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Adherence to Disease Modifying Anti-Rheumatic Drugs in Rheumatoid Arthritis Patients: A Narrative Review of the Literature

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Abstract

Aim—This paper synthesizes findings from available research about medication adherence to disease modifying anti-rheumatic drugs (DMARDs) in the rheumatoid arthritis (RA) population.

Results—This review of literature included 35 articles. Medication adherence to DMARDs ranged from 30% to 107%. Adherence rates greater than 100% indicated that patients took more than the prescribed amount of medication. There were no consistent risk factors for nonadherence to DMARD prescriptions identified, but some evidence was provided for self-efficacy, patient-health care provider relationships, social support, patient beliefs about medications, and age as factors affecting medication adherence. Support for educational interventions focused on medication adherence was equivocal.

Conclusion—Further research is necessary to develop a comprehensive, theoretically-based understanding of medication adherence in RA patients.

Keywords

rheumatoid arthritis; medication adherence; disease modifying anti-rheumatic drugs; review of the literature

Introduction

"Rheumatoid arthritis (RA) is an autoimmune disorder of unknown etiology characterized by symmetric, erosive synovitis and in some cases, extraarticular involvement" (American College of Rheumatology [ACR] Subcommittee, 2002; Harris, 1990). Rheumatoid arthritis has been diagnosed in approximately 1.3 million U.S. adults with an increased prevalence in women and the elderly (ACR, 2008; Center for Disease Control [CDC], 2007; Helmick et al., 2008). The standardized mortality ratio for RA patients has been estimated at 2.26; therefore, when a person with RA is compared to the average person in the population, they are twice as likely to die at the same age (Wolfe et al., 1994). Maetzel and colleagues (2004) estimated the yearly direct costs, the costs of treatment for RA, are nearly twice that of osteoarthritis (OA). Similarly, the indirect costs, the costs due to decreased productivity, are five times that of OA. The estimated total yearly cost of RA and OA per individual patient was $9,300 and $5,700,

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respectively. A systematic review of the costs of RA found that 12% to 26% of patients studied were hospitalized, which accounted for a significant portion of these costs (Cooper, 2000).

Current guidelines recommend treating the majority of RA patients with disease-modifying anti-rheumatic drugs (DMARDs) within three months of diagnosis (See Table 1). When taken as prescribed, these medications can result in remission of the disease as evidenced by normal tests of inflammation (i.e. erythrocyte sedimentation rate and/or C-reactive protein), lack of joint pain and swelling, and lack of radiographic progression of the disease. Remission of the disease achieves the goals of therapies, which are to prevent damage to joints, maintain functional status, and decrease pain (ACR Subcommittee, 2002).

Medication Adherence, Compliance and Persistence

Compliance and adherence are often used interchangeably in theoretical, clinical, and research literature. However, these terms must be considered within an historical and theoretical context. In the 1950's, health care providers embraced compliance to describe patient behavior. A health care provider determined the required treatment and the patient was expected to follow the treatment regimen as prescribed; the patient was passive in this relationship (Steiner & Earnest, 2000). If the treatment was not followed, the patient was deemed non-compliant, a deviant behavior. When the health care plan was followed as directed, the patient was labeled compliant and expected to achieve the goal of health.

More recently, there has been a paradigm shift away from the medical model of care to a more collaborative model of care and adherence has become a more commonly used term (Steiner & Earnest, 2000). Proponents of the term adherence, suggested this word considered the role of the patient in the process of determining the prescribed treatment regimen, as well as, following the prescription (Horne et al., 2005). Thus, patient autonomy was clearly imbedded in this phenomenon. In the majority of studies involving patients with RA, compliance and adherence have been operationally defined as taking 80% or more of the designated medication over the duration of the study time (de Klerk et al., 2003; Dunbar-Jacob et al., 2004). The effect of the 80% cutoff determination of adherent versus nonadherent behavior on RA disease outcomes has not been researched.

Another related phenomenon found in the RA medication taking literature, medication persistence, is reflective of the period of time a patient continuously takes a medication (Cramer et al., 2008). Medication persistence has been determined by evaluation of prescription renewals or refills for a specified time and calculating the time between medication refills (Cramer et al., 2008). In the RA population, medication persistence may also be related to physiological responses to drugs, like immune suppression or the presence of infection, which requires the drug be discontinued. Although there are a number of factors that influence medication persistence, some investigators use persistence as a marker of medication adherence.

The Review

Aim

The aim of this review is to describe the current state of understanding of medication adherence to DMARDs in RA patients as reported in the research literature.

Design

This narrative review followed the guidelines described by Colliver, Kucera, and Verhulst (2008).

Search Methods

Medline, PubMed, CINAHL and the Clearinghouse guidelines databases were searched using the terms: rheumatoid arthritis, inflammatory arthritis, adherence, medications, compliance, non-adherence, co-operative behavior, treatment refusal, and patient compliance as keywords and MeSH terms which are indexed articles for MEDLINE/PubMed (National Center for Biotechnology Information, 2009). The years 1985 through 2008 were included in this search. Studies (qualitative and quantitative methods) were included if they were published in English and addressed medication adherence to DMARDs in adult RA patients. Studies of adherence to non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions for RA were not included because they are used to treat pain from RA as opposed to altering the disease process (ACR Subcommittee, 2002). Medication adherence in juvenile inflammatory arthritis patients was also not included in this review as different variables may affect adherence in these two populations. Letters, editorials, and opinion articles were also excluded from this review. Handsearching and footnote c hasing were not used in the search process.

