Adherence to and patient's knowledge of self-management of subcutaneous biologic therapy in chronic inflammatory rheumatic diseases: results of a multicentre cross-sectional study

V. Gaud-Listrat[1,2], C. Lopez-Medina[1,3,4], C. Hudry[5,6], M. Nguyen[1,5], A. Lebrun-Foisnet[1,5,6], A. Sacchi[7], S. Labatide Alanore[5,8], E. Dernis[9], P. Ledevic[1,10], J. Fechtenbaum[1,11], C. Richard-Miceli[1,3], P. Le Goux[12,13], S. Dadoun[1,6], A. Moltó[1,3], A. Blanchais-Behr[1,14], S. Neveu[1,15], M. Benhamou[16,17], B. Giraud[14,16], C. Roux[1,3], M. Dougados[1,3]

[1]Department of Rheumatology - Hôpital Cochin. Assistance Publique-Hôpitaux de Paris, Paris, France; [2]Office based in Saint Michel sur Orge, France; [3]INSERM (UMR1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité. Paris, France; [4]University of Cordoba/ IMIBIC/ Reina Sofia Hospital, Cordoba, Spain; [5]Office based in Paris, France; [6]CeSOA MGEN action sociale, Paris, France; [7]Department of Rheumatology, Hôpital de Mantes la Jolie, Mantes-la-Jolie, France; [8]Department of Rheumatology, Hôpital la Croix St Simon, Paris, France; [9]Department of Rheumatology, Centre Hospitalier du Mans, Le Mans, France; [10]Office based in Montigny le Bretonneux, France; [11]Office based in Pantin, France; [12]Office based in Puteaux, France; [13]Department of rheumatology, Hôpital Ambroise Pare, Boulogne-Billancourt, France; [14]Office based in Gif sur Yvette, France; [15]Office based in Meudon, France; [16]Department of Re-education, Hôpital Cochin, Paris, France; [17]Office based in Versailles, France. on behalf of the RHEVER network (Hospital and City in Rheumatology Network).

Abstract

Objective

Non-adherence to biologic therapy is an issue in chronic inflammatory rheumatic diseases (CIRDs) and might be related to poor patient knowledge of the risk of these therapies.Our aim here was to evaluate the level of patient adherence to and knowledge of self-care safety skills for biologic therapy.

Methods

This was a multicentre, cross-sectional study in which out-patients visited an office- or hospital-based rheumatologist. All the patients received subcutaneous biologic therapy for CIRDs. We collected data on: 1. the level of CIRD patient adherence to current subcutaneous biologic therapy using both the self-administered Compliance Questionnaire Rheumatology 5 items (CQR5) and a simple adherence question; 2. patients' knowledge of self-management of biologic therapy by the self-administered BIOSECURE questionnaire; 3. sources of information related to biologic therapy.

Results

In all, 285 patients (rheumatoid arthritis, n=103; spondyloarthritis, n=153; psoriatic arthritis, n=25) were enrolled by 19 rheumatologists. The mean (SD) biologic therapy duration was 5.9 (4.9) years. Adherence to the current biologic therapy was high (79.3% and 57.5% according to the CQR5 questionnaire and the adherence question, respectively). Level of knowledge of self-care safety skills (median BIOSECURE score 71) was in the acceptable range. Level of adherence and level of knowledge of self-care safety skills for biologic therapy were not associated. Patients declared that the main sources of information were their rheumatologist (92.6%) and the rheumatology team (30.5%).

Conclusion

According to the patients' estimation, adherence to biologic therapy and the level of knowledge of self-care safety skills related to biologic therapy are acceptable, and these domains are not related (e.g. level of adherence and level of knowledge of risks).

Key words

adherence, biologic agent, BIOSECURE questionnaire, chronic inflammatory rheumatic diseases

Véronique Gaud-Listrat, MD
Clementina Lopez-Medina, MD
Christophe Hudry, MD
Minh Nguyen, MD
Agnès Lebrun-Foisnet, MD
Antoinette Sacchi, MD
Sylvain Labatide Alanore, MD
Emmanuelle Dernis, MD
Patricia Ledevic, MD
Jacques Fechtenbaum, MD
Corinne Richard-Miceli, MD
Patrick Le Goux, MD
Sabrina Dadoun, MD
Anna Moltó, MD
Anne Blanchais-Behr, MD
Séverine Neveu, MD
Mathilde Benhamou, MD
Bernard Giraud, MD
Christian Roux, MD
Maxime Dougados, MD

Please address correspondence to:
Veronique Gaud-Listrat,
Rheumatology Department,
Cochin Hospital,
27 Rue Faubourg Saint Jacques
750014, Paris, France.
E-mail: rhumato.gaudlistrat@gmail.com

Received on December 8, 2020; accepted in revised form on April 19, 2021

Competing interests: none declared.

Introduction

The prognosis of chronic inflammatory rheumatic diseases (CIRDs) has been greatly improved during the last decades, mainly due to an early initiation of disease-modifying anti-rheumatic drugs (DMARDs) and a sustained control of the activity (*e.g.* inflammatory component of the disease) (1-5). This optimal use of disease-modifying drugs (DMARDs) reduces disease activity and radiological progression and improves long-term functional outcome, notably in rheumatoid arthritis (RA) (5, 6).

Biologic therapies have greatly improved these outcomes (*e.g.* control of disease activity, radiographic progression, long-term functional outcome). The route of administration of the biologic therapy used in rheumatology has changed during the last years, with an increasing use of the subcutaneous route (1, 4). The switch from the intravenous to subcutaneous route had several potential consequences in terms of treatment adherence. In most cases, in contrast to intravenous injections, subcutaneous injections are self-administered, without any control by the rheumatology team. Moreover, intravenous injections are sometimes performed in a rheumatology unit, which requires an iterative (*e.g.* every 4–8 weeks) stay in the hospital. During these stays, educational programmes concerning the risk-benefit ratio for the biologic therapy can be included. Therefore, the subcutaneous route of administration might affect treatment adherence for at least two reasons: no control by the rheumatology team and poor knowledge of the risk-benefit ratio for the biologic therapy.

