Joint Bone Spine 86 (2019) 491–496

Available online at ScienceDirect www.sciencedirect.com

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Original article

Patients' information and perspectives on biosimilars in rheumatology: A French nation-wide survey

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ARTICLE INFO

Article history:
Accepted 3 January 2019
Available online 16 January 2019

Keywords:
bDMARD
Biosimilar
Information
Patient perspective
Treatment

ABSTRACT

Objective: To assess the patients' information about biosimilars and to identify the patients' incentives and deterrents to concur with the use of biosimilars.
Methods: Nation-wide cross-sectional study assessing information and concerns about biosimilars of French patients treated for rheumatic inflammatory diseases, whether they were treated or not by a biological DMARD. The assessment was available online from March to July 2017.
Results: Among the 629 respondents, 43% knew what biosimilars were. The main sources of information were rheumatologists and patient associations. Among patients treated with a biosimilar, 44% were not informed before they received the treatment. The patients' concerns focused on the non-similar molecular structure (46%), efficacy (60%) and safety (57%) comparatively to the originator biologic. 15% of respondents would refuse to switch their biologic to its biosimilar. More than 50% of respondents would warily accept to switch medications and interrupt the treatment if in doubt. Being informed about biosimilars and a good understanding of the definition of biosimilars were characteristics associated with better adherence to biosimilars. The rheumatologist was considered the most influent source of information about biosimilars and was considered reliable when deciding to switch a biologic to its biosimilar. Patient were reluctant to substitution of the medications by pharmacists (2%). Medico-economical issues acted as an incentive and a deterrent to accept the switch of medication.
Conclusion: Biosimilars are largely unknown to patients. Information seems to be instrumental in improving the patients' adherence to biosimilars and could help preserving the therapeutic relationship and avoiding a nocebo effect.

1. Introduction

Biological agents have revolutionized the clinical outcome for patients with rheumatic inflammatory diseases. The high cost of these medications has also dramatically increased the cost of the medical care [1,2]. Biosimilars of products whose data patent protection has expired are now available in clinical practice. Highly similar to the originator biological drug, they provide similar efficacy and safety at a lower price.

However, because the biosimilar molecular structure can slightly differ from the originator bDMARD structure, concerns have been raised by both physicians and patients. Those worries are about the efficacy and the safety of being treated with a biosimilar agent and of switching from an originator bDMARD to its biosimilar. Since comforting "switch data" were published [3–5], health agencies have conducted wide information campaigns to reassure and support physicians in their first biosimilar prescription [6]. This sometimes led to wide switching medication policies from originator bDMARDs to their biosimilar. Nevertheless, a recent sur-

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https://doi.org/10.1016/j.jbspin.2019.01.001
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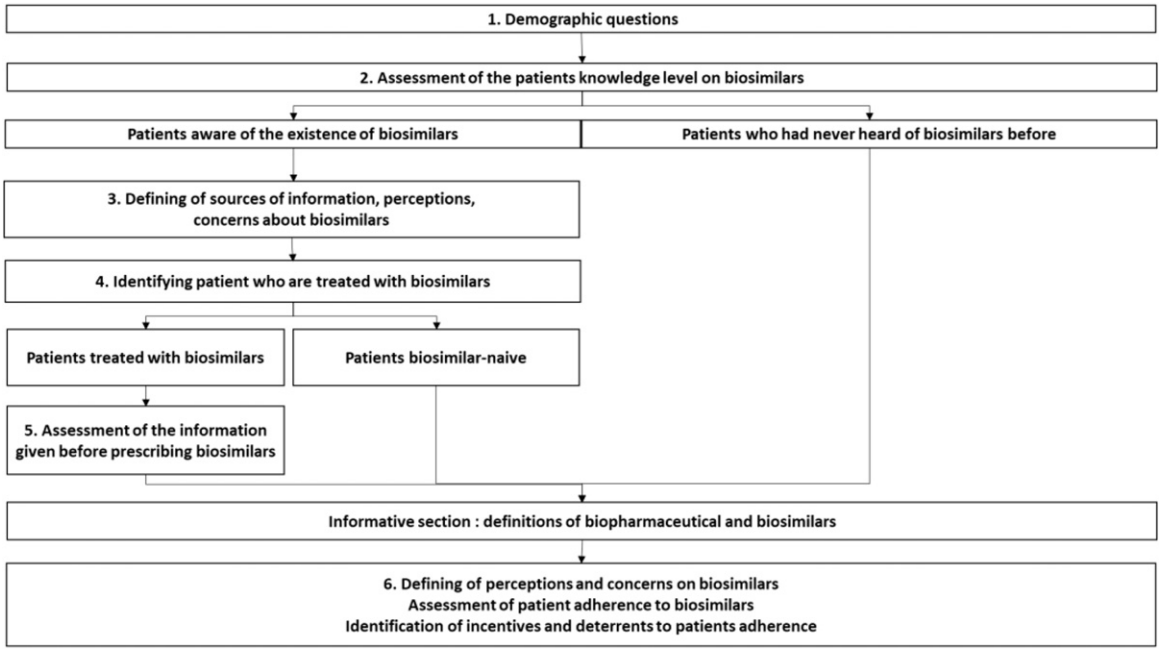

