

DECISION MAKING ABOUT MEDICATIONS IN RHEUMATOID ARTHRITIS

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ABSTRACT

Understanding the issues surrounding decision making about medication treatments has important implications for public health, including improving the quality of care for patients with chronic conditions. This dissertation examines medication decisions in one chronic condition, rheumatoid arthritis (RA).

Chapter one introduces the context of decision making about medications in RA. Guidelines recommend treating RA to the target (T2T) of low disease activity (LDAS) with disease-modifying antirheumatic drugs (DMARDs). T2T requires regularly monitoring for moderate/high disease activity (MHDAS), and adjusting DMARDs at least every 3 months until the patient reaches LDAS. The chapter provides background on the challenges of implementing T2T, and summarizes chapters two through four.

Chapter two addresses delays in DMARD adjustment for patients with MHDAS. Survival analysis is used to examine the extent of delays in DMARD adjustments and whether delayed DMARD adjustment leads to delayed LDAS. Forty percent of RA patients with persistent MHDAS wait longer than 3 months to receive DMARD adjustment, and timely DMARD adjustment is associated with reaching LDAS sooner. There may be a need to reduce delays in DMARD therapy adjustment for many patients.

Chapter three examines patients' perspectives on medication decisions, exploring how feelings in response to events and information motivate decisions to accept or resist medications. Patients' feelings towards the benefits and dangers of medications, their identity as an ill person, the act of taking medication, and the decision process itself affect willingness to accept medications. Awareness of feelings motivating resistance to taking medications may allow physicians to better support patients confronting threatening information and difficult treatment decisions.

Chapter four compares patient joint assessments with physician joint assessments to examine their suitability for disease activity monitoring between visits. Although agreement on joint assessment items is modest, agreement on detection of MHDAS is better. Patient joint assessments may be useful for disease monitoring between visits, potentially reducing delays to DMARD adjustment.

This dissertation provides a multi-level view of treatment guideline implementation in RA. Understanding the interdependency of patient, provider, and system level factors in medication decisions is valuable for improving the quality of care for patients with chronic conditions.

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To my husband and Tesla Bird

1.0 INTRODUCTION

Understanding the issues surrounding decision making about medications has important implications for improving the quality of care and health outcomes for patients with chronic conditions who require ongoing treatment with medications. This dissertation examines these decisions in one chronic condition, rheumatoid arthritis (RA).

RA is a musculoskeletal condition causing pain and progressive damage to joint tissues. The disease requires ongoing treatment with medications called disease-modifying antirheumatic drugs (DMARDs) to control symptoms and progression. Evidence-based guidelines recommend treating RA to the target (T2T) of low disease activity or remission (LDAS), an approach in which DMARD therapy is escalated whenever patients develop moderate to high disease activity (MHDAS). However, implementing the T2T approach in clinical practice is challenging. Patient and physician preferences may conflict with recommended DMARD therapy escalation, and infrequent disease activity monitoring may cause MHDAS to persist undetected. All of these reasons contribute to delays in escalating DMARD therapy when needed, resulting in worse disease outcomes and quality of life for patients.

This dissertation addresses the challenges of implementing the T2T approach in care for RA patients. Chapter 2 quantitatively examines delays in DMARD therapy adjustment for RA patients with MHDAS and how this affects time to LDAS. Chapter 3 presents a qualitative study

of patients' internal motivations for accepting or resisting DMARD medications. Chapter 4 considers the usefulness of patient joint assessments for detecting MHDAS by quantitatively examining the agreement between patient and physician joint assessments.

The rest of this introductory chapter presents the general context of RA and its treatment, and the more specific contexts for each of the three studies included in the dissertation. First, the RA disease process is explained, followed by an overview of T2T in RA. Next, three challenging aspects of implementing a treat-to-target approach in RA in a clinical setting are discussed. The first challenge pertains to the patient and physician's decision during the visit to modify the treatment regimen in response to MHDAS. The second challenge concerns patient reluctance to accept the treatment regimen during the visit or take prescribed medications at home. The third challenge concerns inadequate disease monitoring during and between patient visits to the clinic. Each of the studies included in the dissertation addresses one of these three challenges. A brief description of each study and its major findings and implications is provided following the discussion of each challenge.

1.1 RHEUMATOID ARTHRITIS

RA is an autoimmune disease that causes chronic inflammation of joint tissues, damaging and deforming joints as the disease progresses. Chronic pain, fatigue, and limited physical function have a heavy impact on the quality of life (1-3) and ability to work (4, 5) for RA patients. Worldwide, the prevalence of RA is estimated to be 0.4-1.3% (6, 7); in the United States, RA affects about 1.5 million adults, 70% of whom are female (8, 9).

Disease outcomes in RA are driven by disease activity (RA-related inflammation). Higher levels of disease activity are associated with worse pain and fatigue symptoms, poorer physical functioning, and progression of joint damage (10-12). Flares, or brief periods (under 3 months) of increased disease activity, have also been shown to be associated with these outcomes (12-14). Bykerk et al. (15) conducted a study to characterize flares in an observational cohort of RA patients receiving treatment in the US. They found that the duration of flares ranged from less than 6 days to more than 2 weeks, and that patients reported experiencing as many as 6 flares during a 6 month period (15). While patients with MHDAS were more likely to experience frequent flares than those with LDAS, patients with LDAS experienced flares as well; 30% of RA patients experiencing 6 or more flares in a 6 month period were documented as having LDAS (15).

1.2 TREATING TO TARGET IN RHEUMATOID ARTHRITIS

Although there is no cure for RA, there are many medications currently available to control and prevent the symptoms and long-term effects of RA. Medications targeted at reducing RA-related inflammation are called DMARDs. Clinical trials have shown that systematically treating to the target (T2T) of LDAS with DMARDs leads to better disease outcomes compared to usual care (16). Rheumatology guidelines have recommended adoption of the T2T approach in clinical practice since 2010 (17-22). The T2T approach entails regularly monitoring patients' disease activity with a quantitative measure such as the Disease Activity Score with 28-joint count (DAS28) (23) and responding to the occurrence of MHDAS by adjusting (increasing dose,

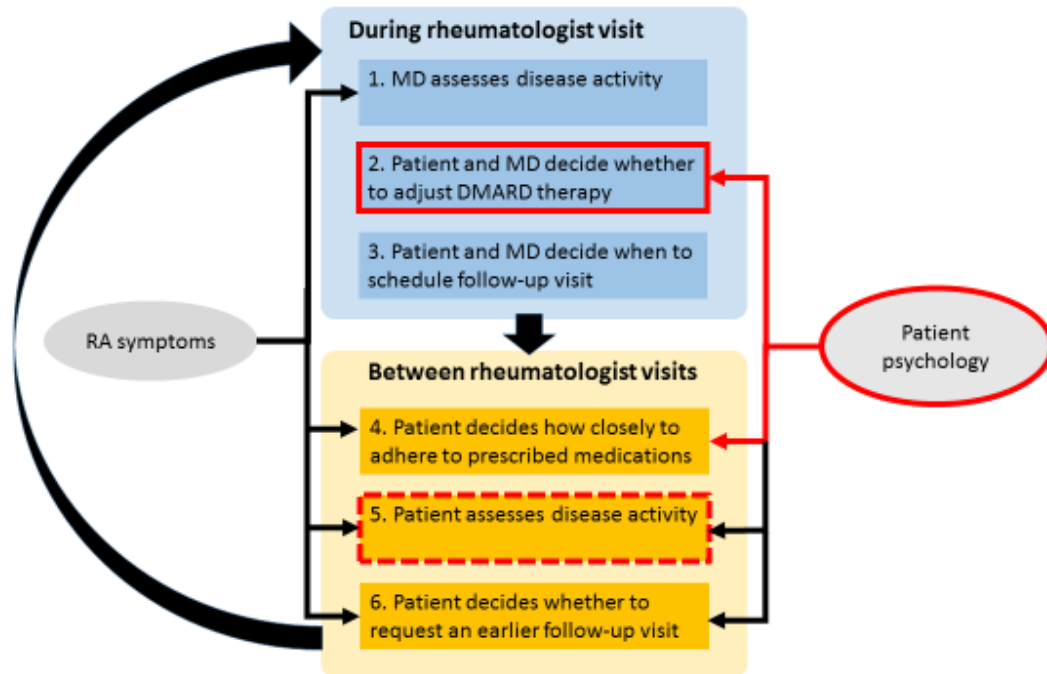


Figure 1-1. Conceptual diagram of the T2T process in clinical practice.

Rectangles are actions and ovals are states. The ordering of rectangles and the thick arrows indicate the cyclical sequence of events. Thin arrows indicate the influence of RA symptoms and patient psychology on actions. Topics covered in the dissertation are outlined in red. Step number 5 (outlined with a red dashed line), “Patient assesses disease activity” is proposed in Chapter 4 as a potentially useful part of the T2T process.

adding, or switching) DMARD therapy at least every 3 months until the patient reaches LDAS (18-22). The process of monitoring disease activity and adjusting DMARD therapy in response to MHDAS must continue indefinitely in order to minimize patients’ disease activity level, since treatments can cease to be effective and disease flares are prevalent among all RA patients, even those with LDAS (14, 15). Promptly addressing RA disease flares is critical, because even brief periods (under 3 months) of MHDAS are associated with progression of permanent joint damage, worsened short-term and long-term pain and physical functioning (12-14).

Figure 1 illustrates how the T2T approach might be implemented in a clinical practice setting where strict algorithms are not imposed on treatment decision making and scheduling of follow-up visits. Events occurring both during and between visits to the rheumatologist

contribute to the care process. During the rheumatology visit, the physician assesses the patient's disease activity with a quantitative measure, which then informs the recommended treatment regimen. The patient and physician then make a decision about which treatment regimen the patient will take, and finally a follow-up appointment is scheduled depending on the need for toxicity monitoring and further disease activity assessments. If the patient's disease activity is stabilized at a low level, follow-up appointments may be scheduled as infrequently as every 6 months, but if the patient has MHDAS, more frequent follow-up may be required until LDAS is attained (18-19). Between visits to the rheumatologist, patients take responsibility for managing their prescribed medications, reporting serious side effects of medications, and monitoring their RA symptoms. If the patient's RA symptoms worsen before their scheduled follow-up visit, they decide whether to request an earlier follow-up visit. In addition to informal symptom monitoring, formal disease activity assessment using quantitative measures could inform patients whether an earlier follow-up visit is needed.

The three decisions which play a central role in the success of the T2T strategy are 1) decisions about adjusting DMARD therapy for RA patients with moderate/high disease activity, 2) decisions about scheduling follow-up visits, and 3) patients' decisions about taking prescribed medications. These three decisions are interrelated. Decisions about adjusting therapy for RA patients with MHDAS require regular disease activity assessments by the physician, which in turn require that follow-up visits are scheduled with sufficient frequency. Therefore, delays in scheduling follow-up visits when patients develop MHDAS contribute to delays in DMARD therapy adjustment. Without formal disease activity assessment between visits, patients must rely on their subjective experience of symptoms rather than an objective measure of disease activity to decide whether to request an earlier follow-up, potentially delaying DMARD therapy

adjustment when it is needed. In addition, patients' decisions about taking prescribed medications influence the effectiveness of the chosen treatment. When patients do not adhere to the prescribed regimen, this may hinder efforts to bring MHDAS under control. Treatment decisions made during the visit and patients' medication adherence decisions are both influenced by patient psychology—patients' beliefs and emotions towards their illness and the act of taking medication treatments.

In this dissertation, it is assumed that treatment decisions in RA should be the result of shared decision making (SDM) between physicians and patients, and that SDM should be integrated into the implementation of T2T in RA. The concept of SDM in health care has been defined as an approach to treatment decision making where the patient and health care provider(s) exchange information about the benefits and risks of available treatment options and their treatment preferences, deliberate together about the options, and reach a mutual agreement on how to proceed (24). A SDM approach is important because it allows patients to participate in an informed choice of a treatment that will affect their health and well-being. In chronic conditions, because patients themselves are responsible for managing their illness in daily life and taking the prescribed treatment, a SDM approach is also beneficial for promoting patient engagement in their own care (25). Guidelines recommending the T2T approach in RA treatment acknowledge the importance of shared decision making between patients and physicians. For example, the American College of Rheumatology 2015 guidelines emphasize that the ideal treatment decision making process requires patient-physician dialogue and consideration of the patient's preferences (21). EULAR guidelines also recommend that patients and physicians collaborate in setting treatment targets as well as selecting treatment regimens (18-19).

While T2T guidelines in RA define a standard regarding the content of care (the medical goal of treatment is LDAS), the principle of SDM defines a standard for the process of care. Tension can arise between the goals of T2T and SDM when the patient prefers not to take the recommended course of treatment (such as adding or switching DMARDs in response to MHDAS). Although T2T guidelines recognize the importance of SDM, they offer little guidance on how to manage situations in which the patient is reluctant to accept the recommended treatment regimen. This dissertation assumes that in such situations, patient preferences are not ‘incorrect’, but rather are a valuable and essential input for treatment decisions. One goal of the dissertation is to provide knowledge that can be used to improve integration of SDM in the implementation of T2T.

1.3 CHALLENGES IN IMPLEMENTING TREAT-TO-TARGET IN RA

The studies presented in dissertation chapters 2 through 4 address three challenging aspects of implementing a T2T strategy for RA in a clinical practice setting where strict algorithms are not imposed on treatment decision making and scheduling of follow-up visits: 1) decisions about adjusting DMARD therapy for patients with MHDAS, 2) patient decision making about taking DMARD treatments, and 3) the lack of formal disease activity assessment between visits. This section highlights what is known about each of these aspects and critical gaps in the existing knowledge. After the context for each challenge has been described, a summary of the relevant dissertation chapter is provided.

1.3.1 Decisions about adjusting DMARD therapy for patients with MHDAS

Context

Although clinical trials have shown that systematically monitoring disease activity and adjusting DMARD therapy for RA patients with moderate to high disease activity leads to better disease outcomes compared to usual care, in US clinical practice, patients with MHDAS receive DMARD therapy adjustment only 30-50% of the time (26).

In clinical settings where treatment algorithms have been adopted in order to encourage the practice of T2T, rates of DMARD therapy adjustment for patients with MHDAS have been found to be higher than in clinical settings such as the US without such treatment algorithms in place. In the Dutch Rheumatoid Arthritis Monitoring cohort (27), DMARD therapy was adjusted at 56.8% of visits where patients had MHDAS, while at an Australian hospital 70.5% of those not in remission escalated DMARD therapy (28). In both these clinical settings, treatment protocols guided physicians to adjust DMARD therapy for patients not in remission and disease activity was monitored every 6-12 weeks at follow-up visits, yet treatment decisions still did not always adhere to the T2T strategy. Physicians have reported not adjusting DMARD therapy according to T2T treatment protocols when there were medical reasons that therapy adjustment should not be pursued (drug toxicity concerns or comorbidities) (28-29). In addition, patient-related reasons (patient preference not to intensify therapy, medication nonadherence) and physician-related reasons (physician thought the patient's disease activity score was inflated by irreversible joint damage or non-inflammatory musculoskeletal pain, physician preferred to wait longer to assess the effect of the current therapeutic regimen) were reported for not adjusting DMARD therapy as recommended by the treatment protocol (27-29). The results of these studies

suggest that similar factors might also inhibit decisions to adjust DMARD therapy for patients with MHDAS in clinical settings without T2T treatment protocols.

Most studies evaluating the implementation of T2T strategies in clinical practice have examined rates of DMARD therapy adjustment for patients with MHDAS, but not how long it takes for patients with MHDAS to receive DMARD therapy adjustment. Only one study by Suarez-Almazor et al. (30) examined time to initiation of DMARD therapy after onset of RA symptoms for patients at two rheumatology clinics in Houston, Texas. Their study found that, controlling for patient age, sex, and year of first rheumatology visit, non-White patients took longer than White patients to initiate DMARD therapy. While White patients took a median of 1 year to initiate DMARD therapy, non-White patients took a median of 7 years to initiate therapy. The results of this study suggest that race may be associated with the timing of treatment decisions for RA patients. Constantinescu et al. (31) have also found that race is associated with treatment decisions in RA. Their study found that African-American patients were more likely to be risk averse compared to White patients. These results suggest that it is worthwhile to examine whether race is associated with the timing of DMARD adjustments for patients with MHDAS as well.

Little is known about what proportion of RA patients with MHDAS in clinical practice receive DMARD therapy adjustment within 3 months as recommended by T2T guidelines, or about whether adjusting DMARD therapy within 3 months in response to MHDAS results in shorter times to LDAS. Nor is it known how time to DMARD therapy adjustment and time to LDAS vary depending on demographic and disease characteristics. Learning about these topics is important for understanding how consistent treatment decisions actually are with T2T guidelines in a clinical practice setting where fixed treatment algorithms have not been adopted,

as well as understanding which RA patients are more likely to experience delays in receiving appropriate treatment for MHDAS or delays in reaching LDAS. It will also help to elucidate the benefits of timely DMARD therapy adjustment in clinical practice.

The study presented in Chapter 2 of the dissertation addresses this gap in the knowledge about treatment decisions for RA patients with MHDAS in clinical practice.

Summary of Chapter Two

Title: “Timing of decisions to adjust disease-modifying antirheumatic drug therapy for rheumatoid arthritis patients with moderate to high disease activity and impact on time to low disease activity”

Purpose of the study: The purpose of the study presented in Chapter Two of the dissertation is to examine times to DMARD therapy adjustment and times to LDAS for RA patients with MHDAS receiving care in a clinical practice setting where fixed treatment algorithms are not employed, as well as the factors associated with delays in receiving DMARD therapy adjustment and delays in reaching LDAS.

Research questions:

1. To what extent is the timing of DMARD therapy adjustments for RA patients with MHDAS consistent with T2T guidelines in clinical practice?
2. Do patients who adjust DMARD therapy in response to MHDAS within the recommended time frame of 3 months have shorter times to LDAS?
3. Which RA patients are more likely to experience delays in receiving appropriate treatment for MHDAS or delays in reaching LDAS?

Description of the study: Using observational data from the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Research (RACER) clinical registry, survival analyses of time to DMARD therapy adjustment and time to LDAS were conducted. A competing risks regression was conducted to identify factors associated with longer times to DMARD therapy adjustment, and a Cox regression was conducted to identify factors associated with longer times to LDAS.

Main findings: 40% of RA patients with persistent MHDAS waited longer than 90 days to receive DMARD therapy adjustment. Controlling for baseline patient demographic variables, overall health, disease-specific characteristics and treatment factors, adjusting DMARD therapy in response to MHDAS within 90 days was associated with shorter times to LDAS. Elderly age, lower baseline disease activity, longer baseline duration of RA, and biologic use at baseline were significantly associated with longer times to therapy adjustment. African-American race and higher baseline disease activity were associated with longer times to LDAS.

Main implications: The results suggest that timely DMARD therapy adjustment in response to MHDAS reduces the time RA patients spend with MHDAS, and therefore that the timing of therapy adjustments in response to MHDAS is an important issue to address in the implementation of T2T. There is a need for improvement with respect to the timing of DMARD adjustments for RA patients with MHDAS. Although most patients in our study received DMARD therapy adjustment within 3 months as recommended, a significant proportion did not, exposing them to an increased risk of poorer current and future disease outcomes. The results suggest that there are three main groups of RA patients at risk for delays in DMARD therapy adjustment in response to MHDAS: those with established disease and greater amounts of disease-related joint damage (the elderly and those with longer duration of RA), those using

biologic medications, and those with less severe disease activity (moderate vs. high disease activity). Although we could not directly assess the influence of patient-related factors (preferences and medication nonadherence) or physician-related factors (disagreement with the DAS28 score, waiting to see if therapy will take effect), it seems possible that physician-related factors could account for delays in therapy adjustment for the elderly, those with longer duration of RA, and biologic users, while patient-related factors could account for delays in therapy adjustment for those with less severe disease activity. African-American patients appear to be at risk for delays in reaching LDAS, even when controlling for receipt of DMARD therapy adjustment within 90 days. Further research is needed to understand the different mechanisms leading to delays in treatment adjustment and achievement of LDAS, and how they can be addressed.

1.3.2 RA patients' decisions about taking DMARD medications

Context

When RA patients refuse the treatment regimen recommended by their physician or decide not to take prescribed medications, this presents an important challenge to the implementation of T2T. In Wabe et al.'s (28) study of T2T protocol implementation, 24.2% of patients refused recommended treatment changes, accounting for 10.5% of all treatment protocol deviations. A systematic review found that medication adherence rates among RA patients have been reported to range from 30-80%, depending on the medication and the method for measuring adherence (32). When adherence to the prescribed treatment regimen is poor, this limits the effectiveness of the treatment and results in poorer control of disease activity (33). There is a need for more

effective interventions addressing medication adherence in chronic conditions (34). Researchers are also showing increased interest in developing interventions such as decision aids to support patient decision-making about treatments in RA (35-39). However, finding the optimal approach to presenting information about the benefits and risks of treatment options to patients is difficult. For example, Li et al. found that use of their methotrexate decision aid amplified frustration with the decision process and reluctance to use the methotrexate in some patients (36). A better understanding of patient decision making is needed to address nonadherence and treatment refusal in RA.

Studies have shown that RA patients are often unwilling to escalate therapy to treat MHDAS. Wolfe and Michaud (40) surveyed 6,135 RA patients about their willingness to try new medications, finding that RA patients were often reluctant to change medications due to concerns about side effects and whether new medications would adequately control their disease. 63.8% of respondents agreed with the statement “As long as I don’t get worse I wouldn’t want to change my arthritis medications.” The study also drew attention to the discrepancy between patient-reported symptoms and satisfaction with current therapy; 77.3% of respondents reported being satisfied with their current therapy, although 71.3% of those who were satisfied with their therapy also had symptoms of MHDAS. Studies by Fraenkel and colleagues have also demonstrated how RA patients can be reluctant to accept the risks of new medications (41-43). When asked to consider taking a hypothetical medication that would effectively treat their RA symptoms, RA patients reported a low level of willingness to accept the risks of adverse events ranging from nausea to cancer (41). In another study by Fraenkel et al. (42), RA patients were asked to make a hypothetical choice between taking a new biologic medication and maintaining their current therapy. This study found that the level of impact experienced by the patient due to

the disease had a complex relationship with their treatment choice (42). While most patients experiencing low impact due to RA preferred to stay with their current therapy, not all patients experiencing high impact due to RA preferred to escalate therapy. Some patients highly impacted by RA felt they could not accept the risks of a new treatment because of the severity of their RA. This suggests that high disease activity is not enough to motivate all RA patients to accept recommended treatment changes (42-43).

Researchers have suggested that RA patients' perceptions about the risks and benefits of medications may influence their decisions about accepting recommended treatments and taking prescribed medications (32, 44). The link between patients' medication-related beliefs and decisions is consistent with social cognition theories of health behavior such as the Health Belief Model (45) and the Necessity-Concerns Framework (46), a model which was developed to describe medication adherence in patients with chronic conditions. Social cognition theories assume that people's beliefs influence how they interpret information and experiences, and how they choose to act. The decision making process is assumed to be deliberate and rational; individuals choose whether to perform health behaviors by weighing the relative benefits and risks of the options and then selecting the option which is optimal from their perspective. For example, the Necessity-Concerns Framework predicts that better medication adherence will be associated with stronger beliefs in the benefits and lower concerns about the risks of taking medications (46). This prediction has been supported in a meta-analysis of studies of patients' beliefs about medications across many chronic conditions (47).

Survey studies have demonstrated that RA patients often have ambivalent attitudes towards taking medications, with strong beliefs in the necessity of medications for controlling their disease, yet also strong concerns about the risks of RA medications (34, 48-49). Research

utilizing the Necessity-Concerns Framework suggests that patients with ambivalent attitudes towards taking medications (high necessity and high concern beliefs) are less likely to adhere to prescribed medications than patients with accepting attitudes (high necessity and low concern beliefs) (50-51). Qualitative studies of RA patient beliefs and decision-making about medications have also found that patients often have ambivalent attitudes towards taking medications, struggling to balance beliefs about the necessity of medications against their concerns (44, 52-53). RA patients in these studies were motivated to take medications to alleviate current symptoms of RA (pain, stiffness, fatigue) and to prevent future consequences of RA progression (disability and disfigurement). Improvements in their symptoms also helped patients to believe that their medications were effective and necessary. At the same time, worries about the aggressive nature of their medications and concerns about potential and experienced side effects made patients reluctant to take medications. Patients had difficulty assessing whether medications were needed or if they were as effective as expected, leading them to doubt whether they should continue taking them.