The full benefit of pharmacological interventions and biologic therapy in particular can only be achieved if patients follow drug regimens closely. Medication adherence can be defined as "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider "(7). Adherence is low in patients with chronic medical conditions (8-17). The implications of non-adherence are far-reaching: non-adherence may severely compromise the effectiveness of treatment and increase healthcare costs (18-20). Thus, improving adherence to therapy could substantially improve the efficacy of medical treatments and reduce costs associated with CIRDs.

A recent systematic review has emphasised that curing non-adherence is challenging, and poor adherence might be prevented by several actions (21). In this area (*e.g.* preventing non-adherence), educational activities seem effective (22). A recent initiative proposed that "to optimise drug adherence, any prescription of anti-rheumatic treatment must be accompanied by patient information and education" (23).

These preliminary remarks raise the question of the concordance/association between the level of a patient's adherence to a biologic therapy and knowledge of self-care safety skills for biologic therapy.

The optimal way to measure non-adherence is debated. In daily practice, the current recommendation is to evaluate adherence at each visit by at least one open question (21, 23). For research purposes, several methods have been proposed: subjective methods such as self-reporting methods and physician's estimation; direct methods such as drug concentration; and indirect methods (*e.g.* pharmacy refill, tablet counts, electronic monitors, questionnaires) (24-33). A recent initiative proposed a self-administered questionnaire, BIOSECURE, consisting of multiple-choice questions and clinical scenarios that measures the patient's knowledge of management of biologic therapy (34).

In this study, we evaluated 1) the level of CIRD patient adherence to current subcutaneous biologic therapy, 2) the level of patient knowledge of self-care safety skills for their biologic therapy, 3) any association between the above two domains, and 4) factors associated with poor adherence and non-optimal knowledge of self-care safety skills for biologic therapy.

Materials and methods

Study design and study settings

This was an observational cross-sectional multicenter study conducted during out-patient visits to an office- or hospital-based rheumatologist. All

patients gave their informed consent to participate in this study and all collected data were anonymised.

Patients

Consecutive patients with either rheumatoid arthritis, spondyloarthritis or psoriatic arthritis were enrolled in the study by their treating rheumatologist as soon as they were older than 18 years and had received a subcutaneous biologic therapy for at least 3 months.

Data collected

The following self-administered questionnaires were collected once (just before the visit to the rheumatologist).

1) The "adherence question" "Have you ever not taken your biologic therapy according to the modalities agreed with your rheumatologist?" was self-answered on a 0- to 4-point scale, from 0, not taking it at all; 1, more than 50% of drug intakes; 2, 20% to 50% of drug intakes; 3, less than 20% of drug intakes; 4, never not taken. Patients who answered "never missing a drug intake" were considered "high adherent". Right after this simple question, the patient had to answer the following: "In case you have not taken your therapy according to the modalities agreed with your rheumatologist what was the reason(s)?" with 11 potential answers: I forgot, I was not feeling well, I felt very good (no longer need the treatment), I considered my treatment not effective, I did not tolerate the treatment, I was afraid of the side effects of this treatment, I had difficulty remembering to take this treatment, I couldn't stand taking this treatment anymore, I was not at home (vacation, travel, etc.), I no longer wanted to think about this treatment/my illness, I followed the advice of my pharmacist, dentist, or other health professional.

2) The 5-item version of the Compliance Questionnaire for Rheumatology (CQR5) (36), a short version of the CQR19 developed to measure compliance with drug regimens in rheumatic patients (37) was administered. The score allows for classifying patients as "low adherent" and "high adherent" by using Fisher's weighted regression equation: two parameters (Q for question, five questions): D0=-27.611 + (4.407*Q1) + (0.939*Q2) + (6.101*Q3) + (2.366*Q4) +(2.531*Q5), and D1=-33.304 + (2.801*Q1) +(5.008*Q2) + (6.471*Q3) + (1.215*Q4) + (3.252*Q5). If D1 is greater than D0, the respondent should be classified as likely to be high adherent, if D0 greater than D1, low adherent.

3) The BIOSECURE self-administered questionnaire was developed to check the level of knowledge of patients in terms of different situations concerning the safety issues of their biologic therapy (*e.g.*, vaccination, infection, travel, pregnancy . . .). The questionnaire has 55 questions. The final score ranges from 0 to 100, higher scores indicating better skills (34). During the elaboration and validation steps of this questionnaire, the median score was 71 (34, 35). Therefore, a score >71 was considered satisfactory.

4) Additional data were collected: a) in case of non-adherence, why patients did not take their medication as agreed upon with their rheumatologists, b) any "tricks" to avoid "forgetting" treatment intake, (four proposals: paper book, electronic agenda, no reminder needed, open answer), c) and the means deemed most useful by patients to obtain information on their treatment (seven potential answers were proposed: their rheumatologist, their pharmacist, during a therapeutic education session, their rheumatology team, any patient organisation, any website, other sources of information, with the possibility to choose up to three of the seven proposals).

The rheumatologist had to collect the following socio-demographic data (age, sex, educational level, employment status, marital status, having children and living alone), the rheumatic disease (diagnosis, age at symptom onset, disease duration) and treatments, including concomitant medication, such as the use of methotrexate and biologic DMARDs (including type, duration, dose and interval), and use of corticosteroids and non-steroidal anti-inflammatory drugs.

Statistical analysis

The level of adherence was evaluated by both the adherence question (a binary variable expressed as the percentage of patients who answered "never") and the CQR5 score (a binary variable expressed as the percentage of patients considered "high adherent").

The level of knowledge of self-care safety skills for biologic therapy (BIOSECURE score) was analysed in two ways: 1) as a continuous variable (mean ± SD, median) and 2) as a binary variable, using as a cut-off a score ≥71, representing the median in the overall population.

