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Biosimilars in Italy: a gastroenterologist's view

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The introduction of biological therapy has revolutionized the paradigm of treatment in the last two decades. This is expected to lead to corresponding amelioration of the course of several immune-mediated diseases, including inflammatory bowel diseases (IBD). However, this may come with an appreciable increase in expenditure on drugs. Due to ongoing patent expiry of some biologicals, the introduction of biosimilars is creating the opportunity for substantial financial savings to be made, leading to easier, wider and earlier access to therapy for some patients, and possibly to changes in resource allocation by health services. However, the complexity and potential immunogenicity of the first monoclonal biosimilar of infliximab introduced to the market, and the extrapolation of its indications to all diseases approved for the originator, despite the absence of controlled trials in all diseases at time of market authorization, have initially raised concerns in the scientific community. In Italy, the uptake of this biosimilar (CT-P13) is already close to the European mean, although the utilization and regulation at regional levels is highly heterogeneous.

Keywords: Adalimumab, biosimilar, Crohn's disease (CD), inflammatory bowel disease (IBD), switching, ulcerative colitis (UC)

Introduction

In recent years, biologicals have gained significant traction in the pharmaceutical industry, and by 2020 they are predicted to generate US$290 billion in revenue, covering about one third of the pharmaceutical market [1]. In addition, approximately half of sales come from 11 biologicals that face loss of exclusivity over the next seven years [2]. For these reasons, it is expected that the worldwide biosimilars market will reach US$25–US$35 billion by 2020 [3]. This, along with the increasing worldwide focus on improving healthcare access and the reducing cost of care, make biosimilars attractive, but they are also a challenge for stakeholders.

Since the approval of the first biosimilar in the European Union (EU) in 2006, 21 biosimilars have now been approved [4], at least 13 are under evaluation [5] by the European Medicines Agency (EMA), and there are many others in the pipeline globally [6]. In major markets like the EU, regulators and payers have recognized the potential financial benefit of biosimilars and are driving their uptake. The introduction of CT-P13, the first monoclonal antibody (mAb) of infliximab on the market, and the forthcoming arrival of many others, has stimulated a great debate and some concerns in the scientific community. The regulatory processes of agencies in the EU and the US (based on what are known as comparability exercises) are rigorous and strict. They are similar to the processes that originator products are subject to following manufacturing changes. The focus of concern is largely on extrapolation to all the indications of the originator, despite the fact that controlled clinical trials of the biosimilar having been performed for only some indications.

In this paper, the Italian National Health Service's situation and position is analysed. Specific emphasis is given to the gastroenterologist's perspective, a year after the introduction of CT-P13 for the treatment of inflammatory bowel disease (IBD).

The Italian healthcare system

After World War II, the healthcare system in Italy was funded by health insurance from 'sickness funds'. As there was a substantial difference in the coverage provided by different funds, and a large proportion of population were uninsured, in 1978, the *Servizio Sanitario Nazionale* (SSN – Italian National Health Service) was established. As a result, health care is now provided to citizens and residents with universal coverage and receives tax funding through a mixed public-private system. The system is highly decentralized, with 20 Regional Health Authorities (RHAs) which are responsible for planning healthcare services and allocating financial resources. In principle, local autonomy implies stronger financial accountability, which means that regions develop different economic strategies.

Data regarding the evaluation of the performance of the healthcare system are complex and discordant. In Bloomberg's 2015 ranking of countries with more efficient healthcare systems, Italy is ranked sixth, with a life expectancy of 82.29 years (–0.6 relative to the previous year), cost as per cent of the gross domestic product of 9.02% (+0.12% relative to the previous year), and cost per capita of US$3,155 per person (+US$123 relative to the previous year). However, in the same year, according to the Euro Health Consumer Index, Italy was 22nd in Europe, whereas

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the OECD (Organisation for Economic Co-operation and Development) survey scored Italy as fourth for life expectancy and 18th for cost expenditure.

The uptake of biosimilars in Italy

The substitution and interchange of biosimilars with biological reference products at the pharmacy level is not permitted by the Italian pharmaceutical system due to possible differences between such products. The official position of AIFA (*Agenzia Italiana del Farmaco,* Italian Medicines Agency), is that biological medicines and biosimilars cannot be approached in the same way as other generic medicines, with respect to their therapeutic substitutability.

