

Treatment adherence to disease-modifying antirheumatic drugs in patients with rheumatoid arthritis and systemic lupus erythematosus

Treatment adherence is critical in the management of rheumatic diseases. Recent advances in therapy for rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are promising, although the impact on quality of life may be limited due to nonadherence. Databases including Ovid Medline, Scopus and the Epub-ahead-of-print subset of PubMed were searched for the period of the last 10 years using combined keywords patient compliance, medication adherence, disease modifying antirheumatic drug (DMARD), rheumatoid arthritis and systemic lupus erythematosus. Additional references from retrieved papers were considered. Inclusion criteria were the following: identification of a quantitative measure of adherence to medications including DMARDs and biologics; inclusion of well-defined measures of adherence; and patients with RA or SLE. Studies in RA and SLE patients demonstrated overall inadequate treatment adherence. Adherence was measured using multiple methods including pharmacy records, electronic monitoring, self-report and physician report. The evidence for interventions to improve treatment adherence was limited and demonstrated various results. Future research should further explore determinants of nonadherence and continue to examine the efficacy of implementing various strategies to improve medication management in this patient population.

KEYWORDS: adherence • disease-modifying antirheumatic drugs
■ rheumatoid arthritis ■ systematic review ■ systemic lupus erythematosus

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Treatment adherence can be defined as the extent to which patients follow recommendations and take medications as prescribed by their healthcare provider [1–3]. The concept of concordance has recently been added to that of adherence, indicating agreement between the patient and the prescriber upon the treatment to be taken. Concordance includes patient-centered informed decision-making, an approach that by including agreement on appropriate treatment could increase adherence. Recommendations may include timing, dosage and/or frequency of medication over a period of time. The terminology involving treatment adherence varies greatly in the literature, creating insecurity in the reliability of published results. Medication persistence refers to the maintenance of the prescriber's recommendations and much of the time is not included in treatment adherence assessments [4].

Nonadherence to treatment has been linked to negative outcomes. Most studies have been conducted in patients with chronic diseases, most frequently HIV/AIDS and hypertension [101]. Treatment adherence is of particular concern in rheumatic diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) because of the chronicity of these disorders, requiring lifetime therapy, which

unfortunately is not curative. Furthermore, RA and SLE patients have multiple comorbidities and often require polypharmacy, with a need for continuous assessment of adherence to multiple regimens [5,6]. Recent advances in therapy for the rheumatic conditions have provided a promising impact on quality of life and life expectancy. Unfortunately, the impact of non-adherence to the emerging therapy can limit their potential benefit [7] and may contribute to poor outcomes, including permanent joint and/or organ damage and increased utilization costs [8–11].

In this article we summarize several aspects related to therapeutic adherence in patients with RA and SLE. We provide a short summary of commonly used adherence measures, a systematic review of studies documenting adherence in usual practice in patients with RA and SLE, and finally, a short overview of what determines adherence in patients with chronic diseases, particularly in those with rheumatic disease.

Measures of adherence

Multiple methods of measuring adherence have been proposed and utilized over time. No one method has been capable of accurately measuring treatment adherence although various

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have shown to be more effective than others. The majority of these methods have been utilized in patients with rheumatic diseases. Adherence can be assessed using direct or indirect methods.

■ Direct methods

Direct methods include observation and biologic assays, which may be impractical in certain settings. In a rheumatologic practice, single-dose therapy may be documented, such as infliximab (IFX) infusions at a specific center, providing direct adherence measurements. Serum or urine levels of a drug or concentration of a metabolite are objective measures. However, their accuracy measuring adherence may vary due to individual pharmacokinetics, and is also affected by the time interval since the drug was taken. These methods are costly and may be perceived as invasive [12,13].

■ Indirect methods

Pill counts

Pill counts have widely been used in clinical trials. Although overall or average compliance may be estimated, it is difficult to establish daily adherence or adherence per dose. Patients may combine refills or throw away pills to appear adherent. Unannounced home visits to count pills may give more accurate results, but could be perceived as intrusive by patients.

Pharmacy records

These provide information on medications dispensed, but do not provide evidence of whether patients actually took the medication or when they did so. Pharmacy records can measure gaps or days without medications, treatment persistence or time until the gap occurs, and medication:possession ratio (MPR). The MPR is estimated as the number of days the medication was dispensed during a specific period divided by the number of days between the index (first day) to the end of the follow-up period. Numerous studies in patients with RA and SLE have used pharmacy claims data [14–19].

