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Recommendations for the assessment and optimization of adherence to disease-modifying drugs in chronic inflammatory rheumatic diseases: a process based on literature reviews and expert consensus

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Key words: adherence; compliance; rheumatoid arthritis; spondyloarthritis; recommendations

Highlights:

1. Non-adherence to medications in chronic inflammatory rheumatic diseases is a frequent and deleterious issue.
2. Using an evidence-based approach followed by expert consensus, recommendations to assess and improve medication adherence in CIRDs have been developed.
3. Adherence should be assessed at each outpatient visit, at least using an open question.
4. Patient information and education, and patient/physician shared decision, are key to optimize adherence.
5. Formalized education sessions, motivational interviewing and cognitive behavioral therapy may be useful to improve adherence.

Abstract (237 words)

Background: Adherence to treatment is a key issue in chronic inflammatory rheumatic diseases (CIRDs).

Objective: To develop recommendations to facilitate in daily practice, the management of non-adherence to disease-modifying drugs in patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, connective tissue diseases or other CIRDs.

Methods: The process comprised (a) systematic literature reviews of methods (including questionnaires) to measure non-adherence, risk factors for non-adherence and efficacy of targeted interventions; (b) development of recommendations through consensus of 104 rheumatologist and nurse experts; (c) assessment of agreement and ease of applicability (1-5 where 5 is highest) by the 104 experts.

Results: (a) Overall, 274 publications were analysed. (b) The consensus process led to 5 overarching principles and 10 recommendations regarding adherence. Key points include that adherence should be assessed at each outpatient visit, at least using an open question; questionnaires and hydroxychloroquine blood level assessments may also be useful. Risk factors associated to non-adherence were listed. Patient information and education, and patient/physician shared decision, are key to optimize adherence. Other techniques such as formalized education sessions, motivational interviewing and cognitive behavioral therapy may be useful. All health professionals can get involved and e-health may be a support. (c) The agreement with the recommendations was high (range of means, 3.9-4.5) but ease of applicability was lower (2.7-4.4).

Conclusions: Using an evidence-based approach followed by expert consensus, this initiative should improve the assessment and optimization of adherence in chronic inflammatory rheumatic disorders.

1. Introduction

Drug adherence is defined by the World Health Organization (WHO) as "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (1). Drug adherence is usually conceived as drug intake and is usually considered satisfactory for adherence rates above 80% (meaning that more than 80% of the prescribed doses are absorbed by the patient) (2). Adherence is different from persistence, which is defined as the length of time a specific drug is taken without interruption.

Depending on the definition of drug adherence, the methodology used and the drugs concerned, adherence is variable but overall insufficient (3,4). In 2003, the WHO reported that, in developed countries, 50% of patients with chronic disease were adherent to prescribed treatment (1). In the field of rheumatic and musculoskeletal disorders, and in particular chronic inflammatory rheumatic diseases (CIRDs) such as rheumatoid arthritis, or connective tissue diseases, this non-optimal adhesion is confirmed. In these diseases, adherence to disease-modifying drugs is only moderate over the long term. Adherence has been mostly studied in RA and reported rates of adherence are 30 to 80% (3,5). Non-optimal patient adherence compromises therapeutic efficacy. In RA in particular, poor adherence has been shown to be linked to increased disease activity (6-9). Furthermore, non-adherence may lead to complications, unnecessary treatment switches and heightened costs (10). Thus, adherence is a key issue when dealing with chronic patients and there is a need for new care models addressing the problem of medication adherence, integrating this problem into the patient care process.

However, several questions remain unanswered. Firstly, assessment of non-adherence is an issue. Physicians tend to overestimate how well patients take their medication as prescribed. This can lead to missed opportunities to change medications, solve adverse effects, or propose the use of reminders in order to improve patients' adherence. Thus, better assessment of non-adherence would be useful. Adherence to treatment can be assessed by several methods, direct (such as blood tests) and indirect (such as questionnaires) (11). However to date, no gold standard method has been defined and clinicians may feel at a loss on how and when to measure adherence in their patients (12, 13). Secondly, as patients' lack of adherence to treatments is multifactorial, it would be useful to better understand the determinants of non-adherence (14-17). And finally, a better understanding of interventions to improve adherence and their efficacy is needed (18).

The objective of the present initiative was to develop recommendations to facilitate in daily practice, the management of non-adherence to disease-modifying drugs, in patients with CIRDs.

2. Methods

This process included literature reviews and a consensus process in France, in accordance with previous Rencontres d'Experts en Rhumatologie (RER) and 3E (Evidence, Expertise, Exchange) initiatives (19, 20) Of note, the recommendations were developed by a group of rheumatologists from a single country (France), the steering committee was issued from 9 university hospitals and one private practice, and the project was conducted thanks to an unrestricted grant from Abbvie France.

