Journal of
Clinical Pharmacy and Therapeutics

Journal of Clinical Pharmacy and Therapeutics, 2016 doi: 10.1111/jcpt.12477

Letter

Position Paper from the Portuguese Association of Hospital Pharmacists for biosimilar therapeutic antibodies

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Received 11 July 2016, Accepted 10 October 2016

Keywords: **ankylosing spondylitis, automatic substitution, biosimilar, extrapolation, infliximab, interchangeability, position paper, review, rheumatoid arthritis, switching**

SUMMARY

What is known and Objective: **Biopharmaceuticals are an important class of drugs for the treatment of autoimmune/inflammatory and oncologic diseases. With patent expiries, biotechnological manufacturers can now develop biosimilar drugs. Due to timeliness of introducing new and more complex biosimilars, the Portuguese Association of Hospital Pharmacists gathered to develop a common positioning on the use of biosimilar monoclonal antibodies.**

Main issues: **The European pathway to biosimilar approval was developed to improve affordability and access to biological therapies, but it remains a work in progress because unresolved issues remain. Due to the present reality of biosimilar monoclonal antibodies, hospital pharmacists must play an important role in ensuring the safe, effective and cost-effective use of biosimilars in health systems; and educating healthcare administrators, providers, legislators, policymakers, payors and patients about these products.**

What is new and conclusion: **The conclusions presented in this work focused on the proposal for optimal biosimilar prescription criteria, the preparation of original biologics and biosimilars in the pharmacy, the management and selection of suppliers, extrapolation issues, the specific role of pharmacovigilance and risk management for the optimal use of biosimilar monoclonal antibodies.**

INTRODUCTION

Biosimilars are approved biotechnological medicines with quality, safety and efficacy comparable to the original medicines, with no relevant differences in chemical, biological, preclinical and clinical characteristics. They can be classified in first generation, including epoetin, somatotropin and filgrastim, and second generation, including monoclonal antibodies (mAb).[1] The advantage of the biosimilar commercialization is to facilitate the access of patients to expensive biotechnological medicines. However, their clinical use has raised some concerns.[1–3]

Biosimilar is a regulatory concept based on criteria of quality, efficacy and safety. The development of biosimilar monoclonal antibodies follows the principle of comparability of these products with the original reference product and should aim to determine the similarity between two biotech drugs, trying to detect differences between them. However, from the clinical point of view these differences should not be relevant. According to the guidelines published by European Medicines Agency (EMA) and FDA (US Food and Drug Administration), the comparison methodology during the production, characterization, preclinical and clinical development ensures that there are no significant differences in safety, quality/purity and efficacy/potency between the biosimilar mAb and the reference product.[4,5] Currently, and from a scientific point of view, the guidelines for biosimilar development published by these two organizations are the most advanced, allowing to differentiate the products that are wrongly categorized as 'biosimilars'. Several products marketed in some non-Union European countries do not meet the most demanding regulatory processes of EMA and FDA for the approval of biosimilars, particularly with respect to comparability.[6–9] Recently, based on dossiers that addressed all regulatory guidelines, EMA approved three biosimilars of infliximab and one biosimilar of etanercept.[2,3,10]

The concept of biosimilarity has evolved over the last ten years.[11–14] The vast experience of EMA with the approval of 23 biosimilars and the publication of seven guidelines for specific classes of biosimilars introduced preclinical and clinical advanced specific characteristics that support the entry of more complex

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Meeting members are in Acknowledgements.

biosimilars, such as monoclonal antibodies. Over the last 20 years of pharmaceutical biotechnology, regulatory science has gained substantial experience in assessing the comparability of biotechnology medicines. The comparability exercise requires applicants to provide adequate guarantees that any changes in the production process will not adversely affect the quality, safety and the effectiveness of the product.[2] These data can be obtained by physicochemical methods and biological characterization (which in most cases is sufficient), or further preclinical or clinical studies. It may be argued that extrapolation of evidence has already been applied in this case, as most processes of changes submitted do not include efficacy and safety data for all the clinical indications of monoclonal antibodies' reference.

