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EDITORIAL

Preconceived notions about biosimilars—a French experience

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Abstract
Since the arrival of the first biosimilar monoclonal antibodies into the market, many information has been circulating, leading to preconceived notions for patients and healthcare professionals. In a pressing economic context and faced with a growing number of available biosimilars, we (clinician, patient association, biologist, pharmacists, health economists) propose to take stock by trying to distinguish facts from misconceptions.

Keywords Biosimilars · Patient · Preconceived notions · Rheumatology

At a time when many ideas circulate around biosimilars, it seems today essential to break down some of these commonly held beliefs. Associating rheumatologist, patient association, biologist, pharmacists, and health economists and approaching the subject on the original mode of the misconceptions, this editorial addresses issues around misconceptions about biosimilars. The ideas came from literature reviews, our field experiences with the patients, and several surveys conducted on the theme of biosimilars.

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Preconceived notions

"Biosimilars have value beyond the economic benefit"

The principle of biosimilarity is based on the concept of therapeutic equivalence and the interest of biosimilars remains above all economic. As with generic medicines—for the patient to whom interchangeability would be proposed—there is no clinical benefit, but satisfaction of participating in the citizen effort. The introduction of this new competition leads to an emulation between pharmaceutical companies, which can lead to an improvement in the characteristics of the products themselves (injection technique, packaging, practicality of use, etc.) or services (support, training, logistics) without constituting a major therapeutic innovation. However, even if the main argument is economic, the magnitude of direct and indirect savings in this sector of innovative and expensive products can only be beneficial.

"A reference biomedicine, having undergone several modifications since its commercialization, can be considered a biosimilar of itself"

Even if it is true that the manufacturing process for a reference biopharmaceutical evolves throughout the marketing life of the drug, it is worth remembering that each modification is the subject of a comparative study between the batches before and after the effective change. These changes, of which health professionals and patients are most often unaware, present in the majority of cases a minor risk of altering the efficacy or

safety of use of the biomedicine [1]. Therefore, no clinical trials have been requested to date following a change in the manufacturing process of a biologic. This is a main difference with the requirements for a marketing authorisation application (MAA) for a biosimilar. Indeed, a biosimilar is not considered a generic; thus, it necessitates to go through a longer pre-MAA trial phase than only bioequivalence implying phase 3 clinical trials. Thus, even if this shortcut is intended for educational purposes [2], caution must be exercised regarding its use, which is not scientifically valid.

"Explaining to the patient what a biosimilar is takes too much time"

One of the barriers to communication with the patient could come from the fear of the prescriber about spending extra time for a result he predicts disappointing [3].

At initiation, the presentation of the different options including the biosimilar does not take longer, whereas in interchangeability, whether the patient is in remission or waiting for efficiency, the change is more difficult to justify as no better efficiency is expected - that would be the case with a biobetter. Since the objective is not to immediately win the agreement of the patient, it is possible to split the information, to consider a time for reflection and thus to adapt to the rhythm of the patient by accepting the possibility of his refusal. If the intervention of other professionals is not subrogative according to the legal requirements of the prescriber, it is complementary and favorable to an informed decision-making [4]. Furthermore, this informed decision-making is provided by the Charter of Fundamental Rights of the European Union [5].

Even if some prescribers are convinced that specifying the biosimilar nature of treatment is not essential and may generate unnecessary concerns, it is demonstrated that patients are sensitive to the cost of their treatment and almost half of them adhere to the principle of generating savings with biosimilars [6]. However, they judge information on the biosimilar nature necessary and place it as a factor of acceptance at both initiation and interchangeability. Even though 15% declare fear, it remains compatible with the achievement of significant savings and is not immutable, just like refusal, provided that the approach is to propose and not to impose [7]. As an example, a European patient organization in rheumatology recently claims that "No patient should be switched from an original product to a biosimilar against the patient's decision just to reduce costs. A switch should always be based on a shared decision between patient and doctor." [8]. It is interesting to underline that in France, a regulatory agency—the National Authority for Health (HAS)—has recently taken a position on the subject by stating that the physician must not inform or decide alone but have to collaborate with the patient in the context of the shared medical decision based on the non-superiority between several therapeutic options [9].