Decisions on target population and target aspects of adherence

A face-to-face meeting of the steering group took place in October 2016. The group included a convenor (MD), 2 methodologists (LG and AM), 3 fellows for the literature review (XR, DP and ML), 9 rheumatologist experts, one pharmacist and one rheumatology nurse. The steering group decided to elaborate these recommendations with the objective to facilitate the daily practice of health care providers in charge of this aspect of patient's management (e.g. nurses, general practitioners, pharmacists and rheumatologists). It was decided to limit the project scope to CIRDs, defined here as RA, spondyloarthritis (SpA), psoriatic arthritis (PsA), connective tissue diseases as well as some other inflammatory diseases such as crystal-induced arthritis, vasculitis and auto-inflammatory diseases. In terms of treatments, the project scope was limited to disease-modifying anti-rheumatic drugs, DMARDs (defined here as mainly conventional synthetic DMARDs, biologics and targeted synthetic DMARDs, but also checking the literature for data on glucocorticoid intake, non-steroidal drugs in SpA, and uric-lowering drugs as well as colchicine for crystal-induced arthritis). It was also decided to focus on 3 aspects of adherence, namely how to assess it, which patients to target more specifically for assessment (i.e., risk factors of non-adherence), and interventions to improve adherence (**supplementary table 1**).

The process then comprised 3 steps.

Systematic literature reviews

Between December 2016 and February 2017, 3 fellows performed systematic reviews of methods (including questionnaires) to measure non-adherence, risk factors for non-adherence and management options for non-adherence with their reported efficacy. The

searched were performed in CIRDs but were also enlarged as non systematic reviews, to cover other diseases where non-adherence is an issue, namely diabetes, high blood pressure, HIV infection and osteoporosis.

A systematic review of the literature in CRIDs was performed according to the Cochrane guidelines The data were issued from PubMed Medline, Embase, Cochrane central register of clinical trials; up to February 2017. Associations of key words around the disease names and “medication adherence” or “patient compliance” were used (**supplementary Table 1**). The search was completed using congress abstracts from the American and European congresses of 2016 and 2017; and several websites were searched: Clinicaltrials.gov, World Health Organisation and French High Authority of Health. Finally, hand search was performed using the references of the most relevant studies provided by the initiative’s scientific committee of experts in the field. Inclusion criteria were studies of adults, published in English or in French, on the diseases considered which were: RA, SpA, PsA, connective tissue diseases including systemic lupus, crystal related diseases including gout and chondrocalcinosis, vasculitis including ANCA-associated vasculitis, giant cell arteritis and polymyalgia rheumatica, and Still’s disease. Pharmacological medications considered were: conventional synthetic DMARDs, biological DMARDs, immunosuppressive drugs (cyclophosphamide…), non-steroidal anti-inflammatory drugs in SpA, glucocorticoids, colchicine and urate-lowering therapy. Articles were screened and all studies fitting the inclusion criteria and related to methods to measure non-adherence, risk factors classified in 5 domains according to WHO and management options for non-adherence with their reported efficacy classified in 5 modalities (educational, behavioral, cognitive behavioral, multicomponent interventions or others) were selected. The flow chart shows this selection process (**figure 1**).

Data were extracted and meta analyses were considered but given heterogeneity, were not performed (21). The most relevant information to answer each main question was discussed and reviewed with the steering committee and presented in a condensed form during the consensus process. ***Consensus process***

In October 2017, during a 2-day face-to-face meeting, recommendations were developed through consensus of 104 rheumatologists/pharmacists/nurse experts (with a high predominance of rheumatologists). The final recommendations were anonymously evaluated by the participants for agreement and ease of applicability (on a Likert scale 1-5 were 5 is highest).

Dissemination, evaluation, implementation and update

For the dissemination and evaluation steps, the steering committee decided that the results of this initiative would be evaluated and disseminated via small, regional, face to face meetings throughout France over one year. Finally, these recommendations should be updated systematically after a 5 years period or before in case some new relevant information in this area is available sooner.

3. Results

The consensus process led to 5 overarching principles and 10 recommendations regarding adherence (**Table 1**). The French version is presented as **Online supplementary Table 1**.

There was high agreement within the Task Force regarding these points: the agreement with the recommendations was high (range of means, 3.9-4.5 on a 1-5 scale) but ease of applicability was lower (range of means, 2.7-4.4).

Overarching principles (Table 1)

A-Drug adherence covers 2 complementary notions: compliance, i.e., treatment intake as prescribed, and persistence, i.e., maintenance of intake over time.

This overarching principle reminds the reader of the definition of drug adherence. Drug adherence refers to both a notion of drug intake and of long-term adherence, as recognised by the WHO (1, 22). This point is for information and was not the subject of debate.

B- Non-adherence to disease-modifying anti rheumatic drugs is frequent. It can be detrimental, leading to lower drug efficacy and potential cost increases.

This principle is again informative and was not debated. Many studies have shown that non-adherence is a detrimental process: it can lead to periods of disease intensification which in turn are detrimental (23). In several chronic diseases, the management of patients not adhering to their treatment is associated with higher health costs compared to that of adherent patients (10). In RA, poor patient adherence can compromise treatment effectiveness, decrease quality of life and appears to increase health care costs by around 33% (24, 25).

C- In non-adherence, factors known as "unintentional" (simply forgetting, ...) and "intentional" (linked to the patient's beliefs and fears, ...), are often intertwined.

This principle refers to causes of non-adherence and was again for explanatory purposes. Patients often cite unintentional causes of non-adherence such as having 'forgotten' to take the drug. But health professionals should be aware that this may 'hide' other reasons for non-adherence.

D- Knowledge both of the disease and of the treatment, and patients' perceptions of the benefit/risk of the treatment are key elements in drug adherence.

This overarching principle and the next one both introduce later recommendations on how to improve adherence since they refer to causes of non-adherence. Patient beliefs play a key role in non-adherence (26). Studies have shown that non-adherence is more frequent if the perceived necessity of a drug is lower than its perceived risk (26).

