# Why Do Patients with Chronic Inflammatory Rheumatic Diseases Discontinue Their Biologics? An Assessment of Patients' Adherence Using a Self-report Questionnaire

Anne-Laure Betegnie, Aurélie Gauchet, Audrey Lehmann, Laurent Grange, Matthieu Roustit, Magalie Baudrant, Pierrick Bedouch, and Benoît Allenet

***ABSTRACT.*** ***Objective.*** Concerns have been raised about nonadherence behavior among patients with chronic inflammatory rheumatic diseases (CIRD) receiving biologics. This nonadherence may be caused by various factors. The main objective was to explain why patients discontinue their biologics of their own accord.

***Methods.*** A quantitative and descriptive study was performed using a self-report questionnaire that was sent through the Internet to members of different patient associations. Sociodemographic data, medical and therapeutic history, management of biologic administration, previous experiences, and patients' beliefs and perceptions about treatment efficacy and side effects were studied to explain self-discontinuation (SD).

***Results.*** A total of 581 patients answered the questionnaire between June 16, 2012, and July 4, 2012, including patients with ankylosing spondylitis (351/581, 60.4%), rheumatoid arthritis (196/581, 33.7%), psoriatic arthritis (30/581, 5.2%), and other CIRD (4/581, 0.7%). More than 1000 different biologics were described by the 581 patients, with a median of 2 lines per patient. Eighty-six patients discontinued their biologics of their own accord (14.8%). In a multivariate analysis, factors that were significantly related to SD were low level of pain, more than 1 line of biologics tried, self-administration of biologics, negative beliefs about the treatment, and a lack of medical and social support.

***Conclusion.*** Five predictive factors of this SD were identified, which should be assessed in routine with patients with CIRD receiving biologic treatment: pain, treatment history, self-administration of injections, negative beliefs about treatment, and a lack of perceived medical and social support. (J Rheumatol First Release February 15 2016; doi:10.3899/jrheum.150414)

*Key Indexing Terms:*

| | | |
|---|---|---|
| RHEUMATIC DISEASE | BIOLOGICS | DISCONTINUATION |
| ADHERENCE | BELIEFS | PATIENT EDUCATION |

Compared with conventional disease-modifying antirheumatic drugs (DMARD), biologics have brought significant therapeutic advantages to the treatment of chronic inflammatory rheumatic diseases (CIRD): rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and others. The high effectiveness of biologics on the evolution of CIRD has been demonstrated by randomized controlled trials and described in clinical practice[1,2,3,4,5,6]. However, many studies have also reported high discontinuation rates with biologics[7,8,9,10], the main causes being side effects and lack of efficacy[11].

Given these results, the issue of self-discontinuation (SD), discontinuation that is decided by the patient himself/herself, needs to be addressed. There is ample literature describing "adherence," a term that covers the 2 aspects of medication taking: regularity, which refers to "patient compliance," and

*From the Pharmacy Department, University Hospital; Interuniversity Laboratory of Psychology: Personality, Cognition, Social Change (LIP/PC2S), University Grenoble-Alpes; Rheumatology Clinic, and Clinical Research Center, Grenoble University Hospital; University Grenoble-Alpes/Centre National de la Recherche Scientifique (CNRS)/ Techniques de l'Ingénierie Médicale et de la Complexité - Informatique, Mathématiques et Applications, Grenoble Unité Mixte de Recherche CNRS #5525 (TIMC-IMAG UMR 5525)/Themas, Grenoble, France.*

*Funded by a grant from the French Society of Rheumatology.*

*A.L. Betegnie, PharmD, Pharmacy Department, University Hospital; A. Gauchet, MS, PhD, LIP/PC2S, University Grenoble-Alpes; A. Lehmann, PharmD, Pharmacy Department, University Hospital, and the University Grenoble-Alpes/CNRS/TIMC-IMAG UMR 5525/Themas; L. Grange, MD, PhD, Rheumatology Clinic, Grenoble University Hospital; M. Roustit, PharmD, PhD, Clinical Research Center, Grenoble University Hospital; M. Baudrant, PharmD, PhD, Pharmacy Department, University Hospital, and the University Grenoble-Alpes/CNRS/TIMC-IMAG UMR 5525/Themas; P. Bedouch, PharmD, PhD, Pharmacy Department, University Hospital, and the University Grenoble-Alpes/CNRS/TIMC-IMAG UMR 5525/Themas; B. Allenet, PharmD, PhD, Pharmacy Department, University Hospital, and the University Grenoble-Alpes/CNRS/TIMC-IMAG UMR 5525/Themas.*

*Address correspondence to B. Allenet, Centre Hospitalier Universitaire de Grenoble, Service Pharmacie, CS 10217, 38043 Grenoble, France. E-mail: BAllenet@chu-grenoble.fr*

*Accepted for publication January 6, 2016.*

continuity, which refers to "persistence"[12]. Adherence is an emerging aspect in the field of rheumatology, particularly among patients with CIRD treated with biologics[13]. In a review by Koncz, *et al*, compliance rates ranged between 63% and 90% and persistence decreased steeply over time[14]. Another review from Blum, *et al* gave an overall range of persistence of 32.0% to 90.9% after 12 months of treatment[15].

