Patient Preference and Adherence

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REVIEW

Medication adherence and persistence in patients with autoimmune rheumatic diseases: a narrative review

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Background: Several drugs are available for the treatment of autoimmune rheumatic diseases; however, their effectiveness may be negatively influenced by inappropriate adherence. Low adherence and persistence rates have a significant impact on patient quality of life and are associated with health-related expenses.

Purpose: To provide an up-to-date narrative review on treatment adherence and persistence rates, and discuss the factors that influence them, in patients with autoimmune rheumatic diseases.

Materials and methods: We searched the PubMed database for studies among patients with a diagnosis of rheumatoid arthritis (RA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), or psoriatic arthritis (PsA), published from January 2015 to February 2017. Only studies with a well-defined measurement of adherence/persistence and those that carried out an evaluation of the influencing factors were included.

Results: Fifteen relevant studies that evaluated adherence and/or persistence were included. Adherence rates varied between 9.3% and 94%, and persistence rates between 23% and 80%. Most of the studies used one method to evaluate adherence or persistence (different questionnaire scores, proportion of days covered, and mean treatment duration). A high concordance was found between the adherence measurements of the Medication Event Monitoring System and Visual Analog Scale. Factors of economic, demographic, and clinical nature were only moderately linked to treatment adherence or persistence. However, patient-related factors – such as positive and increased beliefs in medication necessity, strong views of the chronic nature of the diseases, and increased knowledge of the disease – were related to better treatment adherence.

Conclusion: Owing to the heterogeneity of the study results, we consider that the use of more than one method to assess adherence/persistence should yield more comprehensive and accurate data about patient adherence behavior. Patient-related factors should be included and analyzed more often in adherence studies as the former may be modified to improve patient adherence.

Keywords: drug therapy, rheumatology, patient nonadherence, risk factors

Introduction

As reported by the World Health Organization (WHO), patient adherence to long-term therapies is alarmingly low in both developed and developing countries.[1] The impact of poor adherence on the effectiveness of chronic disease treatment is severe – both in terms of poorer health outcomes and increased health care costs. Low adherence impacts the quality of life of patients, affecting their ability to function in society. Furthermore, it increases the costs associated with the required medical interventions, rates of hospitalization, and increased visits to physicians.[1–4]

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Studies in this area have validated the following statement: "Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments".[1,4]

Medication adherence is a complex issue, and the different terminology used when analyzing this may cause debate and confusion. It is common to find studies that have the same measures referred to by different names: compliance, adherence, concordance, persistence, and discontinuation. These terms describe different aspects of patients' medication-taking behavior (extent of drug use, continuation of therapy, etc.) that are related to patients' knowledge and understanding of their treatment and disease, and also reflect the relationship with their health care professionals. Occasionally, some of these terms are used interchangeably; however, this is not entirely correct. Moreover, the use of multiple terms is even more confusing as most of these terms do not have a clear or direct translation into different European languages.[1–7]

As defined by the WHO, adherence represents "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with the agreed recommendations from a health care provider".[1] In other words, adherence refers to "the extent of drug use during a period of persistence".[2,4–7] In some cases, adherence and compliance are used as synonyms; in others, adherence is referred to as part of the compliance process.

Persistence is described as "the time of continuous therapy", referring to "the continuation of drug use for an overall duration of drug therapy".[2–8] Depending on the source, persistence can be defined alternatively as the time between pharmacy refills or renewal of prescription (in most cases, allowing a gap of 30, 45, or 60 days).[6–8]

Parameters most often used to evaluate adherence and persistence are: medication possession ratio (MPR), proportion of days covered (PDC), survival time, retention rate, and different scores – depending on the method used for assessing them.[2–11] There are both direct and indirect approaches to evaluate treatment adherence, each with advantages and disadvantages; however, ultimately, there is no single method that can accurately measure treatment adherence.[2–18] Direct methods such as therapeutic drug monitoring and measurements of the drug or a metabolite provide a quantifiable value that offers evidence of drug ingestion. These are often referred to as the most "objective" and "direct" approaches to measure treatment adherence as they are subject to low bias; however, these approaches may be expensive and, sometimes, inconvenient for patients. Indirect methods such as pill count, electronic monitoring devices, electronic databases, and self-reported methods are most popular but can be subjective and overestimate adherence.

Autoimmune rheumatic diseases are a heterogeneous group of rare inflammatory conditions that share common immunopathogenic mechanisms. They are characterized by various clinical features and multiple organ involvement, and are associated with increased morbidity and mortality.

As in other chronic conditions, treatment adherence is an important part of their therapy. Because they involve lifetime treatments, the impact of low adherence is serious and can influence the effectiveness of the medication regimen. Unrecognized nonadherence could be wrongfully interpreted as an underestimation of treatment effectiveness.

International and national treatment guidelines exist: although they cover the management of these diseases, such guidelines offer no specific information or recommendations in regard to treatment adherence.[19–22]

Disease management for autoimmune rheumatic diseases consists of various pharmacological or non-pharmacological approaches. Diverse pharmacological options are available and include: corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, and disease-modifying antirheumatic drugs (DMARDs). DMARDs comprise two major classes: conventional synthetic DMARDs (csDMARDs) and biological DMARDs (bDMARDs).[19–22] Disease activity and clinical manifestations, comorbidities, and safety issues are some of the aspects taken into account when choosing an appropriate approach to offer patients the best possible quality of life and prevent inflammation and further structural damage.[19–22] This can only be achieved if patients adhere to their treatments.

