

Challenges in post-marketing studies of biological drugs in the era of biosimilars: a report of the International Society for Pharmacoepidemiology 2019 Mid-Year Meeting in Rome, Italy

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Abstract

Several controversial issues related to challenges in the post-marketing studies of biological drugs, including biosimilars, were discussed at the International Society for Pharmacoepidemiology (ISPE) 2019 Mid-Year Meeting in Rome in April. In recent years, the marketing of biosimilars has been growing thus offering opportunities for wider access by patients to high-cost biological drugs as well as ensuring the economic sustainability of national healthcare systems. Through the comparability exercise required for marketing approval, the similarity of biosimilars to the reference products in terms of efficacy, safety and quality has to be demonstrated in pre-marketing studies. In Europe, the 15 years of experience of marketing of biosimilars has allowed the accumulation of a significant amount of scientific evidence confirming the comparability of the benefit-risk profile of biosimilars and originators. However, some aspects remain to be addressed both from a scientific and regulatory perspective, such as interchangeability and the automatic substitution of originators and biosimilars. The (long-term) monitoring of all biological drugs, including biosimilars, in real world settings is warranted with the ultimate goal of integrating pre- and post-marketing evidence about the aforementioned open questions. This conference report describes priorities, data sources, and methodological strategies for the post-marketing surveillance of biological drugs in the era of biosimilars.

1. Introduction

The International Society for Pharmacoepidemiology (ISPE) is an international organization dedicated to advancing the health of the public by providing a global forum for the open exchange of scientific information and for the development of policy, education, and advocacy for the field of pharmacoepidemiology, including such areas as pharmacovigilance, drug utilization research, comparative effectiveness research, and therapeutic risk management. The ISPE 2019 Mid-Year Meeting was held in Rome (Italy) from the 6th to the 9th April 2019 on the topic “Challenges in Post-marketing Studies of Biological Drugs in the Era of Biosimilars”. This Conference was co-chaired by **Prof. Gianluca Trifirò** from the University of Messina and **Dr. Ursula Kirchmayer** from the Department of Epidemiology of Lazio Region. In general, 215 people from all over the world attended the meeting, which was endorsed by the Italian Association of Epidemiology (AIE), Italian Society of Pharmacology (SIF), Italian Biosimilar Group (IBG), International Society of Pharmacovigilance (ISOP), Italian Society of Hospital Pharmacy (SIFO), and National Institute of Health (ISS). The speakers included a variety of stakeholders, such as officers working in European and American drug regulatory agencies, as well as researchers from international scientific societies, such as the European Crohn's and Colitis Organization (ECCO), the American Society of Clinical Oncology (ASCO) and the European League Against Rheumatism (EULAR), as well as prestigious academic centres and industry with consolidated expertise on regulatory affairs, pharmacoepidemiology and biologics including biosimilars specifically.

The first day of the meeting started with the welcome address of Co-chairs **Gianluca Trifirò** and **Ursula Kirchmayer**, **Dr. Alison Bourke** (FISPE, International Society for Pharmacoepidemiology [ISPE] President), **Dr. Luca Li Bassi** (Director of the Italian Medicines Agency), **Professor Alessandro Mugelli** (President of the Italian Society of Pharmacology) and **Dr. Salvatore Scodotto** (President of the Italian Association of Epidemiology). There was a general consensus on the need for the different stakeholders to work in concert on the topic of biological drugs and biosimilars specifically and to pool their combined expertise. The conference was divided into four sessions: regulatory and industry perspectives on biological drugs including biosimilars, perspectives from scientific societies, interchangeability of originators and biosimilars, and infrastructures for real world evidence (RWE) generation on biological drugs including biosimilars.

