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## Assessment of the adherence to disease-modifying drugs in patients with chronic inflammatory rheumatic diseases: results of a survey of 1594 patients

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## **ABSTRACT**

**Objectives:** a) to describe the self-reported adherence to disease modifying drugs (DMARDs) (methotrexate and biological DMARDs) among patients with chronic inflammatory rheumatic diseases (CIRDs); b) to assess factors associated with non-adherence.

**Methods:** An observational, cross-sectional, nationwide study was conducted through the use of an electronic survey, which was released via patient organizations in France to rheumatic patients. The main outcome was the rate of non-adherence to DMARDs, which was evaluated with the following question “Have you ever tried to stop or space out your treatment in contrast to what was planned with your doctor?”. A positive answer was considered “low adherent”. Sociodemographic variables, type of CIRD and treatment information were also collected.

Factors associated with low adherence to methotrexate and bDMARDs were explored by univariate and multivariate logistic regressions.

**Results:** Among the 1594 participants who completed the survey, 795 (49.9%) were receiving methotrexate and 709 (44.5%) bDMARDs.

A total of 159 (20.0%) were identified as low adherents to methotrexate, and being a woman was independently associated with low adherence (OR 1.90 [95%CI 1.07 – 3.36]) to this drug.

Regarding bDMARDs, 177 (25.0%) were identified as low adherent, and the factors independently associated with low adherence were being employed (OR 1.47 [95%CI 1.04 – 2.09]) and no concomitant use of methotrexate (OR 0.51 [95%CI 0.36 – 0.73]).

**Conclusions:** This study suggests that more than 20% of CIRDs patients are low adherent to their DMARDs, and this is more frequent when bDMARDs are administered as a monotherapy.

**Keywords:** adherence, disease-modifying drugs, rheumatic disease

# 1. Introduction

Drug adherence is defined as the degree to which a patient takes medication in accordance with physician instructions [1]. Long-term treatment is essential to patients with chronic diseases; however, only 50% of these patients have been reported to be adherent to their prescribed treatment in developed countries [1,2]. Specifically, regarding chronic inflammatory rheumatic diseases (CIRDs), this inadequate adherence has also been reported, with approximately 30% to 80% adherence among patients with rheumatoid arthritis (RA) [3]. However, there is a great heterogeneity in the published data about disease-modifying drugs (DMARDs) adherence in these patients.

Assessment of non-adherence in CIRDs is still difficult due to the limited number of validated tools and the short time available during each medical visit to assess adherence. Self-reported questionnaires and open questions seem to be the most frequent tool used to evaluate this issue. In addition, knowing the factors associated with non-adherence is of importance with the aim of being able to detect potentially non-adherent patients in daily clinical practice.

Recently, Gossec et al. published a national set of recommendations for the assessment and optimization of adherence to DMARDs in CIRDs, aiming to facilitate the management of non-adherence in patients with RA, Spondyloarthritis (SpA), Psoriatic Arthritis (PsA), Connective Tissue Diseases (CTD) and other CIRDs in daily practice [4]. The process of developing these recommendations included systematic literature reviews and a face-to-face meeting of the steering group, which included a convenor, 2 methodologists, 3 fellows, 9 rheumatology experts, one pharmacist and one rheumatology nurse. The above arguments prompted us to conduct this study with the following main objectives: a) to describe the self-reported adherence to DMARDs (methotrexate and biologic DMARDs (bDMARDs)) among patients with CIRDs; b) to assess factors associated with non-adherence; and c) to describe the most common sources used by patients to obtain information about their disease and their treatment.

## **2. Methods**

### **2.1. Study design and patients**

An observational, cross-sectional, nationwide study was conducted through the use of an electronic survey between January and June 2018. The questionnaire and the objectives of the study were presented to representatives of different rheumatic patient organizations in France at one meeting in December 2017; subsequently, this survey was released via these associations to rheumatic patients included in their database (affiliated and non-affiliated) around the country.

The only inclusion criterion was being older than 18 years of age. The study followed ethical and good practice guidelines in compliance with local regulations.