AIFA published a new concept paper on biosimilars for public consultation on 16 June 2016 [7]. This is the second such concept paper issued by the agency, the previous report having been published in 2013. Importantly, although the main elements of the paper are consistent with AIFA's initial report, the agency did not make any specific reference to prefer the use in the treatment-naïve patients in the second paper. With respect to this, the last concept paper states that all patients should be considered appropriate for treatment with biosimilars. In the latest report, AIFA has now concluded that using a biosimilar instead of the originator is a possibility that should be left to the clinical judgement of the doctor involved. AIFA also concludes that biosimilars offer a favourable opportunity to develop a competitive market, and to aid in the rationalization of public spending.

However, within the biological class, there are 'simple products (first generation)' and 'complex products' (second-generation) [8]. Here, 'simple' refers to those with less structure, instability and changeability, e.g. growth hormones, epoetins and granulocyte colony-stimulating factor (G-CSF) drugs; and 'complex' refers to monoclonal antibodies [9]. The latter are characterized by greater structural complexity; they are derived from a more complex manufacturing process, which in turn, leads to a higher probability of post-translational changes; and they perform a more critical curative function, as in the case of adjuvant oncology therapy. In the case of biosimilar registration of monoclonal antibodies, it is challenging to assume total overlap and interchangeability with the originators unless post-marketing studies and consistent pharmacovigilance data confirm this in a real world, evidence-based, context.

Based on the 2016 IMS Health report [5], the uptake of 'simple' biosimilars in Italy in 2015 ranged from 23% for human growth hormone, to 88% for G-CSF, compared to their originators. However, there were pronounced differences across the country, mainly due to different strategies and regulations at regional levels. In general, Italian gastroenterologists were not impacted by the first 'wave' of biosimilars, with the exception of few epoetin prescriptions.

The first mAb biosimilar in Italy

In February 2015, the patent for infliximab expired in Italy and two CT-P13 products, based on the same documentation, are now on the market: Remsima (Celltrion Healthcare Hungary Kft, HU-1023 Budapest) and Inflectra (Hospira UK Limited, Maidenhead, UK). As the infliximab indications approved by EMA are: rheumatoid arthritis (RA), ankylosing spondylitis (AS), adult and paediatric Crohn's disease (CD) and ulcerative colitis (UC), psoriatic arthritis (PsA), and chronic plaque psoriasis (CPP), the infliximab biosimilar has therefore been licensed for all of these indications. Although biosimilars may lead to significant cost savings, larger access to biologicals and a sustainable level of care in immune-mediated diseases, there was a lack of confidence in the use of biosimilar infliximab for IBD treatment at the time of its launch [10], and concerns had been raised by several national [11] and international societies [12] with regard to extrapolated indications, and especially to switching from the originator.

To date, no randomized controlled trials are available for the use of CT-P13 for treatment of IBD. A randomized, double-blind, parallel group study, the NOR-SWITCH study [ClinicalTrials.gov identifier: NCT02148640], is currently underway in Norway. The purpose of this study is to assess the safety and efficacy of switching from infliximab to the Remsima biosimilar treatment for all indications for which the originator is approved. It has been designed as a non-inferiority study with an estimated completion in May 2016 with the first report due in October 2016. The primary outcome desired is to evaluate the occurrence of disease exacerbation (Δ 30%) in a time frame of 52 weeks. Another study, sponsored by Celltrion, has been designed to assess non-inferiority in efficacy, and to assess overall safety of CT-P13 compared to infliximab in patients with active CD, up to week 54 [ClinicalTrials.gov Identifier: NCT02096861]. This study that enrolled 214 patients will also provide information about switching from infliximab to CT-P13, and from CT-P13 back to infliximab; the study enrolment is now closed, but no data are available yet.