Poor adherence may undermine the potential therapeutic benefits of biologics by contributing to treatment failure, progression of disease, and potential comorbidities[16,17]. Moreover, the economic burden of nonadherence is high given the high cost of biologics and the lack of benefits from partial treatment[18]. Therefore, identifying the reasons for this lack of adherence is a priority. Several authors have studied the association between adherence to biologics (estimated from pharmacy records) and some factors related to patients with CIRD, the disease, or the treatment[19,20,21,22], but to our knowledge none have used patient self-report to assess reasons for SD.

Between December 2011 and February 2012, we performed a preliminary qualitative analysis of medication adherence of patients receiving biologic therapy[23] and revealed 5 main categories to explain this behavior. The main objective of our present study was to confirm the previous figures and identify predictive factors of SD among patients with CIRD. We expected that chronology of the disease and treatments, healthcare organization, previous experiences, beliefs, relationship between the patient and the healthcare provider, perception of social support, and self-efficacy were related to SD.

## MATERIALS AND METHODS

*Design and study population*. Ours was a prospective descriptive study. A self-report questionnaire was developed in March 2012 based on the initial qualitative phase[23]. The questionnaire consisted of closed-ended and multiple choice questions grouped into 5 categories: (1) disease-induced impairment, (2) drug regimen complexity, (3) demographic and socioeconomic characteristics of the patient, (4) relation between the patient and the healthcare system, and (5) the patient's own resources (knowledge, beliefs, experience, motivation). The questionnaire was tested in May and June 2012 on 10 patients from the Rheumatology Clinic of the Grenoble University Hospital. After validation, the questionnaire was posted on the Internet and the link was sent by e-mail to the members of 3 major French patient associations: *Association Nationale de Défense contre l'Arthrite Rhumatoïde* (3500 members), *Association Française de Lutte Anti-Rhumatismale* (3000 members), and *Association France Spondylarthritites* (750 members). Data were collected between June 16, 2012, and July 4, 2012. Inclusion criteria were age > 18 years and CIRD treated (or formerly treated) with at least 1 biologic DMARD. All concomitant treatments were allowed.

We left the questionnaire posted online until we reached around 10% of respondents from the initial potential pool of targeted patients.

*Measurements*. Various methods, direct or indirect, are approved to measure medication adherence[24]. In our quantitative analysis, we decided to look at the "SD" of biologics, which was better adapted to our self-declaration model than "nonadherence."

*Assessment of discontinuation and SD*. We defined discontinuation as stopping injections of a biologic either definitively, with possibly a switch to another biologic, or temporarily. Discontinuation was assessed in 2 distinct parts of the questionnaire. First, patients were asked to name their first biologic and whether this therapy was still in progress. If not, they were asked to explain the reason for the discontinuation and who had decided on it ("the physician," "in agreement with the physician," "alone and then validated by the physician," or "alone without validation by the physician"). These questions had to be answered for each biologic used. Second, patients were asked if they had already tried to space out the injections of their biologic(s). If so, they were asked the name of the specific biologic and to explain the reason behind the interruption, who made the decision, and the duration of the break (questionnaire available from the authors on request).

SD was defined as the patient's decision to stop biologic injections. Patients were considered "SD patients" if they declared having discontinued their biologic injections by themselves ("alone" or "alone and then validated by a physician"), with the exception of patients who declared having spaced out their injections because of a sign of infection or planned surgery (situations where the action was considered appropriate).

*Exploration of reasons for SD*. A total of 21 different factors grouped into 3 domains were tested with SD patients in the univariate analysis:

(1) Sociodemographic data (6 factors): age, sex, marital status, work status, highest level of study, and place of residence.

(2) Pain, type of CIRD, disease duration, time to diagnosis, time since first biologic, number of biologic lines, number of physicians consulted since first symptoms.

(3) Medical and therapeutic history (7 factors): pain over the last 8 days assessed by a visual analog scale (VAS) from 0 (no pain) to 10 (maximum pain), type of CIRD (RA, AS, PsA, or other), disease duration, time to diagnosis, time since first biologic, number of biologic lines, and number of physicians consulted since first symptoms. We defined a "biologic line" as each biologic drug treatment 1 patient had during their medication history (1 patient could accumulate several biologic lines).

