BioDrugs
DOI 10.1007/s40259-016-0202-5

ORIGINAL RESEARCH ARTICLE

Rheumatologists' Perceptions of Biosimilar Medicines Prescription: Findings from a French Web-Based Survey

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Abstract

Background Healthcare cost savings are closely linked to prescribers' confidence in and acceptance of the prescription of biosimilar drugs.

Objectives The aim of this study was to assess the knowledge, experience and opinions of hospital-based and office-based French rheumatologists with regard to biosimilar medicines and to identify the barriers to and possible options to promote their prescription.

Methods A web-based, self-administered survey was conducted among French rheumatologists from June 8 to August 2, 2015.

Results A total of 116 rheumatologists responded to the survey. Many reported having little knowledge and a lack of available information about biosimilar drugs, especially office-based rheumatologists. 98.3% of the respondents had at least one question about biosimilars, and seven in ten raised issues regarding substitution, iatrogenic effects or cost savings that might be achievable. Only eight rheumatologists had already prescribed a biosimilar drug. The most common barriers reported were indication extrapolation and a lack of data about tolerability. Nine out of ten physicians thought that starting a treatment with a biosimilar drug in biologic treatment-naïve patients was possible. The rheumatologists' opinions were rather favorable towards the implementation of biosimilars, but a majority expressed a negative opinion about substitution by the pharmacist.

Conclusions Our survey gave a better appreciation of the concerns associated with biosimilar prescriptions. Targeted communication initiatives, deeper experience and availability of new clinical data may help to address the outstanding questions and should overcome the misunderstandings surrounding biosimilar drugs among rheumatologists.

Key Points

Many French rheumatologists, especially office-based rheumatologists, are not familiar with and feel poorly informed about biosimilar medicines.

The major concerns regarding biosimilar prescription are a lack of available data about tolerability, extrapolation of efficacy and safety from one therapeutic indication to all indications of the reference biological product, and substitution by the pharmacist of a reference medicinal product with its biosimilar product.

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Electronic supplementary material The online version of this article (doi:10.1007/s40259-016-0202-5) contains supplementary material, which is available to authorized users.

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Published online: 15 November 2016

1 Introduction

Infliximab was the first monoclonal antibody to be approved in the European Community as a biosimilar medicine, and was launched across several European countries in February 2015 [1]. Biosimilar medicines are complex molecules whose commercialization is authorized when branded biological drugs have become off-patent. Due to inherent variability in their manufacturing process, biosimilar drugs are highly similar but not strictly identical to their reference medicinal products. Compared to generic drugs that have chemical structures identical to their reference medicines, biosimilar medicines have to meet a much greater number of requirements to be approved. These include rigorous preclinical studies, a phase I clinical study demonstrating pharmacokinetic/pharmacodynamic equivalence and a phase III clinical study, in order to confirm there are no meaningful differences between the biosimilar and the originator drug in terms of quality, safety and efficacy. Extrapolation of efficacy and safety from the indication that was assessed in clinical studies to all indications of the reference medicinal product is authorized by the European Medicines Agency (EMA), under the condition of providing adequate justification [2–8].

Several studies showed there is a very promising potential for healthcare cost savings associated with biosimilar medicines prescription [9–11]. Indeed, seven biological drugs [adalimumab (Humira®), infliximab (Remicade®), rituximab (Mabthera®), etanercept (Enbrel®), insulin glargine (Lantus®), bevacizumab (Avastin®) and trastuzumab (Herceptin®)] were among the top ten highest selling drugs worldwide in 2014 [12]. All have lost or will lose their patent in years to come, offering pharmaceutical companies the opportunity to focus their drug development strategies towards biosimilar medicines [13, 14].

However, those cost savings are closely linked to prescribers' confidence in and acceptance of the prescription of biosimilar drugs. Numerous issues related to biosimilar drugs, such as manufacturing process, efficacy, safety, indication extrapolation or substitution by a pharmacist, have been raised [3, 5, 15]. It seemed essential to determine whether rheumatologists are in real need of a broader range of information about biosimilar medicines, and to gather their views on such issues. To date, some biosimilar surveys have been carried out among physicians from different fields [16–19]. Apart from a Japanese study conducted by Tanabe et al. in May 2015 among 100 eligible rheumatologists who answered they "were aware of biosimilar medicines," the surveys involved only a few rheumatologists per country [16].

Our study aimed to produce a comprehensive picture of the knowledge, experience and opinions of both hospital-based and office-based French rheumatologists related to biosimilar medicines and to identify expectations, barriers and possible options to promote prescription.