Theory in psychology and cognitive science suggests that it may be fruitful to explore the impact of emotions on RA patients' decisions about taking medications. Although many definitions of emotion and emotion-related phenomena have been proposed, here the definitions of psychology researcher Scherer are adopted to clarify the discussion (54). Scherer defines emotions as temporary episodes of intense mental and physical response to events. In contrast, attitudes (persistent beliefs towards specific objects, events or persons) and preferences (habitual positive or negative evaluations of objects) are relatively stable, long-lasting affective phenomena of milder intensity. Attitudes and preferences can be shaped by experiences and emotions over time (54). Scherer defines feelings as the subjective experience of emotion

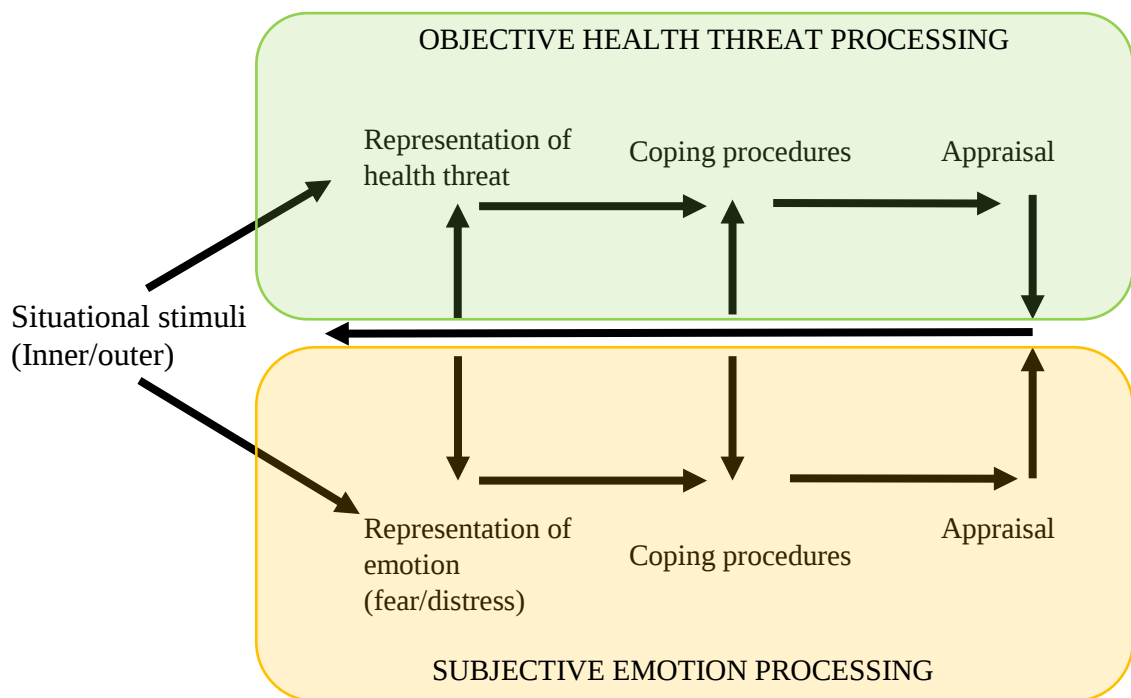


Figure 1-2. Leventhal's Self-Regulatory Model.

Adapted from Leventhal et al., "Illness cognition: using common sense to understand treatment adherence and affect cognition interactions." *Cognitive Therapy and Research* 1992;16:143-163.

episodes (54). In the field of cognitive science, Leventhal and colleagues developed a theory of health behavior, called the Self-Regulatory Model (55), which incorporates emotions into decision making. The Self-Regulatory Model proposes that feelings play an important role in patient treatment decision-making by affecting how individuals perceive health threats, choose coping strategies to respond to threats, and assess the outcomes of chosen strategies (**Figure 2**). Leventhal argued that individuals confronted with health threats respond in a process involving management of actions and feelings, which occur simultaneously and independently. The Self-Regulatory Model envisions feelings as part of a rational decision-making process, a component which can sometimes support and sometimes discourage decisions to adopt recommended or prescribed treatment. For example, the fear that accompanies symptoms that a patient associates with high blood pressure may encourage a patient to take their antihypertensive medication when they have headaches or facial flushing, while the absence of fear when they are asymptomatic

may discourage them from taking antihypertensive medications at other times (55). The patient's experience of fear may undermine the idea that hypertension is asymptomatic, that sustained treatment is necessary, and lead to intermittent nonadherence to antihypertensive medication (55).

Experimental studies support the idea that feelings can influence perceptions of health threats and subsequent health behaviors. Croyle and colleagues (56) conducted a series of experiments to investigate how people respond to ambiguous health threats. Healthy subjects were given a diagnostic test for a fictitious enzyme deficiency, which they were told was a risk factor for a pancreatic disorder, and randomly assigned a positive or negative test result. They then rated the seriousness of the enzyme deficiency on a scale from 0 (not at all serious) to 100 (life-threatening), and were asked to complete a symptom checklist. Subjects who received a positive result rated the condition as less serious than those who received a negative test result, but also reported more symptoms. This result suggested that subjects who received a positive test result were minimizing the seriousness of the condition because they felt threatened by the information (56). Other variations of the experiment manipulated the provision of information about treatment and the accuracy of the diagnostic test (75% or 95% accurate). These experiments found that subjects testing positive were less likely to minimize the seriousness of the enzyme deficiency if treatment information was provided, and more likely to request a follow-up test if they were told their test results were 95% accurate. Overall, results of the enzyme deficiency experiments suggest that people's perception and responses to health threats are affected by the need to maintain a positive view of one's health (56).

An understudied topic is the effect of emotions on RA patients' decisions about taking medications. A better understanding of how feelings in response to events and information

motivate RA patients' decisions about taking medications will contribute to the existing knowledge about how RA patients weigh the risks and benefits of treatment options.

The study presented in Chapter Three of the dissertation addresses this gap in the knowledge about how RA patients decide whether to accept recommended treatments or take prescribed treatments.

Summary of Chapter Three

Title: "Rheumatoid arthritis patients' motivations for accepting or resisting disease modifying anti-rheumatic drug treatment regimens"

Purpose of the study: The purpose of this qualitative study is to explore RA patient perspectives on internal (psychological and emotional) factors motivating their decisions about taking DMARD medications.

Research questions: The central research question is, "How do RA patients' feelings in response to events and information affect their decisions about taking DMARD medications?"

Subquestions are:

1. How do RA patients' experiences and feelings support decisions to take DMARD medications?
2. How do RA patients' experiences and feelings motivate them to resist (refuse or stop taking) DMARD medications?

Description of the study: 48 RA patients participating were interviewed about their experiences living with RA, taking DMARD medications and making decisions about DMARD medications. The interviews were transcribed, coded, and analyzed for themes relating to their internal

motivations for accepting or resisting DMARD treatment regimens, using a narrative analysis approach.

Main findings: Combining with their beliefs and attitudes, patients' feelings in response to information and experiences motivated decisions to accept or resist DMARD medications. They reported being motivated by feelings towards the benefits and risks of medications, as well as feelings related to their identity as an ill person, the act of taking medication, and their experience of the decision process. Patients reported simultaneously experiencing motivations to accept and resist medications, creating ambivalence towards taking medications. For patients' motivations to accept DMARD treatment regimens, two themes emerged: 1) *desire to return to a "normal" life* and 2) *fear of future disability due to RA alleviating current symptoms*. For patients' motivations to resist DMARD treatment regimens, five themes emerged: 1) *fear of medications*, 2) *maintaining control over health*, 3) *denial of sick identity*, 4) *disappointment with treatment*, and 5) *feeling overwhelmed by the cognitive burden of deciding*.

Main implications: This study has important implications for the practice of SDM in treatment decisions for RA.

One implication is that effective communication about the benefits and risks of treatment requires more than just the exchange of information, but also needs to take into account patients' feelings about illness, treatment and the decision process. Most guides to SDM, patient decision aids, and patient-physician communication interventions focus on the exchange of information, but do not specifically encourage addressing the emotional aspects of decisions (57-62). An underlying assumption of many of these interventions is that if the patient receives the right information, they will be prepared to engage in shared decision making about treatments. Our findings in this study suggest that RA patients' feelings play an important role in their decisions

about taking medications. Sometimes, being confronted with threatening information or events can lead patients to avoid information, deny the need for treatment, or postpone important decisions. Patient-physician communication strategies, educational materials and patient decision aids that address or account for patients' feelings may help to provide better support for patients facing difficult decisions involving threatening outcomes and information. For example, eliciting a patient's emotional reactions to information presented in a discussion may help a physician understand and respond to the patient's concerns, and in the long run, aid in building a trusting patient-physician relationship.

Another implication is that physician communication strategies that address patients' negative emotional reactions to illness and treatments may help patients resolve ambivalence towards taking DMARDs and gain confidence in navigating treatment decisions. Although addressing patients' negative emotions cannot guarantee that all patients will always decide to accept treatment with DMARDs, it may help patients to become more receptive towards physician treatment recommendations. For example, instead of dismissing a patient's resistance to taking medications as irrational, a physician can learn about the patients' feelings towards their illness (anger, powerlessness) and help them to overcome those feelings and see their illness and medication taking in a new light.

Further research is needed to determine how patient feelings can be better addressed in patient-physician dialogues about treatment decisions, patient decision aids, and educational materials.

1.3.3 Challenges in monitoring disease activity in RA

Context

Regular disease activity monitoring is an important component of implementing T2T in RA, since delays in detecting MHDAS contribute to delays in adjusting therapy for patients with MHDAS. T2T guidelines recommend monitoring disease activity with quantitative measures every 1-3 months for RA patients with MHDAS, and every 3-6 months for RA patients with LDAS (18-19). However, this is challenging to implement in clinical practice, due to limited access to rheumatologists, resource costs, and restrictions on time during appointments (63-67). In clinical practice settings where fixed treatment algorithms have not been adopted, RA disease activity is typically monitored during patients' follow-up visits, but not between visits. Follow-up visits are typically scheduled as needed depending on the patient's condition and current medications, rather than at regular intervals. Many RA patients receive an insufficient frequency of disease monitoring due to infrequent visits (66, 68). Furthermore, disease activity may not always be assessed using quantitative disease activity measures. Adhikesavan et al. (69) found that 31% of RA patients in a Pennsylvania health care system did not receive disease activity assessment with quantitative measures in a 1-year period. In a survey of 550 rheumatologists from around the world, 45% reported conducting formal joint counts in less than a quarter of RA patient visits (70).

In addition to ensuring adequate disease activity monitoring at clinic visits, addressing the lack of disease activity monitoring with quantitative measures between clinic visits is important in clinical settings where visits are scheduled as needed rather than at regular intervals. RA patients whose disease activity has stabilized at a low level may have follow-up visits

scheduled less frequently. However, these patients are also at risk for disease flares. Patient-reported joint counts (assessments of tenderness and swelling in joints) are a potential means to detect MHDAS between visits and inform patients and their physicians of the need to schedule earlier follow-up visits.

Joint counts conducted by physicians are considered to be a central component of disease activity measurement in RA (70-71). Physician-reported joint counts have been incorporated into several disease activity measures recommended by the American College of Rheumatology (ACR) for disease activity monitoring in RA, including the DAS28 measures (23). Studies have demonstrated moderate correlation between patient and physician tender and swollen joint counts (71-72). Using data reported in studies comparing patient and physician joint assessments, a meta-analysis by Barton et al. (71) estimated summary Spearman correlation coefficients for patient and physician tender joint counts (0.60; 95% CI: [0.30, 0.90]) and swollen joint counts (0.54 [0.35, 0.73]). Cheung et al. (72) conducted a systematic review of studies examining the inter- and intra-observer reliability of joint counts performed by patients and healthcare providers. Their review found that inter-observer reliability of patient and physician tender joint counts was excellent (estimated summary intraclass correlation coefficient (ICC) [95% CI]: 0.82 [0.73, 0.89]), and that inter-observer reliability for swollen joints was moderate (summary ICC [95% CI]: 0.44 [0.24, 0.60]). Patient-physician inter-observer reliability of joint counts was comparable to inter-observer reliability between physicians and other healthcare providers for tender joint counts (summary ICC [95% CI]: 0.86 [0.81, 0.89]) and swollen joint counts (summary ICC [95% CI]: 0.67 [0.06, 0.92]), suggesting that patient joint counts may be useful in assessing disease activity.

Although previous studies have examined the correlation between patient and physician joint counts, it is not known how well patient and physician joint counts agree in the detection of MHDAS. Furthermore, it is not known whether patient-physician joint count agreement varies with patient and disease characteristics, or across different types of joint count items. Investigation of these topics is important for assessing the usefulness of patient joint counts for monitoring RA disease activity between clinic visits. Examining the factors associated with patient-physician joint count disagreements will also help identify challenging aspects of performing joint counts, where patients and physicians may benefit from training to improve the accuracy of checking for tenderness and swelling in joints.

The study presented in Chapter Four of the dissertation addresses this gap in the knowledge about the agreement of patient and physician joint counts in the detection of MHDAS.

Summary of Chapter Four

Title: “Discrepancies between physician and rheumatoid arthritis patient assessments of tenderness and swelling in joints”

Purpose of the study: The purpose of this study is to assess the usefulness of patient joint counts for detecting MHDAS by comparing them with physician joint counts, and to identify factors associated with poorer agreement between patient and physician joint counts.

Research questions:

1. How closely do patient and physician joint counts agree in total number of tender and swollen joints (ICC) and in the detection of MHDAS (sensitivity, specificity, and positive predictive value of patient joint count compared to the physician joint count)?

2. Do patient and physician joint counts exhibit poorer agreement on the presence of tenderness or swelling in joints for certain types of items (such as swelling items or small hand joint items) or according to other factors (patient demographic, health, and disease characteristics; medication use)?
3. Do patient and physician joint counts exhibit poorer agreement on the presence of MHDAS according to patient demographic, health, and disease characteristics, or medication use?

Description of the study: This study used data from the RACER registry from visits where both patients and physicians had completed 28-joint counts (assessments of tenderness and swelling in 28 joints). The patient and physician joint counts were used to calculate Clinical Disease Activity Index (CDAI) scores, which were then used to categorize patients as being in MHDAS or LDAS. The sensitivity, specificity, and positive predictive value of patient joint counts compared to physician joint counts for detecting MHDAS was calculated. Using a two-stage logistic regression procedure to account for agreement due to chance, we assessed the association of the factors described above with patient-physician agreement on individual joint count items and on the detection of MHDAS.

Main findings: The ICC [95% CI] for absolute agreement between patient and physician joint counts was higher for tender (0.46 [0.43, 0.49]) than for swollen joints (0.36 [0.32, 0.40]). Patient joint counts had a sensitivity of 86.8%, specificity of 74.6%, and positive predictive value of 74.5% relative to physician joint counts for detection of MHDAS according to the CDAI measure. Patients and physicians were more likely to disagree on joint count items when the patient had a longer duration of RA, had augmented/switched DMARD therapy at the previous

visit, and for swelling joint and small joint items. No covariates were found to be significantly associated with patient-physician disagreement on the presence of MHDAS.

Main implications: Patients and physicians in our study had lower levels of agreement on total swollen and total tender joint counts compared to previous studies. Yet the sensitivity, specificity and positive predictive value of patient joint counts compared to physician joint counts for detecting MHDAS was relatively good. Furthermore, the regression analysis showed that agreement on detection of MHDAS did not systematically vary according to patient demographic variables, general health status, disease characteristics, and medication use. This suggests that even without perfect agreement on joint count items between patients and physicians, patient joint counts might be useful for detecting MHDAS between visits. Levy et al. (73) showed that providing training on how to distinguish between a chronically enlarged joint and a swollen joint can improve the agreement between patient and physician joint counts. It is possible that offering patients training on distinguishing tenderness and swelling due to RA inflammation and other conditions may further improve the usefulness of patient joint counts for detecting MHDAS.

On individual joint count items, patients-physician disagreement was associated with a longer duration of RA, augmenting/switching DMARD therapy at the previous visit, swelling joint items and small joint items. These may indicate aspects of joint counts which may make it more challenging for patients (and also physicians) to achieve accuracy in their assessments. Previous studies have also found that patient-physician agreement is poorer for swelling joint items compared to tenderness joint items (71-72). It may also be more difficult for patients and physicians to assess tenderness and swelling in the smaller hand joints, and when the patient has joint damage and deformities resulting for long-term disease progression. Assessments of

tenderness and swelling in joints at a visit following a DMARD therapy adjustment may be accompanied by expectations that bias the results. Further research is needed to understand the mechanisms producing these associations, and to explore approaches to training that can improve the accuracy of joint counts performed by patients as well as physicians.

Overall, our results suggest that a patient joint count performed at home in between visits might be useful for detecting MHDAS and alerting the patient and physician of the need to schedule a follow-up visit. Patient joint counts can be combined with a patient global disease activity rating and a laboratory test of inflammatory markers (C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)) to calculate a patient-derived Disease Activity Score 28 joint (DAS28), a measure recommended by the ACR for quantifying disease severity in RA. DAS28 can be readily calculated by patients at online websites such as “DAS28 - Home of the Disease activity score” (<http://www.das-score.nl/das28/en/>) (74), smartphone apps, or by using a simple scientific calculator or spreadsheet program such as Microsoft Excel. Early detection of MHDAS and scheduling of follow-up visits in response could create opportunities to consider adjusting DMARD therapy if necessary and potentially reduce the time it takes for MHDAS to be addressed.

1.4 SUMMARY

Implementing T2T in RA is a complex process that requires increased systematization of certain aspects of care, such as disease monitoring, but also attention to the expectations and needs of patients, who ultimately decide whether to accept or reject treatments offered by physicians.

Using a combination of quantitative and qualitative methods to study different aspects of the treatment decision process for RA patients has yielded insights into care patterns, patient perspectives, and potential solutions that can inform future efforts to improve implementation of T2T in RA, and lead to better quality of care and health outcomes for RA patients.

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**2.0 TIMING OF DECISIONS TO ADJUST DISEASE-MODIFYING
ANTIRHEUMATIC DRUG THERAPY FOR RHEUMATOID ARTHRITIS PATIENTS
WITH MODERATE TO HIGH DISEASE ACTIVITY AND IMPACT ON TIME TO
LOW DISEASE ACTIVITY**

ABSTRACT

Objective: Current guidelines recommend that rheumatoid arthritis (RA) patients with moderate to high disease activity (MHDAS) adjust disease-modifying antirheumatic drug (DMARD) therapy at least every 3 months until reaching low disease activity (LDAS) or remission. Our goal was to learn how quickly RA patients with MHDAS adjust DMARD therapy in clinical practice, and whether those who adjust DMARDs within 90 days in response to MHDAS reach LDAS sooner.

Methods: Using data from the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry, we conducted a competing risks regression on time to DMARD therapy adjustment and a Cox regression on time to LDAS for RA patients with MHDAS.

Results: We identified 558 eligible subjects with MHDAS and subsequent follow-up for a total of 943.5 patient-years of observation. 60% of patients with persistent MHDAS adjusted

DMARDs within 90 days. Among all subjects, median time to DMARD adjustment was 168 days, and median time to LDAS was 301 days.

Being elderly (subdistribution hazard ratio (SHR)=0.62, $p=0.02$), lower baseline disease activity (SHR=0.70, $p<0.01$), longer duration of RA (SHR=0.99, $p<0.01$), and biologic use (SHR=0.70, $p<0.01$) were significantly associated with longer times to therapy adjustment. African-American race (hazard ratio (HR)=0.63, $p=0.01$), higher baseline disease activity (HR=0.72, $p<0.01$), and not adjusting DMARD therapy within 90 days (HR=0.76, $p=0.01$) were associated with longer times to LDAS.

Conclusion: We found that adjusting DMARDs within 90 days was associated with shorter times to LDAS, but that 40% of RA patients with persistent MHDAS wait more than 90 days to adjust DMARDs. Our results indicate the need for interventions addressing the timeliness of DMARD therapy adjustments for RA patients with MHDAS.

2.1 INTRODUCTION

Current evidence-based guidelines for the treatment of rheumatoid arthritis (RA) recommend treating to the target (T2T) of low disease activity or remission (LDAS). Specifically, the guidelines recommend that patients with moderate to high disease activity (MHDAS) have disease-modifying antirheumatic drug (DMARD) therapy adjusted at least every 3 months until patients reach LDAS (1-3). Clinical trials have shown that employing a T2T strategy leads to lower disease activity and reduction of progressive joint damage, compared to routine care (4). Furthermore, observational studies have demonstrated that improvements in these disease-

specific outcomes are associated with reduced pain and improved physical function, health-related quality of life, and work productivity (4-6). This evidence supporting the adoption of T2T strategies in clinical practice suggests that minimizing the amount of time RA patients spend with MHDAS is beneficial. Even brief periods of MHDAS (< 3 months) are associated with progression of joint damage and worsened short-term and long-term pain and functional deterioration (7-9). It is important to address delays in therapy adjustment for RA patients with MHDAS, which may increase the negative impact of the disease on current and future symptoms and quality of life.

Understanding the timing of decisions to adjust therapy for RA patients with MHDAS is critical because it affects their disease outcomes and quality of life (4-9). It is also important to understand whether adjusting therapy within the recommended timeframe (3 months) actually helps patients to reach LDAS sooner in clinical practice. To our knowledge, no other studies have examined how long it takes for RA patients with MHDAS to receive DMARD therapy adjustment, or the impact of timely DMARD adjustment on times to LDAS. Although previous studies have evaluated implementation of the treat to target approach in trials and in clinical practice, these studies have only reported the prevalence of therapy adjustment in response to MHDAS, not the timing (10-15). Observational studies of clinical practice in the US have reported rates of therapy adjustment for patients with MHDAS ranging from 43-85% (12-13). The variation in these studies' results may originate from differences in the time frame used to evaluate the occurrence of therapy adjustment. Because the studies did not provide information on times to DMARD adjustment, we do not know what percentage of therapy adjustments occurred within 3 months of the patient developing MHDAS. Previous studies report that patient preference, medication nonadherence, and physician disagreement with the disease activity index

were all reasons for not adjusting therapy in spite of the patient having MHDAS (10-11, 15), however no studies have identified demographic, overall health- and disease-related characteristics of patients at greater risk for not adjusting therapy.

We wanted to find out how quickly RA patients with MHDAS receive DMARD therapy adjustment in a clinical setting where predefined treatment protocols are not employed, and to what extent treatment for these patients is consistent with T2T recommendations about the timing of therapy adjustments. We also wanted to identify characteristics of patients at greater risk for not receiving timely therapy adjustment, and to see whether patients who take longer to adjust therapy also spend more time with MHDAS. To examine these questions, we conducted survival analyses of times to therapy adjustment and LDAS for RA patients using data from an observational clinical registry.

2.2 PATIENTS AND METHODS

2.2.1 Data source

Data came from the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry. RACER, which began enrolling subjects in 2010, collects data for over 1000 RA patients seen at 4 University of Pittsburgh Medical Center (UPMC) rheumatology clinics (representing about 28% of all RA patients seen within the UPMC health system). Data on subjects' disease activity status, RA-related medications, and patient-reported outcomes (pain, functioning, and health-related quality of life) are collected at every clinic visit. On average,

RACER subjects have follow-up visits every 4.6 months. A list of current and new RA-related medications and dosages is verified by study coordinators at every visit in consultation with the patient, the electronic medical record, and the physician, and the information is entered via tablet into the RACER database. Medications documented include DMARDs (biologic and nonbiologic DMARDs) as well as corticosteroids. Subjects gave informed consent to participate in the registry and the study was approved by the University of Pittsburgh Institutional Review Board.

2.2.2 Study Population

We selected patients who had MHDAS according to the Disease Activity Score 28-joint with C-reactive protein (DAS28-CRP >3.2) (16) and medication data available at a baseline visit, and at least 1 subsequent follow-up visit with a DAS28-CRP measurement and medication data available.

