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Original article

Impact of a clinical pharmacist in a multidisciplinary consultation on the switch to a biosimilar for inflammatory rheumatic diseases

Clara Levivien[a,*], Cécile Bottois[a], Clementina López Medina[b,c], Sophie Dumas[a], Julien Hubert[a], Sephora Belo[a], Christian Roux[b,d], Ornella Conort[a], Maxime Dougados[b,d]

[a] Département de pharmacie clinique, hôpital Cochin, université de Paris, AP–HP centre, Paris, France
[b] Département de rhumatologie, hôpital Cochin, université de Paris, AP–HP centre, Paris, France
[c] Rheumatology department, Reina Sofia University Hospital, IMIBIC, University of Cordoba, Cordoba, Spain
[d] Inserm (U1153), clinical epidemiology and biostatistics, PRESS Sorbonne Paris-Cité, Paris, France

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ABSTRACT

Objective. – Despite several studies proving the efficacy and safety of biosimilars compared with original drugs, switching to a biosimilar remains challenging when the decision is at the discretion of physicians with mandatory consent from patients. Educating patients about biosimilars seems important to increase the prescription rate of biosimilars. This study aimed to evaluate the impact of a clinical pharmacist consultation on the switch to and retention rate of a biosimilar for patients with inflammatory rheumatic diseases.

Methods. – This retrospective study compared 2 groups of adult patients receiving (intervention) or not (control) a consultation with a pharmacist right before the rheumatologist consultation. The primary outcome was the frequency of patients who switched to a biosimilar at the end of the rheumatologist visit.

Results. – We analysed 141 patients (50% women, 50 ± 15 years old, on original adalimumab (62%) or etanercept (38%)) who had never used biosimilars: 85 in the intervention group and 56 in the control group. The switch rate to a biosimilar significantly differed between the groups: 69.4% versus 41.1% in the intervention group versus the control group respectively ($P < 0.01$). After a 1-year follow-up period, 72.5% versus 81.3% of patients who switched were still on biosimilar in the intervention versus control group respectively.

Conclusions. – This study highlights the positive impact of a pharmacist consultation before the physician's one on switching to a biosimilar, but more studies are needed to assess the impact of this pharmacist consultation on preventing the nocebo effect and therefore on improving the retention rate of biosimilars.

1. Introduction

Over the last decade, the development of biological disease modifying anti-rheumatic drugs (bDMARDs) has greatly improved the management of inflammatory arthritis. In rheumatology, the use of bDMARDs to treat rheumatoid arthritis, spondyloarthritis or other severe inflammatory arthritis has significantly improved the quality of life of patients living with these diseases but remains costly [1]. The development of biosimilar bDMARDs (bsDMARDs), defined as biologic drugs assessed to be similar to a licensed original drug in terms of quality, safety, and efficacy, has significantly reduced the costs of these treatment strategies. As the original drugs lost patent exclusivity, the availability of biosimilars has led to reduced costs [2].

Despite several studies proving the safety and efficacy of biosimilars as compared with the original drugs, the interchangeability or switch from the original drug to a biosimilar has raised several questions [3,4]. Regulation laws on the switch from original drugs to biosimilars can differ among countries. In France, unlike for generic drugs, the switch to biosimilars is not offered by pharmacists but remains at the discretion of the physician with the consent of the patient.

* Corresponding author at: Département de pharmacie clinique, hôpital Cochin, université de Paris,AP–HP centre, 27 Rue du Faubourg Saint-Jacques, 75014 Paris, France.
Adresse e-mail : clara.levivien@aphp.fr (C. Levivien).

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A French-nationwide study have found that the major obstacle in switching to a biosimilar is the lack of information offered to patients. In this regard, physicians have a key role in helping patients to accept the switch to a biosimilar. The information given to the patient also seems essential to prevent the nocebo effect (i.e. a negative outcome due to a belief that the intervention will cause harm), which may be responsible for a return to the original drug [5]. Several studies revealed a nocebo effect in 15% to 30% of patients, which may result in medication non-adherence and waste, over-utilization of healthcare resources, polypharmacy, loss of patient trust, and treatment with second-line therapies and suboptimal outcomes [6].

Therefore, to improve the penetration rate of biosimilars and better educate patients about the management of their treatments, several departments of rheumatology have developed a multidisciplinary consultation including information about biosimilars. Different healthcare professionals can provide this information. Clinical pharmacists can assist in counseling patients with inflammatory diseases about managing their treatment, in particular for administration, storage and disposal, adverse effects and adverse effects management [7]. In inflammatory arthritis, education by a pharmacist has already shown a positive impact on patients' knowledge of their treatment [8]. The implementation of this type of consultation might address the 2021 European League Against Rheumatism recommendations on self-management strategies in patients with inflammatory arthritis [9].

