affect adherence behavior. Therefore, a stepwise forward elimination multivariate analysis was performed to study possible confounders. All variables with a significant univariate association were entered into a forward stepwise logistic regression model with the continuous adherence measured by the CQR as the dependent variable. Data were analyzed using SPSS (version 12.0).

RESULTS

Demographics and clinical characteristics. Between December 2004 and May 2005 a total of 1419 patients with RA taking DMARD were scheduled to visit our outpatient rheumatology ward. The 692 patients visiting the clinic on a day scheduled for this study (Thursday or Friday) were considered for inclusion. For each time slot, an average of 3 patients had an appointment with a rheumatologist. Within each time slot patients were selected by alphabetical order, resulting in 235 patients who were invited to participate in the study, 228 of whom (96% of invited patients) agreed to take part and returned completed questionnaires. Reasons for not participating were unrelated to the content of this study.

Demographic characteristics, medication use, and physical functioning of the study population are described in Table 1. Most patients used methotrexate (56%), prednisolone (18%), hydroxychloroquine (10%), etanercept (8%), sulfasalazine (8%), or adalimumab (5%) as DMARD.

In 17% of the patients the prescribed medication was restricted to DMARD and analgesics. All other patients used additional medication. The most frequently used medicines were those that prevent or treat gastrointestinal (GI) complaints (30% of patients), osteoporosis (16%), and cardiovascular diseases (36%). Fifty-eight percent of patients reported side effects, and the most frequently reported side effects were GI complaints. The patients attributed these complaints to the following medicines (percentages of patients with side effects): corticosteroids (52%), DMARD (39%), biologicals (27%), bisphosphonates (20%), NSAID (16%), and cardiovascular medicines (11%).

Table 1. Demographic and clinical characteristics of patients (n = 228).

Characteristic	
Mean age, yrs	56.2 (± 12.2)
Female, %	67.5
Married/living together, %	84
Education, %	
Primary (0–6 yrs)	15
Secondary (7–12 yrs)	67
Higher (> 12 yrs)	18
Tobacco use, nonsmokers, %	77
No. of medicines, median (25th-75th percentile)	5 (3–7)
Disease duration, yrs	4.6 (± 3.3)
HAQ, mean (SD)	0.93 (± 0.63)

Self-reported adherence. In the structured interview with the specialist pharmacy assistant, irrespective of the type of medication, 81% of patients declared they never missed a dose, and 16% reported missing one dose a month, at the most. Allowing less than one missed dosage in a week, these face-to-face answers suggest that 98.5% of the patients were adherent. Based on the CQR, 67% of the patients were adherent with prescribed medicines. Using the MARS, 60% of the patients were rated as adherent.

Relationship between demographics/clinical characteristics and adherence. A number of demographic, clinical, and psychological variables were tested for possible associations with adherence (Table 2). In short, age, sex, marital status, education level, and smoking were not significantly associated with adherence. Disease duration, however, was found to be associated with adherence expressed as a continuous variable rather than a dichotomous variable. In additional analyses, adherence in recently diagnosed patients (disease duration < 3 yrs; n = 78) was compared with adherence in patients with RA of longer duration (n = 155). More patients with recent-onset RA were adherent compared with patients with RA of longer duration (respectively, 76% and 62%; chi-square = 4.1, p = 0.05). Adherent and nonadherent patients did not differ in terms of the number of prescribed medicines, NSAID use, or physical functioning (HAQ). Fewer adverse effects were reported in the CQR-defined adherent group compared with the nonadherent group.

Relations between patient characteristics and adherence. The average levels of necessity beliefs were high (mean score 19.9 ± 3.6); most patients believed in the necessity of their medication to maintain their health. The mean necessity score for CQR-defined adherent patients was 20.3 (± 3.5) compared to a necessity score of 19.1 (± 3.6) in the nonadherent group (t = –2.4, p = 0.02; Table 3). This statistical

Table 2. Comparison between demographic, clinical, and psychological characteristics of adherent and nonadherent patients. Adherence, measured with the Compliance Questionnaire—Rheumatology, is expressed as dichotomous (< 80% or ≥ 80% adherence) and as continuous variable.