(4) Management of biologics in daily life (8 factors):

- Management of biologic administration: the person who administered the biologic ("myself," "a carer," "a nurse," or "other").
  - Previous experience of treatment: Side effects with biologic drugs and consequences on daily life (4-level scale); and use of complementary and alternative medicines (CAM).
- Beliefs and perceptions about the efficacy of the biologic and side effects. From the qualitative analysis data, a series of 14 questions were developed to assess beliefs about disease and treatment among patients with CIRD receiving biologics. After a factorial analysis, questions were grouped into 5 factors:
  - Beliefs about treatments (3 statements: "In the past 3 months, I sometimes did not take my biologics because I feel that my treatment hurt me more than did good to me," "In the past 3 months, I sometimes did not take my biologics because certain weeks I was not convinced of its benefits," "In general, I find that drug treatment is poison.")
  - Perception of self-efficacy of self-injection (2 statements: "I'm afraid to make injections by myself," "I feel capable of making my injections.")
  - Perception of treatment efficacy (3 statements: "Concerning my daily routine I globally need help of a third person," "Thanks to my biologics, I was able to go back to a regular activity," "With the treatment I see things in a positive way.")
  - Medical and social support (3 statements: "In general, I feel involved by my doctor in the choice of my medical care," "My objective with the treatment is to be cured," "Close relatives and friends help me to pursue my treatment.")
  - Expected objective of the treatment (3 statements: "When I stop my biologics, I feel consequences in my body," "The perspective of suffering frightens me," "My objective with the treatment is to run a normal life.")

*Statistical analyses*. Categorical data are reported as frequency and percentage, and continuous data as average or median when appropriate.

Regarding data on patients' beliefs and perceptions about treatment efficacy and side effects, an exploratory factor analysis of the questionnaire was conducted using the nonorthogonal (Direct Oblimin) method of rotation as recommended by Kline[25] and Cattell[26]. Results showed a 5-factor solution as suggested by factor scree plot explaining 59% of the variance. Then scores were calculated by adding items from each factor (or subgroup), with the hypothesis that the higher the score, the more likely patients were to self-discontinue. Univariate analyses were performed to compare characteristics between patients with RA and patients with AS, and between SD patients and other patients. The chi-square test was used for categorical data or the Fisher's exact test when appropriate, and the Student t test was used for continuous data (only for belief scores) or the Mann-Whitney U test when appropriate. The independent SD factors were tested using multivariate logistic regression, entering only variables associated with SD with a p value < 0.2 in univariate analysis. A backward stepwise selection was then performed to give the final model, which included only significant variables. The OR for SD against no SD and the associated 95% CI are reported for these variables. We considered p values < 0.05 significant. Statistical analyses were performed with STATA 12.0 (StataCorp).

This research was approved by the CECIC ("comité d'éthique des centres d'investigations cliniques") Rhône-Alpes Auvergne (No. IRB: 5891).

## RESULTS

*Characteristics of the population*. Out of the 606 patients who responded to the questionnaire during the inclusion period, 581 were retained. Twenty-five patients were excluded: 15 answered twice, 9 gave inconsistent and/or inadequate data, and 1 was under 18 years old. From the majority of patients, 60.4% had AS (351/581), 33.7% RA (196/581), 5.2 PsA (30/581), and 0.7% other CIRD (4/581). Results were reported according to 3 groups: AS group (n = 351), RA group (n = 196), and other CIRD group (n = 34).

*Sociodemographic data*. The median age was 46 (42 for AS, 55 for RA, and 49 for other CIRD). Sociodemographic characteristics are presented in Table 1. All counties in France except 8 were represented, indicating a good geographical distribution of our sample throughout the country.

*Medical and therapeutic history*. The mean duration of the disease since first symptoms was 14.9 years for the AS group, 16.5 years for the RA group, and 18.5 for the other CIRD group. The mean time between first symptoms and diagnosis for the AS, RA, and other CIRD groups was 5.9 years, 2.5 years, and 5.9 years, respectively. Finally, the mean period between diagnosis and the first biologic line tried was 5.3 years, 8.5 years, and 6.1 years, respectively.

Average pain over the previous 8 days was estimated as 4.2/10 on the VAS, 4.5/10 for the AS group, 3.8/10 for the RA group, and 4.1 for the other CIRD group (p = 0.002). Patients reported having consulted an average of 4.7 different physicians since their first symptoms. A total of 1044 biologic lines were described (for each patient, this corresponded to a sequence of 1 or more biologic drugs), with a median of 2 biologic lines per patient (range from 1 to 7). The most cited biologics were etanercept (37.4%, 390/1044 biologics), adalimumab (29.8%, 311/1044), and infliximab (19.6%, 205/1044) for the AS group (39.8%, 33.6%, and 23.2%, respectively), RA group (33.7%, 23.4%, and 12.9%), and other CIRD group (36.4%, 31.8%, and 25.8%).