The aim of this study was to evaluate the impact of a clinical pharmacist consultation on the switch rate (i.e., switch from the original drug) and retention rate (i.e., prevention of the nocebo effect) of biosimilars.

2. Methods

2.1. Study design

This was a retrospective, controlled, mono-centric, interventional non-randomized study conducted in a tertiary department of rheumatology. In daily practice in our hospital, all patients living with an inflammatory arthritis and treated with a bDMARDs were offered the choice to meet with a clinical pharmacist before their appointment with the hospital rheumatologist. The study took place between April 2019 and February 2021 and received ethics approval provided by an independent local ethics committee, the *Comité de Protection des Personnes Ile de France (July 1, 2020) n°2020-A01380-39*.

2.2. Study arms

2.2.1. Intervention arm

The intervention group was composed of patients who agreed to see a pharmacist and who therefore underwent a multidisciplinary consultation. Those patients had a consultation with a clinical pharmacist right before their appointment with the rheumatologist on the same day.

2.2.2. Control arm

The control group was composed of patients who did not see a clinical pharmacist before their consultation with the rheumatologist. Those patients were selected for a multidisciplinary consultation, as they were treated with a sub-cutaneous bDMARDs, but did not see the pharmacist before their consultation with the rheumatologist, for different reasons, such as a patient's refusal to participate, a physician's refusal or a lack of clinical pharmacist available to provide the educational intervention. Those patients, not seen by the pharmacist but only by the rheumatologist, were part of the control group.

All patients (in both groups) were then monitored under usual care conditions and at the discretion of their treating rheumatologist.

2.3. Inclusion criteria

We analysed patients living with an inflammatory arthritis treated with original subcutaneous bDMARDs (Enbrel or Humira) at the time of the multidisciplinary consultation, also called the baseline visit for this study. All patients were adults $\geq$ 18 years old. We excluded patients for whom a switch to a biosimilar before the baseline visit failed (patients for whom a switch had already been done but who returned to the original drug) and those who had to change or stop their sub-cutaneous bDMARD at the time of the visit for medical reasons. Patients for whom a switch to a biosimilar has been previously proposed but refused by the patient were included in this study. Finally, we analysed patients who had never used biosimilars.

2.4. Role of the clinical pharmacist

Before visiting their rheumatologist during an out-patient clinic, patients were offered the possibility to have a 45- to 60- min consultation with a clinical pharmacist on the same day as and right before the rheumatologist consultation. This visit was prepared by a coordinator who gave patients questionnaires (BioSecure questionnaire on safety skills, 5-item Compliance Questionnaire for Rheumatology, Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Functional Index, Routine Assessment of Patient Index Data 3) to complete before the consultations and insured the link between the healthcare professionals [10–13]. During the pharmaceutical consultation, management of treatment was addressed. In case of a patient receiving original bDMARDs (adalimumab or etanercept), the pharmacist presented and discussed a document explaining the biosimilarity to the patient; this document has been validated by the staff members of the departments of pharmacy and rheumatology. The pharmacist then presented the different biosimilars in the form of a pen or pre-filled syringes, described their characteristics allowing the patients to choose the one that best suited them and collect the patient's oral consent to switch to a biosimilar, before informing the rheumatologist. If the patient and the rheumatologist agreed to the switch, the clinical pharmacist then contacted the community pharmacist by phone in order to explain the rationale for this switch (In France, the prescription is done by the treating rheumatologist and the sub-cutaneous biotherapy can be delivered in any pharmacy in the country). The clinical pharmacist also provided information on the new treatment chosen by sending an email with documentation to the patient's community pharmacist.

2.5. Data collected

Patient data were collected from the hospital electronic medical record and included socio-demographic characteristics (age, sex), underlying rheumatic disease (specific diagnosis, disease duration), treatment data (actual treatment, number of previous bDMARDs, and duration of the current bDMARD, concomitant methotrexate or/and corticosteroids). Physician data collected included sex, age and administrative function.