2 Methods

A web-based, self-administered survey was conducted in France over 8 weeks, from June 8 to August 2, 2015. This study was conducted by the OMEDIT (Observatoire des MÉdicaments, des Dispositifs médicaux et de l'Innovation Thérapeutique) of Alsace, which functions within the regional health agency (Agence Régionale de Santé—ARS).

2.1 Development of the Survey Questionnaire

A questionnaire was designed especially for the study by a task group made up of four pharmacists, one rheumatologist and one public health physician and epidemiologist. This questionnaire, made up of 22 questions, was divided into four parts in the following manner: (1) characteristics of respondents, (2) knowledge, (3) experience and (4) opinion related to biosimilar medicines (see the electronic supplementary material, online resource 1). The main part of the web questionnaire was composed of closed-ended questions since these were more convenient for rheumatologists to answer, required less coding and were easier to analyze. A last open-ended question permitted the rheumatologists to express their views on the subject.

2.2 Pilot Study

A pilot study was conducted with seven rheumatologists to ask them for feedback about difficult or ambiguous questions and completeness with regard to the research topic. The time taken to complete the questionnaire was also recorded, and the survey was expected to take $\sim$10 min to fill in. This pre-test enabled us to discard or modify any unnecessary, difficult or ambiguous questions, to re-word or re-scale any question that was not conveniently answered and to check that all questions were answered.

2.3 Target Population

Nearly 500 French rheumatologists were invited by email to take part in the web survey. Participation was also enhanced by the "National Union of Rheumatologists" (Syndicat National des Médecins Rhumatologues) and the "Inflammatory Joint Disease Working Group of the French Society for Rheumatology" (Club "Rhumatismes et

Inflammations") via a newsletter. A reminder was sent at the mid-point of the investigation period to stimulate the rheumatologists' participation.

2.4 Ethical Approval

Information strictly required for the purpose of the study was collected in the form of anonymized data. A file containing the electronic addresses of the rheumatologists was created using data from the CFMR ("Collège Français des Médecins Rhumatologues) website and stored with respect to the approval of the French data protection authority CNIL (Commission nationale de l'informatique et des libertés). The study was registered on a data protection register (Registre informatique et libertés) kept up to date by the local CNIL correspondent of ARS Alsace, warranting compliance with the conditions under which the survey was held.

2.5 Statistical Analysis

Major changes to the questionnaire were made following the pilot study; thus, questionnaires of the pilot study were not combined with the main study for analysis. Data were gathered and analyzed using Microsoft Excel® 2007. Descriptive statistics were reported using numbers, averages and standard deviations, proportions and 95% confidence intervals (CIs). Pearson's Chi-squared tests with Yates' continuity correction (χ^2 tests) were performed using R, version 3.1.0. A p value below 0.05 was considered to be of statistical significance.

3 Results

3.1 Respondents' Characteristics

A total of 116 rheumatologists participated in the survey, which represents 4.5% of rheumatologists in 2015 in France [20]. Of these, 76 respondents were men. They were between 32 and 77 years old, with an average age of 53.8 (standard deviation ±8.8). Most of the respondents (79 rheumatologists, i.e., 68.1%) reported more than 20 years of work experience in rheumatology. Among all respondents, 34 (29.3%) were hospital-based rheumatologists, 38 (32.8%) were office-based rheumatologists and 44 (37.9%) were both hospital and office based. Note, as on January 1, 2014, 2598 rheumatologists were working in France, 57.2% were men, they were aged 52.8 years on average, and 70.9% were office based or both hospital and office based [21].

3.2 Knowledge and Information Needs About Biosimilar Medicines

Many respondents stated they had little [64 rheumatologists, i.e., 55.2% (95% CI 46.1–64.2)] or even no knowledge [four rheumatologists, i.e., 3.4% (95% CI 0.1–6.8)] about biosimilar medicines (Fig. 1). Only six physicians [i.e., 5.2% (95% CI 1.1–9.2)] felt very well-informed about this issue. Hospital-based rheumatologists were more likely to be familiar with biosimilar drugs compared with office-based rheumatologists. In fact, 64.7% (95% CI 48.6–80.8) of hospital-based rheumatologists stated they had good or very good knowledge of biosimilar drugs, versus 26.3% (95% CI 12.3–40.3) of office-based rheumatologists ($p < 0.01$, χ^2 test). In the same way, 61.8% (95% CI 45.4–78.1) of hospital-based rheumatologists reported being well-informed or very well-informed about biosimilar medicines, versus only 23.7% (95% CI 10.2–37.2) of office-based rheumatologists ($p < 0.01$, χ^2 test).