Electronic monitoring

This method is considered one of the most accurate measures of adherence; however, it is costly and does not measure how much of the medication was ingested. This method requires the patient to take medication from a special pill bottle or unit dose package. A microchip records the time and day the bottle or package is opened and software can calculate multiple adherence

measures, including overall percent of doses taken over a specific timeframe and for multiple medications, among others. This method is still considered indirect since the patients are not directly observed and can open the bottle but not take the medication [101,12,20,21].

Self-report

Subjective indirect methods include diaries, single-item measures and self-report questionnaires. Although these methods are inexpensive, easily used in multiple settings and in many patient populations, they are limited in that they are subjective, and only provide an overall estimate of adherence over the period of time included in the assessment. Most single-item measures do not inquire about the proportion of doses missed, but instead use Likert scales on the frequency of missed doses (e.g., rarely, occasionally or often) or visual analogue scales. Other measures include multiple items in self-report. Some of which have been used in rheumatic diseases including the Compliance Questionnaire Rheumatology [22] and the Medication Adherence Report Scale (MARS) [23]. Other self-reported measures commonly used in chronic diseases include the Adherence Questionnaire of the Adult AIDS Clinical Trial Group [24] and the Medication Adherence Rating Scale [25,26]. Self-report methods commonly overestimate adherence in comparison to pill counts or electronic monitoring, and can be influenced by recall and reporting bias [12,21,27].

Physician assessment

Physician (or other healthcare providers) evaluation of patients' adherence to treatment has also occasionally been used as an indirect method.

Adherence in patients with RA & SLE

We have conducted a systematic review to ascertain adherence to disease modifying antirheumatic drugs (DMARDs) in patients with RA or SLE. Electronic database searches were performed using Ovid Medline, Scopus and the Epub ahead of print subset of PubMed. Due to the changes in treatment options available for RA and SLE, including the addition of DMARDs and biologic agents, the search was limited to the last 10 years. Keywords included the following terms: patient compliance, medication adherence, modifications to the term 'adherence', and modifications to the term 'compliance', drug and DMARD were combined using the 'OR' function. Both

rheumatoid arthritis and systemic lupus erythematosus were combined using the 'OR' function. Additional studies were also included from reference lists of articles included in the initial search and systematic reviews. The searches were restricted to the English language and editorials and letters were excluded.

A total of 661 citations were identified in the preliminary search. A single reviewer reviewed the titles and abstracts of these identified citations; 137 were identified as potentially relevant. Available full text articles were then printed and reviewed by two reviewers. Inclusion criteria were the following: identification of a quantitative measure of adherence to medications including DMARDs and biologics; inclusion of well-defined measures of adherence; and patients with RA or SLE. After review, a meeting of the two reviewers took place to determine the final selection of appropriate articles. A total of 113 articles were excluded for one or more of the following reasons:

- No quantitative estimate of adherence was reported;
- Clinical trials, due to the likelihood that the experimental setting would increase treatment adherence with closer patient follow-up and patients participating in clinical trials may be different than the general population, including less comorbidities;
- Inclusion of other diseases besides RA and SLE, without clear differentiation of adherence according to disease.

A total of 22 studies were included in the review: 11 assessed adherence in only patients with RA, 10 assessed adherence in patients with SLE, and one in both RA and SLE. The majority of studies included in this review utilized self-report as the measure of adherence. Most commonly, with pharmacy records, pill counts, or monitoring, individuals were considered adherent if the measures used reported them as being at least 80% adherent. This cutoff has been used by multiple studies, implementing and comparing various adherence measures [21,27]. For the studies utilizing self-report methods, multiple definitions of adherence were used. Some included a time-frame of adherence, for example "in the last 6 months" while others used more general definitions [28–30].

In some studies, adherence to multiple medications was assessed in different populations. Some studies did not restrict adherence measures to only DMARDs or biologics, but

instead utilized "adherence to medications" as a measure [10,31–33]. Other studies specifically assessed DMARDs, biologics or other treatments for RA or SLE, including nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids [14–18,28–30,32,34–42].

■ Rheumatoid arthritis

TABLE 1 shows the characteristics of the 11 studies evaluating adherence in patients with RA. No studies used direct observation, biological measures or pill counts to determine adherence.