2.2.3 Dependent variables

There were two dependent variables of interest: time to DMARD therapy adjustment in response to MHDAS, and time to LDAS (DAS28-CRP ≤ 3.2), measured in days from the date of the baseline visit. DMARD therapy adjustment was defined as adding, switching, or increasing the dose of DMARD medications (not including corticosteroids).

2.2.4 Independent variables

In all regression analyses, we controlled for factors that could impact the disease trajectory and decision making about treatment. Covariates used in the analyses included indicators for demographic characteristics including male gender and African-American race. African-American race was included because in previous analyses we have found a negative association with decisions to adjust DMARDs in response to MHDAS. Constantinescu et al. have also shown that African-American race is associated with increased perceptions of medication risk and lower perceptions of medication benefit in RA patients (17). We included an indicator for elderly age (age ≥ 75) and a comorbidities covariate (Charlson group) because patients with elderly age and multiple comorbidities may have more restricted RA treatment options due to contraindications. The comorbidities covariate Charlson group was defined as a categorical variable equal to 1 if the Deyo-Charlson index was 0-1; 2 if the Deyo-Charlson index equaled 2 or 3; and 3 if the Deyo-Charlson index ≥ 4 . Missing Deyo-Charlson index was imputed by carrying forward the most recent Deyo-Charlson value where possible. We included baseline RA disease severity (DAS28-CRP) and baseline RA disease duration (years). RA patients with higher baseline disease severity and shorter baseline disease duration may be treated more aggressively and adjust therapy sooner than patients with lower baseline disease severity and longer baseline disease duration. RA patients with increased baseline disease severity and duration may take longer to reach LDAS. We included baseline Short Form 12 mental and physical component summary scores (SF12-MCS and SF12-PCS), which document patient-reported mental and physical quality of life. The SF12-MCS and SF12-PCS may capture aspects of disease severity not reflected in the DAS28-CRP, which may affect decisions to adjust therapy

and time to LDAS. We also included baseline use of a biologic DMARD, because in previous analyses we found that biologic use was associated with lower likelihood of DMARD adjustment in response to MHDAS.

The analysis of time to LDAS also included an indicator for adjusting DMARD therapy within 90 days in response to MHDAS (equal to 1 if therapy was adjusted in 90 days or less and the subject had not yet reached LDAS when therapy was adjusted, 0 otherwise). We used a 90 day threshold to operationalize the recommendation that DMARD therapy should be adjusted at least every 3 months until the patient reaches LDAS. This allowed us to investigate whether timely therapy adjustment helps patients to reach LDAS sooner, controlling for other covariates.

2.2.5 Statistical Analyses

We performed descriptive analyses of the baseline characteristics of subjects included in regression analyses: age, gender, race, number of comorbidities, duration of RA, mental and physical quality of life (SF12-MCS and PCS), and Multidimensional Health Assessment Questionnaire (MDHAQ) physical functioning component scores, and use of medications (biologics, corticosteroids, and nonbiologic DMARDs). We also described the distribution of time to DMARD adjustment and time to LDAS, percentage of patients who adjusted DMARDs within 90 days in response to MHDAS, and types of DMARD adjustments made.

We conducted survival analyses on time to DMARD therapy adjustment and time to LDAS for RACER subjects with MHDAS. First, competing risks regression using Fine and Gray's proportional subhazards model (18) was used to assess the impact of covariates on time to DMARD adjustment in response to MHDAS. The competing risks approach is appropriate

when subjects are at risk for experiencing a secondary competing event which changes their probability of experiencing the main event of interest (19). Fine and Gray's competing risks regression models the influence of covariates on the subdistribution hazard function, or the instantaneous rate of the event of interest among those who have survived to time t , after accounting for those who experienced competing events. The regression model estimates subdistribution hazard ratios (SHR), which are interpreted as the ratio of the subhazard rates associated with two different levels of a covariate. A SHR greater than 1 indicates that the event of interest occurs at a faster rate for higher levels of the covariate, and that all else being equal, a subject with a higher level of the covariate would experience the event sooner. We defined DMARD adjustment in response to MHDAS as the main event of interest and reaching LDAS before therapy adjustment as a competing event. Follow-up began when the subject was first known to have MHDAS (DAS28-CRP>3.2) and ended with one of three outcomes: 1) DMARD therapy adjustment before reaching LDAS (DAS28-CRP≤3.2), 2) reaching LDAS before adjusting DMARD therapy, or 3) loss to follow-up (due to no further clinic visits observed, death, or withdrawal from the registry).

Second, a Cox proportional hazards regression was used to assess the impact of covariates on time to LDAS. Cox regression models the influence of covariates on the hazard function, or the instantaneous rate of the event of interest among those who have survived to time t . The Cox regression estimates hazard ratios (HR), which have an interpretation similar to that of the SHR described above. Here, the event of interest was reaching LDAS. Follow-up began when the subject was first known to have MHDAS and ended when 1) the subject reached LDAS, or 2) when the subject was lost to follow-up (due to no further clinic visits observed, death, or withdrawal from the registry).

For all regression analyses, we included subjects adjusting therapy at the baseline visit by resetting their survival time to 1 day.

Sensitivity analyses were conducted to check whether the results changed when adjustment of corticosteroids was included in the definition of DMARD adjustment. Use of corticosteroids for the treatment of RA varies among different communities of rheumatologists around the world; while in the US corticosteroids are not generally considered a long-term treatment solution, in other practice communities corticosteroids may be used together with other DMARD medications to control RA disease activity.

2.3 RESULTS

We identified 558 out of 1041 RACER registry subjects with DAS28-CRP>3.2, follow-up disease activity measurement, and data on medication use, representing a total of 943.5 patient-years of observation. The average follow-up time for each subject was 617 days. The clinic visit dates for these subjects ranged from February 2010 to November 2013. **Table 1** shows baseline characteristics of subjects.

543 subjects had complete data on all covariates and were included in regression analyses. A flowchart (**Figure 1**) illustrates inclusion/exclusion of subjects for the regression analyses.

The status of the 558 subjects (MHDAS, DMARD adjustment in response to MHDAS, or LDAS) was plotted over time in **Figure 2**, while a survival plot of time to LDAS is shown in **Figure 3**. By the end of follow-up for the 558 subjects, 60.8% of subjects (n=339) adjusted

DMARD therapy in response to MHDAS, 31.7% of subjects (n=177) reached LDAS before adjusting DMARDs, and 7.5% (n=42) remained with MHDAS. Among the 42 subjects lost to follow-up before adjusting DMARD therapy in response to MHDAS or reaching LDAS, 40 did not have further follow-up visits documented, 1 died (after 158 days of follow-up), and 1 withdrew from the registry (after 364 days of follow-up). The median time that subjects awaited DMARD adjustment in response to MHDAS (n=558, 339 events) was 168 days. The median time to LDAS (n=558, 398 events) was 301 days.

Table 2 shows the distribution of time spent awaiting DMARD adjustment. Among all 558 subjects with MHDAS, 56.7% waited more than 90 days to adjust DMARD therapy. Among 403 subjects with persistent MHDAS (i.e. the patient does not reach LDAS before therapy adjustment), 40% waited more than 90 days to adjust DMARD therapy.

Among all DMARD adjustments documented (see **Table 3**), initiating new DMARDs (66%) was more common than increasing the dose of existing DMARDs (34%). Initiating new DMARDs was relatively more common among DMARD adjustments taking place within 90 days of the baseline visit (71%) than among adjustments taking place more than 90 days later (51%), while the reverse trend was seen for dose increases.

The results of regression analyses (n=543) are shown in **Table 4**. For the competing risks regression, the following covariates were significantly associated with longer times to DMARD adjustment in response to MHDAS, taking into account the competing risk of reaching LDAS before DMARDs were adjusted (subdistribution hazard ratio (SHR), p-value): being elderly (SHR=0.63, p=0.03), having lower disease activity at baseline (SHR=0.71, p<0.01), having a longer baseline RA disease duration (SHR=0.98, p<0.01), and use of a biologic DMARD at baseline (SHR=0.71, p<0.01). Sex, African-American race, number of comorbidities, and SF12-

MCS and SF12-PCS at baseline were not significantly associated with time to DMARD adjustment in response to MHDAS. The estimated cumulative incidence function of DMARD adjustment in response to MHDAS is shown in **Figure 4**.

For the Cox regression of time to LDAS, the following covariates were significantly associated with longer times to LDAS (hazard ratio (HR), p-value): being African-American (HR=0.63, p=0.01), having higher disease activity at baseline (HR=0.75, p<0.01), and not adjusting therapy within 90 days (HR=0.76, p=0.01). In addition, higher baseline SF12-MCS (HR=1.01, p=0.02) and higher baseline SF12-PCS (HR=1.01, p=0.02) were significantly associated with shorter times to LDAS. Elderly age, sex, number of comorbidities, disease duration at baseline, and use of biologic at baseline were not significantly associated with time to LDAS.

2.3.1 Sensitivity analyses

Even when we included corticosteroids in the definition of DMARDs, the results of our regressions remained robust for the most part (see **Table 5**). For the competing risks analysis of time to DMARD adjustment, including use of corticosteroids in the definition of DMARD adjustment increased the number of events from 339 to 390, but did not change results for any covariates except for elderly age, which was no longer significantly associated with longer times to DMARD adjustment in response to MHDAS.

Inclusion of corticosteroid use in the definition of DMARD adjustment slightly increased the proportion of subjects that adjusted therapy within 90 days from 43% (n=242) to 48%

(n=267), and the Cox regression results for the analysis of time to LDAS were robust to this change.

2.4 DISCUSSION

Current treatment guidelines recommend that RA patients with MHDAS have DMARD therapy adjusted at least every 3 months until LDAS is achieved. Although some studies have reported the frequency of therapy adjustment for RA patients with MHDAS in clinical practice, (12-13), to our knowledge, there have been no other studies examining times to DMARD adjustment and LDAS for RA patients with MHDAS. Our study found that 40% of subjects with persistent MHDAS waited more than 90 days for DMARD therapy adjustment, while 32.3% waited more than 180 days to adjust therapy. We found that 50% of all subjects with MHDAS took more than 301 days to reach LDAS.

We found that being elderly, having lower disease activity at baseline, having longer disease duration and use of biologics were associated with longer times to DMARD adjustment in response to MHDAS. However, a sensitivity analysis showed that elderly age was no longer associated with longer times to DMARD adjustment when corticosteroids were included in the definition of DMARDs. The effect may disappear when including corticosteroids because elderly patients frequently receive treatment with steroids (instead of other DMARD medications) in response to MHDAS. RA patients with moderate disease activity may take longer than patients with more severe disease activity to receive therapy adjustment because patients with less severe disease activity and their physicians may perceive therapy adjustment to be less urgent.

Alternatively, if patients and physicians are unwilling to adjust therapy, this may influence their assessment of disease activity, resulting in a lower DAS28-CRP score. Disease severity may also affect how soon the patient returns to the clinic for a follow-up visit, potentially accelerating DMARD adjustment for patients who return sooner because of more severe disease. Patient or physician willingness to tolerate MHDAS might contribute to delays in receiving timely DMARD adjustment.

RA patients with longer disease duration may have tried more medications and have less therapeutic options to choose from, and therefore it may be more difficult for them to switch medications. Kievit et al. (20) found that disease duration was one of the least influential factors in rheumatologists' decisions about escalating therapy, when presented with a hypothetical treatment scenario. However, longer disease duration may be associated with more joint damage, which may affect how a rheumatologist interprets a patient's symptoms, DAS28-CRP score and recommends treatment. Tymms et al. (21) found that in 19.7% of cases where DMARD therapy was not adjusted in spite of the patient having MHDAS, rheumatologists indicated "irreversible joint damage" as a barrier to optimal disease control. RA patients with MHDAS who are using biologics may take longer to switch off because the process of getting payer approval for a new biologic can be burdensome, or because of waiting to see if the medication will take effect. The latter mechanism is also supported by Tymms et al. (21), where rheumatologists reported not escalating DMARD therapy when patients had active disease due to "insufficient time to assess response to recently initiated DMARDs" in 9.2 % of cases.

In contrast with our study, which relied primarily on observational data to examine patterns in treatment decisions, other studies have surveyed rheumatologists in order to better understand factors influencing treatment decisions. Kievit et al. (20) surveyed rheumatologists

using a hypothetical treatment scenario involving a decision about switching biologic treatment for an RA patient to learn which attributes were most influential in their decision-making. They found that DAS score, patient age, and bone erosions were the most influential factors in respondents' decisions. Tymms et al. (21) used the electronic medical record to ask rheumatologists to indicate reasons that RA patients failed to achieve LDAS. Their study found that at visits where patients had MHDAS but DMARD therapy was not modified, the most common perceived barriers to disease control recorded were irreversible joint damage (19.7%), patient preference not to escalate therapy or nonadherence (14.7%), rheumatologist preference not to escalate due to disagreement with the DAS score (9.9%), non-inflammatory musculoskeletal pain (9.2%), and insufficient time to assess response to recently initiated DMARD (9.2%). Studies of RA patient preferences for treatment have also shown that many RA patients may prefer not to treat their disease aggressively, and that their perceptions and preferences can result in more conservative treatment decisions. In a survey of 6,135 RA patients, Wolfe et al. (22) found that 64% would not want to change therapy unless they got worse, and 68% were worried that a new treatment would not be as effective as their current treatment. Fraenkel et al. (23) found that high disease activity alone was not enough to motivate RA patients to escalate therapy, when unaccompanied by perceptions of high physical and emotional impact of their disease. Wolfe et al. and Fraenkel et al. (23, 24) have found that concerns about the risks of medications are common among RA patients. Unfortunately, we were unable to assess the impact of patient or physician perceptions and preferences on time to DMARD adjustment as we lacked data on these which could be operationalized as a covariate.

We found that African-American race, higher baseline disease activity, lower SF12-MCS, lower SF12-PCS, and not adjusting DMARDs within 90 days were significantly

associated with longer times to LDAS. African-American patients may take longer than other patients to reach LDAS due to poorer access to health care providers and treatments, or possibly poorer medication adherence. A study by Constantinescu et al. (17) about the effects of race on treatment decision-making by RA patients found that African-American patients were more likely to be risk averse compared to White patients, and assigned greater importance to the risks of medications, while Whites focused more on the benefits of medications. Suarez-Almazor et al. (25) also found that non-White newly diagnosed RA patients took longer than White RA patients to initiate DMARDs after onset of symptoms. This suggests that race may have complex effects on treatment decision-making and subsequent outcomes for RA patients. Those with more severe baseline disease activity may take longer to reach LDAS because their RA is more resistant to treatment. Similarly, patients with lower self-reported mental and physical functioning according to the SF12 at baseline may take longer to reach LDAS because of having more severe disease at baseline that is more resistant to treatment. The SF12-MCS and SF12-PCS may capture additional aspects of disease severity not accounted for by the DAS28-CRP. Controlling for other covariates, adjusting DMARDs within 90 days in response to MHDAS was associated with a higher likelihood of reaching LDAS during follow-up. This provides further evidence from clinical practice that timing of DMARD adjustments affects how soon RA patients achieve LDAS, and indicates that attention to timing is important in implementing treat-to-target guidelines in RA.

Our analysis has some limitations worth noting. First, certain aspects of our data constrained our ability to examine our questions of interest. We lacked data to assess the impact of patient preferences on the timing of treatment decisions. Although we were not able to incorporate patient preferences into our analyses, other researchers with access to such

information in an observational setting might consider doing so in future analyses. We could not account for specific medical conditions that might make it more complicated for an RA patient to receive DMARD therapy adjustment even if they had MHDAS. Although we did attempt to account for this by controlling for number of comorbidities in the Cox regressions, the Deyo-Charlson comorbidity index may not perfectly capture cases where DMARD escalation is contraindicated. Future studies should find some way to capture valid medical circumstances that might be barriers to DMARD therapy adjustment, such as comorbid conditions, medical procedures, or contraindications with other non-RA medications. The nature of administering biologic medications for RA made capturing DMARD ‘intensification’ from medication records complicated for these medications. If biologics are not effective or lose efficacy, they might not be immediately switched due to administrative (payer approval) and safety reasons. For example, switching from one biologic to another may take a few months while approval for insurance coverage is obtained; consequently, the switch would not appear in our data as a DMARD adjustment until the very end when the new biologic was added. Finally, for 63% of the eligible subjects, follow-up began at the first RACER visit; thus, it is not known whether they had MHDAS at previous visits as well. If they did have MHDAS at previous visits which we were unable to observe, this would lead to an underestimate of their time to therapy adjustment and time to LDAS, and possibly bias our regression results. However, there is no reason to expect systematic differences between subjects who had MHDAS at their first RACER visit and subjects who were documented with MHDAS at later visits, since recruitment for RACER was not based on any clinical characteristics other than having a diagnosis of RA. Our study’s estimate of the median time to therapy adjustment and time to LDAS may be considered conservative.

The advantage of our study design, compared to other studies that have used surveys to learn what patients and rheumatologists consider to be influential factors in treatment decisions, is that we relied on observational data of actual treatment patterns to draw our conclusions. Our inclusion of the time dimension in analyzing treatment decisions and outcomes also contributes a new perspective to research on the implementation of the treat-to-target approach in rheumatoid arthritis.

The results of our survival analyses suggest that among RA patients with MHDAS, the elderly, those with less severe disease, those with longer duration of RA, and those who use biologics and may take longer to have DMARD therapy adjusted. Our results also suggest that among RA patients with MHDAS, African-Americans, those with more severe disease, and those who do not adjust DMARD therapy within 90 days may take longer to reach low disease activity/remission. Further investigation is needed to understand how and why biologic use may be associated with delays to DMARD adjustment for RA patients with MHDAS, as well as how race might be related to disease outcomes for RA patients.

2.5 TABLES

Table 2-1. Baseline characteristics of subjects (n=558).

Age in years, mean (sd)	59.8 (12.9)
Age ≥ 75 , %	11.1%
Female sex, %	79.4%
African-American, %	11.5%
Charlson group 1, %*	58.5% N=557
Charlson group 2, %*	28.9% N=557
Charlson group 3, %*	12.6% N=557
DAS28-CRP, mean (sd)	4.3 (1.0)
Duration of RA, mean (sd)	14.7 years (13.2)
SF12 mental component score (0-100), mean (sd)	46.8 (11.5) N=544
SF12 physical component score (0-100), mean (sd)	35.0 (10.0) N=544
MDHAQ physical functioning component (0-10), mean (sd)	2.7 (1.8) N=544
On biologic, %	38.9%
On corticosteroids, %	60.4%
On nonbiologic DMARDs, %	80.5%
On biologic monotherapy, %	12.7%
On any DMARD (biologic or non-biologic), %	93.2%
On combination therapy (biologic and non-biologic DMARD therapy), %	26.2%

*Subjects were classified according to Deyo-Charlson comorbidity index (group 1: index of 1; group 2: index of 2-3; group 3: index ≥ 4).

Table 2-2. Distribution of time spent awaiting DMARD adjustment.

	All subjects (total=558; n=419 events; 139 censored)	Subjects with persistent active disease* (total=403; n=330 events; 73 censored)
Time waiting for DMARD adjustment (t=days)	N (%)	N (%)
t=0	197 (35.3%)	197 (48.9%)
0<t≤30	9 (1.6%)	9 (2.2%)
30<t≤ 60	18 (3.2%)	18 (4.5%)
60<t≤ 90	18 (3.2%)	18 (4.5%)
90<t≤180	35 (6.3%)	31 (7.7%)
t>180	281 (50.4%)	130 (32.3%)

* Patient does not reach LDAS before therapy adjustment

Table 2-3. Types of DMARD adjustments made (n, row percent).

Set of DMARD adjustments	Added biologics only	Added non-biologic DMARDs only	Added both biologics and non-biologic DMARDs	Increased dose of biologic or non-biologic DMARD
All (n=419)	104 (24.8%)	158 (37.7%)	16 (3.8%)	142 (33.9%)
at t=0 (n=197)	32 (16.2%)	97 (49.2%)	10 (5.1%)	56 (28.4%)
Those occurring after t=0 and before/simultaneously to reaching LDAS (n=133)	50 (37.6%)	39 (29.3%)	5 (3.8%)	39 (29.3%)
Those occurring after reaching LDAS (n=89)	22 (24.7%)	22 (24.7%)	1 (1.1%)	47 (52.8%)

Table 2-4. Rheumatoid arthritis patient characteristics associated with time to DMARD therapy adjustment in response to MHDAS and time to low disease activity/remission.

	Competing risks regression Main event of interest: DMARD therapy adjustment in response to active disease ⁺ Competing event: Reaching LDAS before adjusting DMARDs		Cox regression: Time to LDAS	
	N=543, 331 main events, 172 competing events, 40 censored [#] (7.4% censored)		N=543, 387 events, 156 censored [#] (28.7% censored)	
Parameter	Subdistribution hazard ratio	P-value	Hazard ratio	P-value
Age at baseline ≥ 75	0.63	0.03	1.07	0.71
Male	0.89	0.35	1.08	0.56
African-American	0.85	0.31	0.63	0.01
Charlson group 2 vs. 1*	1.03	0.75	1.06	0.60
Charlson group 3 vs. 1*	0.85	0.36	0.93	0.67
DAS28-CRP at baseline	1.40	<0.01	0.75	<0.01
Disease duration at baseline	0.98	<0.01	0.99	0.19
SF12-MCS at baseline	1.00	0.30	1.01	0.02
SF12-PCS at baseline	1.00	0.52	1.01	0.02
Using biologic at baseline	0.71	<0.01	1.07	0.52
Adjusted therapy in ≤ 90 days	-	-	1.32	0.01

⁺DMARD therapy adjustment is defined as adding, switching or increasing dose of biologic or nonbiologic DMARD therapies.

[#]Subjects who had not achieved the outcome (adjusted DMARD therapy or exited active disease) by the end of followup were marked as censored.

*Subjects were classified according to Deyo-Charlson comorbidity index (group 1: index of 0-1; group 2: index of 2-3; group 3: index ≥ 4).

Table 2-5. Competing-risks regression on time to DMARD adjustment including corticosteroids as DMARDs⁺.

	Competing risks regression Main event of interest: DMARD therapy adjustment in response to active disease ⁺ Competing event: Reaching LDAS before adjusting DMARDs		Cox regression: Time to LDAS	
	N=543, 381 main events, 139 competing events, 23 censored [#] (4.2% censored)		N=543, 387 events, 156 censored [#] (28.7% censored)	
Parameter	Subdistribution hazard ratio	P-value	Hazard ratio	P-value
Age at baseline ≥ 75	1.05	0.73	1.04	0.81
Male	0.83	0.11	1.08	0.54
African-American	1.06	0.65	0.63	0.01
Charlson group 2 vs. 1*	0.90	0.30	1.08	0.49
Charlson group 3 vs. 1*	0.92	0.57	0.94	0.71
DAS28-CRP at baseline	1.35	<0.01	0.75	<0.01
Disease duration at baseline	0.99	<0.01	0.99	0.14
SF12-MCS at baseline	1.00	0.48	1.01	0.03
SF12-PCS at baseline	1.00	0.61	1.01	0.01
Using biologic at baseline	0.75	<0.01	1.07	0.55
Adjusted therapy in ≤ 90 days	-	-	1.34	<0.01

*The main event was DMARD therapy adjustment, and the competing event was reaching LDAS before adjusting DMARD therapy. Those who adjusted at t=0 were included in the analysis by resetting their survival time to t=1.

⁺Corticosteroids are counted as DMARDs for the purposes of defining DMARD therapy adjustments.

[#]Subjects who had not adjusted DMARD therapy or reached LDAS by the end of their followup were censored observations.