Characteristic	Adherence Expressed as Dichotomous Variable			Adherence Expressed as Continuous Variable	
	Nonadherent, n = 73	Adherent n = 148	p	r	p
Mean age, yrs	54.3	56.9	0.12	0.10	0.16
Female, %	51 (70)	100 (68)	0.7	—	0.6
Married/living together, %	57 (78)	127 (86)	0.15	—	0.07
Education, %					
Primary	8 (11)	23 (16)			
Secondary	51 (70)	100 (67)			
Higher	14 (19)	25 (17)	0.6	–0.007	0.3
Tobacco use, nonsmoker	54 (74)	116 (78)	0.5	—	0.9
No. of medicines, median	5.0	5.0	0.5	0.08	0.2
No. of side effects, median	1.0	1.0	0.02*	–0.16	0.02*
Disease duration, median yrs	3.9	3.2	0.05	–0.21	0.004*
HAQ, mean	0.9	0.9	0.7	0.04	0.58
BMQ necessity score, mean	19.1	20.3	0.02*	0.11	0.11
BMQ concerns score, median	16.0	15.0	0.95	0.05	0.5
SIMS action score, median	19.0	19.6	0.8	0.03	0.6
SIMS adverse effects score, median	22.0	22.0	0.6	–0.01	0.9

* $p < 0.05$. HAQ: Health Assessment Questionnaire; BMQ: Beliefs about Medicines Questionnaire; SIMS: Satisfaction about Medication Scales.

association could not be confirmed with the continuous CQR scale.

More than 90% of the patients also had one or more concerns about potential adverse effects. Most patients expressed their concern about potential longterm adverse effects of their medications and medication dependency. There was no significant difference between the mean concern score for adherent patients compared with nonadherent patients.

Patient satisfaction with medication information (Table 4) was highest on the items concerning information on how to obtain followup prescriptions, on how to use the medication, and the medicine's name and what it is supposed to do (> 90% satisfied patients). Patients were least satisfied (< 70% satisfied patients) with information on the risks of side effects (including drowsiness and effects on their sex life), information about what to do when side effects are perceived, the effect of combining medication with alcohol use, and length of therapy. There was no difference in satisfaction with information about medication total or subscale score between adherent and nonadherent patients. Both adherent and nonadherent patients were more satisfied about the information they received about effects and usage (7.3 on a 9 point scale) compared to information about potential medication problems (a score of 6.1 on a 9 point scale) ($t = 7.2$, $p < 0.01$).

Coping scores were similar to mean scores reported in similar studies[10]. The UCL subscores (mean ± SD) were:

Table 3. Beliefs about necessity and concerns in adherent and nonadherent patients (n = 221).

Necessity Scale (% agreeing or strongly agreeing)			Concern Scale (% agreeing or strongly agreeing)		
Necessity*	Adherent Patients	Nonadherent Patients	Concerns	Adherent Patients	Nonadherent Patients
At present, my health depends on medication	83	75	Having to take medicines worries me	59	51
My life would be impossible without medication	80	78	I sometimes worry about the longterm effects of my medicines	79	89
Without medication I become very ill	58	52	My medicines are a mystery to me	21	19
My future health depends on medication	77	66	My medicines disrupt my life	15	11
Medication protects me	81	86	I sometimes worry about becoming too dependent on my medicines	46	41

* Although the total score on the necessity beliefs differed significantly ($p = 0.02$) between the adherent and nonadherent patients, none of the individual items differed significantly.

Table 4. Satisfaction about medicine information in both adherent and nonadherent patients (n = 228).

Effects and Usage	% Satisfied	Potential Problems	% Satisfied
Medicine name	93	Which side effects	72
Indication	94	Side effect risk	64
Effects	81	What to do when side effects occur	67
Mechanism	72	Interactions	77
Duration effects	75	Alcohol use	64
Perceived effects	73	Drowsiness	67
Duration medicine use	59	Effect on sex life	46
Usage	94	Missed doses	77
Followup prescriptions	91	Effects on the unborn child	81

active coping, 17.4 ± 3.8; palliative reaction, 17.8 ± 3.1; avoidance, 16.1 ± 3.3; seeking social support, 12.2 ± 3.4; passive reaction pattern, 11.0 ± 3.2; expression of emotions, 5.6 ± 1.6; and comforting cognitions, 12.7 ± 2.2. None of the coping scales were related to differences in adherence.

Using the stepwise forward elimination procedure, with a removal level set at $p = 0.05$, logistic regression of noninteracting variables resulted in a 3-variable risk model ($R^2 = 0.11$) consisting of number of adverse effects ($p < 0.01$), disease duration ($p < 0.01$), and necessity of the medication ($p = 0.04$).

Associations with the MARS questionnaire. Similar results were found when either the dichotomized CQR or the dichotomized MARS was used to distinguish patient characteristics between adherent and nonadherent patients.

DISCUSSION

Using a self-report questionnaire, roughly two-thirds of the patients in this large random selected sample were adherent to DMARD. These levels of self-reported adherence are much lower compared to the 98.5% of patients declaring themselves to be adherent when asked face to face by a specialist pharmacy assistant. Nonadherence is hard to identify using general characteristics: only the beliefs about the necessity of the medication, the perceived side effects, and the disease duration were weakly associated with nonadherence. The proportion of nonadherent patients (60%–67%) is in agreement with previous studies indicating that 60%–80% of patients with RA taking DMARD are adherent[5-7].