2. Regulatory and Industry Perspectives

The first session, moderated by **Patrizia Popoli**, President of the Scientific Committee of the Italian Medicines Agency, and **June Raine**, from the English Medicines and Healthcare Products Regulatory Agency (formerly chair of the Pharmacovigilance Risk Assessment Committee (PRAC)) gave a detailed overview of the regulatory and industry perspectives comparing the European experience to the United States (US) experience. **Dr. Thijs Giezen**, from the Biosimilar Medicinal Products Working Party of the European Medicines Agency (EMA), described the differences between originator and biosimilar development: while the conduct of pharmaceutical quality studies and the submission of risk management plans (RMPs) are required for all biological drugs, the focus of biosimilar development is to compare safety, efficacy, pharmacokinetics, pharmacodynamics and immunogenicity versus the reference product. It was emphasised that the aim of a biosimilar development program is not to establish the benefit of treatment but to establish biosimilarity (i.e. comparability of biosimilar and reference product). This has implications for biosimilar clinical studies, which have different aims with respect to clinical studies that are required for the reference product. In the post-marketing setting, drug regulatory requirements are the same for reference products as well as for biosimilars in terms of submitting RMPs, collecting spontaneous adverse drugs reaction (ADR) reports, and submitting Periodic Safety Update Reports (PSURs). The RMP of biosimilars should use the knowledge and experience gained from post-marketing monitoring of reference products, while again emphasising that the focus of biosimilar post-marketing monitoring is primarily aimed at comparing the biosimilar safety profile to the reference product. The importance of batch traceability was discussed, as several safety and efficacy issues identified in the real world setting may be batch-specific [1]. Another important topic that was discussed was the difference between switching, i.e. a decision taken by the treating physician to switch one medicine for another one having the same therapeutic effect, and automatic substitution, i.e. the practice of dispensing one medicine in place of another that is an equivalent and interchangeable medicine, occurring at the pharmacy level and without consultation with the

prescriber. It was noted that interchangeability is outside the remit of the EMA, which defers to European individual member state decisions on this topic.

Dr. Gerald Dal Pan, from US Food and Drug Administration (FDA), gave an overview of the American regulatory experience concerning biological drugs, including biosimilars. The experience of biosimilar post-marketing monitoring is relatively limited in the US, as the first biosimilar drug was marketed in 2015. At the time of writing, 18 biosimilars have already been approved in the United States (compared to 60 approved in Europe) although not all are on the market. In same year as the introduction of the first biosimilar drug in the US, the FDA published guidance entitled “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, Guidance for Industry”, outlining specific considerations for post-marketing monitoring of biosimilars [2]. Such considerations include evaluating efficacy and safety issues concerning the reference product as well as those emerging during biosimilar development and, whenever possible, related the use of the biosimilar in other countries where it is already on the market. Further considerations include the need to develop a good understanding of the conditions of use as well as the target patient population as well as the need to ensure the traceability of reference product vs. biosimilar use at batch level. Overall, the FDA’s approach to the post-marketing surveillance of biosimilars is multi-modal, multi-disciplinary, lifecycle-based and risk-based. The tools used to implement biosimilar surveillance are the FDA Adverse Event Reporting System (FAERS), manufacturer regulatory dossiers (e.g. Periodic Safety Reports, study reports, etc.), drug utilization data and epidemiological data (e.g. Sentinel System). The US experience with FAERS in the context of biosimilar drugs is currently limited but preliminary data suggests that approximately 15% of filgrastim FAERS reports may not have adequate product-identifying information to determine if the patient took the biosimilar or the originator. Several studies using the Sentinel System are under way to describe originator and biosimilar use in detail, in order to inform FDA policy on the traceability of these drugs.

The pharmaceutical industry’s perspective on biosimilars was discussed by **Drs. Uwe Gudat** and **Annalisa Iezzi**, from Fresenius Kabi SwissBioSim and Abbvie, respectively, two biotechnology companies that produce biosimilars. They highlighted the need to define the priorities of post-marketing surveillance of biological drugs and biosimilars in particular. Small observational studies of limited quality may not increase the evidence on biosimilarity, while, on the contrary, may potentially generate controversial results. In addition, it appears redundant to investigate issues that have already been fully addressed in the pre-marketing setting. Both speakers remarked that a large volume of evidence on drug use, safety and efficacy has been already generated on biological drugs, including biosimilars, by studies funded by the pharmaceutical industry. It was recently reported that such industry-funded studies are much more likely to be of high quality compared to studies that are not [3]. Dr. Iezzi attributed this to the stringent regulations on behalf of national and international drug agencies and compliance to such regulations. The importance of being able to trace biological drugs at batch level was emphasised in agreement with other speakers. The role of available Italian data sources, such as claims databases, electronic health records, or medical registries, along with their potential for studying biosimilar use, safety and equivalence was described in detail. The use of these data sources is, however, not without limitations: the difficulty of tracing biologic batch number and of investigating multiple switching are two such examples. Future steps to improve the post-marketing surveillance of biologic drugs could include the integration of different data sources with complementary strengths such as claims databases and clinical registries [4].