2.6 FIGURES

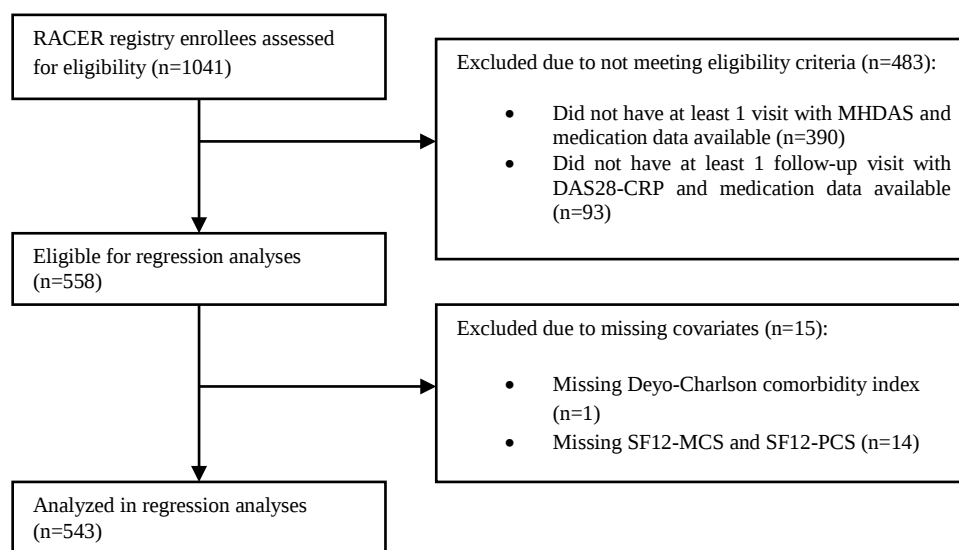


Figure 2-1. Inclusion/exclusion for regression analyses.

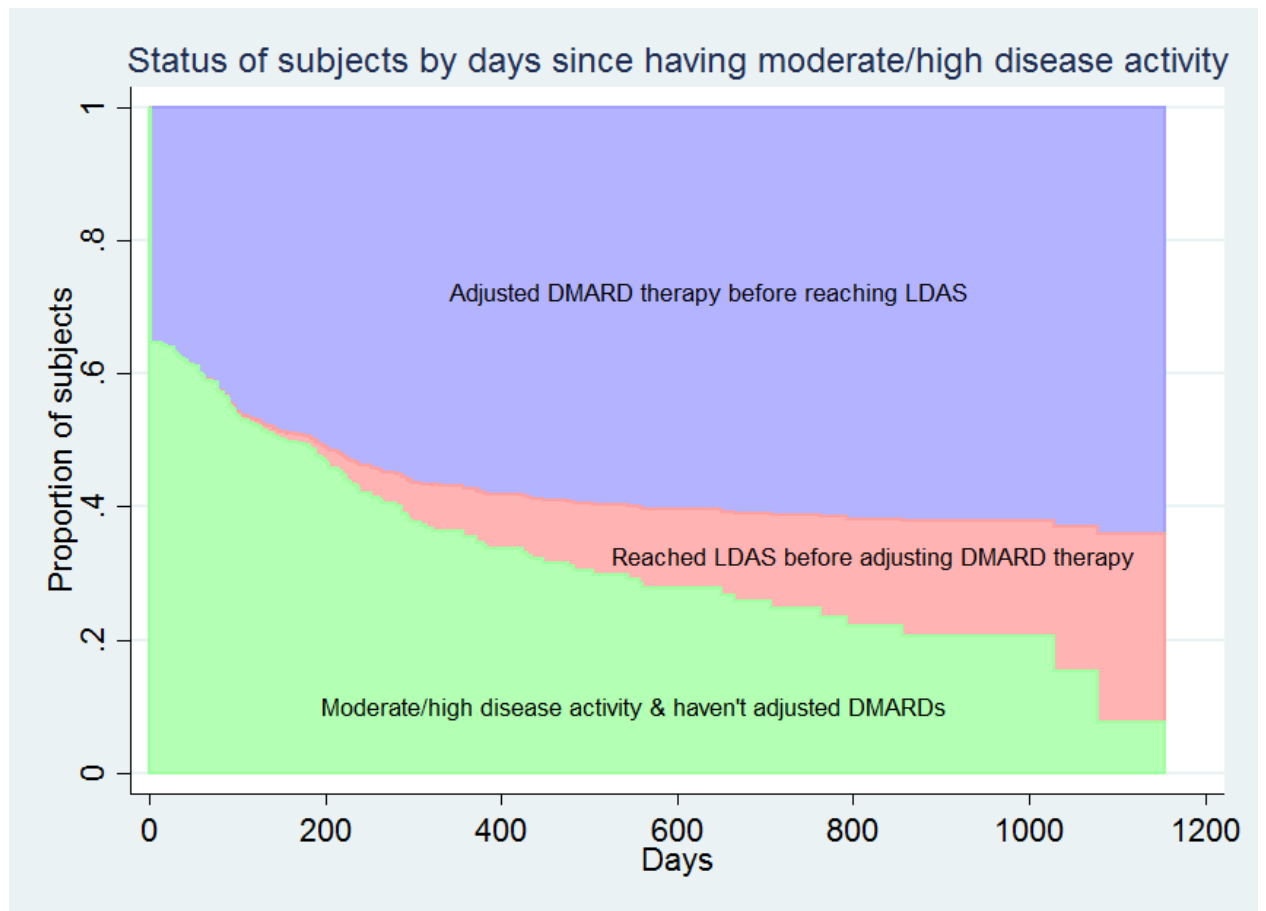


Figure 2-2. Status plot of subjects over time.

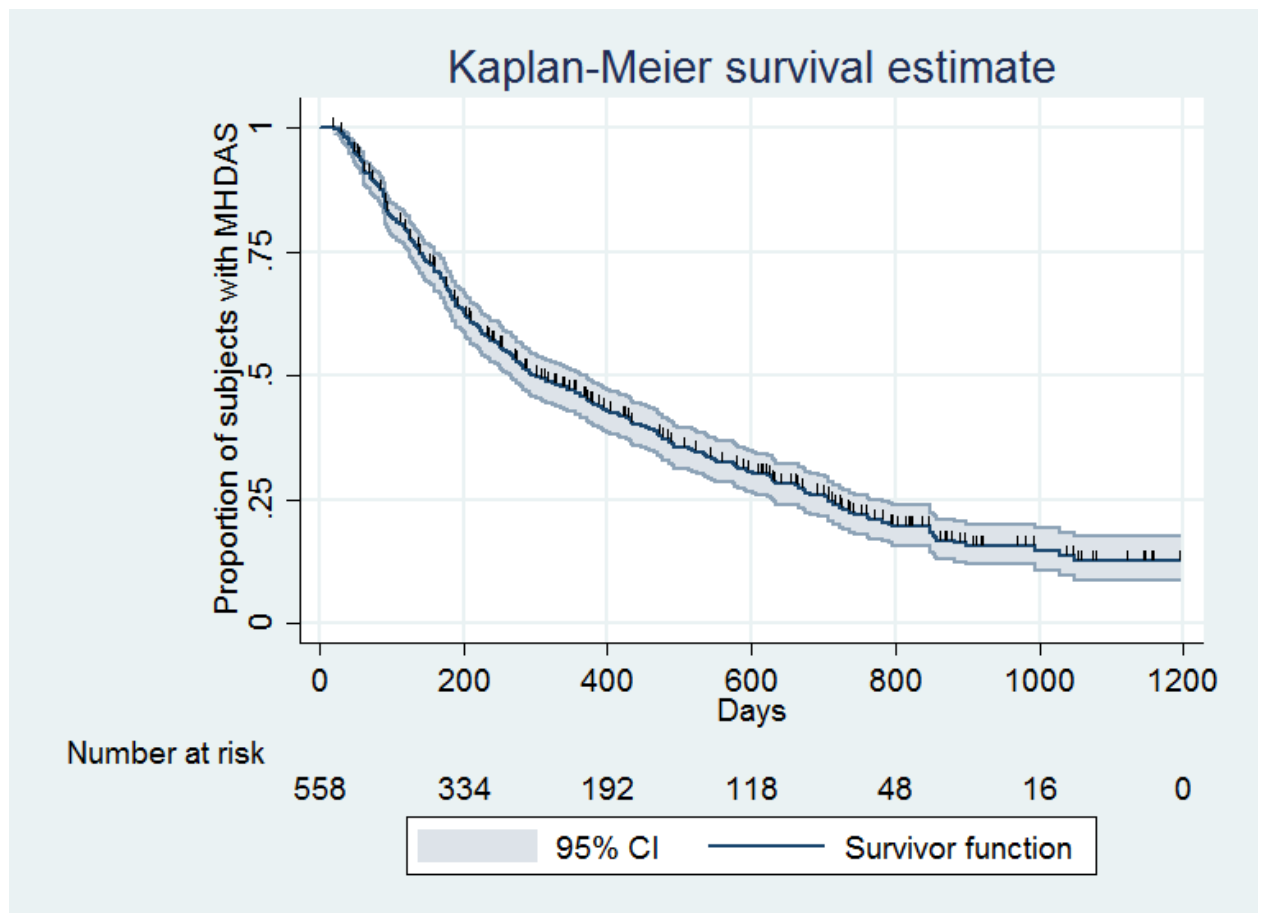


Figure 2-3. Survival plot of time to low disease activity/remission (n=558). Hash marks indicate censored subjects.

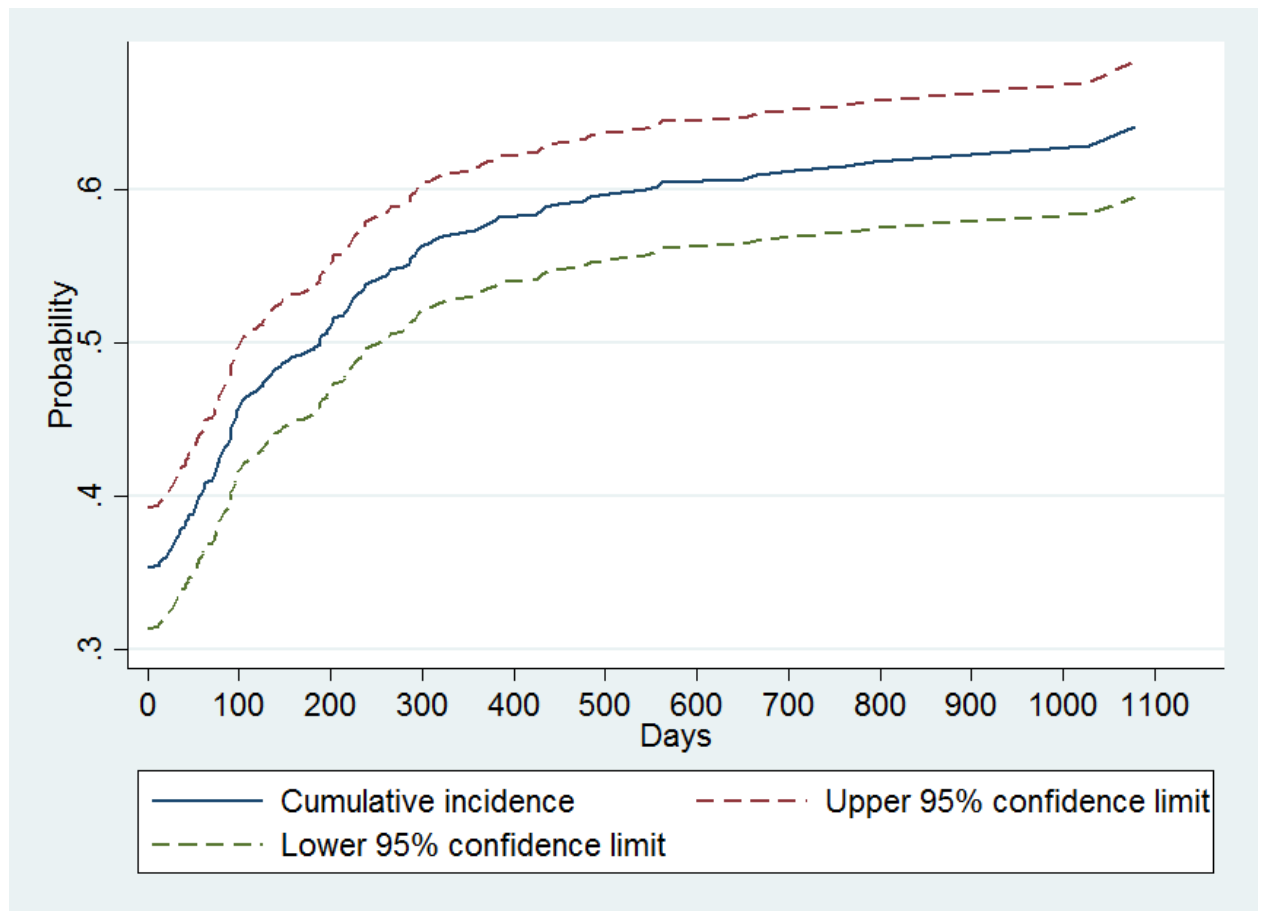


Figure 2-4. Competing-risks regression: estimated cumulative incidence of DMARD adjustment in response to moderate/high disease activity.

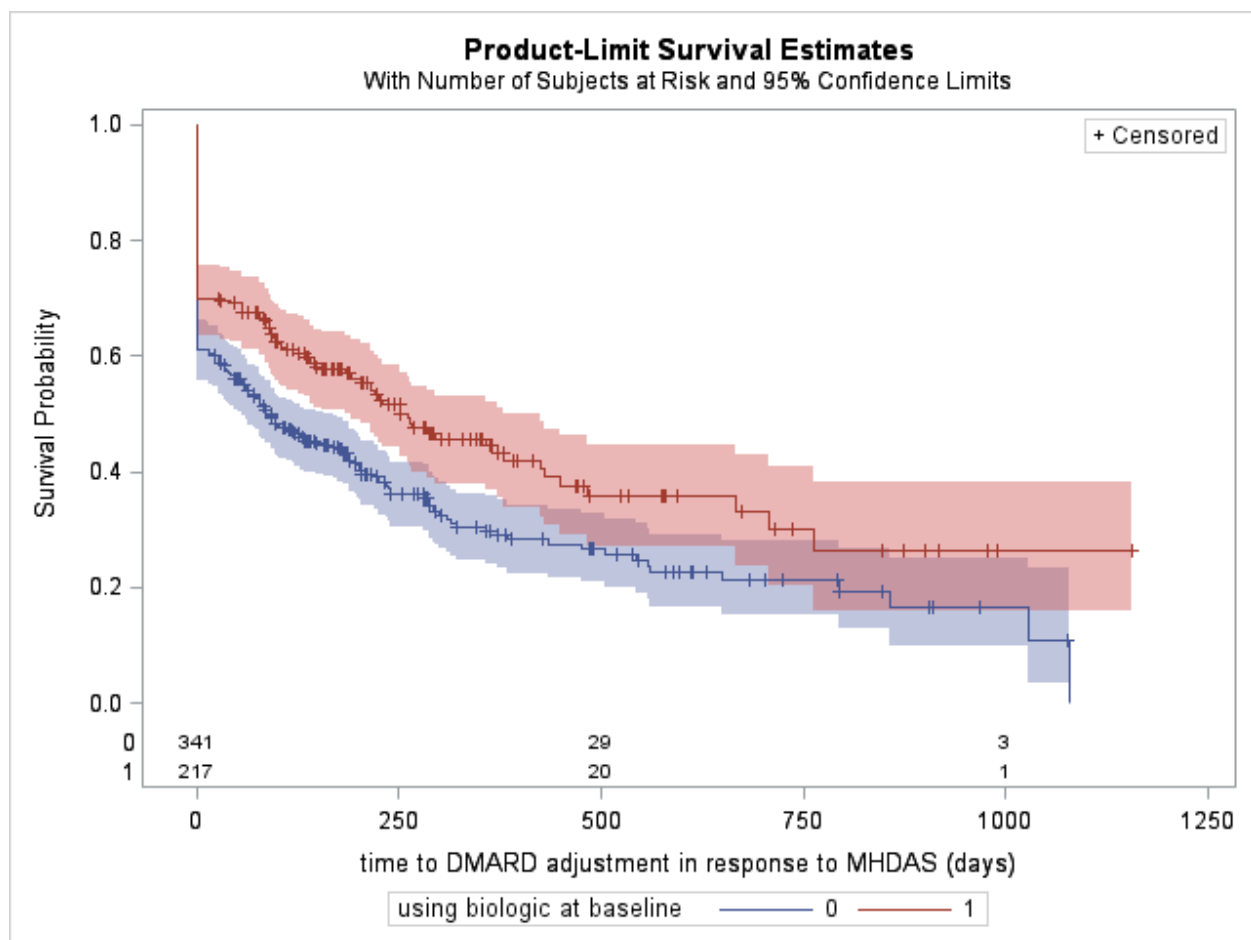


Figure 2-5. Survival plot for time to DMARD adjustment in response to moderate/high disease activity, stratified by baseline use of biologic therapy.

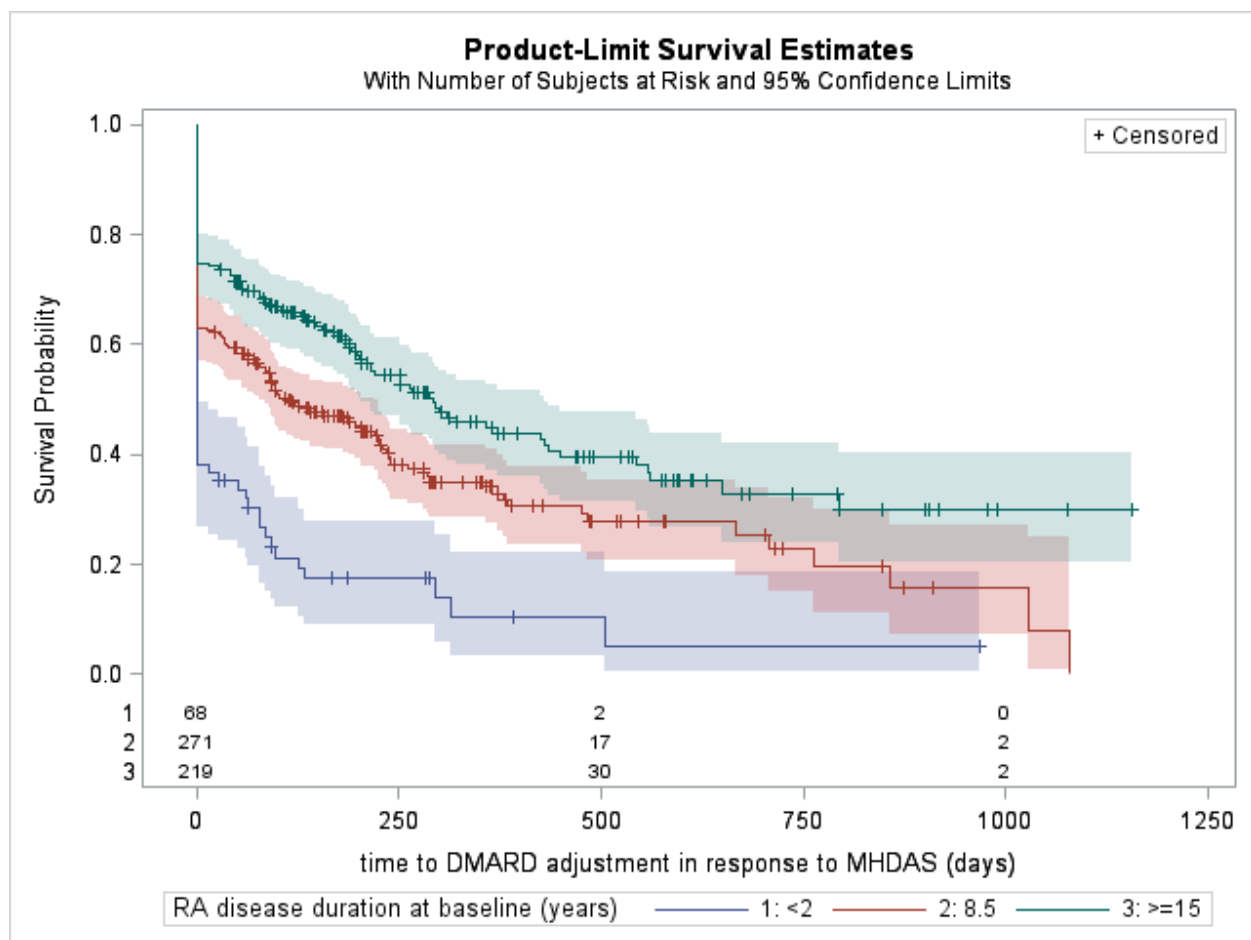


Figure 2-6. Survival plot for time to DMARD adjustment in response to moderate/high disease activity, stratified by RA disease duration.

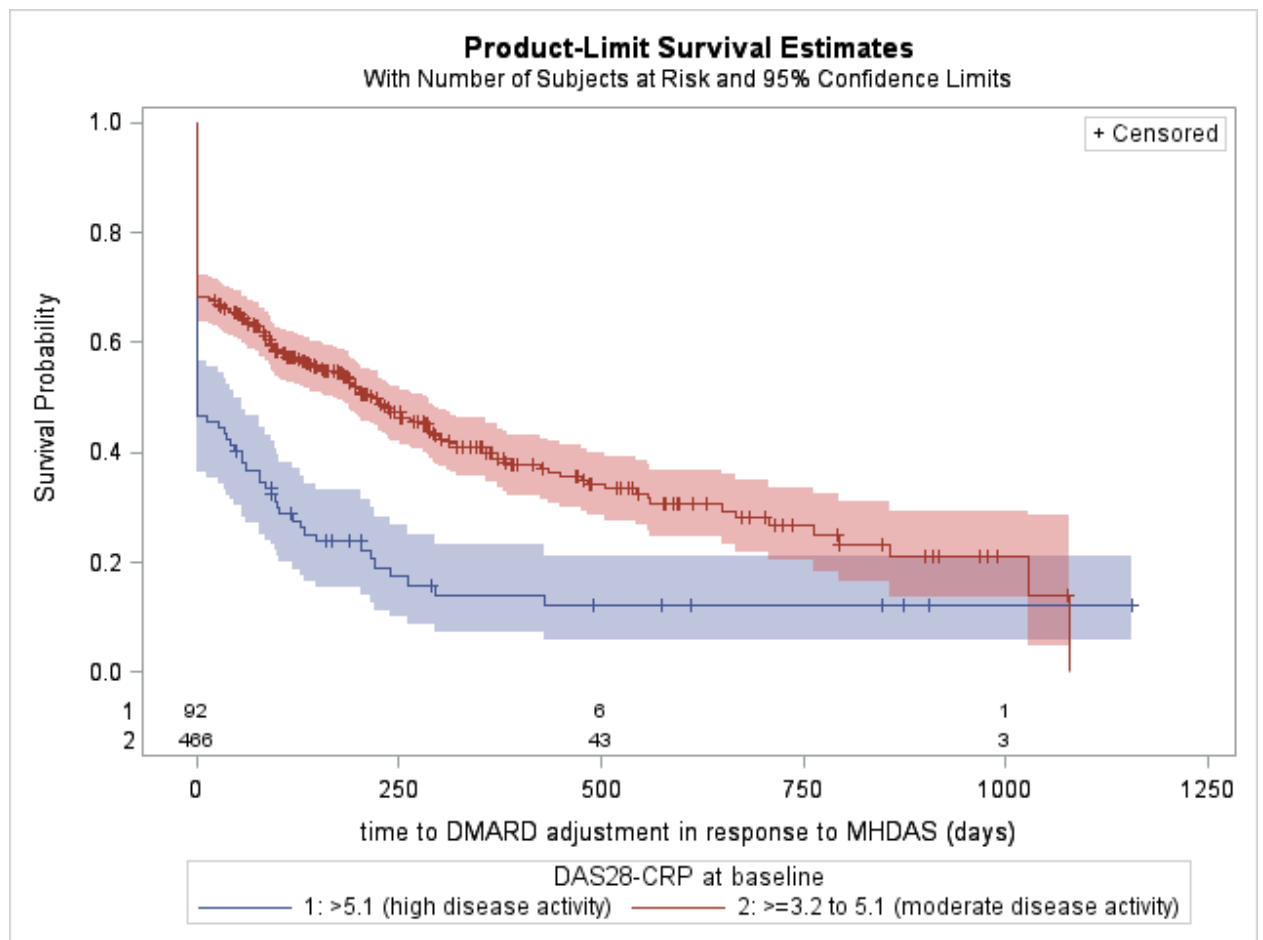


Figure 2-7. Survival plot for time to DMARD adjustment in response to moderate/high disease activity, stratified by baseline disease activity.