Search Outcome

A total of 1630 articles were initially retrieved and evaluated for inclusion through abstract and/or title review. Once exclusion criteria were applied, 35 articles remained. These articles described research findings which were naturally grouped into five categories based on the overall goal of the research study. These groups included: 1) rates of medication adherence (2 articles), 2) factors affecting medication adherence (9 articles), 3) TNF alpha inhibitor rates of medication adherence (13 articles), 4) education programs to effect medication adherence (2 articles) and 5) patient beliefs about medications and medication adherence (9 articles) (See Tables 2 to 6). The administration of TNF alpha antagonists as either a subcutaneous injection or intravenous infusion differs from prior medication used to treat RA. Therefore, this classification of medications was grouped separately (ACR Subcommittee, 2002).

Quality Appraisal

Due to the limited research in this area, all research methods and studies were included in this review. Because the goal of this review was to determine the existing understanding of medication adherence to DMARDs based on the research literature, a systematic critique of these studies was not undertaken. We did perform an informal critique of the study methods; particularly those that might limit the generalizability of the findings (See Tables 2 to 6, Limitations column). This lack of critical appraisal of research methodology is a limitation of this review.

Data Abstraction

Data extracted included study design and methods, sample, DMARDs investigated, measures of adherence, major findings, and identified limitations.

Synthesis

The 35 studies included in the review represented a wide variety of research methods and some heterogeneity in sample. Because of this, meta-analysis was not possible and a narrative synthesis was chosen as the review method (Colliver et al., 2008). Data extracted from each reported study was examined, compared with other studies, and all were synthesized to provide a representation of the findings related to medication adherence to DMARDs in RA patients.

Results

Initially, studies were naturally grouped by the purpose of the study; however, several studies had results that fit in more than one of these groups. Thus, several studies are discussed in multiple sections and are located in more than one data table (Tables 2–6).

Rates of Medication Adherence

Rates of adherence to DMARD prescriptions were reported in 10 articles and were highly variable across studies. Cross sectional studies reported that only 58% to 63.5% of RA patients were adherent to prescribed medication regimens (Doyle et al., 1993; Owen et al.; 1985; Pullar et al., 1988). In contrast, Taal and colleagues (1993) found that 93% of patients were adherent to medication regimens (Taal et al., 1993). The discrepancies in the adherence rate may be attributed to the different measures of medication adherence used in these studies. These measures included urinary assays and serum measurements of drug levels or drug byproduct concentrations, pill counts, health care provider assessment, and self-report (Doyle et al., 1993; Owen et al., 1985; Pullar et al., 1988; Taal et al., 1993). Small sample sizes were also used in many studies and could also have contributed to the variation in adherence rates (Doyle et al., 1993; Pullar et al., 1988).

Discrepancies in adherence rates were also reported in longitudinal studies. Medication adherence rates were reported to range from 30% to 107% (de Klerk et al., 2003; Park et al., 1999; Tuncay et al., 2007; Viller et al., 1999). Adherence rates greater than 100% indicated that patients took more than the prescribed amount of medication. The variance in adherence rates could again be attributed to the multiple measurement methods. Longitudinal studies most often used self-report questionnaires and electronic monitoring devices (de Klerk et al., 2003; Viller, et al., 1999). Electronic medication monitoring devices are medication containers with microprocessors in the cap which monitor medication taking behaviors. The opening and closing of the container is counted as a medication taking event (Aardex, 2008). Electronic medication monitors are considered the “gold standard” of measurement and thus, may provide more reliable data (de Klerk et al., 2003). Longitudinal studies also investigated a number of different DMARDs and included patients with several different rheumatologic disorders, so were not strictly investigations of RA patients (de Klerk et al., 2003). Medication adherence may differ between diseases because of the side effects and efficacy of the medications used.

One retrospective study examined whether the medication prescribed influenced adherence rates. These investigators used medication possession ratios, an indirect method of determining medication adherence. Medication possession ratios are calculated by taking the number of days the patient had a supply of medication and dividing this by the number of days the drug was prescribed. These investigators concluded that the type of medication and the use of medications as monotherapy (single drug therapy) or in combination with other medications affected adherence to medication regimens (Grijalva et al., 2007). A higher ratio indicates improved adherence. Those patients taking sulfasalazine or infliximab as monotherapy were more likely to stop the medication or switch to a new medication when compared to patients taking methotrexate alone, and therefore had a lower medication possession ratio. Those taking etanercept as monotherapy or methotrexate and adalimumab in combination were less likely to stop or switch medications when compared to those taking methorexatev alone and thus, had a higher medication possession ratio (Grijalva et al., 2007). Medication possession ratios, a proxy indicator of adherence, can be influenced by pharmacy records. These records are used to calculate medication possession ratios, and thus, inaccurate records can result in inaccurate data (Dunbar, Dunning, & Dwyer, 1989). Thus, the use of medication possession ratios does not provide information about actual medication-taking activities, a significant limitation (Grijalva et al., 2007).

In summary, the rates of medication adherence to DMARDs were variable (30% to 107%), small, heterogeneous samples were studied and multiple indicators of medication adherence were used which may have contributed to the variable rates reported. However, the variability in reported adherence rates remained when comparing studies which used similar measures of adherence (de Klerk et al., 2003; Tuncay et al., 2007). The use of proxy indicators of adherence was particularly problematic, as there was no direct measure of medication use, only purchase. There was some evidence that the medication prescribed may have influenced adherence rates, but further study is required (de Klerk et al., 2003; Grijalva et al., 2007) (See Table 2 for studies that reported Rates of Medication Adherence).