Pharmacy data

Four studies evaluated adherence using pharmacy data. Of these, two assessed adherence to biologic agents only, and two to both DMARDs and biologics. Borah *et al.* conducted a retrospective cohort study utilizing pharmacy claims data with participants stratified into four groups. Two groups of patients were treated with etanercept (ETA) and two were treated with adalimumab (ADA). Within each drug group, a proportion were first-time users while others were receiving these in an ongoing fashion. Adherence was estimated with the MPR. After 1 year of observation, results indicated a slightly higher level of adherence (>80%) in patients taking ETA in comparison to ADA in both the naive and existing users. Those new to the treatments were less adherent than existing users [14]. Another retrospective cohort study included a large sample of 2285 RA patients initiating subcutaneous therapy with ETA or ADA. They were followed up for 12 months and had a mean MPR of 0.52 [15]. Prescription refill information was also used as a measure of adherence in the large retrospective cohort of RA patients by Grijalva *et al.* [16]. Multiple therapies, including DMARD monotherapy and combination therapy with DMARDs and biologics, were assessed using data from new prescriptions. Adherence was measured using the MPR. Of all of the single and combination therapies assessed, IFX alone had the highest compliance, perhaps this was due to the method of delivery of this therapy, by infusion. This was followed by leflunomide and ADA as single therapies, both with a MPR of 0.85. The lowest level of adherence was in patients taking methotrexate (MTX) and ETA. The study also dichotomized adherence using 80% or less as an indicator of adherence. In a retrospective cohort study of RA naive users of IFX, ETA and MTX, levels of adherence (indicated by a ratio of ≥ 0.80) varied from

Table 1. Summary of rheumatoid arthritis studies.

Study (year)	Study design	Study size (n)	Population description	Medication	Duration of observation period (follow-up)	Adherence measurement	Adherence definition	Adherence (%)	Ref.
Borah <i>et al.</i> (2009)	Retrospective cohort	703	Naive users	ETA	1 year	Pharmacy data: MPR	≥80% adherent	41.96	[14]
		1834	Existing users	ETA				51.25	
		527	Naive users	ADA				40.99	
		765	Existing users	ADA				47.06	
Curkendall <i>et al.</i> (2008)	Retrospective cohort	2285	Naive users	ADA (75%) and ETA (25%)	12 months	Pharmacy data: MPR	Mean MPR	Mean: 52	[15]
Grijalva <i>et al.</i> (2007)	Retrospective cohort	14932 (total)	At least one prescription filled	MTX	Start date of DMARD prescription fill to last refill	Pharmacy data: MPR	Mean MPR	Mean: 80	[16]
				HCQ				79	
				SSZ				77	
				Leflunomide				85	
				MTX + HCQ				66	
				IFX				90	
				ETA				83	
				ADA				85	
				MTX + IFX				66	
				MTX + ETA				64	
				MTX + ADA				72	
				Anakinra, MTX + Anakinra				71	
Harley <i>et al.</i> (2003)	Retrospective cohort	141	Naive users	IFX	365 days	Pharmacy data: compliance ratio	Ratio ≥ 0.80	80.9	[17]
		853		ETA				68.4	
		1668		MTX				63.7	
de Klerk <i>et al.</i> (2003)	Prospective cohort	25	Naive users	SSZ	6 months	MEMS	"Taking compliance" (percentage of prescribed doses taken)	72	[36]
		23		MTX	6 months			107	

ADA: Adalimumab; CQR: Compliance questionnaire on rheumatology; DMARD: Disease-modifying antirheumatic drug; ETA: Etanercept; HCQ: Hydroxychloroquine; MARS: Medication adherence report scale; MEMS: Medication event monitoring system; MPR: Medication possession ratio; MTX: Methotrexate; NA: Not applicable; NSAID: Nonsteroidal anti-inflammatory drug; Pred: Prednisone; RAM: Reported adherence to medication; RA: Rheumatoid arthritis; RCT: Randomized control trial; SES: Socioeconomic status; SLE: Systemic lupus erythematosus; SSZ: Sulfasalazine; VAS: Visual analog scale.

Table 1. Summary of rheumatoid arthritis studies (cont.).