3. Perspective from Scientific Societies on biological drug and biosimilar use

The second session was moderated by **Professor Alessandro Mugelli** from University of Florence, President of the Italian Society of Pharmacology, and by **Professor Sebastian Schneeweiss**, from Harvard Medical School/Brigham & Women’s Hospital. Lectures were focused on the perspectives of scientific societies, such as ECCO, ASCO and EULAR, concerning originator and biosimilar use. **Dr. Gionata Fiorino**, from the Inflammatory Bowel Disease (IBD) Center of Humanitas Clinical and Research Institute in Milan, explained the point of view of ECCO on biosimilar use. He introduced the lecture by showing a survey conducted in 2014 on a total of 307 IBD specialists from ECCO. More than half of respondents declared to be not confident enough with biosimilars (34.6% not confident at all). In Europe, since marketing authorization of biosimilars, different prospective studies were conducted in patients with IBD [5,6]; results from these studies confirmed the comparability of the benefit-risk ratio of biosimilar infliximab versus originator. Data from a prospective,

nationwide cohort study including a large population of IBD patients from 33 referral centres confirmed again the absence of difference in effectiveness and safety of biosimilar infliximab versus originator in IBD patients [7]. Finally, a summary was given of the second ECCO Position Statement on the use of biosimilars for IBD, which confirms that a biosimilar product, registered in the EU, is considered as efficacious as the reference product when used in accordance with the information provided in the Summary of Product Characteristics [8]. However, demonstration of the safety of biosimilars requires large observational studies with long-term follow-up of IBD patients. This should be supplemented by registries supported by all involved stakeholders (manufacturers, healthcare professionals and patients' associations). Moreover, ECCO supports switching from the originator to a biosimilar in patients with IBD, but this should be based on appropriate discussion among physicians, nurses, pharmacists, and patients, and according to national recommendations. On the other hand, ECCO considers that additional efforts should be made to investigate in real world settings the clinical effects of reverse switching, multiple switching, and cross-switching among originator and different biosimilars in IBD patients due to the current lack of scientific and clinical evidence.

Professor Tore K. Kvien from the Department of Rheumatology Diakonhjemmet Hospital in Oslo (Norway), as a member of EULAR, summarized results of four large clinical studies of switching to biosimilar infliximab in patients previously treated with reference product infliximab in rheumatology, and presented the EULAR recommendations for the management of rheumatological diseases [9–12]. In the extension of the PLANETAS and PLANETRA studies, which explored the efficacy and safety of switching to biosimilar infliximab in patients previously treated with reference product infliximab for the treatment of ankylosing spondylitis and rheumatoid arthritis, respectively, antidrug antibody (ADA) incidence as well as response rate were comparable between maintenance and switch infliximab groups [9,10]. Recently, the largest nationwide Norwegian randomised controlled trial (NOR-SWITCH) in patients with immune-mediated diseases (Crohn's disease, ulcerative colitis; psoriasis; psoriatic arthritis; rheumatoid arthritis and ankylosing spondylitis) showed the non-inferiority of switching from originator infliximab to the biosimilar vs. the continuity of the treatment with the originator, according to a prespecified non-inferiority margin of 15% [11]. The NOR-SWITCH extension trial, which aimed to assess efficacy, safety and immunogenicity in patients taking biosimilar infliximab throughout the 78-week study period (maintenance group) versus patients switched to biosimilar infliximab at week 52 (switch group), confirmed the results of the main trial [12]. In the randomized, double-blind EGALITY study on the efficacy, safety and immunogenicity of etanercept biosimilar compared to the reference product in patients with moderate-to-severe chronic plaque-type psoriasis [13] a total of 531 patients were randomized to self-administer etanercept biosimilar or reference product twice weekly subcutaneously. This study demonstrated comparable efficacy, safety and immunogenicity of etanercept biosimilar and reference product. In the recently published consensus-based recommendations of EULAR, the use of biosimilars to treat appropriate patients was considered as comparable to their originators [14]. Concerning single switch between originators and biosimilars, currently available evidence has confirmed its safety and effectiveness; moreover, there is no scientific rationale to expect that switching among biosimilars of the same active substance would result in a different clinical outcome but patient perspectives must be taken into account. Concerning post-marketing challenges, EULAR suggests that harmonized methods should be established to obtain reliable pharmacovigilance data, including traceability of both biosimilars and originators. Multiple switching among different biosimilars or between biosimilar and reference product in a real world setting should be assessed through clinical registries.