Factors Affecting Medication Adherence

Factors affecting medication adherence in RA patients were reported in 11 articles. Several studies suggested that higher levels of self-efficacy and social support were associated with improved medication adherence (Brus et al., 1999; de Klerk et al., 2003; Lorish et al., 1989; Taal et al, 1993). Self-efficacy has been defined as an individual's belief that current health behaviors will impact future health (Lorig et al., 1989). Social support has been described as group of friends and family members that offer help in times of need (National Cancer Institute, 2009). However, other investigators did not find that social support influenced medication adherence (Treharne et al., 2004; Wong & Mulherin, 2007). The absence of children at home, the use of corticosteroids, prescription of a greater number of medications, the presence of strong beliefs about the overuse of medications, and belief in the necessity of medications were all associated with better medication adherence (Treharne et al., 2004). Several investigators found that patients who were satisfied with their communication with their health care provider and had increased knowledge about RA had improved medication adherence (Treharne et al., 2004; Viller et al., 1999). Patients with low levels of education and income, a more positive perception of health at baseline, experiencing increased medication side effects, and paying higher drug costs exhibited reduced adherence to their prescribed medications (de Klerk et al., 2003; Lorish et al., 1989). Demographic factors have also been investigated (Park et al., 1999).

Several investigators reported that age was an important factor affecting medication adherence in patients with RA (Park et al., 1999; Viller et al., 1999). Older age has been demonstrated to be associated with greater medication adherence. Other investigators found that factors such as age, degree of pain experienced, and number of medications did not significantly influence medication adherence (Owen et al., 1985; Wong & Mulherin, 2007).

Few studies have investigated the role of ethnicity as a factor affecting medication adherence in patients with RA (Dunbar-Jacob et al., 2004; Garcia-Gonzalez et al., 2007). Garcia-Gonzalez and colleagues (2007) found that ethnic Hispanic and African-American patients have significantly reduced medication adherence when compared to whites. These investigators attributed these findings to greater feelings of depression and perceptions of medication as harmful in the ethnic minority groups; however these results have not been replicated. Further studies should investigate the importance of ethnicity to DMARD adherence, so that culturally appropriate interventions may be developed if this is a significant factor that influences adherence.

In conclusion, self efficacy, the quality of the patient-health care provider relationship, social support and age may be factors affecting medication adherence in patients with RA (de Klerk et al., 2003; Lorish et al., 1989; Park et al., 1999; Taal et al., 1993). However, there are conflicting results about the factors that affect medication adherence in RA patients. These contrary findings may be the result of a number of methodological issues that included small sample sizes, the use of convenience samples, and measurement of different indicators of adherence that were not equivalent. These studies also lacked a clear, comprehensive, and

consistent theoretical framework upon which to base the variables chosen for measurement (Brus et al., 1999; Treharne et al., 2004) (See Table 3 for Factors Affecting Medication Adherence).

Interventions to Affect Medication Adherence

Only two studies were found that tested interventions to improve medication adherence in RA patients. Both studies evaluated the effect of an education program on medication adherence (Brus et al., 1998; Hill et al., 2001). Brus and colleagues (1998) based their education program on Bandura's Social Learning Theory. This theory states that environment, individual factors and behavior continually interact when humans function (Bandura, 1986; Brus et al., 1998). These investigators studied 65 RA patients taking sulfasalazine over a one-year period. No significant difference in either medication adherence or disease activity was found between the education and control groups. In contrast, Hill, Bird, and Johnson (2001) conducted an assessor-blind, randomized clinical trial (RCT) to test the effects of an education program on adherence to D-penicillamine and therapeutic outcomes in RA patients ($n = 100$). Patients were stratified by educational level and serum pharmacologic markers were used to measure adherence. The education program significantly increased medication adherence in comparison with the control group ($p < 0.05$). Disease activity as indicated by degree of joint pain and swelling and serum tests of inflammation was not changed by the intervention. These investigators suggested that these measures of disease activity might not be sensitive to changes that were produced by the intervention or the measures were made too soon after the intervention to demonstrate effectiveness. Both intervention studies included small samples of RA patients taking medications not commonly prescribed for this disease because their effectiveness is questionable (Brus et al., 1998; Hill et al., 2001). Thus, the utility of these findings is limited (See Table 4 for Educational Programs to Effect Medication Adherence).

TNF Alpha Inhibitor Rates of Medication Adherence

Tumor necrosis factor (TNF) alpha antagonists, relatively new, biologically engineered medications, block the actions of inflammatory cytokines, which mediate the inflammatory response in RA (ACR Subcommittee, 2002). TNF alpha antagonists are currently recommended for moderate to severe RA and are administered as either subcutaneous injections or intravenous infusions (ACR Subcommittee, 2002). Patients are taught to discontinue TNF alpha antagonists in the presence of infection, as these medications likely increase susceptibility to infection and slow the resolution of an infection once it is established (Ledingham & Deighton, 2005). Discontinuation rates, medication persistence, and patterns of use of TNF alpha antagonists (etanercept, infliximab and adalinumab) were the focus of 13 studies. Medication persistence is the duration of time a patient remains on a medication (Cramer et al., 2008).

Retrospective study designs were used in many studies investigating medication persistence to TNF alpha antagonists. Medication persistence in RA patients taking TNF alpha antagonists using retrospective designs ranged from 82% to 89% at 6 months, 48% to 78% at 12 months; 70% at 13 months; 71% at 18 months; 62% to 67% at 24 months; 20% at 36 months; 50% at 50 months; and 67% at 60 months (Agarwal et al., 2005; Brocq et al., 2007; Ostergaard et al., 2007; Wendling et al., 2005). Randomized clinical trials tested various TNF alpha antagonists also investigated persistence to these medications. In RA patients taking TNF alpha antagonists, medication persistence was reported to range between 73% to 86% at 13.5 months and 55% to 68% at 25.5 months (Flendrie et al., 2003; Lipsky et al., 2000; Maini et al., 2004). Prospective, observational studies found medication persistence rates of 84.5% at 12 months; 62% to 73% at 13 months, 73% at 24 months, 59% to 74% at 36 months, and 18% to 53% at 48 months. Thus, as time elapsed, patients were less likely to remain on this class of

medication (Hetland et al., 2008; Kristensen et al., 2006; Voulgari et al., 2005). These studies did not provide reasons for why a patient was no longer taking the medication.