*Management of biologic administration*. A large majority of patients self-administered their biologic: 72.5% (235/324) for the AS group, 58.3% (102/175) for the RA group, and 76.7% for the other CIRD group (23/30; p = 0.003).

*Previous experiences*. Seventy-four percent of patients with AS (243/326), 63.6% of patients with RA (112/176), and 86.7% of patients with other CIRD (26/30) reported having already felt side effects (p = 0.006), and more than 85% agreed that it had disrupted their daily activities. CAM use was reported among 55.7% of patients with AS (177/318), 42.9% of patients with RA (72/168), and 66.7% of patients with other CIRD (20/30; p = 0.007).

*Patients' beliefs and perceptions about the efficacy of biologics and side effects*. Scores were calculated for each factor with the hypothesis that the higher the score, the more patients actually experienced SD (Table 2).

*Discontinuation*. About 74% of patients discontinued their biologics (431/581) at least once, and 79% of biologic lines were discontinued (823/1044). Among these discontinuations, 56.7% involved a switch to another biologic (467/823), 13.1% were definitive (108/823), and 30.1% were restarted (248/823). Regarding patients who restarted biologics, 39.6% (203/581) declared having spaced out their biologic injections, with a mean gap of 24.1 days. Among the 431 patients who discontinued their biologics at least once, 86 patients were included in the SD group, which means that 20% of discontinuations were the patient's decision.

Among the 581 patients of our study, 14.8% experimented with SD. Fifty-seven percent (49/86) were patients with AS, 36% (31/86) were patients with RA, and 7% (6/86) were patients with other CIRD (p = 0.638), representing about 10% of biologic lines (112/1044). Reasons for these SD are presented in Table 3.

*Factors related to SD*. Factors significantly related to SD by univariate analysis (for a p value < 0.05) were more than 1 line of biologics tested, self-administered biologics, use of CAM, negative beliefs about treatment, and lack of medical and social support (Table 4 and Table 5). Significant factors related to SD in the univariate model for a p value < 0.2 were entered into the multivariate model. Factors associated with SD in our sample of patients with CIRD (for a p value < 0.05) were lower level of pain, more than 1 line of biologics tried, self-administered biologics, negative beliefs about treatment, and lack of perceived medical and social support.

Type of CIRD or sex were not associated to adherence.

## DISCUSSION

In our study, 14.8% of patients with CIRD self-discontinued their biologics. Five predictive factors of this SD were identified: pain (low level), treatment history (more than 1 line of biologics tried), self-administration of injections,

*Table 1*. Sociodemographic characteristics. Values are n (%) unless otherwise specified.

| Characteristics | All Diseases, n = 581 | RA, n = 196 | AS, n = 351 | Other CIRD, n = 34 | p |
|---|---|---|---|---|---|
| Female sex | 434 (74.7) | 164 (83.7) | 245 (69.8) | 25 (73.5) | 0.002 |
| Marital status | | | | | |
| Married | 326 (56.1) | 118 (60.2) | 195 (55.6) | 13 (38.2) | < 0.001 |
| Living with someone | 97 (16.7) | 26 (13.3) | 68 (19.3) | 3 (8.8) | |
| Single | 95 (16.3) | 22 (11.2) | 62 (17.7) | 11 (32.3) | |
| Divorced | 49 (8.4) | 19 (9.7) | 23 (6.6) | 7 (20.6) | |
| Widowed | 14 (2.4) | 11 (5.6) | 3 (0.8) | 0 (0.0) | |
| Children, yes | 426 (73.3) | 157 (80.1) | 247 (70.4) | 22 (64.7) | 0.024 |
| Work status | | | | | |
| Active | | | | | < 0.001 |
| Permanent employment | 258 (44.6) | 55 (28.5) | 189 (53.8) | 14 (41.18) | |
| Self-employed | 29 (5.0) | 8 (4.1) | 18 (5.1) | 3 (8.8) | |
| Temporary employment | 26 (4.5) | 3 (1.5) | 23 (6.6) | 0 (0.0) | |
| Unemployed | 37 (6.4) | 11 (5.7) | 25 (7.1) | 1 (2.9) | |
| Others | 2 (0.3) | 2 (1.0) | 0 (0.0) | 0 (0.0) | |
| Inactive | | | | | |
| Temporary or definitive cessation of work | 107 (18.5) | 38 (19.6) | 61 (17.4) | 8 (23.5) | |
| Retired | 105 (18.2) | 68 (35.2) | 29 (8.3) | 8 (23.5) | |
| In training | 9 (1.6) | 4 (2.1) | 5 (1.4) | 0 (0.0) | |
| Others | 5 (0.9) | 4 (2.1) | 1 (0.3) | 0 (0.0) | |
| Level of study | | | | | |
| No academic qualification, or school-leaving certificate only | 30 (5.2) | 7 (3.6) | 20 (5.7) | 3 (8.8) | 0.028 |
| High school graduation | 238 (40.9) | 90 (45.9) | 138 (39.3) | 10 (29.5) | |
| Higher education, undergraduate degree, or vocational training | 313 (53.9) | 99 (50.5) | 193 (55) | 21 (61.7) | |

RA: rheumatoid arthritis; AS: ankylosing spondylitis; CIRD: chronic inflammatory rheumatic diseases.