2.6. Outcomes

The primary outcome was the percentage of patients who switched to a biosimilar (e.g. proportion of patients who were prescribed a biosimilar by the rheumatologist during the visit. The study

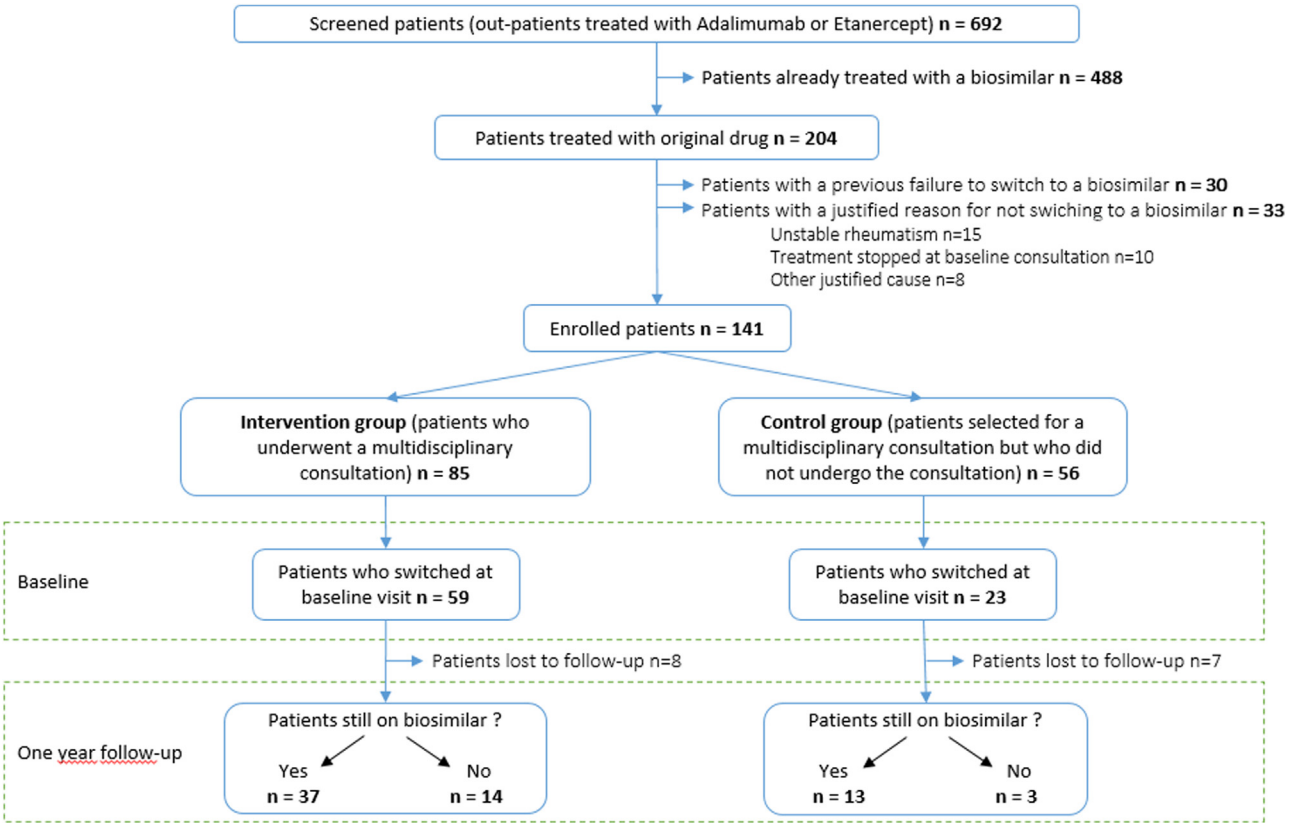

Fig. 1. Patients flow chart.

also looked at the proportion of patients, among those who switched at the baseline visit, who continued the biosimilar during the 12-month follow-up (retention rate).

2.7. Statistical analysis

Absolute and relative frequencies were calculated for categorical variables mean and standard deviation (SD) for continuous values. Baseline characteristics of the intervention and control groups were compared by Student *t* test or Mann-Whitney U test for quantitative variables and chi-square or Fisher test for categorical variables. A complete case analysis for each outcome was conducted. Two-sided $P < 0.05$ was considered statistically significant. Data were analysed by using R Studio 1.3.1073.

3. Results

3.1. Study course and baseline characteristics

We analysed the files of 174 patients who had never used biosimilars (Fig. 1). Among those patients, we excluded patients with a justified reason for not switching to a biosimilar at the time of baseline consultation ($n = 33$) such as 1. an unstable rheumatic disease ($n = 15$), 2. pregnancy ($n = 1$), 3. patients for whom current sub-cutaneous original anti-tumor necrosis factor agent was discontinued with ($n = 3$) or without ($n = 7$) a switch to another bDMARD, 4. another justified reason ($n = 7$).