Medication persistence may be longer than intended in certain patients. Dziadzio, Keat, and Higgins (2007) observed patients camouflaging infections to continue their TNF alpha antagonist medication. In 78 RA and ankylosing spondylitis patients who self-administered TNF alpha antagonists, 27% of patients did not comply with the recommendation to discontinue TNF alpha antagonists while experiencing an infection. Investigators suggested that patients were willing to risk serious adverse effects related to infections because the TNF alpha inhibitors produced such beneficial reductions in their symptoms, particularly pain (Dziadzio et al., 2007).

Studies that compared adherence to TNF alpha antagonists alone to that when these drugs were combined with other DMARDS produced conflicting results (Grijalva et al., 2007; Harley et al., 2003; Kristensen et al., 2006; Voulgari et al., 2005). Some investigators found that medication persistence was greater in patients who were prescribed TNF alpha antagonists alone when compared to those who were prescribed combinations of medications (Harley et al., 2003). Other investigators found that medication persistence to TNF alpha antagonists improved with concomitant use of MTX (Kristensen et al., 2006; Voulgari et al., 2005).

In summary, medication persistence rates to TNF alpha inhibitors were reported to be 20% at 36 months for infliximab to 89% at 6 months for all TNF alpha antagonists (Brocq et al., 2007; Wendling et al., 2005). The primary issue of these studies is the use of medication persistence as a proxy measure of medication adherence. Medication persistence evaluates behaviors that are different from daily medication adherence and it may be influenced by an individual response to these drugs that may necessitate discontinuation (immune suppression). There is no actual indicator of whether patients took their medication as scheduled in these studies (See Table 5 for TNF Alpha Antagonist Rates of Medication Adherence).

Patient Beliefs about Medication Adherence

Patient beliefs about medications may be an important factor in medication adherence (Horne et al., 2005). Studies investigating patient beliefs about medications reported that RA patients weighed risks versus benefits when taking these medications (Berry et al., 2004; Lorish et al., 1989). Perceived risks of medications included side effects and dependence on both medications and the health care system. Perceived benefits included a decrease in symptoms (i.e., pain, stiffness, joint swelling, well-being, insomnia, and fatigue), prevention of functional loss, and cure of disease (Berry et al., 2004; Lorish et al., 1989; Morrison et al., 2003).

Similarly, the necessity of medications versus concerns about medications was weighed by patients with RA (Neame & Hammond, 2005). Rheumatoid arthritis patients believed that medications were necessary to maintain current and future health. Greater pain, fatigue, helplessness, number of DMARDs along with physical disability and longer disease and treatment duration significantly increased the belief in the necessity of medications ($p < 0.01$) (Neame & Hammond, 2005). Other factors that had a significant increased effect on patient beliefs included higher reported disability, older age, lack of family history of disease, lower educational status, and the specific DMARD (TNF alpha antagonists, leflunomide, or hydroxychloroquine) prescribed (Kumar et al., 2008). Degree of pain, fatigue, physical disability, perceived helplessness, and number of DMARDs prescribed had a significant positive effect on patient's concerns about medications ($p < 0.01$) (Neame & Hammond, 2005). Similarly, the number of medications prescribed, degree of forgetfulness, fear of adverse effects, lack of medication efficacy, costs of medications, and inadequate knowledge about the health care system were barriers to taking medications (Popa-Lisseanu et al., 2005). Leeb and colleagues (2005) reported that 26.6% of RA patients wanted to increase the number of

medications taken, 27.5 % wanted to decrease the number of medication taken, and 45.9% wanted to remain on their current treatment regimen. In contrast, Wong and Mulherin (2007) investigated the relationship between psychosocial factors and medication persistence in 68 first-time DMARD users with RA and found that beliefs about medications did not have significant relationship with medication persistence. These investigators hypothesized that the measurement of drug persistence as opposed to medication adherence may be an explanation for this finding.

Some investigators attempted to identify reasons for medication non-adherence. Lorish, and colleagues (1989) found that participants used reminder cues to remember to take medication doses, but physical limitations and lack of medication refills were reasons for missing medication doses. Although a there was a lack of information about medications used to treat RA (Lorish et al., 1989; Morrison et al., 2003), knowledge derived from experience, health care providers, and community contacts positively affected RA patient perception of medications (Lorish et al., 1989). Medications were perceived by many RA patients as “powerful,” “strong,” and “toxic” (Goodacre & Goodacre, 2004, p. 584; Lorish et al., 1989). Even if a medication effect was not observed, Lorish and colleagues (1989) found that an estimated 45% of participants believed the information provided by their health care provider concerning the effects of medications. This suggests that trust is a dimension of medication adherence in those with RA.

Goodacre and Goodacre (2004) found that participants described a delay in reporting side effects because there was the perception that the body required a period of adjustment to medications. Information about side effects provided in written information was described as “confusing” and “scary” (Goodacre & Goodacre, 2004, p. 584). Side effects were tolerated when medications were efficacious and other options for treatment were perceived as limited. Similarly, joint preservation, increased functioning, and decreased symptoms contributed to participant perception of drug effectiveness. Fears were voiced about withdrawal from DMARDs and the limited number of available treatment options.

Several investigators have suggested that ethnicity affected RA and systemic lupus erythematosus (SLE) patient beliefs about medications (Kumar et al., 2008; Popa-Lisseanu et al., 2005). Kumar and colleagues (2008) found that South Asian patients when compared to White British patients, had significantly increased concerns about the overuse, dependency, and harm of DMARDs.

Only three studies investigated the effect of beliefs, attitudes, and knowledge level on medication adherence, and conflicting results were reported about the role of patient beliefs and medication adherence (Neame & Hammond, 2005; Popa-Lisseanu et al., 2005; Wong & Mulherin, 2007). Pain increased the belief in the necessity and also increased patient concerns about medications (Neame & Hammond, 2005). Other investigators primarily described the beliefs, attitudes, and knowledge (See Table 6 for Patient Beliefs about Medication Adherence).