Demographic and economic aspects as well as therapy and disease-related factors, along with patient-related factors, are frequently assessed in adherence studies; however, to date, no predictors have been found to be strongly related to – or to influence – nonadherent behavior.[5,8–15] Furthermore, contradictory results have been reported. The inclusion of disease- (clinical factors, disease duration, and activity) and therapy-related factors (medication type, dosing frequency, previous treatments) in adherence studies focusing on autoimmune rheumatic diseases is based on existing knowledge of their relationship with adherence in other chronic diseases.[1] Adherence is simultaneously influenced by several factors; some of these are potentially modifiable, with potential for use in screening to identify nonadherent patients. These factors demonstrate the importance of accurate identification of the various reasons for patient nonadherence to treatment plans.

Nonadherence is commonly categorized into two groups: unintentional – which can be related to inaccessibility to medication, language barriers, polypharmacy, and forgetfulness – and intentional, which is strongly related to patients' personal beliefs, decisions, and treatment.[4,8–16,23]

This study was conducted to offer an up-to-date overview of the existing information available on rates of adherence and persistence in patients affected by autoimmune rheumatic diseases, and to include factors that potentially influence these rates. An accurate view on this subject would contribute to increased knowledge and improve the effectiveness of therapies. We included studies that evaluated either adherence or persistence because, in essence, both are distinct aspects that relate to the same topic.

Materials and methods

We conducted a literature search to identify studies on patient adherence to their treatments and the factors that potentially influence it.

Search strategy

A PubMed search was conducted with the start date January 1, 2015, and end date February 20, 2017. This interval was chosen on the basis of relevance; only the latest studies were included as reviews including older studies are already available.

Terms used in the search

The terms "persistence" or "adherence" or "compliance" or "discontinuation" AND "rheumatoid arthritis" or "ankylosing spondylitis" or "systemic lupus erythematosus" or "psoriatic arthritis" AND "treatment" or "therapy" or "medication" were searched.

Only English-language articles and those conducted on adults (>18 years) were included.

Reviews, case reports, letters, and editorials were not included as primary data in this review. Each article was screened and assessed for relevance of results on adherence by reading the abstracts or the full text.

Findings based on search criteria

Briefly: 186 articles on rheumatoid arthritis (RA) were selected, of which 28 articles were considered potentially relevant; 35 articles on systemic lupus erythematosus (SLE) were identified, of which 11 were considered potentially relevant; 23 articles on ankylosing spondylitis (AS) were found, of which six were considered potentially relevant (after eliminating duplicates, only two remained); and 26 articles on psoriatic arthritis (PsA) were short-listed, of which five were considered potentially relevant (after eliminating duplicates, two remained).

Full-text articles were retrieved for the remaining 43 articles and, in the present narrative review, we included only those articles that met the following inclusion criteria:

- Studies containing a well-defined measurement of adherence/persistence and reporting adherence/persistence as an outcome.
- Studies reporting an analysis of associated, predictive, or risk factors related to adherence.

Following these criteria, 15 studies were included in the present narrative review.

Results

Adherence, as an outcome, was assessed in ten out of 15, persistence in two, and drug discontinuation in three studies. One study evaluated both adherence and treatment abandonment,[24] and two studies reported results for both adherence and persistence rates.[25,26] The sample size in the studies ranged from 80 to 12,893 participants. Participants were derived either from the outpatient clinic[27–32] or were recruited online[33] through social media or forums, or were patients from established cohorts in medical databases.[24–26,34,35] In two studies, the Danish nationwide DANBIO Registry, which includes clinical data on patients with rheumatic diseases treated with biologics in routine care, was used.[36,37] Another study recruited patients through the British Society for Rheumatology Biologics Register for RA – a UK-wide prospective observational cohort study established in 2001 for the purpose of monitoring the long-term safety of biologic therapy.[38] In regard to study design, four had a cross-sectional design,[27,28,31,32] five were retrospective cohort studies,[24–26,34,35] and six were prospective studies.[29,30,33,36–38]

Adherence and persistence rates and measurements

There was considerable variation in regard to the terms and concepts related to adherence and persistence between studies. Different definitions were used, as presented in Table 1.

The majority of the studies estimated adherence for RA patients,[24–31,33–35,38] and some included both RA and AS patients.[31,33–35] PsA patients were included in three studies,[33,34,37] and one study included patients with SLE.[32]

Most of the studies applied a single method to evaluate adherence, whereas only two studies used more than one method.[28,29] Self-reported adherence was the most

Table 1 Adherence and persistence

Study	Population and rheumatic disease	Study size	Type of medication	Adherence/persistence definition and measurement	Study outcome	Adherence/ persistence (%)
Morgan et al[38] UK Prospective cohort Follow-up at baseline, 6, 12, and 18 months	First-time ADA users RA	329	ADA ADA+csDMARDs	Self-reported questionnaire CQR19 (mail) CQR score (0–100) CQR <65 low-adherence The extent to which a patient's behavior in taking their medication corresponds to agreed recommendations by their health care provider	Adherence 6 months 12 months 18 months	 76.76 76.32 76.7
Kumar et al[27] UK Cross-sectional	Existing users RA	180	csDMARDs or anti-TNFα	Self-reported questionnaire (interview) MARS-6 score (6–30) MARS ≥26 (high adherence) No definition cited in the article	Adherence White British South Asian	 76.9 58.4
Gadallah et al[28] Egypt Cross-sectional	Existing users RA	140	csDMARDs+NSAIDs	Self-reported questionnaire Interview 1. MMAS-8 score (<6 low, 6–7 medium, and >8 high adherence) 2. Rate of prescription refilling Late/on time The extent to which patients take medications as prescribed by their health care providers 3. DAS28 score: DAS28>5.1 high disease activity. DAS28<3.2 low disease activity. DAS28<2.6 remission.	Adherence Low Medium High Rate of prescription refilling Late On time	 90.7 9.3 0 75.7 24.3
Salaffi et al[30] Italy Observational 16 consecutive weeks Longitudinal 12-month follow-up	First-time users of bDMARDs RA	209	Subcutaneous anti-TNFα (ADA, ETN, GOL, or CET) ± MTX	Self-reported questionnaire (via post or email) A combination of compliance and persistence. MMAS-4 score 0 points = high adherence 1–2 points = average adherence 3–4 points = poor adherence	Adherence	79.4
Chu et al[24] USA Retrospective 1 and 2 years follow-up Claim database	First-time users of ADA or ETN RA	2,151	ADA or ETN ± csDMARDs, NSAIDs or analgesics	Adherence was measured with PDC (%) and treatment abandonment with attrition rate (%) $\text{PDC}(\%) = \frac{\text{Total days drug available}}{\text{Days of follow-up}} \times 100$ PDC ≥80% adherent PDC <80% nonadherent $\text{Attrition} = \frac{\text{No. of patients abandoning medication}}{\text{No. of patients initiating medication}} \times 100$ Rate (%)	Adherence Treatment abandonment ADA ETN	26.8 42.9 32.2