First, we explored the level of agreement between the two methods evaluating adherence by using Kappa and PABAK statistics (38, 39). Second, we tested the association between the level of adherence and the knowledge of self-care safety skills for biologic therapy by using the chi-square test.

Two independent univariate and multivariate logistic regressions were conducted to evaluate the variables associated with "high adherence" and "acceptable knowledge" (BIOSECURE score ≥71), respectively. The multivariate logistic regressions involved backward stepwise procedures and included variables with $p<0.20$ on univariate analysis. Interactions and confounding factors were tested and all comparisons were bilateral considering $p<0.05$ as a significant result.

Finally, additional data such as reasons for low adherence, tricks for remembering to take the biologic agent and sources of information most frequently used by the patients were described. All data are presented as mean and standard deviation (SD) for continuous variables and number (%) for categorical variables.

The statistical analysis involved using SPSS 25.0 (SPSS, Inc., Chicago, IL)

Results

Study course and patient characteristics

Between April and July 2018, 293 patients were enrolled by 19 rheumatologists. Because of a different route of administration of the biologic agent (*e.g.* intravenous in 1 patient) and missing data concerning the CQR5 questionnaire (7 patients), data for 285 patients were analysed (female: 59%, mean (SD) age: 53 (14) years, employed: 66%

Table I. Univariate analysis of factors associated with adherence to biologic therapy by high and low adherence according to the Compliance Questionnaire Rheumatology 5 items (CQR5)*.

	Total n=285	High adherent n=226 (79.3%)	Low adherent n=59 (20.7%)	OR (95%CI)**	*p*-value
Sex (female) (%)	168 (58.9)	135 (59.7)	33 (55.9)	1.17 (0.65–2.08)	0.597
Age (years), mean (SD)	52.91 (14.14)	53.56 (14.01)	50.43 (12.85)	1.02 (0.99–1.04)	0.132
University-level education (%)	177 (62.1)	139 (61.5)	38 (64.4)	0.88 (0.49–1.60)	0.682
Not working (%)	98 (34.4)	83 (36.7)	15 (25.4)	1.70 (0.89–3.25)	0.106
Have children (%)	221 (77.5)	174 (77.0)	47 (79.7)	0.85 (0.42–1.73)	0.662
Living alone (%)	80 (28.1)	69 (30.5)	11 (18.6)	1.92 (0.94–3.91)	0.074
Spondyloarthritis (%)	153 (53.7)	120 (53.1)	33 (55.9)	0.89 (0.50–1.59)	0.697
Rheumatoid arthritis (%)	103 (36.1)	81 (35.8)	22 (37.3)	0.94 (0.52–1.70)	0.837
Psoriatic arthritis (%)	25 (8.8)	22 (9.7)	3 (5.1)	2.01 (0.58–6.97)	0.270
Disease duration (years), mean (SD)	16.82 (11.57)	16.90 (11.69)	16.54 (11.16)	1.00 (0.98–1.03)	0.831
Biologic therapy (%)	285 (100)	197 (87.2)	51 (86.4)	1.07 (0.46–2.47)	0.882
Anti-TNF alpha agent (%)	248 (87.0)	197 (87.2)	51 (86.4)	1.07 (0.46–2.47)	0.882
Biologic therapy duration (years), mean (SD)	5.88 (4.89)	5.80 (4.94)	6.22 (4.73)	0.98 (0.93–1.04)	0.552
>1 year (%)	224 (78.6)	176 (77.9)	48 (81.4)	0.81 (0.39–1.67)	0.562
≥4 years (%)	159 (55.8)	120 (53.1)	39 (66.1)	0.58 (0.32–1.06)	0.075
≥2 Different biologic agents (%)	74 (25.9)	61 (27.0)	13 (22.0)	1.31 (0.66–2.59)	0.440
Interval of biologic therapy spaced out (%)	76 (26.7)	59 (77.6)	17 (28.8)	0.87 (0.46–1.65)	0.873
No concomitant treatment (%)	81 (28.4)	63 (27.9)	18 (30.5)	0.88 (0.47–1.64)	0.690
Corticosteroids (%)	21 (7.4)	16 (7.1)	5 (8.5)	0.82 (0.29–2.34)	0.715
BIOSECURE score, mean (SD)***	69.86 (13.18)	69.34 (69.33)	71.87 (12.17)	0.98 (0.96–1.01)	0.189
BIOSECURE score ≥ 71 (cut-off) (%)	137 (48.1)	107 (47.3)	30 (50.8)	0.87 (0.49–1.54)	0.632

OR: odds ratio; 95% CI: 95% confidence interval; SD: standard deviation; TNF: tumour necrosis factor.
*high adherent: D1>D0, low adherent D0>D1.
**Univariate logistic regression.
***level of knowledge of safety issues of biologic therapy, a higher score indicating better knowledge.

(Table I). The underlying rheumatological disease was RA (36%), SpA (54%) or PsA (9%), with a mean disease duration of 17 (11) years. The mean duration of the current biologic therapy was 6 (5) years and was administered as at least the second biologic agent in 74 (26%) patients.

Methotrexate was co-administered with the current biologic agent in 116 (40.7%) patients (75.7%, 13.7%, and 60.0 % with RA, SpA and PsA, respectively). The current biologic agent was etanercept (n=131, 46.0%), adalimumab (n=75, 26.3%), golimumab (n=26, 9.1%), certolizumab (n=16, 5.6%), abatacept (n=14, 5.0%), secukinumab (n=13, 4.6%), tocilizumab (n=8, 2.8%) and ustekimumab (n=2, 0.7%).

Level of knowledge of adherence of biologic therapy

1) Using the "adherence question" "Have you ever not taken your biologic therapy according to the modalities agreed with your rheumatologist?", 164 (57.5%) patients answered "I never missed a dose", and were considered highly adherent.

