Review

The use of biosimilars in immune-mediated disease: A joint Italian Society of Rheumatology (SIR), Italian Society of Dermatology (SIDeMaST), and Italian Group of Inflammatory Bowel Disease (IG-IBD) position paper

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Abstract

Biological agents are widely used in rheumatology, dermatology and inflammatory bowel disease. Evidence about their efficacy and safety has been strengthened for all those therapeutic indications over the last decade. Biosimilar agents are monoclonal antibodies similar to previously approved biologics. In the European Union, they have been approved for all the indications in the management of immune-mediated inflammatory diseases (IMIDs), although data only in rheumatoid arthritis and ankylosing spondylitis are currently available. Direct evidence on efficacy, safety, and immunogenicity of biosimilars is mandatory in psoriasis, psoriatic arthritis, and inflammatory bowel disease, as well as in children. Based on the current evidence in the literature, we present the joint official position of the Italian Societies of Rheumatology, Dermatology and Inflammatory Bowel Disease on the use of biosimilars in IMIDs.

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http://dx.doi.org/10.1016/j.autrev.2014.02.004
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1. Introduction

The introduction of monoclonal antibodies, commonly known as biologics and fusion proteins has dramatically changed the clinical management and the course of immune mediated inflammatory diseases (IMIDs), such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis (PsO), Crohn’s disease (CD) and ulcerative colitis (UC) [1–3]. The use of anti TNFs, such as infliximab, etanercept, adalimumab, certolizumab, and golimumab, and new molecules, such as ustekinumab, an anti-IL-12/23 monoclonal antibody, represents important therapeutic options in patients refractory to conventional immunosuppressive treatments, or that need prolonged and frequent courses of steroids. In addition, prolonged maintenance therapy with anti TNFs may avoid severe complications and improves patients’ quality of life.

The main limitation of biologics is related to their costs [4]. Biologics are very complex and large molecules (about 1000 times the size of chemically synthesized drugs) produced by living cell cultures, thus requiring large investments. In spite of a better control of immune-mediated inflammatory diseases, their use may result very expensive overtime [4–6], especially for National Healthcare Systems. In times of expense reduction, this issue becomes highly important, and may limit their use.

2. General aspects of biosimilars

The concomitant patent’s expiration of some biologics, such as infliximab, and the development of their biosimilars have raised an important debate on their use to save resource for the treatment of chronic inflammatory diseases [7]. Although the strictly controlled manufacturing process makes biosimilars very similar to originators, the lack of solid data on their long-term safety and effectiveness raises some concerns.

The European Medical Agency (EMA) defines a biosimilar as a biological medicinal product, which is similar to a biological medicine that has already been authorized, the so-called “reference medicinal product”. A biosimilar and its reference product are expected to have the same safety and efficacy profile, and are generally used to treat the same conditions. The reference product is defined as a medicinal product which has been granted a marketing authorization by a Member State or by the European Commission on the basis of a complete dossier, i.e. with the submission of quality, pre-clinical and clinical data [8]. As far as the biosimilar product is concerned, such comparability must be clearly supported by scientific evidence. Between 2003 and 2005, the EMA has addressed this challenge by establishing that the development of biosimilars should satisfy the so-called “comparability exercise”. As far as comparability is concerned, however, some issues have raised. Because of the complexity of the molecule itself and the diversity of manufacturing processes, it is generally clear that an identical copy of a biological agent cannot be made. Even minor differences may result and their clinical relevance could be potentially very challenging. Thus, clinicians may be reluctant to switch to a biosimilar agent which has not been tested enough [9,10]. Moreover, the clinical comparability exercise is the least sensitive method to detect differences. Even if present, disparities may not be revealed in clinical studies with a limited sample size, particularly when the biosimilar differs from the reference product mostly for safety, immunogenicity or rare adverse events. The scientific principles underlying the required comparability for changes in the manufacturing process (also known as microheterogeneity) of a given biological drug and for the development of a biosimilar medicinal product are the same. However, data requirements for biosimilars must be higher than those imposed to assess the microheterogeneity [11–14]. Therefore, in 2012, the European Commission changed its position on the use of the reference medicinal product in the comparability exercise [15]. Previous requirements of an exclusive use of products licensed in the European Economic Area (EEA) were changed in accepting critical data for comparisons from reference products authorized in regulated markets outside EEA. This new position left the applicant the responsibility to establish the equivalence from the non-EU to the EU reference product, and to demonstrate that the former is representative of the latter with additional comparisons of both originators.