When asked about the diversity of information resources, a significant proportion of rheumatologists reported being informed through self-study and scientific publications [83.6% (95% CI 76.9–90.4)], pharmaceutical companies [75.9% (95% CI 68.1–83.6)], continuous training [72.4% (95% CI 64.3–80.5)] or colleagues [physician in 54.3% (95% CI 45.2–63.4) or pharmacist in 19.0% (95% CI 11.8–26.1) of cases]. Many also quoted seminar and conference attendance. It is noteworthy to mention that the national health insurance was identified as an information resource about biosimilar drugs by only a single rheumatologist out of 116.

A large proportion of respondents held the view that a biosimilar drug is similar to a reference medicinal product that has gone off-patent [99 rheumatologists, i.e., 85.3% (95% CI 78.9–91.8)]. They also pertinently stated that a biosimilar medicine has no meaningful differences from a reference medicinal product in terms of quality [85.3%

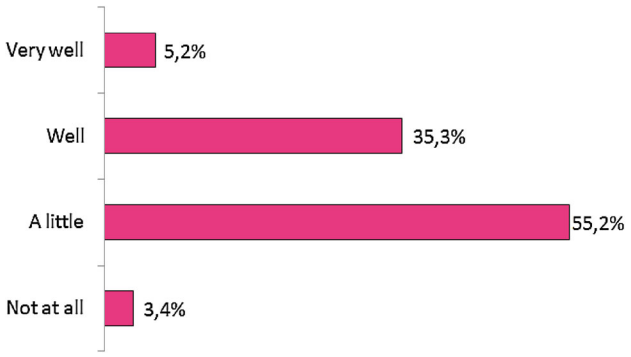

Fig. 1 Survey respondents' ($n = 116$) responses to the question "Overall, how well do you know biosimilar medicines?"

(95% CI 78.9–91.8)], safety [80.2% (95% CI 72.9–87.4)] and efficacy [89.7% (95% CI 84.1–95.2)]. However, 45.7% (95% CI 36.6–54.8) of rheumatologists believed that a biosimilar medicine is a drug for which marketing authorization is granted on the sole investigation of pharmacokinetic bioequivalence with its reference medicinal product. Only 64.7% (95% CI 56.0–73.4) answered that assessment of biosimilarity requires more comprehensive data than generic drugs.

Many rheumatologists expressed a lack of confidence in biosimilar medicines prescription because they did not feel sufficiently informed, especially about safety matters (Fig. 2). Almost all survey participants [114 rheumatologists, i.e., 98.3% (95% CI 95.9–100.0)] had at least one remaining question about biosimilar medicines. Approximately seven out of ten rheumatologists raised concerns regarding substitution [69.8% (95% CI 61.5–78.2)] or iatrogenic effects, side effects or immunogenicity issues [69.8% (95% CI 61.5–78.2)], and more than a half had questions about quality [58.6% (95% CI 49.7–67.6)], manufacturing processes [57.8% (95% CI 48.8-66.7)] or efficacy [51.7% (95% CI 42.6–60.8)]. Cost issues were also addressed by rheumatologists, many questioning the savings that may be associated with biosimilar drug uptake [68.1% (95% CI 59.6–76.6)] or the acquisition cost of biosimilar medicines [53.4% (95% CI 44.4–62.5)].

3.3 Experience of French Rheumatologists

At the time of the survey, only eight rheumatologists [6.9% (95% CI 2.3–11.5) of the respondents] had already prescribed at least one of the following biosimilar medicines available in France: biosimilar epoetin (Binocrit® or Retacrit®), biosimilar filgrastim (Ratiograstim®, Tevagrastim®, Nivestim® or Zarzio®), biosimilar somatropin (Omnitrope®) or biosimilar infliximab (Remsima® or Inflectra®) [14]. Five rheumatologists had already prescribed biosimilar infliximab, while the others had prescribed biosimilar filgrastim or biosimilar epoetin. Three rheumatologists indicated they prescribed biosimilar drugs on an exceptional basis, another physician prescribed biosimilar drugs less than monthly, and the last four on at least a monthly basis.

