Non-Adherence to Disease-Modifying Antirheumatic Drugs in Early Arthritis

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Chapter 1

General introduction

When patients receive their first medication for their rheumatic condition, it is essential that they use the medication as prescribed by their physician. If not, not only their disease will get worse, but the rheumatologist might wrongfully conclude that more intensive medication is needed. In this thesis we investigate the consequences of non-adherence in early arthritis patients and what causes patients to be non-adherent to the medication prescribed by the physician.

Early arthritis

Inflammatory rheumatic diseases present themselves in different forms, all being characterized by persistent synovitis and systemic inflammation. Rheumatoid arthritis (RA) is prevalent in about 1% of the Western population, and each year in 5-50 per 100.000 persons RA is diagnosed. The disease is more common in women and elderly.[1] Another form of inflammatory arthritis is accompanied with psoriasis; psoriatic arthritis (PsA). This diagnosis is made in slightly more males than females. Annual incidence rates range from 6 per 10.000 to 6.8 per 10.000 of the adult population.[2] Spondyloarthritis presents itself with inflammatory back pain and peripheral oligoarthritis. The incidence rate of spondyloarthritis ranges from 6.9 to 7.3 per 100.000 person years.[2]

What these diseases have in common is that, in the early stage of the disease, they present themselves with joint inflammation, leading to pain and loss of function. When poorly managed, the disease can cause joint damage, cardiovascular and other co-morbidities and a decreased quality of life. Therefore it is essential that patients adhere to the physician's treatment instructions in this early stage of the disease.

Treatment

Over the last decades the outcome for early arthritis has improved hugely, since it is treated timely and intensively, following the treat to target principle.[3, 4] Early arthritis is commonly treated with one or a combination of more disease-modifying antirheumatic drugs (DMARDs). The primary target of treatment is to reach a state of clinical remission, or at least a state of low disease activity. With a timely and intensive treatment in the first year after diagnosis, remission will be reached. Until remission is reached, treatment should be adjusted every three months, following the treat to target guidelines.[4] The first step-up in therapy is to higher DMARD dosages or additional DMARDs. When treatment with conventional, synthetic DMARDs fails, a step up to more expensive and advanced biological therapy is made. Decisions whether or not to step up are based on the effectiveness of the treatment as seen by patient and physician. Obviously, when the patient is non-adherent to the treatment, this insight is blurred and decisions about stepping up the treatment are made prematurely.

Non-adherence to treatment

Although the importance of adherence to medication is clear, still a large proportion of patients is non-adherent to their therapy. Research mainly focused on patients with chronic diseases, where the problem of non-adherence is more serious than in acute diseases. Non-adherence ranges from 0% to 95.4% with an overall average of 24.8%.[5] For HIV disease, adherence seems to be highest with an average of 88.8% and the lowest in sleep disorders, with an average adherence percentage of 65.5%.[5] The differences in non-adherence between various diseases might be due to the symptoms with which the disease expresses itself, and the experienced effect of the medication. For example, adherence to preventive medicine for hy-

pertension tends to be low, because patients might not feel ill, and do not experience the effect of medication but only the side-effects.

Patients with rheumatic diseases are reminded of their disease by pain, disability and fatigue, but might not experience the effect of medication right away. Compared with other chronic illnesses, patients with rheumatoid or inflammatory arthritis are rather adherent; on average 81.2% of the patients are adherent,[5] but the adherence rates vary widely from 49% to 99%.[6] When patients do not adhere to the therapy, their disease might worsen, and patients might present themselves as non-responders to therapy when in fact these patients are not adhering to their medication. By not adhering to their therapy, it will take longer for patients to obtain remission and the chance of obtaining joint damage will become higher. Non-adherence might also lead the rheumatologist to think that treatment is failing prematurely. The rheumatologist will then make an unnecessary premature switch to expensive biologicals. Non-adherence thus not only influences the individual patient, but also the rheumatologists' treatment decisions, probably leading to higher health care costs. In addition, due to non-adherence, symptoms and complications may worsen, leading to increased use of hospital and ER services, office visits, and other medical resources.[7] Non-adherence also implies that money has been wasted for unused medication.[8]

Definition of adherence

Adherence to medication is generally defined as 'the extent to which a person's behaviour – taking medication, following a diet, executing lifestyle changes – follows medical advice'.[9] This definition does not imply to what extend a patient should follow medical advice to be regarded as adherent or non-adherent. In studies on anti-rheumatic drugs, the most frequently used definition of adherence is defined as taking 80% or more of the prescribed medication over the duration of the study time.[6, 10, 11] However, there is no general accepted or empirical motivated cut-off when 'not following medical advice' can be regarded as non-adherence.

Because there is conceptual confusion about terms used, there is the need for a sound taxonomy. Recently, an European adherence working group (the ABC project) proposed the standardization of adherence terms and definitions. A differentiation between initiation, implementation and discontinuation was made.[12] The adherence process starts with initiation of the treatment, in which the first doses of a prescribed medication are taken. Implementation of the dosing regimen is defined as the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen. Discontinuation marks the end of therapy.

For patients with early arthritis, the initiation phase is the time it takes for the DMARDs to show its effects and this period can take up to three months. According to the guidelines for the management of RA, this period of three months is needed before deciding if a step-up in therapy is needed.[4] In this phase, the patient also learns to accept the need for the medication and learns to fit the medication schedule into daily life.[13] The implementation phase can be lifelong, since inflammatory arthritis is a chronic disease.

In this thesis we will focus on non-adherence in the initiation phase.

Measurement of non-adherence

Adherence can be assessed either by direct methods that measure drug metabolites or drug levels in blood, urine or tissue, or by indirect methods, such as pharmacy records, healthcare provider assessment, self-report and electronic monitoring.[14] Different adherence

measurement methods produce various adherence rates.[15, 16] Each method has his own advantages and disadvantages. Self-report is sensitive to socially desirable answers, since non-adherence is often seen by patients as deviant behavior. Measurement of drug metabolites may be inconvenient for patients and may give unstable results because of high biological variability. Indirect prospective measurement with electronic monitoring holds the assumption that medication is taken when the package is opened.[17]

There is no consensus about the preferred measurement of adherence to treatment with DMARDs. Direct methods were up till now not available for the measurement of DMARDs. Recently the measurement of methotrexate polyglutamates is upcoming for the measurement of methotrexate build-up, which is the anchor DMARD in early arthritis treatment.[4] This method might however be hard to use as an adherence measure, because there is high variability in pharmacokinetics and pharmacodynamics.[18, 19]

Self-report questionnaires that are available for the measurement of adherence in rheumatology patients are general questionnaires, such as the Morisky Medication Adherence Scale,[20] and specific questionnaires such as the Compliance Questionnaire Rheumatology.[21, 22] However, these questionnaires rely on the assumption that patients have experience with taking medication, and are not validated for the initiation phase of adherence behavior.

Electronic adherence measurement is nowadays regarded as a 'gold standard', because it objectively measures a small, but nevertheless necessary behavioral step of adherence 'real-time'. A frequently used electronic measurement method, is measurement with so called 'Medication Event Monitoring System (MEMS). This system consists of a medication vial with a cap. The medication vial cap contains a microprocessor that records the day and time of each vial opening. The data stored in the MEMS cap is transferred into a web-based data platform, which compiles hour-by-hour drug dosing histories over the treatment period, and medication regimen changes. With this measurement method, distinctions can easily be made between the different phases of adherence and persistence, which is not as easy with other measurement methods.

It is yet unclear how these different measurements relate to each other, which hampers research into non-adherence. For this reason, we will measure non-adherence in several ways, and investigate the relation between them.

Determinants of non-adherence

It seems counterintuitive to rather be in pain than to adhere to the treatment given. Why some patients do and some patients do not adhere to their treatment is unclear and depends on several factors. Patients may report intentional or unintentional poor adherence behavior.[9] Unintentional non-adherence (not being aware of not taking the medication, f.i. due to forgetfulness) might have other determinants than intentional non-adherence (not wanting to take the medication). Intentional non-adherence is mostly due to perceptual (affective) barriers, whereas unintentional non-adherence is mostly due to practical barriers.[23] A framework that is used to explain and understand perceptual barriers is the necessity-concerns framework.[24] This framework proposes that patients weigh the perceived necessity of the treatment against the concerns related to taking the medication. In addition to beliefs about the pharmaceutical treatment, beliefs or perceptions about the illness might play a role in adherence behavior.[25]

Non-adherence might not only be influenced by perceptual barriers, but also by medication characteristics, socio-economic and demographic factors, disease features, the doctor-patient relationship, and depression.[9, 26, 27]

For patients with rheumatic diseases specifically, there is a small body of evidence for determinants of adherence in the implementation phase.[28-32] Four barriers to medication adherence in RA patients in the implementation phase are reported: fear of side effects, perceived lack of efficacy of therapies, cost of medication and difficulty in obtaining treatment in a publicly funded health care environment.[28] Other factors found to influence medicine intake in RA patients in the implementation phase are ignorance and confusion about the medication regimen and interruptions to the daily routine.[29]

Although a large body of research has been done, there is still no consensus about the true determinants of adherence. This is partly due to heterogeneity across studies that examine factors related to adherence: heterogeneity in the study population (diseases studied, study period, type of study, recent onset or established disease), heterogeneity in the measurement of adherence behavior, and heterogeneity in the measurement of determinants. The other reason for the absence of true knowledge of the determinants of non-adherence is that human behavior is not always the product of a rational decision and therefore hard to predict.

Of the determinants that seem to influence adherence behavior, it is unknown in which phase of adherence behavior they are applicable. Since new patients are not familiar with their disease and medication, they may have certain perceptions and expectations about their disease and medication. It will take a while for the medication to have an effect, and factors such as concerns about having to live with a long-term condition may play a role in adherence behavior.[33] In the implementation phase, other factors might become more important, because patients have then more experience with their disease, with taking medication and have experienced the effect of the medication. Knowing which determinants are important in which phase may help clinicians to optimize treatment effectiveness.

There are several reasons why focusing on non-adherence in the initiation phase is important. First, in inflammatory arthritis, treatment is beneficial on the long-term when it is given early in the disease, and when it is targeted, i.e. adjusted according to the patient's disease activity. From this point of view, it is important to focus on determinants of non-adherence to the treatment especially in the initiation phase, so that there can be intervened early on.

Second, intervening on determinants of non-adherence in the initiation phase instead of in the implementation phase is more efficient, since in the initiation phase non-adherence behavior is being shaped. It is easier to change behavior before it has become a habit.

Third, from an economic perspective, identifying only patients at risk to become non-adherent is more efficient than focusing on all patients starting treatment. Only when knowing the determinants of non-adherence, interventions can be targeted and potentially be started.

Even though the importance of finding out what determines non-adherence in the first phase of medical treatment is clear, most studies on the determinants of non-adherence focused on the implementation phase ignoring the part that precedes the implementation phase: the initiation of medication. In this thesis adherence in the initiation phase is investigated. For that reason, a cohort study was set up. In this one-year cohort study, the associations between disease activity, health care costs, psychosocial variables and non-adherence are assessed. All subjects in the cohort study are patients who are recently diagnosed with either RA, PsA or undifferentiated arthritis and start taking one or more DMARDs for the first time.

Aims and outline of this thesis

The aims of this study were to:
1) assess the consequences of non-adherence to DMARD therapy on disease activity and hospital costs;
2) determine which measurement methods are feasible in daily practice for the measurement of adherence to DMARD therapy in early arthritis patients;
3) find factors associated with non-adherence to DMARDs in early arthritis patients;
4) develop a prediction tool to identify patients at risk for low adherence to DMARD therapy in the first three months of treatment.

This thesis gives a detailed description of DMARD intake behavior in the first year after diagnosis. Chapter 1 gives an introduction in the topics described in this thesis. Chapter 2 defines the association between non-adherence and disease activity in the first year of treatment (aim 1). Chapter 3 describes the hospital costs of RA, PsA and undifferentiated arthritis patients in the first year of treatment and explores the associations between hospital costs and non-adherence (aim 1). In chapter 4, different measures of non-adherence are described and compared with each other in a cohort of early arthritis patients that started DMARD treatment for the first time (aim 2). Chapter 5 systematically reviews the literature on factors associated with pharmaceutical treatment for rheumatoid arthritis patients (aim 3). In chapter 6, the patient perspective on DMARD non-adherence in the first phase of treatment is given (aim 3). In chapter 7, a stepwise procedure for the development of a prediction tool to predict which patients are at risk for non-adherence to DMARDs in the first months of treatment is outlined (aim 4). Chapter 8 describes the development and internal validation of a prediction tool for the identification of patients who are at risk for non-adherence at the start of treatment (aim 4). In chapter 9 the significance and clinical implications of the study results are discussed in the light of current literature. In addition, this chapter gives recommendations for the clinical practice and future research.

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Part 1

Consequences of non-adherence

Chapter 2

Non-adherence to Disease-modifying Antirheumatic Drugs is associated with higher disease activity in early arthritis patients in the first year of the disease

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Abstract

Introduction Non-adherence to disease-modifying antirheumatic drugs (DMARDs) hampers the targets of rheumatoid arthritis (RA) treatment; obtaining low disease activity and decreasing radiological progression. This study investigates if, and to what extent non-adherence to treatment would lead to a higher 28-joint count disease activity score (DAS28) in the first year after diagnosis.

Methods Adult patients from an ongoing cohort study on treatment adherence were selected if they fulfilled the EULAR/ACR2010 criteria for RA, and were to start with their first DMARDs. Clinical variables were assessed at baseline and every 3 months. Non- adherence was continuously electronically measured and was defined as the proportion of days with a negative difference between expected and observed openings of the medication container out of the 3-month period before DAS28 measurement. Generalized linear mixed models were used to investigate whether the DAS28 related to non-adherence. Covariates included were age, sex, baseline DAS28, Rheumatoid factor positivity, anti-cyclic citrullinated peptide antibodies (ACPA) positivity, anxiety, depression, weeks of treatment, number of DMARDs used, education level, use of subcutaneous methotrexate and biological use.

Results One hundred and twenty patients met the inclusion criteria for RA. During the study period 17 patients became lost to follow up. There was a decline in adherence over time for all DMARDs except for prednisone. Non-adherence is a predictor of disease activity in the first 6 months of therapy, adjusted for weeks of treatment, baseline DAS28, and baseline anxiety.

Conclusion Non-adherence relates to disease activity.. Therefore, interventions towards enhancing adherence can improve disease outcome.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease, which is characterized by joint inflammation with pain, swelling, damage and disability.[1] Early and adequate treatment with disease-modifying antirheumatic drugs (DMARDs) will prevent the disease from becoming worse. According to the guidelines, rheumatologists should strive for remission, or at least low disease activity within 3 months, in order to obtain the best functional and radiological outcomes.[2, 3]

Adherence to DMARD therapy is important to reach the desired treatment outcome as stated in the guidelines, especially at the start of treatment. Following the guidelines for the treatment of RA, drug therapy should be adjusted at least every 3 months until the desired treatment target is reached.[1, 3] When patients are non-adherent to their drug therapy, it seems as if treatment fails, whereas in fact patients are not taking their medication. When treatment with synthetic DMARDs fails due to overlooked non- adherence, a step-up in therapy will be made. The first step-up is treatment with higher DMARD dosages or adding other synthetic DMARDs, and adds unnecessary risks to the treatment. When this step-up also fails, treatment with biological, and more expensive DMARDs will be considered, adding even more costs and risks.[3] When prognostic unfavorable factors are present, an even earlier switch to biological DMARDs can be made according to the guidelines.[3]

At the individual level, large differences in treatment response, as measured with the 28-joint count disease activity score (DAS28), are observed.[4] It is unclear which factors attribute to these differences. Studies have shown that amongst many factors, part of them are explained by age, sex, baseline DAS28-score, presence of Rheumatoid Factor (RF) or Anti-cyclic citrullinated peptide antibodies (ACPA), type of treatment given, anxiety, coping with pain, locus of control (the extent to which patients believe they can control the pain).[5-11] Non-adherence would also be a logical contributor to individual differences in DAS28.

Early and adequate treatment of RA will prevent the disease from becoming worse, and therefore adherence to the treatment is important for the management of RA. The consequences of non-adherence will not only affect the patient's disease activity, but also the rheumatologist's treatment decisions,[12-14] which may lead to higher health care costs. Adherence in this early phase of disease has not been explored before. Furthermore, the extent to which non-adherence contributes to higher DAS28 in the first year of treatment is not yet determined. This study investigates if, and to what extent non-adherence to DMARDs would lead to higher DAS28 scores in the first year after diagnosis.

Patients and methods

Patients

A sample of 300 patients was consecutively recruited in 11 regional hospitals in the Southwest of the Netherlands from January 2012 to July 2014 for a cohort study on DMARD adherence. Patients who were willing to participate were followed up for one year. Patients were included if they were at least 18 years old, were started on one or more DMARDs for RA for the first time, and were able to sufficiently read and understand the Dutch language. For the present analysis, we only selected those patients included before January 2014 and who were diagnosed with RA according to the EULAR/ACR 2010 criteria for RA.

Participants in the study were on a fixed time interval seen by a research nurse or specialized

rheumatology nurse after their regular rheumatologist consultation. Because the time interval on which the patient is seen by the rheumatologist differed per hospital, the time intervals vary. In the first year after diagnosis, RA patients are mostly seen every three months, but this time interval varied depending on the rheumatologist follow-up appointment.

The Erasmus MC Medical research ethics commitee gave their approval to perform the study. Each hospitals' board of directors gave their approval for participation in the study. All participants gave written informed consent for their participation and for retrieving relevant clinical data from their patient file.

Primary outcome

Every 3 months the DAS28 was measured by a trained rheumatology nurse. The score comprises 4 domains: swollen joint count (SJC), tender joint count (TJC), erythrocyte sedimentation rate (ESR) and a patient general health assessment using a visual analogue scale (VAS). For patients that dropped out of the study, but did not withdrew their consent, the DAS28 score was retrieved from the patient files.

Clinical covariates

Clinical variables assessed at baseline included symptom duration before diagnosis, ACPA, RF, ESR (or CRP) and joint involvement. ACPA and RF were combined for a RF/ACPA positivity score. Symptom duration was dichotomized in more or less than 6 weeks, according to the EULAR/ACR 2010 criteria for RA. The number of DMARDs used was counted and analyzed as a continuous measure. The use of either subcutaneous methotrexate (MTX) or biologicals was noted from the patient file and entered as a binary variable.

Psychosocial covariates

Symptoms of anxiety and depression were measured at baseline with the Hospital Anxiety and Depression Scale (HADS).[15] The questionnaire has two subscales: one for anxiety and one for depression. The scores range between 0 and 21, higher scores indicating more symptoms of anxiety or depression.

Adherence measurement

Non-adherence was measured per DMARD using a 'Medication Event Monitoring System' (MEMS) device, which consists of a medication vial and a MEMS cap. The MEMS uses a microprocessor in the medication container cap to record day and time of each vial opening. The data stored in the MEMS cap is transferred into a web-based data platform, which compiles hour-by-hour drug dosing histories, and in which medication regimen changes are noted. Indirect adherence measurement with MEMS is regarded as a gold standard, since it objectively measures a necessary behavioural step for adherence in 'real time' over a continuum. Disadvantages of using MEMS are the high price, the fact that it does not proof ingestion of medication and that it might be seen as an intervention, although this intervention effect is regarded as negligible.[16] Nursing and medical staff were blind to the adherence data throughout the study.

Extra openings of the MEMS cap were ignored, because these mostly do not represent medication intake, but openings by pharmacists. These would otherwise lead to an overestimation of adherence.

When patients stopped using one or more DMARD on rheumatologist's advice, for example

in case of lab abnormalities, this was noted as a non-monitored period, which means that this period was not assigned as a non-adherence event.

For each individual patient and per DMARD, we calculated per day if there was medication underuse. Underuse was defined as a negative difference between the amount of observed openings minus the amount of expected openings. For methotrexate, we calculated the underuse not per day, but per week, since this medicine only needs to be ingested weekly. For the 12-week period before each DAS28 measurement, we calculated the proportion of days of DMARD underuse. If a patient used multiple DMARDs in the 12-week period, the mean underuse proportion was calculated. Adherence was also dichotomized using a non-adherence proportion above 0.2 (80% or less adherence) and using a non-adherence proportion above 0.1 (90% or less adherence).

When a patient used subcutaneous MTX, the patient was asked to put their folic acid in the MEMS container. The openings of the medication cap to take folic acid would then represent the use of subcutaneous MTX. Adherence to biologicals could not be measured. Patients that used biologicals also used other synthetic DMARDs to which adherence could be measured.

Statistical analysis

Characteristics of the study population and non-adherence per DMARD were described with means, standard deviations, medians, interquartile ranges and percentages as appropriate. Four regression models were run with DAS28 as dependent continuous outcome; at T1, over the period T1 to T2 (2 time points), the period T1 to T3 (3 time points), and the period T1 to T4 (4 time points) respectively.

First, univariate linear regression was performed for the T1 model to identify eligible predictors for the DAS28 score at T1. Predictors entered in the univariate regression were: standardized age, sex, baseline DAS28, RF/ACPA positivity, baseline anxiety, baseline depression, number of weeks using DMARDs, education level (low, medium or high), non-adherence, number of DMARDs used, use of subcutaneous MTX and biological use. Non-adherence and covariates with a p-value lower than 0.2 were entered in the multivariate model.

For the influence of non-adherence on DAS28 over T1 to T2 (2 time points), T1 to T3 (3 time points) and T1 to T4 (4 time points), multilevel regression models were performed with patients in the upper level and their repeated measures in the lower level. Variables that were taken into account in the models to predict DAS28 over time were: standardized age, sex, baseline DAS28, RF/ACPA positivity, baseline anxiety, baseline depression, number of weeks using DMARDs, education level (low, medium or high), non-adherence, number of DMARDs used, use of subcutaneous MTX and biological use. All possible predictors were entered in a univariate multilevel regression, taking into account the evolution of disease activity over time. Non-adherence and covariates with a p-value lower than 0.2 were entered in the multilevel model. Because of potential collinearity between anxiety and depression, only one of these covariates will be included in the multivariate models.

If our study was a hypothesis testing study, a Bonferroni correction should have been applied because of the number of possible covariates in the analysis. However, because of the explorative character of our study this requirement would be too strict, since then we would need a p-value below 0.004 to reach statistical significance, and then no covariates would be left over. A p-value below 0.05 was considered as statistical significant.

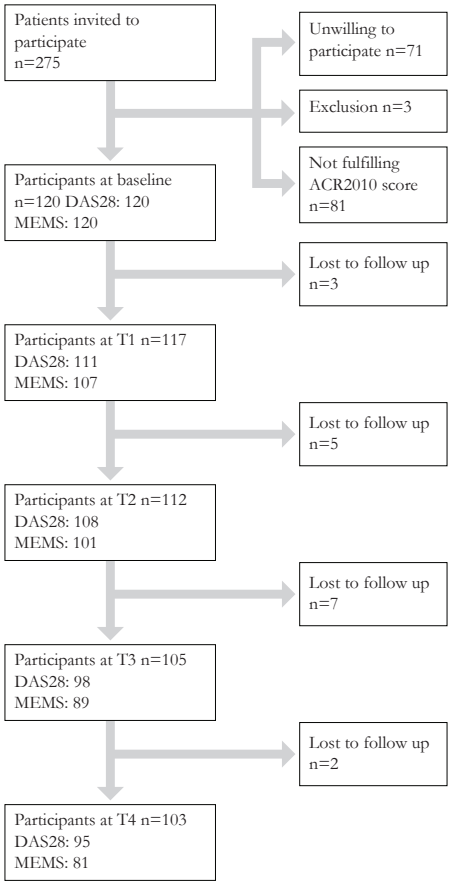
Results

Participants

Before January 2014, 275 patients were asked to participate. Of those, 71 patients declined to participate and 3 were excluded. The EULAR/ACR 2010 criteria for RA were fulfilled by 120 of the 201 participants. During the study period, 17 patients became lost to follow up (figure 1). Reasons for dropping out varied. Two patients stopped because of serious comorbidities, 4 patients did not show up at the study visits. Table 1 depicts the baseline variables. There are no significant differences between patients who became lost to follow up and patients with complete follow-up.

T1 (3 months) ranged from 5 to 20 weeks (mean 12 weeks), T2 (6 months) ranged from 16 to 33 weeks (mean 26 weeks), T3 (9 months) ranged from 20 to 49 weeks (mean 38 weeks) and T4 ranged from 41 to 68 weeks (mean 52 weeks). The distribution of weeks per time point was normal.

Figure 1. Flowchart of respondents



Abbreviations: DAS28: 28-joint count disease activity score, MEMS: medication event monitoring systems

Table 1. Baseline characteristics

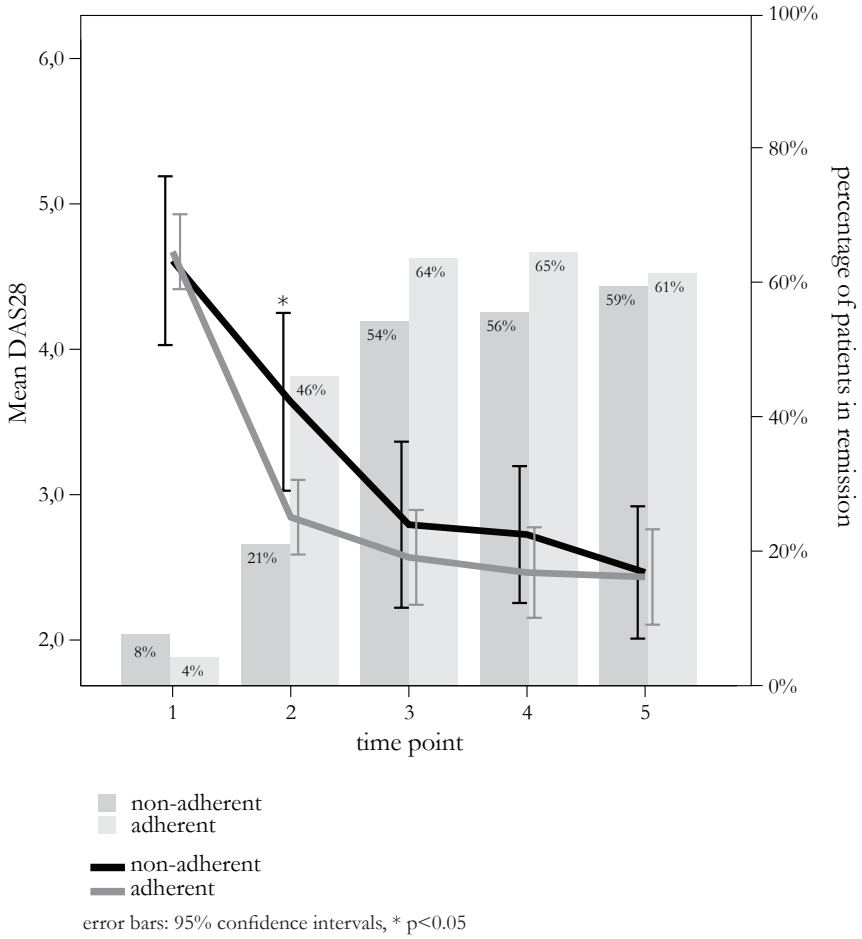
		All patients n=120	Patients with complete follow up n=103	Patients who became lost to follow up n=17
Age (years), mean (SD)		55.7 (13.2)	55.6 (13)	56 (15.3)
Sex, female, n (%)		80 (66.7)	71 (68.9)	9 (52.9)
TJC, median (IQR)		5 (2-11)	4 (2-11)	6 (3-10)
SJC, median (IQR)		3 (2-7)	4 (2-8)	3 (1-7)
ESR, mean (SD)		30.5 (23.3)	30.9 (24.1)	27.7 (17.9)
DAS28, mean (SD)		4.66 (1.3)	4.66 (1.29)	4.6 (1.4)
HAQ, median (IQR)		0.75 (0.38 – 1.13)	0.75 (0.38-1.14)	0.75 (0.25-1)
RF positive, n (%)		93 (77.5)	79 (76.7)	14 (82.4)
ACPA positive, n (%)		85 (70.8)	75 (72.8)	10 (58.8)
Symptom duration, >6 wk, n (%)		104 (86.7)	91 (89.2)	13 (81.3)
Nr of DMARDs at baseline (%)	1	54 (45)	44 (42.7)	10 (58.8)
	2	39 (32.5)	34 (33)	5 (29.4)
	3	23 (19.2)	21 (20.4)	2 (11.8)
	4	4 (3.3)	4 (3.4)	-
Subcutaneous use of MTX during one-year follow up, n (%)		20 (16.7)	16 (15.5)	4 (23.5)
Use of biologicals during one-year follow up, n (%)		11 (9.2)	10 (9.7)	1 (5.9)
Education level, n (%)	Low	58 (50.4)	48 (48)	10 (66.7)
	Intermediate	34 (29.6)	29 (29)	5 (33.3)
	High	23 (20)	23 (23)	-
HADS depression, mean (SD)		4.5 (SD 2.7)	4.4 (2.7)	4.6 (2.9)
HADS anxiety, mean (SD)		5.7 (SD 4.4)	5.9 (4.5)	4.5 (4.1)

Abbreviations: TJC: Tender Joint Count, SD: Standard Deviation, IQR: Interquartile Range, SJC: Swollen Joint Count, ESR: Erythrocyte sedimentation rate, DAS28: 28-joint count Disease Activity Score, HAQ: Health Assessment Questionnaire, DMARDs: Disease-modifying Antirheumatic Drugs, MTX: methotrexate, HADS: Hospital Anxiety and Depression Scale, RF: rheumatoid factor, ACPA: anti-cyclic citrullinated peptide antibodies

Disease activity

The mean DAS28 changed over time from 4.7 to 3.7 (3 months) to 2.7 (6 months), and 2.5 (9 and 12 months). For patients who became lost to follow up during the cohort, the mean DAS28 improved more in the first 3 months of treatment (from 4.6 to 2.5), but worsened slightly after 9 months (from 2.5 to 3.0). Figure 2 depicts the course of the DAS28 over time for adherent (underuse proportion less than 0.1) and non-adherent (underuse proportion more than 0.1) patients. Non-adherent patients have especially at T2 (3 months) a higher DAS28 ($p=0.01$). The proportion of patients achieving remission (DAS28<2.6) is at baseline 5%, 41.4% at T2, 58.3% at T3, 61.2% at T4, and 57.9% at T5. When we split the patients up in adherent and non-adherent especially at T2 (3 months of treatment), two times more adherent patients are in remission (figure 2) ($p<0.05$).

Figure 2. Mean disease activity and percentage of patients in remission for patients more or less than 10% adherent

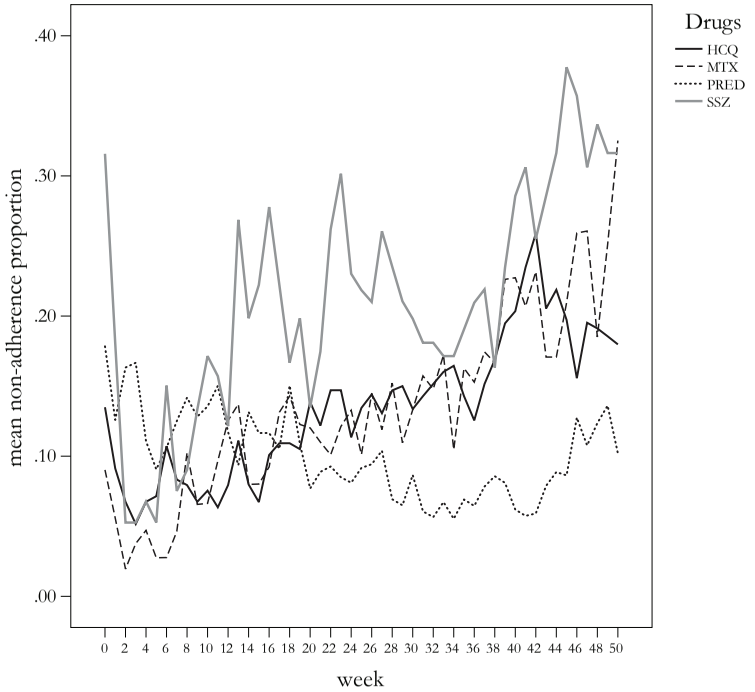


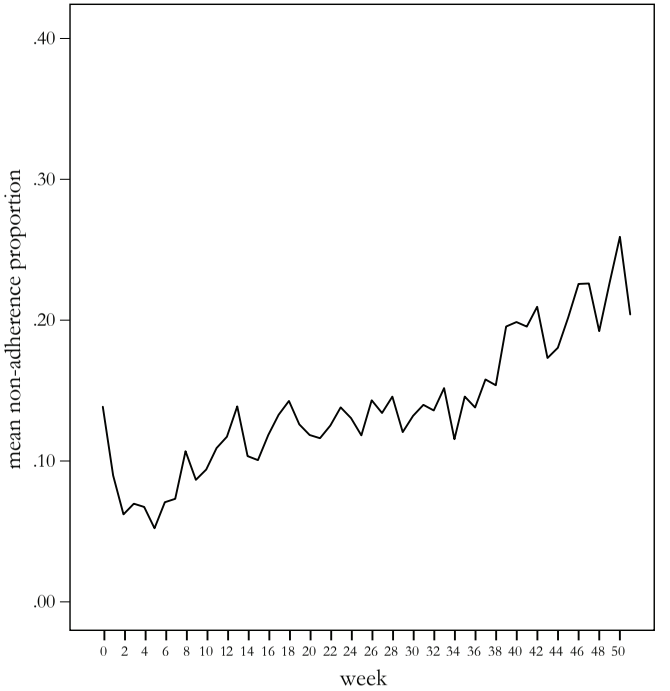
error bars: 95% confidence intervals, * p<0.05

Non-adherence

Most patients were started on monotherapy, of which MTX was prescribed the most often (43.3%). A combination of methotrexate and prednisone bridging therapy with or without an additional DMARD was started for 32.5% of the patients. Triple therapy following the O'Dell' scheme was started for 13 patients (10.8%). Mean non-adherence proportions increase over time (figure 3). Non-adherence proportions per DMARD also increased over time, except for prednisone (figure 3). Non-adherence proportions were highest for sulfasalazine. Methotrexate was the most used DMARD, but for this drug, the non-adherence proportion also increased to 0.3 after week 50. Using an 80% adherence cut-off, for sulfasalazine the least patients were adherent, declining from 80% (3 months) to 53.8% (12 months). For methotrexate, adherence declined from 91.2% (3 months) to 69.3% (12 months). Over the study period, oral MTX was tapered the most. Two patients used leflunomide, which was not depicted in the graph.

Figure 3. Non-adherence over the one-year follow-up period for the separate DMARDs (left) and mean non-adherence (right)





Nr. of patients using each DMARD per month

	1	2	3	4	5	6	7	8	9	10	11	12
DMARD												
MTX	116	109	107	103	99	100	98	90	86	84	82	78
PRED	45	41	39	38	38	37	35	33	31	30	29	27
HCQ	36	36	36	36	34	34	34	33	33	33	32	30
SSZ	19	19	19	19	18	18	17	15	15	14	14	14
ARA	-	-	1	1	1	1	1	2	1	-	-	-
MTXsub	-	-	2	5	7	8	11	13	15	17	19	20
Anti-TNF*					1	1	2	3	3	5	5	8

* 3 patients started anti-TNF just after month 12
Abbreviations: DMARD: disease-modifying antirheumatic drugs, MTX: methotrexate, PRED: prednisone, HCQ: hydroxychloroquine, SSZ: sulfasalazine, ARA: leflunomide, MTXsub: subcutaneous use of methotrexate, anti-TNF: anti-tumour necrosis factor

T1: 3 months

Table 2 shows the univariate and multivariate regression analyses for each time period. In the multivariate regression model for DAS28 outcome at 3 months, non-adherence, weeks of treatment, baseline DAS28 and baseline anxiety were entered as predictors. The influence of non-adherence on disease activity is strongest in the first months of treatment. At T1, being non-adherent increases the DAS28 the most with 1.18 (95% CI - 0.07, 2.42), but is not significant with a p-value of 0.07.

T1-T2: 3 to 6 months

In the time period 3 to 6 months, non-adherence, weeks of treatment, baseline disease activity, standardized age and baseline anxiety were entered in the multivariate model. Non-adherence is a significant predictor of disease activity over time (independent of weeks of treatment, and baseline disease activity). Biological use was not taken into account in the multivariate model, since only 1 patient used biologicals at that time.

T1-T2-T3: 3 to 9 months

For the time period 3 to 9 months, non-adherence, weeks of treatment, baseline disease activity, standardized age, and baseline anxiety were entered in the multivariate model. Non-adherence was not a significant predictor of disease activity in this time period adjusted for the other variables.