The other answers were as follow: "I missed less than 20% of the doses" (n=100, 35.1%), "I missed between 50 and 20% of the doses" (n=16, 5.6%), "I missed at least 50% of the doses" (n=3, 1.1%), and "I never took the prescribed biologic agent" (n=2, 0.7%).

2) Using the CQR5, 226 (79.3%) patients were considered at high adherence.

However, the level of agreement between the two methods evaluating the adherence was low (Kappa=0.092) (38).

Table II. Association between level of adherence to and knowledge of self-management of biologic therapy.

A: Adherence defined by the adherence question

		Level of knowledge (BIOSECURE score ≥71)	
		Yes	No
High adherent*	Yes	72	92
	No	65	56

*Patients answering "never" to the question "Have you ever not taken your biologic therapy according to the modalities agreed with your rheumatologist?"
Chi-square test: p=0.101

B: Adherence defined by the Compliance Questionnaire Rheumatology 5 items (CQR5)*

		Level of knowledge (BIOSECURE score ≥71)	
		Yes	No
High adherent*	Yes	107	119
	No	30	29

Chi-square test: p=0.632. *D1 greater than D0, (Q for question, 5 questions)
D0 = -27.611 + (4.407*Q1) + (0.939*Q2) + (6.101*Q3) + (2.366*Q4) +(2.531*Q5)D1=-33.304 + (2.801*Q1) +(5.008*Q2) + (6.471*Q3) + (1.215*Q4) + (3.252*Q5).

Table III. Univariate and multivariate logistic regression analysis of factors associated with high adherence according to the adherence question*.

	High adherence n=164 (57.5%)	Low adherence n=121 (42.5%)	Univariate analysis OR (95%CI)	*p*-value	Multivariate analysis OR (95%CI)	*p*-value
Sex (female) (%)	102 (62.2)	66 (54.5)	1.37 (0.85–2.21)	0.195		
Age (years), mean (SD)	53.58 (15.02)	52.0 (12.85)	1.01 (0.99–1.03)	0.350		
≥52 (%)	89 (54.3)	58 (47.9)	1.29 (0.81–2.06)	0.291		
≤30 (%)	6 (3.7)	4 (3.3)	1.11 (0.31–4.03)	0.873		
University level education (%)	98 (59.8)	79 (65.3)	0.79 (0.49–1.19)	0.342		
Not working (%)	67 (40.9)	31 (25.6)	2.01 (1.2–3.35)	0.008	2.56 (1.47–4.45)	0.001
Have children (%)	124 (75.6)	97 (80.2)	0.77 (0.43–1.36)	0.363		
Living alone (%)	43 (26.2)	37 (30.6)	0.81 (0.48–1.36)	0.419		
Spondyloarthritis (%)	90 (54.9)	63 (52.1)	1.12 (0.79–1.79)	0.638		
Rheumatoid arthritis (%)	61 (37.2)	42 (34.7)	1.11 (0.68–1.82)	0.666		
Psoriatic arthritis (%)	12 (7.3)	13 (10.7)	0.66 (0.29–1.49)	0.315		
Disease duration (years), mean (SD)	15.42 (11.14)	18.72 (11.91)	0.98 (0.96–0.99)	0.019	0.98 (0.95–0.99)	0.044
Disease duration <15 years (%)	91 (55.5)	53 (43.8)	1.60 (0.99–2.57)	0.052		
Anti-TNF alpha agent (%)	139 (84.4)	109 (90.1)	0.61 (0.29–1.27)	0.189		
Biologic therapy duration (years), mean (SD)	5.24 (4.63)	6.76 (5.13)	0.94 (0.89–0.98)	0.011	0.94 (0.89–0.99)	0.038
>1 year (%)	125 (76.2)	99 (81.8)	0.71 (0.40–1.28)	0.256		
≥4 years (%)	83 (50.6)	76 (62.8)	0.61 (0.38–0.98)	0.041		
No concomitant treatment (%)	46 (28.0)	35 (28.9)	0.96 (0.57–1.61)	0.871		
NSAID (%)	54 (32.9)	35 (28.9)	1.21 (0.72–2.01)	0.471		
Corticosteroids (%)	13 (7.9)	8 (6.6)	1.22 (0.49–3.03)	0.675		
≥2 Different biologic agents (%)	39 (23.8)	35 (28.9)	0.77 (0.45–1.31)	0.328		
Interval of biologic therapy spaced out (%)	45 (27.4)	31 (25.6)	1.10 (0.64–1.87)	0.731		
BIOSECURE score, mean (SD)	68.94 (14.00)	71.10 (11.92)	0.99 (0.97–1.01)	0.174		
BIOSECURE score ≥ 71 (%)	72 (43.9)	65 (53.7)	0.67 (0.42–1.08)	0.102		

*"Have you ever not taken your biologic therapy according to the modalities agreed with your rheumatologist?".
Hosmer-Lemeshow test multivariate: chi-square=6.394, *p*=0.603.
OR: odds ratio; 95%CI: 95% confidence interval; NSAID: non-steroidal anti-inflammatory drugs; SD: standard deviation

For example, the answer to the adherence question for the 226 patients considered at high adherence by the CQR5 questionnaire was "I never missed a dose" (n=136,60.2%) and "I missed less than 20% of the doses," (n=81, 35.8%) and the answer to the adherence question for the 59 patients considered at moderate adherence by the CQR5 questionnaire was "I never missed a dose", (n=28, 47.5%) and "I missed less than 20% of the doses" (n=19, 32.2%).

The association between the level of adherence and level of knowledge of self-management of biologic therapy is summarised in Table II. The mean (SD) BIOSECURE score was 68.9 (14.0) *vs*. 71.1 (11.9) (*p*=0.164) and 69.3 (13.4) *vs*. 71.9 (12.2) (*p*=0.189) for patients considered at high adherence *vs*. non-high adherence by the "adherence question" and by the CQR5 questionnaire, respectively.