Study (year)	Study design	Study size (n)	Population description	Medication	Duration of observation period (follow-up)	Adherence measurement	Adherence definition	Adherence (%)	Ref.
Dunbar-Jacob et al. (2004)	Prospective cohort	419	White	NSAIDs or DMARDs	3 weeks	MEMS (14 day) and recall report (7 day)	Ratio: recorded daily administrations/prescribed daily	37.7	[37]
		33	African-American					36.4	
Garcia-Gonzalez et al. (2008)	Cross-sectional	70	Ethnically diverse, low SES	All medications	Not specified	Self-report: CQR	0 (complete noncompliance) to 100 (perfect compliance)	Mean CQR: 69.6	[31]
Neame et al. (2005)	Cross-sectional	331	Existing users	DMARDs	NA	Self-report: "I often do not take my medications as directed" – strongly disagree–strongly agree	Strongly disagree/disagree = adherent group; strongly agree/agree = nonadherence.	92	[42]
Trehanne et al. (2004)	Cross-sectional	85	Existing users	All: DMARDs, NSAIDs and steroids	NA	Self-report – CQR and two items from RAM	CQR: range 0–3 (strongly disagree); RAM: never/rarely = adherent	CQR mean: 2.04; RAM: 90.6	[44]
Tuncay et al. (2007)	Prospective	86	Existing users	All: DMARDs, NSAIDs and steroids	1 year	Self-report: "Adherence to prescribed dose and timing: strictly, quite, not really or not at all"	Strictly or quite = compliant	30.2	[45]
van den Bemt et al. (2009)	Cross-sectional	228	Existing users	All: DMARDs, NSAIDs and steroids	NA	Self-reported: CQR; combined with MARS and personal interview	MARS total score >23 = adherent; adherence = less than once a week missed	CQR: 67, MARS: 60; Face-to-face: 98.5	[46]
Fernandez-Nebro et al. (2007)	Retrospective	161	Failed DMARDs	All medications	Not specified	Physician report	Good = "demonstrated willingness and capacity to follow recommendations"	86.3	[39]

ADA: Adalimumab; CQR: Compliance questionnaire on rheumatology; DMARD: Disease-modifying antirheumatic drug; ETA: Etanercept; HCQ: Hydroxychloroquine; MARS: Medication adherence report scale; MEMS: Medication event monitoring system; MPR: Medication possession ratio; MTX: Methotrexate; NA: Not applicable; NSAID: Nonsteroidal anti-inflammatory drug; Pred: Prednisone; RAM: Reported adherence to medication; RA: Rheumatoid arthritis; RCT: Randomized control trial; SES: Socioeconomic status; SLE: Systemic lupus erythematosus; SSZ: Sulfasalazine; VAS: Visual analog scale.

63.7% to 80.9%. IFX adherence was the highest, followed by ETA (68.4%) and then MTX (63.7%). The authors attributed the differences in adherence to IFX versus the other drugs to the method of administration [17].

Electronic monitoring

de Klerk *et al.* evaluated various adherence measures that can be obtained from electronic monitoring using a medication event monitoring system (MEMS) in patients with RA. They were able to calculate not only “taking compliance”, but also compliance with dosing and with timing with multiple medications over time. In patients with RA, 25 patients receiving sulfasalazine (SSZ) and 23 receiving MTX were assessed for adherence over 6 months. The taking compliance among this cohort was 72% for patients taking SSZ and 107% for patients on MTX. This difference was statistically significant and was also noted between these two groups when assessing correct dosing and timing compliance, MTX adherence always being higher than adherence to SSZ [36]. Another prospective cohort study, utilizing MEMS 14-day monitoring and 7-day self-report, measured adherence in RA patients over 3 weeks. Unfortunately, the adherence measure was combined with self-reported adherence, making it difficult to assume the MEMS adherence was the measurement utilized in the final reported results. They found that 38% of White patients to be adherent overall versus 36.4% of African-Americans [37].

Self-report

The compliance questionnaire rheumatology (CQR) was used to assess adherence among patients with RA or SLE in a cross-sectional study by Garcia-Gonzalez *et al.* [31]. The responses were scaled from 0 (indicating complete noncompliance) to 100 (indicating perfect compliance). The authors utilized transformed average scores to a 0–100 scale. Participants in this ethnically diverse, low socioeconomic cohort had low levels of compliance with mean CQR scores of 69.6 for the RA group. The most common reason for “sometimes” or “often” missing medications among this cohort was because they felt “depressed” or “overwhelmed.” Statistically significant associations were noted between adherence and education and severity of side effects [31]. Neame *et al.* used a cross-sectional study to assess the adherence to DMARDs among existing users [42]. The Rheumatology