It is often referred that nearly undetectable differences in impurities and/or degradation products can cause serious health implications. Likewise, small changes in the manufacturing process can change the characteristics, efficacy and safety of the biotech medicines. These assumptions stem from the knowledge that existed at the time of the launch of the original biotech medicines. The technological breakthroughs of the last 15 years allow us today to measure the most significant changes that alter the proteins functions.[11,15,16] Microheterogeneity, an inherent feature across the different batches of any biotech medicines, may be exacerbated by modifications in the production processes. Following these changes, the quality of the product is always controlled by comparison. As production processes are being optimized, the number of biotech medicines batches decreases because the amount of medicine produced in each batch is greater.[17–19] To be compared with the original product, the biosimilars need to establish an acceptable variability. The greater the number of batches evaluated by comparison, the smaller the range of variability between the original and biosimilar.[20]

Nowadays, the production of therapeutic antibodies is more scientific than 15 years ago. The most important aspect in the evaluation of biosimilar antibodies is their physicochemical and biological characterization using the most advanced techniques to characterize the quality of the product.[21–23]

Is immunogenicity of mAb a risk factor for biosimilars?

Immunogenicity of therapeutic proteins, still one of the major issue to be solved, has multifactorial causes.[24,25] The protein structure, in combination with factors related to the patient, the disease, type of administration, storage and logistics preparation, can elicit an unwanted immunogenic response.[26] Of note, this is true for both the original and biosimilar therapeutic antibodies.

Protein aggregation, especially subcutaneously, is a critical factor in the development of immunogenicity. Thus, changes in biotechnological production can cause the development of anti-drug antibodies (ADA), which in a first phase (up to 6 months post-administration) can be of low affinity and then of high affinity (between 6 and 9 months post-administration).[24,26,27] These ADA can reduce the serum concentration of the mAb, neutralize mAb functionality and develop adverse effects due to the formation and precipitation of immune complexes. This tachyphylaxis process will also depend on type of the disease such as autoimmune and inflammatory responses, which can be exacerbated under some of the above-described conditions. Thus, it is important that the duration and extent of clinical studies to test comparability should be adequate to determine immunogenicity rates and adverse drug reactions.[28]

How is biosimilarity demonstrated?

The extension of the protein modifications such as oxidation, glycosylation and deamination that may occur during and after production will influence the conformational integrity.[27,29,30] These protein modifications affect tertiary and quaternary conformational structures, that determine the affinity and selectivity and will, therefore, affect the functional activity and immunogenicity of the mAb. Glycosylation pattern depends on the physiological process of cell growth.[31–33] Thus, small variations during production process can modify the mAb glycosylation profile. Pharmaceutical companies should therefore find the best conditions of similarity throughout the production process before starting clinical trials to demonstrate equivalence.[34,35]

All biological aspects of a biosimilar, even those not involved in the mAb mechanism of action, should be evaluated during its development. For example, anti-TNF-α biosimilar antibodies are evaluated not only by their ability to bind and neutralize this cytokine, but also by their cellular activity and complement activation. Even though these analyses are not necessary to determine the mAb mechanism of action, they provide information regarding the quality and conformation of the mAb.[36,37] Similarly, binding to FcRn and its comparison with the original mAb allows the identification of structural changes and predicts the impact on the pharmacokinetics of mAbs biosimilar.[38,39] It is therefore important, and as recommended by FDA and EMA, that despite all these possible modifications that may occur to demonstrate efficacy and safety, similarity of these medicines was found in controlled and randomized clinical trials.[31,34,35]

EMA and FDA guidelines establish that to achieve clinical equivalence with statistical significance, clinical trials should have an adequate size.[29–32,35] The first step for clinical testing includes the comparison of pharmacokinetics, in combination with pharmacodynamics. Secondly, the pharmacodynamic parameters can substantially contribute to the exercise of comparability for certain mAbs and in certain indications. Thirdly, the aim of the clinical studies is to determine the biosimilarity and not provide clinical benefit (which was already determined by the reference mAb). Fourthly controlled and randomized clinical trials evaluate an homogeneous population of patients and compare the effectiveness (or activity) and safety between the biosimilar and original mAb in the most sensitive clinical condition.[27,29,30] As for the original mAb, the rare adverse events and long-term efficacy and safety of biosimilars mAb will be assessed by post-marketing authorization studies.[35]

Is biosimilar interchangeability a risk factor?

If a drug is approved as a biosimilar, this decision should be interpreted as the result of an extensive comparability exercise establishing a therapeutic equivalence to the original drug. From a regulatory point of view, this decision means that these drugs are interchangeable.[19,40]

Is the extrapolation of clinical indication for biosimilar mAb scientifically acceptable?

