Impact of a pharmacist-led programme on biologics knowledge and adherence in patients with spondyloarthritis

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Abstract

Objective

In spondyloarthritis (SpA), improving patients' knowledge on their biologics is a key factor to enhance adherence. The information given to the patient has to ensure the acquisition of safety skills regarding their treatment. The aims of this trial were to evaluate the impact of a pharmacist's educational interview on knowledge and adherence to biologics in these patients.

Methods

Consecutive adult patients with well-controlled axial SpA, stable on biologics were enrolled in a randomised, controlled, single-centre, open-label, 6-month trial. A pharmacist's educational interview provided information on biologics management at baseline in the intervention group and at month 6 in the control group. The changes in a weighted knowledge score concerning the management of biologics and the change in the Medication Possession Ratio (MPR) at month-6 were primary outcomes. The changes in disease activity (BASDAI) and patients' satisfaction regarding the pharmacists' interview were secondary outcomes.

Results

Patients' characteristics at baseline were comparable among the 89 included patients (46 in the intervention group, 43 in the control group). The patient's knowledge score concerning biologics management improved at a greater magnitude in the educational group (+11.0±11.5 vs. +3.0 ±10.6 in the intervention versus the control group, respectively, p<0.0001). There was also a trend in a better adherence (+2.2±13.9 vs. -0.6±18.9 in the intervention versus the control group, respectively, p=0.691). The disease activity remained stable in both groups.

Conclusion

This study is strongly in favour of the benefit of a pharmacist's educational interview in the management of patients with axial SpA.

Key words

adherence, knowledge, biologics, spondyloarthritis, therapeutic education

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Introduction

Adherence to long-term therapy is defined by the World Health Organization (WHO) as the "extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from the health care provider" (1). Various definitions and terms can be found in the literature to express adherence to medication. According to Vrijens *et al*., this process take place over time and can be described into 3 stages: initiation (starting prescribed medication), followed by implementation (the extent to which the patient takes medication as recommended by the prescriber during a period of time) and it ends with discontinuation (stopping treatment) (2). The length of time between initiation and discontinuation can be called persistence.

In 2003, the WHO reported that, in developed countries, only 50% of patients with chronic disease were adherent to prescribed treatment (1).

In chronic inflammatory rheumatic diseases (CIRDs) such as axial spondyloarthritis, (SpA) rheumatoid arthritis (RA), or connective tissue diseases, this non-optimal adherence is confirmed. Adherence to bDMARDs and csDMARDs has been mostly studied in RA and reported rates of adherence were 30 to 80% (3-6). Despite variability in definitions of adherence between studies, in assessment methods, and in the profile of patients included, results highlighted a non-optimal adherence for CIRD patients treated with bDMARDs. Consequences of poor adherence are multiple, and first of all, it compromises therapeutic efficacy. In RA, non-adherence is associated with a higher disease activity and a progression of disease with an increased morbidity (7-9). Furthermore, non-optimal patient adherence can lead to the need for more aggressive and unnecessary treatments or switches that can have a substantial economic impact (9).

Different factors are likely to influence adherence such as: the patient (*e.g*. age, socio-professional status, knowledge, beliefs), the disease (*e.g*. severity, prognosis, duration of treatment), treatment (*e.g*. efficacy, tolerance), health professionals involved (*e.g*. doctor-patient relationship, delivered information) or the health care system (*e.g*. coordination between partners). Among these, the patient's lack of knowledge or misunderstanding regarding her/his treatments are significant factors of non-adherence (10). Thus, among methods to improve medication adherence in CIRD patients, educational interventions have been the most studied and have the highest level of evidence (11). Patient education is recommended as an integral part in established recommendations for the management of early RA and SpA (12, 13). Subcutaneous bDMARDs, especially TNF-alpha inhibitors are currently widely used in the treatment of axial SpA. These treatments are effective but the risk of adverse events (particularly infections) and the complex management on a daily basis emphasise that the acquisition of knowledge and safety skills by the patient is essential (14, 15). The challenge is to make patients understand the importance of adherence in their therapeutic management while providing them with the knowledge and information they need to manage their daily treatments.