T1-T2-T3-T4: 3 to 12 months

Over the whole first year of treatment, non-adherence and the same variables as in the 3 to 9 month model were entered in the multivariate model. Over this time period, non- adherence was also not a significant predictor of disease activity adjusted for the other variables.

Other predictors

The number of weeks of treatment influences the DAS28 at all time periods. The longer time on treatment, the lower the DAS28. The influence of time on treatment is at T1 (3 months) the highest and decreases when lengthening the time period.

The DAS28 score at the start of treatment is a predictor of the disease activity in the first year of treatment. The effect of the baseline DAS28 on the DAS28 decreases over time, but remains a significant predictor and lowers over time from 0.38 (T1) to 0.25 (T4).

Anxiety as measured with the HADS was multivariate not a significant predictor of disease activity.

Table 2. Univariate and multivariate generalized Linear Mixed Model for repeated data: determinants for DAS28 over the first year for rheumatoid arthritis patients over a 3, 6, 9 and 12-month period

	T1: 3 months				**T1-2: 3-6 months**				**T1-2-3: 3-6-9 months**				**T1-2-3-4: 3-6-9-12 months**			
	Univariate	p-value	Multivariate	p-value	Univariate	p-value	Multivariate	p-value	Univariate	p-value	Multivariate	p-value	Univariate	p-value	Multivariate	p-value
Intercept			2.02	<0.01			1.45	<0.01			1.57	<0.01			1.65	<0.01
Non-adherence	1.22	0.06	1.14	0.08	1.18	0.01	1.04	0.03	0.71	0.07	0.52	0.18	0.28	0.40	0.19	0.57
Weeks on DMARDs	-0.10	0.25	-0.08	0.10	-0.02	0.02	-0.02	<0.01	-0.02	<0.01	-0.02	<0.01	-0.01	<0.01	-0.01	<0.01
Baseline DAS28	0.36	<0.01	0.38	<0.01	0.35	<0.01	0.32	<0.01	0.32	<0.01	0.28	<0.01	0.30	<0.01	0.25	<0.01
Age (standardized)	0.01	0.17	0.001	0.92	0.02	0.07	0.01	0.29	0.02	0.03	0.01	0.11	0.02	0.03	0.01	0.11
Baseline anxiety	0.04	0.15	0.02	0.49	0.05	0.08	0.04	0.13	0.05	0.06	0.04	0.07	0.04	0.06	0.04	0.09
Education level	-0.17	0.63			-0.16	0.27			-0.16	0.23			-0.16	0.20		
biological use	#				1.73	0.02	#		0.09	0.83			-0.09	0.78		
subcutaneous MTX	0.38	0.51			0.43	0.23			0.32	0.24			0.16	0.51		
Gender	0.22	0.39			0.19	0.44			0.14	0.53			0.08	0.72		
Baseline depression	0.05	0.31			0.04	0.33			-0.03	0.43			0.02	0.62		
ACPA/RF	-0.11	0.40			-0.04	0.73			-0.04	0.74			-0.002	0.98		
Nr of DMARDs	0.08	0.54			0.03	0.79			0.02	0.83			-0.02	0.84		
Symptom duration > 6 weeks	-0.07	0.84			0.04	0.92			0.05	0.88			0.03	0.92		

Abbreviations: DAS28: 28-joint count Disease Activity Score, MTX: methotrexate, ACPA/RF:Anti-citrullinated protein antibody, RF: rheumatoid factor
no / only 1 patient received biologicals at this time point

Discussion

The results of the present study indicate that non-adherence is a serious problem in the treatment of RA and that non-adherence corrected for other predictors hampers achieving remission in the first 6 months of treatment. Non-adherence increases over time for all DMARDs, except for prednisone. It was a strong predictor of higher disease activity and thus contributes to failure in obtaining remission. In addition, weeks on treatment and baseline disease activity influence the disease activity over time in the first year of treatment.

The effect of non-adherence disappeared after T2. A likely explanation for this effect is that if disease activity remained too high, a step-up in therapy was made following the treat-to target principle, regardless of unknown underlying non-adherence behavior.[3] Patients are probably more likely to adhere to the next step-up in treatment. An explanation for this is that they might need time to get used to taking medication or might be more adherent to more expensive and advanced therapy.[17] Unfortunately, we could not measure adherence to subcutaneous MTX and biological treatment, which was given to respectively 19.4% and 7.8% of patients, so we could not confirm if this was in fact the case. The course of the DAS28 over the first year of treatment in our cohort is similar to that of other studies in which patients were treated according to the treat to target principle,[18] which supports our explanation that patients were treated to target.

Time on treatment significantly influences the DAS28 at each time point. This is what we expect, because the more time the patient is on treatment, the lower the DAS28 is, especially in the early phase of treatment. The effect of time on treatment is highest after 3 months, and decreases during the course of the treatment. During the first months, time on treatment has larger effects than later in the course of the treatment, because the disease activity is then diminished.

Baseline disease activity is a significant predictor of the DAS28, regardless of the time period the patient has been treated. This is a known predictor of disease activity after 3 months,[9] but no studies have been conducted on the influence of baseline disease activity on DAS28 after a longer period of time, except one study, which showed that baseline disease activity was a significant predictor of disease activity in established patients after a two-year period.[11] There is a tendency for the effect of baseline disease activity becoming less over time, which is what we would expect when patients are treated to target.

Interestingly, non-adherence increased over time, except for prednisone. This is probably due to the immediate effect it has on the arthritis symptoms. For other DMARDs, it can take up to several weeks for an effect to be felt. It is logical that patients are more often non-adherent to drugs that have a delayed effect on the symptoms. For rheumatologists, it is important to be aware that patients are more often adherent to prednisone than to other DMARDs.

Although all patients in this study were diagnosed with RA according to the EULAR/ACR2010 criteria, there was high variability in treatment strategies used. From the data that we have, it is hard to determine if all patients were indeed treated according to the treat to target principles. Patients in this cohort might have been subjected to over- or undertreatment, which might increase or reduce the effects of non-adherence. Undertreatment occurs when the patient does not receive a step-up in treatment when needed according to the DAS28. Research has shown that rheumatologists' non-adherence to the EULAR treatment guidelines in fact results in not obtaining remission.[19] In the case of undertreatment, being non-adherent will probably have larger effects on the DAS28 score, whereas in the case of overtreatment, the effect of non- adherence might be smaller. To overcome this possibility of confounding, we took in the regression analysis the number of DMARDs prescribed at each time point into account.

When a patient has an increase in DAS28 and does not receive a step-up in treatment with additional DMARDs, this patient could be undertreated. In all the regression models, the number of DMARDs was not a significant predictor of disease activity. The effect of non-adherence still remained.

The outcomes of this study might have been subjected to the 'adherer effect'.[20] Patients who adhere to the rheumatologists' prescription have better disease outcomes, regardless of the underlying treatment. This theory is based on the finding that behaviors of adherent people are different from the behaviors of non-adherent people. Adherent people have better global health outcomes, since they have more healthy lifestyles, do not engage in risky behaviors and are more adherent to nonpharmacologic prescriptions.[11, 21, 22] If we take this limitation into account, we can conclude that we are dealing with a rather adherent cohort. If more non-adherent patients would be in the study, there would have been more variation in adherence and maybe a stronger effect of non-adherence on disease outcome.

A limitation of this study is that the effect of patient education on adherence is unknown. Literature suggests that poor education about the disease and its treatment may have limited and short-term effects on non-adherence.[23] In our study, all patients received at least once education from the specialized rheumatology nurse, unless they were unwilling to receive such education. However, the education given needs to be congruent with the patients' lay beliefs.[23] We do not know whether this was the case. It may have been better if patient education was standardized over the participating hospitals and measured in this cohort. Another limitation is that there are a few missing DAS28 observations, which we chose not to impute. Because of the exploratory character of this study no multiple testing correction is applied. This might have caused arbitrary findings. However, if we would have corrected for multiple testing our selection criteria for the multivariable model would have been too stringent. A strength of our study is that we measured adherence to DMARDs with the most accurate method we have up to now : electronic monitoring. Monitoring with MEMS might be seen as an intervention, but this effect is regarded as negligible.[16]

Furthermore, patients can 'cheat' with MEMS, for example by opening and closing the pill box but not taking the prescribed medication. Nonetheless, electronic monitoring has been proven to be superior to patient self-reports and pill count in measuring adherence.[24, 25] In this study, electronic monitoring offered the advantage of studying adherence over a continuum, allowing to select specific adherence period previous to DAS28 measurement. This would not have been possible with the use of questionnaires. Furthermore, using MEMS resulted in adherence data on the separate DMARDs, which would not have been possible if we had used conventional questionnaires.

During the follow-up time of the cohort, 17 patients became lost to follow up. It could be that these patients are less adherent than the patients that completed the follow-up. We reviewed the patient files for information on the disease activity from the patients that became lost to follow up. Strikingly, the disease activity from these patients was after three months 0.54 point lower than for the patients that stayed in the cohort, whereas the disease activity for these patients was after a year 0.58 point higher than for the patients who remained in the study. This finding suggests that these patients reached low disease activity relatively soon. Experiencing no or minimal symptom severity might trigger these patients to become less adherent, because they do not experience the need for taking their medication.[17] Non-adherence to their treatment might have caused in a later stage a higher disease activity.

Conclusion

This study showed that in the first half year of treatment non-adherence is an important predictor of higher disease activity in the first 6 months of treatment. Since we know from literature that it is important to reach remission as soon as possible to avoid permanent damage, the so-called window of opportunity, non-adherence needs extra attention especially in the first year of treatment. Rheumatologists should above all be aware that non-adherence is an important factor to take into account when treating the patient and evaluating DMARD efficacy and side-effects. Shared decision making is seen as an important overarching principle of care and has been added to the European League Against Rheumatism (EULAR) recommendations for the management of rheumatoid arthritis in 2010.[1] Shared decision making is indeed a way in which the rheumatologist can improve patient adherence.[26-28] In daily practice, the rheumatologist should build towards an open and trustworthy relationship with the patient, in which non-adherence can be openly discussed. .When the rheumatologist has a trusting relation with the patient, the rheumatologist will be able to know if non-adherence is hampering the treatment goal.

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Chapter 3

Does non-adherence to DMARDs influence hospital-related healthcare costs for early arthritis in the first year of treatment?

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Submitted

Abstract

Introduction Non-adherence to disease-modifying anti-rheumatic drugs (DMARDs) is suspected to relate to health care costs. In this study we investigated this relation in the first year of treatment.

Methods In a multi-center cohort study with a one year follow up, non-adherence was continuously measured using electronic monitored medication jars. Non-adherence was defined as the number of days with a negative difference between expected and observed opening of the container. Cost measurement focused on hospital costs in the first year: consultations, emergency room visits, hospitalization, medical procedures, imaging modalities, medication costs, and laboratory tests. Cost volumes were registered from patient medical files. We used Spearman rank correlations to measure the association between non-adherence and costs, and other variables (age, sex, center, baseline disease activity, diagnosis, social economic status, anxiety and depression) and costs.

Results Of the 275 invited patients, 206 were willing to participate. 74.2% had rheumatoid arthritis, 20.9% had psoriatic arthritis and 4.9% undifferentiated arthritis. 23.7% of the patients were more than 20% non-adherent over the follow-up period. Mean costs are € 2117,25 (SD € 3020,32). Non-adherence was positively correlated to costs (rho 0.146), in addition to baseline anxiety, baseline depression, and baseline disease activity.

Conclusion Non-adherence is associated with health care costs in the first year of treatment for arthritis. This suggests that improving adherence is not only associated with better outcome, but also with savings.

Introduction

Reviews have shown that in rheumatoid arthritis (RA), 49% to 99% of patients are adherent, depending on the measurement method of adherence.[1] Up till now, it is unclear what the actual impact is of non-adherence to disease-modifying antirheumatic drugs (DMARDs) to direct health care expenditures. Non-adherence to DMARDs is suspected to increase health care costs.[2] The aim of this study is 1) to examine the magnitude of the health care costs for inflammatory arthritis in the first year after diagnosis and 2) to determine whether non-adherence to DMARDs has an impact on health care costs.

Health care expenditures for rheumatoid arthritis care comprise of 0.6% of the Dutch healthcare expenditures.[3] These costs consist of 51% medication and aids for rheumatoid arthritis, 19% elderly care, 18% hospital care and 9% primary care (GP visits).[3] Healthcare costs for RA impose a burden on individual RA patients, health services and society.[4] Studies suggest that drug treatment reduces overall healthcare costs by reducing patients' need for expensive medical services such as hospitalization and emergency room (ER) treatment.[5] This observation also suggests that improved adherence reduces health care costs.

Over the last decades the outcome for early arthritis has improved tremendously, since it is treated timely and intensively, following the treat to target principle.[6, 7] The primary target for treatment is to reach a state of clinical remission or at least a state of low disease activity. With a timely and intensive treatment in the first year after diagnosis, remission can be reached. This intensive treatment will benefit the long term disease outcome. Therefore, drug therapy is given in an early phase, which consists of DMARDs and corticosteroids.[7] Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 months.[6, 7]

When treatment with conventional, synthetic DMARDs fails, a first step-up will be made to higher DMARD dosages or additional DMARDs. This can, for some patients, lead to undesirable side effects, such as gastro-intestinal problems, liver or kidney abnormalities.[8] When this occurs, patients may be referred to other medical specialists, which causes more health care expenditures. When step-ups to conventional DMARDs fail, a step-up to treatment with advanced, but also much more expensive biologicals will be made. That suggests that especially in the first year of treatment, adherence is related to treatment success and costs.

Non-adherence can be expected to cause either more or less health care costs. Usually, the relation in which non-adherence leads to ineffective treatment and higher costs due to substituting expensive treatment, is emphasized. Indeed, the burden of a complex and inconvenient dosing regimen, which commonly causes side-effects, has a negative impact on adherence to treatment and this can hamper to achieve the full benefits of the therapy and logically to poorer long-term outcomes.[9-12] Symptoms and complications may worsen, leading to increased use of hospital and emergency room (ER) services, office visits, and other medical resources.[13] Non-adherence can also imply that money has been wasted for unused medication.[10]

On the other hand, non-adherence to DMARDs might also lead to less experienced side-effects. Patients reported that if side-effects outweigh the experienced benefits of the treatment, this is one of the reasons for them to stop taking the medication.[14] This might mean that non-adherent patients are less often referred to medical specialists because of adverse events. From previous studies it is also known that a small amount of patients are not only non-adherent to medication, but also to rheumatologist appointments. These patients avoid health care consumption and might therefore cause even less direct health care expenditures, regardless of possible worsening of their disease activity.

In this study we investigated the hospital costs of arthritis psoriatica (PsA), RA and undifferentiated arthritis in the first year after diagnosis and its association with adherence.

Patients and methods

Patients

From an ongoing adherence cohort study with a one year follow-up, we selected the patients who had finished their participation in the study between March 2013 and December 2014. Patients were recruited in 11 regional hospitals in the Southwest of the Netherlands. The hospitals consisted of one academic hospital, one specialized clinic and 9 general hospitals. Patients were included if they were at least 18 years old, started using DMARD therapy for RA, PsA or undifferentiated arthritis for the first time, and were able to read and understand sufficient Dutch. Clinical variables were assessed at baseline (diagnosis, symptom duration before diagnosis, anti-cyclic citrullinated peptide antibodies (ACPA), RF and joint involvement) and every three months (28-joint count disease activity score (DAS28)) by the specialized rheumatology nurse or a research nurse. At baseline, patients filled out the Hospital Anxiety and Depression scale (HADS),[15] which consists of two subscales: one for anxiety and one for depression. The scores range between 0 and 21, higher scores indicating more symptoms of anxiety or depression. At baseline, the Health Assessment Questionnaire (HAQ)[16] was filled out to measure physical functioning. This self-administered questionnaire is a validated measure of disability which includes 20 specific functions that are grouped into categories: dressing and grooming, arising, eating, walking, personal hygiene, reaching, gripping and other activities. The average of these scores represents a physical functioning score. HAQ scores range from 0 (no difficulty) to 3 (unable to do).

Ethics statement

The Erasmus MC Medical Ethics board approved this study. The hospitals' board of directors of the Bronovo, Haga hospital, Groene Hart, Amphia, Sint Maartenskliniek, Sint Antonius, Reinier de Graaf Gasthuis, Sint Franciscus Gasthuis, Lievensberg and Franciscus hospital gave their consent for participation in the study. All participants gave written informed consent for their participation and for looking up clinical data in their patient files.

Estimating direct healthcare volumes

In health economics, preferably all costs associated with the treatment are included. This would include not only the treatment costs made in the hospital, but also medical costs made outside the hospital, travel costs and costs of productivity loss. However, in this investigation we had only access to hospital files. These hospital files contain information about care at the department of rheumatology and the other departments in the hospital.

The number of visits to the rheumatologist and the specialized rheumatology nurse as well as visits to other medical specialists, medical procedures , imaging modalities, hospital admissions, laboratory tests and use of biologicals and/or subcutaneous use of methotrexate were extracted from the patient hospital files by two investigators (AP, LS) from the date of diagnosis until one year after diagnosis. We only extracted information from the patient files from the hospital in which the patient went to the rheumatology outpatient clinic. The number of comorbidities per patient was measured as the number of separate medical specialists the patient went to without

being referred by the rheumatologist. The number and type of DMARDs (including prednisone) used were derived from an online system in which the rheumatology nurse had entered the prescribed DMARDs, dosage and regimen during the one year follow up period.

To gain more insight into which costs are affected by adherence, the hospital costs were divided into three categories: rheumatology outpatient clinic costs, rheumatology referral hospital costs (including rheumatology outpatient clinic costs) and all other hospital costs (including the rheumatology clinic and rheumatology referral costs). Each cost part was subdivided into: a) costs for consultations (including telephonic patient consultations), b) medical procedures (therapeutic as well as diagnostic), c) imaging modalities, d) admissions (including day admissions), and e) ER visits. For rheumatology outpatient costs, we also subdivided the costs in f) laboratory costs, and g) medication costs (costs for synthetic and biologic DMARDs, costs for prednisone). For visits to other specialists, no data was available on laboratory costs and medication costs.

Due to time constraints it was impossible to register per individual patient all types of blood tests that were conducted in one year. Because the standard strategies of rheumatology lab monitoring differ per hospital, we randomly selected a number of 10 patients per hospital to determine which set of laboratory tests are commonly conducted. We calculated the total costs for these test sets and then counted per patient how many times laboratory tests were requested for monitoring.

Unit prices

To assign unit prices to the different cost categories we used costs derived from the Dutch manual for cost of illness studies[17] and the Dutch price list for medical treatments, supplement 2.[18] For medication costs, we used the Dutch price list for medication.[19] In case of the existence of different medicine manufacturers, the mean medication price was used. All unit prices were corrected for inflation to June 2014 using the inflation numbers from the Central Bureau of Statistics.[20]

Non-adherence measurement

Non-adherence was measured using Medication Event Monitoring System (MEMS) devices, which consist of a medication vial and a MEMS lid. The MEMS uses a microprocessor in the medication jar lid to record the day and time of each vial opening. The data stored in the MEMS lid is transferred into a web-based data platform, which compiles hour-by-hour drug dosing histories over extended periods, and in which medication regimen changes are noted. Nursing and medical staff were blind to the adherence data throughout the study.

Extra openings of the MEMS cap will be ignored, because these are mostly not representing medication intake, but openings by pharmacists. This could otherwise lead to an overestimation of adherence. Each day when the medication cap was not opened when it should have been opened, was assigned as a non-adherence event. When a patient stopped taking their DMARD medication on rheumatologist advice, for example in the case of lab abnormalities, this was not assigned as a non-adherence event. For the whole one-year period an underuse proportion was calculated by adding all non-adherence events and dividing them by the expected amount of days with openings. If a patient used multiple DMARDs in the one-year follow-up period, the mean of the DMARD underuse proportions was calculated.

Missing data

Patients were excluded when a patient became lost to follow up in the clinic, and the hospital files did not include the healthcare consumption of the whole year. For some patients, adherence data was incomplete because of lost to follow up in the study. If a patient had less than one month of adherence data, the patient was excluded from analysis. For patients who had less than one year monitoring data, the mean underuse proportion for the observed amount of days was used to estimate adherence over the whole year. The disease activity from patients who were lost to follow up from the study was extracted from the patient files.

Statistical analyses

We used univariate descriptive measures to report demographic and disease characteristics of the study population. Statistical comparison of the baseline characteristics between patients lost to follow up and patients with complete follow up were made with Student t-tests and chi square tests. Cost data is usually skewed, with some patients making much more costs that the mode. For this reason, non-parametric Spearman rank correlations were calculated between non-adherence (continuous scale), anxiety, depression, number of comorbidities, education level, baseline disease activity, age, gender and the three cost categories. For the association between non-adherence and costs, x-rays of the hand and feet were not included, because they were taken for most patients, but sometimes just within the one-year timeframe and sometimes just outside the timeframe. This could otherwise lead to an over- or underestimation of the associations between variables and costs. They were, however taken into account in the description of the costs.

To check for interaction effects between non-adherence with anxiety, depression, number of comorbidities, education level, baseline disease activity, age and gender, Spearman rank correlations were calculated.

To visualize the association between non-adherence and costs, non-adherence was categorized per 0.05 non-adherence proportion, resulting in an ordinal scale with 20 categories. The mean patient costs were plotted per non-adherence category.

Non-adherence was also dichotomized using an 80% adherence cut-off. The proportional distribution of costs were visualized in pie charts for adherent and non-adherent patients. Mann-Whitney U tests were used to compare the median costs per category for adherent and non-adherent patients.

Results

Patients

Of the 275 invited patients, 206 were willing to participate. Twelve patients were lost to follow up either in the clinic or during the study period and were excluded from analysis, which left 194 patients with complete cost data (figure 1). Of the 206 patients who were included in the study, for 144 patients, 1-year adherence data was available, for 171 patients, more than 200 days of adherence monitoring data was available.

In table 1, the demographic and disease characteristics of the study population are presented. Most patients (74.2%) had rheumatoid arthritis. Patients who became lost to follow up were younger, more often male and they had a lower baseline disease activity than the patients with complete follow up. The mean HADS anxiety score is much higher for the patients who became lost to follow up than for the patients with complete follow up (10.0 versus 5.5; p=0.015).

Figure 1. Flowchart of respondents

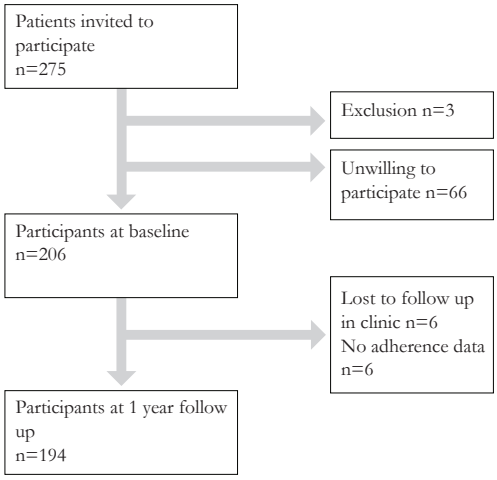


Table 1. Demographic and disease characteristics and adherence percentages

		Total (n=206)	Patients with 1-year follow up (n=194)	Patients lost to follow up (n=12)
Age in years, mean (SD)		53.7 (14.2)	54 (14)	46.3 (16.4)
Gender, female, n (%)		130 (63.1)	123 (63.4)	7 (58.3)
Type of hospital, n (%)				
General		175 (84.9)	165 (85.1)	10 (83.3)
Academic		31 (15.1)	29 (14.9)	2 (16.7)
Diagnosis n (%)	RA	153 (74.2)	145 (75.9)	8 (66.7)
	PSA/ arthritis with Crohn	43 (20.9)	41 (21.1)	2 (16.7)
	other	10 (4.9)	8 (4.1)	2 (16.7)
Baseline DAS28, mean(SD)		4.24 (1.36)	4.26 (1,36)	3.87 (1.43)
Baseline HAQ, median (IQR)		0.75 (0.29-1.13)	0.75 (0.25-1.13)	0.94 (0.69-1.34)*
Education level, n (%)	Low	87 (42.2)	85 (43.8)	2 (33.3)*
	Medium	63 (30.6)	61 (31.4)	2 (33.3)*
	High	43 (20.9)	41 (21.1)	2 (33.3)*
HADS anxiety, mean (SD)		5.6 (4.5)	5.4 (4.4)	10 (5.3)*
HADS depression, mean (SD)		4.5 (3)	4.5 (3)	5.6 (3.4)*
Medication characteristics				
Subcutanuous MTX , n (%)		39 (18.9)	37 (19.1)	2 (16.7)
Use of biologicals, n (%)		20 (9.7)	19 (9.8)	1 (8.3)
Mean 1-year non-adherence proportion (1 = non-adherent)	MTX	0.3 (n=194)	0.14 (n=184)	# (n=10)
	PRED	0.17 (n=70)	0.12 (n=65)	# (n=5)
	SSZ	0.22 (n=31)	0.17 (n=28)	# (n=3)
	HCQ	0.19 (n=47)	0.15 (n=45)	# (n=2)
	ARA	0.03 (n=2)	0.03 (n=2)	-

Abbreviations: DAS28: 28 joint count Disease Activity Score; HAQ: Health Assessment Questionnaire; DMARDs: Disease-modifying Anti-Rheumatic Drugs; MTX: methotrexate, PRED: prednisone; SSZ: sulfasalazine; HCQ: hydroxychloroquine; ARA: arava, #: no adherence data was available, *6 patients had missing data

Furthermore, there were no statistical significant differences between those patients lost to follow up and patients that completed the cohort.

Health care costs

The average costs for the rheumatology outpatient clinic over the one-year period are € 1455,76 (SD € 2402,04), the average one-year costs including referrals are € 1620,47 (SD € 2471,14) and the average total costs for this patient group are approximately € 2117,25 (SD € 3020,32) per year. As expected, among the patients, there was high variability in health care consumption, which results in skewed data. The number of patients using the various types of health care is given in table 2. The mean number of rheumatology visits is 4.64 (range 2-11) and the mean number of specialized rheumatology nurse visits is 3.2 (range 0-5). Of the imaging modalities, x-rays were mostly used in the rheumatology outpatient clinic (83.7%), followed by ultrasound (10.5%). Therapeutic procedures in the rheumatology outpatient clinic only consist of intra-articular or intra-muscular corticosteroid injections.

Referrals to other specialists by rheumatologists were given to 75 patients (38.7%), ranging from 1 to 4 different specialists. Most referrals were to dermatology (16), pulmonary specialists (12), eye care specialists (12) and orthopedic surgeons (14). Diagnostic procedures in the category 'rheumatology referrals' were mostly for tuberculosis screening for patients who needed a step up in therapy to biological use.

Sixty-three patients (32.5%) went to other medical specialists for comorbidities, ranging from 1 to 8 different specialists per patient. Most occurring specialist visits for comorbidities were surgery (14), cardiology (10), eye care (8), dermatology (8), and internal medicine (8).

Non-adherence

Adherence differed per DMARD type. Using an 80% adherence cut-off, for MTX, 77.7% of patients were adherent, as for hydroxychloroquine 77.8% were adherent. For prednisone, 80.0% of patients were adherent and for sulfasalazine, 71.4% were adherent.

Most patients started treatment with a combination of 2 DMARDs. During the first year of treatment, 20 patients (10.2%) were switched to biologic DMARDs and 40 patients (20.4%) were switched from oral to subcutaneous use of MTX.

Figure 2 depicts that as the adherence percentage decreases from 100% to 60% (40% of the amount of medication not taken), the mean costs increase as well. However, this relation disappears when patients are more than 40% non-adherent. Note that the patients who are more than 40% non-adherent are a small minority. The overall study population is adherent: 90.7% of the patients are between 100 and 60% adherent. More than 75% of the study population is more than 80% adherent. The increase in costs with the increase of non-adherence seems to be driven by the costs of biologicals. This is probably because some non-adherent patients start using biologicals early, and these drugs are substantially higher priced.

Figure 3 depicts the distribution of the costs for adherent and non-adherent patients. An adherence cut-off point of 80% is used. Patients who are less than 80% adherent make more costs for biologicals. In all three cost categories, patients who are less than 80% adherent have relatively more costs for hospital admissions than adherent patients. However, the medians of the costs for biologicals do not differ significantly.

Table 2. Components of healthcare costs for early arthritis

	Rheumatology outpatient clinic	Mean costs	Rheumatology referrals	Mean costs	Comorbidities	Mean costs
Consultations with medical specialist						
No. of patients	196 (100%)		74 (37.8%)		62 (31.6%)	
Mean no. per patient ± sd	4.6 ± 1.8	€ 245,87	3.2 ± 3.4	€ 295,24	4.3 ± 4.6	€ 401,09
Consultations with specialized nurse/nurse practitioner						
Mean no. per patient ± sd	3 ± 2.51	€ 100,70	N/A		N/A	
Imaging modalities						
No. of patients	84 (42.9%)		17 (8.8%)		34 (17.5%)	
Mean no. per patient ± sd	3.1 ± 2.0	€ 198,94	2.12 ± 1.5	€ 295,86	2.12 ± 1.95	€ 254,28
Medical procedures						
Diagnostic procedures						
No. of patients	11 (5.7%)		40 (20.6%)		27 (13.9%)	
Mean no. per patient ± sd	1.18 ± 0.4	€ 122,59	1.8 ± 1.3	€ 70,65	1.59 ± 1.0	€ 162,67
Therapeutic procedures						
No. of patients	52 (26.8%)		2 (1%)		3 (1.5%)	
Mean no. per patient ± sd	1.44 ± 0.7	€ 8,54	15 ± 7.0	#	2 ± 1	##
ER visits						
No. of patients	2 (1%)		3(1.5%)		16 (8.2%)	
Mean no. per patient ± sd	1 ± 0	€ 163,75	1 ± 0	€ 163,75	1.31 ± 0.6	€ 214,92
Hospital admissions (including day admissions)						
No. of patients	9 (4.6%)	€ 6082,38	4 (2.1%)	€ 607,84	22 (11.3%)	€ 2488,24
Laboratory tests						
Mean no. per patient ± sd	8 ± 4.6	€ 146,93	N/A		N/A	

Abbreviations: SD: standard deviation, N/A: not applicable, ER: emergency room
no unit price available ## Not all the unit prices were available (2 out of 3 not available)

Figure 2. Association between costs and adherence percentage

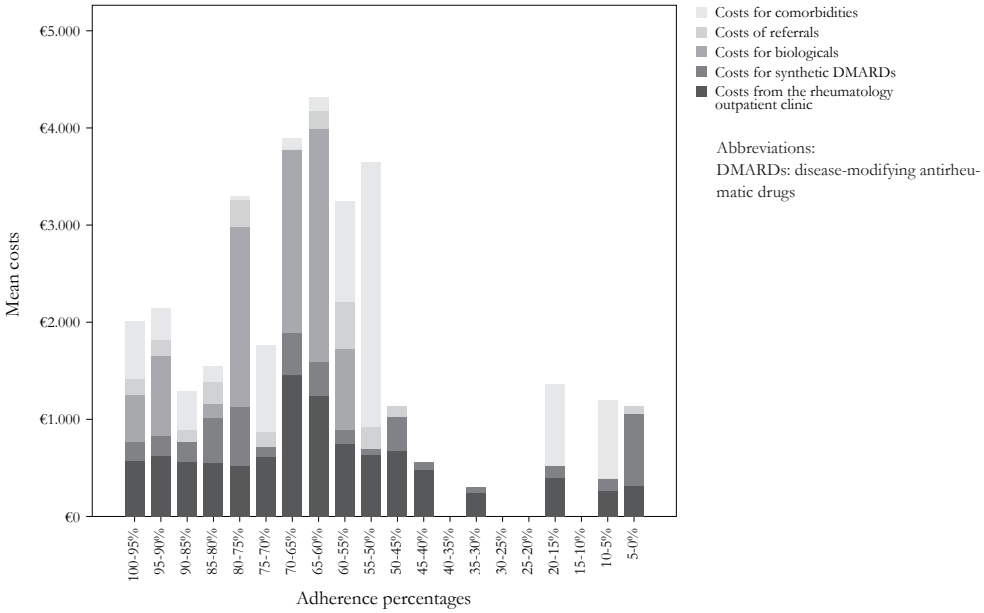
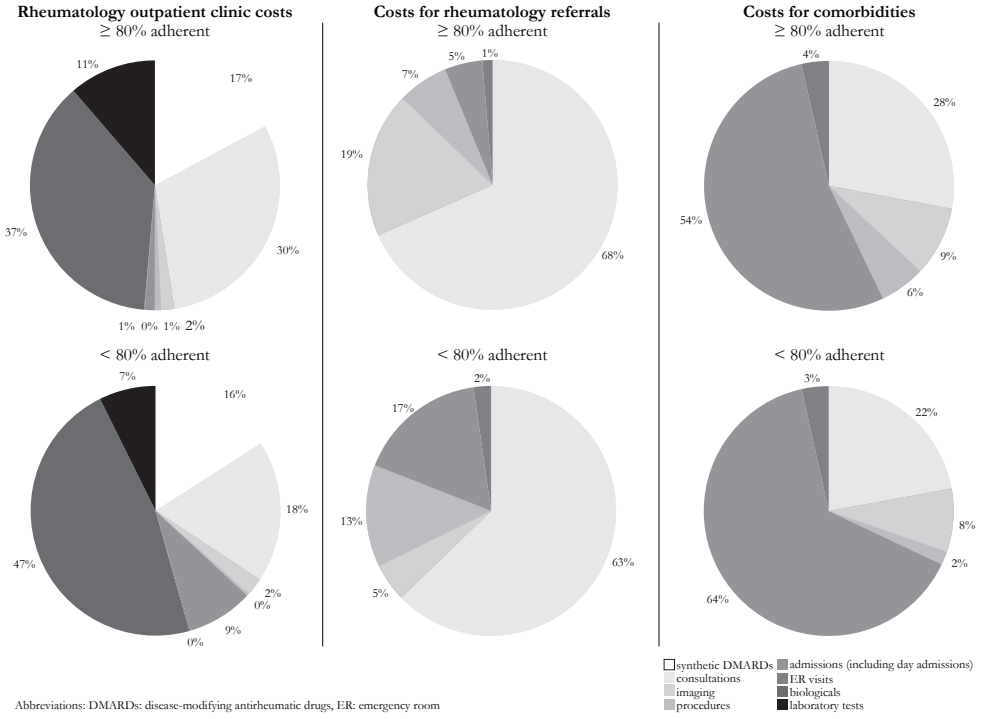


Figure 3. Percentage distribution of costs categories for patients 80% or more adherent and patients less than 80% adherent



Associations with costs

Table 3 depicts the associations between non-adherence and costs. There is a statistically significant correlation between non-adherence and costs made at the rheumatology outpatient clinic (rho 0.182) and total hospital costs (rho 0.146). Spearman rank correlations show that non-adherence is not significantly correlated to rheumatology referral costs (rho 0.125, p=0.083). A low education level was related to higher total hospital costs (rho 0.192), but not to rheumatology outpatient, and rheumatology referral hospital costs. Baseline disease activity was associated with rheumatology-related costs (rho 0.18) and to total hospital costs (rho 0.207). Age (rho 0.244) and the number of comorbidities (rho 0.448) are both correlated to total hospital costs. Anxiety and depression are correlated to costs made at the rheumatology outpatient clinic (rho 0.198 and rho 0.169) and rheumatology related costs (rho 0.188 and rho 0.161).

As shown in table 3, no variables are significantly correlated to non-adherence, though there is a tendency (p=0.052) for age to be negatively correlated to non-adherence (older patients being more adherent). Hence, we can conclude that the relations with the costs are not significantly influenced by interactions with non-adherence.

Table 3. Spearman rank correlations of possible predictors of costs

	Rheumatology outpatient clinic costs		**Rheumatology-related costs**		**Total hospital costs**		**Non-adherence**	
	Spearman rho	p-value	Spearman rho	p-value	Spearman rho	p-value	Spearman rho	p-value
Non-adherence	0.182	0.012	0.125	0.083	0.146	0.043	-	-
Number of comorbidities	0.073	0.313	0.062	0.389	0.448	0.000	0.084	0.249
Low education level	0.112	0.128	0.131	0.074	0.192	0.009	0.007	0.921
High education level	-0.030	0.680	-0.068	0.360	-0.141	0.054	-0.054	0.467
Baseline DAS28	0.108	0.135	0.180	0.012	0.207	0.004	-0.011	0.883
Age	0.066	0.361	0.102	0.160	0.244	0.001	-0.140	0.052
Baseline HADS anxiety	0.198	0.008	0.188	0.012	0.098	0.191	0.059	0.432
Baseline HADS depression	0.169	0.025	0.161	0.032	0.107	0.157	0.127	0.090

Abbreviations: DAS28: 28-joint count disease activity score, HADS: Hospital Anxiety and Depression Scale

Discussion

This is the first study to find evidence that non-adherence is associated with hospital health care costs in the first year of treatment of arthritis. In addition to non-adherence, baseline disease activity, and symptoms of anxiety and depression are associated to rheumatology-related costs.