Fig. 1. Assessment composition.

vey shows that rheumatologists seemed reluctant to inform their patient because they were afraid that it could increase the patients' fears [7]. The patients' understanding of biosimilars and their concerns about biosimilars remain unknown.

Thus, a French multidisciplinary group called CERBER (*Comité d'Etudes et de Réflexion sur les Biosimilaires en Rhumatologie*) was convened to assess the patients' information, knowledge about biosimilars and to assess the patients' perspectives on these medications.

2. Methods

2.1. Inclusion criteria

The assessment aimed at French patients aged 18 and more and suffering rheumatoid arthritis or spondyloarthritis. Respondents did not have to be treated by a biological agent to be included in the study.

2.2. The questionnaire

The assessment was developed by CERBER in collaboration with three rheumatologists, a pharmacist, a biologist, three patients including two representatives of the patients' association AFS (Association France Spondylarthrite) and the director of the patients' association ANDAR (*Association Nationale de Défense contre l'Arthrite Rhumatoïde*). The assessment is described in the Fig. 1. It first assessed the patients' level of knowledge about biosimilars and questioned patients about their sources of information about biosimilars. The second part of the assessment incorporated an informative section developed by CERBER about biological drugs and biosimilars. After the informative section, all respondents were asked about their perspectives on biosimilars. The last part of the assessment aimed to identify influent sources of information, incentives and deterrents to patients' concurrence to switch from the originator bDMARD to its biosimilar.

The final assessment was available online from March to July 2017. Several rheumatology departments, rheumatologist associations and national patient associations, were responsible for relaying the assessment to the patients. Leaflets were sent to several rheumatology departments and rheumatologists offices. Weblinks were published on patients associations websites and journal. The recruitment was self-selective.

2.3. Ethics and consent

Responders were informed on the purpose of the assessment. Their volunteering to respond the assessment was considered as a consent to publish the material. This work has received the ethics committee approval.

2.4. Statistical considerations

Results were described by usual basic statistical variables. In order to identify the main factors that encourage or deter the patients to accept switching from the originator bDMARD to its biosimilar, univariate and multivariate statistical tests were conducted with a α risk of 5%, and a 1-β risk of 10%. Considering multiple comparisons, Bonferroni correction was used to adjust the risk.

3. Results

3.1. Respondents demographics

Owing to the large assessment spreading methods, the number of requested patient and the response rate could not be determined. By the closing of the survey, a total of 629 respondents had participated. The median age was 57 and 77% of respondents were women. Out of the 629 respondents, 65% had Rheumatoid Arthritis (RA) and 35% had Spondyloarthritis (SA); Most of respondents (68%) had already been treated with biological agents but only 7% had already been treated with biosimilar agents. The characteristics of population are detailed in Table 1.

The flow chart is detailed in Fig. 2. Out of the 629 respondents, 273 patients knew what biosimilars were. Only 44 respondents were treated with biosimilars. Most of the 229 biosimilar-naive

Table 1
Characteristics of respondents.

