**Patient motivation for non-persistence with medication impacts self-reported compliance.**

**Running title:** Patient motivation impacts in compliance.

Contreras-Yáñez I1, Pérez-Román DI1, Pascual-Ramos V1.

1 Department of Immunology and Rheumatology. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. DF. México.

**Address for Correspondence**

Virginia Pascual-Ramos

Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Vasco de Quiroga 15, Colonia Belisario Domínguez, Sección XVI, Tlalpan 14500. México DF. México.

virtichu@gmail.com

1. **ABSTRACT**

**1.1 Introduction**

In 2004, an inception cohort of recent-onset rheumatoid arthritis patients was initiated. From 2008 onward, compliance with therapy was assessed through a questionnaire that additionally investigated 15 predefined motivations for non-persistence with therapy, and a visual analogue scale (VAS). **Objectives** were to examine the correlation between the questionnaire and the VAS to assess compliance, and to investigate if the selection of patient-independent motivations for non-persistence predicted better self-reported compliance.

* 1. **Materials and methods**

Up to January 2016, the cohort comprised 180 patients with variable follow-up. Each motivation for non-persistence was classified as patient-dependent or patient-independent by 50 patients randomly interviewed (≥70% agreement). Descriptive statistics as well as multiple regression analysis were used. Written informed consent was obtained.

**1.3 Results**

Length of follow-up from 160 patients for which data were completed was 6.7±3.4 years; all the patients scored 1516 pairs of questionnaire and VAS, and the correlation between them was moderate, r=0.468, p=0.001. Optimal VAS cut-off value to predict compliance as per questionnaire was ≤7.5 mm.

During follow-up, there were 670 questionnaires scored as with non-persistence among whom, 654 had at least one motivation for non-persistence selected; of them, 549 (70.2%) corresponded to non-persistence patients who selected only patient-independent motivations. The selection of exclusively independent motivations for non-persistence predicted better VAS and questionnaire´s scores. Also, the selection of exclusively independent motivations for non-persistence predicted compliance either per VAS (OR: 15.6, 95%CI: 5.4-45.3, p≤0.001) or per questionnaire (OR: 2.25, 95%CI: 1.1-4.7, p=0.034).

**1.4 Conclusions**

Patient motivation for non-persistence with medication impacts self-reported compliance.

**Key indexing Mesh terms**: rheumatoid arthritis, adherence medication, health behavior.

1. **INTRODUCTION**

Rheumatoid arthritis (RA) is a chronic inflammatory disease that frequently results in disability and morbidity, and is associated with increased mortality (Kosinski M et al, 2002, Sanderson T & Kirwan J 2009, Wolfe F et al, 1994). Aggressive and early use of disease modifying anti-rheumatic drugs (DMARDs), targeted to achieve remission or mitigate disease activity, is the mainstay of treatment and has been shown to be the most effective strategy in improving patient outcomes (Grigor et al, 2004). Nevertheless, poor adherence to therapy is common and progressive during patient follow-up (Scheiman et al, 2016, Van der Bemt BJF et al, 2012). Patients from Latin-America present unique and distinctive epidemiological, serological and clinical disease features compared with Caucasians (Mody GM & Cardiel MH 2008, Author, 2009). These patients are frequently uninsured, have low socioeconomic status and are less educated than RA patients from developed countries. All of these factors ultimately impact patient access to health care and commitment to prescribed treatment.

In 2004, we established an early arthritis clinic for patients with recent-onset RA. Once enrolled in the inception cohort, patient compliance with DMARDs was prospectively assessed. Poor compliance was progressive during follow-up and was associated with an increased number of disease flares, decreased rates of remission, and worse physician- and patient-reported outcomes (Author, 2009, Author, 2010, Author 2013). C was assessed initially through an interview; however, from 2008 onward, it was assessed using a 22-item questionnaire (The ‘Concordance Questionnaire’ [CQ], formerly the ‘Compliance Questionnaire’), which evaluated the constructs adherence to (A) and persistence with DMARDs (P), and investigated patient motivations for non-P. The CQ demonstrated high sensitivity and satisfactory specificity to assess P with DMARDs when compared with serum determination of methotrexate levels (Author, 2010). In conjunction with the CQ, a compliance visual analogue scale (C-VAS) was constructed and administered.