Based on current published data, which report some differences in terms of pharmacokinetics and dosing properties [16], the Italian Medicines Agency (AIFA) states that biosimilars cannot be considered interchangeable or simple substitutes of originators, except on case of documented equality [17]. Moreover, it also states that in case of multiple indications (as it is the case for anti TNF-alpha) the biosimilarity has to be demonstrated for each indication. Finally, the decision to prescribe the originator or the biosimilar is left to the clinician [18]. Whether the clinicians are aware of all the issues concerning biosimilarity is still to be investigated.

3. Traceability and interchangeability

Particular emphasis should be placed on the traceability, which means to provide a reliable identification system, related to all production and distribution phases, either the originator or the biosimilar used in clinical practice, so that the frequency and severity of adverse events can be certainly identified for each product. The interchangeability, that means the possibility to switch among similar molecules as they are the same molecules, cannot be defined in the approval phase due to the possible difference in rare adverse events and different susceptibility to induce anti-drug antibodies. This topic has been discussed by the World Health Organization since 2006 [19]. They recognize that ‘biosimilar’ is a regulatory and legal term distinct from the International Non-proprietary Name (INN) assignment process. Although the policy for the assignment of INNs should be applicable to biologicals in general, according to the EU position, the variability related to different glycosylation is to be considered, and they recognize that significant variability can be found between innovator biological products with the same INN, or even for the same manufacturer [19]. Japan and South Korea proposed to add every time the commercial name after the assigned INN, in order to better identify the molecule, rather than only the active principle [19]. The needed post-marketing process to identify relevant safety issues related to biosimilars cannot be performed precisely if differentiation between molecules, beyond the INN, is not specified in the safety reports.

Traceability will be possible only through large databases accumulated in post-marketing surveillance from safety studies or specific registries. It should be possible to detect any significant difference in side effects or immunogenicity, if these data will be effectively and accurately collected. In this way, the clinical community will be given enough assurances about the safety of biosimilars with greater favorable response. For the same concerns, interchangeability between the originator and its biosimilar is an important issue to discuss. If two molecules are considered interchangeable, then it will be possible to switch from one to another. Currently, there are limited data on switching to a biosimilar in terms of maintenance of response, immunogenicity or other safety issues [20,21]. Probably, in some cases, switching can be possible, but the final decision should be tailored on the patient by the clinician; in the case of automatic replacement, a certain risk of loss of response and loss of tolerance should be taken into account.

In the present paper, we report the current literature evidence regarding biosimilars in chronic inflammatory rheumatic diseases, PsO, and inflammatory bowel diseases, and the perspective of the Italian Society of Rheumatology (SIR), Italian Society of Dermatology (SIDeMaST), and Italian Group of Inflammatory Bowel Disease (IG-IBD).

4. Biosimilars in rheumatology

Clinical trials on efficacy and safety comparisons between biosimilars and originators are undertaken with a sample size usually smaller than
normally required for the development of a biologic product. The extrapolation of information related to clinical comparability with other previously licensed originators is easier if the same mechanism of action of the monoclonal antibody is involved. Nevertheless, for certain indications, not only the reactions of Fab fragments with the target, but also the interaction of monoclonal antibody with some FcyR sub-types, may play a role in the mechanism of action and, in this case, it is important to consider further experimental results [22]. In particular, as far as the first biosimilar monoclonal antibody to infliximab (CT-P13) is concerned, which was approved for marketing in South Korea for all the six indications of infliximab, the approval was based on a single equivalence trial conducted in patients with RA [23], and supplemented by a pharmacokinetic study in patients with AS [24]. They showed that infliximab and its biosimilar result are not different in terms of clinical efficacy, safety and immunogenicity, both at 30 and 104 weeks [20,21].

The FDA and the EMA require at least one clinical study in the most sensitive patient population, measuring the most sensitive clinical endpoint(s) to detect clinically meaningful difference both for efficacy and safety, including immunogenicity. Caution is recommended for different safety risk profiles across indications due to different comorbidities and concomitant medications. The large sample size required for a comparative exercise trial [22] is the main reason to give a particular warning when considering the use of infliximab biosimilars in the pediatric population, since the pharmacokinetics of biologics and biosimilars in children is still poorly defined and must represent an aspect to be investigated before approving the free administration of biosimilars as equivalent to original products. Moreover, we should consider that the non-inferiority (or equivalence) evaluation margin of biosimilars is based on the difference in efficacy between the reference product and the placebo (placebo-adjusted response) [25] and that RA was associated with the smallest placebo-adjusted response to infliximab, compared to other indications. In other words, RA is likely to be the less sensitive clinical model to detect a potential difference in efficacy between CT-P13 and infliximab, particularly as studied in the equivalence trial of CT-P13 patients [22].