Discussion

Research studies to date have found medication adherence rates to DMARD therapy in RA patients ranged from 30% to 107% (de Klerk et al., 2003; Tuncay et al., 2007). A number of factors have been suggested to be associated with medication adherence in this population, but clear, consistent associations have not been supported by large, well designed studies with consistent replication of these findings. One serious deficit in these studies of medication adherence is the lack of a consistent theoretical framework to explain medication adherence in the RA population. Brus and colleagues (1998) used Bandura’s Social Learning Theory to

guide their educational program and Goodacre and Goodacre (2004) discussed the Health Belief Model, Self Regulatory Theory and Theory of Planned Behavior as foundations to understanding the beliefs of RA patients about medication adherence. Yet, the contribution of these theories to the understanding of medication adherence in RA patients has not been fully explored. Future studies should focus on the adaptation of established theories and the development and empirical testing of theories of medication adherence in patients with RA.

Surprisingly, there were no published studies that directly investigated the effect of medication adherence on disease outcomes in patients with RA. However, Darmawan and colleagues (2003) reported that patients who dropped out of a drug clinical trial for RA had worse disease outcomes as indicated by tests of inflammation. Although two educational programs intended to improve medication adherence showed no effect on disease activity, these studies used small samples of patients with RA who were taking medication not commonly prescribed to treat this disease (Brus et al., 1998; Hill et al., 2001). Thus, future research should be conducted with measures of RA disease activity as an outcomes measure. These may include functional status, joint mobility, grip strength, pain, inflammatory cytokine concentrations, C-reactive protein, and erythrocyte sedimentation rate (van der Heijde et al., 1990).

Over the past two decades, clinicians have developed an aggressive approach to treatment of RA and pharmacological research has provided a greater number of and more effective medications to treat RA. As a result, many of the medications previously studied are not currently recommended therapies (ACR Subcommittee, 2002; Brus, et al. 1997). Several of the newer medications require injection or intravenous infusion; thus, the route of administration may be a significant factor affecting adherence and this requires systematic investigation.

Biological therapies are currently recommended for the treatment of RA and these are associated with improved patient outcomes (ACR Subcommittee, 2002). A majority of the studies of TNF alpha antagonist administration reported medication persistence as the outcome variable (Lipsky et al., 2000; Maini et al., 2004). Although medication persistence was used as an indicator of medication adherence, it is not a direct measure of medication adherence; a variety of factors like adverse effects may influence these persistence rates. In a systematic review of medication adherence in randomized controlled trials of chronic disease patients, Gossec and colleagues (2007) discussed the importance of medication adherence as an outcome of disease management and criticized the use of reporting medication completion as a measure of medication adherence in randomized controlled trials. Gossec and colleagues state, “Completing treatment includes the notion of taking the medication (ie. adherence)” (2007, p. 248).

The various methods used to measure medication adherence used throughout this review of literature make conclusions about medication adherence in patients with RA difficult to determine. These methods include: pill counts, self-report measures (ex. *Compliance-Questionnaire-Rheumatology* (de Klerk et al., 1999), serum measurements of medication concentrations, and electronic devices. Limitations have been discussed of the various methods such as the indirect nature of self-report and electronic devices and the feasibility issues of serum measurements (de Klerk et al., 2003; Garber, Nau, Erickson, Aikens, & Lawrence, 2004). Currently the “gold standard” for measurement of medication adherence is electronic medication monitoring devices (de Klerk et al., 1999). Consistent use of this measure of medication adherence would provide the most accurate and reliable data for analysis and improve our understanding of medication adherence in this patient population.

Limitations

To attain an understanding of the state of the literature on medication adherence in the RA population, this review included all study designs. This could be considered a limitation of this review as it prohibited the application of strict evaluation criteria. This means that studies did not go through systematic evaluation process (Burls, A. 2009). Only published literature identified in the designated databases was included in this review. The exclusion criteria applied to this review limited the scope of the literature reviewed. However, this review provides the most current review of studies about medication adherence in adult RA patients

Conclusion

The dramatic change in the approach to treatment of RA over the past three decades and the increased numbers of effective medications available to treat RA has resulted in improved patient outcomes (ACR Subcommittee, 2002; Weisman, 1989). Currently, there is not a clear understanding of the factors that influence medication adherence in these patients and rates of adherence vary widely. Further research is necessary for a comprehensive understanding of the phenomenon of medication adherence in persons with RA. A clearly articulated theoretical foundation specific to the patient with RA can guide the development of theoretically-based interventions aimed to improve medication adherence and subsequent outcomes in this population.

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Table 1

List of DMARDs Used to Treat RA

DMARD	Abbreviation	Classification	Indications for use
methotrexate (Trexall)	MTX	Folic acid antagonist	Initial DMARD‡
hydroxychloroquine (Plaquinil)	HCQ	Anti-malarial	Mild disease‡
sulfasalazine (Azulfidine)	SSZ	Anti-inflammatory	Mild disease‡
leflunomide (Arava)	LEF	Pyrimidine synthesis inhibitor	Alternative to MTX‡
azathioprine (Imuran)	AZA	Immunosuppressive antimetabolite	Rarely used‡
d-penacillamine (Cuprimine)	*	Chelating agent	Rarely used‡
minocycline (Minocin)	MIN	Tetracycline antibiotic	Rarely used‡
etanercept (Enbrel)	*	TNF alpha antagonist (biologic)	Failed prior DMARD‡
infliximab (Remicade)	*	TNF alpha antagonist (biologic)	Failed prior DMARD‡
adalinumab (Humira)	*	TNF alpha antagonist (biologic)	Failed prior DMARD‡
abatacept (Orencia)	*	Selective costimulation modulator-inhibits the costimulation of T cells.	Failed prior DMARD‡
rituximab (Rituxan)	*	Modulator of CD20 positive B-cells	Failed prior DMARD‡

* no abbreviations referenced

‡ ACR Subcommittee, 2002

Table 2

Studies Reporting Rates of Medication Adherence (*n* = 10).