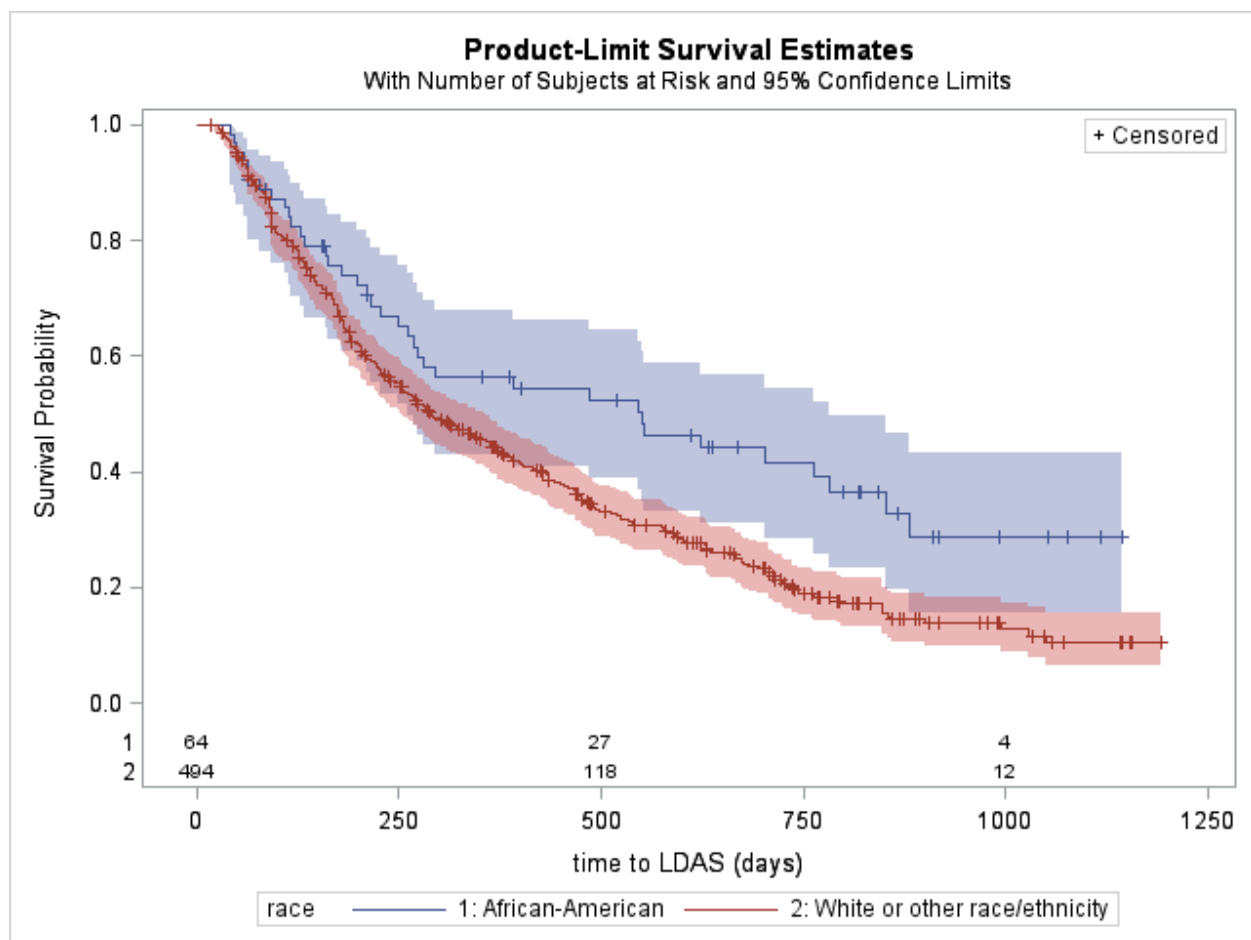


Figure 2-8. Survival plot for time to low disease activity/remission, stratified by race.

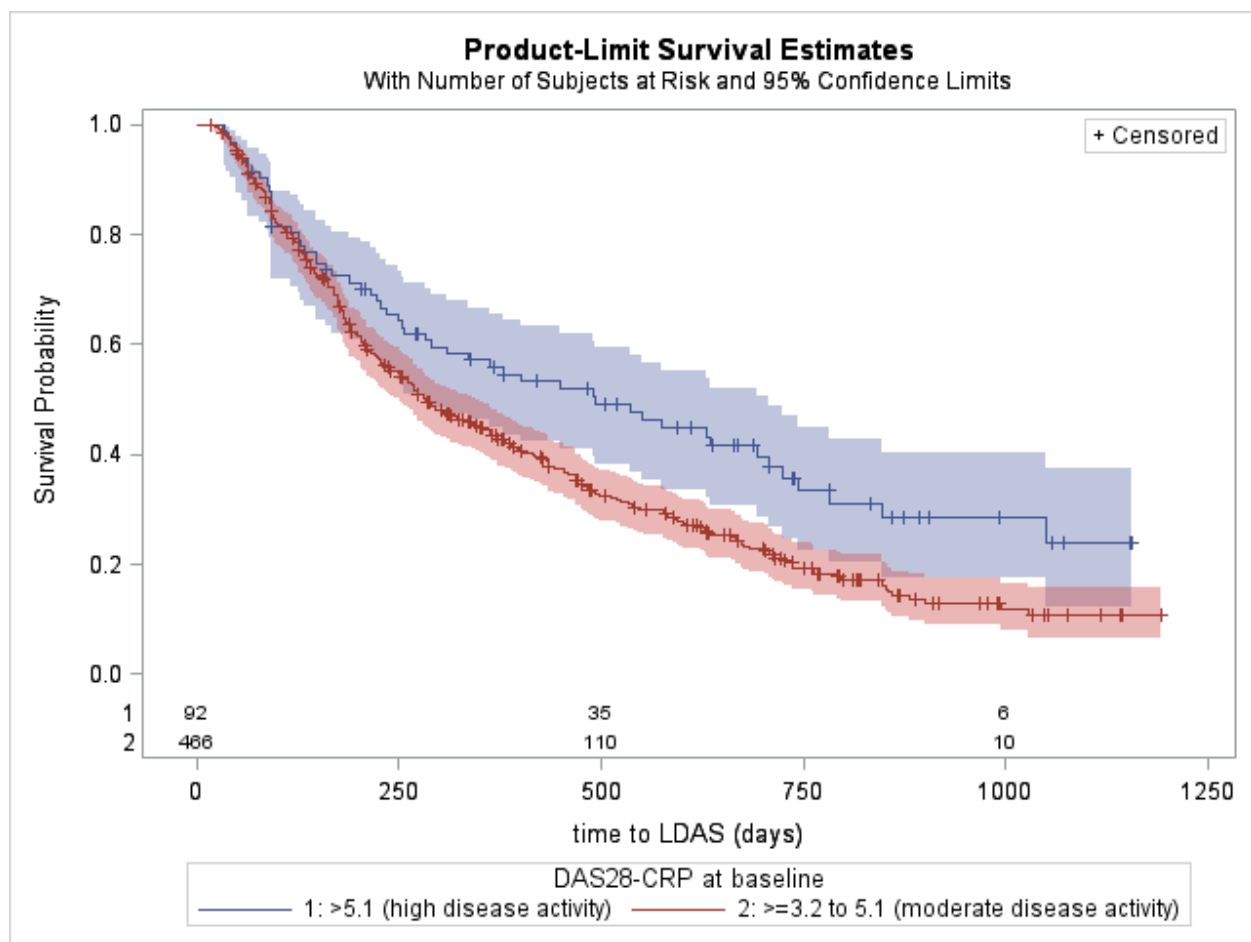


Figure 2-9. Survival plot for time to low disease activity/remission, stratified by baseline disease activity.

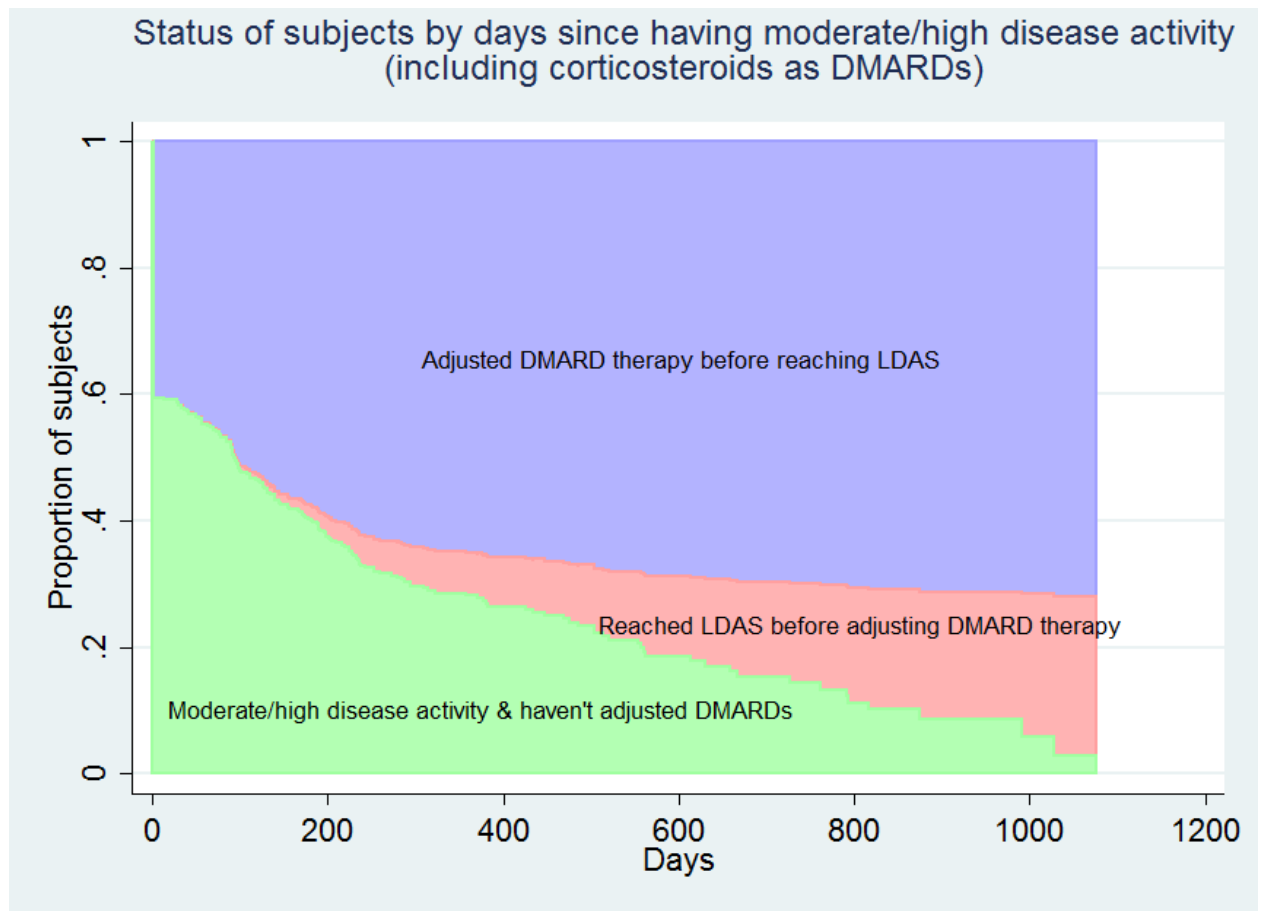


Figure 2-10. Status of subjects over time (including corticosteroids as DMARDs).

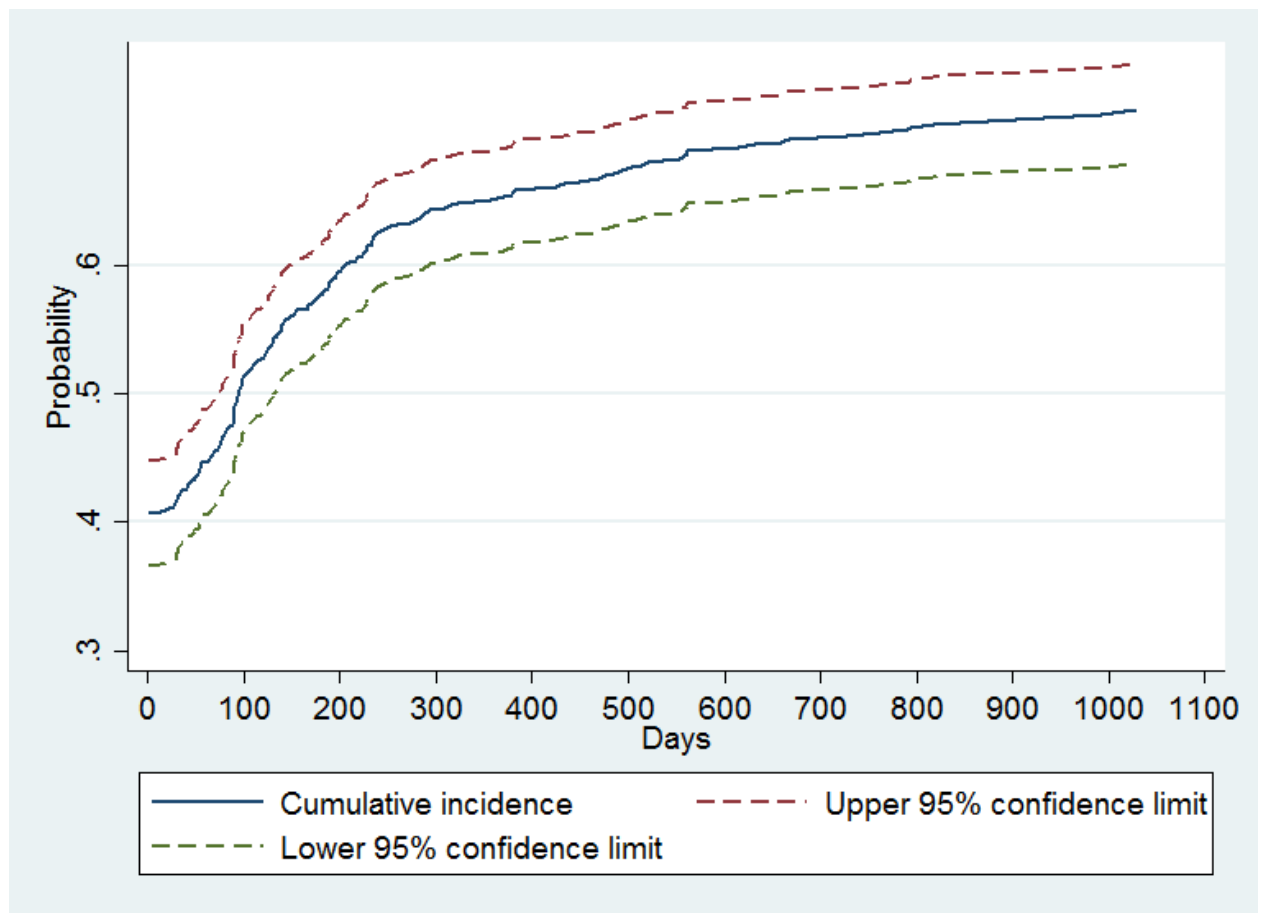


Figure 2-11. Competing-risks regression: estimated cumulative incidence function (including corticosteroids as DMARDs).

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3.0 RHEUMATOID ARTHRITIS PATIENTS' MOTIVATIONS FOR ACCEPTING OR RESISTING DISEASE-MODIFYING ANTIRHEUMATIC DRUG TREATMENT REGIMENS

ABSTRACT

Objective: Patient refusal of and nonadherence to treatment with disease-modifying antirheumatic drugs (DMARDs) can adversely affect disease outcomes in rheumatoid arthritis (RA). The goal of this qualitative study was to describe how RA patients' feelings in response to events and information affected their decisions to accept (initiate and continue) or resist (refuse, avoid and stop) recommended or prescribed DMARD treatment regimens.

Methods: 48 RA patients were interviewed about their experiences making decisions about DMARD medications. The interviews were transcribed, coded, and analyzed for themes related to their internal motivations for accepting or resisting DMARD treatment regimens, using a narrative analysis approach.

Results: In addition to feelings related to the necessity and dangers of medications, patients' feelings towards their identity as an ill person, the act of taking medication, and the decision process itself were important drivers of patient's decisions. For patients' motivations to accept DMARD treatment regimens, two themes emerged: 1) *desire to return to a "normal" life* and 2)

fear of future disability due to RA. For patients' motivations to resist DMARD treatment regimens, five themes emerged: 1) *fear of medications*, 2) *maintaining control over health*, 3) *denial of sick identity*, 4) *disappointment with treatment*, and 5) *feeling overwhelmed by the cognitive burden of deciding*.

Conclusion: Feelings in response to events and information played a major role in how RA patients weighed the benefits and costs of treatment options, suggesting that it may be important for rheumatologists to address patients' feelings when they counsel about therapeutic options. Further research is needed to learn how best to address patients' feelings throughout the treatment decision making process.

3.1 INTRODUCTION

Current rheumatology guidelines recommend treating rheumatoid arthritis (RA) with disease modifying anti-rheumatic drugs (DMARDs) to the target of low disease activity or remission (1-3). Minimizing RA disease activity is critical for managing inflammatory symptoms and pain as well as preventing long-term joint damage (4-6). However, many RA patients do not receive treatment consistent with the treat-to-target (T2T) guidelines (7-10). One contributing factor to this is when RA patients resist (refuse, avoid, or stop) DMARD medication regimens that have been prescribed or recommended by physicians. In a study of T2T protocol implementation, Wabe et al. (11) found that 24.2% of RA patients refused recommended treatment changes at least once during the 12-year follow-up period. A systematic review by van den Bemt et al. (12) found that medication nonadherence rates among RA patients have been reported to range from

20-70%. Patients' resistance to DMARD treatment regimens can increase the risk of suboptimal treatment, prolong time spent with painful symptoms, and lead to progression of joint damage, diminishing patients' current and future quality of life (4-6, 13).

Learning about RA patients' perspectives on decision making about medications is valuable for understanding nonadherence and treatment refusal in RA. Previous qualitative studies have identified beliefs and perceptions of medications and illness that influence RA patients' decisions about taking medications (14-18). For example, Nota et al. (16) found that beliefs in the necessity of medications for controlling symptoms and preventing future joint damage motivated patients to initiate DMARDs. However, concerns about potential side effects and negative perceptions of medications as "aggressive" and "harmful" made patients reluctant to initiate DMARDs (16). Hayden et al. (14) examined RA patients' adherence-related beliefs about methotrexate, finding that experiences of taking the medication modified their initial beliefs and expectations about taking methotrexate. Improvement in symptoms reinforced perceptions of the necessity of taking methotrexate, while occurrence of side effects increased patients' uncertainty about continuing to take methotrexate (14). RA patients in these studies were often found to have ambivalent beliefs and perceptions about DMARDs, sometimes leading them to struggle with decisions about taking these medications (14-16).

The influence of emotions on patient decision making was also acknowledged in some qualitative studies of RA patients' decisions about medications (16-18). For example, Nota et al. identified 'emotional impact' as an additional category of reasons reported by patients for not wanting to initiate DMARDs, distinct from other concerns which dealt directly with the risks of medications. Patients reported being reluctant to initiate DMARDs because it made them feel that they were now "seriously ill" (16). Pasma et al. (17) found that patients often did not want to

initiate DMARDs because of negative feelings related to medication side effects, such as the perception that medications are “poison”, but also related to other reasons, such as the perception that medications were “not natural”, or that taking medications symbolized an unwelcome new status as a patient with a serious chronic illness.

Theory in psychology and cognitive science suggests that it may be fruitful to explore the impact of emotions on RA patients’ decisions about taking medications. Psychology researcher Scherer (19) defines emotion as temporary episodes of intense mental and physical response to events, and feelings as the subjective experience of emotion episodes. One theory of health behavior, Leventhal’s Self-Regulatory Model (SRM) (20), suggests that feelings play an important role in how patients with chronic conditions make decisions about taking medications and performing other health behaviors. The SRM envisions health behavior as the product of a rational decision-making process in which people simultaneously regulate threats to their health and emotional well-being (**Figure 1**). On the ‘objective’ level, people interpret health threats (such as illness), respond with coping actions, and appraise the outcomes of their coping actions in an ongoing cycle. The same cycle occurs on the ‘subjective’ level, where people manage coping strategies for feelings that arise. The objective and subjective level processes occur in parallel but independently of each other. This model proposes that in carrying out health behaviors, patients continually manage not only their health state, but also their feeling state. Experimental research by Croyle and colleagues (21) supports the idea that regulation of emotions affects perception of health threats and health behavior choices. They investigated how healthy subjects react to a false diagnosis of an unfamiliar health condition; their results suggested that people’s perception and responses to health threats are affected by the need to maintain a positive view of one’s health (21).

Understanding how RA patients make decisions to accept (initiate or continue) or resist (refuse, avoid, stop) taking medications is critical to help rheumatologists better understand how to work with their patients to implement treat-to-target recommendations in clinical practice. It is not well understood how patients make decisions about taking medications when they have ambivalent beliefs and perceptions of their medications. Furthermore, it is not well understood how feelings in response to events and information shape patients' decisions. Our study objective was to describe treatment decision making from the perspective of RA patients. We conducted a qualitative study using individual interviews with RA patients, analyzing their narratives of treatment decision making. In this article, we describe how feelings affected RA patients' decisions to accept or resist DMARD treatment regimens offered or prescribed by their rheumatologist.

3.2 METHODS

3.2.1 Study design

We chose a qualitative study design to learn about RA patient perspectives on treatment decision making without imposing the structure of survey instruments or questionnaires on collection and interpretation of data. Qualitative research methods explore a deeper, nuanced understanding of participants' beliefs, feelings and experiences expressed in their own words and allow the possibility for obtaining new insights previously undescribed or unimagined by researchers (22-

24). We chose to use individual interviews to follow the details of each subject's individual narrative.

3.2.2 Study participants

The study participants were recruited from a population of RA patients already enrolled in a local registry of RA patients, the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry. Participants were recruited by RACER study coordinators at their regular rheumatology clinic visits, over the phone, and by a letter mailed out to RACER enrollees. We chose a sampling strategy to allow us to capture a maximum diversity of patient perspectives on medication decision making (25). Our criteria for adequate sampling size were: 1) thematic saturation among participants with and without experiences of medication side effects, and 2) representation of minority subgroups of RA patients including male patients and African-American patients (since most RA patients in RACER are female and white). We continued to recruit patients for interviews, taking care to include RA patients who were male or African-American, until thematic saturation was noted among patients with and without experiences of medication side effects. Informed consent was obtained by the interviewer before each interview. Participants were assured that their identities would remain anonymous. Each participant received a \$20 cash card and free parking for their participation. The study was approved by the Institutional Review Board of the University of Pittsburgh.

3.2.3 Data collection

The interviews were conducted at two rheumatology clinics, in the clinic exam room either before or after each participant's regular rheumatology appointment, in a private conference room, in the RACER research coordinators' office or at a café near the participant's residence, depending on space availability and the participant's convenience. The interviews were all conducted by the same investigator (YS).

Each interview lasted 30-90 minutes and was audio-recorded using a digital voice recorder. The interviews were semi-structured, following a standardized interview guide but allowing for discussion of other topics as they emerged during the interview. The interview guide contained questions prompting discussion about experiences with RA and DMARDs, interactions with physicians and others, and decision making about treatment regimens (see **Supplementary Materials Table S1**). This manuscript will focus on their emotional motivations for deciding to accept or resist DMARD treatment regimens.

3.2.4 Data analysis

The interviews were transcribed verbatim using Transana 2.53 software. Names of people and places were removed from the interviews. Following the template organizing style described by Crabtree and Miller (26), an initial template of codes was developed by YS based on the interview guide, preliminary analysis of the first 15 interviews, and relevant conceptual models and theories of medical decision making and the experience of chronic illness (27-30).