Variables associated with level of adherence to biologic therapy

When defining the level of adherence by referring to the CQR5 questionnaire, no single variable was identified by the analysis (Table I). When defining the level of adherence by referring to the "adherence question", short disease duration, biologic therapy duration, and absence of current professional activity were the three factors associated with high adherence (Table III).

In both analyses, the level of knowledge of self-management of biologic therapy (BIOSECURE questionnaire) was not significantly associated with level of adherence.

Level of knowledge of self-management of biologic therapy

The mean level of self-management of biologic therapy estimated by the BIOSECURE score was 70±13. The percentage of patients with a BIOSECURE score ≥71, defining a high level of knowledge of self-management, was 48.1% (n=137). The variables of high level of self-management of biologic therapy are summarised in Table IV. Better knowledge was associated with female sex, age <52 years and university-level education.

Reasons for low adherence

For patients who answered that they had not taken their therapy according to the modalities agreed upon with their rheumatologist, the reasons were as follows: I forgot (43/121, 36%), I was not feeling well, (14/121, 12%), I felt very good (no longer need the treatment) (17/121, 14%), I considered my treatment not effective (1/121, 1%),I did not tolerate the treatment (3/121, 3%), I was afraid of the side effects of this treatment (1/121, 1%), I had difficulty remembering to take this treatment (2/121, 2%), I couldn't stand taking this treatment anymore (0/121, 0%), I was not at home (vacation, travel, etc.) (39/121, 32%), I no longer wanted to think about this treatment/my illness (0/121, 0%), and I followed the advice of my pharmacist, dentist, or other health professional (16/121, 13%).

Tricks for remembering to take the biologic agent

These tricks are summarised in the Venn diagram (Fig. 1). Most patients reported that they had no particular trick (n=123,

Table IV. Univariate and multivariate logistic regression analysis of factors associated with level of knowledge of self-management of biologic therapy.

	BIOSECURE score ≥71 n=137	BIOSECURE score <71 n=148	Univariate analysis OR (95%CI)	*p*-value	Multivariate analysis OR (95%CI)	*p*-value
Sex (female) (%)	94 (68.6)	74 (50.0)	2.19 (1.35–3.54)	0.002	2.56 (1.53–4.28)	<0.001
Age (years), mean (SD)	51.09 (12.14)	54.60 (15.62)	0.98 (0.97–0.99)	0.037		
<52 (%)	77 (56.2)	61 (41.2)	1.83 (1.14–2.93)	0.012	1.92 (1.16–3.17)	0.011
≤30 (%)	3 (2.2)	7 (4.7)	0.45 (0.11–1.78)	0.256		
University level education (%)	100 (73.0)	77 (52.0)	2.49 (1.52–4.09)	<0.001	2.46 (1.47–4.12)	0.001
Not working (%)	41 (29.9)	57 (38.5)	0.68 (0.42–1.12)	0.128		
Have children (%)	108 (78.8)	113 (76.4)	1.15 (0.66–2.02)	0.616		
Living alone (%)	34 (24.8)	46 (31.1)	0.73 (0.41–1.23)	0.240		
Spondyloarthritis (%)	74 (54.0)	79 (53.4)	1.03 (0.64–1.63)	0.914		
Rheumatoid arthritis (%)	44 (32.1)	59 (39.9)	0.71 (0.44–1.16)	0.174		
Psoriatic arthritis (%)	17 (12.4)	8 (5.4)	2.48 (1.03–5.95)	0.042		
Disease duration (years), mean (SD)	15.96 (11.18)	17.62 (11.90)	0.99 (0.97–1.01)	0.229		
<15 years (%)	78 (56.9)	64 (43.2)	1.73 (1.09–2.77)	0.021		
No concomitant treatment (%)	36 (26.3)	45 (30.4)	0.82 (0.49–1.37)	0.440		
Methotrexate (%)	57 (41.6)	59 (39.9)	1.08 (0.67–1.73)	0.765		
NSAID (%)	51 (37.2)	38 (25.7)	1.72 (1.04–2.85)	0.036		
Biologic agent duration (years), mean (SD)	5.93 (4.84)	5.85 (4.95)	1.00 (0.96–1.05)	0.891		
≥4 years (%)	78 (56.9)	81 (54.7)	1.09 (0.68–1.75)	0.708		
>1 year (%)	111 (81.0)	113 (76.4)	1.32 (0.75–2.34)	0.338		
≥2 different biologic agents (%)	38 (27.7)	36 (24.3)	1.19 (0.70–2.03)	0.512		
Interval of biologic therapy spaced out (%)	37 (27.0)	39 (26.4)	1.03 (0.61–1.45)	0.900		
High adherence according to CQR5 (%)	107 (78.1)	119 (80.4)	0.87 (0.49–1.54)	0.632		

Hosmer-Lemeshow test: chi-square=3.086, *p*=0.798
OR: odds ratio; 95%CI: 95% confidence interval; NSAID: non-steroidal anti-inflammatory drugs; SD: standard deviation.

43.2%). The most frequent trick was the use of a paper agenda (n=79, 27.7%) or electronic agenda (n=80, 28, 1%). For patients using *versus* not using a trick, the proportion considered at high adherence by the adherence question and the CQR5 questionnaire did not differ: 58.6% *vs*. 56.0% (*p*=0.667) and 50.3% *vs*. 44.8% (*p*=0.364).

Sources of information concerning the risk-benefit of biologic therapy

Sources of information are summarised in the Venn diagram (Fig. 2). The treating rheumatologist was mentioned by 92.6% of patients, followed by the rheumatology team (*e.g.* during hospitalisation or educational activities) by 30.5%, from a website by 16.5% and other sources by 2.8% (family or friend, medical journals).

Discussion

This cross-sectional study suggested that in CIRDs, the level of adherence to biologic therapy and level of patient's knowledge of the self-management of their biologic therapy are acceptable. However, we did not find an association between level of adherence and level of knowledge of the self-management of biologic therapy.