Attitudes Index was used, in particular one item: “I often do not take my medication as directed.” Participants who strongly disagreed or disagreed with the statement were considered to be adherent. Using this measure and definition, 92% of the participants were adherent to their DMARDs. Another study by Trehanne *et al.* included 85 patients and used two questionnaires: the CQR, and two questions from the Reported Adherence to Medication (RAM) scale from Horne *et al.* [43]. Among this group of patients, the mean CQR score was 2.04 (1–4). Using the RAM, 90.6% reported “never” or “rarely” missing a dose or “adjusting a dose to suite their own needs.” [44] Tuncay *et al.* in a prospective study of RA patients examined dose and timing [45]. The respondents were given a four point scale in which they reported adherence in the last year (“strictly, quite, not really or not at all”). Those who responded “strictly” or “quite” were considered compliant. According to this scale, 30.2% were compliant over a 1-year period (“consistently compliant”). van den Bemt *et al.* recently reported a cross-sectional study of 228 existing users of RA therapy using the CQR, another self-reported measure, including the Medication Adherence Reporting Scale (MARS) and a personal interview [46]. The face-to-face interview asked the participant the following: “Do you sometimes decide to skip a dose or do you sometimes forget a dose?” The responses ranged from 1–6; 1 indicating “never”, 2 indicating “once a month”, 3 indicating “three times a month”, 4 indicating “once a week”, 5 indicating “several times a week” and 6 indicating “I never take this medication.” Differences between methods of measurement were noted: 67% of participants were considered adherent using the CQR, 60% (total score of >23) using MARS and in the face-to-face interview 98.5% were considered adherent. This study shows the variability with the use of different measures, as well as the potential effects of social desirability responses in face-to-face interviews.

Physician report

Only one study included in the review measured adherence through physician-reported measures [39]. In a retrospective study of 161 RA patients, 86.3% were considered adherent (“demonstrated willingness and capacity to follow recommendations indicated”). Adherence was assessed for all DMARDs, not for biologic therapy.

Table 2. Systemic lupus erythematosus: summary of studies.

Study (year)	Study design	Study size (n)	Population description	Medication	Duration of observation period (follow-up)	Adherence measurement	Adherence definition	Adherence	Ref.
Ward <i>et al.</i> (1999)	Cross-sectional	100	Existing users	Not specified	NA	Pill counts	Number of pills taken/number prescribed	70.6%	[33]
Koneru <i>et al.</i> (2007)	Cross-sectional	41	Existing users	PDN	NA	Pharmacy data: (total number of medication doses dispensed/total number prescribed) × 100	≥80% = adherent	61.0%	[18]
Koneru <i>et al.</i> (2008)	Cross-sectional	37	Existing users	HCQ				48.6%	
		41	Existing users	PDN	NA	Pharmacy data: MPR	≥80% adherent	61%	[40]
		37		HCQ				49%	
		23		Other immunosuppressive drugs				57%	
Chambers <i>et al.</i> (2008)	Cross-sectional	75	Existing users	SLE medications	NA	Self-report: Do you always take them as prescribed in the last 6 months?	≥85% adherent	56%	[28]
Chambers <i>et al.</i> (2009)	Cross-sectional	199	Not specified	All	NA	Self-report: General pill-taking practice in previous 6 months; VAS (cm): 0 = never take; 10 = always take	Not specified	Median: 9.7	[29]
Costedoat-Chalumeau <i>et al.</i> (2007)	Prospective	203	Existing users	HCQ	NA	Self-report: Stopped HCQ or taken no more than once or twice a week	Percent adherent	93%	[35]
Garcia-Gonzalez <i>et al.</i> (2008)	Cross-sectional	32	Demographics ethnically diverse, low SES	Not specified	NA	Self-report: CQR	1 (complete noncompliance) to 100 (perfect compliance)	Mean (SD) CQR: 68.0 +/- 8.3	[31]
Julian <i>et al.</i> (2009)	Prospective cohort	834	Not specified	Not specified	NA	Self-reported: Cognitive symptoms	Never = adherence; nonadherence = at least some of the time.	54.4% – adherent	[10]
Mosley-Williams <i>et al.</i> (2002)	Cross-sectional	68	Existing users African-American	Lupus medication	NA	Self-report: Frequency you failed to take lupus medications when prescribed during the past year	Failing to take medication (mean score)	2.3	[41]
		54	Existing users white					2.5	

CQR: Compliance questionnaire rheumatology; HCQ: Hydroxychloroquine; MPR: Medication possession ratio; NA: Not applicable; PDN: Prednisone; SD: Standard deviation; SES: Socioeconomic status; SLE: Systemic lupus erythematosus; VAS: Visual analog scale.

Table 2. Systemic lupus erythematosus: summary of studies (cont.).