*Table 2*. Patients' beliefs and perceptions about the efficacy of biologics and side effects. Values are mean (median, minimum–maximum) unless otherwise specified.

| Various Subgroups | All Patients | SD Patients | Other Patients | p |
|---|---|---|---|---|
| Beliefs about treatments, out of 12 patients, high score = negative beliefs | 5.6 (5, 3–12) | 6.8 (7, 3–12) | 5.4 (5, 3–12) | < 0.001 |
| Perception of SE of self-injections, out of 8 patients, high score = low SE perceived | 3.8 (3, 2–8) | 3.6 (3, 2–8) | 3.9 (3.5, 2–8) | 0.253 |
| Perception of treatment efficacy, out of 12 patients, high score = low efficacy perceived | 6.0 (6, 3–12) | 6.0 (6, 3–12) | 6.0 (6, 3–11) | 0.927 |
| Medical and social support, out of 12 patients, high score = lack of support | 6.4 (6, 3–12) | 6.9 (7, 3–11) | 6.3 (6, 3–12) | 0.003 |
| Expected objective of the treatments, out of 12 patients, high score = negative expected objective | 6.1 (6, 3–11) | 6.1 (6, 3–9) | 6.1 (6, 3–11) | 0.810 |

SD: self-discontinuation; SE: self-efficacy.

*Table 3*. Reasons for self-discontinuation.

| Reasons* | n = 112 | % |
|---|---|---|
| "I felt better." | 43 | 38.4 |
| "I felt side effects." | 32 | 28.6 |
| "Treatment didn't work." | 15 | 13.4 |
| "I was fed up." | 10 | 8.9 |
| "I was afraid about health effects." | 8 | 7.1 |
| Other reason | 4 | 3.6 |

* One reason per discontinued biologic.

negative beliefs about treatment, and lack of perceived medical and social support.

Only 1 study, from Bluett, *et al*[17], used a self-reported questionnaire to quantify nonadherence, defined as whether the previously due dose of biologic therapy was reported as not taken on the day agreed with the healthcare professional. To our knowledge, even if our questionnaire was validated on a small sample, our study is the only one trying to predict nonadherence with a self-questionnaire, exploring treatment management, previous experiences, and patient's beliefs and

*Table 4*. Variables associated with SD in univariate analysis for a p value < 0.2 and included in the multivariate analysis.

| Various Factors | All Patients, n = 581, n (%) | SD Patients, n = 86, n (%) | Others, n = 495, n (%) | p |
|---|---|---|---|---|
| Pain, VAS between 0 and 4 | 316 (54.4) | 55 (63.9) | 261 (52.7) | 0.054* |
| Time since first symptoms, longer than 10 yrs | 361 (63.3) | 58 (69.9) | 303 (62.2) | 0.181* |
| No. biologics tried, more than 1 line | 299 (51.8) | 55 (63.9) | 244 (49.7) | 0.015 |
| Person who does the injection, self-administration | 360 (68.0) | 67 (77.9) | 293 (66.1) | 0.032 |
| Experiences of side effects | 381 (71.6) | 68 (79.1) | 313 (70.2) | 0.096* |
| Consumption of alternative medicine | 269 (52.1) | 53 (62.3) | 216 (50.1) | 0.039 |
| Factors about "patient's beliefs and perceptions about treatment efficacy and side effects" | All Patients, Mean (Median, Min–Max) | SD Patients, Mean (Median, Min–Max) | Other Patients, Mean (Median, Min–Max) | p |
| Beliefs about treatments, out of 12 patients, high score = negative beliefs | 5.6 (5, 3–12) | 6.8 (7, 3–12) | 5.4 (5, 3–12) | < 0.001 |
| Medical and social support, out of 12 patients, high score = lack of support | 6.4 (6, 3–12) | 6.9 (7, 3–11) | 6.3 (6, 3–12) | 0.003 |

* Factor not significant in univariate analysis (p > 0.05) but included in multivariate analysis (because p < 0.2). SD: self-discontinuation; VAS: visual analog scale.