Here an overview is given of the models of decision making and chronic illness experience that informed the initial code template. Codes were created to label instances of decision making according to the 4 models of medical decision making described by Gafni (27): paternalistic (physician decides for the patient, maybe without taking account of patient preferences), informed decision making (patient receives information in order to make the decision, while the physician provides expertise only), professional-as-agent (physician elicits patient's preferences and uses expertise to decide in the best way possible according to the patient's preferences), and shared decision making (doctor and patient decide together). Codes were also created to label decision making interactions according to Elwyn et al.'s (28) three step guide for clinicians implementing shared decision making with their patients in clinical practice: choice talk (clinician brings attention to the need for a decision and makes sure that patients know that reasonable options are available), option talk (clinician provides the patient with more detailed information about options), and decision talk (clinician works with the patient to decide based on their treatment recommendations and the patient's preferences). A code was created to label the phenomenon of distributed decision making as conceived by Rapley (29), the idea that medical decisions are not single events taking place only between the patient and doctor at clinic visits, but in reality can be distributed across multiple actors (including other providers or family members and friends) and multiple settings/occasions (at home or over the course of multiple visits). Finally, codes were created to label different stages of patients' narratives of coming to terms with RA, according to Bury's (30) conception of the experience of RA as biographical disruption, or an event that radically disrupts patients' previous life narratives. The three stages of biographical disruption are onset (the patient's recognition of symptoms, decision to seek help, and receipt of formal diagnosis), disruption (the disruption of the patient's previous life

narrative and self-image, and rethinking of personal narrative and self-concept or identity), and response (the patient's response to disruption by mobilizing resources to face the altered situation) (30).

The template codebook was refined iteratively in a process where 2 coders (YS and either IDM or JCC) applied the codes to a selected group of transcripts. Involvement of multiple coders is a type of investigator triangulation, where we sought to avoid analytic bias that could occur with a single person's subjective viewpoints (22). The coders individually coded each transcript then met to compare coding and interpretation. Codes were added, refined, merged and split to create a final codebook. The final codebook was then used to recode all transcripts, then the coded statements were analyzed to identify major themes. The authors used ATLAS.ti 7 software to manage the coding and analysis of the data.

Analysis of coded statements was conducted using a narrative analysis approach (31). First, a story of the sequence and context of events as experienced by each patient was reconstructed from patients' individual narratives. Second, we read the patients' narratives closely to develop an understanding of the meanings and feelings that patients associated with having RA, taking medications, and specific events. Third, we identified cases where patients had accepted or resisted DMARD treatment regimens. Fourth, we examined groups of coded statements to identify patterns of events, feelings and decisions across all patients. For example, statements with the code "concern for medication risk" were examined (with reference to the patient's full narrative) to identify the event triggering concern, the feeling in response to the event, and the subsequent decision. Similar sequences of events, feelings and decisions were grouped together as patterns. These patterns were then organized and summarized as themes.

3.3 RESULTS

In this section we present the characteristics of interview participants, followed by the resulting themes from our analysis of patients' motivations to accept or resist DMARD treatment regimens.

3.3.1 Characteristics of interview participants

Forty-eight RA patients participated in interviews conducted from November 2011 through April 2013. Participant characteristics are presented in **Table 1**. The participants' ages ranged from 36 to 90 years (mean=59.7 years), and their duration of RA ranged from 2 to 50 years (mean=14.6 years). Most participants were female and white, corresponding to the demographic composition of the RACER registry population. Out of all participants, 35.7% were employed full or part-time, 91.7% reported taking DMARD medications, and 70.8% reported having experienced side effects due to RA medications. Resistance to DMARD treatment regimens was reported by 29.1% of participants; 22.9% of participants reported refusing recommended medications or dose increases, while 18.8% reported discontinuing or not adhering to prescribed medications.

3.3.2 RA patients' motivations for accepting or resisting DMARDs

Patients discussed how feelings in response to events and information and ways of thinking motivated them to accept (initiate or continue taking) or resist (refuse, avoid, or stop taking) DMARD medications offered or prescribed by their rheumatologist. Feelings towards the

experience of symptoms, the threat of future disease outcomes, the positive and negative effects of medications, their identity as an ill person, the act of taking medication, and the decision process itself were important drivers of patient's decisions. Patients often reported simultaneously experiencing motivations to accept and resist medications, leading them to feel ambivalent about taking medications. Some patients also reported a change in their decision-making behavior, reflecting on how in the past they refused medications, but gradually became willing to try new medications. Example quotations for all themes are presented in **Table 2**.

Motivations for accepting DMARDs

For patients' motivations to accept DMARDs, two themes emerged: 1) *desire to return to a "normal" life* and 2) *fear of future disability due to RA*. The experience of living with RA precipitated feelings of loss, shame, helplessness, and fear towards future effects of the disease. These feelings motivated patients to accept DMARD medications to avoid short-term and long-term effects of RA.

Desire to return to a "normal" life

Pain and fatigue symptoms due to RA impacted heavily on patients' physical and emotional quality of life, profoundly disrupting their lives. Patients described being motivated to take DMARDs because they helped alleviate pain, fatigue, and other symptoms of RA which were physically difficult to bear: "You can't believe how bad this hurts when it hurts. I mean it's totally disabling. So, anything you can do to make that pain not be there, you're going to do or you would be a fool, I guess." For some patients, alleviating pain was important enough to outweigh concerns about medication side effects:

I worry about the side effects, the liver disease, the risk with each individual pill. But what's worse, the RA, or what you may get? I'd rather have it [the medications] and take the chance, than not have it and be in pain all the time. That's the bottom line.

Patients' negative experiences with RA symptoms were also related to negative feelings they felt as they struggled to live with RA. Alleviating RA symptoms was important to patients because it helped them to return to a "normal" life again and regain at least some of their pre-RA function.

[My goal for treatment is] to be able to function as normally as possible, with the disease. Cause I was to the point where I was almost constantly in bed, where I couldn't move. So I wanted to get as normal. . . my life back. You know, get my life as normal as possible.

The desire to reclaim a "normal" life was associated with various powerful feelings that drove people to accept DMARD treatment. Patients felt a deep sense of loss when RA symptoms disrupted their 'normal' lives and they had to give up activities (such as sports) or a way of life (such as carrying stylish handbags) they used to treasure. Patients felt shame and helplessness when forced to confront their inability to fasten a child's ponytail, open a bottle of water, or get up after having fallen to the ground. Their social and work roles exerted pressure on them to remain as independent as possible to avoid becoming a burden to their family or being seen as incompetent at work. These various feeling states motivated patients to view medications as a "necessary evil" they were willing to tolerate to alleviate RA symptoms: "So I've kind of come to that point in my thought process, it's [medications are] kind of like the necessary evil that I have to put up with in order to feel generally good about my health and be able to function."

Fear of future disability due to RA

Patients were also motivated to accept DMARD medications by their fears about future disability due to RA. Disability had different meanings for different people. Some patients associated RA-related disability with being confined to a wheelchair or losing the use of one's hands—their fears were focused on being physically immobilized by the disease and becoming unable to lead an active, productive life. One patient felt so strongly about the importance of medication treatment for RA that when she encountered other RA patients who expressed doubts about taking medications, she warned them that RA would turn them into a “cripple”:

I said, do you really realize what rheumatoid arthritis can do to your body? 'It'll mess up my joints a little bit.' I said, no no no. It will make you a cripple! You will be in a wheelchair. Your hands, your body will not work! Are you willing to risk that because you don't want to get around to it right now? Get busy!

Other patients associated RA-related disability with loss of independence and social isolation. As one subject stated, “That's one of my biggest worries, is that I'll get to the point where I can't be taken care of, and I'll end up in a home. And I don't want that.”

Motivations for resisting DMARDs

In addition to motivations to accept DMARDs, many patients simultaneously experienced motivations to resist DMARDs. Five themes emerged: 1) *fear of medications*, 2) *maintaining control over health*, 3) *denial of sick identity*, 4) *disappointment with treatment*, and 5) *feeling overwhelmed by the cognitive burden of deciding*. Perceptions and feelings towards taking medications, protecting health, being ill, and deciding about treatment contributed to patients' desire to avoid DMARDs.

Fear of medications

Fear of medications often led patients to resist taking DMARDs. Patients expressed various reasons for being afraid of taking DMARD medications. Occurrence of life-threatening adverse events could be a traumatic experience that left a lasting impression that certain types of medications, such as biologics, were dangerous. Chronic side effects such as nausea, fatigue, boils, and hair loss decreased the quality of life for patients and created feelings ranging from mild aversion to repugnance towards medications. These negative experiences and feelings led them to question whether the benefits of medications were worth the ill effects they suffered. Patients who hadn't experienced side effects still worried about those they learned of online, in advertisements and drug information materials, or from other RA patients.

Certain medications were viewed as aggressive treatments, and this perception of the medication's potency led subjects to prefer alternatives which they perceived to be milder and more conservative. For example, one patient was reluctant to take methotrexate because she knew it is also used to treat cancer:

I mean the drug itself scares me, just the name of the drug. Methotrexate. It sounds like some kind of big bad horrible thing that somebody's putting in my body. Due to the fact that it's a cancer pill, and then due to the fact that the side effects could be developing cancer, or lymphoma and different diseases...that doesn't make me happy either. Do I want bad rheumatoid arthritis, or do I want lymphoma or leukemia or something? Uh, I don't know, I think I might rather have the rheumatoid arthritis than having to deal with a bad cancer!

Patients also perceived medications to be unnatural, harmful chemical substances, and preferred more 'natural' remedies such as adopting a gluten-free diet or consuming naturopathic supplements. Although the above-mentioned patient agreed to take methotrexate, she would have preferred a less threatening non-medication alternative: "I just wish there was an alternative, that

I didn't have to...Can I take less, or can I take something holistic or something that I know it's not this chemical in my body for X amount of years.” Concerns about becoming addicted to medications also strengthened patients’ fears of using DMARDs.

Maintaining control over health

Patients valued the feeling of being in control over their health—of being able to take actions to contribute to their health and limit the risk of negative health outcomes. Taking medications threatened patients’ sense of having control over their health because it introduced uncertainty about whether they would suffer life-threatening adverse events. They also worried about becoming addicted to medications—of becoming subject to the control of medications. Taking medications exposed patients to these risks, making them feel vulnerable. Resisting medications was an action that limited uncertainty about their health outcomes by reducing the risk of serious adverse events or addiction, helped patients avoid feelings of vulnerability, and ultimately helped patients feel that they were still in control over their health. From the perspective of patients, the predictable risks of RA were sometimes preferable to the unpredictable, more severe risks of certain RA medications. The desire to maintain control over health by resisting medications was sometimes associated with having experienced unpleasant or frightening side effects. One subject described how she avoided medications after being hospitalized for an adverse reaction to a DMARD:

But ever since then, just by taking it [medication] straight like that makes me very leery and I'm so scared of any pills. . I'm just like, I don't even want a painkiller, I'll just take a nap, I'll be all right. I'll put a heating pad, or something warm, maybe that'll do, stay off my feet, give myself bed rest. I try not to take pills, cause I'm scared. I can't afford to get sick and get wiped out for the little strength that I do have, you know what I mean?

The reaction that her body had to methotrexate was unexpected and frightening. Because of the incident, the subject worried that taking other medications might cause other unpredictable reactions. She worried so much that she avoided medications when possible, and sometimes did not take her prescribed medications. Doing this helped her to limit the risk of another unforeseen adverse event and stay in control of her health, carefully guarding her remaining “little strength”.

Denial of sick identity

Some patients did not want to take medications because they associated this action with being a sick person, a role which they rejected. They found it difficult to accept their RA diagnosis and the idea that they were no longer healthy. Inability to accept the diagnosis of RA even led one patient to avoid seeking any treatment until years later. One patient felt angry about developing RA:

At first I was like, I don't have rheumatoid arthritis. There's denial. . . And then I was angry. And I was angry at God. I was like, 'How could you let this happen to me? I serve you, I do this and. . . This isn't fair!'

Being told by doctors that she needed to take medications was upsetting to her, because she felt she had worked hard to take care of her health: “So I resent the fact that I try to take very good care of myself, and I still have to take drugs.”

Patients also resisted the idea of taking biologic medications because of the perception that they were a ‘last resort’ only to be used for the most severe cases of RA: “To me, injections is my last resort. And if I have to go there, and it doesn't work, then I'm hosed.” Taking biologics had negative implications because it signaled to patients that one’s RA was doing poorly, and that there were few therapeutic options left.

Another patient described the behavior of ‘stoic’ patients who refused to take medications out of pride—for patients with this mentality, taking medication meant admitting that they are weak and not fit to take care of others. In order to maintain their role within the family as caregiver or someone who is reliable, they pretend that their symptoms do not bother them and ignore prescribed treatments.

Disappointment with treatment

Feeling that their medication was not helping as much as they had hoped sometimes made patients disillusioned, leading them to consider giving up and stopping their DMARD treatment. One patient described feeling so dejected that she told her rheumatologist she wanted to give up on treatment: “But sometimes when I get down, like when I emailed Dr. A, I said, 'I'm just getting sick of all this, I don't think nothing is helping me, I think I oughtta just chuck the whole thing.' And she said, no. Because then it'll really flare up.”

Feeling overwhelmed by the cognitive burden of deciding

Patients found it overwhelming to navigate and process information about treatment options (and their accompanying risks) which they received from physicians or encountered online and in advertisements. One subject described being overwhelmed by information she found online:

And I read everything. When I got sick, every web site, everything that I could read on rheumatoid arthritis, I did. And it overwhelmed me. I became that person [I read about online]. And that person and that person. Cause I seen something about what I was feeling or what I was going through in every person—I never individualized it.

Digesting the available information in order to make a treatment decision caused anxiety—patients worried about making a bad decision and suffering negative health outcomes

as a result. Unable to handle the cognitive burden of making a treatment decision, some patients preferred to postpone the decision.

Patients also discussed how the lack of certain kinds of information contributed to their feelings of uncertainty and made the decision making process more difficult. While it was easy for them to learn which side effects could occur with each medication, they did not have more detailed information about the nature of the risks: the magnitude of risk for each side effect, which patients are at greater risk for each side effect, and how the risks could be managed. Patients expressed the desire for guidance from physicians on interpreting risk information, and for more information about the experiences of actual patients with medications—effectiveness, safety, and personal narratives about taking different medications. They valued being able to meet, ask questions, and compare experiences with other RA patients. Patients felt that more access to these kinds of information could have supported them throughout the difficult process of weighing the benefits and risks of treatment options.

3.4 DISCUSSION

Quantitative and qualitative studies have shown that RA patients are often risk averse in decisions about DMARD treatment regimens, preferring to avoid the risks of therapy escalation even when they have active disease (32-35). Wolfe et al. (34) conducted a survey of 6,135 RA patients, finding that 63.8% of respondents were not willing to change their therapy provided their condition did not worsen. Fraenkel et al. (32) asked RA patients to rate their willingness to accept various adverse events for a hypothetical medication that could effectively treat their

symptoms, finding that 33% of respondents were unwilling to accept adverse events under any circumstances. Our study, by exploring RA patients' perspectives on their decisions about taking medications, provides insight into the thought processes that affect willingness to accept the risks of therapy.

For the RA patients in our study, feelings of pain, loss, helplessness, shame, fear, protectiveness, anger, disappointment, anxiety, and uncertainty played an important role in motivating decisions to accept or resist DMARD treatment regimens. These feelings were in some cases related to illness symptoms or concerns about the effects of medications, but in other cases were unrelated. For example, patients described their decisions being affected by feelings towards the decision making process (anxiety about navigating available information and making a final choice) as well as towards their identity as an RA patient (anger about developing a chronic illness). Patients reported feelings of fear and worry towards RA as well as DMARD medications, as both were perceived to threaten health and well-being. Those who chose to accept their DMARD regimens tended to view medications as a "necessary evil", while those who chose to resist DMARD regimens preferred the predictable risks of RA over the uncertain risks and rewards of DMARD treatments. Information that patients encountered in the course of receiving a diagnosis and treatment could have a negative emotional impact, leading to decisions to resist DMARD regimens. For example, being overwhelmed by information about treatment options led to postponing treatment decisions; information about potential side effects led patients to refuse and avoid taking medications; and the distress caused by a diagnosis led to denial of the illness or treatment altogether.

Previous qualitative studies (14-18, 36-38) of how patients with RA and other chronic conditions make decisions about taking medications have identified beliefs and perceptions that

encourage and discourage taking medications that were consistent with those reported by patients in our study. For example, Pound et al. (38) conducted a meta-ethnography of 37 qualitative studies of patient perspectives on medicine taking in a variety of health conditions. Unacceptability of adverse events, concerns about becoming dependent or addicted to medications, being unable to observe tangible benefits of the medication, and non-acceptance of illness were reported as reasons for nonadherence, while hopes for symptom relief, slowing the progression of disease, and normality were reasons for adhering to medications (38). Previous qualitative studies have also reported how various feeling states (such as denial and fear) affected patients' decisions about taking medications (14-18, 36-39). Our study used narrative analysis techniques to draw connections between specific events, their impact on feeling-states, and subsequent choices about medication use. Including emotional aspects of patient decisions in our analysis helped to reveal the logic behind decisions to accept or resist medications. Further research which incorporates analysis of the connection between events, feeling-states, and decisions may be useful for exploring the origins of specific beliefs which influence medication use among patients with chronic conditions, such as beliefs about alternative therapies. Patients in our study and in other studies (36, 38, 40-41) have reported pursuing alternative therapies in an effort to avoid taking recommended medications. This approach may also be useful for further exploration of how patients' decision making patterns can change over time. Some patients in our study reported a gradual transition from a stance of resisting medications to stance of willingness to accept new medications.

3.4.1 Implications for clinical practice

Our findings suggest that because feelings are central to RA patients' experiences of decision making about treatment, to facilitate uptake of recommended DMARD regimens, it may be important to inform patients about the benefits and risks of treatments in a way that takes into account their emotional needs. The recommendations presented below may also be useful to improve care for patients with other chronic conditions as well.

Physician communication strategies that address patients' negative feelings in response to illness and treatments may help patients resolve ambivalence towards taking DMARDs and gain confidence in navigating treatment decisions. For example, eliciting a patient's emotional reactions to information presented in a discussion may help a physician become more aware of how the individual patient interprets the information. Greater awareness of the patient's perspective may help the physician to support the patient as they process potentially threatening information about their illness and treatment options. Physicians can talk to their patients to learn about negative feelings they may have about taking medications. Some patients in our study felt an aversion to taking methotrexate because of their perception of methotrexate as a cancer treatment. Providing reassurance that the dosage of methotrexate prescribed for RA is much smaller than for treating cancer may help such patients to overcome this aversion. Although addressing patients' negative feelings cannot guarantee that all patients will always decide to accept treatment with DMARDs, it may help patients to become more receptive towards physician treatment recommendations.

In recent years, decision aids have been developed to support RA patients' decisions about treatments by informing them of the benefits and risks of medications (42-46). However,

providing patients with information does not always have the intended supportive effect. For example, Li et al. (43) found that use of their methotrexate decision aid increased uncertainty about whether to take methotrexate and frustration with the decision process among some patients. Patients in our study reported that information about side effects which they encountered online and in drug advertisements caused feelings of fear and anxiety about the decision making process. When no information about the probability of side effects and strategies for managing side effects was available, patients felt uncertain about initiating medications and developed the perception that taking the medication would make them very likely to experience the listed side effects. It is important for decision aid designers to present risk information in a balanced but unthreatening way. Providing information to help patients understand the size of treatment risks, whom they are most relevant for, and strategies for managing those risks may be helpful for patients. Patients in our study also expressed the desire for more opportunities to hear about the experiences of other patients with treatments. Finding a way to incorporate the experiences of actual patients into a decision aid, such as through patient testimonies, may improve the usefulness of decision aids for RA patients. Creators of decision aids may also want to consider how the medium of information delivery can impact how patients perceive message content. Being able to receive information in person may have certain advantages over being offered a text or video to passively consume, because a person can actively respond to patients' feelings and concerns if they arise.

More research is needed to identify specific strategies clinicians can use to take patients' feelings into account when communicating with them about the benefits and risks of treatments. A second paper utilizing the same qualitative data from this study will focus on patients' feelings

in response to patient-provider interactions and how these affect treatment decisions, which will further inform specific communication strategies for clinicians.

3.4.2 Limitations

There were some limitations to this study that should be taken into account. The experiences of our study subjects cannot be generalized to the whole population of RA patients. Subjects were recruited from a population of RACER registry participants who were being treated at 4 local arthritis clinics. It is possible that selection bias caused the opinions of our subjects to be unrepresentative of the general population of RA patients. However, it is unlikely that the RACER participants were biased either in favor or against medications, since this is an observational registry without any required treatment protocols. Our study had a larger number of participants (n=48) than most other qualitative studies of RA patients, which include numbers ranging from 15-30 participants. We made efforts to include a diverse selection of subjects to ensure that various perspectives were represented—female and male, white and African-American, and subjects of ages ranging from 36 to 90 years were interviewed. Our subjects had a variety of experiences and attitudes towards medications. The perspectives expressed by our subjects convey similar themes as found in previous qualitative studies of medication decision making among RA patients (14-18).

Another limitation of our study is that recall bias might have affected what opinions and memories subjects shared during interviews. Their current attitude towards medications might have affected how they remembered past events and what they chose to talk about during interviews. Although there is no way for us to know to what extent subjects' current opinions

biased their recounting of past events, we tried to manage this during interviews by asking subjects to clarify the reasons for their opinions and to elaborate on the concrete details of their actual experiences. This way, we had more complete information on specific experiences which could help us to put into perspective their interpretation and reaction to events. Furthermore, there were some cases where subjects acknowledged past experiences and actions associated with a point of view that was different from their current one. This suggests that subjects were able to offer fairly objective accounts of their experiences, even when strong feelings and opinions were involved.

3.4.3 Conclusion

Our study contributes a deeper understanding of RA patients' decisions about medications based on detailed analysis of RA patients' narratives—the origins of their motivations for accepting or resisting DMARD treatment regimens. These findings can be useful for the clinical practice of rheumatologists and other healthcare practitioners working with patients to make treatment decisions, as well as researchers interested in designing interventions to improve patient-provider communication about medication decisions, or patient decision-aids. Our further analyses of this data will explore the impact of patient-provider interactions on RA patients' decisions.

3.5 TABLES

Table 3-1. Characteristics of interview participants (n=48).

Characteristic	Mean (range) or percent
Mean age in years	59.7 (36-90)
% Female	91.7%
% African American	16.7%
Mean duration of RA in years	14.6 (2-50)
% employed (full or part time)	37.5%
% on disability	27.1%
% on any DMARDs	91.7%
% on biologic	43.6%
% reporting experience of any side effects due to RA medications	70.8%
% reporting experience of serious adverse events* due to RA medications	31.3%
% reporting refusal/discontinuation/nonadherence to recommended or prescribed RA medications	29.1%
% reporting refusal of recommended RA medications	22.9%
% reporting nonadherence/discontinuation of prescribed RA medications	18.8%

*Using the US Food and Drug Administration's definition of serious adverse events.

Table 3-2. Example quotations for each theme.