The mean number of visits to the rheumatologist is slightly less than previous studies on health care consumption in a rheumatoid arthritis cohort, that found an average number of 5.7 visits to the rheumatologist per year.[4] However, in this cohort, not the health care consumption in the first year of treatment, but that of established patients was investigated. Health care consumption is expected to be higher in the first year of treatment than in the years thereafter, since treatment has to be tailored and adjusted in the first period of disease, and therefore more visits to the rheumatologist are needed.

The percentage of patients referred to other specialists for arthritis- or DMARD related symptoms was 38.7%. The percentage of patients with comorbidities in our cohort was 32.5%, which is slightly higher than found in other studies (27%),[21] which might explain why our cost in the first years were higher. The difference in comorbidities can be due to the fact that we measured comorbidities as the number of different medical specialists visited instead of the number of additional diagnoses.

Non-adherence is associated with higher healthcare costs at the rheumatology outpatient clinic and higher total healthcare costs. From the data that we collected, it does not appear that patients who are non-adherent make more costs in terms of visits to health care specialists or that they are referred more often to healthcare specialists: the relationship between non-adherence and costs found is related to higher medication costs. It seems that patients who were switched to subcutaneous methotrexate or biologicals were non-adherent to their oral DMARD medication. It could be that because of non-adherence, their disease activity escalated and that they were switched sooner to more expensive medicines such as biologicals.

Although there is not much empirical research about the relation between non-adherence and costs in rheumatology in practice, numerous authors suggest that being non-adherent would lead to higher healthcare cost.[5, 10, 13, 22, 23] We could confirm this suggestion for most patient that are non-adherent, but for patients who are more than 40% non-adherent, costs seem to be lower. These patients do not significantly differ from the more adherent patients in diagnosis, but it might be that these patients have a lower baseline disease activity. Over the course of one year, the disease activity of these patients is slightly lower than the disease activity of the more adherent patients. It might be that being non-adherent is a response to experiencing low disease activity. It might also be that these patients do not have to visit the rheumatologist as often because of mild disease.

In addition to non-adherence, there is also a relationship between baseline symptoms of anxiety and depression and healthcare costs for rheumatology symptoms. The relationship between healthcare costs and depression is well-known.[24-28] RA presents itself often together with depression,[26] and depression causes additional costs on top of the costs for RA.

We were not able to include all costs in our analysis. We had only access to hospital files, and have no data on out of pocket costs and costs of productivity loss. Patient with recent onset arthritis are often on sick leave because of high disease activity, which would contribute to productivity losses and thus to higher societal costs.[29-31] Other studies have suggested that non-adherence does decrease work productivity.[32, 33] It could be that if we had access to this data

of productivity loss, the association between non-adherence and costs might have been larger. Also, costs for supplemental drugs to prevent NSAID induced symptoms and over the counter medication were not measured. They might also attribute to higher costs in RA.[30, 34]

MEMS is up till now the best indirect method to measure non-adherence, and is considered as a 'gold standard'. Because it measures behavior 'real time', it is a very accurate measure. The disadvantage of using MEMS, is that it does not prove ingestion of medication. Participants were instructed to use the MEMS vials for each separate DMARD, but we cannot be sure that they all took their DMARDs from the MEMS vials all the time, which might lead to an overestimation of adherence. Also, we could not measure adherence from patients who were switched to subcutaneous MTX or biologicals, because these medicines do not fit in the medication vial. Electronic measurement of adherence is sometimes seen as an intervention itself and might increase adherence behaviour, but this effect is regarded as small.[35]

The outcomes of this study might be subjected to the 'adherer effect'.[36] Patients who adhere to the rheumatologists' prescription have better disease outcomes, regardless of the underlying treatment and are therefore expected to have less health care costs. This theory is based on the finding that behaviors of adherent people are different from the behaviors of non-adherent people. Adherent people have better global health outcomes, since they have more healthy lifestyles, do not engage in risky behaviors and are more adherent to nonpharmacologic prescriptions.[37, 38] Patients who agreed to participate in this cohort study are probably more adherent than the general patient population, which is also known from other studies.[14] This means that in daily practice the effect of non-adherence on costs might be larger.

In addition, patients who became lost to follow up were or became probably less adherent than the patients who completed follow up. The patients in this cohort are rather adherent to their medication and there is little variation in adherence. This makes it more difficult to study the association between non-adherence and hospital costs.

This study shows that there is an association between non-adherence and costs. This suggests that improving adherence is associated with savings. Most money can be saved in medication costs. The mean medication costs for patients who are switched to biologicals therapy, are almost 30 times more than the costs for patients who use synthetic DMARDs.

Our findings address the need to improve adherence, because money is being wasted and potentially beneficial medication is discarded. It is important to study which patients are at risk for non-adherence, so that interventions to improve adherence can be targeted. While there remains uncertainty about which patients are at risk and how to intervene on adherence behavior, rheumatologists should at least be aware that patients might be non-adherent to therapy. Focusing on the way they communicate with the patient is important, because the patient-doctor relationship is an inescapable factor in establishing good adherence behavior.[39] The rheumatologist should build up towards a trustworthy relationship with the patient so that communication about non-adherence can take place and the importance of adherence to the treatment can be addressed. This is not only better for the patient, but will also save money from a societal perspective.

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Part 2

How to measure non-adherence

Chapter 4

Non-adherence to disease-modifying antirheumatic drugs in the first year after diagnosis: comparing three adherence measures in early arthritis patients

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Submitted

Abstract

Introduction Non-adherence to disease-modifying antirheumatic drugs (DMARDs) is associated with the effectiveness of treatment in early arthritis. Reported non-adherence rates differ, since studies use different adherence measures. We compare 3 measurement methods: the Compliance Questionnaire Rheumatology (CQR), the intracellular uptake of methotrexate in the form of methotrexate-polyglutamates (MTX-PGs) and electronic measurement with Medication Event Monitoring Systems (MEMS).

Methods DMARD naïve early arthritis patients were included in an ongoing cohort study. MEMS were used to measure adherence continuously, while every 3 month MTX-PGs were collected together with the CQR. The associations between the measures were estimated with Spearman rank correlations. Sensitivity and specificity of the CQR against a MEMS cut-off was compared at 3, 6, 9 and 12 months. The same applied to MTX-PGs against a MEMS cut-off and MTX-PGs against a CQR cut-off. For the association between MEMS and MTX-PGs, multilevel linear regressions for different time periods (3, 6, 9 and 12 months) were performed with age, gender, and time of treatment as covariates.

Results We included 206 patients. Non-adherence measured with MEMS varied over time and between DMARDs. The CQR score was not associated with MEMS non-adherence at 3, 9 and 12 months. At 9 months, MTX-PGs was associated with MEMS non-adherence, as well as with the CQR. All correlations were below 0.30.

Conclusion Associations between the three measures are weak. Explanations are individual differences in the uptake of MTX, and little variance in adherence between patients. Moreover, the measurement domains differ: perceptions (CQR), behavior (MEMS) and pharmacokinetics (MTX).

Introduction

The prognosis of early rheumatoid or psoriatic arthritis (RA or PsA) is significantly improved by an early, intensive and tightly controlled treatment with disease-modifying anti-rheumatic drugs (DMARDs) within 3 months of diagnosis.[1-5] These drugs prevent irreversible joint damage, but only if they are actually taken by the patient.[3, 6] A substantial proportion of RA patients does not adhere to treatment. Adherence rates have been reported from 99% to as low as 30%, depending on the methodology and definition of adherence that was used.[2, 3, 6] Non-adherent patients may present themselves as non-responders to the treatment, which may lead to an unnecessary switch to a more expensive treatment, such as biologicals.

There is no consensus about the preferred measurement of adherence in RA patients. Adherence can either be assessed directly by measuring drug levels of its metabolites in blood, urine or tissue, or by indirect methods, such as pharmacy records, healthcare provider assessment and self-report.[2]

A sophisticated indirect adherence measurement method of adherence is measurement with medication jars that register each moment the lid is opened and closed, so called medication event monitoring systems (MEMS).[6] Even though measurement errors can still occur with MEMS, researchers have regarded this as a gold standard, because it objectively measures a necessary behavioral step of adherence in 'real-time' and yields stable results.[7] Electronic monitoring offers the advantage of assessing adherence over a continuum. This method has proven to be superior to patient self-reports and pill counts in the measurement of adherence.[8, 9] Disadvantages of MEMS are the high price, and for some patients it may feel as if their privacy is violated. Furthermore, it remains an indirect method and does not really proof ingestion of medication. It could therefore be that patients only take half of their medication but still appear adherent. Monitoring with MEMS might be seen as an intervention, but this effect is regarded as negligible.[7]

Self-reports with validated questionnaires for the measurement of adherence are easier, and cheaper methods than MEMS, both for the patient and the researcher. However, it is assumed that self-report is not as reliable as MEMS measurement[10] and it does not measure medication intake in real-time. A frequently used adherence questionnaire is the Compliance Questionnaire Rheumatology (CQR), which is validated against MEMS in established rheumatology patients.[11] It is not known whether this questionnaire performs equally well in newly diagnosed arthritis patients as in established inflammatory arthritis patients.

The anchor drug in early arthritis treatment is methotrexate (MTX), which is prescribed to approximately 95% of early arthritis patients. Measurement of MTX in blood could be a good measure for adherence, because it directly measures the monitored drug. However, plasma levels are unstable and therefore unusable. After uptake in the cell methotrexate is polyglutamated leading to cellular retention as the methotrexate polyglutamates (MTX-PGs) are a poor substrate for the efflux transporters.

Although there is high interpersonal variability in the build-up of MTX-PGs due to factors such as age and DNA SNPs,[12-14] adherence likely plays an important role as it has been shown that the erythrocyte MTX-PG levels are dependent on dose and exposure.[12, 13, 15, 16] Therefore it may be possible to detect non-adherence and possibly poor adherence when measuring RBC MTX-PGs over time. Where measurement with MEMS cannot prove actual ingestion of medication, the RBC MTX-PG measurement only detects MTX in the blood if the patient has taken medication and should therefore be able to detect adherence. If accurate, this method will be

cheaper, less invasive and more feasible than measurement with MEMS.

The aim of this study is to measure adherence over time with the CQR, MEMS and MTX-PGs and to compare these three different measurement methods with each other in early arthritis patients in the first year of DMARD treatment.

Methods

Data collection procedure

Data were collected from an ongoing multicentre cohort study measuring adherence in recently diagnosed polyarthritis patients with a one year follow up. A thorough description of the study set-up is described elsewhere.[17] Patients were recruited from January 2012 to January 2014. Inclusion criteria are: being newly diagnosed with rheumatoid, psoriatic or unclassified arthritis, DMARD naïve and age above 18. Patients that are enrolled in the study are asked to take their DMARD medication from a MEMS medication jar. For patients that receive multiple DMARDs, every DMARD is placed in a separate jar. Follow-up occurred every three months. At this time a specialized rheumatology nurse measured disease activity with the DAS28, and records the MEMS data. At baseline, the HAQ[18] was filled out. From patients treated with oral MTX an extra blood sample is drawn during regular blood tests for the rheumatology practice for the measurement of MTX-PG. The measurement of MTX-PGs was added to the already ongoing cohort, therefore MTX-PGs were not measured in all patients. Patients filled out the CQR every 3 months.

Ethics statement

The Erasmus MC Medical Ethics board approved this study. The hospitals' board of directors of the Bronovo, Haga hospital, Groene Hart, Amphia, Sint Maartenskliniek, Sint Antonius, Reinier de Graaf Gasthuis, Sint Franciscus Gasthuis, Lievensberg and Franciscus hospital gave their consent for participation in the study. All participants gave written informed consent for their participation.

Measures

MEMS

The medication jar cap contains a microprocessor that records the day and time of each jar opening. The data stored in the MEMS cap is transferred into a web-based data platform, which compiles hour-by-hour drug dosing histories over the treatment period, and medication regimen changes. Nursing and medical staff were blinded to the adherence data throughout the study. Patients were aware that their medication intake was being monitored.

We only investigate underuse of medication. Extra openings of the MEMS cap are ignored, because these generally do not represent medication intake, but are caused by openings by pharmacists. Underuse was determined per day and per DMARD as a day in which the observed amount of openings was lower than the expected amount of openings of the particular MEMS cap. For a comparison with the other adherence measures, the amount of days with underuse was added in each 3-month period and divided by the total amount of days in the observation period to gain a underuse proportion with 1 being completely non-adherent and 0 being completely adherent. For adherence measurement to MTX, we divided the total amount of days

with underuse by the total amount of weeks in the observation period, since this medicine only needs to be taken once a week.

Adherence was also dichotomized at an underuse proportion of 0.2 (80% adherence). For adherence to MTX, we used a 83% cut-off score (2 weeks not taking the medication out of a 12 week period (1-(2/12)).

CQR

The CQR is a self-report measure consisting of 19 4-point Likert scale statements ranging from 1 (do not agree at all) to 4 (agree very much). The CQR composite score will be calculated following the guidelines from de Klerk et al.[9] The composite score is a continuous variable ranging from 0 (complete non-adherence) to 100 (perfect adherence). We also calculate a dichotomous CQR non-adherence score for correct dosing ≤80%.[9] Correct dosing is defined as the percentage of days on which the correct number of doses was taken, calculated as the total number of days with openings as prescribed / number of monitored days X 100%.[9] An 80% cut-off for taking compliance was also calculated. Taking compliance was defined as the percentage of prescribed doses taken calculated as the total number of openings / total number of prescribed doses X 100%.[9] For details about the calculation procedure see de Klerk et al.[9]

The CQR has been validated in established patients with inflammatory rheumatic diseases (RA, polymyalgia rheumatica, gout) against MEMS.[9] Specificity and sensitivity of a weighed CQR score to detect unsatisfactory correct dosing (≤80%) was 89% and 70%.[9]

MTX-PGs

MTX, which contains one glutamate residue, is polyglutamated with up to four glutamate chains (MTX-PG1-5) intracellularly, which prevents MTX's efflux by various transporters. In low-dose MTX treatment, MTX-PG5 is the highest order of glutamylation detected. MTX-PG1, 2 and 3 build up relatively fast, whereas it takes some months for MTX-PG4 and 5 to reach a steady state.[19]

MTX-PGs were measured in red blood cell pellet using a recently developed and validated Liquid-chromatography tandem-mass-spectrometry (LC-MS/MS) method.[20] The sumscore of MTX-PG1 to MTX-PG5 (MTX-PG1-5) is used as the total MTX-PG content. We also dichotomized MTX-PG1-5 based on the previously found median concentration in RA patients treated with 15 mg,[19] which is 118 nmol/L RBC pellet at 3 months of treatment, 153 nmol/L RBC pellet at 6 months and 170 nmol/L RBC pellet at 9 months of treatment. For 12 months of treatment, we use the median concentration for 9 months of treatment.

Data analysis

The prevalence of non-adherence measured with the various methods is presented with descriptive measures.

ROC curves were used to compare both CQR correct dosing and MTX-PGs (continuous measure) with the electronically measured adherence cut-off score on sensitivity and specificity at four different time points. For the comparison of MTX-PG1-5 and MEMS, we used the cut-off score for electronically measured adherence to MTX.

The internal consistency of the CQR scale will be estimated using Cronbach's alpha. Agreement between MEMS non-adherence proportion (continuous score), the CQR discriminant Z-score for correct dosing ≤80% and total MTX-PG content (continuous score) will be measured with Spearman rank correlation coefficients at the four time-points. We use non-

parametric correlations because the MEMS adherence data are skewed.

To display the agreement between the dichotomized scores for MEMS, CQR correct dosing and MTX-PGs, a classification table is presented.

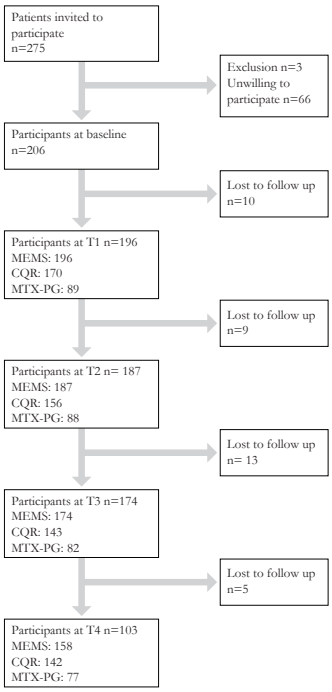
To examine the relation between non-adherence measured with MEMS and the build-up of MTX-PGs over time, linear mixed models for the time slices 3-6 months, 3-6-9 months and 3-6-9-12 months are applied with patients in the upper level and their repeated measures in the lower level. Taking repeated measurements per patient into account, in linear mixed models with MTX-PG1-5 as dependent variable, the following predictors are entered: weeks on MTX treatment, the mean medication underuse proportion determined by MEMS in the 12 weeks before MTX-PG measurement, standardized age, gender and dose.

SPSS version 21 was used for all statistical analyses. A p-value of <0.05 was considered statistical significant.

Results

In total 275 consecutive patients were invited to participate, of whom 206 patients were included. Thirty-three patients were lost to follow up. Figure 1 depicts the flow of patients and the number of measurements available at each time point. The number of available MTX-PG measurements is smaller, because that measurement became available after the start of the study. The differences between the numbers of measurements with MEMS and CQR are due to skipped time-points.

Figure 1. Flowchart of respondents



Abbreviations: MEMS: medication even monitoring system; CQR: compliance questionaire rheumatology; MTX-PG: methotrextrate polyglutamates

Table 1. shows that at baseline most patients were diagnosed with RA and half of the patients received monotherapy after being diagnosed, mostly methotrexate monotherapy. One third of the patients received two DMARDs, mostly consisting of methotrexate and prednisone. All patients that became lost to follow up during the study period had a disease duration longer than 6 weeks, compared to 84% of the patients with complete follow up ($p<0.01$). Patients that became lost to follow up during the study had also more often a positive rheumatoid factor ($p=0.04$).

Table 1. Demographic and disease characteristics of all patients at baseline (n=206)

	All patients (n=206)		**Patients with complete follow up (n=169)**		**Patients lost to follow up (n=37)**	
Age (years), mean (SD)	53.9	(14.2)	53.3	(13.8)	55.5	(15.8)
Sex, female, n (%)	129	(64)	106	(62.7)	24	(66.7)
Diagnosis, n (%)						
RA	152	(73.7)	126	(74.6)	26	(72.2)
PsA / arthritis with Crohn's disease	43	(20.9)	37	(21.9)	6	(16.7)
Unclassified	11	(5.3)	6	(3.6)	5	(13.9)
RF positive, n (%)*	105	(51)	81	(47.9)	24	(66.7)
ACPA positive, n (%)	99	(48)	81	(47.9)	18	(50)
Disease duration >6 weeks, n (%)*	170	(86.7)	137	(84)	33	(100)
Number of medicines, n (%)						
1 (MTX n=116, SSZ n=6, HCQ n=4, PRED=2)	128	(62.1)	109	(64.5)	19	(51.4)
2 (MTX+DMARD= 62)	65	(31.6)	51	(30.2)	14	(37.8)
3 (MTX+2 DMARDs=10)	12	(5.8)	8	(4.7)	4	(10.8)
4 (all DMARDs)	1	(0.5)	1	(0.6)	-	
DAS28, mean (SD)**	4.22	(1.37)	4.19	(1.37)	4.5	(1.28)
HAQ, median (IQR) n=181	0.75	(0.33-1.13)	0.63	(0.25-1.13)	0.75	(0.5-1.25)

Abbreviations: RA: rheumatoid arthritis, PsA: Psoriatic Arthritis, RF: rheumatoid factor, ACPA: anti-cyclic citrullinated peptide antibody,
MTX: methotrexate, HCQ: hydroxychloroquine, SSZ: sulfasalazine, DAS28: Disease Activity Score 28-joint count, HAQ: Health Assessment Questionnaire

*$p<0.05$
**for patients with mono-arthritis (n=3) no DAS28 was calculated

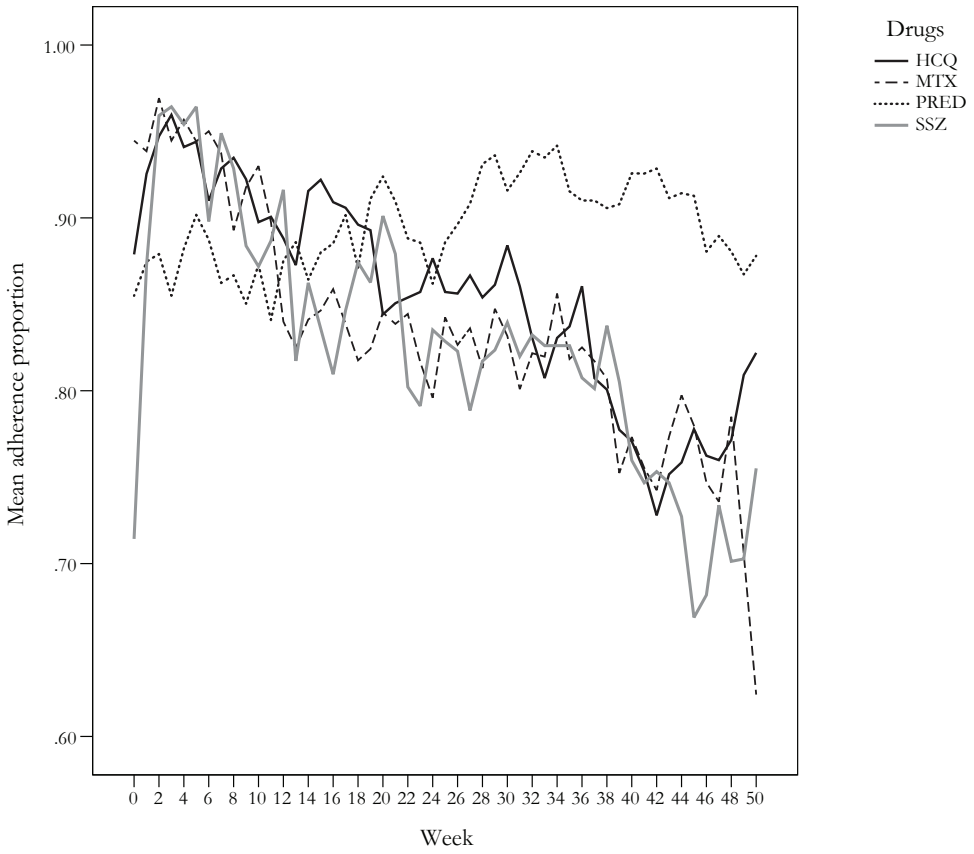
Non-adherence measured with MEMS

Figure 2 shows the weekly DMARD adherence proportion. Underneath the graph, the number of patients using the particular DMARD per month is presented. For methotrexate, prednisone and hydroxychloroquine, there is a trend for more underuse as time passes.

CQR

The mean CQR composite score at the four time points was stable, ranging from 73.0 to 73.6 (SD=12.0 to 13.3). The CQR scale had a high internal consistency within our sample: Cronbach's alpha is 0.94.

Figure 2. Mean adherence proportions measured with MEMS per DMARD per week



number of patients using this DMARD per month												
month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
DMARD												
MTX	180	178	168	163	157	154	149	143	137	134	124	119
PRED	65	62	56	42	37	27	23	21	19	18	17	14
SSZ	16	15	17	21	22	22	21	21	22	21	20	20
HCQ	21	18	19	25	22	23	28	32	32	35	34	32

Abbreviations: DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; PRED: prednisone; SSZ: sulfasalazine; HCQ: hydroxychloroquine

The percentage of patients with correct dosing ≤80% was 8.2% (3 months), 10.9% (6 months), 9.8% (9 months) and 12.7% (12 months). The percentage of patients with taking compliance ≤80% was 30% (3 months), 39.1% (6 months), 44.8% (9 months), and 40.8% (12 months).

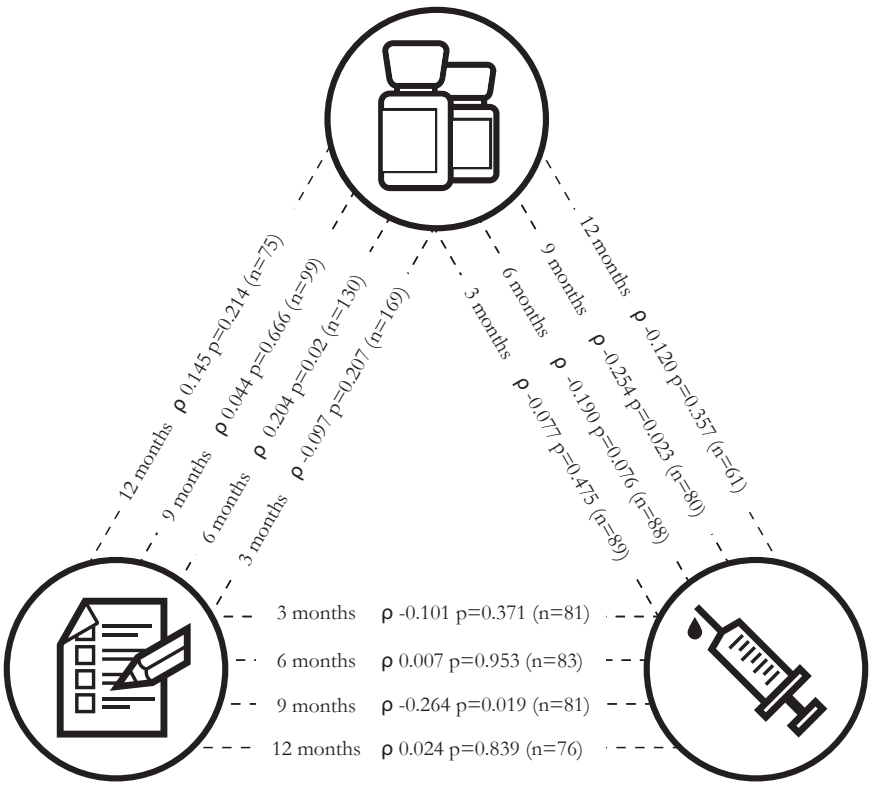
MTX-PGs

The mean MTX-PG1-5 concentration value at T1 is 116.7 (SD=64.2) nmol/L RBC pellet, at T2 147.2 nmol/L RBC pellet (SD=82.1), at T3 163 nmol/L RBC pellet (SD=82.4), and at T4 156.3 nmol/L RBC pellet (SD=84.1).

MTX-PG - MEMS

Spearman rank correlations show the highest correlations between MTX-PG and MEMS non-adherence at T3 (rho=-0.254) (figure 3). The classification table (table 2) shows that there is no satisfactory agreement between dichotomized MTX-PGs and MEMS adherence. At T2 (6 months), the AUC for the continuous MTX-PG score against the 83% MEMS-cut-off is highest with 0.684 (CI 0.551-0.818). Linear mixed models show the trend for non-adherence to influence MTX-PGs at T2 (first 6 months of treatment) and T3 (first 9 months of treatment). At T4 (first year of treatment) non-adherence does not influence MTX-PGs. Also, older age, and weeks on MTX therapy significantly contribute to higher MTX-PG1-5 levels (table 3).

Figure 3. Spearman rank correlations between MEMS non-adherence proportions (1=nonadherent) , MTX-PGs and CQR correct dosing (1=non-adherent) at 3, 6, 9 and 12 months.



Abbreviations: MEMS: Medication Event Monitoring System, MTX-PG: methotrexate-polyglutamates, CQR: compliance questionnaire rheumatology

Table 2. Classification table of the CQR, MTX-PG1 - 5 and MEMS

Months of treatment			CQR taking compliance >80%	CQR taking compliance ≤80%	CQR correct dosing >80%	CQR correct dosing ≤80%	MTX-PG1 - 5* >median	MTX-PG1 - 5* ≤median
3	MEMS correct dosing**	adherent	**58.0%**	26.6%	**76.9%**	7.7%	**36.0%**	57.3%
		non-adherent	11.8%	**3.6%**	14.8%	**0.6%**	3.4%	**3.4%**
6	MEMS correct dosing	adherent	**49.2%**	26.2%	**70.8%**	4.6%	**36.4%**	42.0%
		non-adherent	13.1%	**11.5%**	19.2%	**5.4%**	6.8%	**14.8%**
9	MEMS correct dosing	adherent	**48.5%**	28.3%	**71.7%**	5.1%	**27.5%**	51.2%
		non-adherent	8.1%	**15.2%**	21.2%	**2.0%**	3.8%	**17.5%**
12	MEMS correct dosing	adherent	**46.7%**	25.3%	**66.7%**	5.3%	**19.7%**	47.5%
		non-adherent	10.7%	**17.3%**	24.0%	**4.0%**	11.5%	**21.3%**

* for MTX-PGs we only used MEMS correct dosing for MTX
** Correct dosing is defined as having taken more than 80% of your doses correctly.
abbreviations: CQR: compliance questionnaire rheumatology, MTX-PG1 - 5: methotrexate-polyglutamates 1-5, MEMS: medication event monitoring systems

Table 3. Multilevel multivariate linear regression model of predictors of MTX-PG1 - 5 levels over 1 year

	T2: 3- 6 months		T3: 3-6-9 months		T4: 3-6-9- 12 months	
	estimate	p-value	estimate	p-value	estimate	p-value
Intercept	89.42	<0.001	107.02	<0.001	109.99	<0.001
MEMS non-adherence proportion (1=non-adherent)	-38.66	0.074	-28.54	0.099	-24.18	0.136
Weeks of treatment	2.77	<0.001	1.85	<0.001	1.52	<0.001
Age (standardized)	1.72	<0.001	1.82	<0.001	1.77	<0.001
Mean weekly dose in milligram	-0.075	0.636	-0.14	0.301	-0.1	0.458

Abbreviations: MEMS: medication event monitoring system

MTX-PG - CQR

The ROC curve for MTX-PGs against the CQR correct dosing cut-off shows at 9 months good discriminating ability with an AUC of 0.768 (95% CI 0.57-0.966). With a concentration of 125.2 nmol/L RBC pellet, the sensitivity is 73.6% and the specificity is 71.4%. At the other time points the discriminating ability is insufficient. CQR correct dosing and MTX-PG content were at 9 months also significantly correlated with a rank correlation of -0.264 (p=0.019) (figure 3).

CQR - MEMS

At 6 months of treatment, there is a significant rank correlation between the discriminant Z-score for correct dosing and adherence measured with MEMS (rho=0.204, p=0.02).

At all time points, the discriminant Z-score for correct dosing ≤80% was not able to discriminate electronically measured adherence from non-adherence as measured with MEMS.

The classification table shows that the agreement between CQR correct dosing >80% and MEMS correct dosing >80% is high, but the agreement between both measures for non-adherence is rather low. The agreement between CQR taking compliance and MEMS correct dosing is low, but higher for adherence than for non-adherence.

Discussion

This study simultaneously compared various measurement methods for non-adherence in early arthritis patients who started with DMARD therapy. We compared electronic measurement (MEMS) with a self-report questionnaire (CQR) and measurement of blood levels (MTX-PG) in the first year of DMARD therapy. In the first months of treatment, the measures do not relate to each other. From 6 months on, stronger correlations between MTX-PGs and MEMS appear, whereas after 6 months of treatment, the CQR and MEMS are associated. After 9 months of treatment, blood levels of MTX and CQR correct dosing are related. When MEMS are considered as the gold standard, these results suggest that neither questionnaires nor biological measures are sufficient enough to measure adherence in the first months of treatment.

Overall, there is a decline in adherence as measured with MEMS over time, except for prednisone, which is reported before.[8] This might reflect the immediate effectiveness of prednisone. The mean non-adherence percentage at the first month of treatment was 9.25%, and is comparable to the result of Park et al. (8.5% after 4 weeks 21). Other electronically measured non-adherence percentages over a two year period and 6-month period range respectively from 19 to 22% for methotrexate, 12 to 27% for prednisone, 34% for hydroxychloroquine, and from 41 to 45% for sulfasalazine.[8, 22] These results are close to ours. However, we included the timeframe in our results instead of aggregating all data from a large period in one percentage.

Although all instruments have advantages and disadvantages, we still consider measurement with MEMS as having the least disadvantages. The CQR questionnaire is easy to use and less expensive, but in our case the questionnaire did not relate to MEMS, although the questionnaire was validated using the MEMS. This suggests that the CQR is not a valid measure in the first year of treatment. In established patients, the CQR might be more valid. Questionnaires are nevertheless suitable to get insight into patients' perceptions about medication intake behavior and not so much for the measurement of real behavior.

MTX-PG measurement is relatively cheap, easy to use and insensitive to selection bias. In a multilevel linear model, MEMS non-adherence proportions may be predictive for total MTX-PG content at 6 and 9 months, although the statistical significance is limited to 0.074 and 0.099 respectively. However, there is high inter-individual variability in build-up over time, which is partly due to pharmacokinetics (the rate at which MTX is absorbed, distributed, metabolized and excreted).[12] This makes MTX-PG levels less useful for distinguishing levels of non-adherence. Furthermore, although MTX is the anchor drug for early arthritis, MTX-PGs are only an indicator of adherence to methotrexate, and not to other DMARDs. Finally, other factors such as the number of weeks on methotrexate therapy and age are predictors of MTX-PG levels.[12, 15]

Our CQR composite scores were comparable to those found in established patients,[9] but the percentage of patients with correct dosing was much higher than those found in other studies.[23] Although the CQR was validated against MEMS, we found only weak relationships between these two measures of non-adherence in the first year of treatment. This reflects that in the first year of treatment, the CQR is not a valid measure and needs to be revalidated.

Other studies comparing electronic adherence measures with adherence questionnaires are discordant. One review showed that 7 out of 9 studies had low to moderate concordance between adherence questionnaires and electronic measures of adherence,[10] while another study found that self-report measures are highly correlated with electronic monitoring.[24] The low

correlations between the CQR and electronic measurement of adherence might be because there is not enough variance in adherence behavior in our cohort, although the percentages that we found are comparable to other electronically measured adherence percentages.[8, 21, 22] The results of this study might have been affected by selection bias. Patients who are willing to participate in adherence studies are probably more adherent than others. Patients were aware of being monitored with MEMS, but they were not aware that measuring MTX-PGs was also used as an adherence measure. It could however be that non-adherent patients have dropped out of the study early. Patients who were lost to follow up in the study, were sometimes also lost to follow up in the outpatient clinic. It is very likely that these patients were not adherent to the prescribed medication. Selection bias might have resulted in an overestimation of adherence and a reduction in the variance of adherence.[25-27]

Our study has clinical implications. We showed that in daily practice, when starting a patient on therapy, there is no easy way to find out whether the patient will be adherent to therapy or not. Other studies have shown that the way of communicating with the patient and addressing doubts and fears about DMARDs are techniques to help the patient overcome non-adherence.[28, 29] Considering that we show that the diagnosis of non-adherence is complex and imprecise, rheumatologists should always pay attention to the subject of adherence when communicating with the patient, even when there is no clinical sign of non-adherence.

When measuring adherence in research settings, it depends on the time the patients has been treated which measurement method to use. MTX-PGs might be useable between 6 and 9 months of therapy, but only to assess whether medication has been taken at all or not. The CQR is more suitable to use in established patients for the measurement of adherence, but might be useable to get insight into patient's perceptions about adherence. MEMS remain an indirect measurement method, but give insight in adherence behavior day by day.

We showed that the association between the three measures of adherence are weak in the first year of treatment. Explanations are individual differences in the uptake of MTX, or too little variance in adherence between patients. Moreover, the measurement domains differ: perceptions (CQR), behavior (MEMS) and pharmacokinetics (MTX). This suggests that one has to choose an adherence measurement tool that is concordant with the aim of the intervention. Is the intervention aimed at changing the patient's behavior, then electronic monitoring is the best option; when the aim is to influence the uptake of MTX, MTX-PGs apply. Questionnaires like the CQR will be a good alternative when one tries to change patient's adherence perceptions.

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Part 3

Determinants of non-adherence

Chapter 5

Factors associated with adherence to pharmaceutical treatment for rheumatoid arthritis patients: a systematic review

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Abstract

Objectives To identify factors associated with adherence to medication for rheumatoid arthritis or undifferentiated inflammatory arthritis using a systematic literature search.

Methods PubMed, PsycINFO, EMbase and CINAHL databases were systematically searched from inception to February 2011. Articles were included if they addressed medication adherence, used a reproducible definition, determinants and its statistical relationship. Methodological quality was assessed using a quality assessment list for observational studies derived from recommendations from Sanderson, Tatt and Higgins (2007). Resulting factors were interpreted using the Health Belief Model (HBM).