The VAS has been widely and effectively used in psychological medicine, and provides a simple technique for measuring subjective experiences and behavioural responses (McCormack HM 12). In clinical practice, the simplest method to assess medication compliance is frequently used and involves asking the patient whether he/she is taking the medication as prescribed. We hypothesized that a VAS to assess compliance would be a useful instrument in our population of patients, with the additional benefits of being easier to apply and score than a questionnaire, despite its minimal value for elucidating the factors that impact compliance. These factors have been identified and intensively investigated in previous studies and reviews (Van der Bemt BJF et al, 2012). They can be grouped into domains as recommended by the World Health Organization, and further classified as either ‘intentional’ or ‘unintentional’ – the former reflects a patient’s ability and skill with regard to medicine taking, while the latter describes patient behaviour driven by the decision not to take medication (Jing J et al, 2008, Lorish CD et al, 1989, Clifford S et al, 2008). Drivers of this decision have been suggested to be based on patient beliefs about illness and treatment, which can be further categorized as perceived benefits and perceived concerns (Van der Bemt BJF et al, 2012). The practical implication of this conceptual classification of motivation(s) for non-compliance is that subjectively attributed motivation(s) (ie., patient dependent versus patient independent) may impact self-reported evaluation of compliance. In the present study, we hypothesized that non-P patients who reported independent motivation(s) for their lack of P would score themselves more compliant than those who reported dependent motivation(s). Accordingly, the objectives of the present study were:

1. To examine the correlation between compliance assessed according to the CQ and the VAS.

2. To identify the optimal C-VAS cut-off score to predict CQ compliance.

3. To investigate whether the selection of patient-independent motivation(s) for non-P predicted a better compliance.

**3. METHODS**

**3.1 Setting and study population**

The *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán* belongs to the National Institutes of Health in México. Patients attending the institution have variable government health coverage that includes medical consultations, hospitalizations, emergency room and critical care unit admission(s), laboratory and all available diagnostic procedures. Patients are required to pay for their medication, which is not provided by the local pharmacy.

**3.2 The Early Arthritis Clinic**

Patients attending the clinic had a disease duration <1 year when initially evaluated and no specific rheumatic diagnosis except for RA. Rheumatic evaluations were scheduled at variable intervals; however, all patients underwent fixed six-month assessments. Treatment was prescribed by the rheumatologist in charge of the clinic and was ‘Treat to target’ oriented. Traditional DMARDs were used in 99% of the patients with/without corticosteroids (50% of the patients received low doses of oral corticosteroids during their follow-up). Up to January 2016, the cohort comprised 180 patients with variable follow-up, who were recruited from 2004 onward.

**3.3 Standard rheumatic evaluations**

At cohort inclusion, all patients had their complete medical history and demographic data recorded, and class and levels of disease-specific autoantibodies were determined. Standardized rheumatic assessments included, at minimum, counts of swollen and tender joints, acute reactant-phase determinations, patient- and physician-reported outcomes, and treatment assessments (name[s], dose[s] and schedule[s] of all drug[s] they were taking since last visit).

**3.4 Evaluation of compliance with DMARDs**

From the inception of the Early Arthritis Clinic, patient medication behaviour was prospectively assessed. Since 2008, the CQ and a 100 mm C-VAS were concurrently applied at regular six-month intervals (fixed for all patients).

Briefly, the CQ is a 22-items questionnaire (**Appendix**) that primarily evaluates both A and P on DMARDs; items 12 and 14 correspond to the first construct, while item 10 corresponds to the second construct. In all three items, patients use a Likert scale. Those who score item 10 as 1, 2, 3 or 4 are directed to answer item 11, meanwhile those who score it as 0 are directed to proceed to item 12. Item 11 investigates patient reasons/motivations for non-P and includes 15 predefined answers (most of which were obtained from a literature review (Neame R & Hammond A, 2005) and one open answer. Only patients who defined themselves as ‘non-P’ are directed to select at least one of the 15 pre-defined motivation(s). The CQ has demonstrated high sensitivity and satisfactory specificity to assess P on DMARDs (Author, 2010).

The C-VAS is a 100 mm VAS, in which 0 indicates ‘very good compliance’ and 100 ‘very poor compliance’. Patients score it by following the instruction: “Put a mark on the line that better reflects the way you have taken your RA medication during the past six months; consider the indication given by your rheumatologist”. The C-VAS was constructed following the steps recommended by Scott et al (Scott J & Huskinsson EC, 1976).

**3.5 Definitions**

A patient was considered to be compliance according to the CQ (C-CQ) if A *and* P.