E- In the context of shared decision-making/therapeutic alliance, caregiver-patient communication about treatment is a key factor in drug adherence.

Given the elements above and also as a separate item, patient-physician interactions play an important role in non-adherence. All studies on adherence across diseases point out the importance of the quality of the patient-physician relationship and communication around drugs. Empathy also plays a role, some studies having indicated that empathy can contribute to better disease control (27).

Thus, adherence is a notion which refers to therapeutic alliance, a key notion in chronic disease management.

Recommendations (Table 1)

When and how to assess adherence? (recommendations 1-4)

1. Adherence should be assessed at each patient visit. It must be systematic if the treatment target is not reached and before any therapeutic change.

Healthcare providers are often unaware of adherence problems for their patients. Thus, providing physicians with feedback on medication adherence has the potential to prompt changes that improve their patients' adherence to prescribed medications. A recent Cochrane review did not evidence improvements in patient outcomes in studies with provision of feedback to physicians regarding their patients' adherence to prescribed medication (11). However, the group felt that being aware of adherence and communicating about this issue with patients was key.

The consensus was that adherence should be assessed regularly, ideally at each outpatient visit. If this cannot be done, adherence should at least be assessed when the disease state is unsatisfactory, i.e., when the treatment target has not been reached and when a treatment change is being considered (28, 29).

2. Adherence should be evaluated during outpatient visits by at least one open question.

The literature on assessment of adherence was mainly issued from RA studies and questionnaires were found to be most frequently used in studies (**online supplementary Table 2**). The questionnaires are discussed in Recommendation 2. The group felt it was not possible to reach consensus on a single questionnaire to be used in everyday practice, and furthermore assessment of adherence using a questionnaire was not thought to be feasible in the clinic for every patients. Thus the consensus was to use an open question though this was not data-driven. A minimal assessment of non-adherence can be obtained through an open question such as 'how did it go with your treatment since the last visit?'. Examples of open questions proposed by the steering committee, can be seen in **Table 2**.

3. The assessment of adherence, particularly in the context of multidisciplinary care, can be carried out by more complete methods than an open question alone (self-reported questionnaires, dispensation data, etc.).

When the situation allows it (e.g. in a day hospitalization or when multidisciplinary care is provided), more complete questionnaires may be useful. The literature review allowed us to compare different questionnaires and in particular the Compliance Questionnaire on Rheumatology (CQR), Medication Adherence Report Scale (MARS), Morisky Medication Adherence Scale (MMAS) and Medication Adherence Self-report Inventory (MASRI), as seen in **online supplementary Table 2**. The discussion focused on the MMAS which has been widely used in the literature across several chronic diseases, but given that it is copyrighted, not validated for use in RA, and the items were found to be repetitive, no consensus was reached on which questionnaire should be put forward (30).

4. Adherence to hydroxychloroquine can be verified by a blood test and explaining the results to the patient can improve adherence.

In some cases, other ('more objective') assessments of adherence can be applied. Where available easily, patient-level dispensation data (available in some countries through the health insurance records) may allow to check it the patient has been given his/her drugs. Pharmacists may contribute to this assessment of adherence, as also explained below (31). For hydroxychloroquine, adherence can be verified by a blood test and explaining the results to the patient can improve adherence, as has been shown in lupus (32).

Factors associated to non-adherence (recommendation 5)

5. When assessing adherence, risk factors for nonadherence should be examined, in particular those related to the patient (young subject, fear of side effects, mood disorders,...), treatment (polymedication,...) and environment (caregiver-patient relationship, ...).

The literature review evidenced multiple factors associated to non-adherence, with differing results across studies and across diseases, making the interpretation of the findings difficult. Overall, around 240 different factors related to adherence were evidenced in the literature though they could be broadly regrouped as patient-related, treatment-related and patient-healthcare provider relationship related (33-36). It was difficult to reach a consensus on this part of the project. For this reason, it was proposed (see recommendation 1) to screen all patients for non-adherence. However, particular attention should be given to patients who have characteristics corresponding to the 'non-adherent profile' (**Table 3**): people who are younger, worried of side effects, do not see the necessity of the treatment, and are in psychological distress are more prone to non-adherence.

Interventions to improve adherence (recommendations 6-10)

All studies reporting the results of interventions to improve adherence in CIRDs were analysed in the systematic literature review (21). Interventions were classified as educational, behavioural, cognitive behavioural or multicomponent interventions (37). In all, 22 studies were analysed: most (18) were performed on RA patients. The results were mitigated since of 13 randomized controlled trials (1535 patients), only 5 were positive (774 patients) (10, 24, 25).

6. In order to optimize drug adherence, the patient should be an actor in his disease and his care within the framework of a shared decision (therapeutic alliance).

This is a generic recommendation which refers to the same concept as ocverarching principles D and E. The literature indicates a link between patient involvement and drug adherence though the data is observational rather than in the format of randomized trials. However, the experts felt this was a key point which should be emphasized.

7. In order to optimize drug adherence, any prescription for antirheumatic treatment must be accompanied by patient information and education.