	Characteristic	*n* = 629	%
Sex	Female	486	77.3%
	Male	143	22.7%
Age	Under 30	20	3.2%
	30–65	457	72.7%
	Over 65	152	24.1%
Rheumatic disease	Rheumatoid arthritis	408	64.9%
	Spondyloarthritis	221	35.1%
Date of diagnosis	Less than 5 years before	145	23.0%
	More than 5 years before	484	77.0%
Treatment	Patients who were or already had been treated with a biological medication	393	62.9%
	Patients who were or already had been treated with a biosimilar medication	44	7.0%
Medical follow-up	Exclusive non-hospital follow-up	172	27.3%
	Hospital and non-hospital follow-up	191	30.4%
	Exclusive hospital follow-up	266	42.3%
Patient association	Member of a patient association	376	59.8%
Marital status	Single	173	27.5%
	Attached/Married	456	72.5%
Education level (equivalence)	General Certificate of Secondary education/9th grade	20	3.2%
	Vocational Certificate obtained 2 years after 9th grade	135	21.5%
	High-school Degree	134	21.3%
	Two-year university degree/12th grade	145	23.0%
	More than two-year university degree	195	31.0%
Professional status	Current occupation	303	48.2%
	Retired/Non-working	326	51.8%
Occupation	Craftsman–Trader	42	6.7%
	Executive	191	30.4%
	Intermediary occupations	233	37.0%
	Employee	68	10.8%
	Worker	72	11.3%
	Non-working/Retired/Unemployed workers	23	3.6%

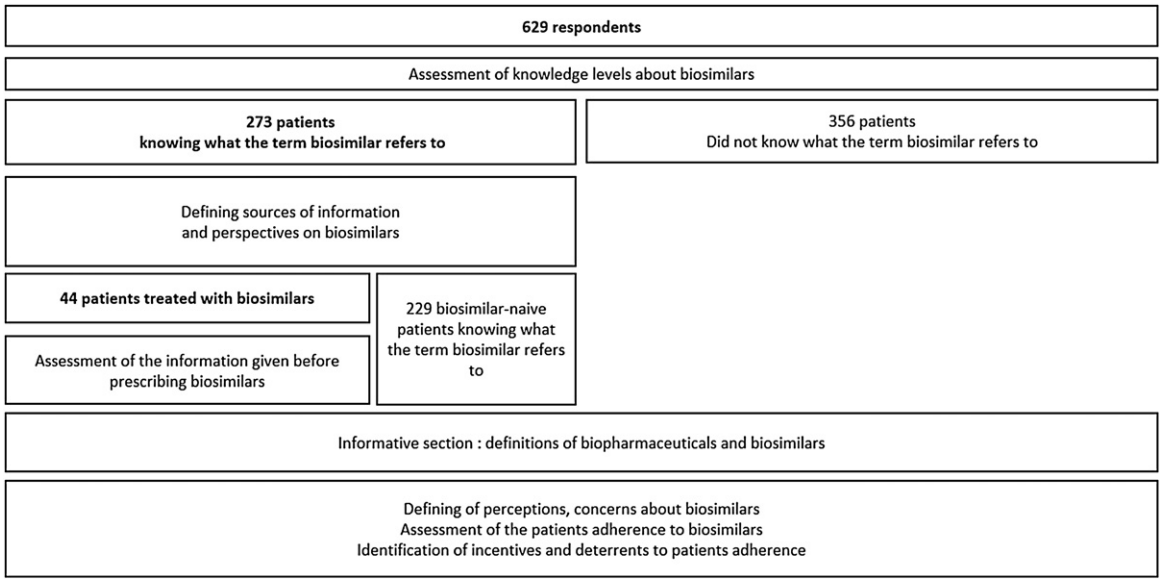

Fig. 2. Flow chart.

patients knowing what the term "biosimilar" refers to (187/229) were members of a patient association.