This study has several weaknesses but also many strengths. How we evaluated level of adherence may be questionable. A potential weakness of this study is that we evaluated the level of adherence by not only the previously validated CQR5 questionnaire but also by a simple, not-validated question. The reason for the choice of this simple "adherence question" was to embark all the rheumatologists, busy clinicians, not expert in this field of research. With this question, they can easily discuss the results provided by their patients. In this study, we used a subjective assessment (*e.g.* patient's self-report), which is usually considered relatively insensitive for detecting non-adherence (32). However, although a wide variety of methods have been used to assess non-adherence and adherence (*e.g.* physician's estimation, drug concentrations, pharmacy refill, tablet counts, electronic monitors), a gold standard for adherence assessment is still lacking.

The level of adherence in our study could be considered at least as acceptable or highly acceptable, with 79.3% of patients considered high adherent according to the CQR5 questionnaire. These results agree with those reported in other studies evaluating the adherence of sub-cutaneous biologic therapy studies (8, 12, 30, 32). Of note, the level of adherence to biologic therapy was previously reported as better than that for conventional synthetic DMARDs (8, 17, 21, 23, 32).

The level of patient's knowledge of self-management of biologic therapy we found agrees with that previously reported (*e.g.* a median BIOSECURE score of 71 and 70 in the Gossec *et al*. study (34, 37) and our study). Although current recommendations emphasise the importance of patient's education for preventing poor adherence or non-adherence to a biologic agent, our cross-sectional study did not find a clear relation between level of adherence to biologic therapy and level of knowledge of self-management of biologic therapy. One potential explanation might be that the BIOSECURE questionnaire evaluates only one domain of the biologic agent (*e.g.* self-management of biologic therapy with regard to specific situations) and not, for example, the patient's feeling of the benefit of these treatments. Another potential explanation might be related to the design of our study. The importance

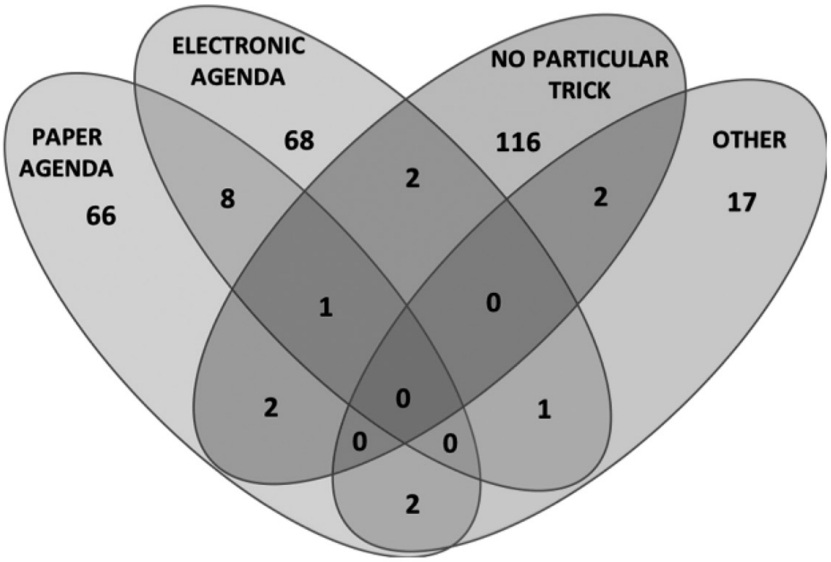

Fig. 1. Tricks for remembering to take the biologic therapy.

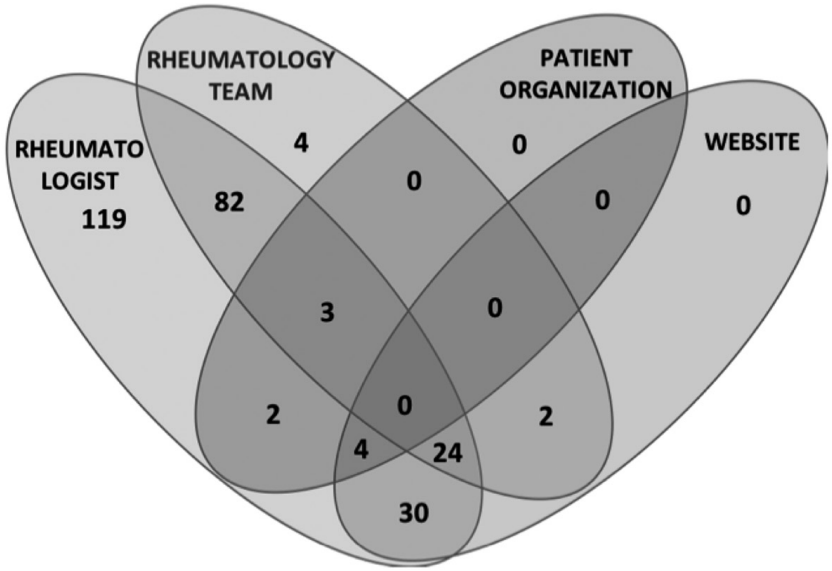

Fig. 2. Sources of information concerning the risk-benefit of biologic therapy.

of educational activities for improving adherence to biologic therapy has been suggested/demonstrated in prospective, longitudinal randomised controlled trials (8, 24, 32, 40). The design used in our study (*e.g.* cross-sectional), as others previously reported, might not be optimal in this field of research.

However, these cross-sectional studies are interesting for determining factors associated with non-optimal adherence. Several factors have been previously reported: In the Align study, (patients receiving not only biologics but also conventional synthetic DMARDs), the variables associated with high adherence: were treatment with biologic agents (*e.g.* anti-TNF) *versus* conventional synthetic DMARDs, shorter disease duration (<9 years), and older age (8, 32). In our study, no single factor was associated with non-optimal adherence by using the CQR5 questionnaire to evaluate adherence. However, when evaluating adherence with the adherence question, three factors were associated with high adherence: short disease and biologic therapy duration and lack of employment. These findings are intriguing. They might be explained by the fact that patients with a long disease duration (and probably previous exposure to biologic therapy) would be more tempted to try to taper their treatment in case such treatment is efficient after a few months of intake.