Immunogenicity of monoclonal antibodies is the most important general safety concern on biosimilars. Anti-drug antibodies, in case of biological products, may cause adverse events and/or inhibit the action of the drug. For example, a minor change in the manufacturing process of an erythropoietin product caused the production of autoantibodies to endogenous as well as exogenous erythropoietin, increasing the incidence of pure red cell aplasia (PRCA), a rare but fatal anemic condition [26]. This means that the immunogenicity profile should be studied in the patient population that carries the highest risk of an immune response and immune-related adverse events [27]. However, RA is associated with the fewest proportion of antibodies to infliximab (10%), mainly at a low titer [28], compared to other IMIDs, thus being the less appropriate population, from whom data on immunogenicity can be extrapolated for the other indications to infliximab.

In conclusion, the Italian Society of Rheumatology states that biosimilars should be limited to the indications for whom the “comparability test” was executed. Any claim must be validated with specific clinical trial, in particular for the extension of use of biosimilars in axial spondyloarthritis, enteroarthritis or psoriatic arthritis, and, overall, pediatric patients. Validation should be conducted by direct comparison of the results coming from well-designed clinical trials on the innovative product and the original treatment. This would result in a great potential for the appropriate use of biological therapies in pediatric rheumatic diseases and enteropathic arthritis, in terms of management of the disease, and in terms of cost reduction.

However, as currently usual for the available biologics, the final clinical decisions should always be made on an individual basis, taking into account both the characteristics of the individual patient and the clinician’s advice.

5. Biosimilars in dermatology

The introduction of biological therapeutics for the treatment of chronic plaque PsO has significantly improved several important patient outcomes including quality of life, and allowing an effective long-term control of the skin disease. Indeed, the proportion of patients who maintain the therapy is significantly higher for those receiving TNF-α blockers than conventional treatments, most likely because the formers are much better tolerated. Conventional drugs more easily induce organ toxicity and negatively affect cardiometabolic comorbidities which are very common in patients with PsO. In particular, cyclosporine induces nephrotoxicity and hypertension, methotrexate liver damage, and acitretin can result in skin and mucosal toxicity [29]. Currently approved biologics for the treatment of chronic plaque PsO include the TNF-α inhibitors adalimumab, etanercept and infliximab, and ustekinumab, an anti-IL-12/23 monoclonal antibody. Although biosimilars may improve access to expensive biological agents, concerns have been raised regarding their clinical use. In particular, due to the complexities of manufacturing copies of biological therapeutics, SiDeMaST has questioned whether biosimilars will confer identical biological function, efficacy and toxicity to reference products, both in the short and long terms. Thus, the key question for biosimilars is not whether differences exist compared with the reference, but whether differences are clinically relevant. The acceptance of biosimilars among dermatologists requires understanding the regulatory processes governing their approval. For EMA and FDA, a biosimilar clinical development program must demonstrate equivalence to a reference product already licensed (and manufactured) for use in Europe or in the USA, respectively. The demonstration of biosimilarity is significantly different from generic drug approval, where only pharmacokinetics equivalence must be shown. Extensive, non-clinical physiochemical and biological characterization is required to address structural, functional and immunogenicity concerns, prior to efficacy and safety trials. Thus, the chemistry, manufacturing and portion controls of a biosimilar application are likely larger and more detailed than that of the reference product. A clinical data requirement that must be demonstrated is equivalent to reference product, as opposed to superior safety and efficacy. Both EMA and FDA require randomized controlled trials (RCT) to be of sufficient size to establish clinical equivalence; however, rare adverse events and long-term efficacy and safety will be assessed only through post marketing surveillance. Thus, as for reference agents, stringent post-approval pharmacovigilance is paramount. Extrapolation of clinical data permits the approval of a biosimilar for a therapeutic indication in which it has not been clinically evaluated, but for which the reference agent is approved. However, extrapolation may be less appropriate when the two therapeutic indications involve distinctly different practices and disease biology, and will therefore be considered by EMA/FDA ‘case-by-case’ [30]. We believe that consideration of separate clinical trials for biosimilars in different therapeutic indications would be therefore very important. Automatic substitution would enable pharmacists to dispense a biosimilar, instead of the reference agent, without prior consent of the prescribing physician. EMA has recently designated a biosimilar as automatically substitutable, although each country will follow its own national guidelines [17,31]. Finally, nomenclature must allow physicians to identify biosimilar products and communicate prescriptions accurately with pharmacists. It is important that physicians distinguish between biological ‘intended copies’ and biosimilars. To attain the biosimilar status, an agent must undergo the required comparability qualification in accordance with scientific principles endorsed by authorities, such as EMA or FDA. Despite these stringent approval processes, significant savings in costs are expected. Once available, physicians who prescribe biological therapies must be aware of any developments concerning biosimilars, and be vigilant in their use. Currently, there are no biosimilar monoclonal antibodies and soluble receptor constructs that have been approved by EMA or FDA for treatment of chronic plaque PsO with specifically designed RCTs, and all
these aspects should be considered at the time of the introduction of biosimilars for the management of skin diseases.