Citation	Method/Sample	DMARDs	Measures	Results:	Limitations
de Klerk et al., 2003	6-month longitudinal (RA, PMR, & gout patients) (*N*=127)	SSZ & MTX	EMM	Adherence: MTX: 107% SSZ: 72%	• Biologic therapies not studied • Heterogeneous diseases in sample
Viller et al., 1999	3-year prospective cohort (*N*= 556)	No specific DMARDs described	Self-report	Adherence:35.7% Non-adherence: 23.8%	• DMARDs taken not discussed • Self-report • Questionable biologic inclusion • 56 lost to follow-up (11%) • 36 missing data (not included in analysis)
Park et al., 1999	Observational (*N*= 121)	No specific DMARDs described	EMM	Adherence: 38%	• DMARDS taken not discussed
Dunbar-Jacob et al., 2004	4-phases of trial recruitment studied (*N*=961)	No specific DMARDs described	EMM	Adherence: African American (AA): 48% White: 47%	• Secondary analysis
Tuncay et al., 2007	1-year longitudinal study (*N*=100)	DMARDS (no specific medications discussed), NSAIDS, and corticosteroids	1 question Self-report	Adherence: 30.2% Non-adherence: 12%	• Small sample • 84.9% of sample -female • Exclusion criteria: those likely to be lost to follow-up were excluded • 14% of sample lost to follow-up • 1-question self-report measure
Grijalva et al., 2007	Retrospective review of Tennessee Medicaid database (*N*=14,932)	MTX, SSZ, leflunomide, HCQ, anakinra, and TNF alpha antagonists	Medication possession ratio	SSZ & anakinra-decreased adherence compared to MTX; MTX+ HCQ, MTX+ infliximab, and MTX = etanercept decreased adherence compared to MTX	• Retrospective • Sample: Primarily white, females, from one U.S. state
Doyle et al., 1993	Cross-sectional (*N*= 59)	D-penicillamine	Urinary assay	Non-adherence: 39%	• Invalid specimens in sample • Small sample • D-penicillamine infrequently used (ACR Subcommittee, 2002)
Pullar et al., 1988	Cross-sectional (*N*=28)	D-penicillamine	Serum measurement of additive phenobarbitone	Non-adherence: 42%	• Small sample • Potential for un-blinding (medication additive)

Citation	Method/Sample	DMARDs	Measures	Results:	Limitations
				-Pill counts and health care provider assessment correctly identified 6 of the 11 non-adherers	• D-penicillamine infrequently used (ACR Subcommittee, 2002)
Owen et al., 1985	Cross-sectional (*N*=178)	DMARDs and NSAIDs (Specific DMARDs not described- although specified as small portion of sample)	Self-report	Adherence: 63.5%	• Number of patients taking DMARDs not specified • Unspecified measure of adherence (no psychometric properties provided)
Taal et al., 1993	Cross-sectional (*N*=86)	No specific DMARDs described	Self-report	Non-adherence: 7%	• Small sample size • DMARDs taken not described

DMARDs = disease modifying anti-rheumatic drug; RA = rheumatoid arthritis; PMR = polymyalgia rheumatica; SSZ = sulfasalazine; MTX = methotrexate; EMM= electronic medication monitoring device; AA = African American; HCQ = hydroxychloroquine

Table 3

Studies Reporting Factors that Affect Medication Adherence (n =11)

Citation	Method/Sample	DMARDs	Measures	Results	Limitations
de Klerk et al., 2003	6 month longitudinal, RA, PMR, & gout patients (*N*=127)	SSZ & MTX	EMM	Self-efficacy and increased perceived health affected adherence	• Biologic therapies not studied • Heterogeneous diseases in sample
Park et al., 1999	Observational (*N*= 121)	No specific DMARDs described	EMM	Age, mood, cognitive functioning affected adherence	• DMARDs taken not discussed
Viller et al., 1999	3-year, prospective cohort (*N*= 556)	No specific DMARDs described	Self-report	Age, health care provider communication, knowledge about RA and RA treatment affected adherence	• DMARDs taken not discussed • Self-report • 56 lost to follow-up (11%) 36 missing data (not included in analysis)
Brus et al., 1999	Clinical trial (*N*= 65)	SSZ	Pill counts	Self-efficacy affected adherence	Randomization not discussed • Pill counts • Only SSZ studied • Small sample size
Treharne et al., 2004	Cross-sectional (N= 85)	No specific DMARDs described	Self-report	Number of medications taken for disease, beliefs about medications affected adherence	• DMARDs not specified • Self-report • Small sample size
Wong & Mulherin, 2007	1-year longitudinal (*N*= 68)	MTX, SSZ, HCQ, gold	Medication persistence measured by chart review	Older age and low anxiety levels produced a negative effect on adherence	• Medication persistence (chart review) • Psychometric properties not discussed (except one tool) • Small sample • Biologic therapies not taken

