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Review Article

Transitioning from first- to second-generation biosimilars: An appraisal of regulatory and post-marketing challenges

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ABSTRACT

Second-generation biosimilars (i.e. monoclonal antibodies or proteins generated by fusion of antibody and receptor moieties) differ in several respects as compared to first-generation ones (e.g. epoetins, bone marrow stimulating factors, somatotropins). In this respect, as second-generation biosimilars are endowed with much greater structural and molecular complexity, which might translate into a number of pharmacological and therapeutic issues, they raise new challenges for manufacturers and regulatory authorities as well as new concerns for clinicians. Based on these arguments, the present article was intended to review information on the main differences between first- and second-generation biosimilars for treatment of immune-mediated inflammatory diseases, as well as their impact on immunogenicity, the design of clinical trials and the critical issue of extrapolation of therapeutic indications. The positions taken by relevant medical associations and the crucial role of pharmacovigilance are also reviewed. According to current knowledge, the initial post-marketing clinical experience with second-generation biosimilars is providing encouraging results, though their long-term safety and efficacy as well as the scientific basis underlying the extrapolation of therapeutic indications are still matter of discussion. There is some consensus that marketing applications should rely on studies supporting the clinical use of biosimilars in their different target diseases and patient populations. In parallel, clinical safety must be ensured by a strict control of the manufacturing processes and a solid pharmacovigilance program. It remains then a responsibility of the physician to drive a proper use of second-generation biosimilars into clinical practice, in accordance with guidelines issued by scientific societies.

Contents

Abbreviations: ACR, American College of Rheumatology; ADAb, anti-drug antibody; ADCC, antibody-dependent cell-mediated cytotoxicity; AIFA, Italian Medicines Agency; CDC, complement-dependent cytotoxicity; CHMP, Committee for Medicinal Products for Human Use; DAS28, 28-joint disease activity score; ECCO, European Crohn's and Colitis Organization; EMA, European Medicines Agency; FDA, Food and Drug Administration; IBD, inflammatory bowel disease; IG-IBD, Italian Group of Inflammatory Bowel Disease; IMID, immune-mediated inflammatory disease; mAb, monoclonal antibody; PASI, Psoriasis Area and Severity Index; PRCA, pure red cell aplasia; RA, rheumatoid arthritis; SIDeMaST, Italian Society of Dermatology; SIR, Italian Society of Rheumatology; WHO, World Health Organization.

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1. Introduction

Over the last two decades, biotechnological drugs, commonly designated as biologics, have revolutionized the therapeutic management of patients, not only in the field of hormone deficiencies as well as solid and hematologic malignancies, but also in the area of immune-mediated inflammatory diseases (IMIDs), and have become blockbusters for healthcare systems worldwide. After data protection or patents covering biopharmaceutical agents have begun to expire, several biosimilar drugs have been developed and approved for use in different clinical conditions. The term 'biosimilar' was first introduced by the European Medicines Agency (EMA) to describe biologic medicines developed as 'copies' of innovative biologics (commonly designated as originators). However, unlike the generic products of small-molecule drugs, identical copies of biologics cannot be obtained. This limitation depends mainly on the circumstance that biologics are produced by living cell systems, whose biosynthetic processes are subjected to intrinsic and unavoidable factors on biological variability, and partly on their high degree of complexity in terms of both molecular structure and manufacturing procedures. Therefore, the term biosimilar refers to a sort of 'copy' of an authorized branded biologic originator that has demonstrated similarity to the originator throughout the various steps of a rigorous comparative procedure designated as 'comparability exercise' [1,2]. While acknowledging the potential favorable impact of biosimilars on the pharmaceutical market, in terms of both cost saving and drug accessibility, the Italian Medicines Agency (AIFA) has taken the position that originators and biosimilars cannot be considered as interchangeable medicinal products, thus excluding the practice of automatic substitution and switching and, in accordance with the concept of biosimilarity issued by the EMA, emphasizing the principle of the dominant role of clinicians in choosing whether patients should be prescribed with an originator or its biosimilar [3].