If, from the regulatory point of view, a biosimilar medicine is considered to be therapeutically equivalent to the original medicine, then it is scientifically reasonable to assume that the biosimilar will behave in a similar manner than the original in all its clinical settings. However, extrapolation may be less suitable when the clinical practice and physiopathology (e.g. oncology and

rheumatology) underlying the two clinical indications are distinct. Thus, the extrapolation of biosimilar mAbs indications is, likely, to be decided in each particular case based on the available evidence.[41]

On this point, uncertainty is a word that is often used without scientific rigour. If there is uncertainty, this shall be included in risk management plans to provide clinical evidence after approval. As extrapolation of clinical indications between original and biosimilar mAb is a possible risk factor, this hypothesis should be included in the post-marketing studies.[41,42]

Thus, the industry and regulators may have to join forces to design a comprehensive system of surveillance of adverse events associated with both original and biosimilar mAbs.[40,43]

METHODS

During the 2nd Meeting of Biological Medicines of the Portuguese Association of Hospital Pharmacists (APFH), hospital pharmacists discussed their concerns about the use of biosimilars. For this aim, several working groups were created led by a facilitator, also a hospital pharmacist, which gathered the information available for review and discussion among peers. The topics under discussion addressed the following issues:

1) Introduction in Form: Prescription criteria and validation of the prescription by the pharmacist. Criteria for providing the biological medicine and records of its administration; selection criteria and evaluation of molecules.
2) Preparation of biological and biosimilar in the pharmacy or by the hospital pharmacists (technical conditions, the drug circuit, technicians, site of preparation).
3) Management and supply.
4) Selection of suppliers (criteria, validation, scientific information, competence). Storage (location and size of stocks, storage conditions and size).
5) Replacement (type, duration of therapy, doctor/pharmacist relationship).
6) Extrapolation (clinical data, criteria, acceptability, indications and therapeutic classes).
7) Risk Management.
8) Safety of the biological and biosimilar drug (risks and weaknesses of the different classes of biologicals; important variables of drug safety monitoring, pharmacovigilance and traceability, medicine epidemiology in the hospital).

The first session of the discussion on the use of biosimilars by hospital pharmacists focused on the compilation of the different points of views among the different groups. The final consensus proposal was completed by a group of members with longer professional experience who compiled and summarized the proposals discussed, adapting them and approving the final recommendations.

RESULTS AND CONCLUSIONS

Based on the preceding discussion, the positioning of Portuguese Association of Hospital Pharmacists on the use of biosimilar therapeutic antibodies is as follows:

1) The validation of biopharmaceuticals and biosimilar prescription should be the limiting step of the drug circuit and performed by the hospital pharmacist. The description of the drug, dose, route of administration, frequency of administration, date and time for administration, period of administration, dosage form, clinical indication and clinical data must be recorded. These data are essential to prevent problems that might occur outside the hospital's internal circuit.
2) The hospital pharmaceutical services should create a circuit of the biotech medicine, where all the participants of the process (doctor, nurse, pharmacist and technician) can have the possibility to track the medicine. Registration of the commercial brand and batch number of the product must exist in the whole circuit of the medication in the hospital.
3) The reconstitution of the original biologic or biosimilar medicine should be carried out by suitably trained technicians and supervised by pharmacists. The site of reconstitution should be the pharmaceutical services where the technical aseptic conditions exist.
4) The reconstitution of the medicine outside the hospital, where it is exempted, should be performed in centralized services under pharmaceutical supervision. In this regard, the revision of biologic medicines transfer guidelines to other clinical institutions is also recommended. This will improve the control of the entire circuit of the drug from its prescription, validation, preparation, transport and administration and consequently the quality of the product.
5) To ensure the accurate identification and knowledge of the reconstituted biologic medicine at any time, its label must follow the standards used in clinical trials and contain the following information: patient identification, date, batch number, time of preparation and expiration date.
6) The transportation of the biologic drug inside the hospital should be performed under a temperature-controlled environment by trained personnel of the pharmaceutical services.
7) The delivery protocol should include the batch record of the biosimilar drug that will be administered to the patient by the nurse and the confirmation that the biotech biologic drug arrived at the infirmary in good technical conditions and stabilized temperature, preferably with an instrumental control of temperature and humidity. All biologic drugs should be kept in the infirmary at the recommended temperature and according to the information provided by the pharmaceutical services. To improve traceability of the medicine, the pharmaceutical services should assign an identifying and an unambiguous number of manipulations.
8) When providing the prescription, all aspects of the reconstitution and delivery of the patient card should be evaluated, ensuring the continuity of the cold chain inside and outside the hospital.
9) If the reconstituted biosimilar medicine is not used, it should be returned to the pharmaceutical services and destroyed.
10) The criteria for the selection of biosimilars should not be limited to the price but also include, among others, proposals to prevent the rupture of stocks, availability of various dosages (if any), expiry dates that respect the turnover of the drug and preferably single batches.
11) An integrated management of biosimilar purchases should be made to, ideally, provide at least 9 months of therapy. Purchasing preferences of the original biologic or biosimilar drug by the pharmacy should not exist. The purchase decision depends on the replacement decision and maintenance of the same brand for a minimum of 9 months of therapy.
12) The rules and procedures for this group of medicines should be published by the hospital, thereby expressing the internal

policy of each institution regarding original biologic drugs and biosimilar supply.

