WHY BIOSIMILARS MATTER: AN INNOVATIVE SOLUTION TO IMPROVE PATIENT ACCESS

Summary of presentations from the Sandoz-supported satellite symposium held at the 20th Congress of the European Hematology Association (EHA), Vienna, Austria, on 13th June 2015

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MEETING SUMMARY

The meeting was introduced by Prof Robin Foà who spoke about the difficulties for patients accessing therapies in the context of rising healthcare costs and reduced budgets. Dr Mark McCamish then explained the biosimilar development process and the analytical techniques involved. Prof Felix Keil discussed the role of biosimilar medicines in haematology using the example of GP2013/rituximab (RTX), and Ms Karen Van Rassel of the Lymphoma Coalition presented the role a patient organisation can play when working with the physician to support a patient's questions and concerns regarding lymphoma.

Introduction

Professor Robin Foà

Prof Foà opened the symposium by highlighting: i) the enormous surge in demand for increasingly expensive treatments, due to an ageing population, and improved biologic age; ii) the rise in long-term chronic conditions, as illnesses become better controlled; and iii) the increased expectations of treatment outcomes by physicians. Providing healthcare is becoming progressively more costly and difficult to manage within the constraints of public resources. The cost of cancer care is increasing at 2-3-times the rate of other healthcare costs; for instance, the average monthly cost of cancer drug therapy has increased from approximately $100 in 1965 to $10,000 in 2013.[1] Patient access to medication is a major problem. An illuminating example is represented by RTX, which has been very successful for the treatment of B-cell chronic lymphoproliferative disorders. In a 2013 global survey of 450 physicians, it was found that patient access was only 39%; cost issues were frequently reported as barriers to RTX access.[2] Biosimilars are approved biologics that are highly similar to their reference product in terms of structure, function, pharmacokinetics (PK), and pharmacodynamics (PD), are comparable with respect to clinical efficacy and safety, and show the same presentation, strength, and mode of action.[3,4]

The first biosimilar was approved in Europe in 2006; currently, there are 19 products approved by the EMA, representing six different biological molecules. In 2013, the first biosimilar monoclonal antibody (mAb) was approved (biosimilar infliximab) and there are many biosimilars currently in development, which may give patients a route to access these important classes of drugs.

Targeted-Directed Development of Biosimilars

Doctor Mark McCamish

Biologics are highly specific and powerful molecules that have revolutionised modern medicine. They are much larger than chemical molecules and smaller peptides, and therefore cannot be chemically synthesised. Synthesis of smaller proteins without sugars can be achieved by inserting the DNA sequence for the protein into a host cell to produce an exact copy, including the protein folding and structure. However, larger glycosylated proteins such as erythropoietin, fusion proteins, and mAbs often experience some post-translational modifications that depend on the cell and the environment, and can vary from one molecule to the next, both during endogenous glycoprotein production in our own bodies and when manufacturing a biologic. Schiestl et al.[5] investigated acceptable levels of change in glycosylation from batch-to-batch and following major manufacturing changes, and found low variability between batches (5% variability) but a large change following a manufacturing change (a specific glycosylation enrichment dropping from 50-30% enrichment). However, this specific glycosylation is not known to impact on biological activity and therefore the change was deemed acceptable by regulatory agencies. Manufacturing changes are monitored closely by the regulating authorities and are only approved when they do not lead to clinically meaningful differences.

There are several reasons for considering the use of biosimilars, including improved patient access, the possibility of using more novel drugs, and reduced healthcare costs. Patient access to biologic medications is suboptimal; for example, only half of patients with severe rheumatoid arthritis (RA) receive biologics in the USA, Japan, and the EU5 countries.[6] In addition, only 30% of patients with moderate severity of RA disease receive biologics;[6] in these patients, the use of biologics could prevent their progression to severe RA, however their cost often limits their use. The use of biosimilar biologics has already been shown to result in large savings in Europe and is estimated to achieve savings of up to $250 billion in the USA by 2024.[7]

The goal of biosimilar development is to engineer a biosimilar to be 'essentially the same' as the reference product.[8] Variability of the reference product is documented over time to establish the variability of various post-translational modifications (such as glycosylations), and this variability helps to establish acceptable variability for the proposed biosimilar. The goal of biosimilar development and production is to reduce the variability to stay within narrow limits as established by the target variability of the reference product, i.e. it is a target-directed development (Figure 1). There are a number of sensitive analytical techniques that can be used to measure variability of the protein structure and glycosylation species; once the comparability of the biosimilar to the reference product has been shown using these techniques, clinical trials can be carried out to confirm biosimilarity, rather than to re-prove efficacy and safety.