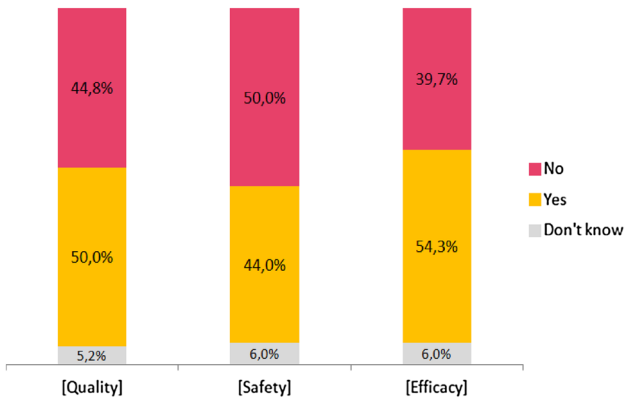

Fig. 2 Survey respondents' ($n = 116$) responses to the question "Do you feel sufficiently informed to prescribe a biosimilar medicine?" (quality, safety and efficacy aspects rated separately)

3.4 Opinion, Incentive Elements and Barriers to Acceptance and Widespread Prescription of Biosimilar Medicines

Nine rheumatologists out of ten [90.3% (95% CI 84.8–95.7)] quoted "healthcare cost savings" as a positive element that might incentivize prescription of biosimilar medicines. "Release of resources allowing treating additional patients" [60.9% (95% CI 51.8–70.0)] and "positive impact on patients' access to innovative drugs" [49.1% (95% CI 39.8–58.4)] were ranked next in importance, followed by "health policy-makers incentives" [46.4% (95% CI 37.2–55.7)].

The most common barriers to the prescription of biosimilar medicines reported were "extrapolation of efficacy and safety from one therapeutic indication of the biosimilar drug to all indications of the reference medicinal product" [67.2% of responses (95% CI 58.7–75.8)] and "lack of information about tolerability" [66.1% of responses (95% CI 57.4–74.7)]. "Risk of increasing patients' worries and concerns," "lack of clinical trials" and "patients' wishes to be treated with the reference medicinal product" followed closely, with those opinions held by 59.1% (95% CI 50.1–68.1), 57.0% (95% CI 47.9–66.1) and 55.3% (95% CI 46.1–64.4) of rheumatologists, respectively.

For most rheumatologists [88.8% (95% CI 83.1–94.5)], it was conceivable to start a treatment with a biosimilar medicine in biologic treatment-naïve patients, namely patients who were not previously treated with the reference medicinal product. Only one quarter of the survey participants (i.e., 29 rheumatologists) answered they could envision a biosimilar switch if patients were previously treated with a reference medicinal product and they responded well to this treatment. In patients treated with a reference medicinal product but experiencing treatment failure, 81.9% (95% CI 74.9–88.9) of the rheumatologists would consider a treatment initiation with the biosimilar drug of another reference product.

Physicians were asked whether they agreed with some statements about biosimilar medicines. Some examples of the survey responses are given. Rheumatologists were rather favorable towards the implementation of biosimilar medicines (Fig. 3), but a majority expressed a negative opinion about substitution by the pharmacist of a reference

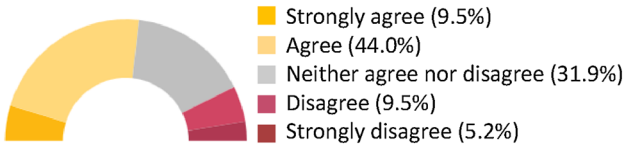

Fig. 3 Survey respondents' ($n = 116$) responses to the question "To what extent do you agree or disagree with the following statement: I am in favor of the implementation of biosimilar medicines?"

Fig. 4 Survey respondents' ($n = 116$) responses to the question "To what extent do you agree or disagree with the following statement: I approve the substitution by a pharmacist of a reference medicinal product by its biosimilar product?"

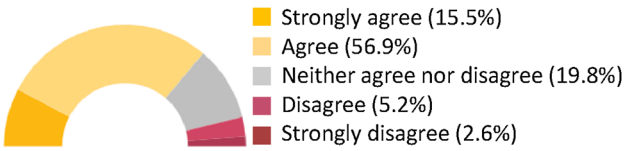

Fig. 5 Survey respondents' ($n = 116$) responses to the question "To what extent do you agree or disagree with the following statement: biosimilar medicines prescription allows reducing healthcare costs?"

medicinal product with its biosimilar compound (Fig. 4). Close to three-quarters of the respondents were aware of the cost-saving potential of biosimilar medicines (Fig. 5). Nevertheless, about a half of physicians thought these savings would be limited [52 rheumatologists, i.e., 44.8% (95% CI 35.8–53.9)] or even negligible [seven rheumatologists, i.e., 6.0% (95% CI 1.7–10.4)].