Study (year)	Study design	Study size (n)	Population description	Medication	Duration of observation period (follow-up)	Adherence measurement	Adherence definition	Adherence	Ref.
Rojas-Serrano <i>et al.</i> (2000)	Cross-sectional	49	Hospitalized	SLE medications	NA	Self-report: 0 (none) – 10 (excellent) compliance	Mean score	7.4	[32]
Sailler <i>et al.</i> (2007)	Cross-sectional	58	Nonhospitalized Existing users	HCQ	NA	Self-report: 0–10 scale	≥8 is compliant	79%	[30]

CQR: Compliance questionnaire rheumatology; HCQ: Hydroxychloroquine; MPR: Medication possession ratio; NA: Not applicable; PDN: Prednisone; SD: Standard deviation; SES: Socioeconomic status; SLE: Systemic lupus erythematosus; VAS: Visual analog scale.

■ Systemic lupus erythematosus

TABLE 2 shows the characteristics of the 11 studies evaluating adherence in patients with SLE.

Direct methods

Costedoat-Chalumeau *et al.* noted a significant difference in hydroxychloroquine (HCQ) whole-blood concentration between SLE patients who reported being compliant versus noncompliant and confirmed nonadherence in 7% [35]. Another study also measured blood concentrations of HCQ and self-reported adherence and found positive correlation within the measurements [30]. Limited research has been completed in this area and further investigation of blood concentrations of medications is needed.

Pill counts

Ward and colleagues measured pill counts in patients with SLE, reporting 70.6% adherence. They did not specify, however, for what medications adherence was being measured. No association was observed between adherence and morbidity, but their sample size was small [33].

Pharmacy data

Koneru *et al.* assessed adherence in SLE patients cross-sectionally of existing users of SLE medications in two studies [18,40]. The first assessed adherence to prednisone and HCQ and noted that 61.0 and 48.6% were adherent (≥80% of prescribed treatments taken) respectively. In another study the next year, they noted a 61% adherence with prednisone, 49% adherence with HCQ and 57% adherence with other immunosuppressive drugs. The method of using prescription refill data is often straightforward in calculation and interpretation. Despite these advantages it is particularly challenging when medications are provided by multiple pharmacies; furthermore, the reasons for discontinuation are not documented, but may be appropriate [4,101].

Self-report

Chambers *et al.* conducted a cross-sectional study assessing the adherence of existing users of SLE medications by asking participants if they always took their medications as prescribed in the past 6 months). Results indicated that 56% reported being over 85% adherent [29]. Another more recent study by Chambers utilized a visual analog scale (VAS) measured in cm to capture the 0–10 scale of taking medications (0 indicating “I never take my medications as prescribed” to 10 “I always take my medications as prescribed”). Of the 199 participants, the median

was 9.7 cm with an interquartile range of 8.8 to 10 cm. Extrapolating these data, over 80% of the participants would be adherent (according to the $\geq 80\%$ standard) [29]. In a study of 203 SLE patients taking HCQ, only 7% were reported as being nonadherent. Adherence in this study was measured by asking participants if they had stopped taking the medication or took it “rarely: no more than once or twice a week” [35]. The cross-sectional study by Garcia-Gonzalez *et al.* previously mentioned, also reported adherence measures, using CQR scores for SLE patients. They noted lower compliance among the SLE patients compared with the RA patients. The mean CQR score for the SLE group was 68.0 [31]. Julian *et al.* recently published results from a prospective cohort of 834 SLE patients in which adherence was measured using the Cognitive Symptoms Inventory developed by Pincus [47]. Participants replied on a four point scale whether they “never had a problem” with adherence or “had a problem all the time.” Patients were considered adherent if they replied they “never had a problem”; only 54.4% of this cohort reported being adherent [10]. Mosley-Williams *et al.* conducted a cross-sectional study, asking how often the patient “failed to take lupus medications when prescribed during the past year.” A 1–5 scale ranged from “never” to “all the time” [41]. The mean score among African–American patients was 2.3, while the mean score among white people was 2.5, indicating the African–American group was more adherent to medications: 30.8% of African–Americans compared with 23.4% of white people reported “never failing to take their medications.” Although this difference was not statistically significant, barriers to adherence did differ among different ethnic groups [41]. One study examined the effect of therapeutic adherence on outcomes. Among patients with SLE visiting an emergency department, those who reported lower compliance with therapy and lower daily in-take of HCQ were more likely to be hospitalized [32]. Sallier *et al.* also assessed compliance using a self-reported questionnaire ranging from 0 to 10, with greater or equal to 8 indicating compliance. Among their 58 existing HCQ users, 79% reported to be adherent [30].