Biosimilars, as all biopharmaceuticals, are endowed with highly complex proteic structures and large molecular weight. They are produced through biosynthesis by genetically manipulated living cell systems [e.g. *Escherichia coli* and Chinese hamster ovary cells], which, depending on growth conditions and other factors, can generate mixtures of related molecules that are quite difficult to extract, purify and characterize. Even having access to the exact DNA sequence coding for the originator biologic, it is very difficult to replicate exactly its end-structure (i.e. tertiary and quaternary structures), including post-translational changes, such as glycosylation, and to reproduce exactly the manufacturing process. Accordingly, each biosimilar, even though closely similar to the reference originator, will never reach the level of identity. In this regard, particular attention must be paid, in a regulatory perspective, to the possibility that a biosimilar might display different patterns of immunogenic activity, with a consequent risk of increased propensity to stimulate the production of anti-drug antibodies (ADAbs), as compared with the originator [4–6]. Thus, to cope with the above issues, some regulatory authorities have developed a specific biosimilar approval pathway, first implemented by EMA in 2005, which requires the demonstration of similarity with the respective originator in terms of physico-chemical properties, pharmacology, efficacy and safety, on the basis of a comprehensive head-to-head comparability exercise. If comparison fails at any level, the biologic product is no longer eligible as a biosimilar. Therefore, only the biologic products that display substantial similarity with their respective originators throughout all steps of the comparability exercise can be designated as 'biosimilar' by the regulatory authority and approved for clinical use [7,8]. In this context, an important point of novelty, which has been matter of much debate, pertains to the possibility for a biosimilar product of getting approval for multiple extrapolated therapeutic indications (ideally all those previously granted to the originator), in the face of a clinical development based on a single phase III comparative trial, documenting its similarity with the originator for only one specific therapeutic indication. This is regarded as an issue of high clinical relevance, since it raises the question of whether data obtained with a biosimilar from patients affected by one specific disease are sufficient to allow the use of such a biosimilar in patients with other diseases, for which a direct demonstration of therapeutic equivalence has not been provided by specific clinical trials. In this respect, most experts agree that it is possible that a biosimilar, demonstrated to be effective for one therapeutic indication, is not effective in other indications for which the originator had been previously approved [9–11].

Notably, second-generation biosimilars (i.e. monoclonal antibodies, mAbs, or proteins obtained by fusion of antibody and receptor moieties) differ in several respects as compared to first-generation ones (e.g. epoetins, bone marrow stimulating factors, somatotropins), and therefore they raise new challenges for manufacturers and regulatory authorities as well as new concerns for clinicians. Based on this background, the present article was conceived to review current information on main differences between first and second-generation biosimilars for treatment of IMIDs, as well as their impact on immunogenicity, the design of clinical trials and the critical issue of extrapolation of therapeutic indications. The positions taken by relevant medical associations and the crucial role of pharmacovigilance have been reviewed as well.

2. First-generation biosimilars

The first biosimilars approved by the EMA Committee for Medicinal Products for Human Use (CHMP) were follow-on products of originator biologics endowed with a relatively low molecular weight, including two biosimilars of somatropin, five erythropoietin biosimilars, and seven biosimilars of filgrastim. Since 2006, more than 20 biosimilar products have been introduced into the European market [12]. Filgrastim and epoetin-alpha were the first biosimilars produced for use in hematology-oncology that overcame the strict quality controls and regulatory requirements for approval by the European agency, and have been used for several years as supportive therapy of patients undergoing anticancer chemotherapy [13].

The regulatory pathway for biosimilars introduced into the European market one decade ago has been taken as a reference by other regulatory authorities, including the US Food and Drug Administration (FDA). According to such a pathway, after a biologic product is generated and intended to be highly similar to an originator, similarity has to be demonstrated in both non-clinical (i.e. in vitro and animal testing) and clinical studies. The design of these studies by the proprietary of the biosimilar product is often subjected to preliminary discussion and agreement with the reg-

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ulatory authorities, such as the EMA or FDA. In all instances, the general background principle underlying the overall approval procedure of biosimilars is that the higher the level of similarity, in terms of structural and in vitro biological/pharmacological properties, the less clinical evidence is needed to demonstrate clinical similarity [14–16]. Moreover, in order to gain long-term evidence on the efficacy and safety of biosimilar products, rigorous programs of post-marketing pharmacovigilance, aimed at confirming the initial patterns of efficacy and safety as well as to minimize and properly manage any risk of unexpected safety issues, are then required by the regulatory authorities [17,18].