Results 18 out of 1479 identified studies fulfilled inclusion criteria. 64 factors were identified and grouped according the HBM into demographic and psychosocial characteristics, cues to action and perceived benefits versus perceived barriers. The belief that the medication is necessary and DMARD use prior to the use of anti-TNF had strong evidence for a positive association with adherence. There is limited evidence for positive associations between adherence and race other than White, general cognition, satisfactory contact with the healthcare provider and the provision of adequate information from the healthcare provider. There is limited evidence for negative associations between adherence and having HMO insurance, weekly costs of TNF-I, having a busy lifestyle, receiving contradictory information or delivered information in an insensitive way by the rheumatologist. Eighteen factors were unrelated to adherence.

Conclusions The strongest relation with adherence is found for prior use of DMARDs before using anti-TNF and beliefs about the necessity of the medication. Because the last one is modifiable, this provides hope to improve adherence.

Introduction

Rheumatoid arthritis (RA) is a chronic auto-immune disease characterized by joint inflammation with pain, swelling, damage and disability.[1] In order to control symptoms, induce disease remission and to prevent disability, RA is commonly treated with disease-modifying antirheumatic drugs (DMARDs), corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs).[2] Adherence to these prescribed drugs is important to prevent irreversible joint damage.[3] However, a recent review shows that a substantial proportion of RA patients does not adhere to their medication. Medication adherence rates reported in this review range from 30% to 99%, depending on which definition of adherence and methodology of measurement was used.[3]

A frequently cited definition of adherence is 'the extent to which a person's behaviour – taking medication, following a diet, executing lifestyle changes – follows medical advice'.[4] This definition does not imply to what extend a patient should follow medical advice to be regarded as adherent or non-adherent. In studies on anti-rheumatic drugs, the most frequently used definition of adherence is defined as taking 80% or more of the prescribed medication over the duration of the study time.[3,5,6] However, there is no general accepted or empirical motivated cut-off when 'not following medical advice' can be regarded as non-adherence.

There is also no consensus about the preferred measurement of adherence in RA patients. Adherence can either be assessed by direct methods that measure drug metabolites or drug levels in blood, urine or tissue, or by indirect methods, such as pharmacy records, healthcare provider assessment and self-report.[3] Since direct measurement methods are for most RA treatments not available, indirect methods need to be applied. The best of these indirect methods is electronic measurement with medication event monitoring systems (MEMS).[7] Although even with MEMS measurement errors can still occur, it is regarded as a 'gold standard', because it objectively measures a small, but nevertheless necessary behavioral step of adherence 'real-time'.

Adherence is thought to be influenced by many factors.[8] Frequently studied factors are medication characteristics, perceptions and cognitions about illness and medication, socio-economic and demographic factors, disease features and doctor-patient relationship.[8] However, up till now, there is no clear overview about the strength of associations between adherence and these determinants in RA and undifferentiated inflammatory arthritis patients. Another problem in studies on medication adherence in RA patients is that a consistent behavioral model to explain medication adherence and non-adherence in the RA population is lacking.[9] A behavioral model directs research, indicates which factors are potentially relevant and helps to gain insight in the relations between the determinants that guide behavior. When a behavioral model is missing, it could be that relevant factors are missed. The lack of a consistent framework makes it also difficult to interpret study results and to decide what should be studied next. Finally, the lack of a theoretical framework makes it difficult to formulate clinically relevant recommendations or to develop an intervention to increase adherence in non-adherent patients.

The most recent review on factors influencing adherence in arthritis patients dates back to 1982.[10] Since then new treatment strategies have been developed and new medication regimens have become available. This implies that adherence rates and factors affecting adherence may no longer be equivalent to those reported in 1982. Furthermore, the review from 1982 did not provide the strength of associations between determinants and adherence.

The aim of the present review is therefore to review adherence rates until 2011, to identify factors influencing adherence and to assess the strength of the association between these factors

and adherence. The identified factors are clustered according to the Health Belief Model (HBM), a frequently used behavioural model in which perceived barriers and benefits of the behaviour are weighted against each other.[11] Finally, recommendations for future research are made.

Materials and Methods

Literature search

EMbase, PubMed, CINAHL and PsycINFO databases were searched from inception to February 2011 to identify studies on factors affecting medication adherence in patients with RA (see search strategy in appendix 1). Studies were eligible if they (i) addressed medication adherence in adult RA or undifferentiated inflammatory arthritis patients, (ii) evaluated factors related to adherence, (iii) used a reproducible definition or validated instrument to measure adherence, and (iv) provided a statistical measure to reflect the strength of the association between the determinant and adherence. Letters, editorials, reviews, RCTs, case reports, qualitative studies and opinion articles were excluded from this review, because our aim was to select studies that included original data and an unbiased measurement of adherence. Reference lists of key articles and articles identified in the systematic search were checked for additional studies. A two-stage screening process was used: first titles and abstracts were screened for eligibility followed by retrieval of relevant full text articles to check further eligibility criteria. One reviewer (AP) screened the titles and abstracts of all citations identified by the literature search. In addition, two other reviewers (AS, JL) screened each half of the titles and abstracts independently. Data was extracted from the studies and considered for pooling. Determinants of adherence were grouped according to the HBM into demographic and psychosocial features, perceived threat of the disease (which, due to the nature of the primary studies, mainly consists of disease features), perceived barriers and benefits of enacting the health behavior, perceived susceptibility to the disease, perceived severity of the disease and cues to action.

Quality assessment

The methodological quality of the studies was assessed using a quality assessment list which was constructed based on recommendations from Sanderson, Tatt & Higgins.[12] The checklist, which is presented in table 1, contains 11 items concerning selection methods, measurement of study variables, design-specific sources of bias, control for confounding, and appropriate use of statistics. The items were adjusted to the features of the studies reviewed in this article. All items had a 'yes', 'no', or 'don't know' answer option. Three observers (AP, AS & JL) assessed the quality of the studies independently. Discrepancies were resolved by discussion until consensus was reached. Each item answered with 'yes' received one point. For each study, a score was constructed by adding up all points. The importance of all items was discussed by all co-authors and 5 of these 11 items (question number 2, 3, 5, 6, and 7) were labeled as 'very important questions'. Studies were determined to be of high quality if they (i) answered 4 out of 5 essential questions with 'yes', and (ii) if their total score was 7 or higher. Studies that scored lower than 7 points and studies that did not score 4 or more points on the essential questions were deemed to be of lower quality.

Table 1. Standardized checklist for the assessment of methodological quality of cross-sectional studies (CS), case-control studies (CC), and prospective cohort studies (PC)

Appropriate methods for selecting study participants				
1	Positive if the main features of the study population are described (sampling frame and distribution of the population by age and sex)	Yes	No	Don't know
2	Positive if the participation is ≥80% or if participation is 60-80% and non-response is not selective (data presented)	Yes	No	Don't know
Appropriate methods for measuring exposure and outcome variables				
3	Positive if method for measuring adherence is reproducible	Yes	No	Don't know
4	The rheumatologist should build towards a trustful relation, for instant by acknowledging fears about medication, and explaining the treatment plan in detail	Yes	No	Don't know
5	Positive if method for measuring adherence is valid (blood serum measurements, MEMS, pharmacy records and a validated questionnaire are considered valid methods, patient questionnaire and/or interviewes and health care provider assessment are considered as not valid methods)	Yes	No	Don't know
Appropriate design-specific sources of bias				
6	Was serious recall bias reduced? (adherence <1 week. For MTX or biological adherence <2 weeks)	Yes	No	Don't know
7	Was serious selection bias reduced? (by inviting consecutive patients/representative sample)	Yes	No	Don't know
Appropriate methods to control confounding				
8	Positive if the analysis is controlled for confounding (such as age/sex) or effect modification.	Yes	No	Don't know
9	Positive if the effect of confounding is quantified in analysis (univariate and multivariate analysis)	Yes	No	Don't know
Appropriate statistical methods (primary analysis of effect but excluding confounding)				
10	Positive if quantitative measures of association are presented (such as r, β, OR), including 95% CI's and numbers in the analysis (totals)	Yes	No	Don't know
11	Positive if the number of cases in the multivariate analysis is at least 10 times the number of independent variables in the analysis (final model)	Yes	No	Don't know

Highlighted questions represent 'essential questions'

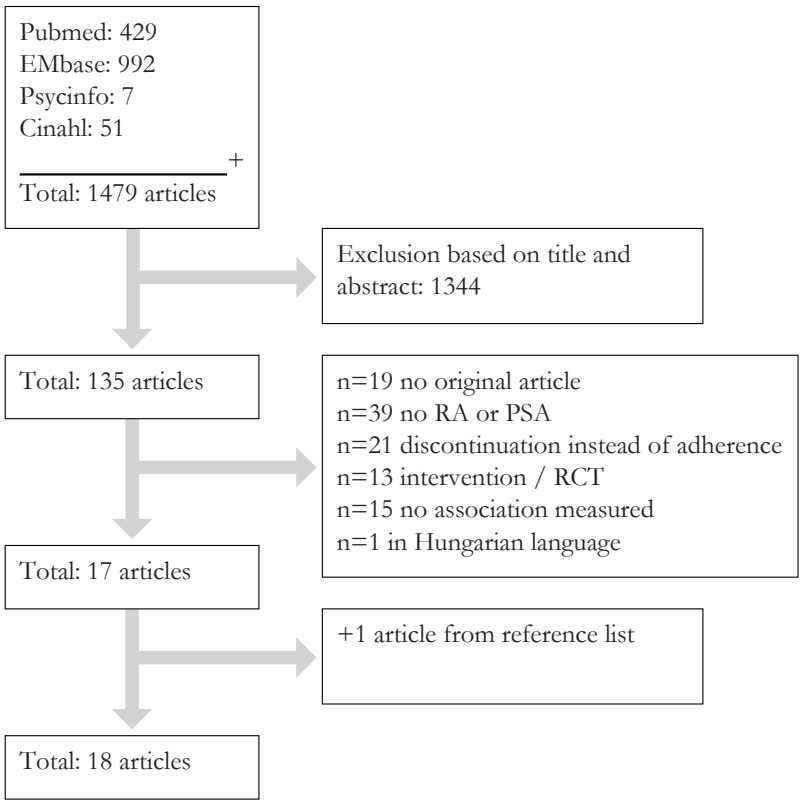
Evidence synthesis

The strength of evidence for factors associated with adherence was assessed by defining 5 levels of evidence, derived from recommendations from van Tulder et al.[13] The level of evidence was divided into the following levels: 1) strong evidence: consistent ≥75% findings among multiple high-quality studies; 2) moderate evidence: findings in 1 high-quality study and consistent findings in multiple low-quality studies; 3) limited evidence: findings in 1 high-quality study or consistent findings in multiple low-quality studies; 4) evidence for no association: ≥75% findings among multiple high-quality or low-quality studies showed no statistically significant associations; and 5) conflicting evidence: <75% of the studies reported consistent findings.

Results

Out of 1479 identified studies, 135 articles were potentially relevant regarding the content of title and abstract and retrieved as full text articles. After applying the inclusion criteria 17 articles remained eligible for the review. One relevant additional study was identified from the reference lists, resulting in 18 included studies (see flowchart figure 1). Data was extracted from each study and summarized in tables 3 to 6 and presented in full detail in the supplemental file.

Figure 1. Flowchart of selection process



Abbreviations: RA: rheumatoid arthritis, PSA: psoriatic arthritis, RCT: randomized controlled trial

Characteristics of the studies

Among the identified articles, the patient selection criteria for RA varied. Three studies included patients that met the ACR '87 criteria,[14-16] 4 studies used the 1958 revision of diagnostic criteria for RA (ARA criteria)[17-20] and 5 studies employed the ICD-9 or ICD-10 disease codes for RA.[21-25] In 6 studies the eligibility criteria for RA were not reported.[7, 26-30] All studies evaluated adherence in established RA patients with disease duration varying from 1 year to 15 years. Comorbidities were reported in 9 studies.[14, 15, 20-25, 30]

The evaluated medication regimen varied between NSAID therapy, DMARD therapy and anti-TNF treatment. Out of the 8 studies that evaluated adherence in DMARD therapy,[14, 21-26, 30] 2 studied methotrexate treatment[22, 25] and 3 evaluated TNF-inhibitors.[21, 23, 24] Adherence to NSAID therapy was assessed in 2 studies[20, 28] while 3 studies evaluated adherence in all medicines prescribed for their rheumatic condition.[15, 17, 29] The 5 remaining studies did not specify which drugs were taken by the patient group they studied.[7, 16, 18, 19, 27] One article studied patients who received for the first time DMARD therapy (no further specification given),[23] two articles studied first time MTX users,[22, 25] and one article studied patients who received either etanercept or adalimumab for the first time.[21] Although these studies state that their study population consisted of patients who were new on some sort of anti-rheumatic treatment, they do not state, however, whether this were newly diagnosed patients.

Information on the number of medicines taken per patient was provided in 6 studies. This ranged from a mean number of 1.5 medicines[17] to a mean of 9.5 medicines[29] per patient.

Sample sizes ranged from 63 to 5390 participants with a median of 152. The largest sample size belonged to the studies that made use of medical claim databases. 8 studies had a cross-sectional design, 4 studies were retrospective cohort studies and 6 studies collected data prospectively.

Methodological quality

The methodological quality of the studies theoretically ranged from 0 to 11 points. The methodological quality of the included studies ranged from a score of 2 points to a score of 10 points. 9 studies scored 'yes' on 4 out of the 5 very important items. Of these 9 studies, 7 also had a score of 7 or higher. One study scored above 7 points, but did not score enough points on the very important items. Overall, retrospective studies had better methodological properties (median 9 points) than prospective studies (median 6.5 points) and cross-sectional studies (median 3.5 points). Most studies showed limitations in the prevention or reduction of selection and recall biases (13 out of 18 studies scored negative), in using a valid method of measuring adherence (9 studies) and in controlling for confounding (11 out of 18 studied scored negative). Quality assessment details are summarized in table 2.

Table 2. Results quality assessment questionnaire

Author	Question number											Score
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Ferguson & Bole 1979 USA[29]	y	dk	dk	n	n	dk	y	n	n	n	na	2
Neame & Hammond 2005[27]	dk	n	y	n	y	dk	y	n	n	n	na	3
Owen, Friesen, Roberts et al. 1985[18]	y	dk	y	n	y	dk	n	n	na	n	na	3
Geertsen, Gray & Ward 1973[28]	dk	dk	y	n	y	dk	dk	na	na	y	na	3
Tuncay, Eksioglu, Cakir et al. 2007[30]	y	y	y	n	y	n	n	n	n	n	na	4
Lee & Tan, 1979[19]	y	dk	y	n	y	n	y	na	na	n	na	4
Lorish, Richards & Brown, 1989[20]	y	y	y	n	n	dk	dk	dk	n	dk	y	4
Beck, Parker, Frank et al. 1988[21]	n	y	y	y	y	y	n	n	n	y	n	6
Contreras-Yanez, Ponce de Leon, Cabiedes et al. 2010[31]	y	y	y	n	y	n	y	dk	n	y	n	6
Treharne, Lyons & Kitas 2004[16]	dk	dk	y	y	y	n	dk	y	y	y	na	6
Li, Blum, Von Feldt et al. 2010[24]	y	y	y	y	y	y	dk	n	n	y	dk	**7**
de Thurah, Norgaard, Harder et al. 2009[26]	y	y	y	y	y	n	y	n	n	y	na	**7**
Viller, Guillemin, Briançon et al. 1999[17]	y	y	y	n	y	n	n	y	y	y	y	8
Van den Bemt, Hoogen, Benraad et al. 2009[15]	y	y	y	y	y	n	y	y	n	dk	y	**8**
De Thurah, Norgaard, Johansen et al. 2010[23]	y	y	y	y	y	y	y	y	n	y	na	**9**
Borah, Huang, Zarotsky et al. 2009[25]	y	y	y	y	y	na	y	y	n	y	y	**9**
Park, Hertzog, Leventhal et al. 1999[8]	y	y	y	y	y	y	n	y	n	y	y	**9**
Curkendall Patel, Gleeson et al. 2008[22]	y	y	y	y	y	y	dk	y	y	y	y	**10**

y=yes, n=no, dk=don't know, na=nop applicable.
The grey columns represent 'very important questions'.
Scores in bold font style represent studies of moderate to high-quality.
Scores in normal font style represent studies of low quality.

Definition and measurement of non-adherence

Most studies used the same, conceptual definition for non-adherence, namely 'not following doctor's instructions'. This was operationalised in 13 studies as 'not following doctor's instructions' or 'taking more or less than the prescribed dosage'. 5 studies did not specify the definition of adherence or compliance.[15, 20-23] However, they did use a measure of adherence, so their data on adherence could be collected. Data on adherence was collected in several ways. 11 studies used a self-report by interview or an ad hoc (unvalidated) patient questionnaire to measure adherence,[7, 14-20, 25, 26, 28-30] 4 studies used a self-report with a validated questionnaire (e.g. CQR) to measure adherence,[14, 15, 25, 26] one study asked the health care provider,[27] 4 based their results on pharmacy records,[21, 23-25] one study used 'medication event monitoring systems' (MEMS)[7] and 2 studies used a serum salicylate assay (n=2).[20, 28] 6 out of 18 studies measured adherence using more than one instrument.[7, 14-15, 20, 28, 30] However, their final analyses were performed using one measurement method. Due to the use of a wide variety of adherence measurement methods, data could not be pooled.

For the definition of the primary outcome, most studies chose to dichotomize their patients in being adherent or non-adherent.[14, 16-18, 20, 23-30] 4 studies used 80% of the prescribed dosage taken correctly as cut-off for their primary outcome[14, 23, 24, 30] of which 2 studies provided a rationale. 11 studies used a self-report questionnaire to determine the patient as being adherent or not. 4 studies defined adherence as a continuous outcome by means of the CQR[14, 15] or pharmacy records.[21, 22]

Occurrence of adherence

Adherence rates ranged from 49.5% to 98.5%. Both the lowest and the highest adherence rate were measured by patient interview.[14, 30]. Adherence frequency measured by the MEMS was 91.5% after 4 weeks,[7] while the 4 cross-sectional studies using validated questionnaires reported adherence rates between 67%[14] and 91.1%[26]. In the prospective and retrospective studies the follow-up period ranged from 4 weeks to 384 days.

Determinants

Factors associated with adherence were measured using self-report by interview (n=11), self-report with a validated questionnaire (n=7) and pharmacy records (n=12). Most studies did not report at what time during treatment the determinants related to adherence were measured. Four studies reported that these were measured at baseline.[7, 20, 23, 24] One of these studies reported on patients that received their first DMARD therapy.[23] One study measured the determinants at three annual assessments.[16] Table 3 provides an overview of the determinants and a simplified rendering of the direction of their association with adherence (detailed information is provided in the supplemental file). Each factor was classified as positively associated with adherence, negatively associated or not statistically significant associated with adherence. In the last column of table 3 the level of evidence for each factor is provided. We did not assign a level of evidence to associations that were reported by only one low-quality study, since this is not determined in the criteria of van Tulder et al.[13]

Twelve factors showed conflicting evidence for an association with adherence. For the following 17 factors there is no evidence for any association with adherence: sex, being single, being employed, coping style, BMQ concerns scale, SIMS action scale, SIMS adverse effects scale, disease duration, Ritchie score, HAQ score, AIMS2 score, number of side effects, frequency of medication schedule, number of medicines, the use of folic acid, a previous inpatient stay, and level of MTX dose.

There is strong evidence for a positive association between a prescription for DMARDs 6 months prior to anti-TNF treatment and adherence to anti-TNF treatment. Related to anti-TNF treatment there is limited evidence for negative associations between weekly costs of anti-TNF, having Health Maintenance Organization (HMO) insurance compared to other types of insurance and out-of-pocket costs for anti-TNF and adherence to anti-TNF[21]; and limited evidence for a positive association between patients of 'other' race as compared to Whites.

Within the category 'Beliefs about medicine and satisfaction with medication', the belief that the medication for RA is necessary to treat the illness, measured with the 'necessity subscale' of the Beliefs about Medicines questionnaire (BMQ), showed strong evidence for a positive association with adherence to DMARDs and NSAIDs.[14, 15, 25, 26]

We could not provide a level of evidence for interpersonal factors, because they were only studied by single low-quality studies. However, the associations within this category all point in the direction that good communication with the healthcare provider is positively associated with adherence.

Table 3. Associations with drug adherence

		Association with drug adherence			Level of evidence
General category	**Specific factor**	**Positive (+)**	**Not significant**	**Negative (-)**	
Demographic factors	Age (higher)	7, 23 (55-64yrs), 16, 29	14, 25 15, 20, 18, 17		Conflicting
	Sex (female)	16	14, 23, 25 30, 15, 29, 18, 17	21	No association
	Education level (higher)	25, 19	14 16, 30, 20, 17		No association
	Number of children		15		
	Children at home			15	
	Single		30, 15, 18		No association
	Divorced		15	19	Conflicting
	Socio-economic status		30, 17, 15	19	Conflicting
	Employed fulltime		15, 30, 19		No association
	Race other than white	23			Limited positive
	HMO insurance			21	Limited negative
	Place of residence	21 (north-eastern US region)	17 (Netherlands versus France) 16 (Norway versus France)		Conflicting
Demographic factors (health-care system)	Weekly out of pocket costs for TNF-I			21	Limited negative
	Proportion of TNF-I costs paid by patient			21	Limited negative
	Cost of visit		20		
	Waiting to see the doctor			27	
	Time spent with doctor		27		
Psychosocial factors (intrapersonal factors)	Coping		14, 7 24		No association
	Optimism		15		
	General cognition	7			Limited positive
	Busy life style			7	Limited negative

Psychosocial factors (beliefs about medication)	BMQ necessity score	14, 25 15, 26			Strong positive
	BMQ general harm	15			
	BMQ general overuse			15	
	BMQ concern score	26	14, 25	15	No association
	SIMS action score		14		No association
	SIMS adverse effects score		14		No association
	Attitude to medication treatment	17	27		Conflicting
	Adverse side effects		20		
	Pain reduction		20		
	Self-prediction regarding taking medication		20		
	Lack of belief in benefit			28	
Psychosocial factors (knowledge of RA)	Knowledge of RA		26		
Perceived benefits versus perceived barriers (disease factors)	Disease duration		22, 25 15, 16, 29, 18, 17, 28	15	No association
	Rheumatoid factor		18		
	Active joint count			18	
	Pain severity		17, 27	18	Conflicting
	CRP		30, 15, 29	22	Conflicting
	Co-morbidity	22, 24	25 15, 30		Conflicting
	Ritchie articular index		16, 29		No association
	Morning stiffness	17	29		Conflicting
	DAS28			30	
	Sedimentation (ESR)	17	15, 29	30	Conflicting
	Disease flare			30	
	HAQ mean score		14, 7, 25 16, 29	30	No association
	AIMS 2 physical function		7		No association
Perceived benefits versus perceived barriers (medication factors)	No. of side effects		16, 20, 28, 17	14	No association
	Frequency of medication schedules		17, 18		No association
	Prescriptions for DMARDs 6 mo prior	21, 23			Strong positive
	No. of medicine	15	14, 7 30, 20, 29, 18, 17		No association
	Use of folic acid		25		No association
	Previous inpatient stay		23		No association
	Level of MTX dose		23		No association

Cues to action	MISS affective: healthcare provider listens, understands	15			
	MISS cognitive: healthcare provider supplies enough info	15			
	MISS behavioural: competent doctor	15			
	Personal nature of relationship with healthcare provider	27			
	Faith in treatment	27			
	Received adequate explanation of disease from healthcare provider	18			
	Satisfactory contact with health care provider	16			Limited positive
	Receiving contradictory info from healthcare provider			16	Limited negative
	Amount of info provided by healthcare provider	16			Limited positive
	Healthcare provider delivered info in insensitive way			16	Limited negative
	Social support	19	7 15, 28		Conflicting

Abbreviations: HMO: Health Maintenance Organisation, TNF-I: tumornecrosis-factor inhibitor, BMQ: Beliefs about Medication questionnaire, SIMS: Satisfaction with Information about Medicines Scale, CRP: C-reactive proteine, HAQ: Health Assessment Questionnaire, AIMS2: Arthritis Impact Measurement Scale, DMARD: Disease-modifying anti-rheumatic drugs, MTX: methotrexate, MISS: Medical Interview Satisfaction Scale

Underlined references: high study quality (score of 7 and higher)
References in normal font style: low study quality (score of 6 and lower)
Positive association means that the presence of the factor increases adherence
Negative association means that the presence of the factor decreases adherence
Strong evidence: consistent ≥75% findings among multiple high-quality studies
Moderate evidence: findings in 1 high-quality study and consistent findings in multiple low-quality studies
Limited evidence: findings in 1 high-quality study or consistent findings in multiple low-quality studies
No evidence: ≥75% findings among multiple high-quality or low-quality studies showed no statistically significant associations
Conflicting evidence: provided by conflicting findings <75% of the studies reported consistent finding.

Table 4. Cross-sectional studies

Author, year, country	Study population (disease, definition of disease)	n (response rate), % ♀, age (SD)	Type of medication	Time period	Determinants, measurement	Theoretical framework mentioned	Adherence, definition and measurement	Adherence rate	Methodological quality
Neame & Hammond, 2005, UK	RA	344 (57.3%) ♀ 67% 49.5% >65 yrs	DMARDs	-	Beliefs about medicine, demographics, disease features, DMARD experience, knowledge of RA	HBM Self-regulatory theory	M:RAI (self-report)	91.1%	3
van den Bemt, Hoogen, Benraad et al. 2009, NL	RA, ACR '87 criteria	228 (96%) ♀ 67.5% 56.2 yrs (SD12.2)	DMARDs	-	Beliefs about medicine, satisfaction about medication, health assessment, coping	-	M: CQ-R>80% MARS > 23 t Self report < One missed dosage a week	Interview: 98.5% CQR: 67% MARS: 60%	8
Treharne, Lyons & Kitas 2004, UK	RA, ACR '87 criteria	85 (?) ♀ 75% 58.88 yrs (SD12.64)	DMARDs / NSAIDs	-	Demographics, satisfaction medical consultation, social support, optimism, beliefs about medicines, medical information	HBM	M: CQ-R RAM Q (self-report)	RAM: 90.6-94.2% CQR mean: 2.04	6
Owen, Friesen, Roberts et al. 1985, Australia	Classical definite/ probable RA, ARA criteria	178 (100%) ♀ 69.7% Median compliants: 60.0 yrs (IQR51.8-70.0) Median noncompliants: 65.0 yrs (IQR55.8-70.3)	NSAIDs, Prednison, SAARDs	-	Socio-economic info, medical and antirheumatic drug history data	-	M:Interview (self-report) D: consistently altering dose of medication from prescriber's instructions	63.5%	3
Geertsen, Gray & Ward 1973, USA	Classical/definite RA	123 ♀ 68% 52 yrs (SD?)	Not specified	-	Doctor-patient communication, temporal factors, measured by SQ	-	D: not following doctor's instructions M: health care provider assessment	51.2%	3
Lee & Tan 1979, New Zealand	RA, 1958 Revision of diagnostic criteria for RA	108 (100%) ♀ 78.7% Compliant: 54.5 yrs (SD13 9) and non-compliant: 52.2 yrs (SD13.1)	Not specified	-	Demographics, disease info	-	D: taking more or less than the prescribed dosages M: self-report	61.1%	4
Lorish, Richards & Brown 1989, USA	Classical/definite RA, 1958 Revision of diagnostic criteria for RA	200 (100%) ♀ 58% 51 yrs (SD27)	Not specified	-	Functional status, list of pre-set reasons	TPB	D: any prescribed arthritis medication not taken within 4 hours of prescribed time M: interview	Not specified	4
Ferguson & Bole 1979, USA	RA	40 (100%) ♀ 75% 44.05 (SD?)	Aspirin	-	Belief in benefit, family support, length of illness, frequency of visits	HBM	D: not taking the prescribed dose of aspirin 'often' M: self-report	78%	2

Abbreviations: RA= Rheumatoid Arthritis, ACR= American College of Rheumatology, ARA= American Rheumatism Association criteria, MARS= Medication Adherence Report Scale, CQ-R= Compliance Questionnaire Rheumatology, RAM= Reported Adherence to Medication scale, DMARDs= disease-modifying antirheumatic drugs, NSAIDs= non-steroidal anti-inflammatory drugs, SAARDs= slow-acting antirheumatic drugs, HBM= Health Belief Model, TPB= Theory of Planned Behavior

Table 5. Retrospective studies

Author, year,country	Study population (disease, definition disease)	n (response rate), % ♀ , age (SD)	Type of medication	Time period	Determinants, measurement	Theoretical framework used	Adherence, definition and measurement	Adherence rate	Methodological quality
Curkendall, Patel, Gleeson et al. 2008, USA	RA, ICD-9CM 714.xx	2285 (100%) ♀ 75% 54 yrs (SD12)	TNF-I	Database search 2002-2004 1-year follow-up	Out-of-pocket costs, patient's share of anti TNF- therapy cost	-	M: MPR (pharmacy record)	MPR=0.52 SD: 0.31	10
De Thurah, Norgaard, Johansen et al. 2010, Denmark	RA, ICD-10 M05.3, M05.9, M05.8, M06.9	941 (100%) ♀ 69% 60.5 yrs (SD?)	MTX	Database search 1996 – 2006 median follow up 384 days	Disease duration, laboratory findings, disease activity, co-morbidity	-	M: CMG (pharmacy record)	Mean CMG: 12.3 (95% CI 11.5-13.2)	9
Li, Blum, Von Feldt et al. 2010, USA	RA, ICD-9CM 714.xx	5390 (100%) E: ♀ 88.4%, A: ♀ 91.8%, I: ♀ 87.6% E: 54.9 yrs (SD16.6), A: 55.9 yrs (SD14.3), I: 63.3 yrs (SD13.6)	TNF-I	Database search 2000-2002 1-year follow-up	Sociodemographics, medical info	-	M: PDC ≥0.80 (pharmacy record)	Mean PDC over 12 month follow-up: E: 0.57, A: 0.36, I: 0.64	7
Borah, Huang, Zarotsky et al. 2009, USA	RA, ICD-9CM 714.xx	3829 (100%) E: ♀ 78.28%, A:♀ 74.77% E: 49.18 yrs (SD13.25), A: 50.55 yrs (SD12.09)	Etanercept, Adalimumab	Database search jan. 2005 – dec. 2005 1-year follow-up	Health care utilization, health care costs	-	M: MPR ≥ 80% (pharmacy record)	MPR: 0.73 (SD0.28) 54.32%	9

Abbreviations: RA= Rheumatoid Arthritis, ICD-9CM= International Classicification of Diseases, 9th revision, Clinical Modification, ACR= American College of Rheumatology, CMG= continuous measure of medication gaps, MPR= Medication Possession Rate, PDC: proportion of days covered, measured as number of days covered with biologic divided by the fixed time interval of 365 days from the date of index biologic therapy initiation, MTX= methotrexate, TNF-I= tumornecrosis-factor inhibitor, E: Etanercept, A: Anakinra, I:Infliximab

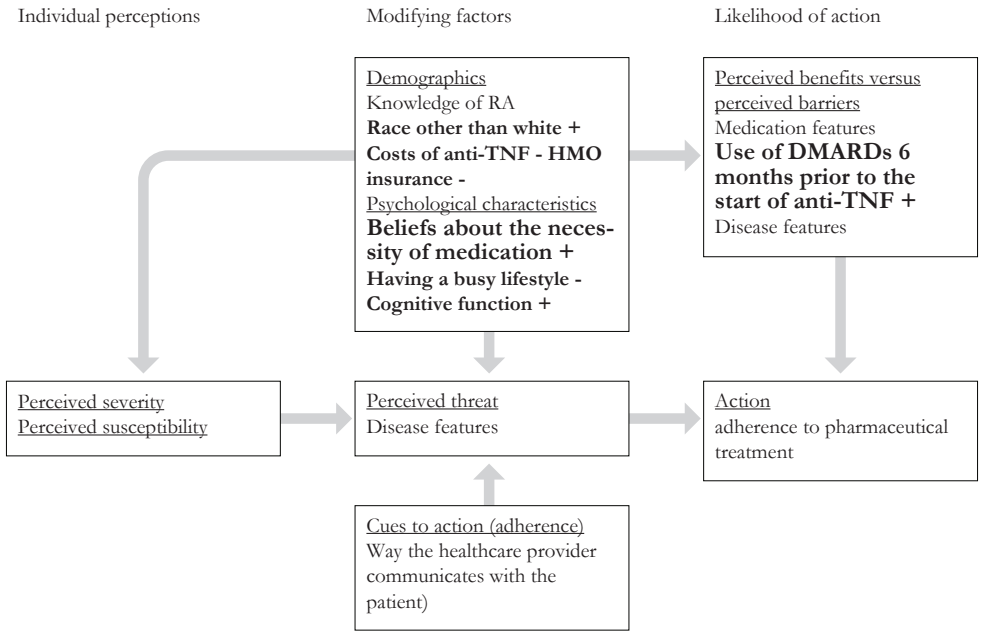
Table 6. Prospective studies

Author, year, country	Study population (disease, definition disease)	n (response rate), % ♀, age (SD)	Type of medication	Time period	Determinants, measurement	Theoretical framework used	Adherence, definition and measurement	Adherence rate	Methodological quality
de Thurah, Norgaard, Harder et al.2009, Denmark	RA, ICD-10 M05.3, M05.9, M05.8, M06.0, M06.9	126 (72.2%), 9 month: 68% ♀ 64% median 63 yrs (IQR 32-80)	MTX	Baseline, 9 months	Beliefs about medicine, health assessment, disease duration, use of folic acid, co-morbidity, demographics	-	M: CQ-R (self-report)	77% at baseline and after 9 months	7
Tuncay, Eksioglu, Cakir et al. 2007, Turkey	RA	100 (86%) ♀ 84.9% 49.3 yrs (SD 11.8)	NSAIDs, Prednison, DMARDs	Baseline, 6, 12 months follow-up	Standardized data collection forms, drug history, disease features, health assessment, morning stiffness	-	M: 4-item scale (self-report)	Baseline 52.3% 6 months: 72.1% 12 months: 60.5%	4
Park, Hertzog, Leventhal et al. 1999, USA	RA, Arthritis Foundation Rating Scale	121 (99%) ♀ 82.6% 56.07 yrs (SD 12.74)	Not specified	Baseline, 4 weeks	Demographics, health and function, illness and medcations beliefs, life style, cognitive function	Cognitive model	M: MEMS Diary notes (self-report)	4 weeks: 91.5%	9
Viller, Guillemin, Briançon et al. 1999, France	RA, ACR '87	556 (86%) ♀ 86% 52.9 yrs (SD 12.2)	Not specified	Baseline, 1, 2 years	Demographics, clinical data, health assessment, subjective definition of rheumatic disease, information provision, satisfaction with health care professionals, treatment	Health belief theory	M: Self-report	77.2%	8
Beck, Parker, Frank et al. 1988, USA	RA, ARA	63 (>95%) ♀ 90.4% 57 yrs (SD?)	NSAIDs	2 outpatient appointments, average 68 days	Demographics, expected success of treatment, behavioural self-predictions, attitudes to medication taking, situational factors, treatment regimen, dosage format	-	M: Serum salicylate assay, questionnaire	53%	6
Contreras-Yanez, Ponce de Leon, Cabiedes et al. 2010, Mexico	RA, disease duration <1 year	94 (98.9%) ♀ 86% 40.8 yrs (SD 13.9)	DMARDs	Baseline, 2, 4, 6 months	Demographic & medical history, health assessment, co-morbidity, treatment	-	M: CQ, DRR ≥80%, quantification of methotrexate	49.5%	6

Abbreviations: RA= Rheumatoid Arthritis, ICD-10= International Classicification of Diseases, 10th revision, ACR= American College of Rheumatology, ARA= American Rheumatism Association criteria, CQR= compliance questionnaire rheumatology, MEMS= medication event monitoring system, DRR= drug record registry, MTX= methotrexate, NSAIDs= non-steroidal anti-inflammatory drugs, DMARDs= disease-modifying antirheumatic drugs,

Intrapersonal factors were studied the least. We identified limited evidence for a positive association with general cognition and a negative association for having a busy lifestyle.[7] In order to identify potentially relevant determinants for future research, we placed the results of our review in the Health Belief Model (HBM)[11] (figure 2). We were able to identify some cues to action (e.g. the communication between patient and doctor). Furthermore, beliefs about the necessity of the medication and the use of DMARDs 6 months prior to the use of anti-TNF are medication features used in the weighing of benefits and barriers towards adherence. Factors with limited evidence (ethnicity, costs of the medication, type of insurance, having a busy life style and general cognition) are also pointed out in the model. Other factors with no or conflicting evidence for associations with adherence were also placed in the HBM and have inconclusive results (e.g. disease features influencing perceived threat, number of medication, type of medication), or are lacking in the literature so far (e.g. intrapersonal factors like coping).