The baseline characteristics of the remaining 141 patients and the physicians' characteristics are summarized in Table 1. The intervention and control groups did not significantly differ in characteristics except for the mean age (52.1 ± 14.1 vs. 46.8 ± 15.5 years; $P < 0.05$; for the intervention vs control group respectively). A total of 17 rheumatologists were involved in this initiative (15 and 14 in the intervention and control groups, respectively). Their characteristics were similar (91.0% vs. 95.9% female, 72.0% vs. 83.8% full-time consultant, and mean age 41.3 ± 10.6 vs. 42.3 ± 13.5 years for the intervention vs control group respectively).

3.2. Frequency of switch at baseline

Among the 141 patients, 82 patients switched to a biosimilar at the end of the consultation (59 vs. 23 patients in the intervention vs. control group respectively). The proportion of patients who switched to a biosimilar significantly differed: 69.4% (59/85) vs. 41.1% (23/56) ($P < 0.01$) in the intervention vs control group respectively (Fig. 2).

3.3. Retention rate of biosimilars after a switch

Among the 82 patients who switched to a biosimilar at the end of the baseline visit, 15 (8 vs. 7 in the intervention vs control group respectively) did not return for a visit with their rheumatologist. Therefore, the analysis of the retention for the switched biosimilar was possible for 67 patients: 51 vs. 16 patients in the intervention vs control group. The characteristics of those patients were similar to the total population and did not differ in both groups except for the mean age (data not shown). During the one year follow-up period, 14 and 3 patients discontinued their anti-TNF biosimilar in the intervention and control group respectively. The anti-TNF biosimilar was switched back to the original drug in 9 and 3 patients in the intervention and control group respectively. Moreover, the anti-TNF biosimilar was switched to another bDMARD with a different mode of action in 5 patients in the intervention group. Finally, the percentage of patient still on biosimilar at the end of the one year

Table 1
Patients' baseline characteristics.

	Total $n = 141$	Intervention group $n = 85$	Control group $n = 56$
Sex (male)	70 (49.6%)	46 (54.1%)	24 (42.9%)
Age, mean (SD)*	50.0 (14.9)	52. 1 (14.1)	46.8 (15.6)
Disease			
RA	37 (26.2%)	19 (22.4%)	18 (32.1%)
SpA	88 (62.4%)	56 (65.9%)	32 (57.1%)
JIA	3 (2.1%)	1 (1.2%)	2 (3.6%)
PsA	10 (7.1%)	8 (9.4%)	2 (3.6%)
Others	3 (2.1%)	1 (1.2%)	2 (3.6%)
bDMARD			
Humira	88 (62.4%)	57 (67.1%)	31 (55.4%)
Enbrel	53 (37.6%)	28 (32.9%)	25 (44.6%)
Concomitant methotrexate	49 (34.8%)	29 (34.1%)	20 (35.7%)
Concomitant corticosteroids	9 (6.4%)	6 (7.1%)	3 (5.4%)
Disease duration			
0–5 years	18 (12.8%)	10 (11.8%)	8 (14.3%)
5–10 years	23 (16.3%)	17 (20.0%)	6 (10.7%)
10–15 years	100 (70.9%)	58 (68.2%)	42 (75.0%)
Number of previous bDMARDs	0.6 (1.2)	0.7 (1.4)	0.6 (0.8)
Duration of the current bDMARD	6.0 (3.8)	6.3 (3.8)	5.6 (3.9)
Sex of the rheumatologist (female)	162 (93.1%)	91 (91.0%)	71 (95.9%)
Age of the rheumatologist	41.7 (11.9)	41.3 (10.6)	42.3 (13.5)
Position of the rheumatologist			
Assistant	61 (35.1%)	35 (35.0%)	26 (35.1%)
Associated	40 (23.0)	28 (28.0%)	12 (16.2%)
Senior	73 (41.9%)	37 (37.0%)	36 (48.7%)

Data are mean (SD) unless indicated. *P*-value are non significant unless indicated. Intervention group: visit with a clinical pharmacist prior to the physician's visit, Control group: Physician's visit only. RA: rheumatoid arthritis; SpA: spondyloarthritis; JIA: juvenile inflammatory arthritis; PsA: psoriatic arthritis; bDMARD: biologic disease-modifying anti-rheumatic drug.
* $P < 0.05$.