The high strictness imposed by regulatory agencies on post-marketing pharmacovigilance programs is widely justified also in the light of some lessons learned from the occurrence of serious adverse events caused by immunogenic reactions against first-generation biologics. The most representative episode in the European area dates back to 2002, when a report described a series of patients affected by chronic renal failure, who had developed severe anemia associated with pure red cell aplasia (PRCA) upon treatment with human recombinant epoetin alpha. All these patients tested positive for neutralizing anti-erythropoietin antibodies, the induction of which was ascribed to changes in the biologic product resulting from variations of the manufacturing process [19]. Subsequently, additional cases of PRCA were reported in patients treated with epoetin beta and darbopoetin alpha [20]. Of interest, cases of PRCA occurred also in the setting of a registration clinical trial on biosimilar epoetin alpha. As a consequence, this study was discontinued and the manufacturer of biosimilar epoetin undertook an investigational program aimed at unravelling the underlying causes of this issue [21].

Despite the strictness of regulatory procedures underlying biosimilar development and approval, in the European Union the use of epoetin and filgrastim biosimilars in the clinical practice has been rather slow, possibly due to an initial lack of trust by patients and physicians in the efficacy and/or safety of biosimilars, and in their interchangeability with the originator product [18]. However, there is now more than a decade of clinical experience accumulated with these 'first-generation biosimilars', and the outcomes, in terms of both effectiveness and safety in the clinical practice, including those concerning the extrapolated therapeutic indications, have been well reassuring. Accordingly, it can be reasonably stated that for these first biologic products the biosimilar approach drawn by the EMA, at both pre- and post-marketing level, has been proven to be successful.

3. Second-generation biosimilars

A second wave of biosimilar medicinal products has started to enter the clinical use since 2013 following the patent expiration of originator biologics with highly complex molecular structures, such as mAbs or proteins generated by fusion of antibody and receptor moieties, approved for treatment of cancer or IMIDs. It is quite clear that these 'second-generation' biosimilars represent a distinct therapeutic class in several respects as compared to epoetins, bone marrow stimulating factors and somatropins. Indeed, the structure and molecular complexity of an immunoglobulin far exceeds that of a first-generation biosimilar. To appreciate the significance of such a difference, it is just enough to consider that the molecular weight of hematopoietic growth factors falls in the range of 15–20 kDa, while that of mAbs is about 150 kDa.

The entry of mAbs and fusion proteins among biosimilars is going to have a significant clinical impact, since the majority of their respective originators are currently regarded as safe and effective drugs available for large numbers of patients as disease modifying therapies in the fields of inflammation and oncology [22–24]. However, second-generation biosimilars raise significant new challenges when compared with their first-generation counterparts, which are employed as replacement therapies or treatments for supportive care. A central issue is that mAbs and fusion proteins are approved for very different therapeutic indications, thus making the extrapolation of their efficacy and safety to other therapeutic indications particularly difficult. In this respect, several experts have claimed that similarity testing between originator and biosimilar mAbs or fusion proteins is more difficult than that required for first-generation biosimilars [25,26]. In keeping with these positions, the EMA and FDA have recognized the difficulty of assessing similarity between mAb products, and EMA, in particular, issued distinct guidelines for biosimilar mAbs in 2012. While the regulatory path for comparability exercise has remained similar to the overarching guidelines, the updated guidelines on mAb biosimilars require more stringent clinical testing and immunogenic assessment [1]. Indeed, there might be relevant differences between a second-generation biosimilar and its respective originator that cannot be detected until extended clinical studies have been carried out. Nevertheless, despite such a cautious approach, further scrutiny and discussion are necessary to understand fully the potential impact of second-generation biosimilars on clinical outcomes in the post-marketing setting.