*Table 5*. Variables associated to self-discontinuation in univariate and multivariate analysis.

| Variable | Univariate Analysis OR (95% CI) | p | Multivariate Analysis OR (95% CI) | p |
|---|---|---|---|---|
| Pain, VAS between 0 and 4 | 1.59 (0.99–2.56) | 0.054 | 2.00 (1.19–3.38) | 0.009 |
| No. biologics tried, more than 1 line | 1.80 (1.12–2.89) | 0.015 | 2.01 (1.20–3.36) | 0.008 |
| Person administering biologic, self-administration | 1.81 (1.05–3.12) | 0.032 | 1.82 (1.02–3.26) | 0.044 |
| Experienced side effects | 1.61 (0.92–2.80) | 0.096 | NS | NS |
| Use of alternative medicine | 1.65 (1.02–2.66) | 0.039 | NS | NS |
| Beliefs about treatments, score 1–12 | 1.40 (1.25–1.57) | < 0.001 | 1.43 (1.27–1.61) | < 0.001 |
| Medical and social support | 1.23 (1.07–1.42) | 0.003 | 1.17 (1.00–1.36) | 0.046 |

VAS: visual analog scale; NS: not significant.

perceptions about treatment to determine reasons for nonadherence among patients with CIRD.

Our sample came from 3 patients' associations: 1 composed of patients with RA, 1 of patients with AS, and 1 of all types of CIRD. Compared with patients with CIRD in a US cohort, the median age of patients with AS and patients with RA was similar (42 and 55 years in our study vs 43 and 50 years in the US study, respectively), but the sex ratio was very different, with a predominance of women (0.4, 0.2, and 0.4 vs 1.5, 0.3, and 1.00, respectively)[27]. Further, we also had more patients with AS in our sample than in a French cohort (60.4% vs 41.6%, respectively) and fewer patients with RA (33.7% vs 50%)[28]. These differences may be explained by our use of the Internet, which may be more accessible for younger people, such as patients with AS, and also by the overrepresentation of women in the patient associations we targeted. The need to use the Internet may have also selected patients with better educational and social status, which was higher in our study compared with the national data (the National Institute for Statistics and Economic Studies, 2009).

Out of the 581 patients included, about 15% self-discontinued. This estimate is in the same range as that of Bluett, *et al* (27% of self-declared nonadherence, all causes confounded)[17]. Our results are in the lower range of rates found in the literature[14]; it may be underestimated because the rate of SD was based on self-reports that required patients to recall details of past experiences (such as dates and names of drugs). Moreover, we should not forget the social desirability bias, whereby patients report an overly optimistic estimate of their adherence to treatment[29].

Concerning our sample size, we consider that the maximum number of explanatory variables that can be included in a multivariate model is 1 for 10 to 15 events (to avoid the risk of overadjustment). In our study, we identified 86 events (86 patients who experimented with SD); therefore, we could include 9 variables maximum in our multivariate analysis. In practice, we included 8 variables (or factors) because these were significantly related to SD for a p value < 0.2 in our univariate analysis (on the 21 factors tested). Finally, a backward stepwise selection was then performed to give the final model, with 5 independent SD factors (for a p value < 0.05).

The first factor related to SD in our study was pain. The more pain the patient experienced, the better their adherence to their biologic. This correlation was independent of the type of disease. Similar results have been reported in fibromyalgia[30]. However, pain was measured over the last 8 days, while participants may have discontinued their biologics far longer ago. Further investigation should analyze the evolution of pain during time and its link to adherence. Relief from pain could be interpreted by the patient as a remission, which may lead to discontinuation[11,31]. In contrast, pain leading up to the next injection may be perceived as a treatment efficacy, which is the most influential factor for longterm persistence according to Brod, *et al*[32].

The duration of therapy seems to be a major component of adherence. Our results show that the number of different lines of therapy tried by the patient is an independent factor for discontinuation. Persistence to biologic treatments decreases with time, as Koncz, *et al* reported in a review of the literature[14].

According to the literature, the previous experience of side effects is also a major driver of discontinuation[32,33,34]. In our study, more than 70% of patients declared having already felt side effects. However, no significant correlation with SD was found.

There is little evidence of the link between CAM and adherence. Our univariate analysis suggests that patients who self-discontinued were more likely to use CAM than others. Westhoff and Zink showed that a preference for CAM was the strongest risk predictor of lack of adherence to DMARD therapy among patients with RA[35]. In our multivariate model, this relationship does not remain significant.

In our study, patients who self-administered their biologics were also more predisposed to discontinue their biologics compared with patients whose injection was given by someone else. A qualitative study has suggested that the most critical period concerning adherence to self-injectable treatment is the first month of therapy[32]. During this period, patients need encouragement and support to continue self-administered treatment.

