Adherence to Synthetic Disease-modifying Antirheumatic Drugs in Rheumatoid Arthritis: Results of the OBSERVAR Study

Adherencia al tratamiento con fármacos moduladores de la enfermedad sintéticos en la artritis reumatoide. Resultados del estudio OBSERVAR

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Abstract

Background: Treatment compliance with disease-modifying antirheumatic drugs (DMARD) is essential to achieve the therapeutic goals in rheumatoid arthritis (RA). However, despite the need for good compliance, there is evidence that patients with RA frequently fail to use DMARD for the control of RA. Thus, the main objective of the OBSERVAR study is to evaluate the reasons for the lack of therapeutic adherence to synthetic DMARD in these patients.

Patients and methods: A Delphi process involving 18 randomly selected Spanish rheumatologists determined the level of agreement with 66 causes of noncompliance selected from the literature in relation to synthetic DMARD in RA.

Results: The reasons for noncompliance were consistent in 75.7%, although 3 reasons (4.5%) were highly consistent: 1) not knowing what to do in the case of an adverse event with DMARD; 2) not having undergone adherence screening by health personnel for early detection of "noncompliant patients"; and 3) not having undergone interventions or strategies that improve adherence.

Conclusion: In order to improve adherence to RA treatment with synthetic DMARD, the patient should be adequately informed of each new treatment introduced, the patient's compliance profile should be incorporated into the clinical routine and the patient's motivation for therapeutic compliance be reinforced through the methods available to us.

Resumen

Introducción. La cumplimentación del tratamiento modificador de la enfermedad es esencial para alcanzar los objetivos terapéuticos en la artritis reumatoide (AR). Sin embargo, y a pesar de la necesidad de una buena adherencia, existe evidencia de que muchos pacientes con AR no cumplen adecuadamente con la prescripción del tratamiento indicado con fármacos moduladores de la enfermedad de acción lenta (FAME) sintéticos o convencionales. Conscientes de la importancia de este hecho, el estudio sobre observancia terapéutica en AR (estudio OBSERVAR) tiene como objetivo principal valorar los motivos de la falta de adherencia terapéutica a los FAME sintéticos en estos pacientes.

Pacientes y métodos. Mediante un proceso Delphi entre 18 reumatólogos españoles seleccionados aleatoriamente se determinó el grado de acuerdo con 66 causas de incumplimiento seleccionadas de la bibliografía, en relación con los FAME sintéticos en la AR.

Resultados. Los motivos de incumplimiento fueron consistentes en el 75,7%, si bien 3 razones (4,5%) destacaron como muy consistentes: 1) desconocer qué hacer cuando se sufre un acontecimiento adverso con el FAME; 2) no llevar a cabo métodos de cribado de la adherencia por el personal sanitario para detectar a los «pacientes incumplidores» de forma temprana y 3) no aplicar intervenciones o estrategias que mejoren la adherencia terapéutica.

Conclusión. Para mejorar la adherencia al tratamiento de la AR con FAME sintéticos se debe informar al paciente de cada tratamiento nuevo introducido, incorporar el perfil de cumplimiento del paciente en la rutina clínica, y reforzar la motivación del paciente al cumplimiento terapéutico mediante los métodos a nuestro alcance.

Keywords

Rheumatoid arthritis; Adherence; Therapeutic compliance; DMARD; Methotrexate

Palabras clave

Artritis reumatoide; Adherencia; Cumplimiento terapéutico; Fármacos moduladores de enfermedad; Metotrexato

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease that requires early diagnosis and treatment to improve symptoms, reduce structural damage and control functional and psychological involvement. The different, both diagnostic and therapeutic, strategies that are currently used, such as *tight control* or *treat to target*, aim to achieve these objectives. Moreover, it has been demonstrated that an early approach also reduces costs, thus improving therapeutic efficiency.[1] However, although most studies take good patient compliance for granted, other studies show that adherence to RA treatment is inadequate and its effectiveness can be diminished.[2] Therefore it is essential to detect the causes impeding therapeutic adherence, and to implement methods to improve it.