In the literature, educational interventions had the highest level of evidence, corresponding to 8 of the 13 randomized controlled trials and 4 (50%) were positive. Briefly, educational interventions aim to enhance patient knowledge of the disease, the benefits and mechanisms

of action of the medication regimen, the consequences of non-adherence, and potential side effects of treatment. The expert consensus was that given that not all patients need formalised, organised therapeutic education and not all patients have access to therapeutic education, the recommendation should be strong for the encouragement to educate patients (ie the term 'must') but should be inclusive of all formats of information and education, rather than limited to formalised patient education (ie the inclusive term of 'patient information and education).

Recommendations 6 and 7 reflect that patient information and education, and patient/physician shared decision, are key to optimize adherence and should be systematic.

8. The detection of nonadherence to medication must lead to the implementation of a specific intervention (therapeutic education, motivational interview, cognitive behavioural methods, etc.) to improve adherence.

In the literature, on top of patient therapeutic education, other interventions such as behavioural interventions, cognitive behavioural interventions or motivational interviewing were also assessed (21). In some cases, the strategies shown to be effective were complex and difficult to implement in clinical practice.

The consensus was that other techniques such as formalized education sessions, motivational interviewing and cognitive behavioral therapy may be useful although it was not possible to hierarchize these interventions or to define profiles of patients who would potentially most benefit from one or the other.

9. The patient information and education process, individual or collective, must be carried out repeatedly by one or several health professionals (doctors, pharmacists, specialized nurses...) alone or in a team.

In the published studies of patient education, patients were informed or educated by different actors (physicians, pharmacists, nurses…).(21) Given this literature and given also feasibility issues (not all rheumatologists have access to formalized group education sessions for their patients), it was felt the recommendation should reflect that all education processes are acceptable. However, we wanted to emphasize that all health professionals should be involved in adherence. In particular, apart from rheumatologists, healthcare teams including nurses are important. Pharmacists will increasingly be involved as well. Advice by pharmacists on drug management has been shown to promote drug adherence, both in rheumatology and in other chronic disease settings (38, 39). The role of pharmacists may vary of course according to the healthcare system.

10. The patient information and education process can be supplemented by tools such as brochures and multimedia to improve therapeutic adherence.

In the published studies, supports and contents of the educational interventions were heterogeneous. (21) Thus the recommendations note the possibility to use different supporting materials in the education process.

Over the past years, the group felt e-health has taken on increasing importance. Patients seek information online and websites or apps can participate in promoting adherence (40). The group was not able to direct patients towards a specific online resource but it was reflected in the recommendations that e-health might be of value.

4. Discussion

Using an evidence-based approach followed by expert consensus, the current work has allowed the development of pragmatic recommendations regarding the assessment and management of non-adherence in CIRDs. This initiative should improve the assessment and optimization of adherence in daily practice.

Adherence is a key issue in chronic diseases but strangely has not perhaps received up to now, the focus it deserves. Non-adherence is frequent and costly at the patient level and at the society level. In its 2003 report on medication adherence, the World Health Organization quoted the statement by Haynes et al that “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). Indeed, among patients with chronic illness, approximately 50% do not take medications as prescribed (1-4) This poor adherence to medication leads to increased morbidity and death and increased costs (10, 41). However, today many more publications are found centred on the prescription of a drug (e.g., management recommendations) than on the intake of the drug (i.e., adherence). It is possible that this relative lack of interest is due to the difficult situation which it puts the physician in, or the fact that many healthcare professionals persist in seeing the non-adherent patient as a problematic patient (rather than, perhaps a problematic prescription) (42-44). In the present work, we felt that a focus on adherence, with the view to develop practical and helpful recommendations, was needed.

The present study has strengths and weaknesses. Well-validated procedures to develop recommendations were followed (19, 20, 45). However, categories of evidence and grades of recommendations were not determined, which is a limitation. Systematic literature reviews were performed and the consensus process allowed everyone's voice to be heard. However, it was not possible to include patients in the process for regulatory reasons. For this reason, the process was followed with a dissemination process among patient associations in France, which is ongoing. Although a strict process was followed, it was in some cases difficult to develop precise and applicable recommendations. This was the case in particular when trying to identify patient characteristics related to non-adherence (33-36). Indeed, it appears it is impossible to define a single non-adherent patient profile. It is possible that non-adherence is more related to a moment / a prescription than to a patient profile; or that all these elements play a part. For this reason, we feel non-adherence should be assessed systematically. It was also not possible to recommend a single questionnaire to assess adherence, since all available questionnaires were found to be unsatisfactory for the context of usual care (30). The inclusive nature of our group is a strength, however, the funding of the project by pharmaceutical industry could be perceived as a pontetial weakness, though adherence was addressed as a generic concept rather than drug-related, throughout the process.

Dissemination and implementation of recommendations is often an issue. In the present case, dissemination was planned in the project from the start through face to face meetings where the literature and recommendations are shared with rheumatologists nationwide. Even so, implementation during patient visits should be further assessed.

Some overlap can be noted between some of the overarching principles, and some of the recommendations which deal with shared decision-making. The group felt strongly that the implication of patients as actors and shared decision making were such key points when discussing adherence, that they had to be emphasized. Shared decision making is still an ongoing subject of research. Overall, we felt interventions to improve drug adherence were disappointing at the group level, as has been also found by other authors (11, 18, 21, 38, 46, 47). There are several potential explanations: perhaps interventions are not targeting the right patients; perhaps the interventions are not sufficiently tailored. Perhaps also non-adherence, due to its multifactorial nature, is difficult to act upon (42-44). Overall, non-pharmacological interventions pose specific methodological problems thus the mitigated results of trials should be interpreted with caution (48).