3.2. Knowledge and sources of information

There were great disparities in patients' knowledge levels about biosimilars. Out of 629 respondents, 176 (28%) had never heard of biosimilars (including 89 patients currently treated with a biological agent), 180 (29%) were aware of their existence without knowing what it was, 211 (34%) knew what the term "biosimilar" referred to, and only 62 (9%) felt familiar with biosimilars (including 14 patients currently treated with a biosimilar agent). Hospital follow-up, a prior or current biological treatment, a prior or current biosimilar treatment and being member of a patient association were demographic factors significantly associated with greater knowledge levels about biosimilars ($P < 0.05$; Table 2).

Out of the 273 patients who were aware of the existence of biosimilars, 65% felt insufficiently informed about biosimilars. Among the 44 patients treated with biosimilars, 29 (66%) felt insufficiently informed about biosimilars. The main sources of information about biosimilars were patient associations (50%), rheumatologists (39%), specialized magazines (30%) and the internet (20%) (Fig. 3).

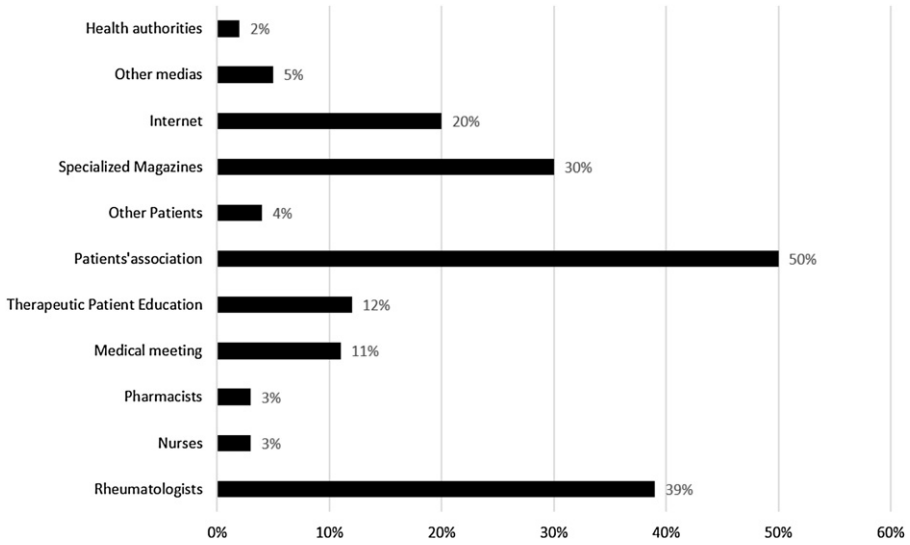

Fig. 3. Main patients' sources of information about biosimilars.

Table 2
Factors statistically associated with greater knowledge about biosimilars.

Factor	OR	IC	*P*-value
Education level ( )	1.44	0.98–2.13	0.06
Date of diagnosis (> 5y/< 5y)	0.93	0.63–1.37	0.69
Previously treated with bDMARD (y/n)	1.83	1.29–2.60	< 0.05
Previously treated with biosimilar (y/n)	3.89	1.45–13.12	< 0.05
Member of a patients' association (y/n)	1.92	1.36–2.71	< 0.05
Hospital follow-up(y/n)	2.01	1.37–2.97	< 0.05

The two sources of information significantly associated with a sufficient information feeling were the rheumatologist (OR 2,31; IC 97.5% [1.35;4.00] ; $P < 0.05$) and the Therapeutic Education of Patient (TPE) sessions (OR 3.67; IC 97.5% [1.61-8.69]; $P < 0.05$).

3.3. Information given before switching from originator to biosimilar treatment

Out of the 44 patients treated with biosimilars, only 33% felt sufficiently informed about biosimilars. Among the 21 converted patients (whose originator biologic had been switched for its biosimilar), 4 patients had not been informed that they were going to be treated with a biosimilar. Among the 17 informed patients, 4 patients had not been asked for their consent.

The given information is detailed in Table 3. None of the 21 converted patients had been informed that the molecular structure was not strictly the same. Only 35% of them were aware of the existence of clinical studies demonstrating equivalent efficacy, safety and immunogenicity. Surprisingly, the argument "it's the same treatment" had been more often used in case of introduction of biosimilar (51%) than in switches (11%).