### **2.2. Collected data**

Non-adherence to DMARDs was evaluated with the following question “Have you ever tried to stop or space out your treatment in contrast to what was planned with your doctor?”. This question was asked twice: once regarding methotrexate and then for bDMARDs. Patients with a positive answer were considered “low adherent”, and those with a negative answer were considered “adherent”. We decided to not use more complete questionnaires because we would to mimic daily clinical practice, in which an open question is usually used.

The following data were also collected: sociodemographic variables (e.g. age, gender, education, profession, employment status, marital status, children and affiliation with patient organizations; type of CIRD; treatment, which included information of concomitant DMARDs, route of administration, and administration interval. We also collected data about the support used by patients to obtain information about their treatment through the use of a multiple-choice question.

### **2.3. Statistical analysis**

All data presented in tables and figures are expressed as the mean and standard deviation (SD) for continuous variables and as the number and percentage for categorical variables.

Factors associated with low adherents were explored first by two univariate analyses (one for methotrexate and the other for bDMARDs) and thereafter by multivariate logistic regressions, which included in the model variables selected by the univariate analysis (i.e. when  $p \leq 0.20$ ). Interactions, confounding factors and collinearity were tested, and all comparisons were bilateral considering  $p \leq 0.05$  as a significant result.

Finally, the sources of information most commonly used by patients were described.

### **3. Results**

A total of 1594 patients completed the survey. Among these, 1285 (80.6%) were female, 850 (53.3%) were younger than 60 years and 964 (60.5%) were affiliated with patient organization (Table 1). Regarding the type of CIRD, 1000 (62.7%) patients suffered from RA, 293 (18.4%) from SpA and 301 (18.9%) from other types of disease (which include PsA and CTD). A total of 795 (49.9%) patients were receiving methotrexate, 709 (44.5%) were receiving bDMARDs (among them, 337 were receiving treatment with Methotrexate, concomitantly), and 427 (26.8%) were not receiving any of these drugs (Figure 1). The frequency of use of bDMARD as monotherapy (e.g. without methotrexate) was 52.5% (372 out of 709) in the whole population, but was 58.4% (264 out of the 452), 76.8% (126 out of 164) and 62.4% (58 out of 93) in RA, SpA and other patients under bDMARD therapy, respectively. Considering the type of drug, 239 out of 468 (51.1%) patients under TNF alpha blockers were receiving bDMARDs in monotherapy. This percentage was 46.2% (36 out of 78) for IL-6 blockers, 55.3% (26 out of 47) for Rituximab, 89.2% (33 out of 37) for IL-17 blockers, 43.5% (30 out of 69) for abatacept and 80.0% (8 out of 10) for IL-12/IL-23 blockers.

A total of 159 out of 795 (20.0%) were identified low adherent to methotrexate. Univariate and multivariate logistic regression (Table 2) showed that being a woman was independently associated with low adherence (OR 1.90 [95% CI

1.07 – 3.36]) to this drug. Methotrexate-low-adherent patients were more frequently younger and not affiliated with patient organizations, but these differences were not statistically significant. In addition, the route of administration for methotrexate (oral or subcutaneous) did not seem to influence adherence.

Regarding bDMARDs, a total of 177 (25.0%) out of 709 were identified as low adherent to this drug. Univariate logistic regression (Table 3) showed that low-adherence was more frequently among patients younger than 60 years (OR 1.44 [95%CI 1.01 – 2.05]) and employed (OR 1.05 [95% CI 1.06 – 2.12]). However, patients treated by bDMARDs and Methotrexate concomitantly were more likely to show a better adherence to bDMARDs than patients treated by bDMARDs monotherapy (OR 0.50 [95%CI 0.35 – 0.72]). Multivariate logistic regression (Table 3) showed that the factors independently associated with bDMARD low-adherence were being employed (OR 1.47 [1.04 – 2.09]) and the absence of concomitant methotrexate (OR 0.51 [0.36 – 0.73]). We did not find differences either regarding the bDMARDs administration interval, nor regarding the type of CIRDs.