Determinants of adherence

Therapeutic adherence appears to be multifactorial for most nonadherent patients. The WHO has identified healthcare systems, provider relationship, disease, treatment, patient characteristics and socioeconomic characteristics to be factors affecting adherence [101].

Nonadherence can be classified as unintentional or intentional [48–50]. Unintentional nonadherence can be related to issues with the system, such as financial costs, pharmacy processes and hours, language barriers, prescription materials and access to pharmacists [51,52]. Patients from disadvantaged populations, in public health-care systems have multiple difficulties adhering to medications due to the barriers imposed by the system itself. Garcia-Popa-Lisseanu *et al.* gathered useful information from focus groups within a disadvantaged rheumatic disease population in Houston (TX, USA). Participants had trouble accessing insurance coverage, had difficulties with the high costs of therapy, were burdened with long waiting times for pharmacy refills, were seen by multiple different physicians within the system and had difficulty handling various changes to medications. Many were Hispanic and reported language barriers. They also stated they had problems with the number of medication they took, and the multiple doses for the various drugs throughout the day [53].

Pill or prescription burden, also referred to as polypharmacy, has been an important predictor of nonadherence in multiple diseases [54]. Studies have also noted decrease in compliance with the increase of times per day or times per week of dosing. Of multiple dosing frequencies, once a day has shown to be the highest in adherence [55]. This is of concern in patients with rheumatic diseases due to the multiple medications with different dosing times for each that are commonly prescribed as treatment. In therapy with biologics, intravenous infusions appear to increase adherence. Many patients may prefer more spaced infusions versus more frequent subcutaneous self-injection [56].

Intentional nonadherence is associated with patient decisions, beliefs and behaviors. Multiple models have been proposed to describe treatment adherence. These include the Health Belief Model (HBM), Social Learning Theory and the Theory of Reasoned Action [49,57,58]. Constructs related to action include disease susceptibility and severity, benefit from treatment, barriers to obtain treatment, self-efficacy and attitudes regarding the treatment. Although research has shown associations between beliefs and behaviors related to adherence, many interventions based on these models have not resulted in significant improvement in adherence among patients with chronic diseases [7]. One specific model, the Medication Adherence Model based on adherence to hypertensive agents, identifies three concepts: purposeful action, patterned

behavior and feedback. The model specifically assesses determinants of adherence to treatment for chronic diseases and incorporates cognitive and noncognitive processes, which can be applicable to nonintentional adherence [49].

Low socioeconomic and educational status have also been associated with poor adherence, in patients with chronic diseases, and specifically, RA and SLE [31]. Whether these findings represent mostly system barriers, or beliefs and attitudes resulting in intentional nonadherence is not well known, however it is likely that they are related to multiple factors. Adherence is also associated with patient knowledge, including knowledge of side-effects and effectiveness of the medication and beliefs about the treatments. Although health literacy may be considered related to unintentional nonadherence, one can also consider the association between health literacy and knowledge to play a part in intentional nonadherence. Patients with difficulties in understanding medication purpose, side effects, or instructions due to limited health literacy are more likely to be nonadherent [51].

Various psychosocial characteristics have been associated with poor adherence. de Klerk *et al.* found no statistically significant association between perceived health state and compliance; however, self-efficacy (measured by the Long Term Medication Behavior Self-Efficacy Scale) and coping (measured by the Utrecht Coping List) were statistically significantly associated with adherence [36]. Depression has been linked to increased forgetfulness and decreased psychological function [10,59]. Depression can also result in poor self-efficacy and coping capabilities, which can in turn affect health-related behaviors. Social support, on the other hand, improves adherence, possibly through improved self-efficacy and reduced depression [60]. Disease severity and organ damage have also shown to be associated with multiple psychosocial variables and to poor treatment adherence and adherence to clinical visits. The relationship is likely to be bidirectional, with low adherence causing deleterious outcomes, and at the same time, in some instances, patients with increased disease severity may be less likely to maintain their scheduled visits and study follow-ups, perhaps because of disenchantment with their treatment [9,33,61,62]. Discontinuation of treatment because of beliefs about need and concerns about toxicity have been documented [63]. One study of patients with chronic disease, including RA, found differences in beliefs about medications