Adherence was defined when a patient selected box 3 (“Almost always”) or box 4 (“Always”) from items 10 (“In the past 2 months, I took my medication exactly at the day/s indicated by my rheumatologist”), 11 (“In the past 2 months, I took my medication exactly at the day-times indicated by my rheumatologist”) and 12 (“In the past 2 months, every time I took my medication, I took the precise amount of tablets indicated by my rheumatologist”). P was defined when a patient selected boxes 0 (“Never”) or 1 (“Almost never”) from item 8 (“In the past 6 months, how often did you completely stop taking your medication?”).

**3.6 Ethics approval**

The present study was approved by the institution’s internal review board. Written informed consent was obtained to have patient charts reviewed, and data presented in scientific forums or published.

**3.7 Statistics**

Descriptive statistics as well as Student’s *t* and chi-squared tests were used when appropriate. Sociodemographic data were presented as mean ± SD, while disease and treatment characteristics were described as median and interquartile range (Q25-Q75). Spearman’s rho was used to correlate compliance defined as per CQ and as per VAS. Receiver operating characteristic curves were plotted to determine the optimal C-VAS cut-off score to predict CQ-compliance.

Each CQ with non-P was classified into one of three categories depending on whether the patient’s motivations for selecting non-P were: exclusively patient dependent (category 1); exclusively patient independent (category 2); or a combination thereof (category 3).

Previously, each of the 15 predefined motivations for non-P was classified as patient dependent or patient independent by 50 patients from the clinic who were randomly selected and directly interviewed for such a purpose. Each motivation was finally assigned to one of the two categories (ie, patient-dependent versus independent) when there was ≥70% agreement among the patients interviewed (**Table 1**).

**Table 1. Percentage of patients who agree to classify each motivation as either patient-dependent or patient-independent.**

|  |  |  |
| --- | --- | --- |
| **MOTIVATIONS** | **% of patients who classified the motivation as patient-dependent** | **% of patients who classified the motivation as patient-independent** |
| **Because I had no money to buy it**  | 84 |  |
| **Because it was not available at the drugstore**  |  | 88 |
| **Because it does not make me feel better**  | 78 |  |
| **Because it may me feel worse when I take it** | 74 |  |
| **Because the medication is very expensive** |  | 72 |
| **Because I forget to take it** | 94 |  |
| **Because nothing happens if I do not take it**  | 96 |  |
| **Because I am taking a lot of medication at this time**  | 84 |  |
| **Because I had to do more things than I usually do through the day** | 94 |  |
| **Because I did fewer things than I usually do through the day** | 94 |  |
| **Because nobody reminded me to take my medication** | 90 |  |
| **Because timing/s when my medication is prescribed is different from mealtime/s**  | 94 |  |
| **Because I was not at home when I had to take my medication** | 96 |  |
| **Because I did not buy it** | 94 |  |
| **Because I went out on a trip** | 96 |  |

Linear regression and logistic regression analysis were used to investigate the impact of patient-independent motivation for non-P on the C-VAS score and the CQ score, and on compliance according to the VAS and the CQ, respectively.

All statistical tests were two-sided and evaluated at the 0.05 significance level. Statistical analysis was performed using SPSS version 17 (IBM Corporation, USA).

1. **RESULTS**

**4.1 Characteristics of the study population**

To January 2016, charts from 180 patients with early RA and at least six months of follow-up were reviewed (the first evaluation of compliance was scheduled at six-months). Of these, 17 were lost to follow-up before 2008 when CQ and C-VAS were added to the standard evaluations, and three additional patients had incomplete evaluation of compliance. The final number of patients for which data were analyzed was 160. At inclusion in the cohort, patients were primarily middle-age ([mean ± SD] age 38.3±1.3 years) female (144 [90%]), with 11.1±3.9 years of formal education, short disease duration (5.4±2.6 months) and high disease activity (Disease Activity Score [28 joints], DAS28: 5.9±1.4). The patients frequently had disease-specific autoantibodies: 137 (85.6%) had rheumatoid factor and 141 (88.1%) had antibodies to cyclic citrullinated peptides. Almost one-half (49%) of the patients were receiving DMARDs and had at least one comorbid condition (48%), and 32.4% were taking low doses of oral corticosteroids.

To January 2016, the mean length of follow-up in the cohort was 6.7±3.4 years, during which patients completed 1516 pairs of CQ and C-VAS; the mean number of paired compliance assessments/patient was 8.2±4.1.