Motivations to accept DMARD treatment regimens	Example quotations
Theme 1: Desire to return to a “normal” life	“I was a very active person [before developing RA]. The only time I ever cried was when my mother-in-law made a comment that I used run everywhere. And then I...started to cry when she said that to me. Just losing my...Well I wasn't particularly athletic, but I just was very busy all the time, and losing that has been the worst thing for me. Although I still do things that most people my age don't do. I still mow my own lawn, and I've got a big lawn, and I paint my walls, and. . .”
	“When I had first started taking the medicine, and things seemed to magically clear up [. . .] I thought that I would never have another flare-up again. I was ecstatic. I was in a really bad place when it first started happening. My fingers were completely misshapen, like I said I couldn't open a jar, put in a ponytail holder, or work a car seat buckle. So it was like a miracle, when I first started taking them.”
Theme 2: Fear of future disability due to RA	“My nephew is also a doctor, although he's a podiatrist, and he told me if I didn't take the meds, I'd go downhill a lot faster. He said, It's going to be debilitating, and at some point, if you don't keep up treatment, you'll be in a wheelchair. You won't be able to get around. So I think that's putting it the way it is. So I try not to think about it, I get up each day and I do what I got to do to get through that day. And so far I'm succeeding. I'm not sitting in a ball crying.”
	“. . . I'm glad that I kept taking the medicine. Because if I would have stopped taking it because of something like hair loss, then where would I be physically? Cause I know a lot of people who have RA. People seem to talk about it who won't take the medicine, and they're all crippled up like a pretzel, and because they're afraid of the liver function problems and all that.”
Motivations to resist DMARD treatment regimens	
Theme 1: Fear of medications	“And I will tell you why I choose not to do that [avoid taking medicines for RA where possible]. Couple of reasons. I took plaquenil [hydroxychloroquine], and I was in the emergency room twice with head to toe hives. Dr. _____ had me on low doses of methotrexate, trying to increase my methotrexate dose and decreasing my prednisone so I could get off the prednisone, and then I started to lose my hair, so

(Table 3-2, continued)

	I panicked. I didn't call him, and I stopped it [the methotrexate]. And so the other reason is I know a lot of those medications depress your T-cells. I don't want my T-cells depressed, because I don't want to end up with a lymphoma or anything else. That scares me. So that's why I'm trying other things other than the drugs.”
	“Like I said, I read information [about the medications], and it's pretty scary when you read. I'd get to where I was turning off the TV or muting my TV when the Humira commercials would come on, because I didn't want to hear all the side effects.”
Theme 2: Maintaining control over health	“[When I was taking my previous medication] I would be drooling. Or I would be moving like I'm running a slow race. I wasn't able to maneuver in my house. I said no, I can't take that. I want nothing that would take my psyche or my independence from me to where I'd have to sit there like I'm a junkie. No no no no, I don't want that. nh-nh. So God is good, the medicine I'm on, it works. If it gets worse, then I'll pray on it. Maybe we may try the infusion. But right now, I'm staying with what I got. I'm in control. I'm in control.”
	“I'm supposed to take it every week, but I refuse to after my experience [being hospitalized with serious infection] with Enbrel. And as long as I do fine with every week, I'm keeping it there. They say the risk isn't that much greater [if I took it every week], but. . .”
Theme 3: Denial of sick identity	“Back in the late 80s, early 90s, what happened was I got up one morning, and I went to stand up out of bed, and I fell down. And the backs of my ankles, my Achilles tendon, I couldn't put any weight on them. So I went to a hospital, podiatry hospital. They turned around and they diagnose me with rheumatoid arthritis. Well I turned around and said I don't have that. I didn't know that it was done through a blood test. So it was way back then, and I've been a hairdresser all my life. Very busy hairdresser, very busy. My hands would blow up like balloons. And I would ice them or I would wear those wristbands. So I was in denial, all those years. Never missed a day of work either. No matter what I had to do, I got through work. So all this time, I was thinking that was from cutting hair.”
	“And I hate to see people [other RA patients who don't seek treatment] who can do something about a disease ignore it and hope it'll go away. I said, putting your head in the sand, being an ostrich, ain't gonna make it go.”

(Table 3-2, continued)

Theme 4: Disappointment with treatment	“Sometimes I don't know, well what should I expect. I know when you're old, everybody has arthritis, but is everything supposed to. . . all this medicine that I take, is it supposed to. . . I know it's supposed to slow down the disease, but is it supposed to make the pain go away totally? Or am I supposed to just grin and bear it? Like I walk like an old person now! Like I'm 100 years old!”
	“As far as the inflammation, the swelling is unbearable. By the end of the day, if you measure yourself, you've gone 2-4 inches wider, than you did at the start of the day from just inflammation...If I didn't have a massager to do what I have to do with it on my joints. . sometimes in the morning, if I had a bad night and I wake up and I'm really sore, it takes me an hour of massaging every joint before I can get out of bed. That's my savior. And that, to me, massage works better than any pill that you could possibly give me. That's kind of where I'm at right now. I definitely need a point in time in between drugs or I can't tell you whether the drug's working or not. So I just took it upon myself to quit. And I feel better without it.”
Theme 5: Feeling overwhelmed by the cognitive burden of deciding	“Cause sometimes, when you go to the internet, there's so much information [. . .] You're googling, you're like, what is this going to do? You keep going down and down [the search results]. . . so that's why I would like a little bit more information from the doctor's office.”
	“If you're saying like, oh, here's a pamphlet on this this...No, to me, that means nothing to me. I don't know what any of that stuff means. [. . .] I never knew what NSAIDs [nonsteroidal anti-inflammatory drugs] was! What the heck is that mess! You could tell me all day long, this does this and this, and I could read all about it. After that, I'd say 90% of that stuff I don't even know, even what the side effects are, I don't understand it! Cause I'm not medically inclined! So to me, that means nothing. [. . .] When I read about all that stuff, I'm like, oh my god I don't want to take this stuff! It's gonna kill me!”

3.6 FIGURES

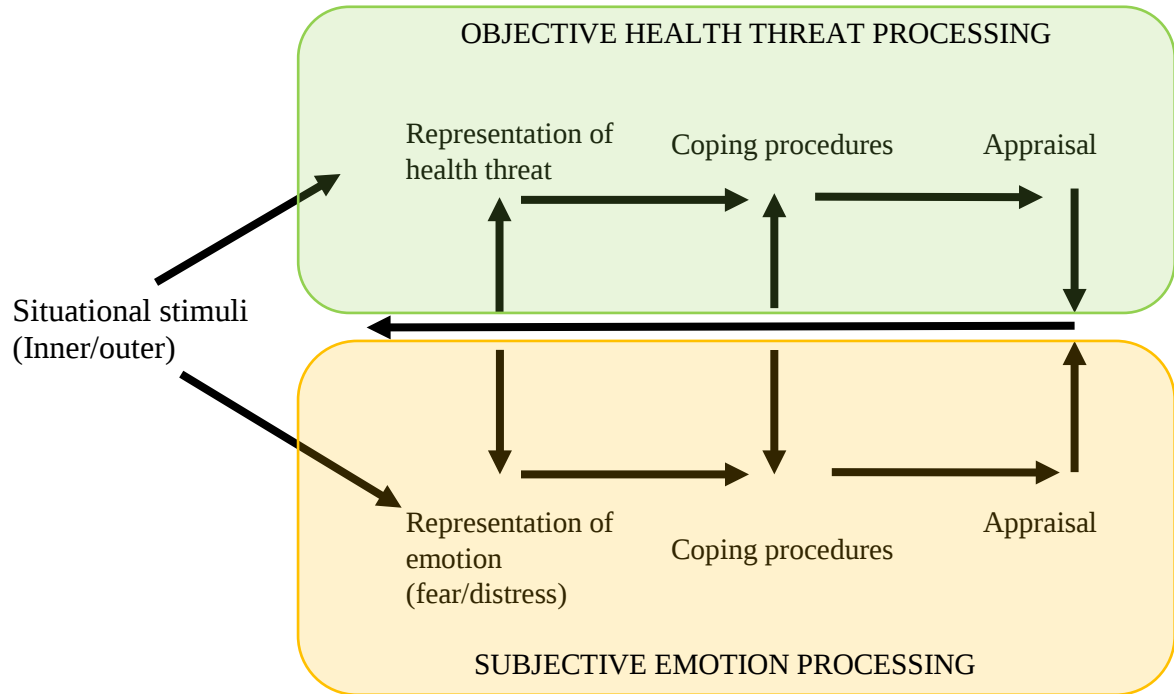


Figure 3-1. Leventhal's Self-Regulatory Model.

(Adapted from Leventhal et al., "Illness cognition: using common sense to understand treatment adherence and affect cognition interactions." *Cognitive Therapy and Research* 1992;16:143-163.).

- Experiences with RA symptoms
- Experiences, attitudes, and emotions towards living with and adapting to RA
- Expectations about the future course of their RA disease
- Experiences, attitudes, and emotions towards taking RA medications
- Experiences with alternative therapies
- Experiences and preferences regarding decision making about RA medications
- Relationship with rheumatologist (and/or other health care providers)
- Acquiring and making sense of information about RA and RA medications
- Interactions with other RA patients

Figure 3-2. Topics discussed in the semistructured interviews.

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4.0 DISCREPANCIES BETWEEN PHYSICIAN AND RHEUMATOID ARTHRITIS PATIENT ASSESSMENTS OF TENDERNESS AND SWELLING IN JOINTS

ABSTRACT

Objective: Guidelines recommend that rheumatoid arthritis (RA) patients be treated to a target of low disease activity/remission. Patient-reported joint counts (assessments of tenderness and swelling) could be used to monitor disease activity between clinic visits, alerting physicians when medication adjustment is needed. Our goal was to determine whether patient joint counts could approximate physician joint counts in detecting moderate/high disease activity (MHDAS) and to determine factors associated with patient-physician discrepancies.

Methods: Patients and physicians participating in the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry independently assessed tenderness and swelling in 28 joints at 1844 clinic visits. We examined how physicians and patients differed in detection of tenderness/swelling and MHDAS, and determined the factors associated with joint count discrepancies.

Results: Patients and physicians agreed 83.6% of the time on joint tenderness/swelling and 80.2% of the time on the presence of MHDAS, with patients typically reporting worse symptoms. Compared to physicians' detection of MHDAS, patient joint counts had a sensitivity

of 86.9%, specificity of 74.6%, and positive predictive value of 74.5%. Longer duration of RA (OR [95% CI]: 1.01 [1.00, 1.02]), augmenting/switching therapy at the previous visit (1.24 [1.07, 1.43]), small joint items (1.28 [1.12, 1.48]), and swelling joint items (1.20 [1.02, 1.43]) were associated with a greater likelihood of disagreement on joint tenderness/swelling. No covariates were significantly associated with patient-physician disagreement on the presence of MHDAS.

Conclusion: While physicians and patients sometimes disagreed on joint count items, they agreed on the presence of MHDAS. This suggests that patient joint counts might be used to monitor patients' disease activity between clinic visits.

4.1 INTRODUCTION

Current American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) guidelines for treating rheumatoid arthritis (RA) recommend systematically monitoring disease activity and treating to the target (T2T) of low disease activity or remission (LDAS) with disease modifying anti-rheumatic drugs (DMARDs) (1-4). The T2T approach for the management of RA has been recommended in published guidelines since 2010 (5). Monitoring disease activity regularly is a critical component of implementing T2T for RA—disease activity measurements indicate when physicians and patients should consider adjusting medication therapy. EULAR recommends more frequent assessment of disease activity (every 1-3 months) when the patient has moderate to high disease activity (MHDAS), but less frequent monitoring (every 6 months) when disease activity has stabilized at the treatment target (4). Physician examination of swelling and tenderness in joints is central to disease activity

monitoring in RA (6). Several composite disease activity measures recommended by the ACR, such as the four versions of the Disease Activity Score 28 joint (DAS28) measure and the Clinical Disease Activity Index (CDAI), include a physician joint count (assessment of tenderness and swelling) in 28 joints (6).

In current clinical practice, most RA patients only have disease activity assessed at clinic visits; therefore, patients with MHDAS may not have disease activity monitored as frequently as would be optimal. Barriers to more frequent clinic visits are the limited availability of rheumatologists, long travel distances between patients' homes and clinics (7), and the burden of increased out-of-pocket expenses for additional visits (8). Kahn et al. reported that 31% of California RA patients in their study had not seen a rheumatologist in the last 3 months, and 14% had not done so in the last 12 months, despite most patients having active disease (9).

One way to increase the frequency of disease monitoring is to have patients perform joint counts between visits. Patients could report their joint count results online using a web-based form or patient portal, or via telephone. Patient joint counts could be combined with blood work to calculate a measure such as the DAS28-C-reactive protein (CRP) (6) and indicate whether the patient has MHDAS. Electronic medical record systems could integrate this information, generating an automated alert to schedule a follow-up appointment when the patient has MHDAS.

The objective of our study was to determine whether patient-reported joint counts could approximate joint counts performed by physicians in the detection of MHDAS. There is conflicting evidence on inter-observer reliability between physicians and patients on joint counts (10-24). Furthermore, not much is known about the circumstances under which disagreement is more likely to occur on patient and physician joint counts. We designed a web-based patient joint

count tool and administered it to RA patients enrolled in a registry where physician joint counts were routinely conducted at clinic visits. We then compared the patient and physician joint counts, examined the extent to which they were discrepant, and determined which patient- and joint exam-related factors were associated with discrepancies.

4.2 PATIENTS AND METHODS

4.2.1 Data source

We used data from the RACER registry, which has enrolled over 1000 RA patients treated by rheumatologists working at four University of Pittsburgh Medical Center (UPMC) arthritis clinics in Pittsburgh, Pennsylvania. RACER began enrolling participants and collecting visit-level data on disease-specific and overall health status, medications, and health-related quality of life in 2010. The RACER study is approved by University of Pittsburgh's Institutional Review Board and participants are enrolled through an informed consent process.

At every RACER clinic visit, physicians conducted joint counts for the 28 joints included in the DAS28 and CDAI measures. Starting in May 2012, at every clinic visit, RACER participants were also asked to complete a patient-reported joint count for the same 28 joints. The 28 joints in the joint count included right and left metacarpal phalangeal (MCP), proximal interphalangeal (PIP), knee, wrist, elbow and shoulder joints. Physicians did not have access to the results of their patients' joint counts when completing joint counts, and vice versa.

Patients completed their joint counts assisted by a web-based tool designed by the RACER research team. The patient joint count tool provided illustrations of the joints to be checked and definitions of “tenderness” and “swelling”, and was based on instructions developed for physicians performing the same joint count (supplementary materials, **Figure S3**). The tool was administered on a computer tablet and a staff member from the research team was available for questions.

We included data from RACER registry visits where both the patient and the physician completed a joint count. Regression analyses included data where there were no missing covariates for the patient and physician.

4.2.2 Dependent variables

The outcome of interest was agreement between each patient and physician on the joint count, and this agreement was measured at both the item level (for each visit there were a maximum of 56 items: tenderness and swelling in 28 joints) and at the visit level. At the item level, agreement was measured as a binary variable equal to 1 if the patient and physician agreed on the presence/absence of tenderness or swelling in the joint or 0 otherwise. At the visit-level, we focused on agreement on detection of MHDAS, since this is the threshold at which treatment change is recommended according to ACR and EULAR guidelines on treating to the target of low disease activity or remission (1-4). We chose to focus on the Clinical Disease Activity Index (CDAI) measure instead of the DAS28-CRP because it does not require the CRP component, thus allowing us to include more observations in our analyses. The CDAI is also recommended for clinical use by the ACR (6), and has been demonstrated to perform similarly to the DAS28-

CRP in disease severity categorization (25). A patient is considered to have MHDAS if their CDAI value is greater than 10 (6). The patient and physician joint counts were used to calculate the CDAI (CDAI=tender joints + swollen joints + patient global disease activity + physician global disease activity), and agreement was measured as a binary variable equal to 1 if the patient- and physician-derived CDAI scores concurred on the presence/absence of MHDAS and 0 otherwise (6).

4.2.3 Independent variables

Predictors of patient-physician agreement on joint counts included covariates for patient demographic characteristics, overall health and RA disease characteristics, medication use, and joint count item characteristics. Patient demographic variables included age and indicators for sex and African-American race. Overall health and RA disease characteristics measured at each clinic visit included Deyo-Charlson comorbidity index, Short Form 12 physical component summary (SF12-PCS) and mental component summary (SF12-MCS), duration of RA, physician global disease activity, patient pain, patient global health, and Routine Assessment of Patient Index Data 3 score (RAPID3). Medication use variables collected at each visit included DMARD use, corticosteroid use, augmenting/switching DMARD therapy at the current visit, and augmenting/switching DMARD therapy at the previous visit. Joint count item characteristics included indicators for large joint items (shoulder, elbow, wrist, knee) and for tenderness items (vs. swelling items).

4.2.4 Statistical Analyses

To assess the unmet need for disease activity monitoring between visits, we examined whether RACER patients completed follow-up visits within the time frame recommended by EULAR (4). We identified RACER visits where patients had MHDAS or low disease activity/remission (LDAS) according to the DAS28-CRP, and determined the proportions where the patient returned for a follow-up visit within 3 months and 6 months, respectively.

We performed analyses to describe characteristics of patients included and excluded from the regression analyses (described below). To assess agreement at the item level, we cross-tabulated frequencies of patient vs. physician item responses, and calculated the sensitivity, specificity, and positive predictive value of patient joint counts compared to physician joint counts for detecting tenderness and swelling. We examined the distribution of patient-physician item disagreements per visit. To assess agreement at the visit level, we cross-tabulated frequencies of patient vs. physician detection of MHDAS and calculated the sensitivity, specificity, and positive predictive value of patient joint counts compared to physician joint counts for detecting MHDAS. We calculated intraclass correlation coefficients (ICC) for absolute agreement between patient and physician tender and swollen joint counts using a two-way mixed effects model, as well as Spearman correlation coefficients.

We used two-stage logistic regression to model the influence of covariates on agreement between patient and physician joint counts. Analyses were conducted at both the item and visit levels. The same patient could be included multiple times.

A two-stage logistic regression approach following that of Lipsitz *et al.* (26) was chosen to account for agreement that might be expected due to chance, since low disease activity ratings

are quite prevalent among patient and physician joint counts and may inflate the overall agreement rate. Four separate first-stage logistic regressions were used to model the influence of covariates on the probability of the patient or physician giving a positive response (either detection of joint swelling/tenderness or MHDAS).

The first-stage logistic regression on the probability of a physician giving a positive response on any of the 56 items was modeled with the following covariates: age, gender, African-American race, duration of RA, Deyo-Charlson comorbidity index, DMARD use, corticosteroid use, augmenting/switching DMARD therapy, indicator for large joint items, indicator for tenderness items, and physician global disease activity. The first-stage logistic regression on the probability of a patient giving a positive response on any of the 56 items was modeled with the same covariates except that physician global disease activity was omitted, and additional patient-reported covariates were included (patient pain, patient global health, SF12-MCS, SF12-PCS). The same first-stage regressions were performed for patient and physician probability of detecting MHDAS, except that the indicators for large joint items and tenderness items were omitted.

The patient's and physician's predicted probabilities of positive response from the first-stage logistic regressions were then used to calculate an offset term,

$$\hat{\eta}_i = \text{logit}[\hat{p}_{i1}\hat{p}_{i2} + (1 - \hat{p}_{i1})(1 - \hat{p}_{i2})]$$

This offset term represents the expected agreement due to chance. To control for expected agreement due to chance, the offset term was included in the second-stage logistic regressions that modeled the probability of patient-physician agreement conditional on covariates. Lipsitz *et al.* (26) showed that if the observed agreement does not exceed that expected by chance, the

coefficients of the covariate predictors will equal zero. To account for underlying correlation between joints within each visit and patient, the second-stage logistic regressions were carried out using generalized linear latent and mixed models (GLLAMM), implemented using Rabe-Hasketh's gllamm program in Stata (27).

To obtain the correct confidence intervals for the second-stage regression parameter estimates, we bootstrapped both the item- and visit-level analyses with 200 iterations, using 80% samples of visit-level clusters (sampled with replacement) for each iteration.

4.3 RESULTS

In the RACER registry, only 49% of patients with MHDAS had a follow-up visit within 3 months, and only 70% of patients with LDAS had a follow-up visit within 6 months.

There were 2049 visits between May 2012 and December 2013 at which 718 RA patients and their physicians had completed joint counts. During these visits, patient and physician ratings were available for a total of 110,768 items. Of these, 1,844 visits (comprising 100,209 items among 676 patients) had all covariate data and were included in regression analyses. Observations were most often excluded due to missing medication data (3.4%), or incomplete physician (2.1%) or patient (2.6%) responses to RACER questionnaires. Since availability of these data was determined by the visit date or by whether the physician or patient had enough time to complete RACER questionnaires, the missing data are unlikely to have biased our results.

4.3.1 Descriptive analyses

Characteristics of patients at visits included and excluded from regression analyses were similar; at included visits, patients were 79.5% female, with a mean age of 62.6 years (**Table 1**). The distribution of disease activity at included visits is shown in **Table 2**, and the distribution of visit-observations among included patients is shown in **Table 3**. The number of patients in each disease severity category was evenly distributed.

The ICC [95% CI] for absolute agreement between patient and physician joint counts was higher for tender (0.46 [0.43, 0.49]) than for swollen joints (0.36 [0.32, 0.40]). Spearman's correlation coefficient [95% CI] was also higher for patient and physician tender joint counts (0.51 [0.48, 0.55]) than for swollen joint counts (0.41 [0.37, 0.45]).

For both tenderness and swelling items, the most common response was that both the patient and physician agreed that there was no swelling (81.7% of cases) or no tenderness (75.4% of cases) in the joint (**Table 4**). Taking physician joint counts as the gold standard, patient joint assessments had an overall sensitivity of 52.3%, specificity of 86.9%, and positive predictive value of 29.5% for the detection of tenderness or swelling in individual joints. For detection of tenderness in individual joints, patient joint counts had a sensitivity of 39.6%, specificity of 90.4%, and positive predictive value of 30.3%. For detection of swelling in individual joints, patient joint assessments had a sensitivity of 65.7%, specificity of 83.2%, and positive predictive value of 29.0%.

For detection of MHDAS according to the CDAI measure, patient joint counts had a sensitivity of 86.8%, specificity of 74.6%, and positive predictive value of 74.5% relative to physician joint counts (**Table 5**). For both patients and physicians, about half of the clinic visit

exams were rated as MHDAS. In the majority of cases (79.9%), the patient and the physician joint count agreed that the patient either had MHDAS (40.0%) or LDAS (39.9%). However, in 20.1% of cases the patient and the physician disagreed on whether the patient had MHDAS. In the cases where there was disagreement, patients typically rated disease activity as being higher than their physicians (13.8% patient moderate-high/physician low; 6.2% patient low/physician moderate-high). A similar pattern of agreement held when comparing DAS28-CRP scores based on the patient and physician ratings (supplementary materials, **Table 6**). Patient-derived DAS28-CRP scores had a sensitivity of 87.5%, specificity of 72.2%, and positive predictive value of 73.0% for detecting MHDAS, compared to physician-derived scores (n=675).

Figure 1 shows the distribution of discrepant items per visit. At 56.8% of visits, there were more than 5 discrepant items. Patients with MHDAS (according to the RAPID3 measure) had greater numbers of discrepant items compared to those with LDAS (**Figure 2**).

4.3.2 Predictors of physician-patient agreement on joint assessments

The second-stage GLLAMM regression results are shown in **Table 7 4**. Covariates significantly associated ($p < 0.05$) with a greater likelihood of patient-physician agreement on joint counts at the item level included (odds ratio [95% confidence interval], p-value) shorter duration of RA (1.01 [1.00, 1.02], $p < 0.01$), not augmenting/switching therapy at the previous visit (1.24 [1.07, 1.43], $p < 0.01$), large joint items (1.29 [1.12, 1.48], $p < 0.01$), and tender joint items (1.20 [1.02, 1.43], $p = 0.03$).

No covariates had a statistically significant effect on visit-level patient-physician agreement.

4.4 DISCUSSION

In the RACER registry, 51% of patients with MHDAS and 30% of patients with LDAS did not return for a follow-up visit within 3 months and 6 months, respectively, as recommended by EULAR guidelines. This suggests that the frequency of disease monitoring at visits may be insufficient for many RA patients, leading to delays in detecting and addressing MHDAS.

Our results suggest that the patient joint count may be an appropriate substitute for the physician joint count, when it is not available, for calculating joint-count based measures of disease activity such as the CDAI or DAS28 to monitor for MHDAS. Despite only modest agreement on individual tenderness and swelling items and joint count totals, patient and physician joint counts demonstrated reasonable agreement in detection of MHDAS using the CDAI for the full study sample, and using the DAS28-CRP for a smaller sample. Unlike the CDAI measure, the DAS28 measures do not require a physician reported global disease activity score, and could be used with patient joint counts to monitor disease activity between visits. Using a combination of patient joint counts and blood work to monitor disease activity remotely may be a useful solution when follow-up visits cannot be scheduled frequently, and may alert patients and physicians when follow-up visits are needed to address MHDAS.

To our knowledge, no previous studies have compared patient and physician joint counts in terms of detection of MHDAS, thus limiting what we knew about the interchangeability of patient and physician joint counts for research or clinical purposes. Instead, previous studies have focused on the correlation or reliability of patient and trained assessor joint counts. Barton *et al.*'s (13) systematic review reported summary Spearman correlation coefficients for patient and physician tender joint counts (0.60) and swollen joint counts (0.54). Cheung *et al.*'s (23)

systematic review reported summary ICCs for patient and physician tender joint counts (0.82) and swollen joint counts (0.44). We found relatively low correlation and reliability for tender and swollen joint counts compared to previous studies. This suggests that our estimates of the sensitivity, specificity, and positive predictive value of patient vs. physician joint counts for detection of MHDAS may be conservative, and that patient and physician joint counts may demonstrate agreement in detection of MHDAS that exceeds the level of agreement shown in our study.