It has been estimated that eight therapeutic mAbs will undergo patent expiration in the European Union and US before 2020, meaning that the pharmaceutical market will be opened to the entry of a wide array of second-generation biosimilar products. The first biosimilar mAb, CT-P13 (having infliximab as the reference originator) was authorised for clinical use within the European Union in September 2013 [27], and it is now available in more than 70 countries worldwide [28]. A substantial pipeline of biosimilars is currently under development, including several mAbs and some fusion proteins, with over 700 products reported to be in the preclinical or clinical phase [28,29]. In particular, the number of mAbs or fusion proteins currently under development as biosimilars for treatment of IMIDs is being greatly growing. Consequently, as a relatively new phenomenon in rheumatology, over 80% of comparative studies (phase III) for biosimilars have been planned to be started from 2013 onward [30,31]. At present, in the setting of IMIDs, biosimilars of adalimumab, etanercept, infliximab and rituximab have reached the stage of clinical development, and the available data have been published or presented at international scientific meetings [32]. While the potential pharmacoeconomic benefits and cost-effectiveness of second-generation biosimilars seem quite clear, several points of concerns still remain pending, and deserve careful consideration.

3.1. Immunogenicity

Unwanted immunogenicity of biologics is a major safety concern during the drug development phase. This issue is acknowledged by health agencies and therefore they strongly recommend assessing the immunogenicity of biologics in clinical trials as well as to monitor patients after drug approval [33]. The EMA recognizes that "immunogenicity of mAbs is complex and there are a number of often poorly understood factors, which make it difficult to predict with any certainty whether a therapeutic or diagnostic mAb is likely to provide a clinically relevant immune response" [1]. Current evidence supports the view that the incidence, characteristics, and clinical consequences of immunogenicity, vary greatly and that such heterogeneity depends on many different factors [34–37]. Indeed, several product quality attributes have been shown to be of importance as determinants of mAb immunogenic activity [38,39], such as the primary aminoacidic sequence, the propensity to generate macromolecular aggregates, the presence of host-cell impurities in the final product, and the glycosylation process. Fur-

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thermore, small fluctuations in the manufacturing process, such as minor changes in cell culture pH, temperature and media ingredients, may impact significantly on the molecular properties of the final product, through the introduction of micro-heterogeneities [40–42]. Even the smallest changes in the molecular shape of a therapeutic protein can modify its solubility or its biological functions, or can even increase its immunogenicity by uncovering antigenic domains over its molecule [43–45]. Owing to all these reasons, the immunogenicity of biologics and, consequently, the immunogenicity of mAb biosimilars, in comparison to their originators, is actually unpredictable and, as such, it must be always subjected to careful investigation before approval as well as to adequate follow-up over the post-marketing phase [6]. However, it must be acknowledged also that the assessment of immunogenicity in clinical studies is hampered by a number of issues, with particular regard for the types of assays employed and the clinical meaning of the results in terms of safety and/or therapeutic efficacy of the biologic drug [46]. Therefore, great caution must be exercised when comparing the immunogenicity patterns of different mAbs on the basis of different assay methodologies, since this comparison could lead to misleading conclusions.

3.2. Design of clinical studies

Phase III clinical trials comparing biosimilars with their respective reference originators are clinical studies designed to assess therapeutic equivalence, at variance with conventional randomized controlled trials that are designed to demonstrate superiority of one treatment compared to another. In the setting of biosimilar development, the appropriate design of therapeutic equivalence studies is faced with a number of methodological challenges. When implementing an equivalence study, the classical rigorous 'intention-to-treat' approach – relying on the concept that more patients leaving an intervention arm due to the occurrence of adverse events would represent a bias in favor of the other treatment, if the analyses were limited only to the patients that completed the protocol – would on the contrary bias toward the conclusion that the biosimilar is equivalent. For this reason, it is recommended that equivalence studies for biosimilars should perform 'per protocol' analyses and present their data with 95% confidence intervals for a difference, rather than with a single p value. In particular, equivalence could be declared, according to the generally accepted standard, if the confidence intervals of the comparator compound (the biosimilar product) lie within ±15% of those estimated for the reference compound (the originator product) [47].

The primary therapeutic indication selected for the comparative evaluation of biosimilars is usually the one considered as sufficiently sensitive, or even the most sensitive for such evaluation. Commonly, this is the therapeutic indication that, in the case of the originator product, demonstrated the greatest effect size. However, it has been appreciated that using the most sensitive therapeutic indication is not necessarily the optimal choice if investigators are not willing to use the originator product to treat that indication [7,12,14]. Moreover, in his own guidelines, the World Health Organization (WHO) suggests that, if extrapolation to other therapeutic indications is being considered for a biosimilar [48], the patient population selected for the comparative study of equivalence should be the one that carries the highest risk of developing immunogenic responses, which may not be necessarily the most sensitive population in terms of effect size.