**4.2 Correlation between the CQ and C-VAS**

The C-VAS significantly correlated with the CQ (r=0.468; p=0.001). C, as assessed per questionnaire, was imputed into the constructs of A and P: C-VAS had a higher correlation with P (r=0.412; p≤0.0001) than with A (r=0.305; p≤0.0001).

**4.3 Optimal C-VAS cut-off values to predict compliance**

Sensitivity, specificity, positive predictive value, negative predictive value, area under the curve and 95% confidence interval (CI) of C-VAS for P, A and compliance (defined as per questionnaire) are summarized in **Table 2**. Cut-off values of C-VAS to predict P and A were 6.5 mm, each, respectively, and to predict compliance was 7.5 mm (**Figure**).

**Table 2. Utility of C-VAS for CQ-persistence, CQ-adherence and CQ-compliance.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **CQ-persistence** | **CQ-adherence** | **CQ-compliance** |
| **Sensitivity** | 0.649 | 0.483 | 0.473 |
| **Specificity** | 0.852 | 0.806 | 0.885 |
| **PPV** | 0.429 | 0.211 | 0.519 |
| **NPV** | 0.066 | 0.064 | 0.135 |
| **AUC** | 0.810 | 0.683 | 0.731 |
| **95% CI** | 0.776-0.844 | 0.633-0.733 | 0.697-0.764 |

**PPV=**positive predictive value

**NPV**=negative predictive value

**AUC=**area under curve

**CI=**confidence interval

**Figure. ROC to define optimal C-VAS cut-off value to predict CQ-compliance**

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**4.4 Impact of patient motivation for non-P on self-reported compliance score**

For this analysis, 670 CQs scored as non-P were identified during the entire follow-up, among whom 654 had selected at least one motivation for non-P; the remaining CQs were discarded for this analysis. All CQs included had a corresponding C-VAS completed.

There were 549 (70.2%) CQs belonging to category 1 (non-P patients who selected only patient-independent motivations), 31 (4.7%) to category 2 (non-P patients who selected only patient-dependent motivations) and the remaining 164 CQs (25.1%) belonged to category 3 (non-P patients who selected both motivations). Non-P patients with category 3 CQ had worse C-VAS scores (ie., higher values on the 0 to 100 mm scale) than non-P patients with category 2-CQ, who additionally scored worse than non-P with category 1 CQ, as summarized in **Table 3**. The number of motivations selected per CQ was also greater in category 3 CQ than in either category 1 or category 2 CQ.

**Table 3. C-VAS score and number of selected motivations according to CQ-category**

|  |  |  |
| --- | --- | --- |
|  | **C-VAS (0 to 100 mm)** | **N° of selected motivations/CQ** |
| **Non-P CQ with only patient-independent motivations (N=459), (Category 1)** | 3 (1-5)¹ | 2 (1-2)¹ |
| **Non-P CQ with only patient-dependent motivations (N=31), (Category 2)** | 13 (10-26)² | 1 (1-2)² |
| **Non-P CQ with combined motivations (N=164), (Category 3)** | 25 (11-44) | 3 (3-5) |

**Data presented as median (Q25-Q75)**

**¹ p≤0.001 for category 1 vs. category 2 and vs. category 3.**

**² p=0.04 for category 2 vs. 3**

The selection of exclusively independent motivations for non-P predicted C-VAS score (ß -0.15 [95% CI -19.2 to -6.8]; p≤0.001) (number of selected motivations was controlled). Also, compliance as per VAS was defined at >7.5 mm. The selection of exclusively independent motivations for non-P predicted compliance according to the C-VAS (OR 15.6 [95% CI 5.4 to 45.3]; p≤0.001).

We confirmed the above results when compliance was assessed as per the CQ. The selection of exclusively independent motivations for non-P predicted CQ score (ß 0.79 [95% CI 0.01 to 0.819]; p=0.045). Also, the selection of exclusively independent motivations for non-P predicted compliance as per CQ (OR 2.25 [95% CI 1.062 to 4.664; p=0.034).

Similar results were obtained when the analysis was repeated for patients selecting ≥1 independent motivation(s) for non-P (data not shown).