The pharmacist, in collaboration with other healthcare professionals, has an important role to play in the evaluation, promotion and improvement of patient's knowledge and medication adherence. Studies have shown improved adherence and knowledge following pharmaceutical interviews for hospitalised patients or at the time of discharge from hospital (16-19). For example, according to Leguenel-Blache *et al*., the outpatient pharmaceutical care improves the primary adherence of patients from 51% to 79.7% (20). If the majority of studies focus on all prescribed drugs or a specific class of drugs and diseases, to the best of our knowledge, no study evaluating the impact of a pharmacist's educational interview on the knowledge and adherence of patients with SpA to subcutaneous bDMARDs has been yet conducted.

The aim of the present study was to assess the impact of a pharmacist's intervention on the knowledge and adherence of subcutaneous bDMARDs in

patients with axial SpA after 6 months of follow up.

Patients and methods

Trial design

This was a randomised, single-centre, 6-month, open label controlled trial (NCT 2016-A01897-44). All applicable regulations were respected and the project was conducted in accordance with ethical standards in France. All participating patients provided written informed consent. The study protocol and informed consent form were approved by the institutional review board (Ile-de-France I Ethics Committee, file 2016-déc.144 23 ND).

Patients

Consecutive outpatients with axial SpA from the Rheumatology Department of our centre were invited to participate if the following criteria were met: older than 18 years, stable disease activity (measured with BASDAI or ASDAS) for at least 6 months, current treatment with subcutaneous bDMARDs for at least 6 months, no change in therapy during the last 3 months and no planned change during the study duration, fluent in French. Exclusion criteria were patients with history of psychological disorders and patients who need other persons to manage their treatment.

Intervention

- Educational intervention

Intervention Group: The intervention was to provide knowledge and information regarding the management of subcutaneous bDMARDs during an educational interview conducted by a pharmacist. The following items were explored and discussed with the patient:

- managing subcutaneous bDMARD injection: storage, preparation, administration and removal;
- benefit of the treatment**:** explanation of the inflammation mechanism and that bDMARDs may be able to slow down the progression of the disease;
- management and prevention of the main adverse events: (1) injection site reaction: to use refrigerated packs to limit oedema, (2) infectious risk: to properly disinfect a wound, to be aware of the signs of infection (*e.g.* prolonged cough, urinary tract infection, abdominal ache, fever over 48 hours), to warn the general practitioner in case of undergoing infection and do not inject bDMARD without medical advice, (3) risk of skin carcinomas: recommendation of limited sun exposure and the use of an high index sunscreen, (4) the need of regular blood tests to be done.
- risk management in case of surgical/dental procedures: the rheumatologist should be notified in order to decide whether there is a need to suspend the injections of bDMARDs and the required duration of the interruption if needed;
- vaccinations: recommended (pneumococcal and influenza vaccines) and contraindicated (lives vaccines);
- recommendations for monitoring by other specialists: annual appointment with a dentist, a dermatologist, a gynaecologist (women) or urologist (man over 50 years old);
- recommendation regarding the management of medication in case of travel: organisation of the refrigerated transport of the required amount of bDMARDs. If travelling by plane, it is necessary to provide the prescription and a certificate stating that the treatment must be transported in cabin.

The educational interview was both standardised to provide the necessary information and also tailored according to the patient in order to take into account her/his specific needs. In order to personalise the educational intervention and involve the patient, the interview was conducted using open questions regarding each item. An empathic listening was used to give the patient the chance to express himself and to share his beliefs or concerns. This gave us the opportunity to detect and discuss potential barriers or issues related on medication adherence with the patient. At the end of the interview, a synthesis on specific recommendations according to the patient's needs was done and a leaflet containing essential information about treatment management was given to the patient. All information given was validated by our hospital multidisciplinary team in charge of educational intervention for CIRD patients.

Control Group: At baseline, the self-administered knowledge questionnaire concerning the management of biologics was collected but no specific comment regarding the results of it were provided. These patients were informed that this information/comment of their answers will be provided at the month-6 visit (M6).

- Intervention allocation

The pharmacist conducted a screening to select patients who met the inclusion criteria. Patients screened were contacted by phone to obtain an oral consent to participate and to plan an interview the same day as the rheumatologist's visit. Once the oral informed consent has been obtained (over the phone) and in order to facilitate the preparation of the baseline visit, the study treatment was randomly allocated via a computer programme by simple randomisation, with an allocation ratio of 1:1 (21). The written informed consent was obtained at baseline prior to any data collection or investigation.