Finally, we evaluated sources used by patients to obtain information about their treatment. The preferred source for these patients was their rheumatologist (78.4%), followed by patient organizations (35.1%) and general physicians (24.5%). However, 8.3% of patients reported that they did not use any information source. Grouping these sources in three categories (Figure 2), the rheumatology team (which included both rheumatologists, nurses and other rheumatology staff) was the most used (1337 patients, 83.9%), followed by the internet (587, 36.8%) and patient organizations (560, 35.1%).

## **4. Discussion**

This work, based on a survey disseminated by patient associations in France, attempts to make an approximate profile of low-adherent patients. This could help us to detect and to pay more attention to these patients in daily practice. Previous studies reported difficulty in identifying patient characteristics related to non-adherence [5,6] due to the large variability of factors, which can be inherent to the disease, treatment or patient, that affect taking medication [3].

In our study, 80% of patients were considered adherent to methotrexate. These results are comparable to those reported in other studies, in which adherence was shown to be between 64% and 92% [7,8]. Regarding bDMARDs, the percentage of adherents decreased slightly to 75%, similar to those reported by previous studies [9,10]. This decrease in adherence to bDMARDs could be associated with increased concerns about side effects and adverse events with these drugs.

All systematic reviews focused on this topic agree that there is a great heterogeneity in the published data about DMARD adherence in CIRDS patients depending on the definition and method used: adherence can be directly assessed by measuring drug levels in blood or by indirect methods, such as patient-level medication dispensation data or self-reported questionnaires [11,12]. For this reason, there seems to be an overestimation of adherence rates when adherence is evaluated with questionnaires or open questions to patients. In addition, it is well known that the social desirability bias plays a role in the responses to self-reporting questionnaires, in that there is a tendency for patients to report socially desirable responses and favourable self-representations [13,14]. For this reason, we are aware that the use of a single question in our study could underestimate the prevalence of low-adherent patients.

Concerning methotrexate, our results report that low adherent patients are more frequently female. This is not in accordance with previous studies, which reported that the compliance of methotrexate and other DMARDs is worse in male patients [15,16]. However, this can be explained by the fact that 80.6% of patients who participated in this survey were female and, consequently, it was easier to find associations with this subgroup of patients. This predominance of women among participants to surveys has also been detected previously in similar studies [5] and may be associated with women having a more participative attitude and a higher level of affiliation with patient organizations than those of men.

Concerning bDMARDs, the univariate logistic regression showed that patients younger than 60 years were less adherent. This result is in line with other studies, which reported that compliance with medication is higher in older populations [17,18]. This could be explained by different perceptions on the necessity of drugs, less patient's knowledge about the disease and medications and also less coping strategies among patients with early diagnosis. Low adherence to bDMARDs was independently

associated with employed patients, which could be contradictory to what is reported in the literature. Some previous studies found that employed patients are more adherent than unemployed patients [19]; while others found associations neither with employment nor with socioeconomic status [20]. Finally, our study confirms that adherence to these drugs is higher when methotrexate is concomitantly prescribed and lower when bDMARDs are administered as a monotherapy. This is more difficult to interpret since theoretically one could expect a better adherence in case of monotherapy. However, one could not merge the concept of “acceptability” (including the facility to take) and the concept of adherence.

In our study, 559 patients (78.8%) were receiving their bDMARD via subcutaneous and 150 (21.2%) via intravenous. Among the 150 patients under intravenous bDMARDs, 31 were low-adherent (they answered that they have tried to stop or space out their treatment in contrast to what was planned with their doctor). Theoretically, self-administration of biologics could be associated with missed doses [5,21], while those parenterally administered in the hospital and supervised by health professionals could encourage a good adherence. However, it has been reported that self-injectable forms may be effective and better tolerated than other administration forms, which may lead to better adherence in patients with subcutaneous treatment [17,22].

Our study had some limitations but also several strengths. A limitation was the use of a single question with two possible responses to evaluate adherence, which has a risk of incurring an underestimation of low-adherence. However, a dichotomized response is useful for identifying the two types of patients [18]. The second weakness is that we did not evaluate the relationship between adherence and disease activity. This has not been possible because the study was based on an electronic survey, and patients were not physically evaluated. Finally, the fact that 60% of participants are affiliated with patient organizations means that these are patients with a greater knowledge about the disease, and maybe are not representative of the majority of patients. The main strength of our study is the large sample size. The use of an electronic survey has allowed us to include more than 1500 patients, an unusual number in this type of study.