Abdul-Sattar et al[32] Egypt Cross-sectional	Existing users SLE	80	csDMARDs	CQR19 score (0–100) Nonadherent (noncompliant) = patients who were taking <80% of their medication correctly	Adherence	52.5
Glintborg et al[36] Denmark Observational DANBIO registry	First-time users of anti-TNFα AS	1,576	Anti-TNFα (ADA, ETN, GOL, INF) ± MTX	Number of years each patient maintained treatment Start date = the date of the first given dose Stop date = the date of the first missed dose	Treatment duration mean (years) Current smokers Previous smokers Never smokers	 2.24 2.71 4.12
Højgaard et al[37] Denmark Observational DANBIO registry	First-time users of anti-TNFα PsA	1,388	Anti-TNFα (ADA, ETN, or INF) ± MTX	Number of years each patient maintained treatment Start date = the date of the first given dose Stop date = the date of the first missed dose	Treatment duration mean (years) Current smokers Never smokers	 1.56 2.43
Bonafede et al[25] USA Retrospective database 1-year follow-up	First-time users of dual or triple therapy RA	4,542	ETN–MTX vs MTX-HCQ-SSZ	Rate of adherence PDC* (%) = the percentage of days based on day's supply of prescription claims during which a patient has medication available during the 1-year post-index period Adherent patient PDC*>80% for all drugs within each regimen Rate of persistence (%) = no treatment gap >45 days for any drug and no addition or switching to other csDMARDs	Adherence ETN–MTX MTX–HCQ–SSZ Persistence ETN–MTX MTX–HCQ–SSZ	 27.9 18.2 29.4 23.2
Hromadkova et al[31] Czech Republic Cross-sectional	RA AS SSc JIA	289	Not mentioned	Self-reported questionnaire CQR19 score CQR19 score ≥80% compliant CQR19 score <80% non-compliant	Adherence RA AS	 55.1 38.3
Betegnie et al[33] France Prospective cohort	Existing users AS RA PsA	581	bDMARDs ± csDMARDs	Questionnaire developed and validated by the authors (via the Internet) SD = patient's decision to stop biologics	Adherence	85.2
De Cuyper et al[29] Belgium Observational 16 consecutive weeks	Existing users RA	129	MTX (oral or injection)	1. MEMS® Medication adherence rate = Every patient was assigned a score 0 (not opened) or 1 (opened). The average of 16 measurements was multiplied by 100 Patient fully adherent = if, over a period of 1 week, the MEMS container was opened once or more in accordance with the prescription 2. MARS-5 (score range 5–25) 3. CQR19 score 4. VAS (ranging from "in 0% of the cases" to "in 100% of the cases")	Adherence 1. MEMS 2. MARS-5 3. CQR19 4. VAS	 92 Mean score 24.2 85.7 Mean score 94

(*Continued*)

Table 1 (*Continued*)

Study	Population and rheumatic disease	Study size	Type of medication	Adherence/persistence definition and measurement	Study outcome	Adherence/ persistence (%)
Lyu et al[34] Germany Retrospective database 12 months follow-up	First-time users of subcutaneous anti-TNF therapy RA AS PsA	881	Anti-TNFα (ADA, ANA, CET, ETN, or GOL) ± csDMARDs	Rate of persistence assessed as time from initiation of treatment until discontinuation Discontinuation was the first day of a period of at least 60 consecutive days (grace period) in which no prescription for the biologic agent was detected (switching to another biologic agent was considered non-persistence)	Persistence RA AS PsA	 51.9 48.1 57.9
Kim et al[26] USA Retrospective claim database	First-time users RA	2,685	csDMARDs (MTX, HCQ, SSZ, or LEF) as mono- or dual therapy	Adherence was measured with PDC PDC = the number of days when drugs were available divided by the number of days in the study period PDC ≥70% adherence PDC <70% nonadherence Persistence was calculated as the number of days in which sDMARD were continuously used during the post-index period before a gap of the last day's supply plus 60 days	Adherence Persistence (days)	10 189
Machado et al[35] Brazil Retrospective cohort Database 1 and 2 years follow up	First-time users RA AS	12,893	Anti-TNFα (ADA, ETN, or INF) ± csDMARDs (MTX, LEF, SSZ, HCQ, or CCQ) users and csDMARDs users	Proportion of persistent patients: At the 1-year follow-up $= \frac{\text{No. of patients who persisted in their therapies for atleast 1 year}}{\text{No. of patients that had a full year of follow-up or more}}$ At the 2-year follow-up $= \frac{\text{No. of patients who persisted in their therapies for atleast 2 years}}{\text{No. of patients who had 2 years follow-up or more}}$ In the anti-TNF group, switching from an anti-TNF drug to another was considered discontinuation of therapy Persistence = the period between the start of treatment until it is discontinued, allowing for an interval of up to 30 days between the prescription end and the start of the next prescription	Persistence Anti-TNFα ± sDMARD 1 year RA AS 2 years RA AS csDMARDs 1 year RA AS 2 years RA AS	 66 80 41 60 54 41 29 20