As treatment options become more numerous in the field of CIRDs, in a financially-limited context in many countries, adherence to medication should become a priority to improve the quality of care for patients with chronic diseases.

Table 1. Overarching principles and recommendations regarding drug adherence in CIRDs

	Overarching principles		Agreement
A	Drug adherence covers 2 complementary notions: compliance, i.e., treatment intake as prescribed, and persistence, i.e., maintenance of intake over time.		4.71 (0.48)
B	Non-adherence to disease-modifying anti rheumatic drugs is frequent. It can be detrimental, leading to lower drug efficacy and potential cost increases.		4.33 (0.87)
C	In non-adherence, factors known as "unintentional" (simply forgetting, ...) and "intentional" (linked to the patient's beliefs and fears, ...), are often intertwined.		3.95 (0.92)
D	Knowledge both of the disease and of the treatment, and patients' perceptions of the benefit/risk of the treatment are key elements in drug adherence.		4.62 (0.64)
E	In the context of shared decision-making/therapeutic alliance, caregiver-patient communication about treatment is a key factor in drug adherence.		4.56 (0.70)
	Recommendations	**Agreement**	**Applicability**
1	Adherence should be assessed at each patient visit. It must be systematic if the treatment target is not reached and before any therapeutic change.	4.45 (0.66)	3.73 (0.80)
2	Adherence should be evaluated during outpatient visits by at least one open question.	4.45 (1.04)	4.38 (0.68)
3	The assessment of adherence, particularly in the context of multidisciplinary care, can be carried out by more complete methods than an open question alone (self-reported questionnaires, dispensation data, etc.).	3.89 (0.94)	3.45 (0.89)
4	Adherence to hydroxychloroquine can be verified by a blood test and explaining the results to the patient can improve adherence.	4.08 (1,15)	2,81 (1.19)
5	When assessing adherence, risk factors for nonadherence should be examined, in particular those related to the patient (young subject, fear of side effects, mood disorders,...), treatment (polymedication,...) and environment (caregiver-	4.29 (0.91)	3.38 (0.80)

	patient relationship, ...).		
6	In order to optimize drug adherence, the patient should be an actor in his disease and his care within the framework of a shared decision (therapeutic alliance).	4.35 (0.78)	2.94 (0.90)
7	In order to optimize drug adherence, any prescription for antirheumatic treatment must be accompanied by patient information and education.	4.47 (0.73)	3.44 (0.82)
8	The detection of nonadherence to medication must lead to the implementation of a specific intervention (therapeutic education, motivational interview, cognitive behavioural methods, etc.) to improve adherence.	3.88 (1.10)	2.69 (0.82)
9	The patient information and education process, individual or collective, must be carried out repeatedly by one or several health professionals (doctors, pharmacists, specialized nurses...) alone or in a team.	4.31 (0.70)	2.96 (0.74)
10	The patient information and education process can be supplemented by tools such as brochures and multimedia to improve therapeutic adherence.	4.35 (0.61)	3.45 (0.91)

Agreement and applicability in daily practice were assessed on 1-5 Likert scales where 1= not at all in agreement and 5= fully in agreement by 104 rheumatologists. Results are presented as mean (standard deviation).

Table 2. Examples of open questions to assess adherence

How did it go when taking your treatment since the last visit?
What difficulties did you meet when taking your treatment since the last visit??
How is it going with your medication?
How do you feel regarding your treatment?
How do you manage not to forget to take your treatment?
I have the impression that you have issues with this treatment
I see that the treatment is less effective, what do you think? Maybe there is a problem with the way you take your medication?
What do you do when you forget to take your treatment?

Table 3. Profile of the 'non-adherent' patient according to the literature

Factor	Characteristic
Age	Young age
Beliefs and knowledge	Concerns about side effects Low perceived need of treatment Low knowledge regarding disease
Treatments	Polymedication
Comorbidities	Presenting with comorbidities (in RA and SpA) or not (in gout and lupus)
Psychological status	Mood disorders
Patient physician relationship	Poor doctor-patient relationship

References

1. World Health Organization. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; accessed on March 23, 2018. http://www.who.int/chp/knowledge/publications/adherence_introduction.pdf?ua=1.

2. Treharne GJ, Lyons AC, Hale ED, Douglas KM, Kitas GD. 'Compliance' is futile but is 'concordance' between rheumatology patients and health professionals attainable? Rheumatology (Oxford). 2006;45:1-5.

3 van den Bemt BJF, Zwikker HE, van den Ende CHM. Medication adherence in patients with rheumatoid arthritis: a critical appraisal of the existing literature. Expert Rev Clin Immunol. 2012;8:33751.

4. Curtis JR, Bykerk VP, Aassi M, Schiff M. Adherence and Persistence with Methotrexate in Rheumatoid Arthritis: A Systematic Review. J Rheumatol. 2016;43:1997-2009.

5. Scheiman-Elazary A, Duan L, Shourt C, Agrawal H, Ellashof D, Cameron-Hay M, et al. The rate of adherence to antiarthritis medications and associated factors among patients with Rheumatoid Arthritis: A Systematic Literature Review and Metaanalysis. J Rheumatol. 2016;43:51223.