In summary, this study suggests that more than 20% of CIRDs patients are low adherent to their DMARDs, and this is lower when bDMARDs are administered as a monotherapy.

Further studies are required to better evaluate the true level of adherence of the use of DMARDs in daily practice together with the link between this adherence and, on one hand, the use of bDMARD in combination or not with csDMARD and, on the other hand, the link with the route of administration of bDMARD.

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Author's contribution: The corresponding author certifies that all authors approved the entirety of the submitted material and contributed actively to the study.

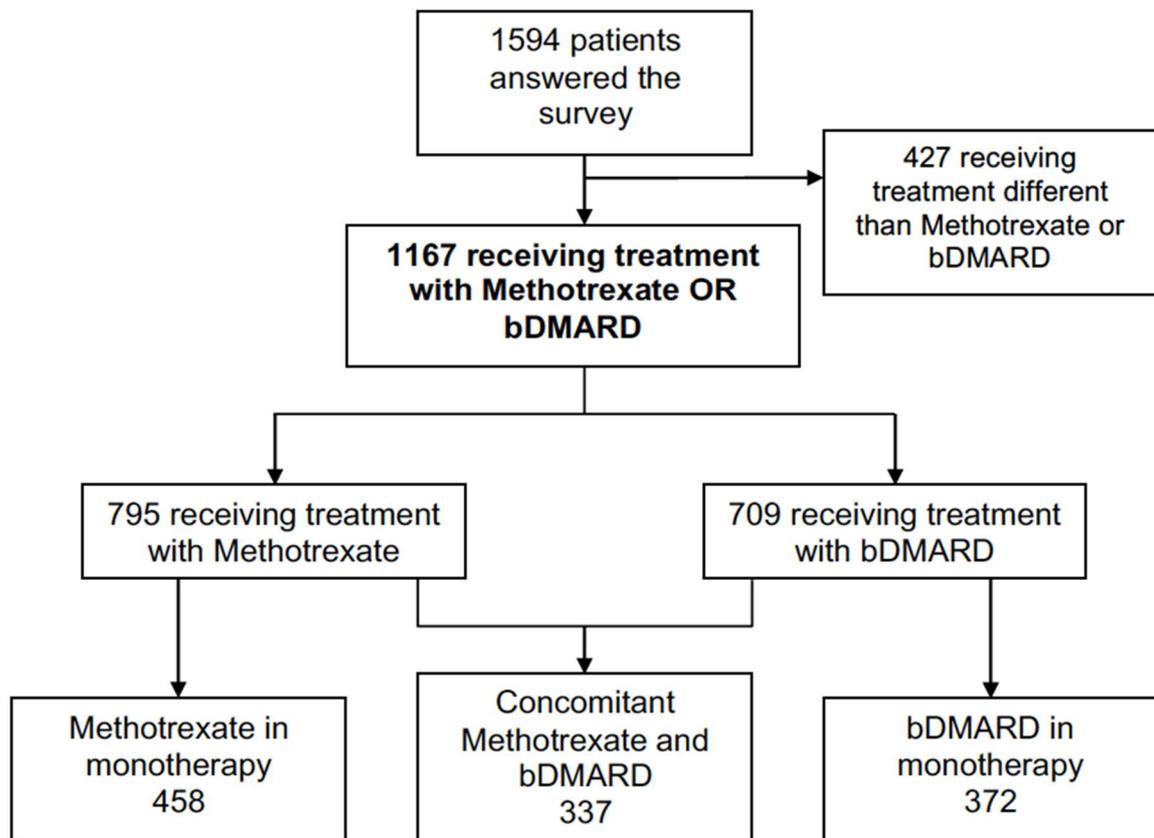
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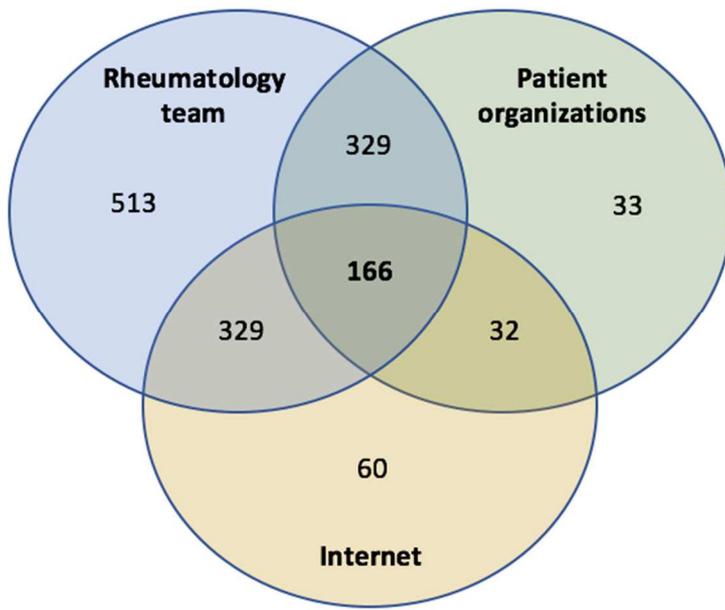
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Figure 1. Flow chart of patients included in the study