According to most of the 629 responders, informing the patient is necessary (97%), useful in order to accept the treatment (91%) and it could improve compliance (88%). Fifteen percent thought the information given could enhance fears.

3.4. The patients' perspective on biosimilars

The questionnaire assessed the 629 respondents' theoretical position about biosimilars. Almost 25% of them had no fear of being treated with biosimilar drugs. Most of them worried about the biosimilar being less effective (60%), less safe (57%) and low-quality (53%) compared to the originator bDMARD. 88% contested the principle of the extrapolation of clinical indication and 49% would prefer having data about efficacy and safety in every indication.

Switching from the originator biologic to its biosimilar made sense for 35% of the 629 respondents.

3.5. The key role of the rheumatologist

A large part (57%) of the 629 respondents thought the switching decision should continue to take place on medical prescription (57%), after a shared-decision-making process between the rheumatologist and the patient (69%). Only 3% of the responders approved the medication substitution by the pharmacist. Rheumatologists also were considered the most influent source of information about biosimilars (78% of respondents) before the patient associations (64%) and health authorities (40%). 57% of respondents trusted the rheumatologist about the switching issue but 11% worried that refusing the biosimilar could alter the relationship between them and their rheumatologist.

Table 3
Given information to patients treated with biosimilar.

Given information	Patients treated with biosimilar (initiation or switch)	Patients switching from originator to biosimilar
The word "biosimilar" has been pronounced	72.0%	70.6%
It is the same treatment	51.1%	11.0%
The molecular structure is not strictly the same	17.9%	0%
Clinical data have shown similar efficacy and safety profile comparatively to the originator bDMARD	32.1%	35.3%
It is a generic treatment	44.4%	47.1%
The word "generic" has not been pronounced	55.6%	52.9%

3.6. Patients ambivalent feelings about medico-economics concerns

Almost all the respondents (99%) considered themselves sensitive to medication costs. Half of them (47%) approved the principle of reducing-health-costs policies; but only 21% had no hesitation concerning the use of biosimilars because of the potential savings for the healthcare system. This ambivalence between the patients' concerns about medico-economical issues and their reluctance to be treated with biosimilars may be partially explained by a common preconception assuming that less expensive is lower quality (30%).

3.7. Prospects about patients' concurrence switching from originator biologic to its biosimilar

After giving their theoretical perspectives on biosimilars, the respondents were also asked about their personal willingness to switch their biological treatment to its biosimilar equivalent. Among the 629 respondents, 15% would strictly refuse the change. Most of the respondents (55%) would accept to change over the medications but would be worried about quality (52%), efficacy (37%) and safety (42%) or would fear a resurgence of their rheumatism during the switch period (37%). Although 36% of respondents declared having no fear of taking a biosimilar, only 15% would accept to change their originator bDMARD treatment to its biosimilar without worrying. Moreover, 42% of respondents would be more attentive to any changes concerning safety and efficacy and 23% would be worried and interrupt the treatment if in doubt.

3.8. Factors associated with fears about biosimilars

A poor understanding of the biosimilar definition was significantly associated with greater fear of being treated with biosimilars in the univariate analysis (OR 2.10 [1.15–3.82] *P*-unitvariate = 0.0006; *P*-multivariate = 0.055.

A strong trust relationship with the rheumatologist and a sufficient information feeling about biosimilars were significantly associated with less fears of being treated with a biosimilar treatment (respectively OR 0,56 [0,34-0,93] *P*-unitvariate = 0.018; *P*-multivariate = 0.14; and OR 0,53 [0.29-0.5] *P*-multivariate = 0.02 ; *P*-multivariate = 0.01). In the multivariate analysis, the only independent factor associated with lower fears of being treated with a biosimilar was the sufficient information feeling about biosimilars.