Abbreviations: ADA, adalimumab; ANA, anakinra; AS, ankylosing spondylitis; CCQ, chloroquine; CET, certolizumab; CQR19, 19-item Compliance Questionnaire for Rheumatology; bDMARDs, biological disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ETN, etanercept; GOL, golimumab; HCQ, hydroxychloroquine; INF, infliximab; JIA, juvenile idiopathic arthritis; LEF, leflunomide; MARS, Medication Adherence Report Scale; MMAS-8, 8-item Morisky's Medication Adherence Scale; MEMS, Medication Event Monitoring System; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; RA, rheumatoid arthritis; PDC, proportion of days covered; PDC*, percentage of days covered; PsA, psoriatic arthritis; SD, self-discontinuation; SLE, systemic lupus erythematosus; SSZ, sulfasalazine; SSc, systemic sclerosis; VAS, Visual Analog Scale.

frequently used method, with different questionnaires being employed – the 19-item Compliance Questionnaire for Rheumatology-19 (CQR19), which was created specifically for and validated to use in rheumatic diseases,[29,31,32,38] eight- and 4-item Morisky's Medication Adherence Scale (MMAS-8 and MMAS-4, respectively), and 6- and 5-item Medication Adherence Report Scale (MARS-6 and MARS-5, respectively);[27–30] in one of the studies, the investigators developed and validated a special questionnaire.[33]

When measuring adherence using medical databases, PDC was used in three of the studies,[24–26] and rates of persistence were the outcome in four others.[25,26,34,35] One study gave information on treatment abandonment, which was assessed with the attrition rate.[24] More details on the methods of calculation for all these studies are presented in Table 1.

Some of the studies included rates of adherence in existing users of medication;[27–29,32,33] however, the majority assessed adherence or persistence for first-time users,[24–26,30,34–38] whereas one study did not mention this aspect.[31] Most commonly, first-time users referred to patients initiating biologic therapy.

Rates of adherence varied widely between 9.3% and 94%, with results depending on the rheumatic disease, the method used to assess adherence, as well as the cutoff point that was used to separate nonadherent from adherent patients. The lowest adherence was detected in a cross-sectional study, with 9.3% of the RA patients being classified as medium-adherent according to the MMAS-8 measurement.[28] None of the patients included met the criteria for being high adherers. The highest rate of adherence was measured in an RA cohort receiving methotrexate (MTX).[29] The results obtained using the Medication Event Monitoring System (MEMS) method (92% of patients adhered to treatment) correlated the highest with the results from the Visual Analog Scale (VAS) mean score of self-reported adherence (94%).[29]

Rates of persistence varied widely across studies, ranging between 23% and 80%. A low persistence was found in RA patients treated with MTX–HCQ–SSZ (methotrexate–hydroxychloroquine–sulfasalazine) triple therapy (23.2%). A high rate of persistence was found in AS patients undergoing anti-tumor necrosis factor alpha (anti-TNFα) therapy with or without concomitant csDMARD use – 80% in the first year of follow-up, decreasing to 60% in the second year.

Factors associated with adherence

A variety of associated/predictive factors were analyzed in all the studies, including sociodemographic and economic factors, therapy- and disease-related factors, and patient-related factors; however, only a small number of these factors was found to influence adherence or persistence.

Social and economic factors

Sociodemographic factors, such as age, ethnicity, gender, marital status, educational level, living situation, and employment status, were among those most commonly included in the analyses.

Results show that older patients with RA were more likely to be adherent,[24,30,38] whereas another study found that younger patients with RA were more likely to adhere to their therapies.[28] No other study reported age as a predictor of patient adherence behavior.

For SLE patients, factors such as very low and low economic status, lower education levels, and rural residency were found to be correlated with adherence in a negative way.[32] Another study detected that RA patients who had a lower income were more likely to be persistent in the first and second year of follow-up than those with better incomes.[35]

The connection between smoking status and treatment adherence was evaluated in two studies from Denmark using data from the DANBIO registry.[36,37] One of them found that AS patients who were current and previous smokers had poorer treatment adherence than never smokers, with this finding being relevant mainly in men.[36] These results were consistent regardless of the TNF-α inhibitor prescribed. When they compared previous smokers with never smokers, the authors found that previous smokers had poorer adherence for adalimumab (ADA) and etanercept (ETN).[36] The same registry was used to assess the influence of smoking status on treatment adherence in PsA patients, and current smoking status was associated with poorer adherence to ETN and infliximab (INF), but not to ADA.[37]

Increased professional or familial support was associated with greater adherence,[33,38] whereas living alone had a negative impact on adherence.[29] Two out of three studies that included the patients' ethnicity found a relevant connection with treatment adherence.[24,27] White British patients with RA had better treatment adherence than South Asians,[27] and African-American patients with RA were more likely not to adhere to their first bDMARD.[24] Details of these factors from all studies are presented in Table 2.