among those that were intentional versus non-intentional nonadherers [64]. Kumar *et al.* compared patients of South Asian and white British origin in their beliefs about medications utilizing the Beliefs about Medicines Questionnaire. They noted differences, with those of South Asian origin being more concerned about adverse events than their white counterparts. They also found that domains of the SF-36 were associated with different beliefs regarding therapy. Those with physical and emotional health problems affecting their daily activities or work, thought medications were more harmful and overused [65]. Other studies have observed that patients with rheumatic disease are fearful of adverse events, or feel their medications are not helping; these beliefs are associated with discontinuation of treatment without a physician's advice [53,66]. However, in one study, no association was observed between actual side effects from medication and adherence in patients with rheumatic diseases [36]. Treatment adherence and persistence has shown to vary by the time since first use. A large cohort of pharmacy data from patients with multiple chronic diseases found 6 months after the initial treatment, adherence declined over the 2-year study period. Differences in the patient populations, in terms of previous exposure to medication, may have an effect on differences in adherence measures across studies [67].

The quality of patient–doctor communication has been associated with patient adherence to recommendations [3,68]. Patient involvement in the decision to take a medication is often overlooked as a decision-making step within the patient–doctor interaction [69–71]. Ward reported that patients with SLE actively participating in the interactions with their physicians had lower organ damage [72]. Trust is an essential part of the relationship between patients and their physicians, related to multiple factors in patients with rheumatic disease including patient-centeredness, showing concern for patient problems and providing patients with information about their disease [73]. In patients with RA, Martin *et al.* identified trust in physicians as one of the highest contributing factors to decision-making regarding initiation of DMARD in community patients. Multiple pathways in which this relationship contributes to patient attitudes and beliefs about treatment decision consequently affects treatment adherence [71]. Treharne *et al.* also found multiple correlations between the medical interaction and adherence including

affective, cognitive and behavioral consultation satisfaction (measured using Wolf's Medical Interview Satisfaction Scale) [44,74].

Treatment adherence interventions

Few studies have shown interventions particular to the RA and SLE population. Research in interventions for patients with other chronic diseases includes attention to both the unintentional and intentional aspects of adherence [75]. Those focused on unintentional determinants of adherence include reminders such as calendars and diaries, pill boxes and notifications through phone, letters or email. In regard to improvements to the system, modifications have been made in some pharmacies to methods of dispensing the medications or managing patient refills. In terms of intentional determinants of adherence, interventions focused on cognitive and behavioral theories have been documented in patients with chronic disease and among those, RA. In particular, treatments consist of knowledge of disease and therapy, psychosocial aspects of the patients' lives, self-efficacy and doctor–patient communication [38]. A recent publication highlighted the scarce and conflicting data regarding interventions for patients with RA [76]. Only two studies were found to meet the review criteria. One study found the educational intervention to have no effect of the adherence of patients [77], while the other did find a positive effect on adherence, but no effect on disease outcomes [78]. Homer *et al.* recently published a pilot study comparing methods of delivery of interventions on DMARD adherence. They found patients randomized into group versus individual therapy tended to have higher DMARD adherence, although not statistically significant, and were satisfied with the group setting [79]. Although multiple determinants of adherence have been addressed in interventions, adherence measures need to be improved to appropriately assess the impact of future interventions [80].

Conclusion

The studies included in this article were published in the last 10 years and examine adherence to DMARDs and/or biologic agents in the treatment of RA and SLE. Methodological

differences in study design and measurement of adherence preclude a precise overall estimate of adherence. Nevertheless, most studies show that adherence is inadequate in many patients, and that it is conceivable that it leads to deleterious health effects. Adherence varies by medication, delivery and dosing schedule, but is also dependent on sociocultural characteristics such as race and education, patients' beliefs about therapy, self-efficacy, and very importantly, the quality of communication with their physicians. Unfortunately, strategies to improve adherence have shown variable and often disappointing results. Future research should further explore the determinants of nonadherence in patients with RA and SLE, and continue to examine the efficacy of implementing various strategies to improve medication management in these patients.

Future perspective

Future research should further explore determinants of nonadherence utilizing reliable methodologies and consistent measures of adherence. Future interventions to examine the efficacy of implementing various strategies to improve medication management in this patient population require evidence-based theoretical models. Clinical outcomes assessments would further reinforce the need for modifications to the current management of medications.

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Executive summary

- Studies in rheumatoid arthritis and systemic lupus erythematosus patients show overall inadequate treatment adherence.
- Methodological differences in study design and measurement of adherence preclude a precise overall estimate of adherence.
- Consistent methods of measuring adherence are needed in patients with rheumatic disease.
- Further interventions examining the efficacy of various strategies to improve medication management are warranted.

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