From the oncologic perspective, **Dr. Donald Harvey** summarized the statements of ASCO [15]. Concerning naming and labelling, to ensure high-quality cancer care, oncologists, patients, and pharmacists should be able to easily identify biological drugs and ensure that patients receive the intended therapy. Oncologists must understand the significance of the name of each specific biosimilar that is being considered for use as treatment, as well as the associated clinical information. Distinction and clarity on the naming and labeling of biosimilars before, during, and after use are critical to avoid unintended alternating or switching of biological drugs that have not been deemed interchangeable by the FDA. The FDA recommends a two-step approach to obtain the interchangeable biologic designation, first gaining approval as a biosimilar and then submitting supplemental data to support interchangeability on the basis of the transition studies (considering at least three switches (back and forward)). However, to date no biosimilars have received an FDA interchangeable status. Moreover, post-marketing evidence development on use, efficacy, and safety of all biological drugs including biosimilars is warranted to enhance patient and provider confidence with biological drugs and biosimilars specifically.

4. Interchangeability of originators and biosimilars

This session, moderated by **Jaclyn Bosco** from IQVIA and **Giuseppe Traversa** from the Italian National Health Institute, focused on interchangeability of originator and biosimilar. Professor **Armando Genazzani** from the University of Eastern Piedmont showed the state of the art of interchangeability of reference products and biosimilars in different countries. Biological drugs are generally large complex proteins that are difficult to characterize and copy. As mentioned by the European Medicines Agency (EMA), however, “*natural variability is inherent to all biologics and strict controls are always in place during manufacturing to ensure that it does not affect the way the medicine works or its safety*” [16]. Thus, it was remarked that biological drugs often undergo post-marketing changes in their production process [17,18], which need to be assessed by the regulatory agencies. Differences in structure between the biosimilar and reference product, small or large, may theoretically impact on the properties of the biosimilar [19]. However, the comparability exercise (now used to demonstrate the biosimilarity of a biosimilar and the corresponding reference product) has been employed for decades to validate that any major manufacturing changes do not impact the quality, efficacy and safety (including immunogenicity) of the drug [20]. In October 2014, publicly available *European Public Assessment Reports* (EPARs) (N=29) for all monoclonal antibodies (mAbs) authorized by the EMA between 1998 and October 2014 were analysed [21]. These 29 EPAR reports included details of 404 manufacturing changes authorized by the EMA. Of these, 22 were categorized as high-risk, 286 as moderate-risk and 96 as low-risk manufacturing changes. The manufacturing change data presented herein indicate that, prior to the authorization of the first biosimilar mAb, the EMA had extensively evaluated the manufacturing process changes of originator mAbs, and gained significant experience in the change process and its impact on the safety and efficacy of biologicals. These comparability exercises became the guiding principles of biosimilarity to confirm that no meaningful differences in quality, safety and efficacy exist. These exercises have been employed in biosimilar development to ensure that sound scientific principles are adhered to. Since the manufacturing process for biosimilars will likely be different from the reference product for proprietary reasons, physicians ought to be able to trust the expertise of regulatory authorities to confirm the similarity of previously approved originator products and their biosimilars akin to their assessment of the pre- and post-manufacturing changes of biological drugs [17].