6. Pasma A, den Boer E, van ’t Spijker A, Timman R, van den Bemt B, Busschbach JJV, et al. Nonadherence to disease modifying antirheumatic drugs in the first year after diagnosis: comparing three adherence measures in early arthritis patients. Rheumatology 2016;55:18129.

6. Gadallah MA, Boulos DNK, Gebrel A, Dewedar S, Morisky DE. Assessment of rheumatoid arthritis patients’ adherence to treatment. Am J Med Sci.2015;349:1516.

8. Contreras-Yáñez I, Ponce De León S, Cabiedes J, Rull-Gabayet M, Pascual-Ramos V. Inadequate therapy behavior is associated to disease flares in patients with rheumatoid arthritis who have achieved remission with disease-modifying antirheumatic drugs. Am J Med Sci.2010;340:28290.

9. Bluett J, Morgan C, Thurston L, Plant D, Hyrich KL, Morgan AW, et al. Impact of inadequate adherence on response to subcutaneously administered anti-tumour necrosis factor drugs: results from the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate cohort. Rheumatology 2015;54:4949.

10. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. Med Care 2005;43:52130.

11. Zaugg V, Korb-Savoldelli V, Durieux P, Sabatier B. Providing physicians with feedback on medication adherence for people with chronic diseases taking long-term medication. Cochrane Database Syst Rev. 2018 Jan 10;1:CD012042. doi: 10.1002/14651858.CD012042.pub2.

12. Lehmann A, Aslani P, Ahmed R, Celio J, Gauchet A, Bedouch P, et al. Assessing medication adherence: options to consider. Int J Clin Pharm. 2014;36:5569.

13. Hansen RA, Kim MM, Song L, Tu W, Wu J, Murray MD. Comparison of methods to assess medication adherence and classify nonadherence. Ann Pharmacother. 2009;43:413-22.

14. Pasma A, van't Spijker A, Hazes JMW, Busschbach JJV, Luime JJ. Factors associated with adherence to pharmaceutical treatment for rheumatoid arthritis patients: a systematic review. Semin Arthritis Rheum 2013;43:1828.

15. Voshaar M, Vriezekolk J, van Dulmen S, van den Bemt B, van de Laar M. Barriers and facilitators to disease-modifying antirheumatic drug use in patients with inflammatory rheumatic diseases: a qualitative theory-based study. BMC Musculoskelet Disord 2016;17:442.

16. Wong PKK. Medication adherence in patients with rheumatoid arthritis: why do patients not take what we prescribe? Rheumatol Int. 2016;36:153542.

17. Delestras S, Roustit M, Bedouch P, Minoves M, Dobremez V, Mazet R, et al. Comparison between two generic questionnaires to assess satisfaction with medication in chronic diseases. PloS One. 2013;8:e56247.

18. Salt E, Frazier SK. Adherence to disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a narrative review of the literature. Orthop Nurs. 2010;29:260-75.

19. Gossec L, Baillet A, Dadoun S, Daien C, Berenbaum F, Dernis E, et al. Collection and management of selected comorbidities and their risk factors in chronic inflammatory rheumatic diseases in daily practice in France. Joint Bone Spine. 2016;83(5):501-9.

20. Gossec L, Bijlsma JW, Bombardier C, Canhão H, Devlin J, Edwards CJ et al. Dissemination and evaluation of the 3E initiative recommendations for use of methotrexate in

rheumatic disorders: results of a study among 2233 rheumatologists. Ann Rheum Dis. 2011;70:388-9.

21. Lavielle M, Puyraimond-Zemmour D ; Romand X, Gossec L, Senbel E, Pouplin S et al. Methods to improve medication adherence in patients with chronic inflammatory rheumatic diseases: a systematic literature review. *in press RMD Open*

22. Brown MT, Bussell JK. Medication Adherence: WHO Cares? Mayo Clin Proc. 2011; 86: 304–14.

23. Ho SC, Chong HY, Chaiyakunapruk N, Tangiisuran B, Jacob SA. Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: A systematic review.J Affect Disord. 2016;193:1-10.

24. De Vera MA, Mailman J, Galo JS. Economics of non-adherence to biologic therapies in rheumatoid arthritis. Curr Rheumatol Rep. 2014;16(11):460.

25. Pasma A, Schenk C, Timman R, van ’t Spijker A, Appels C, van der Laan WH, et al. Does non-adherence to DMARDs influence hospital-related healthcare costs for early arthritis in the first year of treatment? PloS One. 2017;12(2):e0171070.

26. Horne R, Chapman SC, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. PLoS One. 2013;8(12):e80633.

27. Cobos B, Haskard-Zolnierek K, Howard K. White coat hypertension: improving the patient-health care practitioner relationship.Psychol Res Behav Manag. 2015 2;8:133-41.

28 Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis. 2016;75(1):3-15.

29 Smolen JS, Schöls M, Braun J, Dougados M, FitzGerald O, Gladman DD, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis. 2018;77:3-17.

30 Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens (Greenwich). 2008;10(5):348-5431 Readdean KC, Heuer AJ, Scott Parrott J. Effect of pharmacist intervention on improving antidepressant medication adherence and depression symptomology: A

systematic review and meta-analysis. Res Social Adm Pharm. 2017. pii: S1551-7411(16)30372-2.

32 Costedoat-Chalumeau N, Galicier L, Aumaître O, Francès C, Le Guern V, Lioté F, et al. Hydroxychloroquine in systemic lupus erythematosus: results of a French multicentre controlled trial (PLUS Study). Ann Rheum Dis. 2013;72:1786-92.