3.9. Incentives and deterring factors of converting patients to biosimilars

Respondents were asked about most influent arguments and sources of information to either accept or refuse to change the originator biological treatment to its biosimilar. Scientific arguments acted as the best incentive to convert patients to biosimilar prescription, especially the existence of safety and efficacy data (47% of respondents) and the biosimilarity definition (33%). Another motivation was the prospect of savings to-come for the national health system (20%). The most persuasive sources of information were rheumatologists (considered influent by 78% of respondents), the patient associations (64%) and the national health authorities (40%).

According to respondents, the fear of less efficacy (61%) and safety (71%) comparatively to the originator biologic agent and poor trust in the pharmaceutical companies (40%) acted as the main deterring factors.

4. Discussion

This is the first nation-wide study assessing French patients' perceptions of biosimilars in rheumatology.

Considering the patients' associations-mediated propagation of the questionnaire and the self-selective recruitment, we are aware that the patients sample in this survey may not be representative. Indeed, 60% of respondents were members of patient associations, first source of information in this survey. The patients' knowledge level about biosimilars may therefore be overestimated. Biosimilar are still widely unknown by patients. Although the rate of patient who had already heard about biosimilars was enhanced in comparison with previous assessments concerning other populations [8–12], only 43% of responders knew what it refers to and most of respondents considered the information insufficient. This suggests a lack of information from the medical and paramedical communities which were the only sources of information associated with sufficient information feeling.

If the EULAR recently recommended to provide patients with information on biosimilars and obtain the patients' consent to change medications [13], former studies [7,9] showed that rheumatologists were reluctant to provide information, worrying about increasing patients' fears and leading their attention away from major recommendations (for example warning about infectious risks, management of biologics, etc). Thus, rheumatologists seem to provide patients with selective information before proposing to switch medications (as an example converted patients were not aware of the non-strictly identical molecular structure between a biologic agent and its biosimilar) but they also often do not let patients know about the existence of clinical efficacy and safety data about biosimilars (35% of converted patients).

However, this survey suggests that an information given could reassure patients and enhance their concurrence to switch medication and their compliance with the biosimilar treatment. This acknowledgement could enhance rheumatologists' confidence in biosimilars and convince them to inform their patients about biosimilars when thinking of switching medications [14–16].

According to earlier studies, patients suffering rheumatoid arthritis are reluctant to change their treatment, even when the activity of the rheumatic disease requires it [17] because they fear loss of efficacy or adverse effects. In the case of switching from an originator to its biosimilar, these risks seem less acceptable because the rheumatic disease is well-controlled by the originator bDMARD. Patients have no personal or clinical interest in switching from the originator biologic to its biosimilar, but they fear risking losing control of their rheumatism. Patients may also be emotionally tied to their treatment as a chronic disease treatment.

Another deterring factor raised in this survey is the common misconception of biosimilars as lower-grade medicine, "counterfeits", by analogy with generics. Lower cost often means lower quality according to patients who do not differentiate production cost and final cost [18]. Some patients declared they would be more attentive to any change in efficacy or adverse effects. The lack of trust in the treatment could lead to nocebo effect: people may involuntarily interpret symptoms as adverse effects of the biosimilar or recrudescence of their rheumatism. Recent studies [4,19–21] suggest that this nocebo effect may lead to conclude at therapeutic failure or intolerance and lead to abandon the biologic medication. French patients also have an ambivalent conception of the medico-economic issue. Almost all of them are sensitive to the cost of their treatment, but they still are reluctant to agree with cost-reducing-health policies. This ambivalence is probably strongly related to the historical French health care system and the slow realization of its current threatened state.

This survey highlights the lack of patients' information about biosimilars. According to recent EULAR recommendations, switch-

ing medications should be a shared-decision process between the patient and one's rheumatologist. The rheumatologist seems to play a key role in this information. In their recent position statement [22], French Rheumatology Society and Inflammatory Rheumatic Disease club recently considered that rheumatologists have a unique position to predict which patient are good candidates to interchangeability. With the help of available clinical safety and efficacy data and medico-economic considerations, information given could be an incentive for a patient's agreement to switch. It could be reassuring and could help preserving the trust between the patient, one's treatment and one's rheumatologist.

Disclosure of interest

The authors declare that they have no competing interest.

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