The factors we identified to be associated with patient-physician discrepancies may indicate circumstances where joint assessment is especially challenging for patients as well as physicians. We found that disagreements on individual joint count items were more likely to occur for patients with longer duration of RA and those who did augment/switch DMARD therapy at the previous visit. We also found that controlling for all other factors, disagreements were more common for small joint and swelling items. However, we found that none of the covariates were significantly associated with patient-physician agreement on joint counts at the visit-level, when the joint assessments were used to categorize disease severity. Although we have used the physician joint count as the de facto gold standard for calculating the sensitivity, specificity and positive predictive value of the patient joint count, patient-physician discrepancies should not necessarily be interpreted as patient errors. Both patients and physicians may benefit from increased training on how to detect symptoms of swelling and tenderness due to RA. For example, Levy et al. (28) showed that training patients on how to distinguish between a chronically enlarged joint and a swollen joint can improve the agreement between patient and physician joint counts. It is possible that training patients to differentiate between symptoms due

to RA inflammation and symptoms due to other conditions may further improve the usefulness of patient joint counts for detecting MHDAS.

Wong *et al.* previously examined predictors of patient-physician differences in total joint counts (21). They found that greater age and poorer physical functioning were associated with discordance on tender joint counts completed via mannequin format, and that longer disease duration was associated with discordance on tender joint counts completed via textual instruction format. Like Wong *et al.*, our study also found that longer duration of disease was associated with patient-physician disagreement at the item level, but not at the visit level on detection of MHDAS. We did not find a significant association between age or physical functioning and patient-physician agreement on joint counts. We may have had different findings because of differences in how patient joint counts were administered (Wong *et al.* had patients assess their joints at home 1 day before and after the physician assessed their joints at the clinic, while we had patients assess their joints at the clinic on the same day as the physician) or differences in analytic methods (we controlled for expected agreement due to chance, while they did not, and at the visit level we focused on agreement with respect to detection of MHDAS, rather than absolute difference in total joint counts).

Longer duration of RA was associated with a slightly higher likelihood of patient-physician discrepancy at the item level. With an additional 10 years of RA, patients were 1.10 times more likely to disagree with physicians at the item-level. Some patients may develop enlarged bony joints, nodules, and osteoarthritis over the course of many years with RA, making it difficult to assess whether tenderness or swelling is due to RA disease activity.

Augmenting/switching DMARDs at the previous visit was associated with a lower likelihood of item-level agreement. Decisions to augment/switch DMARDs at the previous visit

may have created expectations for improved symptoms that in some cases were not met for either the physician or the patient, leading to more item-level discrepancies.

We found that swelling items were associated with greater likelihood of disagreement between the physician and patient, compared to tenderness items. This was consistent with previous research which has shown higher levels of patient-physician disagreement on swelling rather than tenderness in joints (10-11, 13, 15-19, 21-22). Joint swelling may be more challenging than tenderness for patients and physicians to recognize. Osteoarthritis, nodules, enlarged bony joints, and even weight gain may complicate the assessment of swelling due to RA, often leading patients to find joint swelling where physicians do not. We also found that the small joint items were associated with slightly greater probability of patient-physician disagreement compared to large joint items. This could be because the small joints of the hands are more difficult to check for swelling and tenderness relative to large joints such as the knees and shoulders. It may be more challenging for patients to detect swelling or tenderness by squeezing joints (the technique applied to the small hand joints) rather than through movement of the joint (the technique applied to large joints such as the knee and shoulder).

4.4.1 Study limitations

There were some limitations to our analysis. First, it is possible that in the context of the RACER registry, patient and physician joint counts might have influenced each other, leading to more similar assessments. Although physicians did not watch patients perform joint counts, patients did observe physicians assessing their joints and inevitably participated in the physician joint count by responding to the physician's questions as the exam was performed. Sometimes patients

assessed their own joints before the physician performed the joint count, and sometimes they did so afterwards. If patients observed the physician's joint count before assessing their own joints, it is possible that the physician's evaluation might have influenced the patient's responses. If the patient assessed their own joints before meeting with the physician, it might have prepared them to respond during the physician's joint count, thus also aligning their responses more closely. Unfortunately, it was impossible to simultaneously prevent both types of influence between physician and patient respondents, since the patient must be present and participate in the physician's examination of their joints. Providing patients with clear and thorough instructions on how to assess their own joints and allowing them to do so without the physician present encouraged patients to complete the assessment based on their own judgment, minimizing the degree to which they would be influenced by the physician. In a future study, we could prevent the patient's responses from being influenced by the physician's responses by having all patients assess their joints prior to seeing the physician.

Another limitation was that patients who successfully completed joint counts were possibly more skilled at performing them than those who did not, thus making patient joint counts appear more similar to the physician joint counts than they would be if we had included data from all RACER patients. Since RACER began collecting patient joint counts in May 1, 2012, patients completed joint counts at 74% of visits with a completed physician joint count. Again, our patient joint count tool provided illustrated instructions designed to make completing the assessment as simple as possible for patients. This helped to ensure that we were able to obtain responses from as broad a sample as possible.

Because patients in our study completed their joint counts at the clinic, our study does not show how patients would perform if completing joint counts at home for the purpose of disease

activity monitoring in between clinic visits. Since study patients assessed their joints guided by our web-based tool and with minimal guidance from study coordinators, this leads us to believe that patients would perform similarly well using the same web-based tool (or a paper version) at home. Further study is needed to better understand how to improve the accuracy of patient joint counts performed at home.

A final limitation was that we did not have enough CRP data to compare DAS28-CRP scores using the patient and physician joint counts, or to evaluate the impact of covariates on patient-physician agreement on disease severity according to the DAS28-CRP. The CDAI has been shown to have a high correlation with the DAS28-CRP, and offers a reasonable approximation of DAS28-CRP (25). Although we were not able to conduct our study using the DAS28-CRP measure, our results with the CDAI measure suggest that patient joint counts might be similarly useful in approximating DAS28-CRP when the physician joint count is not available.

4.4.2 Conclusion

In summary, while some amount of disagreement between physician and patient may exist at the item level in joint counts, most of the time (80.2% of visits) RA patients and physicians agreed on the presence/absence of MHDAS. This suggests that patient joint counts might be useful as tools to help rheumatologists monitor their patients' disease activity between clinic visits and prompt scheduling of follow-up visits to address MHDAS. The usefulness of patient-reported joint counts might be further increased if patients are provided with more training on how to perform the assessments accurately. We have identified specific factors (such as longer disease

duration) and types of items (such as swelling) which are associated with lower levels of patient-physician agreement. These can be used to guide efforts to better train RA patients and their physicians to perform joint counts in the future, as well as to better interpret their results.

4.5 TABLES

Table 4-1. Characteristics of patients at visits included and excluded from multivariate analyses*.

Mean, standard deviation (SD) or %	All visits with a patient and physician joint assessment (n=2,040)	Visits included in regressions (n=1,844)	Visits excluded from regressions (n=196)
Age	62.4 (12.6)	62.6 (12.5)	60.5 (13.1)
Female	79.2%	79.5%	76.5%
African-American	10.3%	9.8%	15.8%
Duration of RA, years	16.0 (12.7), n=2,032	16.2 (12.7)	13.9 (12.4), n=188
Deyo-Charlson comorbidity index	2.1 (1.5), n=2,030	2.1 (1.5)	2.3 (1.6), n=186
Physician global disease activity, 0-10	2.6 (2.2), n=2,006	2.7 (2.1)	2.5 (2.3), n=162
Patient pain, 0-10	4.4 (3.0), n=2,022	4.4 (3.0)	4.4 (3.2), n=178
Patient global health, 0-10	4.0 (2.6), n=2,031	4.0 (2.6)	3.9 (2.9), n=187
SF12-MCS, 0-100	49.4 (11.0), n=2,009	49.4 (10.9)	49.6 (11.4), n=165
SF12-PCS, 0-100	38.1 (11.1), n=2,009	37.9 (11.1)	40.4 (11.9), n=165
DAS28-CRP	3.1 (1.2), n=742	3.1 (1.2), n=675	3.0 (1.4), n=67
CDAI	12.0 (10.2), n=1,997	12.1 (10.2)	11.7 (11.0), n=153
RAPID3, 0-10	3.6 (2.2), n=1,988	3.6 (2.2)	3.8 (2.7), n=144
DMARD use (including biologics and traditional DMARDs)	93.5%, n=2,010	93.6%	92.2%, n=166
Biologic use	50.7%, n=2,010	51.7%	39.2%, n=166
Corticosteroid use	48.2%, n=2,010	48.0%	50.6%, n=166
Augmented/switched DMARD therapy at current visit	17.0%, n=2,010	15.9%	29.5%, n=166
Augmented/switched DMARD therapy at previous visit	16.1%, n=1971	16.3%	14.2%, n=127

* Means and percentages across all visit-observations in each subgroup are reported. Patients could have multiple observations; some patients may have had certain observations excluded due to missing covariates. Because item-level analyses required same covariates to be present, the same characteristics were reflected in item-level data as well.

Table 4-2. Distribution of disease activity at visits included in regression analyses (n=1844).

		CDAI [#]				
		High	Moderate	Low	Remission	Total
RAPID3*	High	232 (12.6%)	392 (21.3%)	204 (11.1%)	4 (0.2%)	832 (45.1%)
	Moderate	25 (1.4%)	126 (6.8%)	281 (15.2%)	22 (1.2%)	454 (24.6%)
	Low	3 (0.2%)	55 (3.0%)	133 (7.2%)	55 (3.0%)	246 (13.3%)
	Remission	2 (0.1%)	18 (1.0%)	94 (5.1%)	198 (10.7%)	312 (16.9%)
	Total	262 (14.2%)	591 (32.1%)	712 (38.6%)	279 (15.1%)	1844 (100%)

*RAPID3 score of 0 to 1.0=remission; >1.0 to 2.0=low disease activity; >2.0 to 4.0=moderate disease activity; and >4.0 to 10=high disease activity.

[#]CDAI score of ≤2.8=remission; >2.8 to 10.0=low disease activity; >10.0 to 22.0=moderate disease activity; and >22.0=high disease activity.

Table 4-3. Number of visit-observations among patients for data included in regression analyses (1844 visit-observations for 676 patients).

Number of visit-observations	Frequency (%)
1	151 (22.3%)
2	196 (29.0%)
3	158 (23.4%)
4	90 (13.3%)
5	45 (6.7%)
6	19 (2.8%)
7	11 (1.6%)
8	3 (0.4%)
9	3 (0.4%)
Total	676 (100%)

Table 4-4. Patient vs. physician item responses to joint assessments.

Is the joint tender?	MD: yes	MD: no	Total
Patient: yes	2,137 (3.8%)	4,920 (8.7%)	7,057 (12.5%)
Patient: no	3,261 (5.8%)	46,079 (81.7%)	49,340 (87.5%)
Total	5,398 (9.6%)	50,999 (90.4%)	56,397 (100%)
Is the joint swollen?	MD: yes	MD: no	Total
Patient: yes	3,364 (6.2%)	8,255 (15.2%)	11,619 (21.4%)
Patient: no	1,754 (3.2%)	40,998 (75.4%)	42,752 (78.6%)
Total	5,118 (9.4%)	49,253 (90.6%)	54,371 (100%)
All items (both tenderness and swelling)	MD: yes	MD: no	Total
Patient: yes	5,501 (5.0%)	13,175 (11.9%)	18,676 (16.9%)
Patient: no	5,015 (4.5%)	87,077 (78.6%)	92,092 (83.1%)
Total	10,516 (9.5%)	100,252 (90.5%)	110,768 (100%)

Table 4-5. Patient vs. physician disease severity categorizations (CDAI*).

	MD: moderate/high disease activity	MD: low disease activity	Total
Patient: moderate/high disease activity	799 (40.0%)	274 (13.7%)	1073 (53.7%)
Patient: low disease activity	121 (6.1%)	803 (40.2%)	924 (46.3%)
Total	920 (46.1%)	1077 (53.9%)	1997 (100%)

*CDAI > 10 is considered to be moderate/high disease activity; CDAI ≤ 10 is considered to be low disease activity/remission.

Table 4-6. Patient vs. physician disease severity categorizations (DAS28-CRP*).

.	MD: moderate/high disease activity	MD: low disease activity	Total
Patient: moderate/high disease activity	273 (40.4%)	101 (15.0%)	374 (55.4%)
Patient: low disease activity	39 (5.8%)	262 (38.8%)	301 (44.6 %)
Total	312 (46.2%)	363 (53.8%)	675 (100%)

* DAS28-CRP (DAS28-CRP>3.2 is considered to be moderate/high disease activity; DAS28-CRP≤3.2 is considered to be low disease activity/remission)

Table 4-7. Factors associated with patient-physician agreement on joint assessments: GLLAMM estimated odds ratios.

Outcome	Item-level agreement		Visit-level agreement	
Covariate	Odds ratio [95% CI]*	P-value*	Odds ratio [95% CI]*	P-value*
Age	1.00 [0.99, 1.00]	0.57	0.99 [0.97, 1.01]	0.23
Female	0.85 [0.69, 1.04]	0.11	0.95 [0.48, 1.89]	0.89
African-American race	1.03 [0.83, 1.29]	0.76	1.23 [0.41, 3.70]	0.71
Duration of RA (years)	0.99 [0.98, 0.99]	<0.01	1.00 [0.97, 1.02]	0.74
Deyo-Charlson comorbidity index	1.00 [0.96, 1.05]	0.88	1.03 [0.82, 1.30]	0.81
SF12-MCS	1.00 [0.99, 1.01]	0.93	1.01 [0.98, 1.04]	0.47
SF12-PCS	1.00 [0.99, 1.01]	0.89	1.04 [1.00, 1.08]	0.09
Physician global disease activity	0.98 [0.93, 1.04]	0.49	1.11 [0.95, 1.30]	0.20
RAPID3	1.05 [0.97, 1.14]	0.19	1.22 [0.97, 1.53]	0.09
DMARD use	0.98 [0.77, 1.25]	0.89	0.82 [0.26, 2.59]	0.73
Corticosteroid use	1.13 [0.97, 1.32]	0.11	1.10 [0.64, 1.89]	0.73
Augmented/switched DMARD therapy at current visit	1.11 [0.89, 1.37]	0.36	0.80 [0.40, 1.59]	0.52
Augmented/switched DMARD therapy at previous visit	0.81 [0.70, 0.93]	<0.01	0.85 [0.44, 1.63]	0.62
Large joint item	1.28 [1.12, 1.48]	<0.01	--	--
Tenderness item	1.20 [1.02, 1.43]	<0.01	--	--

*P-values and 95% confidence intervals obtained by bootstrapping the analysis for 200 iterations.

4.6 FIGURES

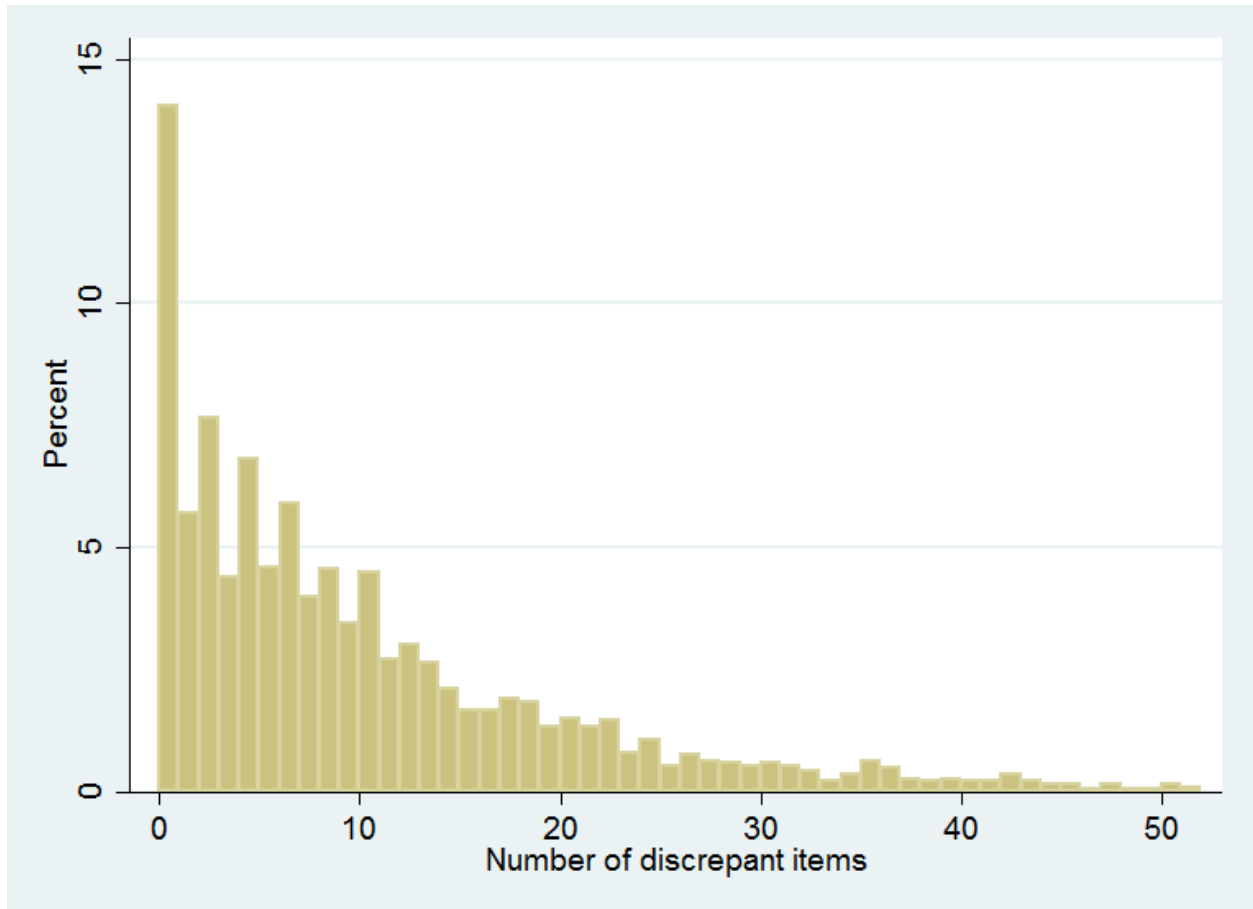
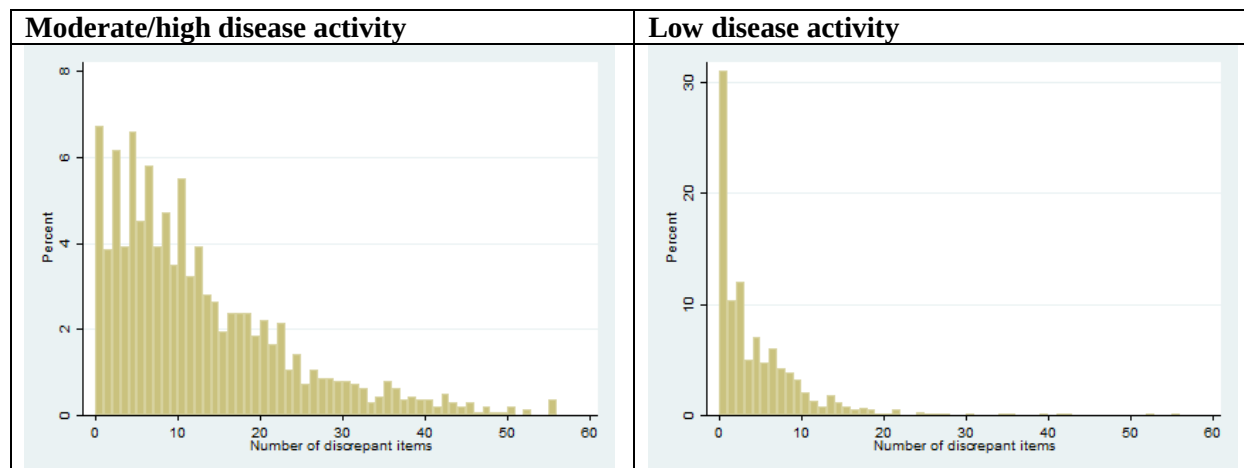
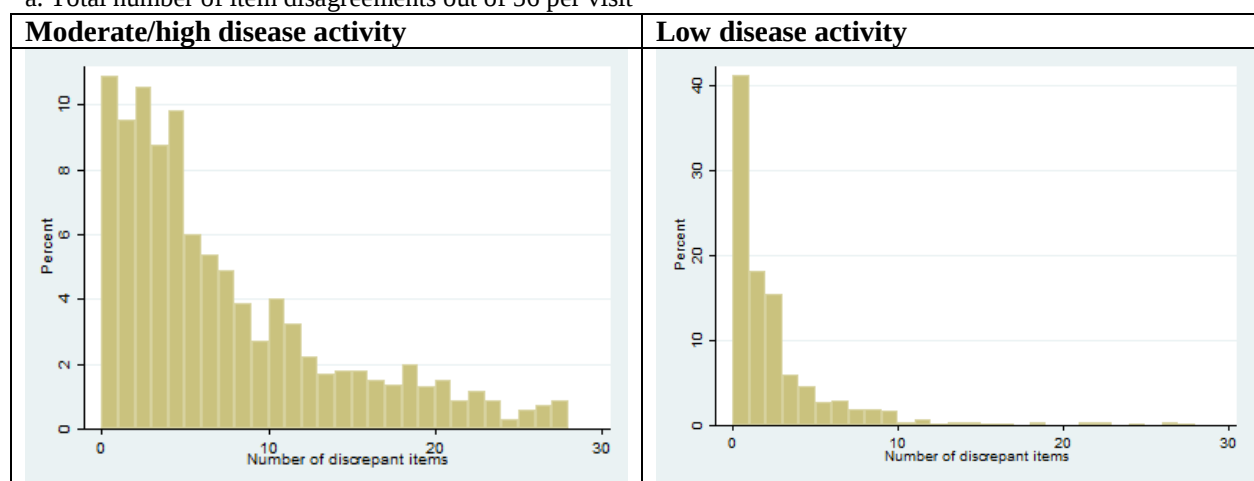


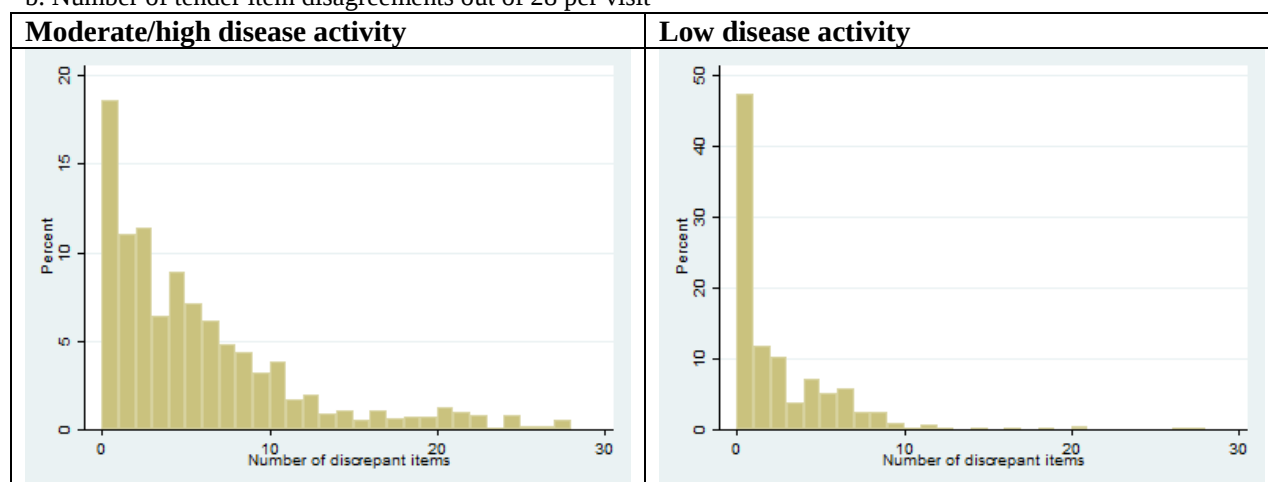
Figure 4-1. Distribution of number of discrepant items out of 56 per visit (n=1844).



a. Total number of item disagreements out of 56 per visit



b. Number of tender item disagreements out of 28 per visit



c. Number of swollen item disagreements out of 28 per visit

Figure 4-2. Comparison of number of disagreements for moderate/high vs. low disease activity patients (RAPID3).

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