Figure 2. Categories inserted in the Health Belief Model.



Underlined: features of the HBM
Normal font style: no/conflicting evidence
Bold font style: limited evidence
Large, bold font style: strong evidence

Abbreviations: RA: rheumatoid arthritis, DMARDs: disease-modifying antirheumatic drugs, anti-TNF: anti-tumour necrosis factor, HMO: health maintenance organization

Discussion

Our study used a systematic literature search to identify and summarize data on adherence rates in RA and undifferentiated inflammatory arthritis, to identify factors influencing adherence to pharmaceutical treatment and to identify the strength of the association between these factors and adherence. Overall 18 studies that fulfilled the inclusion criteria examined the relationship between adherence and factors thought to influence adherence, of which none studied undifferentiated inflammatory arthritis. Adherence rates varied between 49.5% and 98.5% depending on definition and method used. Concerning the factors influencing adherence, 17 factors were not associated with adherence. The lack of these associations may be a true absence of a relationship, but could also be caused by the heterogeneity of the studies. However, for factors that were frequently studied such as gender and education, the lack of associations independent of study methods may also indicate the absence of the association. For 12 factors the evidence was conflicting for a relation with adherence. Nonetheless, there is strong evidence that two factors have a consistent positive relationship with adherence: the use of DMARDs 6 months prior to the start of anti-TNF[21, 23] and the belief that taking the medication is necessary.[14, 15, 25, 26] As for the relation between patient and healthcare provider, the associations all point in the direction that good communication with the healthcare provider is positively associated with adherence. [15, 16, 18, 27]

A number of issues presented in the following paragraphs should be taken into account when interpreting the results of this review. First, the wide range of measures and definitions for adherence complicates the interpretation and summation of results over studies. This wide range could be due to a number of factors. The first and probably the most important is the variation of methods used to measure adherence. Because there is no 'gold standard' to measure adherence to pharmaceutical therapy, the use of multiple measurement methods within one study would be recommended.[10, 31, 32] This data can then be combined to gain more and better results.[31] Although 6 out of the 18 reviewed studies used two or more adherence instruments,[7, 14-15, 20, 28, 30] none of them combined the different instruments in their analysis.

Second, the dichotomization of adherence rates, which was done in 15 studies, also complicates the summation of results. This dichotomization means that more subtle adherence–regimen relationships may be left undetected.[33] Although the use of a continuous scale is preferable because it avoids the normative determination of the cut-off score, the application for daily practice would cause difficulty to identify those patients at risk for non-adherence. When adherence is dichotomized, cut-offs should be based on clinically relevant values.[32] Although dose-titration studies of most drugs show that the dosage for each individual patient may vary, determining the optimal cut off for adherence is difficult.[5] The most used cut-off score was 80% and was applied in 4 studies. However, the choice of 80% as a cut-off point was not explained in terms of clinical relevance, nor is there any other reference that motivates this percentage. Because we do not know what levels of adherence are required for therapeutic benefit,[5] the 80% may be a clinically insignificant cut-off score.

Third, the patient selection methods could have influenced the results. Because only 12 studies used random selection and 5 studies had a response rate of less than 80% it is likely that in part of the studies patients were selected towards those that would have no problems adhering to their medication regimen. This selection may have resulted in higher adherence rates than would be expected in normal daily clinical practice.

Fourth, the relationship between adherence and its related factors might have been affected

by the study design selected in the primary papers. With a cross-sectional design, which was applied in 8 studies, no causal assumptions can be made based on findings from these studies. Retrospective studies using a pharmacy database can only explore the relationship between factors in that database and adherence. Potentially relevant factors that are not in the database will remain undiscovered. To study the dynamic nature of adherence and to find causal relationships a prospective study design would be optimal, but this was only applied in 6 studies.[7, 16, 20, 25, 29, 30]

Fifth the type of medication studied may have influenced the strength of the association between the determinants and adherence. Various medication regimens and treatments that are not commonly used today (e.g. salicylate treatment) were studied by articles selected for this review. Various types of medicines may differ on the effect they have on the disease (slow-working or fast-working) and on the number and sort of side-effects. Besides this, the costs of the medication, for example for TNF-I treatment, may influence adherence to the treatment. When out-of-pocket costs for TNF-I treatment are higher, adherence measured by medication possession ratio decreases, since some patients cannot afford this medicine and therefore do not collect their medicine.[21]

Sixth, the best evidence synthesis required a cut point in the methodological quality score distinguishing high quality studies from moderate to low quality studies. The choice of this cut point is rather arbitrary, although we carefully considered methodological items that could be regarded as essential. If, for instance, the median were to be used, we would have ended up with the same cut-off score of 7. Higher cut-off scores weakened the level of evidence.

Adherence to medication requires behavior change of the patient and could therefore benefit from the use of a theoretical framework to understand what facilitates and what inhibits medication intake. 6 out of the 18 studies used a theoretical framework[7, 15, 16, 19, 26, 28] but none of these explicitly described how they made use of this framework. The most frequently used models were the Health Belief Model and the Theory of Planned Behaviour. These all share the central assumptions that people are capable of forethought, planning and rational decision making.[34] They focus on outcome expectancies, outcome values, self-efficacy expectancies, and intentions (i.e. proximal goals). Concerning the factors studied in the reviewed articles, we see that they lack information about outcome expectancies, self-efficacy expectancies and intentions. These factors and psychosocial determinants of adherence need to be addressed in future research. Results from reviews on other chronic diseases did include psychosocial factors and showed associations between psychosocial factors and adherence.[32, 35, 36] It is important to know whether these factors also play a role in adherence behaviour in RA patients. Once that is known, evidence based interventions to increase adherence can be developed and tested.

Two factors showed strong evidence for a relationship with adherence. First, the use of DMARDs 6 months prior to the use of anti-TNF shows strong evidence for a positive association with adherence. One might argue that it seems more logical that patients who failed on DMARD therapy, might not have been adherent to this medication, and therefore are likely not to be adherent to anti-TNF as well. However, our study showed that patients who used DMARDs before, are more adherent to anti-TNF therapy. We explained this phenomenon with the reasoning that patients who failed on previous therapy, may feel an urgency for using anti-TNF medication.

Second, our results show that there is strong evidence that a patient who does not believe in the necessity of anti-rheumatic medication, is at risk for non-adherence. Beliefs about the necessity of the medication are partly shaped through the information that the rheumatologist

provides about the disease and the pharmaceutical treatment. Consequently, the rheumatologist can play an important role in the patient's adherence behavior. With the provision of sufficient and tailored information about the medication and the disease from the initial consultation onwards, the rheumatologist could persuade, if necessary, the patient to take the medication. By talking about the patient's beliefs about the necessity of medication therapy the rheumatologists may influence these beliefs for the better.

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Appendix 1. Search strategy

Pubmed

((“patient compliance”[mesh] OR “medication adherence”[mesh] OR “Patient Compliance”[tw] OR “Patient Cooperation”[tw] OR “Patient Non-Compliance”[tw] OR “Patient Non Compliance”[tw] OR “Patient Nonadherence”[tw] OR “Patient Noncompliance”[tw] OR “Patient Non-Adherence”[tw] OR “Patient Non Adherence”[tw] OR “Medication Adherence”[tw] OR “Medication Compliance”[tw] OR “Medication Nonadherence”[tw] OR “Medication Non-Compliance”[tw] OR “Medication Non Compliance”[tw] OR “Medication Noncompliance”[tw] OR “Medication Non-Adherence”[tw] OR “Medication Non Adherence”[tw] OR “Medication Persistence”[tw] OR “Patient Non Cooperation”[tw] OR “Patient non-Cooperation”[tw] OR “Patient nonCooperation”[tw] OR “Medication non Persistence”[tw] OR “Medication non-Persistence”[tw] OR “Medication nonPersistence”[tw]) AND ((arthritis[mesh] OR arthriti*[tw] OR polyarthriti*[tw] OR rheumatic diseases[mesh] OR rheumatic disease*[tw]) AND (drug therapy[tw] OR drug therapy[sh] OR drug therapy[mesh] OR pharmacotherap*[tw] OR anti-inflammatory agents[mesh] OR anti-inflammatory agents[pa] OR anti-inflammatory agent*[tw] OR anti-inflammatory drug*[tw] OR anti-inflammatory agent*[tw] OR anti-inflammatory drug*[tw] OR Disease-Modifying Second-Line Drug*[tw] OR prednisone[mesh] OR prednisolone[mesh] OR prednisone[tw] OR prednisolone[tw] OR salazopyrine[tw] OR sulfasalazine[mesh] OR sulphasalazine[tw] OR hydroxychloroquine[mesh] OR hydroxychloro*[tw] OR oxychloro*[tw] OR plaquenil[tw] OR tumor necrosis factor-alpha[mesh] OR tnfalpha[tw] OR tnf-alpha[tw] OR antirheumatic agents[mesh] OR antirheumatic agents[pa] OR antirheumatic agent*[tw] OR anti-rheumatic drug*[tw] OR anti-rheumatic agent*[tw] OR anti-rheumatic drug*[tw])))

EMbase

((arthritis/syn OR ‘rheumatic disease’/syn OR arthriti*:ti,ab,de OR polyarthriti*:ti,ab,de OR rheumatic disease*:ti,ab,de) AND (‘drug therapy:ti,ab,de’ OR ‘drug therapy’/syn OR pharmacotherap*:ti,ab,de OR ‘antiinflammatory agent’/exp OR ‘anti-inflammatory agent’:ti,ab,de OR ‘anti-inflammatory drug’:ti,ab,de OR ‘anti-inflammatory agent’:ti,ab,de OR ‘anti-inflammatory drug’:ti,ab,de OR ‘anti-inflammatory agents’:ti,ab,de OR ‘anti-inflammatory drugs’:ti,ab,de OR ‘anti-inflammatory agents’:ti,ab,de OR ‘anti-inflammatory drugs’:ti,ab,de OR prednisone/syn OR prednisolone/syn OR salazosulfapyridine/syn OR hydroxychloroquine/syn OR ‘tumor necrosis factor alpha’:ti,ab,de OR tnfalpha:ti,ab,de OR tnf-alpha:ti,ab,de OR ‘antirheumatic agent’/exp OR ‘antirheumatic agent’:ti,ab,de OR ‘antirheumatic drug’:ti,ab,de OR ‘anti-rheumatic agent’:ti,ab,de OR ‘anti-rheumatic drug’:ti,ab,de OR ‘antirheumatic agents’:ti,ab,de OR ‘antirheumatic drugs’:ti,ab,de OR ‘anti-rheumatic agents’:ti,ab,de OR ‘anti-rheumatic drugs’:ti,ab,de OR methotrexate:ti,ab,de))

PsychINFO

(Treatment compliance.mp OR treatment compliance/ OR adherence.mp.) AND (exp arthritis/ or arthritis.mp. OR polyarthritis.mp. OR rheumati*.mp.) AND ((drug therapy.mp OR exp Drug Therapy/ OR anti-inflammatory drug.mp. OR exp Anti Inflammatory Drugs/ OR predniso*.mp. OR antirheumtaic drug.mp. OR exp tumor necrosis factor/ OR tumrnecrosis factor.mp.) OR (salazopyrine OR sulfasalazine OR sulphasalaziine OR hydroxychloro* OR oxychloro* OR plaquenil OR tnfalpha OR tnf-alpha OR antirheumatic* OR anti-rheumatic* OR methotrexate).mp)

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((patient compliance OR medication adherence OR Patient Cooperation OR Patient Non-Compliance OR Patient Non Compliance OR Patient Nonadherence OR Patient Noncompliance OR Patient Non-Adherence OR Patient Non Adherence OR Medication Adherence OR Medication Compliance OR Medication Nonadherence OR Medication Non-Compliance OR Medication Non Compliance OR Medication Noncompliance OR Medication Non-Adherence OR Medication Non Adherence OR Medication Persistence OR Patient Non Cooperation OR Patient non-Cooperation OR Patient nonCooperation OR Medication non Persistence OR Medication non-Persistence OR Medication nonPersistence) AND ((arthritis OR arthriti* OR polyarthriti* OR rheumatic diseases OR rheumatic disease*) AND (drug therapy OR drug therapy OR drug therapy OR pharmacotherap* OR anti-inflammatory agents OR anti-inflammatory agents OR anti-inflammatory agent* OR anti-inflammatory drug* OR anti-inflammatory agent* OR anti-inflammatory drug* OR Disease-Modifying Second-Line Drug* OR prednisone OR prednisolone OR prednisone OR prednisolone OR salazopyrine OR sulfasalazine OR sulphasalazine OR hydroxychloroquine OR hydroxychloro* OR oxychloro* OR plaquenil OR tumor necrosis factor-alpha OR tnfalpha OR tnf-alpha OR antirheumatic agents OR antirheumatic agents OR antirheumatic agent* OR antirheumatic drug* OR anti-rheumatic agent* OR anti-rheumatic drug* OR methotrexate OR methotrexate)))

Chapter 6

Facilitators and barriers to adherence in the initiation phase of disease-modifying antirheumatic drugs (DMARD) use in arthritis patients who recently started with their first DMARD treatment

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Abstract

Objective To explore themes associated with adherence in the initiation phase for first time use of disease-modifying antirheumatic drugs (DMARDs) in patients with inflammatory arthritis using focus groups and individual interviews.

Methods 33 patients were interviewed in focus groups and individual interviews. Interviews were transcribed verbatim and imported into ATLAS.ti software. Responses that included reasons for adherence or non-adherence in the initiation phase were extracted and coded by two coders separately. The two coders conferred until consensus on the codes was achieved. Codes were classified into overarching themes.

Results Five themes emerged: 1) symptom severity, 2) experiences with medication, 3) perceptions about medication and the illness, 4) information about medication, and 5) communication style and trust in the rheumatologist.

Conclusion Perceptions about medication and the communication style with and trust in the rheumatologist were mentioned the most in relation to starting DMARDs. The rheumatologist plays a crucial role in influencing adherence behavior by addressing perceptions about medication, providing information and establishing trust in the treatment plan.

Introduction

The prognosis of early arthritis is significantly improved by an early, intensive and tightly controlled treatment with disease-modifying anti-rheumatic drugs (DMARDs) within 3 months of diagnosis.[1-4] This however requires the patients to adhere to the prescribed medication as soon as possible, which is for some patients too big a hurdle. Prevalence data on adherence in this early stage are lacking, but there is a significant amount of patients not adhering to their medication in the later phase of the disease (1.5% to 50.5%, depending on methodology and definition of adherence).[5] We may assume that a considerable amount of arthritis patients also has difficulty initiating medication, since this has also been shown for other diseases.[6] It would be helpful to get insight into the reasons for nonadherence in the initiation phase, so that we could intervene at an early stage to prevent the disease from becoming worse.[7]

Adherence to medication is a continuous process, which can be divided into three parts: initiation (or acceptance), implementation and discontinuation.[8] In the initiation phase, the patient learns to accept the need for the medication and learns to fit the medication schedule into daily life.[9] The length of the initiation phase differs between diseases. For inflammatory arthritis, we set this stage at 3 months of DMARD use, because it takes generally 3 months before the full effectiveness of the DMARDs can be felt and tested. The initiation phase is followed by the implementation phase, in which the patients should maintain their adherence to the therapy. This phase can last lifelong, since inflammatory arthritis is a chronic disease.

Most studies on adherence focus on the implementation phase ignoring the part that precedes the implementation phase: the initiation of medication. For this reason, little is known about determinants of therapy initiation. For determinants of adherence in the implementation phase, on the other hand, there is a small body of evidence.[10-14] Garcia Popa-Lisseanu[10] reported 4 barriers to medication adherence in RA patients in the implementation phase: fear of side effects, perceived lack of efficacy of therapies, cost of medication and difficulty in obtaining treatment in a publicly funded health care environment. Other factors found to influence medicine intake in RA patients in the implementation phase are ignorance and confusion about the medication regimen and interruptions to the daily routine.[11] For other chronic diseases, beliefs about the necessity of medication and concerns about medication as well as illness perceptions seem to play an important role in adherence behavior.[15, 16] The necessity-concerns framework (NCF) is a framework used to improve our understanding of the relationship between patients' beliefs and adherence.[17]

It is unknown if, and to what extent these determinants of adherence in the implementation phase are also applicable to the initiation phase. Since new patients are not familiar with their disease and medication, and since it takes a while for the medication to have an effect, other factors, such as concerns about having to live with a long-term condition may also play a role.[18] A recent study on preferred outcomes in early RA patients shows that patients prefer 'returning back to normal' and pain relief as outcomes.[19] It could well be that these preferred outcomes are also factors influencing adherence behavior. Knowing these factors may help clinicians to identify factors that influence DMARD initiation and thereby optimize treatment effectiveness. In overcoming the gap in literature regarding factors influencing medication initiation, we used qualitative methodologies to study the reasons for DMARD initiation and we visualize the data synthesis in a conceptual model.

Materials and methods

Design

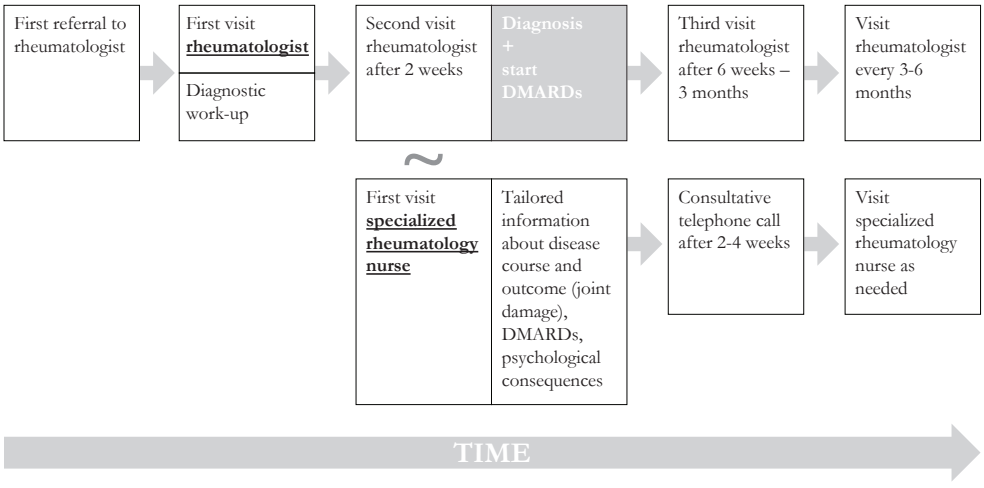
We set up focus groups, which allowed for an interactive discussion on the topic of adherence to generate data.[20] Focus groups were set up until the same topics of adherence kept reoccurring in multiple focus groups. During the recruitment for these group interviews, it became apparent that patients willing to participate, were rather adherent. Because we were interested in barriers to adhere, we also wanted to include less adherent patients in our sample. Therefore, 10 additional individual interviews were conducted with less or non-adherent patients. Individual interviews made it possible to adapt the interview setting to specific preferences of these patients and to ensure that they felt safe to open up about non-adherence.

Recruitment

Forty consecutive patients were invited by their rheumatologists from the Erasmus Medical Center (EMC) Rheumatology department to participate in focus groups, of which 24 were able and willing to participate. Main reasons for non-participation were not being able to travel or no interest. Six focus groups were formed with 3 to 6 patients. One interviewee did not fulfil the inclusion criteria and was excluded from analysis. For the individual interviews, rheumatologists asked patients if they either had a delayed start with DMARDs, altered their medication dose or took their medication intermittently. When patients responded with 'yes', they were invited to participate. Twelve patients were invited, of which 10 were willing to participate.

Inclusion criteria were minimum age 18 years, prescribed treatment with DMARDs which started less than 2 years ago for polyarthritis (RA, PsA and unclassified inflammatory arthritis) to ensure that they could recall starting medication. All patients had symptomatic disease for which they required standard care (figure 1) and DMARDs. Approval was gained by the EMC Medical Ethics Committee and all subjects gave consent for participation.

Figure 1. Standard rheumatology care for arthritis patients in the first 3 months



Measures

A semi-structured interview schedule was developed based on items found during a literature review[21] and on relevant determinants of the 'Health Belief Model', a frequently used behavioral model in health care, in which perceived barriers and benefits of behavior are weighted against each other.[22] Lead questions were: "How did you experience starting with medication" and "What were your considerations on starting with medication?". The interview guide is available upon request.

Procedure

A male psychologist (AS) (PhD) and a female epidemiologist (JL) (PhD) with experience in conducting interviews each led 3 focus groups, which were held at a quiet location in the hospital. During the focus groups participants were invited to discuss and share experiences with each other. The sessions lasted approximately 90 minutes. One female researcher (AP) interviewed 10 participants individually by telephone or face-to-face at the hospital. These interviews lasted 20 to 90 minutes. The interviewers introduced themselves as being interested in the topic of adherence and emphasized the confidentiality of the interviews. Focus groups and individual interviews were audiotaped with prior consent of all participants and transcribed verbatim. Field notes were made during the interviews. To ensure anonymity, identifying information was removed from the transcripts.

Data Analysis

Transcripts were imported into ATLAS.ti software, which facilitates qualitative content analyses. Field notes were used to verify discrepancies in the transcripts. The thematic analysis of the transcripts was inductive: the formation of themes was driven solely by the data content.[23] The inductive analysis followed guidelines described by Arcury and Quandt.[24] One coder (AP) read the interview transcripts several times to familiarize herself with the data. Statements by patients that included reasons for the initiation of DMARDs were coded with the key word that captured the dominant content of the quote. The codes were then categorized and grouped into overarching themes. A second investigator (MW) read and coded two transcripts independently of the first coder. The two investigators discussed the themes until consensus was achieved. A comprehensive model was formed based on the themes. The number of quotes was counted as an indication of the importance of the theme.

Results

Demographics of the participants

Table 1 summarizes the participants' demographic characteristics. Although the inclusion criteria stated that patients had to have a prescription for DMARDs for less than 2 years, 4 participants received their first DMARD prescription more than 2 years ago with a median of 3 years, because they delayed their start with DMARDs.

Themes

Below we describe the themes that influence the initiation of DMARDs and illustrate them with typical quotes. Table 2 summarizes the themes and the number of quotes per theme.

Table 1. Demographics of the participants

Characteristics		Total (n=33)
Female, n		29
Median age (IQR), years		51 (39-59)
Time since diagnosis	≤ 1 year	12
	1 to ≤2 years	12
	> 2 to 5 years	9
Median time since medication	(IQR), months	13 (6-19)
Diagnosis :	RA	23
	PsA	10
Number of DMARDs	1	12
	>1	21

Abbreviations: IQR: interquartile range, RA: rheumatoid arthritis, PsA: psoriatic arthrtis, DMARDs: diseasse-modifying antirheumatic drugs

Table 2. Overview of 5 themes into which the respondents' reasons were grouped

Themes	Examples of reasons mentioned	Nr of quotes
Symptom severity	Pain, fatigue, disability	46
Experiences with medication	Previous experience with medication for other diseases or current experience with DMARDs, side effects	61
Perceptions about medication and the illness	Expectations about medication, confrontation with 'having a chronic illness' by the use of medication	89
Information about medication / knowledge acquisition	In the early phase patients started gathering information. Information obtained from the rheumatologist, the medication information leaflet or by searching the internet	15
Communication style, and trust in the rheumatologist	The rheumatologist should build towards a trustful relation, for instant by acknowledging fears about medication, and explaining the treatment plan in detail	54

Symptom severity

Symptom severity is not only determined by specific arthritis pain, but also by fatigue and feelings of disability caused by arthritis. Patients stated that the more severe their complaints were, the more likely they were to take the medication.

> *"Well, you do take them if it hurts. That's the thing. If it hurts, you take them.(…) It's that simple."* (P1 Female, 62 years old, RA)

Experiences with medication

Previous negative experiences with any kind of medication before starting with DMARDs, could impact perceptions about DMARDs and therefore could affect initiation in a negative way. Some patients received a corticosteroid injection as a bridging therapy, and immediately felt the positive effect of this injection. This caused a positive attitude towards taking DMARDs.

"I took the tablets for the first time and at night I needed to go to the bathroom (…). I walked to the door and noticed that I was there right away. I thought 'wow this seems like a miracle'. And then I started using methotrexate. And my first experience was this positive that I believed it only worked in a positive way." (P2 female, 69 years old, RA)

After their first intakes of DMARD therapy, patients started weighing the symptom severity against the perceived experiences with the medication. If the side-effects of the medication outweighed the symptom severity, this was a reason to stop using DMARDs.

"When I started taking the Sulfasalazine as well, I felt so miserable. I'd just start crying for no reason at all. (…) I felt sick and... I think I'd rather have the darn pain than feel like that." (P3 Female, 47 years old, RA)

Perceptions and feelings about medication and the illness

Having negative perceptions about medication in general or about DMARDs in particular, was the most frequent mentioned reason for reluctance to initiate DMARDs. Most patients had difficulty explaining why they had these negative feelings about DMARDs. Some patients regarded these medicines as 'poison', but when asked to explain further, patients responded with more nuanced expressions like "it is just not natural" or "I don't want this in my body". Participants explained how perceptions about medication were shaped by numerous factors, e.g. previous negative experiences with medication, not accepting the diagnosis, influence from important others, and available information about the medication.

"(…) I often didn't take them because I was like: 'No, this is junk, I'm not putting that in my body. Never had to take any pills and now I have to...' Just reading the leaflet got me saying: 'no way, this is not for me'." (P4 Female, 35 years old, RA)

"But, in the past I didn't want to use any pills. When I had a headache, I thought, oh, it will pass. And then you find yourself standing with a box (of medicines) in your hands" (P3 Female, 47 years old, RA)

"Because I think, it are means from the outside, and why can't my body heal itself? Why am I just not healthy from nature?" (P5 Female, 41 years old, RA)

Mostly, taking medication symbolized for patients that they had become a chronic patient with a serious illness. Non-adherence was a way of resisting this new position. Some patients felt their health depended too much on the medication. Other patients were angry because they felt

betrayed by their own body. The patients seem to be in a state of denial and were reluctant to start with medication.

> *"No. Because then you feel like you really are sick, as it were. That you actually have something. And I didn't want to start, and I... I keep repeating to myself: I don't have arthritis, I don't have arthritis. I'm too young."* (P5 Female, 41 years old, RA)

Fears and doubts about the long-term effects of DMARDs were also mentioned as a reason for non-adherence. Some interviewees felt that if they would take the DMARDs they would live shorter because the medication could have serious side effects on their liver and kidneys. They accepted that non-adherence would result in higher levels of pain. Some patients had the feeling that they had no choice whether to start with the medication. The quote below explains this feeling.

> *"Honestly, I am fed up with it. But I have no choice (but to take the medication). You will not get away without it. Because, how else would I go on?"* (P1 female, 62 years old, RA)

Information about the medication

Information about medication shaped perceptions about medication, which in turn influence adherence. The three main information sources were: the rheumatologist, the medication leaflet and the internet.

> *"And then you start looking and searching on the web. And when I read what a hassle it (the medication) can give, I thought to myself; my God, what if I get all those things! Because I think, then I don't want it (the medication) no longer."* (P1 Female, 62 years old, RA)

Patients used these information sources differently. The medication leaflet mostly focusses on medication effects and side-effects, whereas rheumatologists give tailored information and can also address the patient's emotions. Most patients gained information from the internet from websites with an unclear source.

Communication style and trust in the rheumatologist

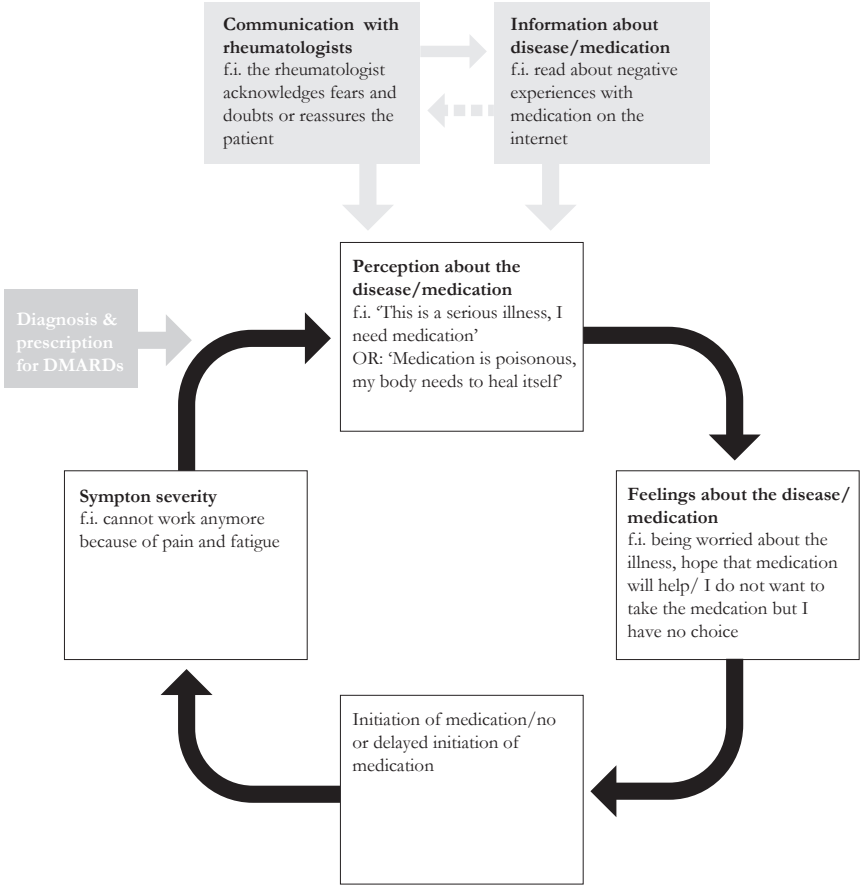
Communication style and trust in the rheumatologists was mentioned frequently as a reason to initiate DMARDs. Patients talked about the need to trust their rheumatologist to feel able to adhere to the medication. In order to build on this trust, the patients felt that the rheumatologist needs to acknowledge the patient's fear of medication. Being interested in the patient's needs, doubt and fears and a thoughtful response to these items were mentioned as important, as was the way of providing information about the medication and its side-effects by the rheumatologist. Indeed an open and trustworthy communication with the rheumatologist was regarded as the most effective way to modify the patient's knowledge and perceptions about medication. Miscommunication about medication types and dosages was reported as a serious event that could easily break the trust in the rheumatologist.

"And she (the rheumatologist) knew how frightened I was, but she just accepted it. And that was really important to me. She didn't say like: 'Yeah, well, what nonsense, if you don't take this then that's your lookout, your loss'. No, she accepted it and dealt with it. And that's what persuaded me quite quickly, from that point on really, to just start taking the pills." (P6 Female, 62 years old, RA)

Data synthesis

To synthesize the data, relationships between the themes were explored by visualizing them in a model (figure 2). When a patient experiences symptoms and becomes a patient, certain perceptions about the disease and the medication start to play a role. The perception that medicines are poisonous for your body could amplify feelings of anxiety about medication. This in turn can delay the patient's medication initiation. This influences the severity of complaints, and the chain goes on as the patient will consult the rheumatologist again. The rheumatologist can address the patients perceptions about medication and the disease and thereby break the chain. Information about medication and the disease can also change patients' perceptions.

Figure 2. Conceptual model



Discussion

This is the first study that explicitly focuses on the initiation part of the adherence process in inflammatory arthritis patients about perceived barriers and facilitators to initiate DMARDS. Five themes emerged: 1) the symptom severity; 2) experiences with medication; 3) perceptions and feelings about medication and the disease; 4) information about medication; and 5) Communication style and trust in the rheumatologist. As depicted in the conceptual model (figure 2), the themes influence each other. Perceptions about medication and illness are the most modifiable and can be targeted through the rheumatologists' communication efforts and through the information received about DMARDs and the disease.

No previous studies were available on factors influencing DMARD initiation, but previous qualitative studies on factors influencing adherence in established disease, reported the same 5 themes.[10, 12-14] This suggests that we could use similar interventions to promote adherence although there will be differences. Believes about the disease and medication play in both stages a role, but they vary. Newly diagnosed patients may have more general beliefs about the harmfulness and expected effectiveness of medication while patients with established disease may have more specific cognitions about the necessity of the medication. In the first part of DMARD intake, the rheumatologist has a better opportunity to influence adherence than in a later stage, because of the often more frequent visits to the rheumatology clinic, and this interaction can be used to build up trust and change perceptions about the disease and medication.

Known demographic variables influence adherence,[5] but are not modifiable. The patient perspective, as studied in this paper, gives us more clues for the development of interventions, since psychosocial variables such as perceptions are modifiable. Our model (figure 2) suggests that the theme to target is 'perceptions about the medication and the illness'. Perceptions are the most modifiable theme in our model, and can be changed,[25] for instance with cognitive behavioral techniques. As trust in the rheumatologist is a key factor, challenging these inadequate perceptions in an empathic way may increase both adherence and the relationship with the rheumatologist.

In patients with established disease, shared decision making is often mentioned as an important topic influencing adherence. In our sample, this was not mentioned. It could be that patients in the months after diagnosis are rather passive and leave decisions to their rheumatologist. In a later stage they become more aware of what they need and might be more open to shared decision making.

When elaborating on symptom severity, patients spoke about pain and not about the preventive effects of taking DMARDs for potential joint damage. Apparently patients do not prioritize the preventive effects of DMARDs, as is also expressed in low adherence rates for other preventive medicines, such as for blood-pressure lowering medication.[21] This might also be an important topic for rheumatologists to address. The speed at which physical improvement takes place might be an important cue for patients that medicines are working and thus influences necessity beliefs.

Although appointments with a specialized rheumatology nurse are firmly embedded in the first months of rheumatology care, interviewees did not mention them in regard to adherence behavior, but they did mention the rheumatologist's role. From our data, it seems that patients view the rheumatologist as an authority and this may cause why patients only mention the role of the rheumatologists.

Our study has several limitations. Interviewees' inclusion in the study depended on the will-

ingness to participate. It could be that we missed patients with particular adherence characteristics that were associated with response to our request to participate. We did not involve patients in the design of the study, which might have been helpful in the study set up. For instance, we missed less adherent patients in the focus groups, and had to conduct additional individual interviews to capture the non-adherent patient's viewpoint. Patients' responses about the start of DMARD intake relied on recall, and could not be verified by other means. Recall bias might have affected feelings about the importance of communication with the rheumatologist as well as feelings about symptom severity. However, all patients were prescribed DMARDs suggesting that the arthritis symptoms were indeed severe. It might have been more desirable to include patients who used DMARDs between 6 and 12 months, but because of difficulties with collecting patients in this disease phase, we expanded our inclusion criteria. Most of the interviewees were women, which may cause that the male viewpoint is slightly underrepresented. However, the topics mentioned by the interviewees were not gender-specific and thus generalizable to both men and women.

Future research should combine quantitative and qualitative methodologies so that the focus lies on both the patient perspective and the healthcare provider perspective. The present study gives insight in which themes play a role in non-adherence behavior. The second step would be to perform a quantitative study, that shows which themes are most prevalent. That way we gain a proper understanding of the extent of the non-adherence problem and we will have a clear body of evidence for determinants to target. The third step is to develop a theory- and evidence-based intervention, such as the intervention mapping protocol describes.[26, 27]

If we would bundle these steps in a protocol, we could test whether these suggestions indeed make a difference on adherence to DMARDs in early arthritis patients. Our findings suggest that the rheumatologists' communication efforts may play a decisive role in patients' initiation of DMARDs. The rheumatologist should be aware that a newly diagnosed patient may have negative perceptions about medication in general or specific to DMARDs, depending on the patient's health literacy. Tailored information by eliciting prior expectations about DMARDs by the rheumatologist can influence these perceptions. Changing the perceptions will, as outlined in our model, improve adherence in the initiation phase of DMARDs.

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Chapter 7

How to study determinants related to medication adherence in newly diagnosed polyarthritis patients for the development of a prediction instrument

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Annelieke Pasma, Johanna M.W. Hazes, Jolanda J. Luime, Jan J.V. Busschbach, Adriaan van 't Spijker. How to study determinants related to medication adherence in newly diagnosed polyarthritis patients for the development of a prediction instrument. Patient Prefer Adherence. 2014;8: 1437-1447.

Abstract

Introduction For patients with a chronic disease, the appropriate use of medication is the key to manage their illness. Adherence to medication is therefore important. Adherence can be divided into three parts: the initiation part, the execution phase and the discontinuation part. Little is known about the determinants of the initiation part. For this reason, we describe the conduct of a stepwise procedure to study determinants of medication initiation for patients with a chronic disease.