As a consequence, a significant proportion of patients was not adherent to medication, and therefore there is a need to develop effective interventions to improve adherence in RA. Current interventions in patients with chronic conditions are not very effective[4,21]. It has been suggested that efficacy of interventions can be improved by tailoring them to the patients' main reason for nonadherence, as there are no barriers for adherence that apply to all nonadherent patients[18,22-25]. This is confirmed in our study — we found that nonadherence is unrelated to demographic and clinical characteristics, satisfaction about information, concerns about medication, and coping styles.

Only 3 variables were related to adherence in this descriptive study: disease duration, the number of attributed side effects of the medication, and beliefs about the necessity of the medicine. Although adherence seems to be higher shortly after a diagnosis, efforts to improve adherence should not exclude patients with short disease durations, as adherence is also not optimal in recently diagnosed RA.

The number of perceived side effects was the second variable related to adherence. In the nonadherent group the number of reported side effects was almost double the number reported by adherent patients. Although it is tempting, it is too early to assume that medication side effects cause lower adherence. An alternative explanation could be that a critical attitude toward medication causes lower adherence and raises the perception of side effects. In general, the level of reported side effects was high in our sample. A majority of the patients (58%) reported one or more medication side effects. This proportion is slightly lower compared to earlier studies observing that 60%–84% of the patients with RA reported side effects[13,26].

Finally, the role of beliefs underlines the complexity of adherence. Beliefs in the necessity of medication were high in our patient sample. Nevertheless, adherent patients had stronger beliefs about the necessity of their medication than nonadherent patients. The association of perceived need for medication and adherence is consistent with previous findings in studies in people with RA using the BMQ[12,26]. Despite strong beliefs about the necessity of their medication, patients in this sample simultaneously reported strong concerns about potential adverse effects, particularly in the long term. However, specific concerns about medications did not relate to adherence, in accord with previous research[12]. Patients seem to make a cost-benefit analysis to consider whether their beliefs about the necessity of medication outweigh their concerns about the potential adverse effects[12,26]. The moderate internal consistency of the concerns subscale, however, implies that future research is necessary to investigate the relationship between different concerns about medication.

Our study was based on data gathered in a large sample of RA patients taking DMARD. The selection ensured that the sample was representative of the patient population at

our clinic. However, the study has several limitations. These include the misclassification of adherence due to the absence of a "gold standard" for adherence, a possible overestimation of adherence, and problems in causal inference due to a cross-sectional design.

There is no gold standard for the assessment of adherence. As a result, the adherence estimates of different studies of the same patient and medication group vary significantly depending on the measurement instrument used[27]. Adherence seems to be underestimated by the MEMS device and overestimated by patient self-report and pill count[28]. In our study, the CQR was chosen because it is the only validated adherence questionnaire in rheumatology. However, the CQR relies partly on behavioral items, which could automatically lead to circularity between specific cognitions and adherence measured with the CQR. Therefore, in addition to the CQR a nonbehavioral questionnaire, the MARS, was used, and the results of these questionnaires did not differ. However, there is as yet no published MARS validation study. As a consequence, previous studies did not consistently use the same cutoff points to dichotomize the MARS scale in adherent and nonadherence patients[29,30]. Further studies are therefore needed to determine the best MARS cutoff point. Additional research is also warranted to differentiate adherence rates between different types of drugs, as both the MARS and the CQR are designed for general, and not drug-specific, adherence.

Another limitation of the study is possible overestimation of adherence due to the so-called Hawthorne effect. Given the design of the study, patients are aware that they are under observation, which may affect their normal behavior and lead to more conscientious medication use and better adherence.

Finally, the cross-sectional design implies that although variables related to adherence could be identified, no causal relationships can be assumed. Another disadvantage of the cross-sectional design is selection bias due to selective survival. For instance, if nonadherent patients are more likely to stop DMARD therapy, then our cross-sectional study may have included fewer nonadherent patients and may thus have underestimated nonadherence. Further research is needed to determine whether altering risk factors has an effect on the adherence rate. Further, the design did not measure changes over time. Adherence is a dynamic process, and patients' behavior can change over time[11,14,27]. Therefore, longitudinal adherence behavior patterns should be studied.

Nonadherence is a major problem that affects roughly one-third of RA patients who use DMARD. There is a need to develop effective interventions to improve adherence in this patient group. Besides practical barriers such as forgetfulness, interventions should also incorporate personal beliefs that may influence medication adherence and discuss patient concerns about medication and side effects. Future research is needed to determine the efficacy of interventions that are tailored to individual primary reason(s) for nonadherence. Only nonadherent patients should be included in this intervention.

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