Data collected

- Knowledge and adherence data

Knowledge data were recorded at baseline and at M6 before the pharmacist's educational interview using a weighted self-administrated questionnaire (0–100 scale, where 100 represents the maximum knowledge score). This questionnaire is composed of 12 items exploring the management of subcutaneous injection, benefit of treatment, adverse events and their management, specific risk situations, recommendations for monitoring by other specialists, management in case of travel (Table I). The questionnaire was created for the study and disseminated among 55 participants (14 patients with SpA, 12 nurses, 17 rheumatologists and 13 pharmacists). All participants have been asked to weigh each item depending on their importance according to their opinion, taking into account that all items must sum 100 points. There were no significant differences in the weighting between patients, nurses, rheumatologists and pharmacists (using Kruskall-Wallis and Tukey *post-hoc* test) (22).

Table I. Items and weighted scores of the knowledge questionnaire.

Item	Maximum weighted score
Q1 Preparation	8
Q2 Administration	8
Q3 Removal	6
Q4 Storage	8
Q5 Benefit of the treatment	8
Q6 Adverse events	12
Q7 Risk management of adverse events	12
Q8 Risk management in surgical/dental procedures	9
Q9 Recommended vaccinations	8
Q10 Contraindicated vaccinations	8
Q11 Recommendation for monitoring by other specialists	7
Q12 Management in case of travel	6
Total	100