Correct therapeutic compliance can be made difficult for many reasons.[3,4] The elements of therapy are highly complex and can be affected by different factors, associated with the patients and their disease, the health professionals and the area where they work, and with the drug used and its possible side effects.[5,6] A Spanish study suggests that young men have the poorest adherence.[7] It is calculated that between 30% and 80% of patients with RA and other chronic illnesses fail to follow their treatment appropriately.[8,9]

It has been demonstrated that follow-up of patients with RA must be rigorous with frequent visits structured according to established therapeutic protocols and programmes.[10] Current routine assessments are increasingly more thorough and cover: disease activity and its relationship with quality of life, functional capacity, comorbidities, disease progression, efficacy of treatment and its possible adverse events (AE).[1] However, in the care of the chronic patient, policies to assess levels of treatment compliance and reasons for it are not often implemented, although there are several strategies for doing so.[11,12]

The synthetic or conventional disease modifying antirheumatic drugs (DMARDs) are the first step in treating RA, and are often accompanied by AE of varying intensity.[5,13] In fact, more than half of RA patients refer to the AE as the main disadvantage of the synthetic DMARDs, hence the consequent lack of adherence.[14] However, there are often other reasons and concerns that must also be considered.[13]

For these reasons, the Treatment Adherence Observatory, in collaboration with the Spanish Rheumatology Society, launched the OBSERVAR study, with the main aim of discovering the reasons why RA patients in Spain are failing to adhere to treatment with the synthetic DMARDs.

Patients and Methods

The study started in January 2014 with a systematic literature review referring to treatment adherence using *PubMed* and the *Google Scholar* search engine based on scientific publications and other trustworthy sites, and we found 66 claims with a low level of evidence (III or IV according to NHMRC, National Health and Medical Research Council, criteria),[15] divided into 3 subject blocks or categories: 24 patient-related reasons, 23 health professional-related reasons, and 19 treatment-related reasons for failing to adhere to treatment.[7,16-18]

Nineteen rheumatologists were invited to take part, selected by a scientific committee, seeking to represent the greatest number possible of autonomous regions, and cover both large and small hospitals.

After contacting all the participants by telephone, the list of selected claims were circulated twice to the participants' personal email addresses. The first questionnaire was sent in July 2014 to the 19 rheumatologists selected, and again one month later to the 18 participants who responded to the first mailing (see attached appendix).

The Delphi process that we applied used validated scientific methodology to enable agreements to be reached, and each participant indicated their level of agreement with the claims using a Likert-type psychometric scale, scoring between 1 (minimum) and 9 (maximum acceptance) following the RAND/UCLA system (RAND corporation and University of California in Los Angeles).[19]

We then performed a descriptive analysis of the 66 reasons selected using the statistical tools of Microsoft Excel 2012 to determine: mean and standard deviation (SD); median and interquartile range (IQR); mode, minimum value, maximum value, and coefficient of variation (COV).

Two different criteria were established to assess the final level of agreement:

1. Criterion based on the group median: although the mean is routinely the most frequently and arithmetically convenient parameter used, we considered the median a

better measure of central tendency, since it is less sensitive to the extreme values in asymmetric distributions.

Based on the median, 1–2 and 8–9 were considered disagreement and very consistent agreement respectively; 3 and 7 disagreement and consistent agreement; and the intermediate values (4.5 and 6), completely inconsistent.

2. Criterion based on simultaneous compliance: given that SD, IQR and COV represent the dispersion with respect to the central value, we considered unequivocal consistency of agreement when the mean and the median were ≥7, the SD and the IQR were ≤1.00, and the COV was ≤.25.

The results obtained were crossed with the aspects of segmentation of the participants, the autonomous region where they worked, and the number of RA clinical histories, applying the Students *t*-test and the χ^2 test.

The study was approved by the clinical research committees of the referral hospital "A Coruña University Hospital Complex", and then by the rest of the participating hospitals.