In this analysis, the level of knowledge of self-management of biologic therapy was not associated with level of adherence to the biologic agent. The factors associated with high level of knowledge of self-management of biologic therapy were female sex, young age and educational level. These patient characteristics have been previously reported in studies evaluating the level of patients' knowledge about their disease and/or treatment (7, 31)

One of the strengths of our study is the evaluation of the tricks used by the patients to remember their biologic agent intake. Most patients reported that they had no particular trick. Exploring new technologies (*e.g.* tablets, smartphones) might help improve treatment adherence. Finally, this study emphasised the importance of the rheumatology team in facilitating/improving/implementing educational programmes. These results agree with the recent published quality standards in CIRDs. For example, in SpA, both an initial review and periodic systematic reviews found strong recommendations for educational activities and evaluating treatment adherence supervised by the rheumatologist and performed by the rheumatology team (21, 23).

Further studies in other settings using different tools are required to confirm our results. These studies will probably facilitate the updating and implementation of the standard of quality to optimally manage CIRDs in daily practice.

Acknowledgements

We thank the patients who participated in the study, the RHEVER network and all its participants' rheumatologists: Veronique Gaud-Listrat, Christophe Hudry, Minh Nguyen, Agnes Lebrun-Foisnet, Antoinette Sacchi, Sylvain Labatide Alanore, Emmanuelle Dernis, Patricia Ledevic, Jacques Fechtenbaum, Corinne Richard-Miceli, Patrick Le Goux, Sabrina Dadoun, Anna Moltó, Anne Blanchais-Behr, Séverine Neveu, Mathilde Benhamou, Bernard Giraud, Christian Roux, Maxime Dougados; and our statistician, Clementina Lopez-Medina.