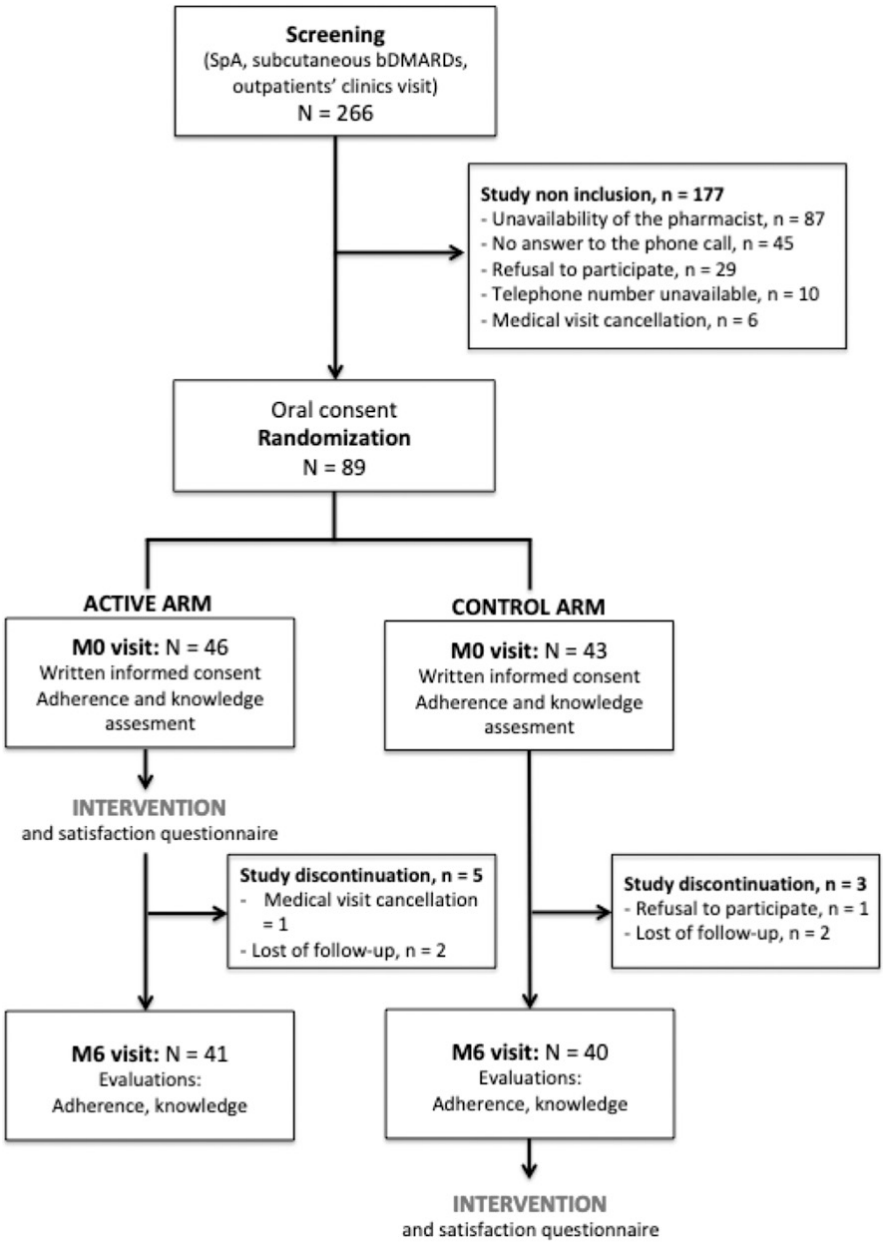

Fig. 1. Study flowchart.

Adherence data regarding subcutaneous bDMARDs were recorded at baseline and M6 using an objective method: calculation of the medication possession rate (MPR) during the last 4 months. To understand this method, 2 characteristics of the French Health Care System has to be recalled: there is one single health insurance called: "Sécurité Sociale". A specific card called "carte vitale" is provided to each citizen. This card contains a chip with all the information related to any medicine delivered by any pharmacy in France. Concerning the biologics, the prescription of any doctor can be delivered by any pharmacy. MPR represents the number of subcutaneous bDMARDs supplied by a pharmacy divided by the number of theorical subcutaneous bDMARDs that the patient should have taken within the observation period (*e.g.* during the 4 months preceeding the baseline or the M6 visit), expressed in percentage. The number of theorical subcutaneous bDMARDs that the patient should have taken is calculated taking into consideration individual circumstances that lead the patient to temporally stop the bDMARDs (*e.g.* pending surgery, infection, …). The patient's "carte vitale" was consulted and her/his usual community pharmacy called to obtain complementary data if necessary.

- Other data collected

At baseline, the following information was recorded: sociodemographic data (age, gender, marital status, educational level, professional status), clinical data (disease duration), treatment characteristics (subcutaneous bDMARD intake duration, concomitant csDMARD, non-steroidal anti-inflammatory drugs (NSAIDS) and/or analgesics, history of previous bDMARD). At both baseline and M6 visits: data on disease activity (BASDAI, C reactive protein,) and time spent in conducting the educational interview were recorded. The patient's satisfaction was assessed using a self-administrated questionnaire regarding the clarity of the information and leaflet provided, the patients' perception of the impact of the pharmacists' intervention on their subcutaneous bDMARD management and on

their skills acquisition. The patient's satisfaction was assessed at the end of the pharmacist's intervention (at baseline for the intervention group and at M6 for the control group).

Outcome measures

Two primary end-points were a priori defined: (1) the changes from baseline to M6 in the patients' knowledge score about subcutaneous bDMARD management and (2) the changes from baseline to M6 in MPR. As secondary end-points, the changes in disease activity and patients' satisfaction regarding the pharmacists' intervention were evaluated.

Statistical analysis

The analysis was based on intention-to-treat. Missing data were handled with the last observation carried forward technique for patients who did not complete M6 and the multiple imputations technique for missing data in questionnaire's variables (only if less than 20% of missing data). Qualitative variables were expressed as numbers and percentages. Quantitative variables with symmetrical distribution were summarised as mean±SD. Changes from baseline to M6 in the intervention and control group regarding the knowledge score, MPR and disease activity were compared using the Student t-test.

Results

Patients and study course

Figure 1 summarises the flow of patient enrolled in the study. Among the 266 patients screened, 89 were randomised (46 in the active arm and 43 in the control arm). The two main reasons for non-inclusion were the unavailability of the pharmacist the day of the rheumatologists' visit (n=87) and the absence of answer to the telephone call (n=45). Of the 89 patients who attend the first visit, 81 (91%) completed the 6 months study period. The reasons for non-completing the study among the remaining 9 patients (n=5 and n=3 in the active arm and control arm, respectively) were patient's refusal to continue (n=1), medical cancellation of visit to the rheumatologist (n=2), lost to follow-up (n=5).

Table II. Patients' characteristics at baseline.