Dr. Bente Glintborg from Department of Rheumatology of Rigs hospitalet in Denmark showed the impact of non-medical switching from originator to biosimilar infliximab in patients with arthritis using the DANBIO registry. The DANBIO registry was set up in 2000 by the rheumatological society to monitor patients with inflammatory arthritis receiving biological drugs, covering more than 95% of adults with rheumatic diseases treated in routine care with biological drugs in Denmark. Results from this registry-based study showed that 802 patients treated with originator infliximab for >6 years were switched to biosimilar infliximab [22]. Disease activity and flare rates were unchanged, with no statistically significant differences during the 3-month period pre- vs. post-switch. Moreover, DANBIO data were used to assess the effectiveness and safety of the switching from originator to biosimilar etanercept in patients with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis [23]. Of a total of 2,061 patients treated with originator etanercept, 1,621 (79%) patients switched to a biosimilar. Disease activity was unchanged 3 months’ pre-switch/post-switch. In both switchers and non-switchers groups, lack of effect was the most common reason for withdrawal. These results indicate the safety of such switching and demonstrate the usefulness of registries for this purpose.

Finally, **Dr. Antonio Addis** from the Department of Epidemiology of Lazio Region provided an overview of Italian observational studies conducted through a network of claims databases from several local Health Units and Regions, covering a total population of around 13 million inhabitants (25% of the Italian population) [24–26]. These studies documented that the practice of switching of biological drugs belonging to the same class is frequent in routine care, irrespective of the marketing of biosimilars. Italian post-marketing database studies have so far provided reassuring data on the comparative effectiveness and safety of originator and biosimilars of epoetins [27,28], demonstrating also the absence of clinical effects in those switching from originator to biosimilar epoetins. The usefulness of the Italian database network to address urgent regulatory questions on several aspects of biologicals including biosimilars was noted.

5. Infrastructures for real world evidence on biological drugs including biosimilars

The last session of the meeting, moderated by **Marina Davoli** from the Department of Epidemiology of Lazio Region and **Susana Perez-Gutthann** from RTI Health Solutions, Barcelona, was focused on the infrastructure for generating RWE on biological drugs in the era of biosimilars. It is important to create a system for the large volume of data to enable storage, sharing and analysis, as well as to set up a governance that allows a prompt reply to public health questions generating robust evidence through real world data. Professor **Jeffrey Brown** from Harvard Medical School and Harvard Pilgrim Health Care Institute showcased the experiences of creating and leveraging the informatics infrastructure that supports database networks in the US. Professor Brown explained that, in 2007, the FDA was given a mandate to launch an active surveillance system. In 2008, the Sentinel Initiative was launched, starting with a 5-year pilot project called Mini-Sentinel. Since then, the Sentinel System has been conducting studies using real-world data as a national medical product monitoring system, partnering with 18 data partners using a distributed data system with data on more than 100 million persons, using a common data model (CDM) approach [29]. The data used by the Sentinel System consists of administrative claims data, electronic healthcare records (EHRs) and laboratory test results for 10% of these EHRs, registries, and a small number of full-text clinical records. The specific challenge of identifying biological drugs within the Sentinel System while conducting real world data (RWD)-based studies on biological drugs mentioned earlier by Dr. Dal Pan were highlighted again. Currently, the US approach to recording biological drugs is evolving to meet these challenges, for example by addition of procedure codes that include not only the name of the biosimilar but also the manufacturer of that specific biosimilar. This can address some of the difficulties in tracing safety and effectiveness issues to a specific biological drug. To further address issues concerning post-marketing biological drug monitoring, the US has developed another network, the Biologics and Biosimilars Collective Intelligence Consortium (BBCIC), a non-profit, multi-stakeholder, scientific public service initiative that aims to conduct robust post-marketing observational research monitoring of biosimilars as well as newly marketed biological drugs for effectiveness and safety in a real-world setting. The infrastructure of the BBCIC leverages the network and expertise of the Sentinel System, although it is not part of the Sentinel System. The BBCIC governance includes a member of the FDA as well as workgroups that develop specific research areas, such as switching, comparative effectiveness research methods, International Classification of Diseases 9 to 10 mapping, and developing best practices to identify biological drugs through the available coding systems in the US.