To achieve regulatory approval, the goal is to produce a biosimilar that is essentially the same as the reference product. Indeed, the concept of 'sameness' has evolved over time with the development of more advanced techniques and complex molecules. Sameness is demonstrated by combining data from multiple sources evaluating more than 100 individual attributes covering primary structure, post-translational modifications, protein folding, biological activity, and impurities. The process of biosimilar development is very different to that of developing a novel drug or the reference product. During development of the original reference product the analytical tests simply describe the molecule, while clinical testing is substantial and designed to show how the molecule works, ultimately demonstrating clinical safety and efficacy in every indication in the label. However, during biosimilar development it is the opposite: analytical testing forms the basis of development to demonstrate that the molecule is essentially the same as the reference product and, once similarity is established, clinical studies are used to confirm the similarity already demonstrated analytically. The clinical trials are not designed to establish safety or to prove efficacy.

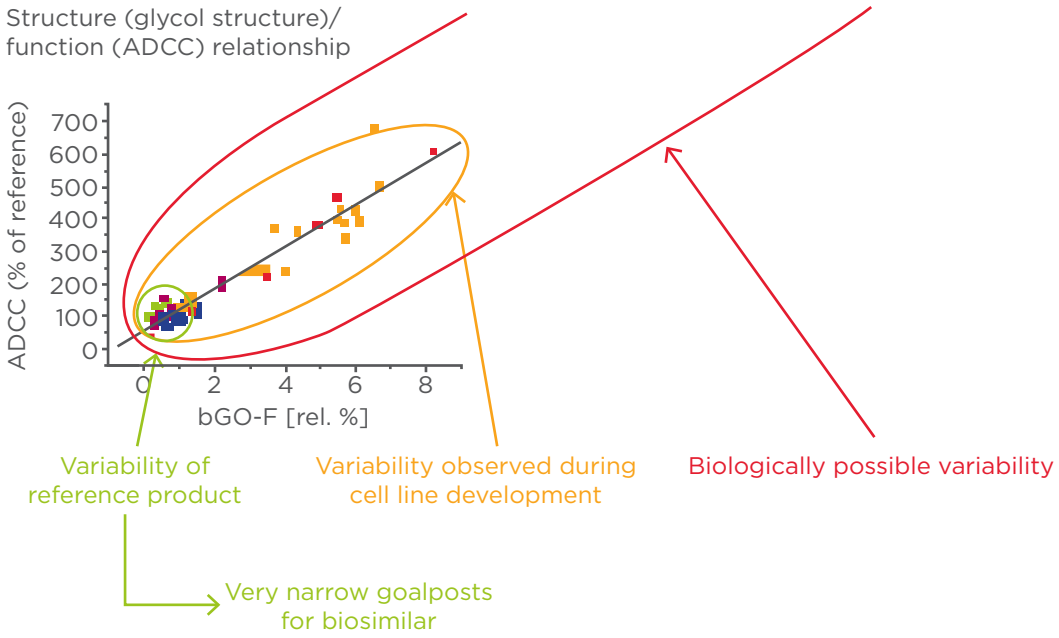

Figure 1: Originator variability is the basis for definition of biosimilarity goal posts.[5]
ADCC: antibody-dependent cellular cytotoxicity.

Biosimilars are recognised around the world as being safe and effective medicines, and have been available for a long time; the first biosimilar medicine was manufactured by Sandoz and approved in the EU in 2006 (biosimilar somatotropin). The EMA and the FDA have developed documents to provide guidance on how to approach biosimilar development; these have evolved over time. The guidelines are similar in both Europe and the USA. There has been more clarity achieved in the USA with the first biosimilar approved by the FDA, biosimilar filgrastim (Zarxio®, Sandoz); this approval demonstrated the development and approval processes in the USA, and has shown that extrapolation for other indications is achievable — a key benefit for biosimilar development. Extrapolation of biosimilar medications for other indications is not based on one small clinical study in one patient population that is then used to extrapolate to other indications on the label; rather, extrapolation is based on the demonstration of similarity between the biosimilar and the reference product in terms of structure, biological function, toxicity, and clinical similarity in a sensitive clinical indication. When it can be proven that the biosimilar molecule is essentially the same as the reference product, extrapolation can be made simply from the biosimilar to all indications of the reference product as they are essentially the same active pharmaceutical ingredients.