1. **DISCUSSION**

In the present study, we assessed compliance with DMARDs in an ongoing cohort of early onset RA patients followed-up from 2004 to January 2016. Assessment was performed using a questionnaire that has been previously shown to be adequate (Author, 2010). Additionally, we developed and applied a horizontal VAS for self-scoring compliance. In busy clinical settings, there is a need for quick and convenient clinical tools to assess repeated subjective experiences (eg. pain) or behaviours (eg. compliance) and, additionally, are easy to score. The VAS has been shown to be adequate and suitable for frequent and repeat use, easily understood by patients and requires little motivation for its completion (McCormack HM et al, 1988, Rampling DJ & Williams RA, 1977, Morrison DP 1983). There was a moderate, albeit significant, correlation between the C-VAS and the CQ. The CQ separates the constructs of A and P using specific items. The C-VAS showed a slightly higher correlation with the P construct than with the A construct. This suggests that patients identified the (temporal) cessation of medication intake (P construct) as inadequate compliance; meanwhile, missing doses or incomplete regimens (A construct) may be perceived by themselves as ‘acceptable’. We also identified the optimum C-VAS cut-off value (7.5 mm) to predict CQ compliance; cut-off values for A and P were identical and similar to the cut-off for compliance (6.5 mm). Finally, we found that among patients who were non-P, the selection of at least one patient-independent motivation for non-P (isolated or combined with patient-dependent motivations) predicted a better self-assessment of compliance. This classification is conceptually different from the distinction between intentional and unintentional non-adherence, in which the former is a behaviour driven by the decision not to take medication (Lorish CD et al, 1989, Clifford S et al, 2008, Horne R & Weinman J, 1999). In our study, the category assignment (patient dependent versus independent) of each particular motivation was based on a 70% consensus obtained from a sample of patients themselves. Our findings suggest that patients had the mis-informed idea that patient-independent motivations for non-P do not correspond with the conceptual construct of (non-) compliance. Moreover, they are not perceived as a motivating factor for non-compliance and, accordingly, appear to be ‘erased from the equation’ when they rate compliance. Van den Bemt et al (Van der Bemt BJF et al, 2012) developed a simplified model to explain adherent behaviour. Patients conduct a risk-benefit analysis based on their beliefs about the necessity of a medication and whether they outweigh their concerns (Rosenstock IM et al, 1988). When the former is stronger than the concerns, patients will take their medications intentionally, and will do so successfully unless unintentional (ie, patient-independent) barriers hinder the patient in taking their medication. In clinical practice, it is recommended that patients rate compliance themselves (Scheiman-Elazary et al, 2016), and our study highlights that careful consideration should be given to how it is assessed. Specifically, motivation(s) for non-compliance affect how patients perceive and score themselves, and may lead to the mis-identification of non-compliant patients.

Limitations of the study need to be addressed. First, we did not use a well-validated questionnaire to assess compliance. We applied a short, locally designed patient-oriented questionnaire, which has shown adequate internal consistency, high sensitivity and satisfactory specificity to assess P with traditional DMARDs (Author, 2010). Second, we applied a VAS, although neither its validity nor its suitability for the population were assessed. When using the VAS, it may be argued that end points were not clearly defined and may not convey the full range of non-compliance. In addition, patients were likely to rate themselves in reference to their personal experience and not relative to the overall number of possible non-compliance behaviours (Lati C et al, 2010, Bellamy N 1989). Nonetheless, our main results reflect how motivation category for non-P impacts a patient’s self-assessment of compliance, and that similar results were obtained with the CQ and C-VAS. The use of multiple measurement methods to assess compliance within one study has been recommended because data obtained can be combined (Pasma A et al, 2013). Also, we presented the C-VAS in a horizontal rather than vertical format and did not define intermediate points as strategies to reduce respondent error (McCormack HM et al, 1988). Third, we investigated a limited number of motivations for non-P, which were selected based on the existing literature, and corresponded with a group of ‘patient-related factors’ published in a WHO report in 2003 (World Health Organization 2016). Fourth, our population was not representative of other populations in terms of sociodemographic characteristics, ethnicity, or treatment and health system; therefore, our results may not be generalized to RA populations with different characteristics (Author, 2009, Author, 2010).

RA outcomes may be impacted by inadequate compliance to prescribed treatment. Identifying patients with poor compliance and its predictors should be recommended in clinical practice, especially in health care systems with poor resources. Patient’s personal beliefs required additional time and attention from physicians because they appeared to impact how patients self-assess compliance. Ultimately, knowledge of the factors associated with medication adherence in RA patients could help health professionals develop adherence-improving interventions. Educational interventions concentrate on changing dysfunctional patient perceptions and beliefs about motivating factors for a particular behaviour (Hill J et al, 2001, Van Dulmen S et al, 2007), and could be adopted to improve an individual’s ability to manage his or her disease through the provision of tailored information.

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