6. Biosimilars in inflammatory bowel disease

Infliximab and adalimumab are the only biologics currently approved for the treatment of Crohn’s disease (CD), and, together with golimumab [32], for ulcerative colitis (UC) in the European Union (EU) [33]. In the Western countries outside EU, also certolizumab pegol and natalizumab are approved for Crohn’s disease. At present, two infliximab biosimilars have been filed for the EMA, Inflectra®, and Remsima® [34,35], although there are currently no studies comparing infliximab and biosimilars in IBD. In this particular case, EMA has accepted the regulatory filing of the biosimilar companies by extrapolating data from chronic inflammatory rheumatic diseases, in particular from the PLANETRA trial [23], which investigated combination therapy with biosimilar infliximab and methotrexate in RA. However, there are several data which show that evidence on rheumatic diseases cannot be directly translated on inflammatory bowel diseases, starting from different mechanisms on pathogenesis [36]. Etanercept and abatacept work well in rheumatic diseases, but are completely ineffective in IBD [37,38]. The dosage of anti TNFs used in rheumatology is sometimes different from those used in IBD, and also the dose optimization is different [39]. It is thus needed to conduct well-designed non-inferiority or equivalence trials to compare biosimilars and infliximab.

The Italian Group for the study of Inflammatory Bowel Disease states that adequate studies and surveillance are urgently required, before approving the use of biosimilars in IBD, in line with the position of the European Crohn’s and Colitis Organization [40].

7. Discussion

The development of biosimilars for the treatment of immune-mediated disease may be important to decrease the costs of biological therapy. However, it is required to demonstrate their equality in terms of efficacy and safety. Studies on erythropoietin demonstrated that a simple change in the formulation of the molecule can lead to relevant unexpected adverse events, especially concerning immunogenicity [9,16,41]. Given the complexity of anti TNFs and their relevant immunogenicity, this point should be carefully considered. Moreover, clinicians often do not know that also original molecules can undergo modifications in manufacturing after the approval from Regulatory Agencies, which can somehow impact on the effects of the agent itself [42]. This should be also taken into account for biosimilars, which come already from a modification in the manufacturing process compared to the originator. Post-translational modifications, such as glycosylation, may occur from changes in cell lines and/or manufacturing processes, resulting in products that are highly similar, but not identical to approved ‘reference’ agents, hence the term is ‘biosimilar’, rather than ‘bioidentical’. The potential for protein modification to alter biological function is especially true for complex therapeutic proteins, such as monoclonal antibodies and soluble receptor constructs. Subtle changes in protein conformation may result in altered function, insolubility or increased immunogenicity that is a major determinant to loss of clinical efficacy in patients who undergo biological treatments [43]. Activity of monoclonal antibodies and soluble receptor constructs depends not only upon interactions with target antigen, but also upon Fc receptor (FcyR) function [44]. Mutations of one amino acid are sufficient to impair Fc interactions, thereby altering complement activation and/or antibody-dependent cytotoxicity, and reducing the efficacy of therapeutic monoclonal antibodies.

The methodological issues in comparing biosimilars and originator are a key point. A non-inferiority comparison is the most correct approach, but it is limited by the large sample size required. Moreover, phase III are usually underpowered for safety, thus a well-designed comparative trial for biosimilars should start with $\alpha = 0.25$ and $\beta = 0.90$, which results in a higher sample size required than the common placebo-controlled trials for efficacy [45]. The absence of placebo and the lower response due to immunogenicity should be also taken into account in the sample size calculation. Li et al. [45] have proposed an asymmetrical biosimilarity margin with different non-inferiority and non-superiority margin, which can improve the feasibility of the trial. Probably, such trial needs an interim analysis to adjust the sample size during the investigation phase, and get statistically significant results [45]. The trial design should also consider the different outcomes, and get an adequate sample size for all of them.