Results

The project was carried out from March to September 2014. Eighteen of the 19 participating rheumatologists (94.74%) completed the 2 circulations of the Delphi process. This included 13 autonomous regions (Andalusia, Catalonia, Madrid, Valencian Community, Galicia, Castilla-León, Basque Country, Castilla-La Mancha, The Canary Islands, The Balearic Islands, Extremadura, Asturias and Cantabria), and Melilla as an autonomous city.

Table 1 shows the patient-related reasons for failing to adhere to the synthetic DMARDs. We must highlight that among the 24 related variables, the level of agreement based on the median was very consistent in 7 (29.10%), consistent in 11 (45.83%), and inconsistent in 6 (25%). There was no disagreement in this section. Based on the simultaneous criterion, there was only consistent agreement in one statement (4.17%).

Table 2 specifies that, among the 23 health professional-related reasons, the level of agreement according to the median was very consistent in 3 (13.04%), consistent in 18 (78.26%) and inconsistent in 2 (8.70%). There were no disagreements in this section either. When the simultaneous criterion was analysed, consistency was found in only 2 agreements (8.70%).

After assessing the 19 reasons for a lack of adherence to the synthetic DMARDs relating to the "treatment itself", the level of agreement was consistent in 11 (57.89%), there was only one disagreement (5.26%) and 7 inconsistencies (37.84%) considering the criterion of the group median. There was no agreement based on the simultaneous criterion (Table 3).

Discussion

In this study, designed to understand the main causes for the lack of adherence to synthetic or conventional DMARDs in the treatment of RA, only 3 reasons stood out as very consistent: (1) not knowing what to do in the event of an AE; (2) not having undergone adherence screening by health personnel; and (3) not having applied the strategies that improve therapeutic adherence.

The therapeutic adherence concept was used as a synonym for therapeutic compliance, defined as the extent that a patient's behaviour, in relation to taking their medication, following a diet or changing lifestyle habits, matches the recommendations agreed with healthcare staff, or the extent that a patient acts in accordance with the dose, dosing regimen and prescribed times, which must be distinguished from persistence of treatment, which is the number of days of continuous usage of the medication over a specific time.[8,9] Another similar term, although not identical, is therapeutic concordance, a concept that is based on a negotiation between clinicians and patients, as equals, and opens the way for the latter to differ from the former in evaluating the benefit-risk balance of the drugs.[19] All the variables analysed in this study only refer to therapeutic adherence or compliance. A strict approach to RA, both from a diagnostic and a therapeutic perspective, clearly improves the progression of the disease and its prognosis.[9,13] However, very often, the therapeutic indications are not clearly followed, and the results and objectives set are not as desired, resulting in diminished effectiveness.[20] Control of pharmaceutical expenditure is optimised if medical prescriptions are strictly followed, and consequently, inadequate adherence reduces therapeutic efficiency.[14,21] The main reasons for poor adherence and reduced therapeutic persistence have been widely studied.[8,21,22]

This study analyses the agreements reached by a panel of rheumatologists chosen to represent the Spanish rheumatological community, randomly distributed throughout the autonomous regions. The hospitals selected were tertiary and regional; we considered

they would provide a significant sample of the opinions of Spanish rheumatologists, and that the consensus reached faithfully illustrates the reality in our setting regarding therapeutic adherence in RA. The Delphi method is widely generalised and validated and its results should faithfully reflect the reality surrounding us.[18,19] However it is possible, since the results come from subjective opinions, that there could be some bias, which is obviously reduced by the methodology itself and the consensus reached over several stages. We only obtained national results, which therefore cannot be extrapolated to other countries or scenarios.