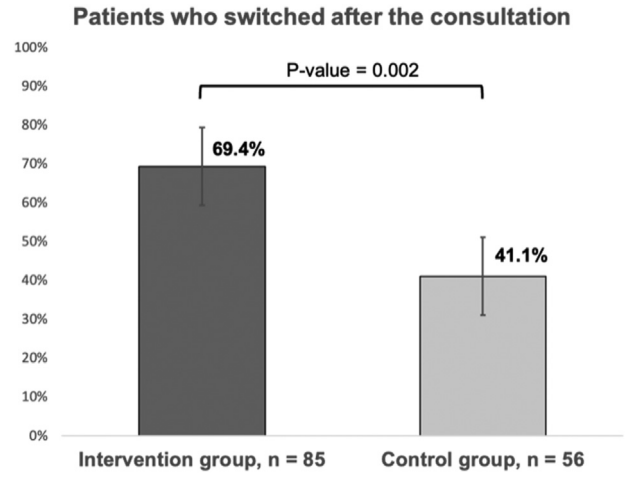

Fig. 2. Percentage of patients who switched to a biosimilar at the baseline visit.

follow-up period was 37/51 (72.5%) versus 13/16 (81.3%) in the intervention versus control group respectively.

4. Discussion

This study showed the positive impact of a clinical pharmacist consultation on the prescription rate of biosimilars. As compared with a physician-only consultation, the addition of a clinical pharmacist consultation before the physician consultation increased the number of patients who switched from an original drug (bDMARDs) to a biosimilar (bsDMARDs) from 41.1% (control group) to 69.4% (intervention group, $P < 0.01$). However, among the patients who switched to a bsDMARD at baseline, the addition of a clinical pharmacist did not affect the retention rate of biosimilars after a 12-month follow-up, which reflects the absence of impact on the nocebo effect, one of the main reasons for discontinuing a biosimilar [14].

This significant impact of the pharmacist consultation could be explained by the time allowed to inform the patient about biosimilars in a 45- to 60-min consultation on top of an average 30-min physician consultation. Having two different healthcare professionals explaining biosimilars to patients instead of one could also have affected their decision to accept the switch from their original drug to a biosimilar. The choice of delivery device left to the patient could influence their decision to accept the switch and the treatment adherence. Another French study offering the same type of information on biosimilars (oral and written) as well as the patient's free choice to accept the switch reported an 85% switch rate from Enbrel to a biosimilar etanercept (SB4, Benepali) [15]. The switch rate we found in the intervention group (69.4%) was therefore higher than the one reported in another study, reporting a 51.6% switch rate for etanercept [16].

We hypothesised that the information given to the patients about biosimilars, their free choice to switch or not and the notification provided by the clinical pharmacist to the patient's community pharmacist after the consultation could have improved adherence to the biosimilar and therefore increased the persistence of the drug intake (e.g., retention rate of the drug). All those factors should have prevented the so-called nocebo effect [17]. In fact, we did not demonstrate a prevention of this nocebo effect with the intervention because the proportion of patients returning to the original drug after the switch at baseline to a biosimilar did not differ between the 2 groups. However, our results seem similar to those from previously reported studies. A French study exploring the impact of the nocebo effect showed a retention rate at 12 months of 84.5% (72.5% in our study) and found a 6.6% biosimilar discontinuation rate due to a nocebo effect after 12 months [18]. Other studies have found a nocebo effect in approximately 15% to 30% of patients or 12.8% when including patients with gastrointestinal or rheumatic diseases [6,19].

To our knowledge, this is the first study evaluating the impact of a clinical pharmacist consultation on the prescription rate of biosimilar bDMARDs. The use of similar groups followed by the same physicians is a strength of the study. However, the single-centre enrollment and the recruitment of patients by a limited number of physicians from the rheumatology department may prevent generalizing the results. The lack of randomization and the retrospective nature of this study could be a limitation to the interpretation of results on retention rate. It has also to be noticed that this study has been conducted using the Biosecure questionnaire version published in 2013, other studies conducted with the 2021 updated version might provide different results [10,11].

This study showed that a clinical pharmacist consultation could improve the proportion of patients who switched from an original bDMARD to a biosimilar and the proportion receiving biosimilar bDMARDs at the end of follow-up. A multi-centred study with other physicians could confirm the positive impact of the pharmacist consultation on the switch rate. Other studies would also be necessary to evaluate the key factors that could improve the retention rate and whether a pharmacist consultation could affect those factors. Some recommendations for preventing and managing the nocebo effect mentioned that education about biosimilars should be tailored to the individual patient, taking into account their risk profile for the nocebo effect, which could then influence and change our practice for educating patients about biosimilars [20].

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Disclosure of interest

The authors declare that they have no competing interests.

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