Health system-related factors

Health system-related factors were evaluated in more than half of the studies,[24,25,27,28,30,33,34,38] referring to either the type of insurance (in studies conducted in databases) or the different aspects relating to physician interaction (language used in

Table 2 Analyzed factors for adherence/persistence

Study	Factors				
	Social and economic	**Health system-related**	**Therapy-related**	**Illness-related**	**Patient-related**
Morgan et al[38] UK	Age, gender, ethnicity, lifestyle (ever smokers), social deprivation, family support	Professional support	Number of baseline csDMARDs	Disease activity, disease duration, functional disability	IPQ-R, HADS, BMQ, EQ-5D, coping (problem/emotionally focused)
Kumar et al[27] UK	Age, gender, occupation, ethnicity (South Asian, white British), IMD, level of education	Language spoke with physician		HAQ, DAS28	BMQ, SIMS, IPQ
Gadallah et al[28] Egypt	Age	High costs of medication, nonavailability of free drugs, communication, time spent with doctor	Duration of medication use, side effects	Duration of diseases, disease activity (DAS28 score)	Patient knowledge about RA, patient beliefs concerning medications, general satisfaction score
Salaffi et al[30] Italy	Age, gender, marital status, employment status, educational level	Patient–physician discordance ratings		Comorbidities, disease activity, laboratory and clinical parameters	
Chu et al[24] USA	Age, gender, ethnicity	Insurance types	RA-related outpatient visits, emergency department visits, hospitalizations, physical and occupational therapy, history of joint or knee replacement, prescription type (corticosteroids, csDMARDs, ADA/ETN)	Comorbidities	
Abdul-Sattar et al[32] Egypt	Age, gender, marital status, educational level, place of residency, socioeconomic status (very low, low, middle, or high)		Total number of medication used	Number of years since diagnosed with SLE, disease activity, presence/absence self-reported SLE disease flare within the past 3 months, depressive symptoms	
Glintborg et al[36] Denmark	Age, gender, smoking status (never, previous, current)		Calendar year of starting TNFi, baseline MTX use (yes/no), TNFi type	Disease duration	
Højgaard et al[37] Denmark	Age, gender, smoking status (never, previous, current)		Calendar year of starting TNFi, baseline MTX use (yes/no), TNFi type	Disease duration	
Bonafede et al[25] USA	Age, gender, urban status (urban/rural), region, index year	Health care plan	Preindex rheumatologist visits (yes/no), preindex total RA-related costs, preindex glucocorticoid use (yes/no), number of preindex distinct National Drug code codes, ETN–MTX therapy vs MTX–HCQ–SSZ therapy	Preindex comorbidity level	
Hromadkova et al[31] Czech Republic	Age, gender, education level			Quality of life (SF-36v2), Health status (HAQ)	

Betegnie et al[33] France	Age, gender, marital status, work status, education level, place of residence, social support	Medical support	Time since first biologic, number of biologic lines, number of physicians consulted since first symptoms, management of biologic administration ("myself", "a carer", "a nurse", "others"), side effects, use of CAM	Pain (over the last 8 days, assessed with VAS), type of CIRD (RA, AS, PsA, other) disease duration, time to diagnosis	Beliefs and perceptions about the efficacy of the biologic and side effects Beliefs about treatments, Perceptions of self-efficacy of self-injection, Perceptions of treatment efficacy, Expected objective of the treatment
De Cuyper et al[29] Belgium	Age, gender, living situation, occupational status		Dosage (MTX), number of doctor visits during the last 6 months, number of prescribed pills per day, possible side effects	Disease activity (DAS28), HAQ, comorbidities, somatic symptoms (PHQ-15), physical and mental health (SF36), depression (PHQ-9), anxiety, disease duration	Illness cognitions (IPQ-K), social support in relation with the disease in general and with medication intake, motivation to take MTX, motivation
Lyu et al[34] Germany Kim et al[26] USA	Age, gender	Health insurance status (private/statutory)	Preindex csDMARDs use, Baseline medication csDMARDs drug type (MTX, HCQ, SSZ, or LEF)	Comorbidities	
Machado et al[35] Brazil	Age, gender, per capita income (low/high income)		Drug type TNFi ± csDMARDs/csDMARDs	Disease (RA/AS)	

Abbreviations: ADA, adalimumab; AS, ankylosing spondylitis; BMQ, Beliefs About Medicines Questionnaire; CAM, complementary and alternative medicines; CIRD, chronic inflammatory rheumatic disease; DAS28, Disease Activity Score in 28 joints; bDMARD, biological disease modifying antirheumatic drugs; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; EQ-5D, EuroQol-5 Dimension; ETN, etanercept; HADS, Hospital Anxiety and Depression Scale; HAQ, Health Assessment Questionnaire; HCQ, hydroxychloroquine; IMD, Index of Multiple Deprivation; IPQ, Illness Perceptions Questionnaire; IPQ-K, Dutch shortened version of the Illness Perception Questionnaire; IPQ-R, Revised Illness Perception Questionnaire; LEF, leflunomide; MTX, methotrexate; PHQ-9, 9-item Patient Health Questionnaire; PHQ-15, 15-item Patient Health Questionnaire; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SF36, Short Form 36; SF-36v2, Short Form 36 version 2; SIMS, the Satisfaction with Information about Medication Scale; SSZ, sulfasalazine; TNFi, TNF inhibitor; VAS, Visual Analog Scale.

communication and professional support with discordance rates). The findings were not conclusive, with just three studies reporting a significant correlation between health system-related factors and adherence.[28,30,33]

Nonavailability of cost-free drugs in the pharmacy is, as expected, one of the barriers to treatment adherence.[28] Lack of perceived medical support[33] and higher patient–physician discordance rates[30] had a negative impact on treatment adherence.

Therapy-related factors

Different factors related to therapy, such as type of medication used, complexity of the treatment regimen, side effects, and duration of medication used were included in 12 of the 15 studies and found to have a relevant connection to adherence or persistence in some of them,[24–26,32–35] being mostly related to the type of medication used.

Factors found to be positively associated with both adherence and persistence were csDMARD monotherapy (with either MTX or LEF)[26] and ETN–MTX use in RA patients.[25] Factors positively influencing persistence were existing csDMARD RA users[34] and anti-TNFα therapy with or without csDMARDs in AS patients.[35]

ETN use in RA patients and an increased number of medications used by SLE patients were found to have a negative impact on adherence.[24,32] More than one attempted and self-administered bDMARD therapy was also a factor that had a negative impact on self-discontinuation, which was defined as the patient's own decision to stop the treatment "alone" or "alone and then validated by a physician".[33]

Illness-related factors

A wide range of illness-related factors, such as type of disease and disease duration, disease activity and functional disability, depressive symptoms, and other comorbidities, was included in most studies. Most of the reported results were inconsistent, making it difficult to establish a coherent pattern.