Poor therapeutic adherence is not specific to RA, it also occurs with other rheumatic diseases such as systemic lupus erythematosus, psoriatic arthritis and ankylosing spondylitis, as well as diseases of other specialities such as infectious, neoplastic, cardiovascular, metabolic, and possibly most chronic diseases.[10,21,23,24]

Overall, we found agreement for 75.8% of the claims surveyed. There was only one disagreement regarding the treatment-related reasons for lack of adherence: "imprecise or not appropriately reassessed diagnosis during follow-up". On the other hand, categorical agreement was reached for three of the claims: "not knowing what to do in the event of an adverse event with the DMARD", "potential non-compliant patients not having undergone adherence screening by health personnel", and "not having applied strategies to improve therapeutic adherence". The only disagreement with regard to the literature concerned an imprecise diagnosis as a cause, since something that could occur in other chronic illnesses, seems less likely in RA, where there are specific programmes for early diagnosis and a differential diagnosis with other diseases that simulate the clinical characteristics of RA, and follow-up protocols that repeatedly confirm diagnosis and improve the comprehensive approach to the disease.[23,25] The 3 reasons for which there was categorical agreement were: improving the doctor-patient relationship, indicating different aspects of a failure to convey information (not knowing what to do in the event of an AE), a failure to detect the problem (lacking adherence screening methods) and lack of action (failing to use interventions to improve therapeutic adherence).

The patient-related reasons for which there was the greatest consistency were grouped under two sections: "reasons relating to an insufficient level of knowledge of the disease, treatment and the importance of adhering to it" and "a lack of knowledge of the repercussions of their disease and therapeutic non-compliance". Believing that

improvement with the use of a biological DMARD rendered a conventional synthetic DMARD unnecessary and stopping treatment after unexpected AE because of not knowing what to do, would also be included in this section. On the other hand, the other aspect was internal in nature: “lack of commitment and responsibility in complying with the prescribed treatment”; “not knowing that they are really ill”; “overestimating one's own adherence profile”; “not understanding and not asking”, “not sharing the same aims as the doctor”, “not taking part in decision-making”.

Each treatment is really personalised, re-evaluated and adjusted if necessary at each follow-up; but just as important as doing so correctly is that the patient should feel that they are receiving really “personalised treatment”, controlled, with specific objectives, that they are appropriately instructed about their illness, the importance of adherence and consequences, thus motivating and reinforcing their efforts.[1] The patient-related variables indicate that medical and nursing information must improve, since often the professionals agree that patients have insufficient knowledge of the need to adhere to their treatment, or lack the necessary involvement to understand the danger of discontinuing it, or the benefits of continuous treatment with synthetic DMARDs for patients receiving a biological DMARD to improve their effectiveness and reduce immunogenicity.

In this regard, there might be differences between the different synthetic DMARDs and also between the biological DMARDs, concomitant medication with MTX having been studied more than with other conventional DMARDs.[3,26] There are also differences with other entities such as psoriatic arthritis or ankylosing spondylitis where monotherapy with biological DMARDs is more frequently accepted and useful.[3] Most of the variables analysed can be improved by providing patients with RA health education plans, and implementing rheumatology nursing clinics.[12]

This study only analysed the synthetic DMARDS, MTX being the most widely used. Although there is literature on both the synthetic DMARDS and the biological DMARDs, there are no major differences in terms of therapeutic adherence or reasons for discontinuation. Low social class was highlighted among the data associated with poorer adherence; this is associated with poorer understanding of the disease and its treatments, and also higher disease activity.

In general, acknowledged among the health personnel-related reasons were “a low awareness on this point among the professionals themselves”, resulting in insufficient follow-up of this aspect, lack of recording it, leaving it out in guidelines and recommendations, etc., and “not using methods to detect non-compliant patients”, “not applying interventions to improve therapeutic adherence”, “not undertaking awareness-raising programmes among healthcare personnel” and even “not relating poor adherence with potential inappropriate response” were highlighted. Again, all the programmes aimed at raising the awareness of health staff could improve the perception of this issue and, once again, providing patients with nursing clinics and information clearly improves awareness of the importance of maintaining the drug to achieve relevant clinical results. However, it is possible that some of the variables analysed relate more to the health structure itself than to the activity of healthcare staff.