Another issue that deserves careful consideration in comparative studies for the approval of biosimilars is the appropriate selection of endpoints, since some regulatory authorities recommend the use of sufficiently sensitive endpoints [7,12,14]. A very important point of interest is that, in equivalence trials for biosimilars, primary endpoints do not have to be necessarily identical to those used for the registrative clinical trials of the originator product. Indeed, based on recommendations by regulatory authorities, different *ad hoc* primary endpoints can be implemented to facilitate the detection of relevant differences between the originator and the proposed biosimilar. In particular, to better assess the therapeutic equivalence of biosimilars, primary endpoints based on continuous versus dichotomous measures have been suggested to be more sensitive. For instance, in the setting of rheumatoid arthritis (RA), the use of 28-joint disease activity score (DAS28) appears to be preferable to response rates based on 20% improvement in American College of Rheumatology (ACR) criteria (ACR20), and likewise, in patients with psoriasis, the mean Psoriasis Area and Severity Index (PASI) is regarded as more convenient than the 75% PASI response rate [49,50]. However, it is noteworthy that, while comparisons and therapeutic use of first-generation biosimilars as well as second-generation biosimilars for IMIDs can rely on the assessment of relatively fast and objective clinical responses, in other fields, and particularly in oncology, the evaluation of clinical outcomes to second-generation biosimilars is a major point of concern. Indeed, in the setting of anticancer therapy, including neoadjuvant treatments, clinical responses may take months before allowing objective evaluations, and they do not always correlate with actual improvements in progression free or overall survival [51].

An additional point deserving consideration is the magnitude of margins set out to determine the equivalence of efficacy between the proposed biosimilar and the reference originator product. Of note, the FDA has issued a guidance for advising on the statistical calculation of equivalence margins, which appears to be acceptable also to the EMA [52]. Accordingly, the statistically estimated margins should be based on available data for the originator in comparison with placebo or standard of care therapy rather than an active control.

With regard for the assessment of immunogenicity, it is noteworthy that several patient- and treatment-related factors can affect immunogenic responses against therapeutic proteins during the implementation of clinical studies [34]. Therefore, when starting a clinical comparative trial aimed at measuring immunogenicity, amongst the other endpoints, the optimal study design should be selected depending on the biosimilar product under investigation. First, validated assays to detect ADAbs are needed, and, when ADAbs are detected, their neutralizing capacity should be tested, as well. The EMA guideline on immunogenicity assessment of mAbs intended for in vivo clinical use suggests assays based on competitive ligand binding as the best choice for ADAb detection in patients' sera [34]. Second, the best patient population for assessing immunogenicity should possibly be the same enrolled in a pharmacokinetic study or, for some mAbs, it could consist of healthy volunteers, who are known to develop a lively immune response following a single dose of biologic within a few days [34,39]. Third, it is crucial to choose the optimal dose of the originator and biosimilar mAb employed for clinical studies, in order to maximise the probability to detect ADAbs. The EMA guideline on mAb biosimilars states that "some mAbs inhibit ADAb formation when administered at high doses, and in these cases studies conducted with low doses can be more sensitive to compare immunogenicity of the mAb biosimilar and original product" [34]. The guideline stresses also the concept that clinical studies on immunogenicity are particularly important when the biosimilar mAb is produced using a different expression cell system as compared to the originator product, recommending that "in some instances, IgE testing prior to clinical administration needs to be considered for patients if the mAb contains non-human carbohydrate structures (e.g. α-Gal), in order to prevent severe anaphylaxis" [34].

Finally, seeking engagement with regulatory authorities early and often is essential to streamline a biosimilar development path-

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way, and it is recommended in both the EMA and FDA guidance documents [7,12,14].