Citation	Method/Sample	DMARDs	Measures	Results	Limitations
					• Disease duration not discussed
Tuncay et al., 2007	1-year longitudinal (*N*=100)	DMARDS (no specific medications discussed), NSAIDS, and corticosteroids	1-question Self-report	Older age had a positive effect on adherence; Gender, disease duration and number of medications had no effect on adherence	• Small sample • 84.9% of sample - female • Exclusion criteria: those likely to be lost to follow-up were excluded • 14% of sample lost to follow-up • 1-question measure
Garcia-Gonzalez et al., 2007	Cross-sectional of RA and SLE patients (*N* = 102; RA = 70; SLE= 32)	DMARDs (specific medication not specified)	Self-report (*Compliance-Questionnaire-Rheumatology*)‡	• Education, severity of side effects, ethnic groups on adherence	• Self-report • Small sample • Various diseases included in sample • 76% female sample
Owen et al., 1985	Cross-sectional of RA patients (*N*=178)	DMARDs and NSAIDs (Specific DMARDs not described-although specified as small portion of sample)	Self-report (unspecified)	• Demographic factors, pain, and number of medications-no significant relationship with adherence; ESR, morning stiffness, reasoning for taking medications, attitudes about medications –significantly affected adherence	• Number of patients taking DMARDs not specified-although described as few • Unspecified measure of adherence (no psychometrics described)
Lorish et al., 1989	Cross-sectional (*N*=200)	No specific DMARDs described	Self-report of missing doses of medication	• Schedule changes & running out of medication= most common unintentional reasons missing medication dose; Side effects & expense= most common intentional reasons; Lack of social support and educational and financial means= significant factors related to missed doses	• Medications taken not described • Self-report

Citation	Method/Sample	DMARDs	Measures	Results	Limitations
Taal et al., 1993	Cross-sectional (*N*=86)	No specific DMARDs described	Self-report (interviews and mailed surveys)	• Social support, self-efficacy	• Small sample • DMARDs taken not specified

‡Self report scale with described reliability and validity (de Klerk et al., 1999)

DMARDs = disease modifying anti-rheumatic drug; RA = rheumatoid arthritis; PMR = polymyalgia rheumatica; SSZ = sulfasalazine; MTX = methotrexate; EMM= electronic medication monitoring device; AA = African American; HCQ = hydroxychloroquine

Table 4

Intervention Studies to Improve Medication Adherence in RA Patients (*n* = 2)

Citation	Description of Program	Method	Results	Limitations
Brus et al., 1998	4 weekly group meetings of RA patients and a 4 and 8-month meeting; meetings included education on RA and treatments for RA and a group discussion	One-year RCT studying the effect of education on medication (SSZ) compliance in RA patients (*N*= 65)	• Patient education did not have a significant effect on medication adherence	• Small sample • Assessor blind • Pill counts as adherence measure • Discussion of education program not provided • Only SSZ adherence studied • No power analysis completed to determine sample size
Hill et al., 2001	Educational program based on self-efficacy theory; provided education about RA and treatments for RA	RCT studying effects education program on adherence with d-penicillamine (*N* = 100)	• Education program did have a significant effect	• Studied over 6 month period • Only d-penicillamine studied • Serum measurements (adherence measurement tool) • No power analysis completed to determine sample size

RA= rheumatoid arthritis; SSZ = sulfasalazine; RCT = randomized control trial

Table 5

Studies Reporting TNF Alpha Inhibitor Medication Persistence (*n* = 13).

Citation	Methods	Measure	Results	Limitations
Ostergaard et al., 2007	Retrospective review of database Medication persistence to infliximab and etanercept (*N*= 417)	Medication persistence	• 52 week medication persistence Infliximab/ etanercept: 70%	• Retrospective review • Observation study • Voluntary database • Medication persistence measured-not a direct indication of adherence
Voulgari et al., 2005	Observation study evaluating a number factors related to treatment with infliximab including discontinuation rates over a 6-year period (*N*= 84)	Medication persistence	• 33% discontinuation rate • Use of MTX decreased discontinuation • Reaction and efficacy accounted for 30% of discontinuation	• Observation study • Number of endpoints • Small sample size
Agarwal et al., 2005	Retrospective review of factors including medication persistence to infliximab (*N* = 183)	Medication persistence	• Mean ± SD duration of infliximab of 58.2 ± 56.6 weeks • Medication persistence at 1 year 52%	• Retrospective review • Medication persistence measured • Not a direct indication of adherence
Kristensen et al., 2006	Prospective study comparing adherence rates between infliximab and etanercept (*N*= 1,161)	Medication persistence	• 4-year adherence Infliximab or etanercept with MTX: 36% Infliximab or etanercept (monotherapy): 18% Infliximab or etanercpet with other DMARDs: 27%	• Lack of randomization • Access to medications • Older patients were taking infliximab as monotherapy
Harley et al., 2003	Review of pharmacy and health records 1998–2000 to compare adherence between infliximab, MTX and etanercept (*N* = 2,662; MTX = 1668; etanercept = 853; infliximab= 141)	Medication possession ratio	• Significantly decreased compliance in patients taking etanercept and MTX when compared with infliximab	• Unequal groups studied (infliximab-141; etanercept-853; methotrexate-1668) • Concomitant use of other medications not discussed • Medical and pharmacy record review
Dziadzio et al., 2007	Mailed survey RA and AS patients, compliance with recommendations to discontinue TNF alpha antagonist treatment while experiencing an infection (*N*=78)	Self-report questionnaire	• 27% of patients reported non-compliance with recommendations • Factors reported included: fear of flare, disregarding infection as serious, advice from healthcare providers and community contacts, & concurrent treatment with antibiotics	• Mailed survey • Small sample size • Few demographics of sample • IRB approval not discussed