References

1. SMOLEN JS, LANDEWÉ R, BIJLSMA J *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017; 76: 960-77.
2. ZANGI HA, NDOSI M, ADAMAS J *et al*.: EULAR recommendations for patient's education for people with inflammatory arthritis. *Ann Rheum Dis* 2015: 74: 954-62.
3. GAUJOUX-VIALAC, GOSSEC L, CANTAGREL A *et al*.: Recommendation of the French society for rheumatology for managing rheumatoid arthritis. *Joint Bone Spine* 2014: 81 : 287-97.
4. GOSSEC L, SMOLEN JS, RAMIRO S *et al*.: European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis* 2016; 75: 499-510.
5. VANGELI E, BAKHSHI S, BAKER A *et al*.: A systematic review of factors associated with non-adherence to treatment for immune-mediated inflammatory diseases. *Adv Ther* 2015; 32: 983-1028.
6. GOSSEC L, TUBACH F, DOUGADOS M, RAVAUD P: Reporting of adherence to medication in recent randomized controlled trials of 6 chronic diseases: A systematic literature review. *Am J Med Sci* 2007; 334: 248-54.
7. WORLD HEALTH ORGANISATION: Adherence to long-term therapy: evidence for action. 2003.http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf.
8. SMOLEN JS, GLADMAN D, MCNEIL HP *et al*.: Predicting adherence to therapy in rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis: a large crosssectional study. *RMD Open* 2019; 5: e000585.
9. VAN DEN BEMT B, ZWIKKER HE, VAN DEN ENDE CH: Medication adherence in patients with rheumatoid arthritis: a critical appraisal of the existing literature. *Expert Rev Clin Immunol* 2012; 8: 337-51.
10. GRIJALVA CG, CHUNG CP, ARBOGAST PG, STEIN CM, MITCHEL EF, GRIFFIN MR: Assessment of adherence to and persistence on disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis. *Med Care* 2007; 45: S66-S76
11. ARTURI P, SCHNEEBERGER EE, SOMMERFLECK F *et al*.: Adherence to treatment in patients with ankylosing spondylitis. *Clin Rheumatol* 2013; 32: 1007-15.
12. BHOI P, BESSETTE L, BELL MJ, TKACZYK C, NANTEL F, MASLOVA K: Adherence and dosing interval of subcutaneous antitumour necrosis factor biologics among patients with inflammatory arthritis: analysis from a Canadian administrative database. *BMJ Open* 2017; 7: e015872.
13. WALLMAN JK, KAPETANOVIC MC, PETERSSON IF, GEBOREK P, KRISTENSEN LA: Comparison of non-radiographic axial spondyloarthritis and ankylosing spondylitis patients - baseline characteristics, treatment adherence, and development of clinical variables during three years of anti-TNF therapy in clinical practice. *Arthritis Res Ther* 2015; 17: 378.
14. HARLEY CR, FRYTAK JR, TANDON N: Treatment compliance and dosage administration among rheumatoid arthritis patients receiving infliximab, etanercept or methotrexate. Am J Managed Care 2003; 9: S136-44.
15. GOLDBERG EL, DEKOVEN M, SCHABERT VF, COYLE A: Patient medication adherence: the forgotten aspect of biologics. *Biotechnol Healthc* 2009; 6: 39-42.
16. LOPEZ-MEDINA C, MOLTO, GERALD F *et al*.: Assessment of the adherence to disease-modifying drugs in patients with chronic inflammatory rheumatic diseases: Results of a survey of 1594 patients. *Joint Bone Spine* 2019; 86: 610-4.
17. SALT E, FRAZIER S: Adherence to disease modifying anti-rheumatic drugs in rheumatoid arthritis patients: a narrative review of the literature. *Orthop Nurse* 2010; 29: 260-75.
18. WAIMANN C, MARENGO M, DE ACHAVAL S *et al*.: Electronic monitoring of oral therapies in ethnically diverse and economically disadvantaged patients with rheumatoid arthritis. Consequences of low adherence. *Arthritis Rheum* 2013; 65: 1421-9.
19. PASMA A, SCHENK C, TIMMAN R *et al*.: Does non-adherence to DMARDs influence hospital-related healthcare costs for early arthritis in the first year of treatment? *PLoS One* 2017; 12: 1-14.
20. HARROLD L, BRIESACHER B, PETERSON D *et al*.: Cost-related medication nonadherence in older rheumatoid arthritis patients. *J Rheumatol* 2013; 40: 1-14.
21. LAVIELLE M, PUYRAIMOND-ZEMMOUR D, ROMAND X *et al*.: Methods to improve medication adherence in patients with chronic inflammatory rheumatic diseases: a systematic literature review. *RMD Open* 2018; 4: 1-8.
22. HILL J, BIRD H, JOHNSON S: Effect of patient education on adherence to drug treatment for rheumatoid arthritis: A randomized control trial. *Ann Rheum Dis* 2001; 60: 869-75.
23. GOSSEC L, MOLTO ANNA, ROMAND X: Recommendations for the assessment and optimization of adherence to disease-modifying drugs in chronic inflammatory rheumatic diseases: A process based on literature reviews and expert consensus. *Joint Bone Spine* 2019; 86: 13-9.
24. DEMONCEAU J, RUPPAR T, KRISTANTO P *et al*.: Identification and assessment of adherence-enhancing interventions in studies assessing medication adherence through electronically compiled drug dosing histories: a systematic literature review and meta-analysis. *Drugs* 2013; 73: 545-62.
25. AALTONEN KJ, TURUNEN JH, SOKKA T, PUOLAKKA K, VALLEALA H: A survey on the medication adherence to methotrexate among rheumatoid arthritis patients treated with self-administered biologic drugs. *Clin Exp Rheumatol* 2016; 34: 694-7.
26. LINEKER SC, BADLEY EM, HUGHES EA *et al*.: Development of an instrument to measure knowledge in individuals with rheumatoid arthritis: the ACREU rheumatoid arthritis knowledge questionnaire. *J Rheumatol* 1997; 24: 647-53.
27. HENNELL SL, DAWSON JK: Development, validation and use of a patient knowledge questionnaire (PKQ) for patients with early rheumatoid arthritis. *Rheumatology* 2004; 43: 467-1.
28. WONG PK: Medication adherence in patients with rheumatoid arthritis: why do patients not take what we prescribe? *Rheumatology Int* 2016; 36: 1535-42l
29. KUMAR K, RAZA K, NIGHTINGALE P *et al*.: Determinants of adherence to disease modifying anti-rheumatic drugs in White British and South Asian patients with rheumatoid arthritis: a cross sectional study. *BMC Musculoskelet Disord* 2015; 16: 396.
30. CALVO-ALÉN J, MONTEAGUDO I, SALVADOR G *et al*.: Non-adherence to subcutaneous biological medication in patients with rheumatoid arthritis: a multicentre, non-interventional study. *Clin Exp Rheumatol* 2017; 35: 423-30.
31. BETEGNIE AL, GAUCHET A, LEHMANN A *et al*.: Why do patients with chronic inflammatory rheumatic diseases discontinue their biologics? An assessment of patients' adherence using a self-report questionnaire. *J Rheumatol* 2016; 43: 724-30.
32. MICHETTI P, WEINMAN J, MROWIETZ U *et al*.: Impact of treatment-related beliefs on medication adherence in immune-mediated inflammatory diseases: results of the global ALIGN study. *Adv Ther* 2017; 34: 91-108.
33. MORISKY DE, GREEN LW, LEVINE DM: Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986; 24: 67-74.
34. GOSSEC L, FAUTREL B, FLIPON E *et al*.: Safety of biologics: elaboration and validation of a questionnaire assessing patients' self-care safety skills: the BioSecure questionnaire. An initiative of the French Rheumatology Society Therapeutic Education section. *Joint Bone Spine* 2013; 80: 471-6.
35. OREFICE D, BEAUVAIS C, GOSSEC L *et al*.; Therapeutic Education Section of the French Society for Rheumatology (SFR) Cross-sectional study of self-care safety skills in 677 patients on biodrugs for inflammatory joint disease. *Joint Bone Spine* 2014; 81: 502-7.
36. HUGHES LD, DONE J, YOUNG A: A 5 item version of the Compliance Questionnaire for Rheumatology (CQR5) successfully identifies low adherence to DMARDs. *BMC Musculoskelet Disord* 2013; 14: 286.
37. DE KLERK E, VAN DER HEIJDE D, VAN DER TEMPEL H, VAN DER LINDEN S: Development of a questionnaire to investigate patient compliance with antirheumatic drug therapy. *J Rheumatol* 1999; 26: 2635-41.
38. VIERA AJ, GARRET JM: Understanding interobserver agreement: the kappa statistic. *Fam Med* 2005; 37: 360.3.
39. CHEN G, FARIS P, HEMMELGARN B, WALKER RL, QUAN H: Measuring agreement of administrative data with chart data using prevalence unadjusted and adjusted kappa. *BMC Med Res Methodol* 2009; 9: 5.
40. TAIBANGUAY N, CHAIAMNUAY S, ASAVATANABODEE P, NARONGROEKNAWIN P: Effect of patient education on medication adherence of patients with rheumatoid arthritis: a randomized controlled trial. *Patient Prefer Adherence* 2019; 13: 119-29.
41. VAN HEUCKELUM M, LINN AJ, VANDEBERG L *et al*.: Implicit and explicit attitudes towards disease-modifying antirheumatic drugs as possible target for improving medication adherence. *PLoS One* 2019; 14: e0221290.
42. CHUNG-TEI C: How to translate basic knowledge into clinical application of biologic therapy in spondyloarthritis. *Clin Dev Immunol* 2013; 2013: 369202.