33. Michetti P, Weinman J, Mrowietz U, Smolen J, Peyrin-Biroulet L, Louis E, et al. Impact of Treatment-Related Beliefs on Medication Adherence in Immune-Mediated Inflammatory Diseases: Results of the Global ALIGN Study. Adv Ther. janv 2017;34:91108.

34. Betegnie AL, Gauchet A, Lehmann A, Grange L, Roustit M, Baudrant M, et al. Why Do Patients with Chronic Inflammatory Rheumatic Diseases Discontinue Their Biologics? An Assessment of Patients' Adherence Using a Self-report Questionnaire. J Rheumatol. 2016;43:72430.

35. Zwikker HE, van Dulmen S, den Broeder AA, van den Bemt BJ, van den Ende CH. Perceived need to take medication is associated with medication non-adherence in patients with rheumatoid arthritis. Patient Prefer Adherence. 2014;8:163545.

36. Curtis JR, Xie F, Mackey D, Gerber N, Bharat A, Beukelman T, et al. Patient's experience with subcutaneous and oral methotrexate for the treatment of rheumatoid arthritis. BMC Musculoskelet Disord. 2016;17:405.

37. Greenley RN, Kunz JH, Walter J, et al. Practical Strategies for Enhancing Adherence to Treatment Regimen in Inflammatory Bowel Disease: Inflamm Bowel Dis 2013;19:1534–45.

38. Ryan R, Santesso N, Lowe D, Hill S, Grimshaw J, Prictor M, et al. Interventions to improve safe and effective medicines use by consumers: an overview of systematic reviews. Cochrane Database Syst Rev. 29 avr 2014;(4):CD007768.

39. Kulchaitanaroaj P, Brooks JM, Chaiyakunapruk N, Goedken AM, Chrischilles EA, Carter BL. Cost-utility analysis of physician-pharmacist collaborative intervention for treating hypertension compared with usual care. J Hypertens.2017;35:17887.

40. Bosworth HD, Zullig LL, Mendys P, Ho M, Trygstad T, Granger C et al. Health Information Technology: Meaningful Use and Next Steps to Improving Electronic Facilitation of Medication Adherence. JMIR Med Inform. 2016; 4(1): e9

41. Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. BMJ Open. 2018; 8(1): e016982.

42. Fung V, Graetz I, Reed M, Jaffe MG. Patient-reported adherence to statin therapy, barriers to adherence, and perceptions of cardiovascular risk. PLoS One. 2018;13(2):e0191817.

43. Kvarnström K, Airaksinen M, Liira H. Barriers and facilitators to medication adherence: a qualitative study with general practitioners. BMJ Open. 2018;8(1):e015332

44. Suh YS, Cheon YH, Kim HO, Kim RB, Park KS, Kim SH, et al. Medication nonadherence in Korean patients with rheumatoid arthritis: the importance of belief about medication and illness perception. Korean J Intern Med. 2017; 27.

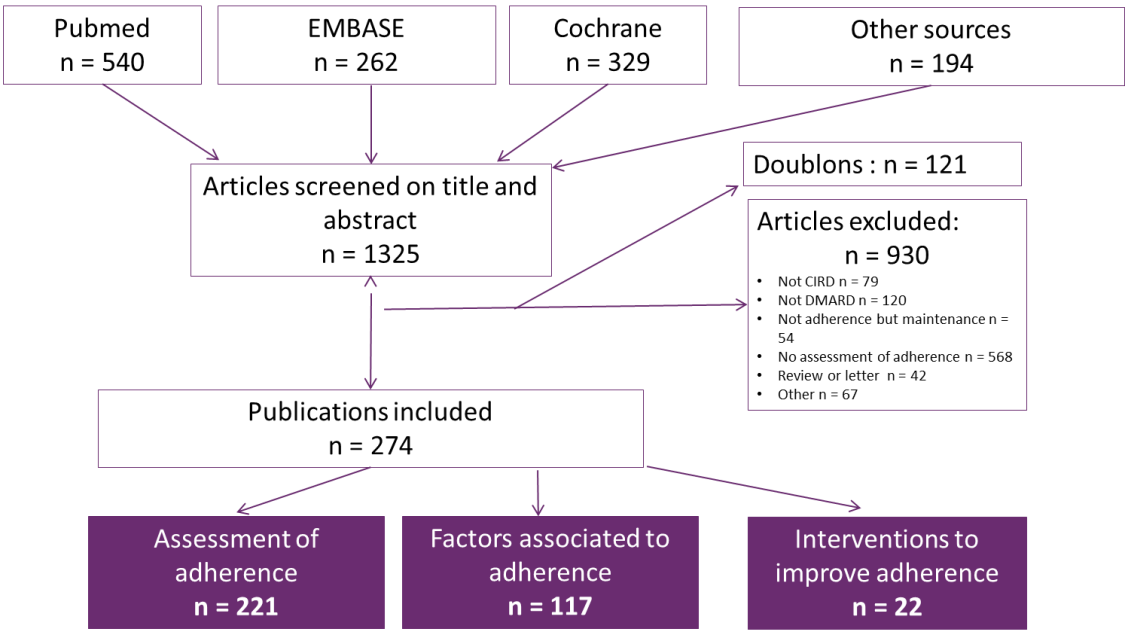
45. van der Heijde D, Aletaha D, Carmona L, Edwards CJ, Kvien TK, Kouloumas M, et al. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. Ann Rheum Dis. 2015;74:8-13.