Citation	Methods	Measure	Results	Limitations
Grijalva et al., 2007	Retrospective review of Tennessee Medicaid database (*N*=14,932)	Medication persistence	Leflunomide, infliximab, adalimumab, and etanercept – higher adherent behaviors compared to methotrexate	• Retrospective review • Sample primarily white females in one U.S. state
Brocq et al., 2007	Retrospective review (Data collected 1999–2005) (*N*= 442 inflammatory arthritis patients; RA 304; AS 92; PsA 46)	Medication persistence	• Medication persistence- 6 months was 89%; 12 months- 78%; 18 months- 71%; 24 months- 62%; and 50 months- 50%. Drug persistence with etanercept and adalimumab significantly greater than infliximab	• Retrospective review • 3 disease groups included in sample • Use of adalimumab was limited due to drug unavailability • Medication persistenc - not a direct indication of adherence
Hetland et al., 2008	Prospective study of Danish Danbio Registry (*N* =1813 in 5 cohorts)	Medication persistence	• Medication persistence at 52- weeks ranged between 62 to 73%.	• Limited data- use of registry • Sample 72% female • Age ranges 45 to 66 • Medication persistence measured- not a direct indication of adherence
Wendling et al., 2005	Retrospective chart review (*N*= 42)	Medication persistence	• Medication persistence at 36, 24, 12, and 6 months were 20%, 67%, 74% and 82% respectively	• Small sample size • Retrospective chart review • Medication persistence measured- not a direct indication of adherence
Flendrie et al., 2003	3-year prospective study (*N*= 237)	Medication persistence	• 1-year -medication persistence l- 73%, 66%, and 74% for adalimumab, infliximab, and etanercept respectively. No difference in medication persistence between the three TNF alpha antagonists	• Medication persistence measured- not a direct indication of adherence • Data collected from registry
Lipsky et al., 2000	RCT (drug trial) (*N*= 428)	Medication persistence	• -Medication persistence at 54 weeks was 73% (3mg/kg every 8 weeks); 77% (3mg/kg every 4 weeks); 86% (10mg/kg every 8 weeks); & 80% (10mg/kg every 4weeks); all subject also took MTX	• Aim: investigate efficacy and safety of infliximab as opposed to determining adherence • Medication persistence- not a direct measure of adherence • Funding for study from manufacturer of infliximab
Maini et al., 2004	RCT (drug trial) (*N*=428)	Medication persistence	• Medication persistence at 102 weeks was 56% (3mg/kg every 8 weeks); 55% (3mg/kg every 4 weeks); 68% (10mg/kg every 8 weeks); & 60% (10mg/kg every 4weeks); all subject also took MTX	• Aim: investigate efficacy and safety of infliximab • Medication persistence- not a direct measure of adherence

Citation	Methods	Measure	Results	Limitations
				• Funding for study from manufacturer of infliximab

DMARDs = disease modifying anti-rheumatic drugs, RA = rheumatoid arthritis; PsA = psoriatic arthritis; AS = ankylosing spondylitis; MTX = methotrexate; RCT = randomized control trial

Table 6

Studies Reporting Patient Beliefs About Medications Taking (*n* = 9)

Citation	Methods	Results	Limitations
Berry et al., 2004	Cross-sectional study evaluating patient beliefs about medications; New and established rheumatology clinic patients (*N*=81)	• Perceived benefits of medications is a decrease in symptoms • Perceived risk included drug dependency • Established patients increased medication adherence	• Cross-sectional study • Self-report • Small sample size
Neame & Hammond, 2005	Cross-sectional study to evaluate the beliefs of RA patients about medication adherence; mailed survey to 600 RA patients (response rate 57.3%) (*N*= 344)	• 74.3%- DMARDs needed for health • 47.4%- concerned about adverse effects • Helplessness and degree of disability affected beliefs • Physical symptoms increased beliefs about necessity of DMARDs • Increased DMARDs, longer use of DMARDs and longer duration of disease increased beliefs in necessity of DMARDS	• Cross-sectional study • Mailed survey (response rate 57.3%) • Possible persons with less sever disease returned the mailed survey; thus altering the study findings
Goodacre & Goodacre, 2004	Qualitative methods; evaluation of beliefs about medications (*N*=29)	• A complicated belief system described • Delay in reporting side effects because there was the perception that the body requires a period of adjustment to medications. • Side effects provided in written information was described as “confusing” and “scary” • Fears were voiced about withdrawal from DMARDs and the limited number of available treatment options.	• 24 of 29 participants short-term use of DMARD at the time of the study
Popa-Lisseanu et al., 2005	Qualitative methods; Focus groups; grounded theory techniques; evaluate factors related to medication adherence (*N*= 40)	• Barriers to adherence identified: costs, knowledge of health system, treatment efficacy, adverse effects	• Various diseases in focus groups
Morrison et al., 2003	Cross-sectional survey of beliefs or attitudes about medication adherence with corticosteroids (*N*=158)	• 68% of those surveyed refused treatment with corticosteroids • Weight gain, bloating, increased B/P, bleeding = side effects feared	• Cross-sectional • Only corticosteroids studied • No scale to measure attitudes
Leeb et al., 2005	Cross-sectional comparison of congruence between patient beliefs about medication adherence and commonly used disease activity measurement tools (*N*= 207)	• 26.6% desired an increase in medications; 27.5% a decrease in medications and 45.9% no change	• Psychometrics of scales- not discussed • Cross-sectional
Wong & Mulherin, 2007	1-year longitudinal (*N*= 68)	• Beliefs about medication did not have a significant relationship with drug survival	• Drug survival measured with chart review • Small sample size
Lorish et al., 1989	Cross-sectional (*N*=140)	• Medication knowledge deficit present	• 60 participants from indigent clinic were excluded

Citation	Methods	Results	Limitations
		• Reminder cues have a role in medication adherence • Harm of medications- a belief affecting missed doses • Physical limitations & lack of medication refills-reasons for missing medication doses • Beliefs about the benefits (decreased symptoms, functional abilities, & cure) • DMARDs perceived - “powerful”. • 45% believed information from their health care provider	• Interview survey
Kumar et al., 2008	Cross-sectional (*N*=200)	• Beliefs about medications were significantly affected by South Asian ancestry.	• Psychometrics of scales were not described for sample of RA and SLE patients • SLE and RA patients analyzed in combination • Majority of sample was female

DMARDs = disease modifying anti-rheumatic drugs; RA = rheumatoid arthritis; BP = blood pressure; SLE = systemic lupus erythematosus