	Whole population n=89	Control group n=43	Intervention group n=46
Gender, male; n (%)	56 (62.9%)	26 (60.5%)	30 (65.2%)
Age, years; mean (SD)	42.4 (10.6)	43.3 (10.4)	41.7 (10.8)
Disease duration, years; mean (SD)	13.4 (10.8)	14.3 (10.8)	12.5 (10.7)
Single; n (%)	31 (34.8%)	11 (25.6%)	20 (43.5%)
Professional status; n (%)			
Employee	77 (86.5%)	38 (88.5%)	39 (84.8%)
Retired	2 (2.3%)	1 (2.3%)	1 (2.2%)
Unemployed	4 (4.5%)	2 (4.6%)	2 (4.3%)
Student	6 (6.7%)	2 (4.6%)	4 (8.7%)
Level of education, n (%)			
Primary school	1 (2.3%)	1 (2.3%)	0 (0%)
High school	22 (24.7%)	9 (20.9%)	13 (28.3%)
University	66 (74.2%)	33 (76.8%)	33 (71.7%)
bDMARD intake duration, years; mean (SD)	3.7 (4.1)	4.6 (4.2)	3.6 (3.2)
Concomitant csDMARDs; n (%)	15 (16.8%)	6 (14.0%)	9 (19.6%)
Concomitant NSAIDs; n (%)	32 (36.0%)	14 (32.6%)	18 (39.1%)
Concomitant analgesics; n (%)	22 (24.7%)	12 (27.9%)	10 (21.7%)
History of ≥2 bDMARDs; n (%)	38 (42.7%)	20 (46.5%)	18 (39.1%)
BASDAI (0-100), mean (SD)	23.5 (17.8)	22.2 (19.5)	24.6 (16.1)
*3/89 missing data CRP, mg/dL; mean (SD)	2.7 (3.1)	2.9 (3.8)	2.5 (2.1)
**11/89 missing data			

Data presented are either mean±SD, number and (percentage)
bDMARDs: biologic disease-modifying anti-rheumatic drug; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drug; NSAIDs: non-steroidal anti-inflammatory drugs; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein.

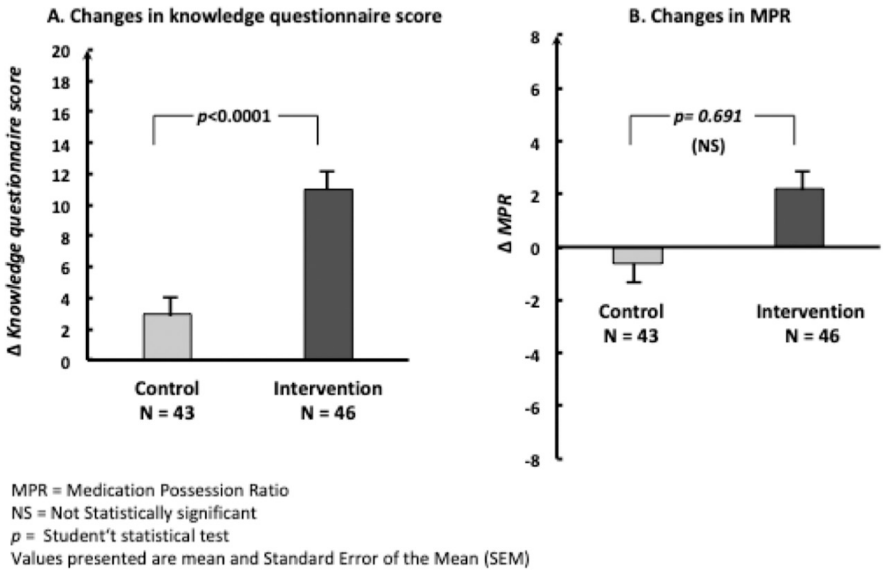

Fig. 2. Changes in knowledge questionnaire score (**A**) and changes in Medication Possession Ratio (**B**) during the study.

Patients' characteristics at baseline are summarised in Table II. There was no difference between the intervention and control groups. Most of patients were men (62.9%), with a mean age of 42.4 (±10.6) years and relatively long disease duration (13.4±10.8 years) with moderate activity (BASDAI (0–100): 23.5±17.8). Most of the patients were employees (n=77) and had a high level of education (university n=66). Regarding their treatment, the mean subcutaneous bDMARD intake duration was 3.7 (±4.1) years and 38 (42.7%) patients had a history of 2 or more subcutaneous bDMARD intake. The mean time spent conducting the educational interview was 39 min ±16 min per patient.