**Figure 2. Sources used by patients to obtain information about their treatment.**



132 patients did not use any information support

**Table 1. Descriptive data of the 1594 patients included in the study.**

|  | <b>Total patients<br/>n = 1594 (%)</b> |
|--|--|
| Age ≤60 years                          | 850 (53.3)                             |
| Sex (female)                           | 1285 (80.6)                            |
| Universitary studies                   | 757 (47.5)                             |
| Blue collar professions                | 868 (54.5)                             |
| Employed                               | 547 (34.3)                             |
| Marital status (married)               | 1127 (70.7)                            |
| Children                               | 1264 (79.3)                            |
| Affiliation with patient organizations | 964 (60.5)                             |
| Spondyloarthritis                      | 293 (18.4)                             |
| Rheumatoid Arthritis                   | 1000 (62.7)                            |
| Methotrexate                           | 795 (49.9)                             |
| bDMARDs                                | 709 (44.5)                             |
| Concomitant methotrexate and bDMARDs   | 337 (21.1)                             |
| Neither methotrexate nor bDMARDs       | 427 (26.8)                             |

bDMARDs: biological Disease-Modifying Drugs.

|  | Total patients under treatment with Methotrexate (%)<br>n = 795 | Low adherent<br>n = 159 (%) | Adherent<br>n = 636 (%) | OR (95%CI)<br>univariate analysis | OR (95%CI)<br>multivariate analysis <sup>1</sup> |
|--|---|-----------------------------|-------------------------|-----------------------------------|--|
| Age ≤60 years                          | 388 (48.8)  | 87 (22.4)                   | 301 (77.6)              | 1.34 (0.95 – 1.91)                |  |
| Sex (female)                           | 675 (84.9)  | 144 (21.3)                  | 531 (78.7)              | 1.90 (1.07 – 3.36)*               | 1.90 (1.07 – 3.36)*                              |
| Universitary studies                   | 376 (47.3)  | 80 (21.3)                   | 296 (78.7)              | 1.16 (0.82 – 1.65)                |  |
| Blue collar professions                | 415 (52.2)  | 88 (21.2)                   | 327 (78.8)              | 1.17 (0.83 – 1.66)                |  |
| Employed                               | 268 (33.7)  | 55 (20.5)                   | 213 (79.5)              | 1.05 (0.73 – 1.51)                |  |
| Marital status (married)               | 556 (69.9)  | 103 (18.5)                  | 453 (81.5)              | 0.74 (0.51 – 1.07)                |  |
| Children                               | 634 (79.7)  | 128 (20.2)                  | 506 (79.8)              | 1.06 (0.68 – 1.64)                |  |
| Affiliation with patient organizations | 477 (60.0)  | 85 (17.8)                   | 392 (82.2)              | 0.72 (0.50 – 1.01)                |  |
| Spondyloarthritis                      | 56 (7.0)  | 14 (25.0)                   | 42 (75.0)               | 1.37 (0.73 – 2.57)                |  |
| Rheumatoid Arthritis                   | 621 (78.1)  | 124 (20.0)                  | 497 (80.0)              | 0.99 (0.65 – 1.51)                |  |
| Subcutaneous methotrexate (ref. oral)  | 376 (47.3)  | 81 (21.5)                   | 295 (78.5)              | 1.20 (0.85 – 1.70)                |  |
| Concomitant bDMARD                     | 337 (42.4)  | 76 (22.6)                   | 261 (77.4)              | 1.32 (0.93 – 1.86)                |  |