Longer disease duration,[28,38] lower levels of pain,[33] and both low levels[30] and high levels[28] of disease activity were found to have a negative impact on adherence. Better mental health status predicted better adherence.[29,32]

The presence of comorbidities (coronary artery disease, hypertension, COPD, renal disease, and liver disease) was found to have both a negative[24,30] and a positive impact on treatment adherence.[29]

Patient-related factors

The patient's knowledge about their disease, motivation to take medicines, and the patient's perceptions about efficacy

and concerns about therapy or side effects are some of the related factors included in the studies.[27–29,33,38] Beliefs and perceptions about treatments were evaluated using the Beliefs About Medicines Questionnaire (BMQ)[27,38] or other scales.[28,33] Positive and increased beliefs in medication necessity were associated with higher rates of adherence,[27,28,33,38] and lower medication concerns had a positive effect on adherence.[27,38] Strong views of the chronic nature of the diseases,[38] increased knowledge of the disease,[28] satisfaction with information received about therapy,[27] and greater satisfaction score[28] were all factors associated with greater treatment adherence.

A simplified list of all the factors enclosed, and the direction of association with adherence and persistence, is presented in Table 3.

Discussion

Adherence and persistence rates and measurements

Patients who adhere to their treatments are three times more likely to achieve desired outcomes, such as improved quality of life and better functional capacity, than nonadherent patients.[39] However, research suggests that adherence rates drastically drop after 6 months of treatment; this is valid in a number of chronic diseases such as cardiovascular conditions and hypertension, asthma, diabetes, and RA.[1,40] Chronic patients might display a number of common adherence characteristics, some being closely related to the specific features of the disease that they suffer from, with each facing unique and distinctive challenges.

We found that rates of adherence vary widely in the four autoimmune rheumatic diseases included in this review, underlining the seriousness and complexity of this aspect. In previous reviews of earlier studies, there are the same wide variations, with reported adherence rates in rheumatic diseases ranging between 7% and 75%.[4]

The diversity of the definitions and methods used to evaluate adherence and persistence might explain the variation in results. There is no standard method to evaluate adherence, and the choice remains entirely at the hands of the investigators conducting the study, and varies based on the resources, desired outcome, and personal interpretations on the matter. However, the different methods used in the studies from this review assessed various aspects of treatment adherence. The findings should, therefore, not be discarded, but rather, analyzed and integrated in the wider context as part of understanding the complex patient-treatment behavior. As there is no "gold standard" for evaluating adherence, using two methods (eg, MEMS and a self-reported method) may lead to more accurate measurement of patients' treatment adherence, as they gather sets of information by using different approaches and perspectives, thereby complementing each other. Using both a subjective and an objective method could also provide additional information on the beliefs and barriers pertaining to adherence.[12] In the study using four methods for evaluating adherence in patients taking MTX, the highest concordance was found between MEMS, an objective method, and VAS, a subjective method – with the latter being frequently perceived to overestimate adherence.[29] However, this study demonstrated that VAS may be used in daily practice as a quick and simple method for screening medication adherence.

Adherence is a dynamic process that changes over time; therefore, a complex image can only be obtained if adherence is evaluated both at the beginning of a treatment and during the continuation phase. This could partly explain the diversity of adherence rates in the studies included here, as some of them measured adherence in patients initiating a new treatment regimen (most frequently, the initiation of an anti-TNFα agent) and some evaluated adherence in existing users. Longitudinal studies – commencing at the start of a treatment and following patients through the years of treatment – could give a complete representation of adherence and inform physicians about the different factors influencing it along the way.

Data on direct comparisons between rates of adherence and persistence between different diseases were available for RA and AS patients. Although it is difficult to draw a clear conclusion, RA patients tended to have slightly higher rates of adherence than AS patients.[31,33,34]

In three of the studies, patients responded to adherence questionnaires online, showing overall better adherence.[30,33,38] The selection of recruitment strategy could bias the results, by choosing some categories of patients (younger, better education, and better social status) and excluding others. Moreover, it could lead to results that reflect reality better, with patients that do not display "white coat adherence behavior".

Factors associated with nonadherence

According to the WHO, there are five dimensions of factors influencing medication adherence: social and economic factors, health system-related factors, therapy-related factors, illness-related factors, and patient-related factors.[1]

A broad range of social and economic aspects that characterize the personal context of the patient have been included in almost all of the studies. These aspects are quite easy to