4 Discussion

This survey provided a depth of insight into the knowledge, experience and opinions of French rheumatologists regarding biosimilar medicines.

The study highlighted the lack of experience of French rheumatologists with the prescription of biosimilar medicines, which may be related to the very recent launch of a biosimilar drug for the treatment of rheumatologic disorders and its exclusive approval for hospital use. The study also revealed that a significant percentage of physicians were not familiar with and felt poorly informed about biosimilar medicines, especially office-based rheumatologists. However, they will soon be fully involved with the challenge of prescribing biosimilar drugs, such as adalimumab or etanercept, that are administered by the subcutaneous route at home. Therefore, it is particularly important to provide them with the appropriate training on these drugs. As a possible provider of information on the biosimilar question, the French health insurance was noticeably absent in the survey responses. Its involvement in supplying information and in enhancing biosimilar medicines uptake is essential, just as it is for generic drugs.

The major issues raised by our survey were related to skepticism and weaknesses in communicating information about the quality, safety and efficacy of biosimilar medicines. Several information resources may help address these concerns, first of all the European Public Assessment Reports (EPAR) that are published by the EMA for every medicine authorized at an EU level. These reports contain the necessary information that has justified the granting or refusal of the marketing authorization of medicinal products, including biosimilar medicines [22, 23]. For instance, the clinical data demonstrating similarity between biosimilar infliximab CT-P13 and the reference biological medicinal product (Remicade®) consisted of two pivotal studies: PLANETAS, a phase I randomized controlled trial in patients with ankylosing spondylitis (AS), and PLANETRA, a phase III randomized controlled trial in patients with rheumatoid arthritis (RA). Both studies, the results of which are published in the EMA reports, showed there were no clinically significant differences in the pharmacokinetics, efficacy, safety and immunogenicity profiles between CT-P13 and the reference medicinal product [1, 24, 25].

The survey responses suggested there was a lack of understanding of the biosimilar concept, such that some respondents did not note any difference in the development philosophies between biosimilars and new active substances [26]. For instance, the indication extrapolation rules led to approval by EMA of biosimilar infliximab CT-P13 for all the indications held by the reference product, including RA and AS, but also psoriatic arthritis, psoriasis, ulcerative colitis and Crohn's disease. This principle is likely to confuse some physicians, especially those who prescribe a biosimilar drug for an indication that was not specifically evaluated through clinical trials during its clinical development. Here again, EMA reports contain information related to the granting of the totality of the indications, in a specific paragraph named "2.6.3 Extrapolation of efficacy and safety". Moreover, some studies are ongoing in order to provide factual evidence, especially in the field of gastroenterology [27–30]. In addition, a growing number of switch studies aiming to support interchangeability have been or are currently being conducted [29–34]. For instance, the NOR-SWITCH study is a national, randomized, double-blind study aiming to evaluate the efficacy and safety of switching from innovator infliximab to biosimilar infliximab in patients suffering

from ulcerative colitis, Crohn's disease, RA, spondyloarthritis, psoriatic arthritis and psoriasis. First results of this study, funded by the Norwegian government, are expected to be reported in the fall of 2016 [35]. As part of a risk-management plan and pharmacovigilance system, European registries enable the monitoring of biosimilar drugs' safety [36].

In spite of the doubts expressed above, rheumatologists were rather favorable towards the implementation of biosimilar medicines and were aware of the potential cost savings associated with biosimilar drugs prescription. Several budget impact analyses have already estimated the cost savings linked to the use of infliximab biosimilar for the treatment of RA and/or some other inflammatory autoimmune diseases in European countries [37–43]. For instance, Kim et al. showed that the total 5 year savings for the management of RA with biosimilar infliximab across the UK, Italy, France and Germany ranged from €96 million to €433 million according to different price discount scenarios [42].

This information about the cost-saving potential is somewhat reassuring, especially since rheumatologists are in agreement with prescribing biosimilar drugs in appropriate cases, particularly in biologic-naïve patients or in patients experiencing treatment failure with another class of biologic drug. However, many rheumatologists did not support substitution of a reference medicine with its biosimilar equivalent by a pharmacist. This opposition is somewhat reminiscent of that already observed with generic drugs.