With regard to “the treatment itself” as the source of non-compliance, rather general aspects were admitted, that might refer to any chronic disease: “polymedication”, “problems synchronising medication intake”, “lack of reminder techniques on containers”, etc. The data is contradictory on whether adherence is better if the drug is administered orally or parenterally, these results occur again with the biological DMARDS where, contrary to what one would imagine, therapeutic adherence with subcutaneous administration is also not as desired.[27,28] In this regard, adherence could be much improved by administering the treatments intravenously, because control is stricter as this must be done in hospital. Although one study indicates that the therapeutic adherence in this subgroup of patients was not as expected either, depending on the combination or otherwise with a synthetic DMARD.[29]

We appreciate that the AE of the conventional DMARDs are considered a lesser cause of lack of adherence, some aspects are even inconsistent, with values that would bring them close to disagreement. This leads us to believe that, since differences were certainly shown between the doctor and their patients in terms of the appreciation of AE and their importance, patients might not be disclosing all their AE. However, different studies show that the AE of both the synthetic and the biological DMARDs are a frequent cause of reduced therapeutic adherence.[4,21,29] In this regard, this subject should be approached from the perspective of an adverse effect as such, or a fear that one will occur, and on the other hand actions to encourage awareness[4] among doctors as well as patients should be

promoted, which would result in early detection of AE and agreed action after their onset, since they should not always involve discontinuing the drug.

Our study has some limitations. Firstly, although the number of rheumatologists consulted might appear small, it was considered sufficient after evaluation by an epidemiological/statistical advisory team. Similarly, the level of health care was heterogeneous with specialists that visit a very different number of patients in hospitals of different care levels. However, this enabled us to cover a large and varied group of rheumatologists with different clinical practice, which seems more a pro than a con. We did not include graduates of nursing or other healthcare professions in the study either, which might also reduce the importance of some of the results obtained. Furthermore, given the great individual variability of the reasons for therapeutic noncompliance, it would have been interesting to define more restricted, specific populations such as: patients with synthetic DMARDs combined with subcutaneous or intravenous biological DMARDS, the treatment time with the different drugs, etc. However, and despite all the aforementioned limitations, we believe that this study is valid and that the results obtained are consistent.

Based on this experience, we consider it essential to inform patients sufficiently about each new treatment introduced and its possible AE, to include an assessment of each patient's therapeutic compliance profile in the clinical routine, and to reinforce patients' motivation for therapeutic compliance throughout their follow-up.

Ethical Responsibilities

Protection of people and animals. The authors declare that no experiments were performed on humans or animals for this investigation.

Data confidentiality. The authors declare that they have followed the protocols of their work centre on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

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Conflict of Interests

The authors have no conflict of interest to declare.

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Appendix A. OBSERVARa Working Group. List of Authors and Collaborating Centres.

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Table 1. Patient-related Reasons for Lack of Adherence.

	Mean	SD	Median	IQR	Mode	COV	Level of consistency
Lack of awareness that they really are ill	5	2.58	7	5	7	.52	Consistent
Lack of motivation to change habits	5	2.56	6	5	7	.49	Inconsistent
Mistrust of healthcare personnel, not expressing concerns, etc. (fear of appearing foolish, etc.)	5	2.44	5	5	7	.52	Inconsistent
Not being aware of the severity of their disease	7	2.27	8	1	8	.34	Very consistent
Not being aware of the efficacy, action, etc. of the treatment	7	1.75	8	1	8	.25	Very consistent
Not knowing factors that determine noncompliance and not attaching sufficient importance to adherence or its impact on the progression of their disease	7	2.20	8	1	8	.33	Very consistent
Overestimating own adherence profile as a patient and/or self-justifying	6	2.30	7	2	8	.37	Consistent
Not understanding the information received	7	2.12	7	2	8	.32	Consistent
Barriers to compliance (sight problems, Lack of dexterity, cognitive impairment, difficulty swallowing, etc.)	4	2.50	4	5	3	.60	Inconsistent
Not feeling a part of decision-making	6	2.18	7	4	7	.38	Consistent
Not feeling that their treatment is personalised and adapted to their circumstances and disease	6	2.45	7	5	8	.44	Consistent
Patient and doctor not sharing the same objectives with regard to treatment	6	2.26	7	3	8	.38	Consistent
Not feeling committed as responsible for taking their medication	7	2.29	8	1	8	.34	Very consistent