Table 3 Direction of association between adherence/persistence and factors

Study	Outcome	Factors			Analysis
		Negative association	**Not significant**	**Positive association**	
Morgan et al[38] UK	Adherence	Longer disease duration	DAS28 score Disease activity and functional disability (high acute-phase reactants HAQ score)	Older age Patients' awareness of the long-lasting nature of RA Increased belief in medication necessity Lower medications concerns. Increased professional or family member support Increased treatment control	Univariate
Kumar et al[27] UK	Adherence	Dissatisfaction with information about csDMARDs (side effects, how do csDMARDs work to control the condition) High concerns about csDMARDs and medication in general (south Asian had more negative views about medicines) South Asians Negative beliefs about csDMARDs and medication in general	IMD score Age Gender Level of education DAS28 score English speaking patients	White British Higher SIMS score	Univariate and multivariate
Gadallah et al[28] Egypt	Adherence Rate of prescription refilling Late/on time	High costs of medications Nonavailability of free drugs Experienced side effects of medication Higher disease activity Higher disease duration		Younger age Higher knowledge score Greater general satisfaction score, communication and time spent with doctor Higher beliefs score of the importance and benefits of RA medications	χ^2 test Student's *t*-test
Salaffi et al[30] Italy	Adherence	Low disease activity, older age, higher patient–physician discordance ratings, high number of comorbid conditions	Employment status, educational level, gender, marital status Laboratory parameters and functional data Radiographic data		Logistic regression
Chu et al[24] USA	Adherence Treatment abandonment	ETN use, csDMARDs use, knee/joint replacement, age <65, African Americans, having physical/occupational therapy, corticosteroid use Age, the presence of at least one comorbidity, ETN use, csDMARDs use, knee/joint replacement			Multivariate linear regression
Abdul-Sattar et al[32] Egypt	Adherence	Lower educational level, very low and low economic status, rural residency, increased number of medications, higher depressive symptoms	Age, gender, marital status, disease duration		Multiple regression
Glintborg et al[36] Denmark	Drug discontinuation	Smoking status (current and previous smokers) statistical significance mainly in men			Univariate multivariate

(*Continued*)

Table 3 (*Continued*)

Study	Outcome	Factors			Analysis
		Negative association	Not significant	Positive association	
Højgaard et al[37] Denmark	Drug discontinuation	None	Smoking status		Univariate multivariate
Bonafede et al[25] USA	Adherence	Triple therapy (MTX–HCQ–SSZ)			Multiple logistic regression
	Persistence	Triple therapy (MTX–HCQ–SSZ)			
Hromadkova et al[31] Czech Republic	Adherence	Increased QoL (PCS) score for AS patients		Higher HAQ score (higher disability rate) – only for RA patients CQR19 score (continuous and dichotomous variable)	Multivariate logistic regression
Betegnie et al[33] France	Adherence	Lower level of pain More than one line of bDMARDs Self-administered bDMARDs Negative belief about treatment Lack of perceived medical and social support	Type of CIRD Gender Experienced side effects		Univariate and multivariate
De Cuyper et al[29] Belgium	Adherence	Living alone		Presence of comorbidities Better mental health status	Logistic regression analysis
Lyu et al[34] Germany	Persistence		Preindex use of csDMARDs (in the SA and PsA cohorts)	Preindex use of csDMARDs (only in the RA cohort)	Multivariate
Kim et al[26] USA	Adherence	Dual therapy		LEF, MTX users Monotherapy	ANOVA, χ^2, Duncan and *t*-test
	Persistence	SSZ users	Monotherapy, dual therapy	LEF users	
Machado et al[35] Brazil	Persistence	csDMARDs use (first and second year) in AS patients		Lower income (first and second year) RA patients Male gender (first year) RA patients Anti-TNF ± csDMARDs users AS patients	Logistic regression

Abbreviations: AS, ankylosing spondylitis; CIRD, chronic inflammatory rheumatic disease; CQR19, 19-item Compliance Questionnaire for Rheumatology; DAS28, Disease Activity Score in 28 joints; bDMARDs, biologic disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ETN, etanercept; HAQ, Health Assessment Questionnaire; HCQ, hydroxychloroquine; LEF, leflunomide; IMD, Index of Multiple Deprivation; MARS, Medication Adherence Report Scale; MMAS-8, 8-item Morisky's Medication Adherence Scale; MEMS, Medication Event Monitoring System; MTX, methotrexate; PCS, Physical Component Scale; PDC, proportion of days covered; PDC*, percentage of days covered; PsA, psoriatic arthritis; QoL, quality of life; RA, rheumatoid arthritis; SD, self-discontinuation; SLE, systemic lupus erythematosus; SIMS, the Satisfaction with Information about Medication Scale; SSZ, sulfasalazine; VAS, Visual Analog Scale.

obtain, regardless of the method used to evaluate adherence or persistence. There are, however, no consistent theories that explain why these factors should be included and what is the extent of their influence on adherence. Moreover, they may have limited value due to the fact that they are not modifiable. However, they could be considered for risk screening and targeted interventions.[10] Altogether, they have been associated with treatment adherence in diabetes, epilepsy, HIV, and statin use, but the association with rheumatic diseases is still unclear.[1,10]

The most studied aspect – the influence of age on adherence – was found to be relevant in few of the studies we analyzed and showed opposite results, consistent with similar findings from other reviews and studies.[8,10,11,13,14,40] We did not find an association between gender and treatment adherence, but there is evidence in literature that links female gender to increased risk of biologic discontinuation.[8,40] One factor in particular – social support (from family and community) – was shown to have a positive impact on adherence,[33,38] whereas living situation (living alone) had a negative impact on adherence.[29] This is valid for other diseases and shows the importance of maintaining an optimal level of interaction and support that patients need in order to adhere to their treatments.[1,41] In a few studies, smoking status has been linked to the effectiveness of treatment in patients with RA and PsA, making it an important factor to be included in adherence research, as it is also potentially modifiable.[42,43] These findings are in line with the ones from two studies in our review.[36,37] Ethnicity, which was found to influence adherence in RA patients,[24,27] does not appear to be a consistent predictor of adherence in some reviews,[4,10,11] whereas it seems to influence adherence in others.[9,44] A strong connection between other social and economic factors has not been established in other studies either.[4,8,10,11,13]

Findings from our review suggests that some of the health system-related factors (eg, patient–physician relationship) contribute to treatment adherence.[30,33] Other studies in this area suggest the same association, that a good relationship with the treating physician improves adherence outcomes, both in rheumatic diseases[9,11,13,15,45] and in chronic conditions.[1,41] This might actually explain the association between adherence and some patient-related factors. Patients likely have an increased trust in the treatment efficacy and stronger treatment beliefs if they feel they can rely on and trust the treating physician. Moreover, international guidelines promote patient implication in the prescription process as a ground principle of therapy.[19–22] The trust RA patients had in their physicians was, in fact, shown to be one of the most important contributing factors when starting and adhering to an sDMARD treatment.[46] This supports the concept that adherence is not just an individual characteristic, but rather, a complex and dynamic experience in which each part – patient, health care practitioner, and the community – plays a specific role.