To date, few studies have assessed physicians' perceptions and experience with biosimilar medicines [16–19]. We can quote the Alliance for Safe Biologic Medicines (ASBM) European physicians survey on biosimilars that was carried out in 2013 in five Western European countries: France, Germany, Italy, Spain and the UK [17]. This survey focused on doctors' prescribing habits and understanding of biosimilars, and included 470 specialists, including 80 rheumatologists. This study showed physicians' knowledge of biosimilars remained insufficient, since only 22% considered themselves as very familiar with biosimilar medicines and a quarter of participants "could not define" or "had never heard" about biosimilar drugs before. Furthermore, 62% considered it was "not acceptable" for a pharmacist to determine which biologic medicine to dispense at initiation of treatment. Our study echoes similar concerns for the French community of rheumatologists.

We chose to focus our survey on rheumatologists, especially because biosimilar prescription constitutes a major topical issue in their field of expertise with the recent introduction of biosimilar infliximab and for the upcoming commercial launch of biosimilar etanercept and adalimumab. It is worth mentioning biosimilar infliximab was the only biosimilar medicine available in the field of rheumatology at the time the survey was conducted. However, many other physicians may prescribe biosimilar medicines, such as gastroenterologists, and they may have a different opinion on biosimilar drugs. Besides, one cannot exclude a potential participation bias, since the majority of the respondents (68.1%) had more than 20 years of professional experience in rheumatology and the view of younger rheumatologists may not have been fully captured. Finally, our study reflects the knowledge, experience and opinion of 4.5% of French rheumatologists (116 out of 2598 rheumatologists in France in 2014), which may prevent the extrapolation of the results to either national or international levels. We note, however, that the rate of rheumatologist participation in other biosimilar surveys has been lower regarding the percentage of the total number of rheumatologists in the country. For instance, we can quote the ASBM Latin American survey, which, while showing a 6.0% response rate (399 out of 6650 prescribers surveyed), collected the responses of 52 rheumatologists from four different countries, thus limiting the value of the results at the country level [18]. Our survey was conducted very recently and thus provides current information on physicians' understanding on biosimilar medicines. This constitutes a major advantage since the only European study on biosimilar drugs was carried out back in 2013, prior to the launch of biosimilar infliximab [16]. To our knowledge, no biosimilar survey so far has focused on such a large number of rheumatologists in a single country.

5 Conclusion

A survey was conducted in 2015 among French rheumatologists in order to assess their knowledge, experience and opinions regarding biosimilar medicines and to identify the barriers to and possible options to promote their prescription. Many French rheumatologists were not familiar with and felt poorly informed about biosimilar medicines, especially office-based rheumatologists. The major concerns regarding biosimilar prescription were a lack of available data about tolerability, extrapolation of efficacy and safety from one therapeutic indication to all indications of the reference biological product, and substitution by the pharmacist of a reference medicinal product with its biosimilar product. Further work is needed to enhance understanding and to overcome misperceptions relative to biosimilar medicines among rheumatologists. Targeted communication initiatives, additional experience in biosimilar drug prescription and availability of new clinical data may help to address these concerns.

Acknowledgements The authors would like to thank all rheumatologists who participated in the pilot study for giving their impressions and advice—Marc Ardizzone, Hélène Bauer, Emmanuel Chatelus, Jacques-Eric Gottenberg, Paul Moreau, Nawal Rahal, Laëtitia Sparsa—and everyone who provided assistance in the survey's dissemination: the "National Union of Rheumatologists" (Syndicat National des Médecins Rhumatologues) and the "Inflammatory Joint Disease Working Group of the French Society for Rheumatology" (Club "Rhumatismes et Inflammations"). The authors would like to thank Valérie Leray for proofreading and linguistic review of the manuscript. Last but not least, the authors would like to gratefully acknowledge all participants in the survey for completing the questionnaire.

Author contributions MB conceived and designed the survey. BM, MCRV, DL, CS and MV were involved in validating the survey questionnaire. MB, CS and JS were involved in the survey's dissemination. MB collected and analyzed the data. All authors checked the accuracy of the results. All authors were involved in drafting the article and revising it critically for important intellectual content. MB acts as guarantor for the content of the paper. All authors read and approved the final manuscript submitted for publication.

Compliance with Ethical Standards

Conflict of interest JS has received grants (<€10,000) from Roche, Pfizer, Abbvie, UCB and consulting fees or honorarium (<€1500) from Roche, Chugai, Bristol Myers Squibb, Abbott, UCB, GSK, LFB, Actelion, Pfizer, Merck Sharp, Novartis, Amgen, Hospira and Abbvie. MB, BM, MCRV, DL, CS and MV declare that they have no conflicts of interest.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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