Methods/Design The stepwise procedure comprises of eliciting a list of all potential determinants via literature review, interviewing patients, and consulting an expert panel. This is followed by embedding the determinants in a theoretical framework, developing a questionnaire, and choosing adherence measurement methods. The consecutive steps that we conducted for the development of a tool for the prediction of adherence in our study sample of early arthritis patients, are described.

Discussion Although we used a thorough procedure, there are still some pitfalls to take into account, such as the choice of theoretical framework. A strength of this study is that we use multiple adherence measurement methods and that we also take clinical outcomes into account.

Introduction

For patients with a chronic disease that respond well to drug treatment, appropriate use of medication is the key to managing their illness. Since a few decades we know that over 30% of prescribed medication is not taken as directed[1]. A meta-analysis from 2004 assessed over 50 years of research on chronic medication adherence and calculated an overall non-adherence rate of 24.8%.[2] For rheumatoid arthritis (RA), the non-adherence rates range between 1.5% and 50.5%.[3]

Non-adherence wastes resources, and is related to preventable morbidity and mortality.[4] For example, in the rheumatology practice, patients with RA, are treated with disease-modifying antirheumatic drugs (DMARDs) to induce disease remission and prevent disability. When not sufficiently adhering to their treatment, they may present themselves as a non-responder to the treatment, resulting in a switch to a more expensive treatment with biologicals. When rheumatologists get better insight in patients who are potentially non-adherent, unnecessary switches to other therapies might be prevented.[5]

To prevent non-adherence, early recognition of potential non-adherence behavior is necessary. This requires patient profiling distinguishing those at risk for non-adherence from adherent patients. A frequently cited definition of adherence is 'the extent to which a person's behavior – taking medication, following a diet, executing lifestyle changes – follows medical advice'.[6] It is a continuous process, which can be divided into three parts: acceptance, execution and discontinuation.[7] In the acceptance phase, the patient learns to accept the need for the medication and learns to fit the medication schedule into daily life.[8] This phase initiates the execution of medication intake. For RA patients, this is the part where they start to experience the effect and side effects of the DMARDs. It takes approximately three months before the full effectiveness of the DMARDs can be felt and tested. Unfortunately, most studies on adherence focus on the execution phase and skip this important phase that precedes the execution phase: the initiation of medication.

The focus of studies on the execution phase means that, although we do have some insight in the prevalence of non-adherence in the execution phase, even in that phase we still do not have a clear view what causes non-adherence. Non-adherence is a complicated phenomenon, and decades of research show unequivocal relationships with both modifiable factors and unmodifiable factors.[6, 9] Frequently studied factors are medication characteristics, perceptions and cognitions about illness and medication, socio-economic and demographic factors, disease features and doctor-patient relationship.[3, 6] Although these factors are widely studied, the evidence for the association with adherence points in different directions.[3] For example, some studies report higher age as a risk factor for nonadherence in RA patients, whereas other studies report lower age as a risk factor for nonadherece in RA.[3] This can be due to a number of factors, such as the use of different adherence measurement instruments. Another problem is that most studies on medication adherence in chronic patients do not include a consistent behavioral model to explain non-adherence. A behavioral model directs research, indicates which factors are potentially relevant and helps to gain insight in the relations between the determinants that guide behavior. When a behavioral model is missing, it could be that relevant factors are missed.

Moreover, research mostly focused on unmodifiable determinants of adherence, such as disease features or demographic characteristics. An example is the work of Curtis et al., who showed which osteoporosis patients are at risk for nonadherence for bisphosphonates, but only

identified unmodifiable risk factors.[10] Although these unmodifiable determinants give us some clues for the target of interventions, we also need to study modifiable determinants, so that interventions on these modifiable determinants can be developed.

We know from the scarce literature on the initiation of medication that a) expecting health problems from not treating the disease; b) the ability to obtain information during treatment; c) negative attitudes toward medication and; d) a relative lack of insight are associated.[11,12] We do not know whether the results of the studies that were conducted on factors influencing medication adherence in the execution phase are also applicable to the starting part.

We aim to study factors that are possibly associated to the initiation of medication therapy, with the final goal to develop a prediction instrument for the early recognition of patients at risk for non-adherence In this article we describe the study protocol as a stepwise procedure with background information to examine possible determinants of medication initiation. We use the population of newly diagnosed inflammatory arthritis patients starting on DMARD therapy as an example. The aim of this paper is to describe how to study possible determinants of adherence by using a stepwise procedure.

Methods/Design

We describe which steps are needed to develop a preliminary set of determinants. Thereafter, we describe the study setup and how to develop the prediction instrument. The process contains the following steps: systematic literature search, patient perspective, expert panel, application of a theoretical framework, selection of questions, and selection of adherence measurement instrument.

Systematic literature search

The first step to gain insight in relevant and modifiable determinants of adherence is systematically reviewing the literature. A large amount of research tried to assess determinants of adherence. Reviewing all the literature on this topic is therefore not advisable. Instead, it is useful to review the literature on the topic that is of interest; concerning a particular disease or medication, or a particular adherence phase, f.i. the initiation or discontinuation of medication. It is important to remember that determinants may differ for various diseases. Patients with arthritis might be driven by feelings of pain to take their medication, whereas for hypertension, patients may have no symptoms, and their adherence behavior might be driven by adverse cardiovascular outcome.

In this example, we wanted to gain insight in factors affecting adherence in recent onset (rheumatoid) arthritis patients. When searching the literature, we discovered that there was no information on recent onset arthritis, so we broadened our search terms into established disease, because then we at least got insight in factors influencing adherence. The literature was systematically searched from inception to February 2012 to identify studies on factors affecting medication adherence in patients with (rheumatoid) arthritis. Studies were eligible if they addressed medication adherence in adult (rheumatoid) arthritis patients, evaluated factors related to adherence, used a reproducible definition or validated instrument to measure adherence and provided a statistical measure to reflect the strength of the association between the determinant and adherence. 18 observational studies remained and were assessed on their methodological quality. All studies were on established RA patients and focused on the execution phase

of adherence. Adherence rates ranged from 49.5% to 98.5%.[3] A level of evidence synthesis was conducted to find the strength of the evidence for every factor. The factor that was associated with adherence to biologicals was having had a prescription for DMARDs 6 months prior to biological treatment. The factor that was associated with adherence to DMARDs is the belief that the medication for RA is necessary to treat the illness. There is also some limited evidence that the communication between the healthcare provider and the patient is influencing medication adherence.

Patient perspective

When searching for relevant determinants of health behavior, it is important to have an overview of possible determinants from all relevant viewpoints. The patient perspective is a very relevant viewpoint. To get to know this viewpoint, individual or group interviews with patients need to be conducted. When interviewing patients on possible determinants of adherence, it is of importance that the interviewees are representative for the group of patients the prediction instrument is targeted on. It is also advisable to keep on conducting interviews until saturation of the themes has been achieved. The main goal of the interviews has to be taken in mind when constructing an interview scheme. Furthermore it is advisable to use a theoretical framework when analyzing the interview data.[13,14]

In the literature we reviewed, the viewpoint of the patient was not present. We also wanted to gain insight into factors affecting the initiation of therapy, because we did not gather information about these factors from the literature review. Therefore we conducted a qualitative study to learn more about the initiation of medication from the patient perspective. This study was a combination of 6 focus groups and 10 individual interviews, with a total of 33 patients. All patients gave informed consent for their participation and were aware that their data would be used for research purposes. The interviews were transcribed verbatim and imported into ATLAS.ti software. To ensure anonymity, all identifying information was removed from the transcripts. Responses that included reasons for adherence or non-adherence in the initiation part were extracted and coded by two coders separately. The same was done for the execution phase. Codes were classified into overarching themes. 7 factors that influenced medication intake behavior emerged: 1) severity of complaints, 2) experiences with medication, 3) perceptions about medication, 4) information about medication, 5) ability to adjust to the medication schedule, 6) need to make autonomous or shared decisions, and 7) communication with and trust in the rheumatologist.

Expert panel

The factors that were extracted from the literature review and the interviews were presented to an expert panel that consisted of 1 rheumatologist, 1 pharmacists, 1 psychologist, 2 specialized rheumatology nurses and 4 researchers in the field of rheumatology. The expert panel ordered the factors according to theme and according to perceived importance. They also proposed other potentially relevant determinants of adherence behavior, which were intended with the other factors in table 1.

All potentially relevant determinants identified in the literature, during patient interviews and expert panel, were gathered, and ordered and clustered according to a theoretical framework in table 1.

Table 1. Possible determinants of adherence

Distal	Demographic	Psychosocial		Perceived benefits versus perceived barriers		Cues to action
	Race other than white	Recent life events		Severity of complaints		Social support
	Costs for TNF-I	General cognition		Experiences with medication		Social norm
	Health system factors	Rigidity	NPV-2			Info about disease and medication
		Need for information				
		Patient delay				
		Anxiety/depression	HADS			
		Coping	Ways of coping questionnaire/ PCCL/ CORS			
		Locus of control	MHLC			
		Acceptance disease / chronic pain	CPAQ			
		Arthritis learned helplessness	AHI			
		Illness-specific anxiety	PASS-20			
		Self-efficacy	MUSE			
		Ability to fit medication schedule in daily life				
		Busy lifestyle				
		Expectations about medication/disease				Need to make shared decisions
		Beliefs about disease	IPQ-R			
Proximal		Belief medication is necessary / beliefs about medication	BMQ	Perceptions about medication	BMQ	Contact with healthcare provider

Underlined text: these factors are taken into account by our study.
Abbreviations: AHI, Arthritis helplessness Index; BMQ, Beliefs about Medicines Questionnaire; CoRS, Coping with Rheumatic Stressors questionnaire; CPAQ, Chronic Pain Acceptance Questionnaire; hAdS, hospital Anxiety and Depression Scale; IPQ-R, Revised Illness Perception Questionnaire; MHLC, Multidimensional Health Locus of Control Scale; MUSE, Medication Understanding and Use Self-efficacy; NPV-2, Nederlandse persoonlijkheidsvragenlijst; PASS-20, short version Pain Anxiety Symptoms Scale; PCCl, Pijn Coping Cognitie lijst; TNF-I, tumor necrosis factor inhibitor.

Theoretical framework

Adherence to medication requires behavior change of the patient and could therefore benefit from the use of a theoretical framework to understand what facilitates and what inhibits medication intake.[15]

Numerous theoretical frameworks have been developed and tested, but how do we know which framework to use? Each model has its own advantages and disadvantages. A brief description of the social cognition models which are commonly used to predict health behavior can be found below.

The Health Belief Model (HBM)[16] has the central assumption that behavior is determined by the perceived threat of the health problem and the evaluation of the health behavior. The benefits of the behavior have to be larger than the possible disadvantages. The Protection motivation theory (PMT)[17] holds that behavior aimed at protecting one's own health is called an 'adaptive response', where behavior that is regarded to be bad for one's health is termed a 'maladaptive response'. Two processes are distinguished: estimating the threat, and estimating the opportunities to cope with the threat. The person estimates the threats and based on these estimations the patient makes an adaptive or maladaptive response. The theory of reasoned action/theory of planned behavior (TRA/TPB)[18] depicts that the intention to follow a certain behavior is the best predictor of behavior. The intention is influenced by 3 determinants: attitude, subjective norms and perceived behavioral control. The social cognitive theory (SCT)[19] describes how human behavior is directed through the expectations that one holds of a certain behavior. Behavior is seen as dynamic and the product of interactions and influences of environmental aspects, the person and this person's behavior.

There are also theories that focus on stepwise behavioral change, these are called 'stage models'. The transtheoretical model of change[20] describes 5 stages of behavioral change; precontemplation, contemplation, preparation, action, and maintenance. The precaution-adoption process[21] is on some aspects comparable to the stages-of-change concept. In this process, the first step in the process from precontemplation to contemplation, is to be aware of the risk behavior. The model distinguishes 3 stages of awareness.

What these models have in common, is that they emphasize the rationality of human behavior. They assume that the health behaviors to be predicted, in our case adherence, are considered to be the end-product of a rationale decision-making process based upon deliberate, systematic processing of the available information.

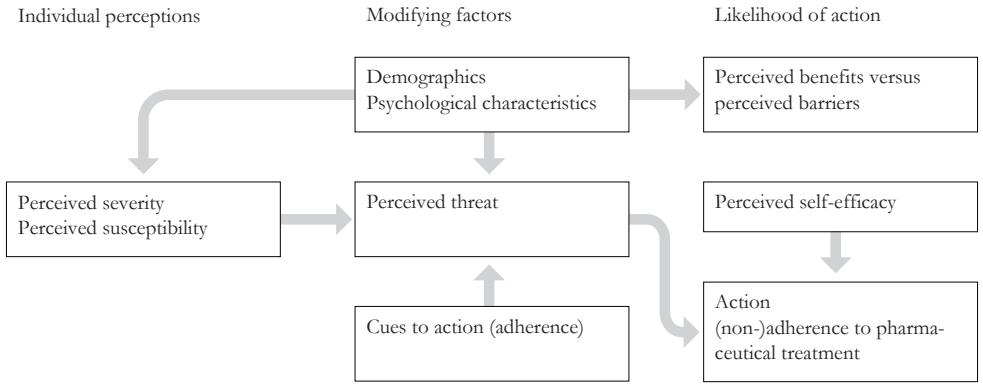
Which theoretical framework to apply should be based on the research question, the target health behavior, and the specific target group. The prerequisites for choosing a model are therefore to have adequate knowledge on the different theoretical frameworks and adequate knowledge on the specific empirical literature. The researcher can also decide to integrate several theoretical frameworks, because the goal is to get optimal insight into the determinants of behavior. One can add some concepts to an existing model or assemble two frameworks together. The drawback of this method is that connections or processes from specific theories can become disconnected or misinterpreted.

We choose to use the extended HBM as a guide to explore and explain the numerous possible determinants of adherence, because it fits the possible determinants of adherence that we found the best (see figure 1, which is explained below). The HBM asserts that the decision to engage in preventive health behaviors, such as adherence, is influenced by four perceptions: perceived severity of an illness, the perceived susceptibility of the individual to that illness, the perceived benefits associated with a health behavior to address the illness and the perceived

barriers to engage in the health behavior. The weighing of pros and cons of performing the health behavior was mentioned repeatedly in the focus group interviews as an important step towards taking the medication. This is also one of the key features of the HBM. The model focuses on severity, susceptibility and perceived utility of the regimen (efficacy and the abundance of benefits over costs). These belief components have been found to affect intentions to adhere to various health-related behaviors.[16] The model is thus in line with our findings from the literature review and the patient interviews.

Another reason for choosing the HBM is that it has been used widely in the prediction of adherence behavior[15] and has a larger level of evidence for the prediction of adherence than other theoretical frameworks.

Figure 1. Extended Health Belief Model.



Selection of questions

In deterministic research, one can distinguish between proximal, distal and ultimate determinants. Proximal determinants are closely related to adherence and usually modifiable, distal determinants influence adherence behavior indirectly and ultimate determinants are even further away from the actual behavior but have an indirect influence on behavior through intermediate processes.[22] Distal and ultimate determinants are mostly unmodifiable. In table 1 factors that are thought to influence adherence behavior are clustered according to the Health Belief Model and ordered hierarchically from distal to proximal determinants. For example, the factor 'race other than white', which was found in the systematic literature review, is a demographic factor and distal. It is also unmodifiable.

It seems logical that only proximal factors will be included in our sample. However, we also choose to include some distal factors in our questionnaire, because we also want to gain insight into the intermediate pathways in which distal determinants can influence adherence. Once we gain insight into all distal and proximal determinants, we can create tailored interventions for special target groups.

The underlined factors shown in table 1. were the base of the constructs we used to develop our questionnaire. We searched in the scientific literature for validated questionnaires that measure the constructs from table 1. The questionnaires that we extracted questions from, were the short version Pain Anxiety Symptoms Scale (PASS-20)[23], Arthritis Helplessness Index (AHI)[24], the Revised Illness Perception Questionnaire (IPQ-R)[25], the Coping with Rheumatic Stressors questionnaire (CORS)[26], Pijn Coping Cognitie Lijst (PCCL)[27], the Ways of Coping Questionnaire[28], the Multidimensional Health Locus of Control Scale (MHLC)[29], the Chronic Pain Acceptance Questionnaire (CPAQ)[30] and a Dutch personality questionnaire: the 'Nederlandse persoonlijkheidsvragenlijst' (NPV-2).[31] We studied the main articles on these questionnaires for the factor structure of the questionnaires and choose per factor the questions with the highest factor loading. We assumed that anxiety, depression, self-efficacy and beliefs about medication might have a high impact on adherence behavior. Therefore we used the complete scales to measure this construct. These scales are described in detail below.

Beliefs about medicines questionnaire (BMQ)

Patient beliefs about medicines were assessed using the BMQ, which has been validated for use in patients with somatic chronic illnesses.[32] 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.

Hospital Anxiety and Depression Scale (HADS)

Anxiety and depression were measured with the Dutch version of the Hospital Anxiety and Depression Scale (HADS)[33], screening anxiety and depression symptoms in a hospital setting on two subscales. The HADS consists of 14 items; 7 items measuring anxiety and 7 items measuring depression. Each item presents a statement, and 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).

Medication Understanding and Use Self-Efficacy Scale (MUSE)

The Medication Understanding and Use Self-Efficacy (MUSE) questionnaire is a research tool that can be used in clinical and research settings to assess patients' understanding and use of prescription medication. The Medication Understanding and Use Self-Efficacy (MUSE) questionnaire consists of two scales: 'learning about medication', with Cronbach's alpha of 0.68, and 'taking medication' with Cronbach's alpha of 0.77.[34] Taken together, the two factors account for 55% of the total variance of understanding medication instructions. MUSE scores are continuous and can range from 0 to 10, with low scores indicating patients' low understanding of prescription medication use.

The final item pool consists of 216 items. Besides the constructs described before, the questionnaire also covers demographic questions such as gender, age, education, work and social situation. The final item pool was tested by 10 individual established rheumatoid arthritis patients. These patients were asked if they found some questions difficult to understand or difficult to answer. They were also asked what they thought of the length of the questionnaire. Following their responses, some questions were adapted.

Methods to measure adherence

Methods to measure adherence are described by de Klerk (2001).[35] They are summarized in table 2. As shown in the table, there are many methods with their own advantages and disadvantages. Measurement instruments can be distinguished in direct measurement methods, which prove that the drug reached the site of action, and indirect measurement methods, where there is no proof of ingestion. An ideal measurement instrument should be: 1) valid, 2) reliable and sensitive to change, and 3) feasible: the patient should not be aware of adherence measurement, the method should not be invasive and the researcher/physician should always have access to the data. However, an adherence measurement instrument that possesses all these features, does not exist. Therefore, when choosing a measurement method from the table below, de Klerk suggests to pay attention to: 1) the objective of measuring adherence, 2) the desired level of precision of the instrument, 3) the need to proof ingestion of the medication, and 4) does the patient have to be unaware of the adherence measurement?

The objective of measuring adherence in our study is to assure that the drug is approximately ingested as prescribed. The desired level of precision of the instrument needs to be high. Although timing adherence is not relevant when using DMARDs, patients in this study will use different DMARDs with different regimens. Since we also need to look for variations in adherence between different DMARDs, we need a precise measurement instrument. Ideally, we want the patients to be unaware of the adherence measurement, but since we are ethically obliged to inform patients about the scope of the study, this is not entirely possible. From daily practice, it is however known that patients easily forget that they are being monitored and that electronic monitoring does not interfere with adherence behavior.[36]

We therefore choose as a primary measurement instrument the electronic monitoring with medication event monitoring systems (MEMS). It is non-invasive and gives stable results. It is also one of the best indirect methods.[3] The MEMS uses a microprocessor in the medication container cap to record the day and time of each vial opening. Electronic monitoring offers the advantage of assessing adherence over a continuum. This method has proven to be superior to patient self-reports and pill counts in the measurement of adherence (in studies of adults requiring chronic medication).[37,38] The only drawback of using MEMS is that it is a method that is relatively high in costs and that it does not prove ingestion of the medication. The primary outcome measure of our study is the adherence rate to oral DMARDs in the first three months of disease measured with MEMS. The MEMS adherence rate will be calculated by dividing medication events or bottle openings by doses prescribed for the interval. The adherence rate varies between 0 (complete non-adherence) and 100 (complete adherence).

Because it is recommended to use multiple measurement methods of adherence to increase reliability[3], we also choose to use questionnaires for the measurement of adherence. Patient questionnaires do not give detailed overviews on the time of ingestion, but they are a cheap way to measure adherence. When a patient needs to start using DMARDs subcutaneously, we cannot use MEMS anymore, but then we still can still use the questionnaires for adherence measurement.

The Compliance Questionnaire Rheumatology (CQR) is a self-report measure consisting of 19 statements, which is related to compliance. 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 noncompliance) to 100 (perfect compliance). The CQR has been validated in patients with inflammatory rheumatic diseases against a MEMS. The 19 item CQR compared well with electronic monitoring over 6 months with a

Table 2. Measurement methods of adherence

Method	Proves ingestion of medication	Gives detailed overview on timing of ingestion	Stable result under stable compliance	Differential result under variable compliance	Patient is aware of compliance measurement	Invasive method	Measurement method requires:
Interviews	No	No	Yes	Possible	Yes	No	Staff
Questionnaires	No	No	Yes	Possible	Possible	No	Questionnaire
Diary method	No	Possible	Yes	Possible	Yes	No	Diary
Physician estimate	No	No	Possible	Possible	No	No	Consultation
Counting returned medication	No	No	Yes	Possible	Possible	No	Consultation
Electronic monitoring	No	Yes	Yes	Yes	Usually	No	Electronic monitors
Concentration measurement	Yes	No	Possible	Possible	Possible	Yes	Drawing blood/urine sample and laboratory analyses
Clinical outcome	No	No	Possible	Possible	No	No	Measurement of clinical outcome
Direct observation	Yes	Yes	Yes	Yes	Yes	No	Staff, consultation
Duration of treatment	No	No	Yes	Possible	No	No	Data collection of prescriptions

Table taken from de Klerk [35]

sensitivity of 98%, specificity of 67% and an estimated kappa of 0.78 to detect non-adherence.[39] As the CQR does not measure adherence directly, but relies partly on behavioral items, the use of the CQR could learn us more about the correlation between specific cognitions and adherence behavior.

We also choose a direct physical method to measure adherence: concentration measurement. The advantage of this method is that it proves ingestion of the medication. The drawback of concentration measurements, is that at the time of measurement, you only measure if the drug concentration is in the body at that moment. So if a patient has taken their medicine the day before, the method will report a perfectly adherent patient. This method is mostly used intermittently, but if you want to retrieve full adherence data, ideally you will have to do concentration measurements every day, which is, of course, invasive and therefore difficult to employ.
For RA patients, it would be interesting to measure levels of DMARDs. RA is commonly treated with one or more DMARDs, of which methotrexate is the first drug of choice. Methotrexate needs to be ingested weekly and it takes 6 to 8 weeks to have an effect on the arthritis symptoms.[40] We expect that this drug will be prescribed to approximately 95% of our study sample. Measurement of methotrexate serum concentration is not possible, since these are cleared rapidly.[41] However, the methotrexate accumulates intracellular into polyglutamates (PG's) when ingested. This process takes approximately 6 months. The longer maintained intracellular red blood cell methotrexate concentrations might be a good indicator for adherence. Incorporating these PG measurement in normal clinical practice is relatively easy, as it is normal practice to draw blood in the rheumatology practice at a regular basis, and that blood can also be used for the methotrexate PG measurement.

Blood samples will be drawn and in these samples intracellular methotrexate will be measured and compared to MEMS adherence data. Patients will be classified as non-adherent, partial adherent and adherent. Non-adherence will be defined as MTX-PG levels below the analytical detection limit.

Clinical outcome

In adherence studies, it is recommended to take clinical outcomes into account. While clinical outcomes cannot stand alone as an adherence measure, they can tell us something about the relationship between the adherence percentage and clinical outcome. Especially when you want to dichotomize an adherence percentage into 'adherent' and 'non-adherent', measures of clinical outcome can be helpful to find a clinically relevant cut-off point. We use the Disease Activity Score 28 (DAS28)[42] and the Health Assessment Questionnaire (HAQ)[43] to measure clinical outcome of disease. These measures are described below.

DAS28

To evaluate disease activity, the DAS28 will be calculated every 3 months. The DAS28 is a composite score of erythrocyte sedimentation rate (ESR) and the number of tender and swollen joints as per the 28 joint count as well as a patient global assessment.

Health Assessment Questionnaire (HAQ)

Physical functioning was measured using the validated Dutch version of the consensus HAQ.[43] This self-administered questionnaire is a validated measure of disability which includes 20 specific functions that are grouped into categories: dressing and grooming, arising, eating, walking, personal hygiene, reaching, gripping and other activities. The average of these scores

represents a physical functioning score. HAQ scores range from 0 (no difficulty) to 3 (unable to do). 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).

Study design

Determinants of adherence in the first 3 months of DMARD use are studied in a cohort study with one year follow-up, which will take place in the rheumatology outpatient clinic of the hospital where the patient is treated. The study will be performed in 11 different rheumatology outpatient clinics of 11 participating hospitals. Adult patients who are diagnosed with rheumatoid arthritis (RA) (according to the new or old ACR criteria for RA), psoriatic arthritis (PsA) or undifferentiated arthritis and are prescribed oral DMARDs will be invited by their rheumatologist to participate in the study. Data will be collected at 5 time points by one of the research nurses or specialized rheumatology nurses in the outpatient clinic where the patient is treated. T0 is the baseline measurement, performed within 2 weeks after the prescription for DMARDs. T1 will be performed 3 months after T0, T2 at 6 months, T3 at 9 months, and T4 at 12 months after start with medication. This study has been approved by the Medical Ethics Committee and all medical boards of the participating hospitals gave their consent for participation in the study. Written informed consent will be obtained before start of the study. When giving informed consent, patients state that they are aware that their data will be used for research purposes and that the data will be anonymized.

Participants are asked to fill in the item pool at baseline (T0) and at 6 month follow up (T2). Every 3 months physical functioning is measured and patients are asked to fill in an adherence self-report measure. In table 3., a schematic overview of measures is presented.

Table 3. Flowchart of measures during follow up

Measure	T0	T1	T2	T3	T4
Adherence					
MEMS	Continuous				
CQR					
MTX polyglutamates					
Clinical outcome					
DAS28					
HAQ					
Factors associated with adherence					
BMQ					
MUSE					
HADS					
Item pool					

Columns in grey: measured at the time point indicated in the column heading. Abbreviations: BMQ, Beliefs about Medicines Questionnaire; CQR, Compliance Questionnaire Rheumatology; dAS28, disease Activity Score 28; hAdS, hospital Anxiety and depression Scale; hAQ, health Assessment Questionnaire; MeMS, medication event monitoring systems; MtX, methotrexate; MUSe, Medication Understanding and Use Self-efficacy scale; T0, baseline; T1, 3 months after T0; T2, 6 months after T0; T3, 9 months after T0; T4, 12 months after T0.

Study population

Inclusion criteria for participation in the study are: being newly diagnosed with RA, PsA or undifferentiated arthritis, being prescribed a DMARD or Prednisone for the first time, aged above 18 years and being able to take their medication without the assistance of others. Reasons for exclusion are illiteracy and the inability to use the MEMS. Patients with cognitive impairments, visual impairments and serious addictions were excluded from participation in the study, because they are mostly not able to take their medication without the assistance of others. We strive to include 300 early IA patients, so that we have enough cases to include approximately 9 predictive factors for adherence in the prediction rule.

Construction of prediction rule

The amount of items will be reduced stepwise: first, items are reduced based on the frequency distribution of answer categories. Second, an exploratory factor analysis will be performed. The minimum amount of questions allowed per factor is 5. Third, per factor, items will be reduced with item response theory. Only those questions will be included that distinguish the most within the latent factor.

Having reduced the items, a multivariate logistic regression with backward selection will be performed. After having fitted the significant factors in the model, we prevent the model from overfitting using a shrinkage method.[45, 46]

Discussion

This article describes how to develop a tool for the prediction of adherence for patients with a chronic disease. It describes the various steps to be taken for the development of our tool for the prediction of adherence to DMARDs for early arthritis patients.

The stepwise procedure that we describe is thorough, but there are some pitfalls to take into account. First, the choice for a theoretical framework can be arbitrary. Although we do feel that the HBM fits our determinants the best, a different framework could have been applied as well. We focused on factors such as social norm and communication with the health care provider, and thus choose the HBM. If we had chosen a different framework, for example the Transtheoretical Stages of Change model, the focus of our study would have been more on intrinsic factors. Using a theoretical framework for the prediction of adherence has many advantages, but it has one major drawback. A social cognition model can only be used to predict conscious and motivated behavior. Unconscious nonadherence, for example through simply forgetting to take the medication, cannot be predicted with a social cognition model.

Second, the selection of questions from validated questionnaires depended on what was available in the literature. This set of questions might therefore not be complete. We also had to make some choices concerning the questionnaires. There are for example many questionnaires available on coping, all based on slightly different theories. We choose to use questions from a general coping questionnaire as well as items from specific coping with chronic pain, and coping with arthritis questionnaires. We choose these questionnaires because these were most often used in research.

The outcome measure of our study is adherence. Previous literature has shown that adherence outcomes strongly depend on the measurement instrument chosen. We gave an overview of the different methods to measure adherence and pointed out the issues around choosing the right method. Because there is no 'gold standard' to measure adherence, we will use in our example three different methods, both direct and indirect, to assess adherence behavior. Within the measurement of methotrexate polyglutamates we can differentiate between nonresponse to MTX treatment and non- or partial adherence to MTX treatment. We can correlate these measurements with the indirect adherence measurements with the MEMS and by that means validate the MTX polyglutamate measure. When validated, this is the first direct measure for adherence to MTX treatment. It is also a relatively cheap method which is easy to implement in daily practice.

The item pool that we constructed is ready to be used in the study. In this phase, we can encounter some pitfalls. First, the patient may find the item pool too long and may find that items are similar. This may cause that patients are not motivated to be followed up in the study. It is therefore important to first try to eliminate the amount of questions in the item pool and secondly to explain to patients that they are not filling out an end-stage questionnaire, but an item pool that has to become a questionnaire. We also expect that our cohort is vulnerable to selection bias. Those patients who do not adhere to their therapy are less likely to participate in the study or are likelier to become lost to follow up. When setting up a cohort study for the measurement of medication adherence, researchers should be aware of this pitfalls and also try to gather information about patients that are not willing to participate or that are lost to follow up.

In this article we described the steps to be taken for the development of a questionnaire for the prediction of adherence in patients with a chronic disease. We discussed for every step the different options and pitfalls. We concluded each section with the choices that we made regarding these steps.

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Chapter 8

Psychosocial predictors of DMARD adherence in the first three months of treatment for early arthritis

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Submitted

Abstract

Objective For early arthritis patients it is important to strictly adhere to their disease-modifying antirheumatic drugs (DMARD) in the first months of disease to induce remission. It remains unknown why some patients do not adhere to therapy. In this study we aimed to identify patients at risk for non-adherence in the first 3 months of treatment.

Methods Adult DMARD-naïve early arthritis patients who started synthetic DMARDs were recruited for a cohort study. At baseline, patients filled out items on potential adherence predictors. Adherence was continuously measured with electronically monitored pill bottles. Items were reduced and clustered using principal component analysis. Latent trait models were constructed to extract the most discriminating items. Per DMARD and per day non-adherence was defined as not opening the pill bottle when it should have been. We used a multivariable logistic regression model to find predictors for non- adherence.

Results 301 patients agreed to participate of which 259 completed follow-up. Adherence was high and declined over time. Principal component analysis led to 7 dimensions, while the subsequent latent trait models analyses led to 15 dimensions. Of these dimensions, 'information seeking' and 'having positive expectations about the disease' were associated with adherence and the dimension 'adjusting to the pain' was associated with non-adherence.

Discussion Rheumatologists may be assured that information seeking behavior and positive expectations about the course of the disease are associated with adherence. They should be alert when patients become passive because of pain: these patients are at risk for non-adherence.

Introduction

Rheumatoid arthritis (RA) and Psoriatic Arthritis (PsA) have in common that they are chronic auto-immune diseases characterized by joint inflammation with pain, swelling, damage and disability.[1] RA or PsA patients both respond well to treatment with disease-modifying antirheumatic drugs (DMARDs).[1-4] For early arthritis patients, it is important to strictly adhere to their DMARDs in the first months of disease to induce remission and prevent disability.[1, 2, 4] Rheumatologists should aim at remission or at least low disease activity within 3 months, in order to obtain better functional and radiological outcomes.[2, 5, 6] It is unknown why some patients do not adhere to DMARDs. In this study we aimed to develop a prediction model to identify patients at risk for non-adherence in the first 3 months of treatment.

Adherence to the prescribed drugs is, especially in the early phase of disease, important to reach the desired outcome.[7] When not sufficiently adhering to treatment, patients may present themselves as non-responders, resulting in a step-up in therapy to more expensive treatment with biologicals.[2] Non-adherence does not only interfere with reaching remission, but may also lead to higher healthcare costs and more side-effects.[8-11] When rheumatologists get better insight in potentially non-adherent patients, unnecessary switches to other therapies might be prevented.

Although patients are advised to take their medication as prescribed, a proportion of RA patients does not adhere to their medication. Adherence rates in established patients range from 49.5%-98.5%, depending on which adherence definition and measurement methodology is used.[12] Adherence in the early phase (first 3 months) of treatment is unknown, but suspected to be as low as in established patients, whereas it is in these first months a necessary condition for effective treatment. It would therefore be helpful to determine which patients are at risk for non-adherence, so that clinicians can direct their attention to these patients when discussing non-adherence.

Why some patients are non-adherent has been studied for decades, but meta-analyses show that many questions about adherence remain unanswered.[13, 14] Intuitively, adherence to drugs that reduce symptoms should be good, and when non-adherence occurs, symptoms might not be that severe. However, it takes a while until the effects of the DMARDs on the symptoms can be felt. In addition, many studies have shown that many more factors besides symptom severity can contribute to non-adherence, such as beliefs about medication.[15] Most studies investigating factors associated to adherence were done in patients with established disease. Frequently studied factors are medication characteristics, perceptions and cognitions about illness and medication, socio-economic and demographic factors, disease features and doctor-patient relationship.[12, 13] Commutable factors that lie within the patient and that can influence adherence, such as psychosocial factors, are regarded as important, but less frequently studied. Psychosocial factors related to non-adherence are for example perceptions about medication and the illness, trust in the rheumatologist,[16] the patient-provider communication,[17] depression[14] and social support.[18] In contrast, other studies found no evidence for the role of psychosocial factors in adherence.[19]

Although several studies described clinical and psychosocial predictors of non-adherence in established patients, it is unknown whether these predictors have a similar impact in early arthritis patients, where adherence is a necessary condition for effective treatment prescription. Different factors may play a role in adherence behavior in the initiation phase than in patients with established disease. For example, a newly diagnosed patient has to learn to cope with the

disease and medication regimen, which can influence adherence.

The objective of this study is to search for psychosocial predictors that would help rheumatologists to identify patients who are likely to become non-adherent in the initiation phase of DMARD therapy.

Materials and methods

Participants

Adult and DMARD-naïve RA, psoriatic arthritis and undifferentiated arthritis (polyarthritis and oligo arthritis) patients were consecutively recruited between January 2012 and June 2014 in 11 regional hospitals from an ongoing cohort.[20] The cohort study involved a 1-year observation period and 3-monthly nurse visits. Reasons for exclusion from the study were illiteracy and the use of a pill organizer. For this study we use the initiation phase (first 3 months) of follow-up.

The study protocol was approved by the Erasmus University Medical Center ethics committee. The board of directors of the participating hospitals gave their approval for performance of the study. Participating patients gave informed written consent for participation in the study.

Participants filled out a pool of 216 items before or at least within 2 weeks of treatment start. Non-adherence was continuously measured using electronic monitored pill bottles (Medication Event Monitoring Systems (MEMS)).

Measures

Item pool

The item pool consists of questions regarding coping, perceptions about medication, the disease and pain, social support, need for information, self-efficacy, acceptance and demographics. The items are phrased as statements and patients are asked to respond to these items on a 5-point Likert scale ranging from 1 (do not agree at all) to 5 (agree very much).