Lacking full and up-to-date information on their particular situation	6	2.47	6	5	3	.43	Inconsistent
Not feeling that they are doing things properly or receiving positive feedback	6	2.11	7	3	8	.34	Consistent
Lack of support of those around them and/or family, carer, social workers, etc.	5	2.55	7	5	8	.47	Consistent
Forgetting or confusion with medications, lacking means of self-control	7	1.82	7	1	7	.28	Consistent
Independently stopping treatment as a reaction to unexpected AE	8	.84	8	2	8	.11	Very consistent
Not being aware of the negative impact on cost-benefit or on quality of life, caused by a failure to adhere to their treatment	8	.83	8	2	7	.11	Very consistent
Lack of planning and inconvenience in routine (holidays, weekends)	5	2.41	6	4	2	.47	Inconsistent
Adherence in RA reduces with the duration of the treatment	6	2.13	7	2	7	.36	Consistent
Not knowing what to do in the event of an AE with a DMARD	7	.85	7	1	7	.12	Consistenta
Perceiving the DMARD as unnecessary (or redundant) since their disease has improved with a biological DMARD	7	2.21	8	1	8	.32	Very consistent
Rejecting MTX relating it with cancer	5	2.21	6	4	6	.42	Inconsistent

AE: adverse events; COV: coefficient of variation; SD: standard deviation; DMARDs: slow acting remission inducers (synthetic); MTX: methotrexate; IQR: interquartile range.

a Level of consistency of agreement based on the simultaneous compliance criterion: mean ≥7, median ≥7, SD ≤1.00, IQR ≤1.00 and COV ≤.25.

Table 2. Health Professional-related Reasons for Lack of Adherence.

	Mean	SD	Median	IQR	Mode	COV	Level of consistency
Considering treatment to be the core element and not the patient	6	2.18	7	2	8	.34	Consistent
Assuming that the patient must cope with and overcome problems with therapeutic non-compliance	7	1.50	7	1	8	.21	Consistent
Not considering it relevant to personalise each case	5	2.52	6	5	8	.48	Inconsistent
Not paying sufficient attention to written and verbal information during the medical visit and nursing follow-up	6	2.62	7	5	8	.45	Consistent
Not keeping a record of treatment adherence in the patient's clinical history and not being aware of the real situation	6	2.31	7	1	7	.36	Consistent
Not paying much attention to adherence in clinical practice guidelines and recommendations	6	2.26	7	3	7	.37	Consistent
Doctors, nurses, etc., not using adherence screening methods to detect potential non-compliant patients.	8	.99	8	1	8	.13	Very consistenta
Lack of awareness-raising programmes and ongoing education to improve adherence, directed at healthcare personnel	7	1.40	8	1	8	.19	Very consistent
Lack of active involvement by the doctor in the follow-up of adherence	7	1.75	7	2	8	.27	Consistent
Lack of active involvement by nursing staff in the follow-up of adherence	6	2.39	7	4	7	.40	Consistent
Lack of active involvement by pharmaceutical staff in the follow-up of adherence	6	2.35	7	4	8	.38	Consistent
Being unaware of possible difficulties for the patient with compliance and adherence to treatment	6	1.82	7	1	7	.30	Consistent