The relationship between drug adherence and beliefs about medication among patients with RA was described by Neame, *et al* using the Belief about Medicines Questionnaire[36]. In line with this, we concluded a significant correlation between negative beliefs and SD (impression that treatment hurts more than does good, and that it is like a poison).

Further, we found that medical and social support were significantly related to SD, which suggests that a supportive environment may improve adherence to a biologic. Regarding internal resources, we found no significant correlation between self-efficacy and SD in our study, although the literature reports this factor as an important determinant of adherence[37,38]. However, de Klerk, *et al*[37] and Brus, *et al*[38] assessed self-efficacy among patients with conventional DMARD only and did not use the same questionnaire.

Our study identified several components of SD behavior among patients with CIRD receiving biologics. Pain, treatment history, self-administration of injections, beliefs about treatment, and medical and social support are all factors to take into consideration when a patients with CIRD is prescribed a biologic. These patterns may be useful to better target patients who are more likely to discontinue their biologics by themselves, and to adapt our patient education programs. In the light of these predictive factors of SD, we have identified 3 major educational objectives for patients with CIRD receiving biologics: (1) to improve knowledge about the efficacy and side effects of biologics, and to identify and help modify negative beliefs, (2) to enhance medical and social support, especially during the first month of self-administered therapy, and (3) to enhance motivation over the longterm with the implementation of a regular followup program to ensure longterm adherence.

## ACKNOWLEDGMENT

We thank the staff of the research laboratory *Techniques de l'Ingénierie Médicale et de la Complexité - Informatique, Mathématiques et Applications, Grenoble*; the patients' associations *Association Nationale de Défense contre l'Arthrite Rhumatoïde*, *Association France Spondylarthritites*, and *Association Française de Lutte Anti-Rhumatismale*, and the Rheumatology Outpatient Clinic team at the Grenoble University Hospital. We also thank Dr. Alison Foote (Grenoble Clinical Research Centre) for critical reading and editing of the manuscript.

## REFERENCES

1. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis [review]. Lancet 2007;370:1861-74.
2. Bingham CO 3rd. Emerging therapeutics for rheumatoid arthritis. Bull NYU Hosp Jt Dis 2008;66:210-5.
3. Krishnan E, Lingala B, Bruce B, Fries JF. Disability in rheumatoid arthritis in the era of biological treatments. Ann Rheum Dis 2012;71:213-8.
4. Hetland ML, Lindegaard HM, Hansen A, Podenphant J, Unkerskov J, Ringsdal VS, et al. Do changes in prescription practice in patients with rheumatoid arthritis treated with biological agents affect treatment response and adherence to therapy? Results from the nationwide Danish DANBIO Registry. Ann Rheum Dis 2008;67:1023-6.
5. Glintborg B, Ostergaard M, Krogh NS, Dreyer L, Kristensen HL, Hetland ML. Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. Ann Rheum Dis 2010;69:2002-8.
6. Pavelka K, Forejtova S, Stolfa J, Chroust K, Buresova L, Mann H, et al. Anti-TNF therapy of ankylosing spondylitis in clinical practice. Results from the Czech national registry ATTRA. Clin Exp Rheumatol 2009;27:958-63.
7. Simard JF, Arkema EV, Sundström A, Geborek P, Saxne T, Baecklund E, et al. Ten years with biologics: to whom do data on effectiveness and safety apply? Rheumatology 2011;50:204-13.
8. Gómez-Reino JJ, Rodríguez-Lozano C, Campos-Fernández C, Montoro M, Descalzo MÁ, Carmona L; BIOBADASER 2.0 Study Group. Change in the discontinuation pattern of tumour necrosis factor antagonists in rheumatoid arthritis over 10 years: data from the Spanish registry BIOBADASER 2.0. Ann Rheum Dis 2012;71:382-5.