3.3. Extrapolation of therapeutic indications

The intrinsic complexity of mAb and fusion protein structures, the heterogeneity introduced by small changes in the manufacturing process and the complications that might arise with the introduction of second-generation biosimilars into the pharmaceutical market are matter of intensive debate among the experts, with particular regard for the issue of extrapolated therapeutic indications. It is well known that monomeric growth factors/hormones or cytokines, endowed with a relatively simple polypeptidic structure, are typically equipped with a single active site that binds the same receptor or family of receptors for each therapeutic indication (in the majority of cases the same receptor, and thereby the same mechanism of action, is involved across all therapeutic indications). On the other hand, mAbs, besides their primary binding sites that interact with specific 'antigenic' molecular targets, are endowed also with additional binding sites, located in their different molecular domains (mainly the Fc region), known to interact with different receptors (e.g. FcRn and FcγR) and to elicit a variety of different 'ancillary' effects [53–55]. Of note, the net contribution of each mode of action in humans, including antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and apoptosis, remains presently unknown, even though there is convincing evidence that such ancillary effects contribute at different extents to the efficacy (or tolerability) of mAbs across their different therapeutic indications [56,57]. Furthermore, it must be considered that, particularly in the field of IMIDs, treatment regimens of the same mAb or fusion protein can vary across the different therapeutic indications in terms of dose strength, dosing time and possible combination with traditional small-molecule drugs (particularly immunosuppressants) [6,58].

When addressing the issue of extrapolation of therapeutic indication, the 2012 EMA guideline on similar biologic medicinal products containing mAbs suggests that, if different mechanisms of action are considered or suspected to be relevant, "applicants should provide relevant data to support extrapolation to all claimed clinical indications", including discussion of published data on antigen receptors and mechanisms of action, potency assays, in vitro assays demonstrating the functionality of the molecule, and any relevant clinical data [1]. Notably, it has been commented that extrapolation should be considered not as a "bonus" for the manufacturer of the biosimilar, but rather as a commitment to provide rigorous scientific evidence [59]. In a recent review, it appears that the majority of biosimilars developed for different IMIDs are evaluated comparatively for efficacy, safety and immunogenicity against the originator in only one therapeutic indication, with RA being the most common condition, followed by psoriasis [30]. Several experts have raised concerns about the oversimplification of clinical biosimilar development. In particular, they claim that, given that mAbs have complex mechanisms of action that in most cases are poorly or only partly understood, and that treatment regimens, study endpoints and study populations often vary among therapeutic indications, granting of extrapolation of therapeutic indication by regulatory authorities should not be straightforward [58–60]. It is therefore not surprising that, in the case of the infliximab biosimilar CT-P13, subjected to clinical evaluation in AR and ankylosing spondylitis, granting of marketing authorization for inflammatory bowel diseases (IBDs) by the EMA and other regulatory agencies through a mere extrapolation of therapeutic indication has led to lively discussions questioning the scientific basis supporting such a decision [10,11,61–63]. Reassuringly, the NOR-SWITCH trial, aimed at examining efficacy, safety and immunogenicity following the switch from originator to biosimilar infliximab in patients with different IMIDs, including Crohn disease, has shown a lack of significant changes in the parameters of therapeutic effectiveness along with a similar incidence of ADAbs detected during the study: (17 [7.1%] with the originator and 19 [7.9%] with the biosimilar) [64].

3.4. Pharmacovigilance

The limited experience with second-generation biosimilars in terms of efficacy, safety and immunogenicity at the time of regulatory approval makes rigorous pharmacovigilance programs a public health concern that needs to be addressed and well implemented, in order to acquire information about long-term patient safety and outcomes, as well as to reassure physicians in their clinical practice. For instance, if subtle, but of potential clinical relevance, differences in the patterns of immunogenicity are unlikely to be detected during the development of biosimilar mAbs, the regulatory authority may require additional post-marketing studies, specifically designed to detect small differences in immunogenicity. Accordingly, a program of active pharmacovigilance should be ensured by means of patient registries supported by sponsors and/or interested scientific societies. Additional post-marketing safety assessment tools might include also targeted questionnaires, phase IV studies, and long-term follow-up programs [65–67]. The importance of a robust pharmacovigilance plan is emphasized also by the lack of a guidance on whether and how product divergence over time should be regulated. Indeed, post-marketing changes introduced by manufacturers into an originator and/or its biosimilar may lead to a long-term loss of similarity (divergence) in their quality attributes as well as pharmacological and immunogenic properties [68], which in turn may result in a loss of equivalence [69,70].