Not involving the patient in the progression of their disease by means of complementary tests: X-rays, ultrasound, blood tests, etc.	6	2.66	7	5	8	.47	Consistent
Healthcare staff failing to adapt or use the “new technologies”	6	2.41	7	3	7	.41	Consistent
Maintaining a distance between the doctor and patient	6	2.49	7	4	7	.42	Consistent
Perceiving that the distance between the nurse and the patient can be maintained	5	2.45	4	5	7	.52	Inconsistent
Perceiving that the distance between the pharmacist and the patient can be maintained	5	2.56	7	4	7	.49	Consistent
Not using motivational interview techniques with the patient	7	1.73	7	1	8	.24	Consistent
Each person being possessive of their role as a healthcare professional in treatment; focussing on their own particular tasks only	6	2.23	7	3	8	.36	Consistent
Failing to make interventions towards improving therapeutic adherence	8	.79	7	1	7	.10	Consistenta
Not relating insufficient adherence to a “poor response”	7	1.70		1	8	.24	Very consistent
Limiting the proximity and accessibility of healthcare staff (although justified for structural reasons)	7	2.15	7	1	7	.32	Consistent
Not undertaking reasoned prescribing with the patient	6	2.56	7	5	8	.44	Consistent

COV: coefficient of variation; SD: standard deviation; IQR: interquartile range.

A Degree of consistency of agreement based on the simultaneous compliance criterion: mean ≥7, median ≥7, SD ≤1.00, IQR ≤1.00 and COV ≤.25.

Table 3. Treatment-related Reasons for Lack of Adherence.

	Mean	SD	Median	IQR	Mode	COV	Level of consistency
Diagnosis that was imprecise or not appropriately reassessed during follow-up	4	2.66	3	5	8	.61	Disagreement
When choosing the drug, failing to appropriately consider its characteristics and adaptability to the patient	5	2.68	4	5	3	.60	Inconsistent
Not paying attention to the number of drugs prescribed, which might be excessive	6	2.45	7	5	8	.41	Consistent
Not paying attention to the high number of drugs taken (e.g., in the case of a synthetic DMARD).	6	2.59	7	5	3	.44	Consistent
Lack of synchronisation when taking medication, at the same time or with routine activities	5	2.61	7	5	8	.49	Consistent
Using the most usual dosing regimen, without attempting to simplify it	5	2.51	5	4	7	.51	Inconsistent
Allowing flexibility in dose and regime…, which can lead to the patient developing bad habits	5	2.60	6	5	2	.50	Inconsistent
Not using reminder techniques on packaging: single dose vials, numbered, in different colours, highlighting medication schedules, etc.	7	1.64	7	2	7	.24	Consistent
Not providing a (clear) explanatory document along with the treatment	6	2.52	7	4	7	.41	Consistent
Changing the administration route of the treatment or drugs without the patient considering it necessary	5	2.47	5	5	2	.51	Inconsistent
Overlooking intolerance to synthetic DMARDs, whether or not shown by the patient	7	1.88	7	1	7	.28	Consistent
Not considering that the patient would attach importance to the risk of AE associated with DMARDs	6	2.03	7	2	7	.32	Consistent

Not considering that the patient would attach importance to the risk of haematological disorders: anaemia, thrombocytopenia, etc. associated with synthetic DMARDs	5	2.61	5	4	3	.53	Inconsistent
Not considering that the patient would attach importance to the risk of contracting an infection (opportunistic, etc.) associated with synthetic DMARDs	5	2.56	4	4	3	.54	Inconsistent
Not considering that the patient would attach importance to the risk of mucositis, mouth ulcers, diarrhoea or other gastrointestinal upsets associated with synthetic DMARDs	5	2.37	6	4	3	.45	Inconsistent
Not considering that the patient would attach importance to the risk of hair loss associated with synthetic DMARDs	6	2.40	7	5	8	.42	Consistent
Not considering that the patient would attach importance to possible impact on sexual functions and/or fertility of DMARDs	6	2.36	7	4	8	.40	Consistent
Not considering that the patient would attach importance to possible fatigue associated with DMARDs	6	2.33	7	3	7	.40	Consistent
Not considering that the patient might be afraid of MTX injections	6	2.18	7	4	7	.36	Consistent

AE: adverse events; COV: coefficient of variation; SD: standard deviation; DMARDs: slow acting remission inducers (synthetic); MTX: methotrexate; IQR: interquartile range.