13) Due to the minimal time of antidrug antibodies' development and good clinical practice, the interchangeability among biosimilar and original biological medicines is not recommended during the first 9 months of therapy. The responsible person of the pharmaceutical services should take the initiative to submit interchangeability proposals of specific classes of biosimilars to the Pharmacy and Therapeutics Committee (CFT), and their decision should be taken based on technical and scientific knowledge, for each type of biosimilar. Therefore, all the quality, safety and efficacy characteristics obtained during the drug development must be taken into consideration. Wherever is possible, the committee should have a clear position about the interchangeability and substitution of different classes of biosimilars. The drug traceability information should be available to other health professionals. The off-label use of biosimilars should be addressed by CFT using the same procedure as for the reference biologic medicine.

14) The criterion of acceptability of biosimilars at the time of their entry in the market is based on the adequate and stringent criteria set by EMA for the approval of these drugs. Thus, and as referred in EMA evaluation, extrapolation is scientifically and technically accepted in naive patients and patients being treated with the original biological medicine, as long it is based on good clinical and pharmacotherapeutic practice, particularly in situations of interchangeability.

15) Risk management plans for original biologic and biosimilar medicines should be known. These plans are part of the marketing authorization for medicinal products and was approved by the EMA. These plans should define specific activities to minimize identified risks for each class of biologic drug and biosimilars. Information about the manufacturing changes or packaging process alterations should be requested to the suppliers and included in pharmacovigilance plan.

16) One of the risk minimization activities that must be provided by the pharmacist is the alert card with safety information, which should be made available to patients using these medicines. Data related to the treatment should be recorded in this card. The contents of this alert card, as well as its inclusion in the package of the reference biologic and biosimilar medicine, were subject to evaluation and approval by the health authorities and are specific for each product (as the Drug Package Leaflet).

17) Due to limited clinical experience of biosimilars during phase I and phase III clinical development, the detection of low-frequency and long-term adverse effects is necessary. To evaluate the biosimilar safety following its approval, particularly in the case of therapeutic indications extrapolation, the active pharmacovigilance plan should be concentrated in the hospital pharmacist, to allow complete data analysis and early detection of safety issues. It is important to compare the clinical, immunogenicity, pharmacokinetics and serum drug concentration data, as well as all aspects related to the quality of the product.

ACKNOWLEDGEMENTS

Paula Matos de Brito is a recipient of the fellowship SFRH/BPD/94373/2013.

We would like to thank the following participants in the meeting for their input in this positioning: Ana Rita Lopes Marques (FFUC); Carla Arriegas (CHLC); Daniela Goulart Garcia (Hospital Santo Espírito - Angra do Heroismo); Deolinda Aires (Hospital Faro); Isabel Chaves (Centro Hospitalar Setúbal); José Ferreira da Costa (Hospital Guimarães); Adriano Castro Gomes (Hospital Guimarães); Ana Paula Roque (Hospital Castelo Branco); Dina Maria Vieira (Hospital Faro); Fernanda Pires (Hospital das Forças Armadas); Luisa Magalhães (Hospital Santa Maria); Maria Cristina Coelho (Hospital Infante D. Pedro); Vera Batista (Centro Hospitalar Setúbal); Ana Rute Filipe (Centro Hospitalar Tamega e Sousa); Isabel Rosete (Hospital Infante D. Pedro); Isabel Sebastião (Hospital Abrantes); Luís Manuel Gomes (IPO, Porto); Patrocinia Rocha (Centro Hospitalar do Porto); Susana Maria Oliveira e Neta (Hospital Fernando da Fonseca); Célia Sofia Vaz (ULS Guarda); Maria Raquel Ribeiro (Hospital São João); Nuno Marques (CHUC – HUC); Olinda Melo (Centro Hospital Povoa Varzim); Silvia Guerreiro (ULSBA – Beja); Sónia Fonseca Jorgensen (HPP Cascais); Luís Filipe Faria (Hospital das Forças Armadas); Maria Adelaide Monteiro (CHUC – HUC); Tânia Mesquita (Hospital São João); Vera Pires (IPO, Lisboa); Carla Ribeiro (Hospital Vila Franca Xira); Carla Paixão (Roche); Helena Farinha (Hospital Egas Moniz); and Rui Mesquita (MSD).

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