Table III. Changes from baseline to M6 in the level of knowledge about bDMARDs management in the intervention group.

Items (score)	Baseline score Mean (SD)	M6 score Mean (SD)	Changes (percentage) in knowledge score
Q1: Preparation (0-8)	8 (0)	8 (0)	0% (0)
Q2: Administration (0-8)	8 (0)	8 (0)	0% (0)
Q3: Removal (0-6)	4.6 (2.6)	5.5 (1.7)	102.2% (231.4)
Q4: Storage (0-8)	6.1 (1.8)	6.3 (1.8)	8.7% (37.0)
Q5: Benefit of the treatment (0-8)	4.9 (3.2)	6.3 (2.6)	140.2% (43.0)
Q6: Adverse events (0-12)	10.7 (3.8)	11.7 (1.8)	104.3% (341.9)
Q7: Risk management of adverse events (0-12)	9.0 (4.1)	10.4 (2.9)	102.2% (307.9)
Q8: Risk management in surgical procedures (0-9)	7.8 (1.7)	8.7 (0.9)	19.6% (44.1)
Q9: Recommended vaccinations (0-8)	5.6 (2.7)	6.0 (2.5)	35.9% (123.0)
Q10: Contraindicated vaccinations (0-8)	2.6 (3.7)	5.0 (3.9)	244.9% (371.9)
Q11: Recommendations for monitoring by other specialists (0-7)	5.1 (2.1)	5.8 (1.6)	45.1% (145.2)
Q12: Management in case of travel (0-6)	3.0 (2.4)	4.6 (2.3)	118.5% (214.3)
Total (0-100)	75.3 (14.2)	86.3 (12.6)	

Outcomes

- Patient's knowledge about bDMARDs

The changes in the knowledge questionnaire score (0–100) during the study are summarised in Figure 2A. The means±SD of the knowledge score were 75.3±14.2 *versus* 73.0±13.2 and 86.3±12.6 *versus* 76.0±14.1 in the intervention versus control group at baseline and at M6, respectively.

The changes in knowledge score between baseline and M6 was significantly higher in the intervention group than the control group (+11±11.5 *vs.* +3±10.6 in the intervention *versus* the control group, respectively $p<0.001$).

The changes during the study in each item of the knowledge questionnaire in the intervention group are summarised in Table III. At baseline the knowledge of the patients were low for the following items: contraindicated vaccinations and management of the biologics in case of travel with a mean score of 2.6 (range: 0–8) and 3.0 (range: 0–6), respectively. After 6 months of follow-up, an improvement in all items was observed and, in particular for the contraindicated vaccinations, the benefit of treatment and the management in case of travel with an improvement in knowledge score of 244.9%, 140.2% and 118.5%, respectively.

- Patient's adherence about bDMARDs

The changes in the MPR during the study are summarised in Figure 2B. The MPR at baseline were very high in both groups (92.9±14.6% *vs.* 96.6±15.6% in the intervention *versus* control group, respectively). During the study, there was a non-statistically significant trend in favour of a better improvement of adherence in the intervention group (+2.2±13.9% *vs.* -0.6±18.9% in the intervention *versus* the control group, respectively).

- Patient's disease activity

At baseline, in accordance to the protocol, the activity of the disease was low according to the BASDAI score (24.0±15.9 and 20.7±17.6 in the intervention and control group respectively). During the study, there was no significant change (+2.9±10.4% and +3.3±12.2% in the intervention and control group, respectively).

- Impact on patient's satisfaction

The satisfaction questionnaire was completed by 80 patients (40 in each group). All the patients were mostly or totally satisfied by the pharmacist's educational interview in general and thought that all patients should benefit of this type of interview. They were also mostly or totally satisfied by the clarity (n=77, 96.2%), the content (n=80, 100%) and the leaflet provided (n=79, 99%). All the patients expressed that they have acquired new competences and 77 (91.3%) of them that the interview will lead to a change in their daily bDMARD management.

Discussion

This study evaluated the impact of a pharmacist's intervention primarily aiming at improving the knowledge of subcutaneous bDMARDs in patients with axial SpA and therefore, at improving their medication adherence. The results showed that the pharmacist's educational interview on subcutaneous bDMARD management improved significantly the level of knowledge of patients. This intervention permitted also a trend in favour of a better improvement of treatment adherence.