As patients with rheumatic diseases use complex treatment regimens, therapy-related factors were also assessed in the majority of the studies analyzed in this review. We have found that patients taking fewer medicines were more likely to be adherent than patients taking more medicines.[25,26,32] Polypharmacy is widely recognized to raise safety concerns and influence adherence to treatment in a number of chronic conditions,[1,47–49] including some rheumatic diseases,[50] although this association was not always consistent among studies conducted on RA patients.[10,11,13] The heterogeneity of these findings might be attributable to the diverse treatment regimens that are usually prescribed for these patients, which makes a direct and conclusive comparison difficult. Thus, adherence to MTX was better when compared to other csDMARDs,[10,26] but not superior to bDMARDs.[14,44] Among bDMARDs, there are studies that support a better adherence to subcutaneous ETN measured in lower discontinuation rates[4,8,40] than the adherence to intravenous INF (probably due to the implication of another health care provider, as INF is administered intravenously). Better adherence to ETN might also be explained by the low level of non-immunogenicity, compared to ADA and INF.[51] Furthermore, we have found lower persistence rates for INF when compared with other anti-TNFα agents used in RA and AS patients.[35]

Factors related to the disease, have been extensively studied in relation with medication adherence in a wide range of chronic disorders. Laboratory parameters that assess the severity of the diseases are routinely measured at doctor visits and can potentially be used for adherence screening, if found related to adherence. The relationship between adherence and disease severity can be bidirectional. Disease severity could be both the cause and effect of adherence, especially in rheumatic diseases where manifestations include symptoms such as severe pain, stiffness, and multi-organ involvement. Until now, a relationship between adherence and disease duration or disease severity has been established in diabetes, hypertension, and epilepsy,[1] but the findings are still inconsistent in autoimmune diseases.[4,10,11,13,14,52] Moreover, we have found conflicting results among the studies screened in this review. It is difficult to state if the results are because of the actual lack of correlation or other confounders that might have influenced the results, such as medication type,

follow-up period, and method of adherence measurement that cannot grasp the association. However, it is known that poor adherence leads to increased disease activity.[53] Better mental status is associated with better adherence – both in our findings[29,32] and in previous reviews.[4,9]

The last category of factors related to medication adherence are those considered to be patient-related – that means factors connected to the patients' attitudes, perceptions, beliefs, and lifestyle habits. They can indirectly influence some of the other factors. People's perceptions of their medications can be divided with respect to beliefs about the necessity of taking the medication and concerns about taking it.[4,16,54,55] These have been found to be consistent predictors of adherence in a number of disorders, namely asthma, renal disorders, cancer, diabetes, mental illness, and coronary heart disease, as well as in immune-mediated inflammatory diseases.[1,4,9–11,13,15,44,54–59] In some diseases, addressing the patients concerns seems more important than pointing out the necessity of treatment,[57,58] whereas, in rheumatic diseases, convincing patients of the treatment's necessity seems more relevant.[13,44,56] Similar consistent associations between adherence and increased necessity beliefs were observed by other groups.[27,28,33,38]

Limitations

Our results may have been influenced by a number of factors: 1) the heterogeneity of the studies included and inequality of the patient population covered (most studies involved RA patients, with the other rheumatic diseases thus being poorly represented); 2) methodological differences might have led to different adherence results (different methods used for assessment, some more "stricter" than others, that could have contributed to the ample variations of the results); and 3) potential confounders or specific elements could have influenced the results.

The ample variations of rates of adherence and persistence resemble the findings from systematic reviews, suggesting that our study – although not representing a systematic review – covers a relevant selection of the literature. Moreover, the results of our cumulative review present the latest findings in adherence research as we included studies published from 2015 to 2017. These studies include therapeutic regimens that are in line with the most recent international treatment recommendations and guidelines, making the present review one of current interest.

From the large number of factors included in all of the studies, only a few were found to have a certain influence on adherence or persistence. This lack of association may be the result of the true absence of a relationship or could be caused by the heterogeneity of the studies. Although studies have shown similar efficacy in RA when compared to TNFα inhibitors, T-cell co-stimulation inhibitors (eg, abatacept) and interleukin (IL)-6 antagonists (eg, tocilizumab) are much less used in clinical practice. None of the studies included in our review had patients treated with either abatacept or tocilizumab; therefore, unfortunately, we could not provide data on treatment adherence or persistence in regard to these agents. One study did include patients with an IL-1 inhibitor (anakinra) but did not report adherence results to it, because the number of patients taking it was too small.[34] The cross-sectional nature of four of the studies makes it challenging to establish a causal relationship between the findings, this being an issue noted by a significant number of systematic reviews. The retrospective database studies could only investigate the factors that were included in the databases; other factors that could have been potentially relevant, therefore, remain unexplored. Prospective data collection may represent a better choice; this was undertaken in only six of the 15 studies included in the present review.

Conclusion

Estimates of treatment adherence and persistence were shown to vary considerably because of differences in patient populations, follow-up durations, different types of adherence definitions, and measurements used.

Factors that suggest a coherent connection with adherence, such as personal beliefs and concerns, should more often be included in adherence research as there is some evidence to sustain their importance. Further research should focus on characterizing the specific relationship between treatment adherence and these factors. Future efforts should additionally aim to develop methods to improve treatment adherence in patients with autoimmune rheumatic diseases, thereby improving treatment effectiveness and patient quality of life.

Disclosure

The authors report no conflicts of interest in this work.

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