The item pool was constructed using information about factors associated to adherence from a literature review,[12] from patient interviews,[16] and an expert panel of rheumatologists and adherence researchers. Inclusion of items was broad and nonrestrictive, which resulted in a large item pool. Details about the construction of the item pool are described elsewhere.[20]

Disease activity

To evaluate disease activity, the 28-joint Disease Activity Score (DAS28) was calculated at baseline and at 3 months.[21]

Health Assessment Questionnaire (HAQ)

Physical functioning was measured using the validated Dutch version of the consensus HAQ.[22] HAQ scores range from 0 (no difficulty) to 3 (unable to do).

Adherence measurement

Non-adherence was electronically measured per DMARD using MEMS, which consists of a medication container (a small plastic bottle) and an electronic MEMS cap. The MEMS

uses a microprocessor in the medication container cap to record the day and time of each vial opening. MEMS are regarded as the 'gold standard' for adherence measurement and has been proven to be superior to self-report and pill count, because they measure a necessary behavioral step of adherence 'real time'.[23] Monitoring with MEMS might be seen as an intervention, but this effect is regarded as negligible.[24]

Data stored in the MEMS cap were every three months transferred by the nurse into a data platform, which compiles drug dosing histories over extended periods, and in which medication regimen changes are noted. Medical staff was blind to the adherence data.

Extra openings of MEMS were ignored, because these mostly represent openings by pharmacists. When patients stopped using one or more DMARD on rheumatologist's advice, for example in case of lab abnormalities, this was not assigned as non- adherence.

In case a patient used subcutaneous methotrexate, the patient was asked to put folic acid in the MEMS container. We assumed that the openings of the MEMS to take folic acid would represent the use of subcutaneous MTX.

Definition of non-adherence

In most adherence studies an 80% cut-off is used for the definition of non-adherence. Because the clinical significance of using an 80% cut-off is unknown, and because non-adherence might differ per DMARD and over time, we used non-adherence over time and per DMARD as outcome measure. For each patient and per DMARD, we defined non-adherence as a day in which the medication container was opened less than expected based on the prescribed medication intake regimen. For methotrexate, we calculated the underuse not per day, but per week, since this medicine is used once a week. Thus, for each patient, per day, and per DMARD non-adherence was dichotomized in yes(1) or no(0). Patients with complete follow-up had 91 days of observations and thus 91 repeated (non-)adherence outcomes.

Data analysis

Descriptive statistics were used to describe the demographics of the study population, baseline DAS28, HAQ, number of medicines per patient and average non-adherence proportion per DMARD. Differences between group means are tested with Student T- tests.

For the prediction of non-adherence in the first 3 months, a 6-stage procedure was used. 1) First, we selected items with good discriminative capacities, by selecting items with a flat or even hollow frequency distribution. A kurtosis-standard error ratio smaller than -1.96 was applied as criterion. We did not seclude items on basis of skewness, because a skewed distribution is an indication that an item is differentiating at one end of the characteristic which is of interest. 2) Second, using principal component analysis (PCA), the major components were selected using the procedure described by Horn [25] with the program Monte Carlo PCA for parallel analysis.[26] Items with component loadings ≥ 0.4 were selected from the item pool. 3) Third, for each major component we constructed a two-parameter logistic latent trait model (LTM), using the LTM package in R.[27] As LTM assumes a dichotomized score, we dichotomized the Likert scale answer categories on the median frequencies. 4) Fourth, the LTM models were tested for unidimensionality. Unidimensionality was anticipated not to be obvious, as the number of extractable components of the principal component analyses was limited due to high variables patient ratio. When the component did not meet the unidimensionality criterion, we performed

an additional PCA until the retrieved components were unidimensional. 5) Fifth, For each model, we divided the latent ability scale in equal sections and selected per section the item with the most discriminating ability. Per component, a sum score was calculated by computing the mean of the items. 6) Finally we fitted a multivariable logistic model including all candidate predictors on the repeated adherence data, with patients and DMARD type as random effects. Subsequently we used LASSO regression to select predictors of non-adherence. The optimal shrinkage parameter was determined using Akaike's Information Criterion. The regression coefficients of the predictors in the final model were multiplied with the shrinkage factor, to prevent too extreme predictors.

Missing data

When more than half of the factors scores was missing, data was not imputed. In other cases, the original missing items within the factors scores were imputed using the other items, proportion of missed doses, days of monitoring covered and type of DMARD. Missing adherence data was not imputed, the total amount of days covered was used in the analysis.
Statistical analyses were performed with SPSS (version 21.0) and R (version 3.00).

Results

Patients

Figure 1 depicts the flow of patients through the study. Of 385 patients who were invited to participate, 20 were excluded. Common reasons for exclusion were participation in a medication trial (n=6), because of previous DMARD use (n=3) or a different diagnosis (n=5). Sixty-four patients were unwilling to participate. Reasons were being overwhelmed by the diagnosis (n=13), being included too late (n=9) and logistic problems (n=11). Patients unwilling to participate were more female (Chi square p=0.052), but did not differ in age from those that were willing to participate. In total, 301 patients (78.2%) were willing to participate. Of these patients, 10 became lost to follow up, which left 291 patients at baseline. During the follow up, 32 patients were lost to follow up, which left 259 patients (89%). Reasons for lost to follow up were having second thoughts about study participation, not wanting to use MEMS because of the use of a week divider, or lost to follow up in the clinic.

The baseline table (table 1) depicts the demographic and disease features of patients with complete follow up and patients lost to follow up. Lost to follow up patients were significantly younger (p=0.012). Three quarters of the patients received the diagnosis RA, which was in 73.3% of the cases based on the ACR2010 criteria for RA.

Figure 1. Flowchart of patients

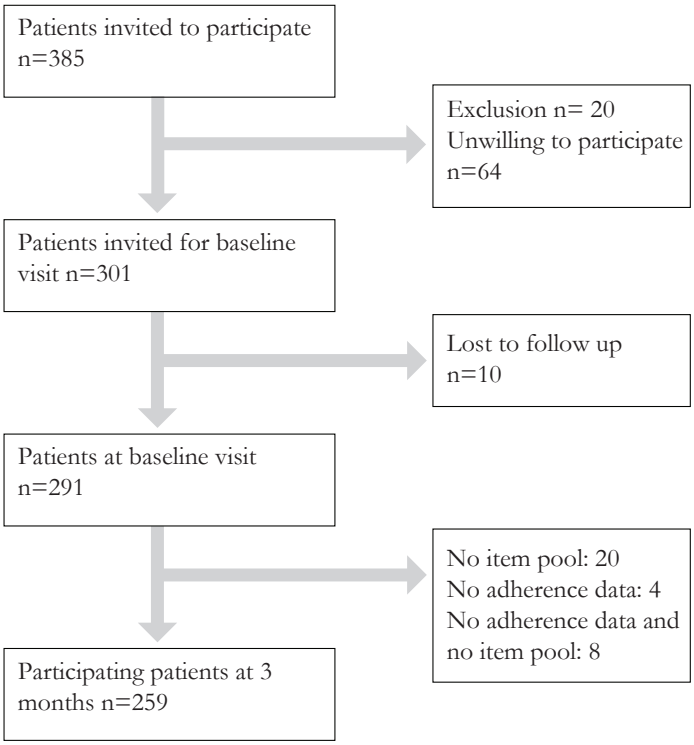


Table 1. Baseline Characteristics

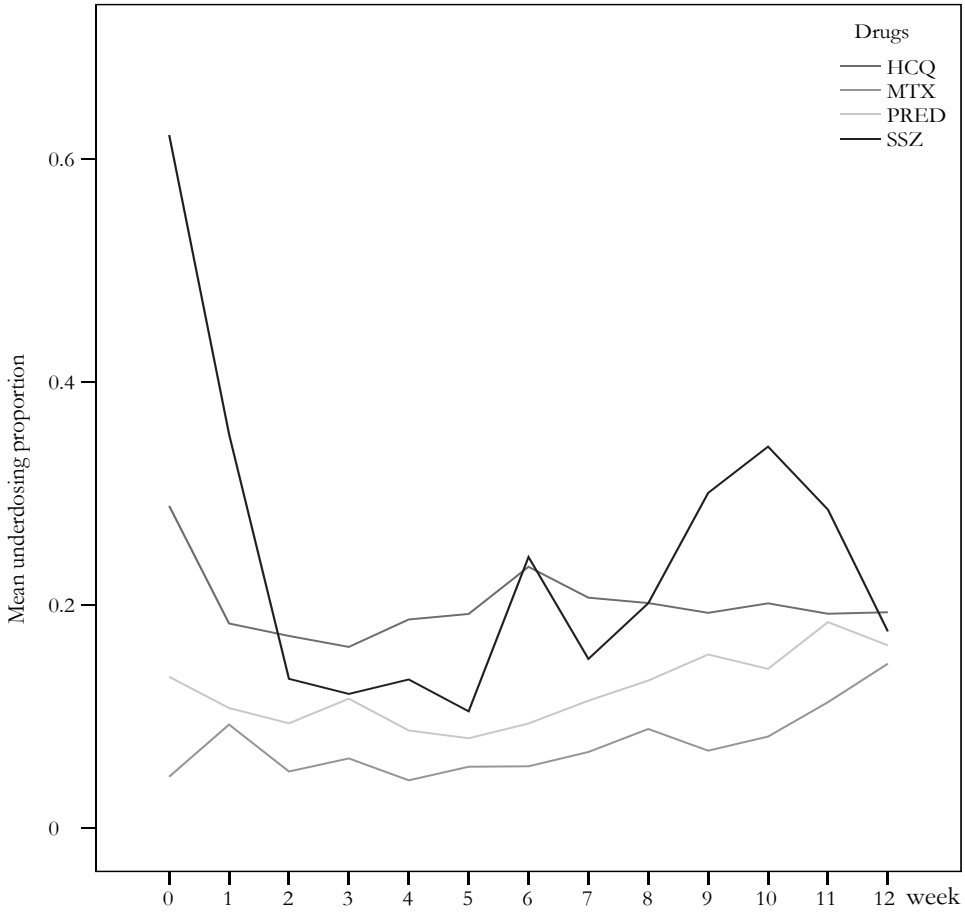
		Total (n=291)	Complete follow up (n=259)	Lost to follow up (n=32)
Gender (female), n (%)		174 (59.2)	154 (59.5)	19 (59.4)
Age, mean (SD)		53.8 (14.5)	54.5 (14.3)	46.9 (14.8)
Diagnosis, n (%)	RA	210 (73.2)	190 (74.8)	20 (62.5)
	PSA	65 (22.3)	56 (21.5)	8 (25)
	Undifferentiated	16 (5.6)	12 (4.6)	4 (12.5)
Disease duration >6 weeks, n (%)		236 (85.5) n=274	206 (84.8) n=244	29 (90.6)
ESR, mean (SD)		25.77 (22.42)	25.6 (22.2)	27.5 (24.4)
TJC, median (IQR)		3 (1-7)	3 (1-7)	0 (0-10)
SJC, median (IQR)		3 (1-5)	2 (1-5)	0 (0-5)
Positive serology (RF or ACPA), n (%)		158 (54.3)	141 (54.4)	17 (53.1)
ACR2010 score >5, n (%)		154 (52.9)	140 (54)	14 (43.8)
DAS28, mean (SD)		4.0 (1.4)	4.1 (1.38)	4.0 (1.59)
Nr of DMARDs at baseline (%)	1	187 (64)	170 (65.4)	18 (58.1)
	2	90 (30.8)	78 (30)	11 (35.5)
	3	14 (4.8)	11 (4.2)	2 (6.5)
	4	1 (0.03)	1 (0.04)	-
Dosing per DMARD in milligram at baseline, median (range)	MTX	15 (2.5- 37.5)	15 (2.5-37.5)	15 (10-37.5)
	PRED	10 (5-45)	10 (5-30)	10 (5-45)
	SSZ	2000 (1000- 2000)	2000 (1000- 2000)	2000 (2000- 2000)
	HCQ	400 (200- 800)	400 (200- 800)	400 (200- 400)
HAQ (n=255) median (ICQ)		0.75 (0.25-1.13)	0.75 (0.25-1.13)	0.5 (0.25-1.25) n=5
HADS-anxiety (n=260), mean (SD)		5.6 (4.45)	5.57 (4.38)	8.1 (7.3) n=5
HADS-depression (n=258), mean (SD)		4.65 (3.0)	4.69 (3.0)	3.8 (2.8) n=5
Education level, n (%)	Low	122 (45)	118 (46.3)	4 (26.7)
	Intermediate	84 (31)	78 (30.6)	6 (40)
	High	65 (24)	59 (23.1)	5 (33.3) n=15
Living situation, n (%). n=266	Married/living together	202 (75.9)	197 (76.1)	2 (40)
	Separated/widower/alone	64 (24.1)	62 (23.9)	3 (60) n=5
Work status n=267	Paid employment, n (%)	157 (58.8)	152 (58.5)	3 (60)
	Working ≥32 hours, %	56.7	56.6	40 n=5

Abbreviations: SD: standard deviation, IQR: interquartile range, RF: rheumatoid factor, ACPA: anti-cyclic citrunillated peptide antibodies, ACR2010: American College of Rheumatology 2010, DMARDs: disease-modifying antirheumatic drugs, RA: rheumatoid arthritis, PSA: Psoriatic Arthritis, DAS28: 28-joint count disease activity score, MTX: methotrexate, PRED: prednisone, SSZ: sulfasalazine, HCQ: hydroxychloroquine, HAQ: health assessment questionnaire, HADS: hospital anxiety depression scale

Non-adherence

Most patients initially received monotherapy: methotrexate. Ninety patients received two DMARDs, of which the combination methotrexate and prednisone was given the most. Adherence was mostly high, but slightly declined over time, except for hydroxychloroquine (see figure 2). Figure 2 shows per week the total proportion of non-adherence events per week. Adherence to sulfasalazine was lower than to other DMARDs in the first 2 weeks of treatment. It could be that patients took sulfasalazine only once a day against the rheumatologists prescription for twice a day.

Figure 2. Non-adherence proportions per week per DMARD as estimated with MEMS



Number of patients using this DMARD per week												
MTX	269 66.3%	259 67.1%	256 67.4%	256 67.2%	258 67.7%	255 67.6%	253 67.6%	249 67.5%	248 68.1%	245 68.6%	244 68.2%	239 67.1%
PRED	84 20.7%	80 20.7%	79 20.8%	80 21%	79 20.7%	78 20.7%	77 20.6%	74 20.1%	71 19.5%	64 17.9%	59 16.5%	58 16.3%
SSZ	19 4.7%	17 4.4%	16 4.2%	16 4.2%	15 3.9%	15 4%	15 4%	16 4.3%	16 4.4%	17 4.8%	21 5.9%	23 6.5%
HCQ	34 8.4%	30 7.8%	29 7.6%	29 7.6%	29 7.6%	29 7.7%	29 7.8%	30 8.1%	29 8%	31 8.7%	34 9.5%	36 10.1%

Abbreviations: DMARD: disease-modifying antirheumatic drugs, MEMS: medication event monitoring system, MTX: methotrexate, HCQ: hydroxychloroquine, PRED: prednisone, SSZ: sulfasalazine

Item reduction and factor construction

At baseline, 267 item pools were returned. Item reduction based on the kurtosis criterion reduced the amount of items to 143 items. The PCA conducted on the remaining 143 items distinguished 7 components, which explained 31% of the variance. Because of multidimensionality, 5 components had to be split up, which eventually led to 15 unidimensional components, with a total of 59 items. Components and accompanying items are presented in Appendix 1.

Prediction tool

Table 2 shows the multivariable repeated logistic regression analysis of the 15 candidate predictors. Both regression coefficients and odds ratios are reported. After backward selection, information seeking (1 item), and positive expectations (4 items) (appendix 1) remain significant predictors of adherence over time and adjusting/limiting activities (4 items) (appendix 1) remains a significant predictor of non-adherence. The shrinkage factor derived with bootstrapping was 226.4. Discriminative performance was moderate with an area under the curve of 0.62 (95%CI=0.60-0.63).

Table 2. Results of the initial multivariable generalized linear mixed model and the results of the multivariable final model after backward selection and correction for over-optimism.

	Multivariable				Multivariable model
Factor	**OR**	**95% CI**	**Regression coefficient**	**p-value**	**Regression coefficient**
1. Negative feelings	1.92	(0.66, 5.62)	0.65	0.24	
2. Disability	1.06	(0.41, 2.72)	0.05	0.91	
3. Depression	1.11	(0.40, 3.10)	0.11	0.84	
4. Anxiety	0.49	(0.18, 1.29)	-0.72	0.14	
5. BMQ specific- necessity	1.05	(0.46, 2.38)	0.05	0.91	
6. Modelling	0.92	(0.33, 2.57)	-0.09	0.87	
7. Adjusting / limiting activities	1.20	(0.43, 3.35)	0.19	0.72	0.11
8. Information seeking	0.70	(0.40, 1.23)	-0.36	0.22	-0.17
9. Not speaking about it	1.97	(0.91, 4.27)	0.68	0.09	
10. Distancing	0.90	(0.35, 2.32)	-0.10	0.83	
11. BMQ - general harm/general overuse	1.01	(0.40, 2.55)	0.01	0.98	
12. BMQ - specific concerns	1.44	(0.60, 3.46)	0.37	0.41	
13. Internal locus of control	1.36	(0.53, 3.54)	0.31	0.52	
14. Active coping	1.31	(0.57, 3.02)	0.27	0.53	
15. Positive expectations	0.35	(0.14, 0.84)	-1.06	0.02	-0.30

Abbreviations: OR: odds ratio, 95% CI: 95% confidence interval, BMQ: beliefs about medication questionnaire

Discussion

This study used a thorough method to relate psychological factors to adherence in the first months of treatment. Adherence was remarkably high but slightly declined over time. Fifteen candidate predictors of non-adherence were retrieved from the item pool: negative feelings, depression, adjusting/limiting activities, distancing, BMQ specific concerns, internal locus of control, anxiety, information seeking, BMQ general, active coping, positive expectations, not speaking about it, BMQ specific-necessity, modelling, and disability. The final model consists of 3 components: information seeking, adjusting/limiting activities and having positive expectations about the course of the disease. The results implicate that patients who adjust or limit activities because of their disease are more prone to be non-adherent. Seeking information on the internet, and having positive expectations about the course of the disease relate to adherence.

Our findings can be linked to the self-determination theory.[28] This theory holds that a patient needs autonomous motivation in order to be adherent. Patients who regulate their behavior autonomously choose to do so because they are convinced that their behavior is important for their health.[29] This means that if a patient experiences pressure, or feels that he or she needs to obey to medical authority contrary to their own conviction, he or she would feel less autonomous and adherence would therefore be threatened. According to the self-determination theory, autonomous motivation is predicted by autonomy support, or perceived support from others for making autonomous decisions with regard to adherence.[29] Self-determination theory also suggests that the relationship between autonomous motivation and adherence is mediated by the patients' confidence in his or her ability to be adherent (perceived competence).

Seeking information on the internet may reflect a search for autonomy support, which is a way in which patients want to regain their autonomy: they try to make the doctor's advice their own decision. Having positive expectations could reflect the outcome of this process: once patients have the idea that they have made an autonomous decision, they become optimistic about the outcome. In contrast, patients that adjust or limit activities might not feel autonomous, their behavior is motivated by feelings of disability and pain. They may feel that they have to 'surrender' to their disease. Furthermore, feeling too autonomous may also cause non-adherence, because the patient is then less likely to follow the clinician's advice.

It seems counterintuitive that patients who adjust to their pain by taking rest have more risk for non-adherence. Adjusting to pain is not necessarily a negative coping technique since it can have a positive effect to adjust activities when in pain. However, research suggests that adjusting to pain also has negative consequences; for instance patients who cope by stopping or altering activities have more risk for sick leave and work disability.[30] The difference may be that adjusting is positive, but surrendering to a disease is not (at least not when the disease is curable).

With an area under the curve of 0.62, our prediction model is insufficient in identifying patients at risk for non-adherence. However, it does give an idea about which factors play a role in adherence in the first months of treatment. In the first phase of treatment, adherence is relatively high compared to a later stage of disease.[31] We also know from interviews that patients in the first phase of disease do not act concordant with their feelings.[16] This means that although they might have negative feelings about medication or actually do not want to take the medication, they still adhere to the therapy. This may cause that the association between

candidate predictors and non-adherence is not as large as we hoped for. The outcomes of this study may help to diminish the decline in adherence, when doctors discuss more openly the patient's negative associations with medication use.

When studying psychosocial factors related to adherence, we may assume that non- adherence is intentional, but it could also be the case that non-adherence is coming from unintentional causes such as forgetfulness or not being used to taking medication.[32] However, from interview studies we know that factors such as forgetfulness start to play a role later on.[16] In the early stage of treatment, patients are often still very aware of their disease and of having to take medication, and reasons for non-adherence are mostly intentional.[33]

Our results are probably affected by selection bias. 78.2% of those patients asked to participate, was willing to participate. From those patients, 86% had completed the follow-up period. It might be that the nonresponse group was less adherent than those who responded. This has been reported under the name of the 'adherer effect': responders tend to be more 'well behaved', than nonresponders.[34-36] Thus selection bias might have caused that our cohort is more adherent than patients in daily practice.[37-39]

Although the results of this study are not powerful enough for external validation of the prediction model, our results give insight in determinants of adherence to intervene on. Numerous interventions have been developed and tested but few have shown to be effective. A recent meta-analysis concluded that there is no evidence that non-adherence can be 'cured'.[40] Perhaps methods to improve adherence had only a short- lasting effect, while in many cases adherence should be lifelong.[40] To ensure this lifelong effect, interventions should be integrated into the healthcare system. The rheumatologist is the one who intermittently keeps contact with patients, and logically this should be the one intervening on non-adherence. Of course time spent with the rheumatologist is expensive, and thus the rheumatologist needs effective and simple tools to target non-adherence.

Interventions might be targeted at fostering the patients' autonomy throughout the disease process. Autonomy is stimulated if the patient feels that he is freely choosing to participate in drug therapy at his own volition. Through patient involvement in the treatment plan, the rheumatologist can help the patient to modify faulty outcome expectations and use the working alliance to help the patient believe in the treatment's utility and value.[41] Research has already shown that patient participation and shared decision making have a positive outcome on adherence.[42-44] In the early stage of treatment, patients are often not ready for shared decision making, because they are not yet experienced with medication.[16] An adapted form of shared decision making is needed in this stage, such as patient adapted paternalism.[43] This holds that the professional decides in accordance with the individual situation of the patient. In this case the patient does not make the final treatment decision, but the patient has the ability to share information about the situation and preferences.

Conclusion

Communication about adherence should not stop after giving out the first DMARD prescription, but rheumatologists should continue to pay attention to adherence throughout the treatment. Rheumatologists should be alert when patients become passive because of pain and should open up a conversation about non-adherence.

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Appendix 1. Unidimensional components with items

Final components selected by backward multilevel logistic regression	
Leading to non-adherence	
7.	Adjusting/limiting activities • After the diagnosis I rediscovered what is important in life • I cope with my restrictions by spreading my tasks during the day • When I am in pain, I stop my activities • When I am in pain, I make sure that I do not have to be physically active
Leading to adherence	
8.	Information seeking • I searched for rheumatic diseases on the internet
15.	Positive expectations • These complaints will improve in time • I expect these joint complaints to slowly pass • My recovery depends on me • When I do the right things, I can control my joint complaints
Components not selected by backward multilevel logistic regression	
Leading to non-adherence	
1.	Negative feelings • I find it difficult to calm my body down after periods of pain • My complaints are puzzling to me • When I think about my illness I get upset • I get angry, when I think about not getting rid of these complaints • I am my pain
2.	Disability • I hate not being able to do everything I could before • Because of these joint complaints I cannot take care of others anymore • These joint complaints hinder my daily tasks • Because of the pain I do not get to all kinds of things
3.	Depression • *I feel cheerful* • *Despite these complaints I still function well* • *I can relax* • I have a tense feeling in my stomach • *I can laugh and see things from the bright side*
5.	BMQ specific- necessity • My health at present depends on my medicines • My life would be impossible without my medication • *I have to take medicines to keep functioning well* • Without my medication I would be very ill
9.	Not speaking about it • When I heard that I had a disease, I tried to keep my feelings to myself • When I heard this diagnosis, I kept my feelings to myself • When I heard that I had a disease, I kept others from knowing how bad things were • I do not want other people to know that I have these complaints

11.	BMQ - general harm/general overuse • Medicines do more harm than good • Doctors place to much trusts in medicines • Doctors use to many medicines • People who take medicines should stop their treatment for a while every now and again • If doctors had more time with patients they would prescribe fewer medicines
12.	BMQ - specific concerns • I sometimes worry about the long term effects of my medication • Having to take medication worries me • My health in the future will depend on my medication
13.	Internal locus of control • I know a way to ease my pain • *It does not matter what I do or try, my pain does not become less* • There are many things which I can do to control my symptoms • I have the power to influence my complaints
14.	Active coping • After the diagnosis I changed or grew as a person in a good way • When I heard the diagnosis I made a plan of action and followed it • When I am in pain, I seek the company of others
Leading to adherence	
4.	Anxiety • I worry • I feel tense • I feel restless • It seems as if my pain becomes more and more predominant
6.	Modelling • I make sure to always have some medicines available • A regular lifestyle suits me best • When I recover from these complaints, I mostly owe this to my rheumatologist • When it comes to managing my arthritis, I feel I can only do what my rheumatologist tells me to do • When I heard that I was ill, I thought about how a person I admire would handle this situation and used that as a model
10.	Distancing • When I am in pain I ignore it • After I heard the diagnosis I went on as if nothing had happened • When I am in pain I tell myself not to be hold back by the pain and keep doing what I want to do • When I am in pain I see it as a challenge and do not let it get me down

Items in italics: the polarity of the statements was reversed
Abbreviations: BMQ: Beliefs about Medication Questionnaire

Chapter 9

Discussion

When patients receive their first medication for their rheumatic condition, it is essential that they use the medication as prescribed by their physician. If not, not only their disease will get worse, but the physician might also wrongfully conclude that more intensive medication is needed. In this thesis we investigate the consequences of non-adherence in early arthritis and what causes patients to be adherent or non-adherent to the medication prescribed by their physician. In that respect we formulated four aims:

1) assess the consequences of non-adherence to DMARD therapy to disease activity and hospital costs;
2) determine which measurement methods are feasible in daily practice for the measurement of adherence to DMARD therapy in early arthritis patients;
3) find factors associated with non-adherence to DMARDs in early arthritis patients;
4) develop a prediction tool for patients at risk for low adherence to DMARD therapy in the initial phase of treatment.

We addressed these aims by conducting a systematic review, interviewing early arthritis patients and by conducting a cohort study in which we electronically measured adherence. Patients eligible for the cohort study were adult DMARD naïve early arthritis patients starting with treatment. In this chapter the results of this thesis are discussed within the current body of literature. Methodological considerations of this thesis and the study of adherence in general are discussed. Finally, recommendations for future research are given.

Aim one - consequences of non-adherence

Disease activity

The present study showed that the consequences of non-adherence to DMARDs in the first year of treatment can be severe; at the individual level the patient is affected by non-adherence, because it causes higher disease activity in the first 6 months of treatment. We found that non-adherence progresses over time. Disease activity diminishes during the first year of treatment, but for patients that are less than 90% adherent, the disease activity is higher after six months of treatment than for adherent patients. Since patients are treated to target, the effect of non-adherence disappears after 6 months of treatment. It could be that because of non-adherence unnecessary and premature treatment switches are made to more advanced and expensive therapy, such as biologicals. Patients are probably more likely to adhere to the next step-up in treatment. The more expensive and advanced therapy may have more authority. In this study we could not measure adherence to biologicals and subcutaneous methotrexate, because these medicines do not fit in the MEMS jar. Reviews report non-adherence to biologicals to be as large as non-adherence to synthetic DMARDs, but on the other hand, patients also appear to be more content with biological treatment.[1]

The present study is not the first to find that non-adherence hampers remission.[2, 3] What the present study adds, is that it is the first to determine in which phase of the treatment non-adherence has the largest impact on disease activity. For the rheumatologist it is important to know that especially in the first 6 months of treatment disease activity is affected by non-adherence. That means that the rheumatologist should assure at the start of treatment that the patient is correctly taking the medication. Moreover, when a patient is not responding to

therapy, the rheumatologist has to take in mind that non-response can in fact be caused by non-adherence.

Hospital costs

It is not only the patient at the individual level who is affected by non-adherence; non-adherence also causes a societal burden in the form of higher hospital costs, which endanger the allocation of budget to more effective interventions. The association between non-adherence and hospital costs in the first year of treatment was only small (rho 0.146). Strikingly, the positive relation between non-adherence and hospital costs disappeared when patients were more than 40% non-adherent. These patients had lower health care costs over the first year of treatment. Thus the relation between adherence and costs seems to be U-shaped. The fact that patients who took less than 60% of their DMARDs had lower health care costs is counterintuitive, since many studies report on the association between non-adherence leading to higher health care costs.[4-8] It may be that patients who experience low disease activity did not feel the need for taking DMARDs anymore and started self-tapering medication.[9] This indicates that patients judge for themselves when their disease is less active and when they can taper medication. Premature self-tapering may cause adverse long-term disease outcomes, because the patient should be in sustained remission for two subsequent visits before DMARDs can be tapered, and the rheumatologist can decide best when the patient is in sustained remission. Studies with a longer follow-up period are needed to investigate if self-tapering happens prematurely and if it causes adverse long-term disease outcomes.

In conclusion, non-adherence to DMARDs hampers remission in the first six months of treatment, and can also influence the rheumatologist's treatment decisions, leading to higher health care costs. The course of events would thus be that non-adherence leads to failure to reach remission, and consequently the rheumatologist may switch to more expensive therapy. When judging the effectiveness of the therapy, the rheumatologist should be aware that non-response to therapy might be caused by non-adherence. When the rheumatologist addresses the patient's issues with medication intake during the first consultations, premature and unnecessary treatment switches might be prevented.

Aim two - measurement methods of non-adherence

Since non-adherence is affecting both disease activity and hospital costs, there is a need for a feasible tool to measure adherence in daily practice from the start of treatment on. We compared three different measures of adherence (electronic monitoring, a self-report questionnaire and blood levels of DMARD uptake) on feasibility and reliability in early arthritis patients in the first year of treatment. For the first six months of treatment, no feasible tool stands out as the most preferable.

Electronic monitoring adherence prevalence

Adherence percentages in the first year of treatment are relatively high, slightly declining over time. Differences between DMARDs are also found; for sulfasalazine, the proportion of underuse over time is highest. This is probably because sulfasalazine, which was mostly prescribed twice a day, was preferably taken once a day. Because we calculated non-adherence as not having opened the medication bottle as often as expected per day, opening the bottle

once a day instead of twice a day also led to being non-adherent. One could also calculate the percentage of adherence by dividing the amount of openings by the amount of expected openings, which results in the patient being only half adherent when a patient takes one out of two medication doses. Other studies have highlighted before that patients are more adherent to once-a day dosing regimens than to twice-a-day dosing regimens.[10] This is in line with our findings. Rheumatologists should be aware that patients are more easily non-adherent to twice-a-day medication than to once-a-day medication. This is also an important consideration to take in mind in the development process of new medication.

Strikingly, non-adherence to prednisone did not occur as often as for other DMARDs. This is not what we expected, since patients are often very aware of the negative connotation around glucocorticosteroids.[11] But if patients immediately experience the effect of prednisone, they become more willing to adhere to it.[9, 11] For the other DMARDs such as methotrexate, hydroxychloroquine and sulfasalazine, it takes more time (for methotrexate even up to 8 weeks) for an effect to occur, which may cause more non-adherence.

Self-report

Studies comparing electronic adherence measures with adherence questionnaires are discordant. One review showed that 7 out of 9 studies had low to moderate concordance between adherence questionnaires and electronic measures of adherence,[12] while another study found that self-report measures are highly correlated with electronic monitoring.[13] This discordance might be due to heterogeneity across studies. For example, questionnaires that have been validated in patients with established disease might not be valid for patients that just started with treatment. Overall, it does seem to be the case that self-report questionnaires highly overestimate adherence.[13] In our study, self-report was not or only weakly related to electronic monitoring. The questionnaire that we used was therefore found unsuitable to measure non-adherence in the first year of treatment. In addition, it was found unsuitable because this questionnaire assumes that patients are familiar with medication intake. It might however be suitable to measure the patient's perceptions about medication taking behavior.

MTX-PGs

MTX-PGs can only be used to measure adherence to MTX, and not to other DMARDs. MTX-PGs can be used to check whether methotrexate has been taken at all, but we could not find a steady cut-off value for non-adherence. This is probably due to individual differences in the uptake of methotrexate. We tried to control for individual differences such as age, but this did only explain a small part of the individual differences. Other studies found that besides age, also higher dose, route of administration, decreased renal function, higher erythrocyte folate status and some genetic factors explain the build-up of MTX-PGs.[14-16] Due to logistic reasons, we could not measure these factors. In daily practice, only renal function could be measured, but previous studies showed that together with age and dosage, renal function explained 26% of the total variability of MTX-PG1 - 5.[15] However, if we had taken this into account we might have explained more variability in the uptake of MTX-PGs over time.

Since there is for the first half year of treatment no feasible tool to measure adherence, it is suggested to use, when possible, electronic monitoring, since this is the most accurate method. Recent developments in electronic monitoring devices have resulted in more easy-to-use methods such as blister packs and multicompartmental pillboxes for polypharmacy. When electronic monitoring is not available, a combination of measures of adherence could be

used.[17-20] Self-reports might be used when no other measure is available, but are not reliable in the first half year of treatment. MTX-PGs can be used, but only as an indication whether methotrexate has been taken at all.

Aim three - Determinants of non-adherence in early arthritis

Non-adherence should be recognized at an early stage to prevent the disease from becoming worse and to prevent unnecessary health care expenditures. To address adherence early, targeted interventions need to be developed. The first step in the development of interventions is to search for determinants of non-adherence. Our aim was to systematically review the literature on factors affecting adherence in rheumatology patients at the start of treatment, but we only found studies targeted at established patients. The factors reported to be associated with adherence seem inconsistent over the different investigations, mainly due to heterogeneity in measures and due to low to moderate study quality of the reviewed studies. Two factors stand out: 1) there is an association between a perceived need to take the medication and adherence,[21-24] and 2) there is a tendency for an association between the information received and the way information has been provided by the rheumatologist and non-adherence.[24-27]

The perceived need to take medication is formed by the amount of complaints and the experienced effectiveness of the medication. Patients starting treatment have experienced the physical complaints caused by their arthritis, but do not have experience yet with taking the medication. Thus they have not experienced the effectiveness of the medication. This may cause that the perceived need to take medication might not be as relevant for newly diagnosed patients as for patients with established disease. The rheumatologist can influence the perceived need by persuading the patient to take the medication and by creating positive expectations about the effectiveness of the DMARDs. The information received and the way information has been provided by the rheumatologist is also relevant in the first phase of treatment, since patient-doctor contact is frequent in this phase and trust needs to be build up between the rheumatologist and the patient.

Because no literature was available on determinants of adherence in patients starting treatment, we conducted patient interviews. Patients report in the early stage of treatment five themes that may influence treatment adherence: 1) symptom severity, 2) experiences with medication, 3) perceptions about the medication and the illness, 4) information about the medication, and 5) communication style and trust in the rheumatologist. The themes relate to each other; perceptions about the medication and the illness are modifiable and may be targeted through communication efforts and through information received. No other qualitative data is available on factors affecting adherence in the first phase of medication intake. However, qualitative studies exist on factors affecting adherence in established patients.[28-31] The same themes apply, but there are (subtle) differences. For example, in both stages of the disease beliefs about medication and the disease play a role, but vary. Newly diagnosed patients may have more general beliefs about the harmfulness and expected effectiveness of medication as they are new users. Patients with established disease may have formed more specific cognitions about the necessity of the medication, because of their experiences with the particular DMARD medication.

In the first year of treatment, the rheumatologist might have a larger window for targeting beliefs about medication than in a later stage of treatment, because there are more frequent consultations with the patients. These interactions can be used to gain trust.

Aim four - Predicting non-adherence

In the first three months of treatment, non-adherence is low, but can be predicted by information seeking, having positive expectations about the disease and adjusting/limiting activities. Information seeking and having positive expectations about the course of the disease are related to adherence while adjusting to the pain by limiting activities is related to non-adherence. These factors are in line with the self-determination theory of autonomy, which states that if the patient's autonomy is threatened, the patient's motivation to perform health behaviors such as medication adherence becomes less.[32] Patients who limit their activities because of pain might not feel autonomous, because their behavior is motivated by feelings of disability and pain. They might feel as if they have to surrender to their disease. Seeking information about the disease may reflect a way in which patients want to regain their autonomy: they try to make the rheumatologist's advice their own decision. Having positive expectations about the disease could reflect the outcome of this process: once patients have the idea that they have made an autonomous decision, they become optimistic about the outcome.