Despite the limited trial data available at present, the uptake of CT-P13 in Italy in 2015, compared to the originator, is already 11%. This is close to the EU mean of 13%, which takes into account 78% uptake in Poland and 100% in Bulgaria [5]. This result has been obtained despite a great heterogeneity of regulation between the 20 RHAs in Italy, which is likely due to either the finances of the local health systems and what is available for pharmacologic expenditure, or more rapid decision-making of some local stakeholders. In two regions, Piemonte and Tuscany, a strict prescription rule has been issued requesting over 65% and 95% of CT-P13 utilization against the originator, respectively. In nine regions across the country, a specific recommendation to use the CT-P13 in all naïve IBD patients has been announced. In the remaining regions there is no specific advice, but it is suggested that patients naïve to anti-TNF products are prescribed the biosimilar in at least 10% of cases. This situation is confusing for doctors and for patients who are often treated in a tertiary referral centre, not in their home region.

The diseases treated with the infliximab biosimilar by gastroenterologists, namely UC and CD, lack a clear-cut effect biomarker, such as haemoglobin or glycaemia. As a result, once starting the therapy with the biosimilar or switching from the originator, a period of months must pass before the clinician might realize that the biosimilar is not working effectively, or is causing a loss of the previously acquired

efficacy. Due to the lack of information on efficacy and safety in IBD sufferers and the limited published open label studies [13], a prospective multicentre trial on the use of CT-P13, the PROSIT study, has been promoted by the Italian Group for the study of IBD (IG-IBD). This cohort is still recruiting patients via their web-based platform, and preliminary data were presented at the 2016 European Chron's and Colitis Organisation (ECCO) [14] and Digestive Disease Week (DDW) meetings. Data from approximately 400 patients, of whom approximately 100 switched from infliximab, so far appear to demonstrate a comparable efficacy and safety when compared to the originator. It is important to note that this was an investigator-driven, non-sponsored trial and to partake, patients signed an informed consent. Paradoxically, the investigators themselves initially had little information on the efficacy or safety profile of CT-P13 for IBD treatment.

It is important that drug safety information is conveyed to patients. Regulations surrounding the compulsory black triangle (included on drug labelling for all new products), apply to both new originator biologicals and newly marketed biosimilars; however, originator biologicals, already on the market, are exempt from needing to include this marker and from being subject to additional monitoring, as they have been on the market for many years and have a proven safety profile. When faced with the choice of new versus old products, doctors must inform the patient when there is no evidence suggesting inferior safety or efficacy of the biosimilar, and also clarify if there are other available drugs with the same active ingredient and a safety profile that is more comprehensively known. However, Italian law unquestionably assigns the final decision over which treatment is administered to the health service operator (not the patient), with the preferential treatment option being that safest for the patient and the operator is completely liable for the choice of treatment adopted. In this context, it is worth noting that, of a sample of 150 gastroenterologists who took part in the IG-IBD's online anonymous survey, only half responded that they feel completely free to decide whether or not the infliximab biosimilar should be prescribed (Annese V 2016, personal communication, October 3).

In view of the arrival of other biosimilars of infliximab, and in the near future those of adalimumab, it is critical that patients and clinicians retain the freedom of choice over therapy adopted, especially in cases where patients are doing well while receiving a specific drug, either originator or biosimilar. In the future, we may see that there are many biosimilars of the same originator on the market, and that every 6–12 months a new, less expensive biosimilar will be added or, paradoxically, we may see the originator becoming the more economic treatment option. Either scenario could lead to the situation of multiple possible treatment switches.

Conclusion

The 'biosimilar era', unlike the non-biological one, is still in its infancy and is likely to increasingly dominate the market. There is no doubt that manufacturing processes and reverse protein engineering have made substantial progress in the last decade, and that the new generation of biologicals and biosimilars are much more completely investigated and evaluated by regulatory agencies globally. This should result in fewer impurities, less heterogeneity among batches and higher consistency. However, according to Hippocrates' oath, doctors are committed to '*primum non nocere*' or 'first, do no harm'; this means they must know and reiterate information surrounding the safety, efficacy and reliability of any new treatment option to their patients. Although the cost and cost-effectiveness of health care are important, patients facing more complex and potentially life-threatening diseases, especially when they are doing well with a specific treatment (either originator or biosimilar), have the right to receive all available information concerning the potential consequences of switching once or multiple times whenever a new, less expensive compound is being considered for use.

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