Overall, pharmacovigilance is of critical importance while using biosimilars in clinical practice and it is necessary to collect safety data across the different countries to detect all safety signals. However, at present there is a substantial lack of consensus on how to implement and maintain an adequate and effective system of pharmacovigilance on biosimilars [71].

3.5. Other issues: naming, traceability and costs

An important challenge to healthcare professionals is to avoid confusion among originators and biosimilars, as well as among different biosimilars of the same originator, to ensure appropriate prescribing and accurate reporting of adverse events in the post-marketing phase. In this respect, experts and clinicians are increasingly claiming that, in order to achieve an adequate use of biologics in the clinical practice, the international non-proprietary name (INN) should not be employed as the only mean for their identification. Indeed, relying on a common naming system of originators and biosimilars makes it difficult to impute adverse events to a specific medicinal product, with an unavoidable negative impact on adequate regulatory actions and safe management of patients [72]. This issue is fostering much discussion, and several solutions are being proposed, including the use of the brand name, the INN in combination with the brand name, or the use of codes, based on letters and/or numbers as a prefix or suffix to the INN, allowing a unique identification of the product. In 2012, the European Commission released the Directive 2012/52/EU, which, for all biologics, including biosimilars, establishes the use of brand names to ensure an unambiguous identification of biologic medicinal products [73]. Despite acknowledging that biosimilars are similar, but not identical, to their originators, in 2013 EMA confirmed that biosimilars must share the same INN with their originators, while differentiations, with particular regard for pharmacovigilance, should rely solely on the use of brand names [74]. Since this position is not shared unanimously by other Countries, possible alternatives to the

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sole use of INN are being considered by a committee of the World Health Organization, and one proposal has been that a 4-digit code might be adopted to differentiate biosimilars from their respective originators [72].

With specific regard for post-marketing surveillance, whatever be the solution taken for biologic naming, it is important to consider that appropriate reporting of adverse events for originators and biosimilars cannot rely solely on their brand names. Indeed, adverse events might stem from inadvertent changes in the manufacturing processes or storing conditions, and therefore it is strongly recommended that, when reporting to the regulatory authority, the batch number should be always provided in addition to the brand name [75]. However, current evidence suggests that the majority of physicians may not comply fully with these recommendations. For instance, in a survey on European and US pharmacovigilance databases, Vermeer et al. [76], when assessing the reports of adverse events to biologics, observed that, while the large majority of physicians had provided appropriate information on brand names, very few of them had taken care of indicating batch numbers, thus hampering the possibility of going back to specific data on production and storing of those specific medicinal products.

Another important issue on the development and clinical use of biosimilars pertains to their economic impact on healthcare systems. Currently, world expenditure for medicines has been estimated to reach 1.4 trillion US dollars by 2020, with up to 60% of this payment burdening on governments. A number of cost-saving measures have been then implemented worldwide to restrain drug costs, including incentives to generic drug use. However, since a substantial portion of global drug expenditure results from therapies with biologics, biosimilars offer the promise of helping to achieve substantial cost savings, which might be reinvested to expand the access of patients to treatments with innovative biologics or to improve the quality of other healthcare facilities. Indeed, consistently with this expectation, in the European area savings from 2.3 to 11.7 billion Euros have been estimated for United Kingdom, Germany and France over the period from 2007 to 2020 as a consequence of first-generation biosimilar marketing [77,78].

Based on current knowledge, it is expected that even higher savings could be achieved with second-generation biologics in the area of IMID therapies. At present, one-year treatment of RA with biologics is quite more expensive than methotrexate (in USA: 10,000–30,000 US dollars for biologicss against about 3000 US dollars for conventional disease modifying anti-rheumatic drugs). In this respect, it is noteworthy that, following approval of the first infliximab biosimilar, some budget-impact evaluations have estimated that, in the United Kingdom, Germany, France and Italy, according to three scenarios of 10%, 20% and 30% discounts, cost savings of about 96, 233 and 433 Euros might be achieved, respectively, after switching RA patients to the infliximab biosimilar [77,79].