9. Glintborg B, Østergaard M, Krogh NS, Tarp U, Manilo N, Loft AG, et al. Clinical response, drug survival and predictors thereof in 432 ankylosing spondylitis patients after switching tumour necrosis factor α inhibitor therapy: results from the Danish nationwide DANBIO registry. Ann Rheum Dis 2013;72:1149-55.
10. Saad AA, Ashcroft DM, Watson KD, Hyrich KL, Noyce PR, Symmons DP; British Society for Rheumatology Biologics Register. Persistence with anti-tumour necrosis factor therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology Biologics Register. Arthritis Res Ther 2009;11:R52.
11. Duftner C, Dejaco C, Larcher H, Schirmer M, Herold M. Biologicals in rheumatology: Austrian experiences from a rheumatic outpatient clinic. Rheumatol Int 2008;29:69-73.
12. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: terminology and definitions. Value Health 2008;11:44-7.
13. Goldberg EL, Dekoven M, Schabert VF, Coyle A. Patient medication adherence: the forgotten aspect of biologics. Biotechnol Healthc 2009;6:39-44.
14. Koncz T, Pentek M, Brodszky V, Ersek K, Orlewska E, Gulacsi L. Adherence to biologic DMARD therapies in rheumatoid arthritis. Expert Opin Biol Ther 2010;10:1367-78.
15. Blum MA, Koo D, Doshi JA. Measurement and rates of persistence with and adherence to biologics for rheumatoid arthritis: a systematic review. Clin Ther 2011;33:901-13.
16. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964-75.
17. 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;54:494-9.
18. Hughes D, Cowell W, Koncz T, Cramer J; International Society for Pharmacoeconomics & Outcomes Research Economics of Medication Compliance Working Group. Methods for integrating medication compliance and persistence in pharmacoeconomic evaluations. Value Health 2007;10:498-509.
19. Borah BJ, Huang X, Zarotsky V, Globe D. Trends in RA patients' adherence to subcutaneous anti-TNF therapies and costs. Curr Med Res Opin 2009;25:1365-77.
20. Curkendall S, Patel V, Gleeson M, Campbell RS, Zagari M, Dubois R. Compliance with biologic therapies for rheumatoid arthritis: do patient out-of-pocket payments matter? Arthritis Rheum 2008;59:1519-26.
21. Grijalva CG, Chung CP, Arbogast PG, Stein CM, Mitchel EF Jr, Griffin M. Assessment of adherence to and persistence on disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis. Med Care 2007;45 Suppl 2:S66-76.
22. Harley CR, Frytak JR, Tandon N. Treatment compliance and dosage administration among rheumatoid arthritis patients receiving infliximab, etanercept, or methotrexate. Am J Manag Care 2003;9 Suppl:S136-43.
23. Betegnie AL, Lehmann A, Baudrant M, Roustit M, Bedouch P, Grange L, et al. [Adherence to biotherapy in inflammatory rheumatism: identifying ways to better support the patient]. [Article in French. Internet. Accessed January 13, 2016.] Available from: www.freepaperdownload.us/1764/Article5569661.htm
24. 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;36:55-69.
25. Kline P. An easy guide to factor analysis. London: Routledge; 1994.
26. Cattell RB. The fallacy of five factors in the personality sphere. Psychologist 1995;8:207-8.
27. Bonafede M, Fox KM, Watson C, Princic N, Gandra SR. Treatment patterns in the first year after initiating tumor necrosis factor blockers in real-world settings. Adv Ther 2012;29:664-74.
28. Régnier-Rosencher E, Farhi D, Lebrun A, Salliot C, Dougados M, Dupin N. Factors associated with severe skin infections in patients treated with biologic therapies for inflammatory rheumatic diseases. Dermatology 2012;224:72-83.
29. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. Circulation 2009; 119:3028-35.
30. Dobkin PL, Sita A, Sewitch MJ. Predictors of adherence to treatment in women with fibromyalgia. Clin J Pain 2006;22:286-94.
31. Du Pan SM, Dehler S, Ciurea A, Ziswiler HR, Gabay C, Finckh A; Swiss Clinical Quality Management Physicians. Comparison of drug retention rates and causes of drug discontinuation between anti-tumor necrosis factor agents in rheumatoid arthritis. Arthritis Rheum 2009;61:560-8.
32. Brod M, Rousculp M, Cameron A. Understanding compliance issues for daily self-injectable treatment in ambulatory care settings. Patient Prefer Adherence 2008;2:129-36.
33. Garcia-Gonzalez A, Richardson M, Garcia Popa-Lisseanu M, Cox V, Kallen MA, Janssen N, et al. Treatment adherence in patients with rheumatoid arthritis and systemic lupus erythematosus. Clin Rheumatol 2008;27:883-9.
34. Kristensen LE, Saxne T, Nilsson JA, Geborek P. Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. Arthritis Res Ther 2006;8:R174.
35. Westhoff G, Zink A. [Basic treatment of early rheumatoid arthritis. Abstaining from rheumatological care and preferring alternative medicine increase the risk of undertreatment]. [Article in German] Z Rheumatol 2007;66:121-4,126-8.
36. Neame R, Hammond A, Deighton C. Need for information and for involvement in decision making among patients with rheumatoid arthritis: a questionnaire survey. Arthritis Rheum 2005;53:249-55.
37. de Klerk E, van der Heijde D, Landewé R, van der Tempel H, Urquhart J, van der Linden S. Patient compliance in rheumatoid arthritis, polymyalgia rheumatica, and gout. J Rheumatol 2003;30:44-54.
38. Brus H, van de Laar M, Taal E, Rasker J, Wiegman O. Determinants of compliance with medication in patients with rheumatoid arthritis: the importance of self-efficacy expectations. Patient Educ Couns 1999;36:57-64.