Our study has strengths and weaknesses. To our knowledge, this is the first study evaluating the impact of a pharmacist's educational interview in SpA patients on subcutaneous bDMARDs. The design of the study (randomised and controlled) and the low attrition rate can be seen as strengths of this study. However, the single centre enrolment, the recruitment of patients who had a relatively long bDMARD intake duration and the high educational level of the participant prevent generalisability of the results observed in this trial. The proportion of patient included is low regarding the number of patients screened. The principal reason for the patients not been included was the unavailability of the pharmacist. During the study, the pharmacist did not benefit from specific time dedicated to this activity and the interviews were carried out among the others daily activities. The positive impact, both on improving knowledge and patient satisfaction, highlights the need to pursue these pharmacists' educational interviews. Thus, a key element to the sustainability success would be having specific dedicated time to this activity.

Concerning the impact of the intervention on knowledge, despite a high level of knowledge at baseline in both groups, a significant improvement was obtained in the intervention group. The high level of patients' knowledge at baseline could be explained by the characteristics of the patients included. Indeed, the proportion of patients with a high educational level was important, and has been previously reported to be associated with a higher skill level regarding bDMARD management in the literature (23, 24). Regarding the items

explored by the questionnaire, the pharmacists' educational intervention has led to improve all the dimensions and in particular essential safety skills such as the management of the adverse events or contraindicated vaccinations. However, one limitation of this evaluation is that the use of a questionnaire is not a real life situation and a good level of knowledge cannot guarantee that patients will used the responses included in the questionnaire to take the good decision. However, the clear improvement in patient knowledge observed in this study suggests the positive role of pharmacist in therapeutic education of patients with chronic diseases. Although we have not found in the literature other studies confirming the impact of a pharmacist's intervention on knowledge regarding the subcutaneous bDMARDs in patients with SpA, the positive role of pharmacists' educational interventions in RA and other chronic conditions (*e.g.* diabetes, anticoagulants) is clearly established (17, 25-28). Choosing the right educational interview format is an essential criterion for facilitating knowledge acquisition. In our study, we used a standardised content in order to give all the information required for safety medication use, but we also personalised the interview in order to be closer to the patient's needs. Furthermore, we also gave a leaflet that can strengthen the transmission of information and represents a useful solution for maintaining long-term knowledge (29).

Concerning the impact of the intervention on subcutaneous bDMARD adherence, a trend in favour of an improvement was observed in the intervention group but did not reach the statistically significant inter-group difference. These results are in line with a recent systematic review by Lavielle *et al*., which states that even if educational interventions have the highest level of evidence, many existing interventions to improve medication adherence in CIRDs patients are not particularly effective (11). There are several reasons to explain the lack of statistically significant difference in our study. First, the level of adherence evaluated *via* the MPR was particularly high at baseline allowing a limited room for improvement. Targeting patients with adherence issue at baseline might have facilitated the demonstration of this intervention. Second, despite the MPR is a widely used tool to measure the level of adherence, it may not reflect the actual medication taking by the patient but only the medication possession and thus overestimate adherence. However the choice of the optimal adherence assessment tool is challenging since most of available questionnaires seem to be unsatisfactory in the context of usual care or to be copyrighted (30, 31). Moreover, these questionnaires have not been studied in patients with SpA and at least, MPR allows avoiding the subjectivity of self-questionnaires (32). Third, the lack of clear benefit of our intervention concerning treatment adherence might be due to other factors influencing the treatment adherence which were not included in our study such as the patient belief, the therapeutic alliance with the rheumatologist or the health care system (1). The improvement in adherence may require several interviews and a better exploration of the different factors of non-adherence. Nevertheless, targeting knowledge about medication remains an understandable choice according to a recent literature review indicating that patient information and education are key to optimise adherence and should be systematic (10).

In summary, this study shows that pharmacists' educational intervention on subcutaneous bDMARDs is effective in improving the knowledge of patients with SpA on their treatment. Further studies with a different design are required to evaluate the impact of such a type of interview on adherence. Nevertheless, the results observed in this study are already an argument to propose to include the pharmacists in the multidisciplinary team in charge of the management of patients with SpA.

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