4. Position statements of medical associations

Several medical societies and other organizations have issued position statements on biosimilars. The Italian Society of Rheumatology (SIR) has published two position papers [11,80], one of which was issued jointly with the Italian Society of Dermatology (SIDeMaST) and the Italian Group of Inflammatory Bowel Disease (IG-IBD). In both papers, the SIR has pointed out a number of criticisms pertaining to the approval of second-generation biosimilars: 1) clinical data are currently available only for RA and ankylosing spondylitis, referring to a relatively small number of patients, and thus providing insufficient information concerning long-term efficacy as well as safety and frequency of rare adverse events; 2) conversely, direct evidence on efficacy, safety and immunogenicity of biosimilars is still lacking in psoriasis, psoriatic arthritis and IBDs as well as pediatric patients; 3) with regard for immunogenicity, longer observation periods are required, since ADAbs may develop after several administrations and sometimes even after one year of treatment; 4) when considering the extrapolation of therapeutic indications, there is a lack of sufficient scientific evidence supporting automatic translation of indications from an originator to its biosimilar, particularly because of the complex and different pharmacological mechanism(s) of action in the different approved clinical indications. Overall, the SIR concluded that, given the limited knowledge on efficacy and safety of second-generation mAbs, it is mandatory to set rules, perform ad hoc clinical trials and implement appropriate drug surveillance programs.

The ACR, in its position statement, recommended that long-term post-marketing registry-based data collection be established to monitor for less common, but potentially important, adverse events, and that the decision of substituting a second-generation biosimilar product should not be taken without support by the knowledge of prescribing physicians [12].

In 2013, the European Crohn's and Colitis Organization (ECCO) released a position statement on the use of biosimilars in the treatment of IBD, stating that "a biosimilar proven effective and safe for one indication may not necessarily be effective and safe for a second indication for which the reference biologic has been shown to be safe and effective". Furthermore, the organization requested specific studies in patients with IBD, in order to establish efficacy and safety for this indication, stating that the experience with biologics has shown that efficacy in IBD does not necessarily correlate to efficacy in other indications, such as RA [10]. However, it is worth mentioning also that, based on early post-marketing experience, the opinion of some scientific societies, such as the ECCO, has gradually changed towards a more confident position on the use of second-generation biosimilars [81].

5. Conclusions

Second-generation biosimilars, namely mAbs and antibody-receptor fusion proteins, differ in several respects as compared to first-generation ones, such as epoetins, bone marrow stimulating factors and somatotropins, having much greater structural and molecular complexity, thus raising new challenges for manufacturers and regulatory authorities, and new concerns for clinicians. Despite some issues remain matter of discussion, with particular regard for long-term safety and efficacy and the scientific basis underlying the extrapolation of therapeutic indication, the initial post-marketing clinical experience with infliximab biosimilars is showing encouraging results [82–87]. The way for biosimilar mAbs and antibody-receptor fusion proteins is now open and paved, and we have to comply with this new context. What really matters to clinicians is to be assured that their patients' treatment is based on solid scientific evidence, obtained by the most sensitive and advanced methodologies. Robust programs of clinical development must be required for each new agent intended to be approved as a biosimilar product. Each marketing application should include studies supporting the use of the biosimilar drug in the different target diseases and patient populations. Safety must be ensured also by a strict control of the manufacturing process and a solid pharmacovigilance program, with full traceability and avoidance of substitution without medical decision. All the above actions will help settling all controversies and increasing the confidence of both physicians and patients in biosimilars.

We believe that it remains a responsibility of the physician, according to scientific society guidelines, to drive the implementation of new biosimilars into clinical practice, while concomitantly continuing to search for better therapeutic approaches. Biosim-

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ilars have certainly the potential of impacting positively on the overall treatment scenario, allowing significant cost savings and greater accessibility to valuable, effective treatments. However, great responsibility and caution is required by the healthcare community to ensure the appropriate development and clinical use of biosimilars. Likewise, from a regulatory standpoint, less emphasis should be given to similarity at detriment of safety, and over-reliance on comparative clinical data should be avoided. In the meantime, additional clinical studies and the implementation of active post-marketing surveillance will hopefully increase physicians' confidence in second-generation biosimilars.

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