"The nocebo effect explains the cases of failure of interchangeability"

With biosimilars, the nocebo effect springs up in rheumatology [10] when it is known for a long time [11]. Regarding biosimilars, it is often presented as a hypothesis to explain the failures of interchangeability. However, there is no formal evidence to support it and caution is still required [12, 13]. According to the drug reaction assessment method [14], it would be permissible to require the reintroduction of the biosimilar to confirm the causal link. However, the positivity of the readministration test (reappearance of the adverse effect and/or flare on subjective parameters) involving the biosimilar would not eliminate the possibility of a "real" difference for the patient. We can also wonder about the emphasis on the subjective part of composite tools to suggest the nocebo effect without doing the same when efficiency is noted.

"The difference between intravenous and subcutaneous biosimilar penetration rates is the result of time-lagged marketing"

Beyond the timing of commercialization, there should be no differences in prescription depending on the route of administration. However, if a faster uptake of etanercept biosimilars than infliximab biosimilars could be seen across Europe [15], there is globally a lower use of subcutaneous biosimilars which could partly be explained by the obligation to justify the choice of prescribing a biosimilar to the patients. Furthermore, for biologics administered intravenously in hospitals, the use of a biosimilar selected is almost automatic and is generally not the result of a discussion with the patient. The patient knows that he receives a biologic medicine but is often not sufficiently informed of its biosimilar status, making this interchangeability almost invisible. This lack of information is also frequently observed in the field at the nursing staff level in day hospitals, who are not always aware of the changes and for whom the use of the international non-proprietary name (INN) no longer makes it possible to distinguish the different biologics [16]. This situation is less conceivable with biologics used subcutaneously, because the medical prescription is done by brand names, the delivery by the pharmacist of one well-identified box with a specific device, and the access to the information on websites. For their part, some European patient associations call for more consistency in the use of biosimilars regardless of the mode of administration [17, 18].

"Financial incentives are needed to promote the prescription of biosimilars"

As for generics, EU members decided to introduce mechanisms to enhance their use: prescription quotas; financial incentives or penalties; prescription guidelines [19]. Depending

on the healthcare settings (ambulatory vs. hospitals) and the organization of the healthcare system, they can be quite different and led to various outcomes. For example in the UK, some 'gain share' mechanisms have been offered whereby the prescribing authorities benefit from the savings made from switching to biosimilars. The University Hospital of Southampton and their local Clinical Commissioning Group (CCG) are often taken as reference. When the switch to infliximab biosimilars was decided, the savings were divided between the hospital and the CCG, which then invested the money back into clinical services. In this case, it seems to lead to some positive results for the healthcare systems locally [20]. In France, the observation is opposite in the ambulatory setting. Complementary pay-for-performance remunerations have been implemented for private doctors in the insulin glargine biosimilars, but for now, they led to quite poor results. Since 2018, regulations target hospitals with the introduction of experimental financial incentives to prescribe biosimilars of adalimumab, etanercept, and insulin glargine. Hospitals can earn 20% or even 30% of the difference between the public price of the originator and its biosimilars [21]. It remains too early to know if such mechanisms could be effective in France. The results of such incentives have to be carefully analyzed country by country or even region by region.

"Substitution is not a problem"

In the EU, this is up to National Members to define their own policies concerning the substitution for biologics. For example, a law was recently passed in Germany that will possibly allow pharmacists to carry out automatic substitution of biosimilars by 2022, whereas the French pharmacists have been prohibited from doing so since early 2020. However, the interchangeability by the physicians remains legal in France. This development was the result of fierce debates in recent years in France, illustrating the scientific and political difficulty of deciding on the question of substitution for EU Members [22].

Conclusion

Biosimilars are an opportunity to allow healthcare professionals to refocus on the founding principles of trust between caregivers and patients: clarity and sincerity. Consideration of the patient as an actor of his or her health is no longer just a personal conviction but a fundamental principle of health democracy enshrined in the French law. Learning to put ourselves in the place of the patient and to abandon the paternalistic model so much criticized but very often found in practice, are challenges that will have to be taken up.

Code availability Not applicable.

Compliance with ethical standards

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