<sup>1</sup>For statistically significant variables which remain in the final model. \*p<0.05

Percentages indicate number of patients with the covariate from the total number of patients in each row.

bDMARDs: biologic Disease Modifying Drugs; OR: Odds Ratio; n.s.: non-significant.

|   | <b>Total patients under treatment with bDMARDs n = 709 (%)</b> | <b>Low adherent n = 177</b> | <b>Adherent n = 532</b> | <b>OR (95%CI) univariate analysis</b> | <b>OR (95%CI) multivariate analysis<sup>1</sup></b> |
|---|--|-----------------------------|-------------------------|---------------------------------------|---|
| Age ≤60 years                           | 419 (59.1)   | 116 (26.7)                  | 303 (72.3)              | 1.44 (1.01 – 2.05)*                   |   |
| Sex (female)                            | 579 (81.7)   | 146 (25.2)                  | 433 (74.8)              | 1.08 (0.69 – 1.68)                    |   |
| Universitary studies                    | 342 (48.2)   | 87 (25.4)                   | 255 (74.6)              | 1.05 (0.75 – 1.47)                    |   |
| Blue collar professions                 | 394 (55.6)   | 97 (24.6)                   | 297 (75.4)              | 0.96 (0.68 – 1.35)                    |   |
| Employed                                | 265 (37.4)   | 79 (30.8)                   | 186 (70.2)              | 1.05 (1.06 – 2.12)*                   | 1.47 (1.04 – 2.09)*                                 |
| Marital status (married)                | 523 (73.8)   | 127 (24.3)                  | 396 (75.7)              | 0.87 (0.60 – 1.28)                    |   |
| Children                                | 563 (79.4)   | 142 (25.2)                  | 421 (74.8)              | 1.07 (0.70 – 1.64)                    |   |
| Affiliation with patient organizations  | 474 (66.8)   | 117 (24.7)                  | 357 (75.3)              | 0.97 (0.67 – 1.37)                    |   |
| Spondyloarthritis                       | 164 (23.1)   | 45 (27.4)                   | 119 (72.6)              | 1.18 (0.80 – 1.75)                    |   |
| Rheumatoid Arthritis                    | 452 (63.7)   | 116 (25.7)                  | 336 (74.3)              | 1.11 (0.78 – 1.58)                    |   |
| Subcutaneous bDMARDs (ref. intravenous) | 559 (78.8)   | 146 (26.1)                  | 413 (73.9)              | 1.36 (0.87 – 2.10)                    |   |
| Administration interval                 |  |                             |                         |                                       |   |
| - 1 week                                | 217 (30.6)   | 51 (23.5)                   | 166 (76.5)              | Reference                             |   |
| - 2 weeks                               | 183 (25.8)   | 41 (22.4)                   | 142 (77.6)              | 0.94 (0.59 – 1.50)                    |   |
| - Other                                 | 309 (43.6)   | 85 (27.5)                   | 224 (72.5)              | 1.23 (0.83 – 1.84)                    |   |
| Concomitant methotrexate                | 337 (47.5)   | 62 (18.4)                   | 275 (81.6)              | 0.50 (0.35 – 0.72)*                   | 0.51 (0.36 – 0.73)*                                 |

<sup>1</sup>For statistically significant variables which remain in the final model. \*p<0.05

Percentages indicate number of patients with the covariate from the total number of patients in each row.

bDMARDs: biologic Disease Modifying Drugs; OR: Odds Ratio; n.s.: non-significant.