Patient autonomy is a well-known concept which is not only associated with adherence, but also with other outcomes such as patient satisfaction.[32, 33] Adherence to medication can be guided by the patients' experienced autonomy, autonomy support, and the patient's perceived competence. Through the working alliance with the patient, the rheumatologist can support the patient's autonomy by involving the patient in the treatment plan. Furthermore, the rheumatologist can enhance the patients' perceived competence to be adherent by addressing practical barriers to medication intake behavior in their consultation.

Limitations

Selection bias

The results presented in this thesis might have been affected by biases. One of the most complex aspects of adherence research is selection bias. In our study, patients had to be informed about the use of MEMS, which made that some patients did not want to participate, because they did not want to be monitored. Studies have reported before that adherent patients are more likely to participate in adherence studies.[34] This may cause what we call the 'adherer effect' or 'healthy adherer bias'.[35] Patients who adhere to the rheumatologists' prescription have better disease outcomes, regardless of the underlying treatment. This theory is based on the finding that behaviors of adherent people are different from the behaviors of non-adherent people. Adherent people have better global health outcomes, since they have more healthy lifestyles, do not engage in risky behaviors and are more adherent to nonpharmacologic prescriptions.[36, 37]

Of those patients invited to participate, 21.8% were unwilling to participate. The group of patients unwilling to participate contained more females than the group of patients who were willing to participate. Based on the 'adherer effect', it could well be that these patients who were unwilling to participate were less adherent than the participating group. A frequently mentioned reason for being unwilling to participate was feeling overwhelmed by the diagnosis. Feeling overwhelmed by the diagnosis could be congruent with loosing autonomy and not feeling 'in control'. Patients who felt this could in fact be patients who experience more difficulty with initiating medication. If we take this limitation into account, we can conclude

that we are dealing with a rather adherent cohort. Adherence proportions are especially in the first months of treatment high, but slightly decline over time. Adherence levels are probably higher in our study population than in a normal population and may not be generalizable to the normal population. If more non-adherent patients would have been in the study, there would have been more variation in adherence and maybe a stronger effect of non-adherence on disease outcome as well as an effect of non-adherence on hospital costs. Furthermore, the components that are predictive of non-adherence, were found in a rather adherent cohort, and might not be as predictive in daily practice, since we assume patients in daily practice to be less adherent. Moreover, the correlation between measures of adherence would have been higher when more variance in adherence was present.

Ways to overcome selection bias are depending on the type of study. For qualitative studies, explicitly inviting patients who have difficulty taking medication might be a solution. For observational or intervention studies, it might be suitable to study adherence with a non-invasive and non-obtrusive method, such as direct measurement of the uptake of medication in blood. Since routine monitoring takes place frequently, it is feasible to draw an extra blood tube for drug monitoring. In the rheumatology practice the only useable measurement tool for this purpose is the measurement of the build-up of methotrexate in the form of methotrexate-polyglutamates. Because it is yet unclear how this measure relates to adherence, it can now only be used to check whether methotrexate has been taken or not at all.

Causality

A limitation in the studies performed in chapter 2, 3 and 8 is that, although with regression analyses causal relationships are modelled, a causal relationship cannot be proved. The most common methodology by which a causal relationship can be proved, is a randomized controlled trial. A randomized controlled trial is unsuitable to study adherence because it is unethical to ask patients to purposefully not take their medication. Remarkably, in many medication trials, causal relationships are masked because of unrecognized non-adherence to the allocated treatment.

However, in observational studies, based on a sound hypothesis and a relevant explanation about how variables are related, causality can be suggested. For example, in chapter 2, the relation between non-adherence and disease activity over time is studied. The hypothesis is that non-adherence leads to disease activity. This is a logical explanation, since we already know from literature that not treating RA leads to a higher disease activity. Furthermore, non-adherence occurred before the measurement of DAS28, we studied the effect of non-adherence on DAS28 over time and controlled for other covariates. One could however also argue that experiencing higher disease activity would lead to non-adherence. This is an interesting explanation, but it would contradict most of the literature and the responses from patients in the interview study, in which they said that experiencing complaints would lead them to be adherent to their medication. Thus, although causality cannot be proved in this study, we may cautiously assume that the causal relationship is that non-adherence leads to higher disease activity.

Strengths

Electronic monitoring

A strength of our study is that we measured adherence with the most accurate method that we have up to now. Electronic measurement of adherence is an accurate method and measures real behavior. In comparison with other measures, it gives detailed 'real-time' descriptions of day-to-day medication intake behavior, instead of a bulk measure or percentage of adherence. The additional value of electronic monitoring, is the opportunity to isolate the monitoring period of interest from the total monitoring time. This was of particular interest in studying the relation between non-adherence and disease outcome over time. We were able to select the exact measurement periods every 12 weeks before the screening of disease activity, which gives accurate results.

However, electronic monitoring still remains an indirect method, which means that it cannot prove ingestion of medication. Some also say that electronic measurement counts as an intervention itself, but this effect is regarded as small.[34, 38, 39] Because electronic monitoring is, as any other adherence measure, still vulnerable for biases, it is advised that researchers should use multiple methods of adherence measurement.[19, 40, 41] In addition to electronic monitoring, we also used objective measures of methotrexate-uptake (MTX-PGs) and self-report questionnaires (CQR). However, there are some issues in integrating and interpreting these multiple measures of adherence. Self-report measures tend to consistently overestimate adherence rates, which is partly due to the desire to appear adherent.[40] The units of measurement among methods are mostly not the same and the frequency distribution of electronically measured adherence percentages is mostly skewed. This means that integrating these measures was not that easy and they were therefore hard to interpret. Eventually, we only used electronic monitoring because the use of multiple measurement methods did not add any value. Until the measurements can be easily integrated and interpreted, the use of multiple measurements does not have any additional value.

Recommendations for future research

Interventions

The studies presented in this thesis address the need for the development of targeted interventions. Over the past decades, numerous interventions have already been developed and tested. Most interventions were carried out by allied health care providers such as nurses and pharmacists. Interventions were complex and mostly aimed at overcoming multifactorial barriers and tailoring support to individual needs, using frequent interaction with patients with a focus on adherence. Overall, interventions targeted at non-adherence behavior were not very effective. Research into enhancing adherence should therefore be more radical and creative. There is also insufficient evidence for newer intervention types, such as mobile text messaging and internet-based care.[42]

Overall, no evidence exists that non-adherence can be prevented.[42] Non-adherence needs to be addressed continuously, since existing interventions do not have long-term effects. This means that clinically applicable and intuitive methods to improve adherence must be maintained for as long as medication is needed, in the case of early arthritis this may be lifelong. Therefore, interventions are required that can be integrated into the health care system.

In the standard rheumatology care, the rheumatologist sees the patient approximately every three months in the first year after diagnosis. After the diagnosis and first prescription by the rheumatologist, the patient mostly sees the specialized rheumatology nurse. The specialized rheumatology nurse informs the patient about the disease and medication and gives advice on how to cope with disability and pain. After this, the patient visits the specialized rheumatology nurse on demand when needed. The specialized rheumatology nurse can influence adherence by the information he or she provides, but often does not see the patient more than once. Since the rheumatologist is the only one who intermittently has contact with the patient, this should logically be the one intervening on medication intake behavior. Furthermore, patients regard the rheumatologists as an authority and state that trust in the rheumatologist is an important condition for being adherent to medication.[9] Time spent with the rheumatologist is expensive, and therefore interventions need to be integrated in daily care in a cost-effective manner.[42, 43] Research is needed on developing and testing the cost-effectiveness of these integrative interventions.

Implications for daily practice

The role of patient-doctor communication

One may wonder whether adherence to medication is either the patient's or the doctors' responsibility. From this thesis it appears that non-adherence has both for the patient and for the clinician consequences, and thus adherence should be seen as a shared responsibility. Because of this shared responsibility the rheumatologist and the patient should together resolve adherence issues.

Until a prediction tool is available, awareness of possible non-adherence can only be created through communication with the patient. The accurate assessment of adherence depends then on the development of a trusting and accepting relationship between the patient and healthcare provider.[44] When the healthcare provider assesses adherence in a nonthreatening and objective manner, the patient will be more likely to disclose non-adherence behavior.

One way to do this is through involvement of the patient, for example through shared decision making. Shared decision making is seen as a form of doctor-patient consultation in which both clinician and patient share relevant information, express treatment preferences, deliberate the options and ultimately agree on the treatment to implement.[45, 46] Shared decision making is the ultimate form of taking shared responsibility for treatment adherence by both the patient and the clinician and research has shown that patient participation and shared decision making have a positive outcome on treatment adherence.[45-47] Furthermore, shared decision making results in having fewer concerns about the medication.[48] Making shared decisions is balancing between a paternalistic clinician who tells his or her patient what to do and a clinician who lets the patient autonomously choose his or her treatment options (informed choice). The professional is still responsible for setting the agenda, but the decision-making process is shared.

From our interview study, it appeared that in the early stage of the disease, the patient is mostly not ready yet to make shared decisions. This is because the patient does not have any experience with medication yet and is mostly overwhelmed by the diagnosis. In this stage, an adapted form of shared decision making is needed. Patient adapted paternalism holds that the professional decides in accordance with the individual situation of the patient.[46] In this case

the patient does not make the final decision about the treatment, but the patient does have the ability to share information about his or her situation and his or her preferences.

Meta-analytic research suggests that doctor-patient communication is indeed an inescapable factor in adherence behavior.[49] Good doctor-patient communication results in 19% higher adherence than poor doctor-patient communication. Furthermore, it is proven that training physicians in communication skills results in 12% improved patient adherence.[49] When the patient is non-adherent, the rheumatologist may explore whether the patients' non-adherence is a result of an autonomous decision and actually in line with his or her preference set. The rheumatologist may also express his or her opinion on what she finds to be in the patients' best interest.

Shared decision making is seen as an important overarching principle of care and has been added to the European League Against Rheumatism (EULAR) recommendations for the management of rheumatoid arthritis in 2010.[50] However, the guidelines do not give any practical advice on what the rheumatologist needs to do or say during his or her consultation to allow for shared decision making. First, the rheumatologist may check which expectations the patient has about the medication and the course of the disease. When expectations are unrealistic, the rheumatologist can alter these expectations. The rheumatologist should use affective communication techniques to encourage the patient to talk about doubts and fears about the medication. The ability to use affective communication is a predictor of the success of a consultation, generates trust and allows for shared-decision making to occur.[51] Second, when planning the treatment strategy, the rheumatologist should let the patient participate and agree on the treatment plan. In further consultations, the rheumatologist should always ask the patient how medication intake is going in an empathic and non-judging manner.

The main condition needed to involve the patient in treatment seems to be the patient's trust in the physician. This point was also mentioned in the patient interviews as an important condition for adhering to the treatment. This entails that trust in the physician is essential for emotional disclosure and a crucial component of the patient-physician relationship. Trusting relationships between physicians and patients can affect patient outcomes for the better.[44] Physicians who promote trust in the therapeutic relationship and who use affective communication can easily establish patient cooperation and adherence.[52, 53]

Conclusion

In patients starting DMARD treatment, non-adherence is a mostly unrecognized burden for both the patient and the healthcare provider. Because existing interventions do not have long-term effects, interventions are needed that are integrated in daily practice. Therefore, the patient and the rheumatologist should together try to resolve adherence issues in a clinically applicable and intuitive way, for example through patient involvement in the treatment. An essential condition in addressing medication intake behavior is the patient's trust in the rheumatologist.

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Summary

Chapter 1 introduces the topic of non-adherence to DMARDs in patients with early arthritis. The importance of good adherence to DMARDs is prescribed, as well as the consequences of non-adherence. Adherence can be divided in different phases: the initiation phase, implementing medication in daily life and persistence or non-persistence with medication. This thesis mainly focuses on the initiation of DMARDs, because especially in the early phase of disease, a tight-controlled treatment is important to prevent joint damage.

There are many ways to measure adherence: with (validated) questionnaires, or with direct methods that measure the uptake of medication intracellularly. A frequently used indirect method to measure adherence is electronic measurement of openings of medication bottles. The jar lid registers every time the medication lid is opened and closed and compares this with when the jar should have been opened. This method is precise and measures real behavior 'real time'.

What determines non-adherence remains unclear. It is suggested that certain perceptions about the medication and the illness may cause non-adherence. Research mainly focused on determinants of adherence in established patients. One can imagine that patients that just started taking medication have other perceptions about their illness and medication than established patients. There is not enough knowledge about the determinants of initiating medication. Therefore this thesis mainly focuses on the first phase of adherence: initiating medication.

We conducted a cohort study in which arthritis patients starting with DMARDs were followed up for one year. We measured adherence electronically, with a validated questionnaire and with the intracellular uptake of methotrexate in red blood cells. Disease activity was measured every three months and healthcare consumption were registered from the patient files. Furthermore, we developed and administered an item pool to measure psychosocial factors that are possibly related to adherence.

The consequences of non-adherence to DMARDs in the first year of treatment are studied in part one. **Chapter 2** describes the relation between non-adherence and disease activity. From the cohort, 120 patients that were diagnosed with RA following the ACR2010 criteria were selected. Every three months disease activity was measured using the DAS28. Electronically measured adherence was measured continuously and aggregated over the 12-week period before each DAS28 measurement. Non-adherence to DMARDs significantly contributes to higher disease activity scores over the first six months of the disease.

The relation between non-adherence and hospital costs is explored in **chapter 3**. From 206 patients that finished the cohort before January 2014, we registered health care consumption from the hospital in which they were treated for their rheumatic condition. The number of visits and telephone consultations with medical specialist and other health care providers, imaging modalities, medical procedures, medication use, laboratory tests, admissions and ER visits were registered and their costs were computed. Cots were divided into three categories: a) costs made at the rheumatology outpatient clinic, b) costs made through referrals from the rheumatologist, and c) costs for comorbidities. Adherence was continuously measured and aggregated over the whole year. We found a positive association between non-adherence and total costs. However, when a patient is more than 40% non-adherent, the patient seems to make less costs. This effect may be explained by the fact that patients with a less active disease (and therefore having less hospital costs) might have self-tapered their medication.

Part two handles various measurement methods of adherence. **Chapter 4** describes three different measurement methods and depicts their mutual associations. From 206 patient that had ended the cohort before January 2014 we measured adherence continuously electronically, and every three months adherence was measured using the Compliance Questionnaire Rheumatology (CQR) and with the measurement of intracellular methotrexate polyglutamylation (MTX-PGs). Electronically measured adherence was aggregated over each 3-month period and correlated to MTX-PGs and the dichotomized CQR adherence score. Especially in the first 6 months of DMARD use, none of the measures correlated well enough with each other. The CQR did correlate with MEMS after 9 months, but not sufficient enough. The same applied to MTX-PGs. MTX-PGs and the CQR did not correlate with each other at all. The results implicate that in the first year of medication use, electronic monitoring of adherence remains the best method, even though this is an expensive and less feasible method. The insufficient correlation of the CQR with MEMS, is probably because these methods measure a different concept: the CQR measures perceptions about nonadherence, where electronical measurement with MEMS measures behavior real-time. MTX-PGs are promising as a nonadherence measure, and are easy to administer in daily practice, but there is too little variation between patients in MTX-PG build-up, which makes it hard to compare the MTX-PG values with electronically measured adherence. This variance in build-up is partly due to biological differences between patients, such as age and DNA.

Part three describes determinants of adherence from different perspectives. **Chapter 5** systematically reviews the literature about factors influencing non-adherence to pharmaceutical treatment in RA patients. Studies that observed adherence in rheumatology patients and that related factors to adherence were included. 18 studies fulfilled the search criteria. The relevant data was extracted from the studies and the studies were subjected to a quality assessment. 61% of the studies had insufficient or moderate quality. In addition, it was hard to compare studies with each other due to hetorogeinity in adherence measurement methods and heterogeneity in the measurement of factors related to adherence. There is an association between the perception that medication is needed and adherence, between adherence to anti-TNF and previous DMARD use, and there is a tendency for an association between the way of delivering information to the patient and adherence.

In **chapter 6**, the patient perspective about factors influencing the initiation of DMARDs is given. We conducted focus group interviews and individual interviews with patients who have been using DMARDs for less than two years for RA or PsA. After interviewing 33 patients, of which 10 self-reported being non-adherent, the following factors were extracted from the interview data: 1) symptom severity, 2) experiences with medication, 3) perceptions about the medication and the illness, 4) information about medication, 5) communication style and trust in the rheumatologist. In summary, it appears that the rheumatologist can influence adherence by addressing ideas about the medication and the illness. The way of communicating to the patient is important to gain a trustworthy relationship with the patient.

Part 4 describes the development of a prediction tool to identify patients at risk for nonadherence in the first three months of treatment. In **chapter 7**, the methodology of developing a prediction model for adherence in patients starting with DMARDs is outlined. This stepwise procedure describes to first extract knowledge from the literature and when needed from the

patient perspective. Secondly, an expert panel can be used to cluster and/or reduce the factors found. Ordering can be done based on distance and proximity, meaning the extent to which the factors are changeable. It is advisory to gain more insight in mutual relations between the factors by introducing a theoretical framework. Which theoretical framework to use depends on the goal for the prediction model. It is important to reflect on how to measure the factors and how to measure adherence.

Chapter 8 describes the construction of a prediction model for the first three months of adherence to DMARDs. Over the first three months of DMARD use, we measured adherence electronically in 291 patients diagnosed with RA, PsA or undifferentiated arthritis. At baseline, patients filled out an item pool, consisting of statements to which they could answer to which extent they agreed to these statements. The items were reduced and clustered. A multilevel multivariable logistic regression with backward selection was ran to find the most predictive components. Fifteen candidate predictors of non-adherence were retrieved from the original item pool: negative feelings, depression, adjusting/limiting activities, distancing, BMQ specific concerns, internal locus of control, anxiety, information seeking, BMQ general, active coping, positive expectations, not speaking about it, BMQ specific-necessity, modelling, and disability. The final prediction model consists of 3 components: information seeking, adjusting/limiting activities and having positive expectations about the course of the disease. The findings suggest that patients who keep feeling autonomous during their disease, for example by seeking information and through having positive expectations, are more adherent, whereas patients who feel less autonomous, expressed by limiting activities because of pain, become less adherent over the first 3 months of treatment.

In **chapter 9** the findings of this thesis are discussed. Limitations of this study are selective patient drop-out. It is likely that patients who become lost to follow up are also less adherent to medication. A strength of our study is that adherence was measured with a very accurate method. Indications for the improvement of adherence can be found in patient-doctor communication. Making shared decisions about the treatment can promote the patients' feelings of autonomy and improve adherence. Necessary conditions for patient participation in treatment decisions are affective communication techniques and trust in the rheumatologist.

Samenvatting

In **hoofdstuk 1** wordt een introductie gegeven op therapie-ontrouw aan antireumatica bij patiënten met vroege artritis. Het belang van therapietrouw wordt onderstreept, evenals de consequenties die therapie-ontrouw met zich meebrengt. Therapietrouw kan verdeeld worden in verschillende fases: het starten met medicatie, het implementeren van het medicatiegebruik in het dagelijks leven en het stoppen of volhouden van de medicatie. Omdat juist in de vroege startfase van de behandeling strikt medicijngebruik belangrijk is om schade te voorkomen, gaat dit proefschrift vooral over de fase waarin gestart wordt met antireumatica.

Er zijn verschillende manieren om therapietrouw te meten: bijvoorbeeld met al dan niet gevalideerde vragenlijsten, of door middel van directe methoden die de opname van een medicijn in het bloed meten. Een veel gebruikte indirecte methode om therapietrouw te meten is door middel van het elektronisch monitoren van het openen en sluiten van medicatiepotjes. Elke keer dat het medicatiepotje is geopend en weer gesloten wordt, wordt geregistreerd door middel van een microchip en vergeleken met de keren dat het potje geopend en gesloten had moeten zijn. Deze methode is precies en meet echt gedrag op het moment.

Wat de determinanten van therapie-ontrouw zijn, blijft onduidelijk. In de literatuur wordt gesuggereerd dat het te maken heeft met overtuigingen die patiënten over medicatie hebben, en met hoe patiënten hun ziekte ervaren. Onderzoekers hebben zich vooral gericht op de determinanten van therapietrouw in een latere fase van medicatiegebruik, maar je kan je voorstellen dat patiënten die net ziek zijn geworden anders over hun ziekte en medicatie denken dan patiënten die al een tijdje medicatie slikken. Over redenen om wel of niet te starten met medicatie is echter nog weinig bekend. Daarom richt dit proefschrift zich vooral op de eerste fase van therapietrouw; het starten met medicatie.

We doen dit door middel van een cohort studie: we hebben patiënten vanaf het moment van diagnose een jaar lang gevolgd. Bij deze patiënten hebben we de therapietrouw elektronisch geobserveerd. We hebben ook een gevalideerde vragenlijst gebruikt om therapietrouw te meten, en via de gefaseerde opname van methotrexaat in rode bloedcellen therapietrouw gemeten. Ziekteactiviteit werd elke drie maanden gemeten en zorggebruik werd uit het patiëntendossier geregistreerd. Daarnaast werd er een itempool ontwikkeld en afgenomen om mogelijke psychosociale determinanten van therapietrouw te meten.

In deel 1 bestuderen we de consequenties van therapie-ontrouw in het eerste jaar van antireumatica gebruik. In **hoofdstuk 2** wordt beschreven van de relatie tussen therapie-ontrouw en ziekteactiviteit is. Voor dit onderzoek selecteerden we uit ons cohort de 120 patiënten met reumatoïde artritis en maten we elke 3 maanden de ziekteactiviteit met de DAS28. We selecteerden de elektronisch gemeten therapietrouw in de 12 weken voor elke DAS28 meting. We zien dat in de eerste 6 maanden van de ziekte het minder dan voorgeschreven slikken van de antireumatica significant samenhangt met een hogere ziekteactiviteit gemeten met de DAS28.

In **hoofdstuk 3** wordt de relatie tussen therapie-ontrouw en zorgkosten behandeld. We registreerden van de 206 patiënten die voor 1 januari 2014 het cohort hadden doorlopen de zorgconsumptie uit het ziekenhuis waar ze voor hun reumatische aandoening behandeld werden. Het aantal bezoeken en telefonische consulten met specialisten en andere zorgverleners, beeldvorming, medische procedures, medicijngebruik, laboratoriumtesten, opnames en eerste hulp bezoeken werden geregistreerd en hier werden kosten aan verbonden. We verdeelden de kosten in: a) kosten gemaakt op de polikliniek reumatologie, b) kosten gemaakt door doorverwijzingen van de reumatoloog, en c) kosten gemaakt voor comorbiditeiten. Therapietrouw werd

elektronisch gemeten gedurende het hele jaar. Er werd een associatie gevonden tussen therapie-ontrouw en totale kosten. Hoe minder antireumatica de patiënt slikt, hoe hoger de zorgkosten. Echter, als de patiënt meer dan 40% ontrouw is, maakt deze juist minder kosten. Dit effect kan verklaard worden door het feit dat dit misschien patiënten zijn die een minder actieve ziekte hebben (en daardoor minder zorgkosten hebben gemaakt), en daarom zelf hun medicatie hebben afgebouwd.

Deel 2 gaat over verschillende meetmethodes van therapietrouw. **Hoofdstuk 4** beschrijft drie verschillende meetmethodes en beschrijft hun onderlinge verbanden. Van 206 patiënten die voor 1 januari 2014 het hele cohort hebben doorlopen, hebben we de therapietrouw op drie manieren gemeten: door middel van elektronisch monitoren, met de 'compliance questionnaire rheumatology' (CQR) en door middel van methotrexaat-polyglutamaten (MTX-PGs). De elektronisch gemeten therapietrouw werd per drie maanden samengevoegd en gecorreleerd aan zowel de MTX-PGs als de CQR. Wat bleek was dat vooral in de eerste 6 maanden van antireumatica gebruik, geen van de maten goed met elkaar correleerden. De CQR was na 9 maanden wel iets beter gecorreleerd aan MEMS, maar nog steeds niet voldoende. Hetzelfde geldt voor de MTX-PGs. MTX-PGs en de CQR bleken alleen na 9 maanden aan elkaar gecorreleerd. Deze resultaten wijzen erop dat in het eerste half jaar van medicijngebruik, het elektronisch monitoren van therapietrouw de meest accurate methode is, ook al is dit een dure methoden en wordt deze door veel patiënten als onhandig ervaren. Dat de CQR zo slecht correleert met MEMS komt waarschijnlijk doordat deze twee methodes wezenlijk iets anders meten; waar de MEMS echt gedrag meten, meet de CQR percepties over therapietrouw. MTX-PGs leken een veelbelovende maat, en deze zouden makkelijk ingezet kunnen worden in de dagelijkse praktijk om therapietrouw te meten, maar er blijkt te veel variatie tussen patiënten te zijn in de opbouw van de polyglutamaten, waardoor het moeilijk is om een goede vergelijking met therapietrouw te maken. Deze variatie in opbouw wordt mede veroorzaakt door biologische verschillen, zoals leeftijd en DNA-profielen.

Deel 3 beschrijft determinanten van therapietrouw vanuit verschillende gezichtspunten. In **hoofdstuk 5** wordt de literatuur systematisch gereviewd op factoren die van invloed zijn op therapie-ontrouw aan medicatie in patiënten met reumatoïde artritis. Er werd gezocht naar literatuur die therapietrouw aan medicatie in observationele studies beschreef bij patiënten met een reumatologische aandoening en daarnaast andere factoren relateerde aan therapietrouw. In totaal werden er 18 studies gevonden die aan de zoekcriteria voldeden. De relevante data werd geëxtraheerd en aan een kwaliteitsassessment onderworpen. 61% van de studies bleek van slechte tot matige kwaliteit te zijn. Daarnaast bleken de studies moeilijk vergelijkbaar met elkaar: er was heterogeniteit in de manier van meten van therapietrouw en in de manier van meten van factoren die gerelateerd werden aan therapietrouw. Er lijkt er een verband te bestaan tussen de perceptie dat de medicatie nodig is en therapietrouw, het gebruik van synthetische DMARDs voor het gebruik van anti-TNF en therapietrouw aan anti-TNF, en er is een zwak verband tussen de informatie en de wijze van informatie verstrekken door de reumatoloog en therapietrouw.

Aan de hand van focusgroepen (groepsinterviews) en individuele interviews met patiënten die maximaal twee jaar antireumatica slikten voor reumatoïde artritis of artritis psoriatica, is in **hoofdstuk 6** vanuit het patiëntenperspectief gekeken welke factoren van invloed zijn op

het wel of niet goed starten met antireumatica. Na het interviewen van in totaal 33 patiënten, waarvan 10 patiënten zelf rapporteerden niet therapietrouw aan hun antireumatica te zijn, zijn de volgende 5 factoren die van invloed zijn op therapietrouw uit de interviews gehaald: 1) ernst van de klachten 2) ervaringen met medicatie 3) ideeën over de medicatie en de ziekte 4) informatie over de medicatie 5) communicatiestijl en vertrouwen in de reumatoloog. Samenvattend lijken het ingaan op ideeën over de medicatie en de ziekte aangrijpingspunten voor de reumatoloog te zijn om therapietrouw bij patiënten die gaan starten met antireumatica te bevorderen. Daarbij is de communicatiestijl van de reumatoloog van belang om vertrouwen bij de patiënt op te wekken.

Deel 4 beschrijft welke determinanten van invloed zijn op therapietrouw in de startfase van antireumatica gebruik. **Hoofdstuk 7** beschrijft de methodologie van het ontwikkelen van een predictiemodel om therapietrouw bij patiënten die starten met antireumatica te voorspellen. De stapsgewijze methode beschrijft om als eerste vanuit de literatuur en eventueel vanuit patiëntenperspectief bestaande kennis te extraheren. Ten tweede zou een expertpanel kunnen worden ingezet om de gevonden factoren te ordenen, dan wel te reduceren. Men zou de factoren kunnen rangschikken op hoe makkelijk men deze factor zou kunnen veranderen. Daarnaast strekt het tot de aanbeveling om meer zicht op de onderlinge verhoudingen van de factoren te krijgen door het inzetten van een theoretisch kader. Welk theoretisch kader te gebruiken hangt voor een groot deel af van het doel wat men voor ogen heeft met het predictiemodel. Het is belangrijk om na te denken over hoe de factoren gemeten gaan worden en hoe therapietrouw gemeten gaan worden.

In **hoofstuk 8** wordt de constructie van een voorspelmodel voor de eerste drie maanden van therapie-ontrouw aan antireumatica beschreven. Gedurende drie maanden is therapietrouw aan antireumatica elektronisch gemeten bij 291 patiënten met reumatoïde artritis, artritis psoriatica of ongedifferentieerde artritis. Voordat patiënten begonnen met het slikken van antireumatica, werd door hen een itempool ingevuld. Deze items zijn gereduceerd en vervolgens geclusterd in componenten. Een multilevel multivariabel logistische regressie met backward selectie werd gerund om zo de meest voorspellende componenten te vinden. Vijftien kandidaatvoorspellers van therapie-ontrouw werden uit de originele itempool gehaald: negatieve gevoelens, depressie, aanpassen/stoppen van bezigheden, afstand nemen, BMQ specifieke zorgen, interne locus of control, angst, informatie zoeken, BMQ generiek, actieve coping, positieve verwachtingen, er niet over praten, BMQ specifiek noodzakelijkheid, modelleren en beperkingen. Het uiteindelijke voorspelmodel bestaat uit 3 componenten: informatie zoeken, aanpassen/stoppen van activiteiten en het hebben van positieve verwachtingen over de loop van de ziekte. De bevindingen wijzen erop dat patiënten die zich autonoom voelen gedurende het ziekteproces, bijvoorbeeld door het zoeken van informatie en door het hebben van positieve verwachtingen, meer therapietrouw zijn. Patiënten die zich minder autonoom voelen, wat uitgedrukt wordt door het stoppen of beperken van bezigheden omdat ze pijn hebben, hebben meer kans om gedurende de eerste 3 maanden van behandeling therapie-ontrouw te zijn.

Hoofdstuk 9 bediscussieert de bevindingen van dit proefschrift. Beperking van dit onderzoek zijn geselecteerde uitval van deelname van patiënten. Waarschijnlijk zijn patiënten die niet deel willen nemen ook minder therapietrouw. Een sterk punt van onze studie is dat we therapietrouw met een zeer precieze methode hebben gemeten. Aanwijzingen om therapietrouw

te verbeteren kunnen gevonden worden in de communicatie tussen arts en patiënt. Het gezamenlijk beslissingen maken over de behandeling kan gevoelens van autonomie bevorderen en daardoor de therapietrouw verbeteren. Voorwaarden voor het betrekken van de patiënt bij de behandeling zijn affectieve communicatie en vertrouwen in de arts.

PhD portfolio

Name PhD student: Annelieke Pasma
Erasmus MC departments: Rheumatology
Psychiatry, section Medical Psychology and Psychotherapy
Research school: NIHES
PhD period: February 2011 – July 2015
Promotores: Prof.dr. J.M.W. Hazes and Prof.dr. J.J. van Busschbach
Copromotor: Dr. A. van 't Spijker

Courses concerning Master in Public Health

2011	
Principles of Research in Medicine (ESP01)	0.7
Introduction to Global Public Health (ESP41)	0.7
Methods of Public Health Research (ESP11)	0.7
Methods of Health Services Research (ESP42)	0.7
Primary and Secondary Prevention Research (ESP45)	0.7
Social Epidemiology (ESP61)	0.7
Biostatistical Methods I: basic principles (CC02)	4.3
Biostatistical Methods II: classical regression models (EP03)	4,3
2012	
Study design (CC01)	4,3
International comparison of Health Care Systems (HS03a)	1.4
IRT course (Leiden University, department of Methods and Statistics)	1.4
Logistic regression (ESP66)	1.4
Repeated measurements (CE08)	1.4
Preventing Failed Interventions in Behavioral Research (MP05)	1.4
Courses for the quantitative researcher (EP17)	1.4
2013	
Missing values in Clinical Research (EP16)	0.7
Site visit to the Municipal Health Service Rotterdam (PU03)	0.3
Advanced analysis of prognostic studies (EWP13)	0.9
Public Health Research: from epidemiology to Health Promotion	5.7
Analysis of Population Health (HS02a)	
Analysis of Determinants (HS02b)	
Intervention Development and Evaluation (HS02c)	
2014	
Integration Module (PU04)	0.3

General courses, seminars and workshops

2011	BROK ('Basiscursus Regelgeving Klinisch Onderzoek'), Erasmus MC, Rotterdam Symposium IRT in healthcare
2012	Scientific English Writing, Erasmus MC, Rotterdam Espacomp scientific meeting educational day, Gent
2013	Espacomp scientific meeting educational day, Budapest
2014	Teaching the Teacher I, Erasmus MC, Rotterdam
2015	Basiskwalificatie Onderwijs (BKO)

National and international conferences and presentations

2011	3e nationale therapietrouwcongres NCPF, Utrecht, poster
2012	Espacomp scientific meeting, Gent, Belgium, 2 posters Nedederlandse Vereniging Reumatologie (NVR) Najaarsdagen, Papendal, oral presentation and poster Meeting of the American College of Rheumatology/American Rheumatology Health Professionals (ACR/ARHP), Washington, USA, poster
2013	Nederlandse Vereniging Reumatologie (NVR) Najaarsdagen Papendal, invited speaker Espacomp scientific meeting, Budapest, Hungary, poster
2014	Meeting of the American College of Rheumatology/American Rheumatology Health Professionals (ACR/ARHP), Boston, USA, poster
2015	Annual European congress of rheumatology (EULAR), Rome, Italy 2 posters Nederlandse Vereniging Reumatologie (NVR) Najaarsdagen Papendal, oral presentation, 2 posters

Teaching activities

2011 – 2015	Teaching course PKV – Communication and Attitude to 1st year medical students at the Erasmus University
2014	Supervising research internship of 4th year medical student

Other activities

2015	Educational grant for the project: Development and pilot of a training in shared decision making skills for rheumatologists
2011 – 2015	Member of Nivel scientific researchers in adherence working group
2011 – 2013	Coordinator students team Rheumatology
2012	Erasmus MC pilot grant for the project: Using intracellular methotrexate levels to monitor patient adherence in rheumatoid arthritis
2012 – 2015	Member of SWORA (sociaalwetenschappelijk onderzoek bij reumatische aandoeningen) working group

Publications

In this thesis

Pasma A, Schenk CV, Timman R, van Busschbach JJ, van den Bemt B, Molenaar E, Noort-van der Laan W, Schrauwen S, van 't Spijker A, Hazes JMW. Non-adherence to DMARDs is associated with higher disease activity in early arthritis patients in the first year of the disease. Arthritis Res Ther. 2015 In press.

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Pasma A, den Boer E, van 't Spijker A, Timman R, van den Bemt B, van Busschbach JJ, Hazes JMW. Non-adherence to disease modifying antirheumatic drugs in the first year after diagnosis: comparing three adherence measures in early arthritis patients. Submitted

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Pasma A, Hazes JMW, van Busschbach JJ, Noort-van der Laan W, Appels C, de Man Y, Nieboer D, Timman R, van 't Spijker A. Psychosocial predictors of DMARD adherence in the first three months of treatment for early arthritis. Submitted

Other publications

Walter MJM, van 't Spijker **A, Pasma** A, Hazes JMW, Luime JJ. Focus group interviews reveal differences in the perception of disease activity in rheumatoid arthritis. Rheumatology. 2015 accepted.

About the author

Annelieke Pasma was born on the sixth of April 1984 in Vlissingen. She grew up in Borne, and finished secondary education (gymnasium) at the Bataafse Kamp in Hengelo in 2002. After her graduation she worked and travelled for a while in Australia and New Zealand. When she returned, she started her study to become an art therapist at Hogeschool Leiden, which she finished in 2007. During her study, she gained more interest in the way the mind influences our physical health, and started with a master in Psychology (Safety and Health) at Twente University in Enschede, which she finished in 2009.

After some more travels and working as a pediatric group leader in kindergarten, she ended up in Rotterdam where she started to work at the research project described in this thesis at the department of Rheumatology of the Erasmus MC under the supervision of Prof.dr. J.M.W. Hazes (Rheumatology), Prof.dr. J.J. van Busschbach (Psychiatry, section Medical Psychology and Psychotherapy) and Dr. A. van 't Spijker (Psychiatry, section Medical Psychology and Psychotherapy).

In addition to working on her research project, Annelieke taught first-year medical students in communication skills and attitude. During her research project, Annelieke graduated from the Master of Science – Public Health at the Netherlands Institute of Health Sciences (NIHES) and achieved her basic training in education at the Erasmus MC Desiderius School.

After finishing her PhD project, Annelieke will combine teaching with developing and implementing a training in shared decision making skills to rheumatologist, for which she received an educational grant.

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