Dr. Andrew Bate from Pfizer described the potential global real-world data-based strategies for biological drug post-marketing surveillance, with particular focus on machine learning. RWD currently has a role throughout the drug development lifecycle [28]. Dr. Bate suggested a three-tiered strategy to leverage RWD, made up of: local analysis of data available in-house, remote use of data, and ad-hoc use of data. In addition to single databases in the form of EHRs, claims databases and registries, there are several multi-database initiatives around the world that are involved in post-marketing drug surveillance, including the Canadian Network for Observational Drug Effect Studies (CNODES), Observational Health Data Sciences and Informatics (OHDSI) and EU-ADR, to name a few. As for other drug classes, for biological drug research it is important to have large data sets with long follow-up periods and good data capture in specialist settings. To collect the level of clinical detail needed, it might be necessary to augment RWD with primary data, for example by asking General Practitioners (GPs) or specialists to provide specific information about disease severity. While all the above data sources are increasingly used to study biological drugs, pharmacoepidemiological experience in this field is still somewhat limited. It is important to leverage the full potential of currently available data sources and identify measures to augment the capabilities of these data sources. In addition, the correct and transparent reporting of observational research is essential to render RWD and the evidence it produces useful for public health purposes [30].

Dr. Nello Martini from Drugs & Health discussed the role of real-world data on biological drugs including biosimilars for informed regulatory decision making. In light of the recent European marketing of different biosimilars of monoclonal antibodies, it is necessary to conduct post-marketing studies in the field of gastroenterology, dermatology, rheumatology and onco-hematology. He presented an Italian Drug Agency-funded pharmacovigilance national project, "Post-marketing evaluation of comparative benefit-risk profile of biological drugs and corresponding biosimilars in dermatology, rheumatology, gastroenterology and onco-hematology using real world data from an Italian network of databases, active surveillance and clinical registries - VALORE project" as an example of a coordinated initiative to leverage several available data sources to study biological drug use. For the purpose of the project, a multi-regional network will be built (covering several

million of inhabitants) in order to integrate and analyze data from different regional claims databases and clinical registries. In line with national rules regarding patient privacy, the construction of a network of different data sources may be a tool that overcomes the traditional limitations of administrative databases (e.g. lack of some clinical details, such as parameters of effectiveness, information on lifestyles, etc.) and from the other side those related to clinical registries (reduced number of enrolled patients and years of follow-up, limited ability to observe the patient in the long term, especially with regard to serious ADRs that lead to hospitalization). It was highlighted that Italy, due to the experience gained in conducting a large number of observational studies on biologicals (and biosimilars specifically) in the last decade, has become a leader in the RWE generation on these drugs. It was added that, very recently, the updated ASCO/American Society of Hematology (ASH) clinical practice guideline for anemia management in cancer patients [31] cited several Italian multi-database studies demonstrating the comparability of epoetin alfa, originator and biosimilar, as well as other epoetins still covered by patents (e.g. darbepoetin, epoetin beta) in terms of effectiveness and safety [27,28,33,34].

6. Conclusions

As for originator biological drugs, post-marketing monitoring of biosimilars is necessary, in line with risk management plans. In particular, some specific issues, such as immunogenicity, interchangeability of originator and biosimilars, the appropriateness of their use, and impact on costs and on access to innovative biotechnological drugs, should be carefully evaluated, to support and integrate with available pre-marketing evidence. Through claims databases and clinical registries it may be possible to monitor the benefit-risk profile of biologicals, including biosimilars.

Author Contributions: GT, UK generated the study idea. YI, GT and JS wrote the final manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Funding: No funding was received.

Conflicts of Interest: Trifirò Gianluca declares his participation on advisory boards on biosimilars, organized by Sandoz and Hospira; furthermore, he coordinates a pharmacoepidemiology research team at the University of Messina, which receives research grants for projects that are not related to the topic of the paper. Ylenia Ingrassiotta, Janet Sultana, and Ursula Kirchmayer declare that they have no conflicts of interest.

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