46. Galo JS, Mehat P, Rai SK, Avina-Zubieta A, De Vera MA. What are the effects of medication adherence interventions in rheumatic diseases: a systematic review. Ann Rheum Dis. 2016;75:667-73.

47. Depont F, Berenbaum F, Filippi J, Le Maitre M, Nataf H, Paul C, et al. Interventions to Improve Adherence in Patients with Immune-Mediated Inflammatory Disorders: A Systematic Review. PloS One. 2015;10(12):e0145076.

48. Page MJ, Boutron I, Hansen C, Altman DG, Hróbjartsson A. Assessing risk of bias in studies that evaluate health care interventions: recommendations in the misinformation age. J Clin Epidemiol. 2018;97:133-136.

Figure 1. Systematic literature review: flowchart



Supplementary data Table 1. Details of the methods of the systematic literature review

Methodology - step	**Information**
Choice of diseases	RA, SpA, PsA, connective tissue diseases including systemic lupus, crystal related diseases including gout and chondrocalcinosis, vasculitis including ANCA-associated vasculitis, giant cell arteritis and polymyalgia rheumatica, and Still's disease.
Choice of treatments	Pharmacological medications considered were: conventional synthetic DMARDs, biological DMARDs, immunosuppressive drugs (cyclophosphamide…), non-steroidal anti-inflammatory drugs in SpA, glucocorticoids, colchicine and urate-lowering therapy
Research questions	WSubject 1 WWhat tools are used to easily assess adherence by health care professionals in CIRDs? What are their performances? Check for questionnaires (specific? generic? from daily practice?), scores, dispensation data, pharmaceutical files. What are their validity? sensitivity? ease of use? Performance of generic vs. specific questionnaires? SSubject 2 What are the predictive factors of adherence to disease modifying therapy in chronic inflammatory rheumatism and other major chronic disease? 1. What are avoidable or non-avoidable factors? 2. What are factors related to the treatment? 3. What are factors related to the physician-patient relationship? 3.1. Impact of characteristic of the physician 4. What are factors related to socioeconomic condition? 5. What are factors related to health system? 5.1. Impact of medical demography 5.2. Impact of reimbursement of care 6. What are factors related to characteristic of the patient? 7. What are factors related to family support? Subject 3

	evidence of interventions proposed in the literature to enhance medication adherence in CIRDs
Databases searched	• PUBMED, Embase , Cochrane central register of clinical trials • Clinicaltrials.gov • Congresses of 2016-2017: SFR, EULAR, ACR - World Health Organisation websiteThe start and lock dates for the literature review were Dec 15, 2016 to Feb 10, 2017
Keywords used for PubMed	("Arthritis, Rheumatoid"[Mesh] OR "Spondylarthropathies"[Mesh] OR "Polymyositis"[Mesh] OR "Lupus Erythematosus, Systemic"[Mesh] OR "Mixed Connective Tissue Disease"[Mesh] OR "Scleroderma, Systemic"[Mesh] OR "Gout"[Mesh] OR "Chondrocalcinosis"[Mesh] OR "Polymyalgia Rheumatica"[Mesh] OR "Giant Cell Arteritis"[Mesh] OR "Still's Disease, Adult-Onset"[Mesh] OR "Systemic Vasculitis"[Mesh] OR "Behcet Syndrome"[Mesh]) AND ("Patient Compliance"[Mesh] OR "Medication Adherence« [Mesh]) AND (English[lang] OR French[lang])
Data extraction	Data were collected by one person using a specific CRF developed for this study. 3 fellows performed the literature review each one dealing with one of the subjects described in the research question: 1Methods used to assess adherence and psychometric properties of each method; 2: Factors shown to be associated to low adherence; 3: Efficacy of interventions: For all studies, we collected data regarding the design of the studies: randomized or non randomized, controlled or not, length of follow up, number of patients in each group (intervention and control). Characteristics of the population were also collected: disease studied, disease duration, activity of the disease, age at baseline, gender, treatment studied. The type of measurement used for adherence and adherence results were also collected. We then collected for subject 3, information on the intervention under evaluation: type of intervention aiming to improve medication adherence (educational…), main components and supports of this intervention, actors of the intervention, patients targeted by the intervention (systematic for all patients or targeted on patients considered to be non-adherent or at high risk of non-adherence). Tools used to measure adherence were noticed and finally, results on adherence were collected in each group of patient if available. •

Risk of bias assessment	Given the observational nature of almost all the studies, is was not possible to assess risk of bias.
Data analysis	Analysis was descriptive

Supplementary data Table 2. Use of questionnaires to assess adherence in CIRDs (literature review)

Questionnaire/validity				
N studies on the questionnaire	44	13	7	58
Reliability	++	++	+++	++
Feasibility	+/+++	+++	+++	+++
Validity	Yes	Not assessed in rheumatology	Yes	Not fully assessed in rhumatology
Copyrighted?	No	No	Yes	Yes

Compliance Questionnaire on Rheumatology (CQR); Medication Adherence Report Scale (MARS); Medication Adherence Self-report Inventory (MASRI); Morisky Medication Adherence Scale (MMAS)

The + represent a semi quantitative summary of the available literature with more + meaning higher / better results (from O to +++)