Finally, clinicians and patients should be aware of all matters concerning biosimilarity. The similarity, but not equality, should be clear, and the current lack of data for biosimilars in certain diseases should be also underlined. The interchangeability and substitution between molecules should be left to the expert and informed clinicians. The point of view of patients’ associations should also be carefully considered. A consensus between clinicians, patients, payers, and/or public health organizations needs to be reached, especially to carefully consider advantages and issues related to the use of biosimilars, from different points of views [46].

In conclusion, we can clearly state that:

- Biosimilars cannot be considered interchangeable or simple substitutes of originator, until recent and preliminary data will be confirmed. The complexity of the molecule, dosing, and immunogenicity issues needs careful investigation on these aspects.
- Biosimilars should be demonstrated to be effective and safe in immune mediated-diseases in RCTs of sufficient dimension. Efficacy assessment merely based on clinical response is not always comprehensive, as specific endpoints should be also investigated.
- The use of biosimilars in children affected by chronic immune-mediated diseases, such as RA, AS, PsA, Pso and IBD needs to be carefully investigated, especially in terms of safety.
- Biosimilars need to be tested by well-designed trials with an adequate sample size calculation.
- Post-marketing surveillance for safety and immunogenicity has to clearly differ the biosimilars from the originator. The name “infliximab” should not be used in the reports, but rather the commercial name, in order to monitor particular effects which can differentiate between the agents. In this context, we did not find anything correct to identify an originator monoclonal antibodies and its biosimilar with the same INN.
- Interchangeability cannot be automatic, unless its effectiveness and safety will be exhaustively demonstrated. It should be currently left to the clinician’s responsibility to choose whether to switch from an originator to a biosimilar, based on patients’ characteristics. Neither other paramedical characters nor Healthcare payers should be allowed to change the prescription or impose the use of biosimilars instead of their originator.

Conflict of interest

G.F. served as a consultant and a member of Advisory Boards for MSD, Takeda Pharmaceuticals, and Janssen Pharmaceuticals; G.G. has received advisory/speaker honoraria and/or research funding from AbbVie, Almirall, Boehringer Ingelheim, Celgene, Dompé, Eli-Lilly, Galderma, GSK, Janssen, Leo Pharma, Otsuka, Merck-Serono, Maruho, MSD, Novartis and Pfizer. G.L. has served as a consultant and a member of Advisory Boards for MSD, Pfizer, AbbVie, BMS, UCB and ROCHE. A.O. has served as an advisory board member for AbbVie and MSD, and received lecture grants for AbbVie, Sofar, Chiesi, and Takeda Pharmaceuticals; S.D. Silvio Danese has served as a speaker, consultant and advisory board member for Schering-Plough, Abbott Laboratories, Merck & Co., UCB Pharma, Ferring, Cellerix, Millennium Takeda, Nycomed, Pharmacosmos,
Take-home messages

- Biosimilar agents are monoclonal antibodies similar to previously approved biologics.
- Biosimilarity for monoclonal antibodies has been investigated only in rheumatoid arthritis and ankylosing spondylitis.
- EMA approved the use of biosimilars for all indications, including psoriasis and inflammatory bowel disease.
- Biosimilars still need to be tested for efficacy and safety by well-designed trials with an adequate sample size calculation, especially for psoriasis and inflammatory bowel diseases.
- Caution is recommended for extrapolation of data across indication, interchangeability and traceability.
- Post-marketing surveillance for safety and immunogenicity is strongly required.

Acknowledgments

We thank the IG-BDB members Fernando Rizzello, Vito Annese, Alessandro Aruzzi, Livia Biancone, Fabrizio Bosa, Emma Calabrese, Fabiana Castiglione, Michele Comberato, Salvadori Cuccioni, Marco Daperno, Walter Fries, Paolo Giannonetti, Giovanni Latella, Anna Kohn, Giannmichele Meucci, Claudio Papi, Maria Beatrice Principi, Antonio Rispo, Simone Saibeni, and Maurizio Vecchi for their suggestions and critical revision of the final version of the manuscript.

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