During the question and answer session, Dr McCamish commented that production of a biosimilar takes twice as long from target selection to first-in-human studies compared with the reference product, due to the various analytical tests required. In addition, he commented on the benefits of having the experience from the reference product in terms of predicting immunogenicity, as decades of clinical experience define what the potential immunogenicity risks are. Dr McCamish commented that although it is challenging to enrol patients into clinical trials, the motivation for patients to take part include altruism, access to medications that are potentially unavailable or too expensive, and the fact that all patients in the trial would receive the active drug. The concept of interchangeability was also discussed. In the USA, interchangeability is related to the ability of a pharmacist to substitute a biosimilar for a reference drug without the intervention of the prescribing physician. In Europe, the term 'interchangeability' is used to imply the ability of the physician to exchange use of a biosimilar in place of a reference biologic, while the term 'substitution' describes the intervention of the pharmacists as above. Although reference products may have minor changes over time related to manufacturing modifications, they are considered the same if approved by regulators. Although biosimilars that are approved to be interchangeable are designed to be essentially

the same as the reference product and whose function has not shown to alter upon switching, Dr McCamish emphasised that interchangeability is still a regulatory issue. Finally, Dr McCamish discussed the need for the education of physicians on the science of biosimilar production.

Biosimilars in Haematology

Professor Felix Keil

Biologics may be categorised as originators, of which they may be innovators (novel drugs/targets, and a significant step forward in efficacy and/or safety) or biobetters (known target, improved binding etc.), or as non-originators, of which they may be biosimilars (clinically equivalent to the originator, robust regulation) or copy biologics (less stringently regulated, often found in the emerging markets).[9] Biologics account for <1% of all prescriptions, but up to 28% of all medicine costs.[10] While generic medicines can result in price reductions of up to 90% compared with the brand-name version, the same cost savings are not achievable with biosimilars due to the complex nature of their production. In the EU, the median price saving for biosimilar epoetin alfa is 35%.[10] In fact, since the introduction of biosimilar epoetin in 2007, Germany has achieved savings of >€550 million.[11] The global costs of cancer care are high and continue to grow,[12] however, the patents on some of the key oncology therapies have expired or are about to expire,[13] presenting an opportunity for biosimilar medicines to provide the same clinical effects at reduced costs.

RTX has been a successful biologic therapy for the treatment of lymphoma, with approved indications for non-Hodgkin lymphoma (primarily follicular lymphoma, diffuse large B-cell lymphoma [DLBCL], and mantle cell lymphoma), chronic lymphocytic leukaemia, and RA. The incidence of DLBCL and mantle cell lymphoma increases with age,[14] resulting in increasing numbers of patients requiring treatment. The proposed biosimilar RTX GP2013 has been shown to be similar to the originator in terms of non-clinical *in vitro* and *in vivo* studies, as well as PK/PD studies (Table 1).[15]

The ASSIST-FL study is being conducted to compare GP2013 with originator RTX in 618 patients with untreated follicular lymphoma receiving a cyclophosphamide/vincristine/prednisone (CVP) chemotherapy regimenn. The primary outcome of this trial is the overall response rate at 24 weeks. The recruitment of the study is now closed, with results expected next year.

Biosimilars provide opportunities for more affordable and sustainable healthcare, greater access to biologic treatments for patients, and the increased opportunity for clinical studies. Additional clinical studies with RTX are important in order to determine the impact of variations in, for instance, body composition (proportion of fat, muscle, etc.) among patients; although they receive the same dose, the amount retained may not be appropriate for their body composition and thus needs to be personalised. Age and gender have been shown to significantly affect RTX clearance, with older men having greater clearance rates than older women.[16] In addition, increased weight in older male patients with DLBCL results in reduced clearance and increased half-life of RTX.[17] Therefore further studies in this area of personalised dosing are important in order to obtain more information about biologics; the only way to do this is to have more companies conducting more trials.

Table 1: GP2013 and the originator rituximab are pharmacologically similar.[15]

GP2013 and originator rituximab are pharmacologically similar
Pharmacological comparability between GP2013 and originator rituximab were confirmed in preclinical studies using clinical scale drug product: - *In vitro* ADCC potency in lymphoma cell lines - *In vivo* efficacy in mouse xenograft models - Pharmacokinetics and pharmacodynamics (CD20 cell depletion) in cynomolgus monkeys

ADCC: antibody-dependent cellular cytotoxicity; PK: pharmacokinetics; PD: pharmacodynamics.

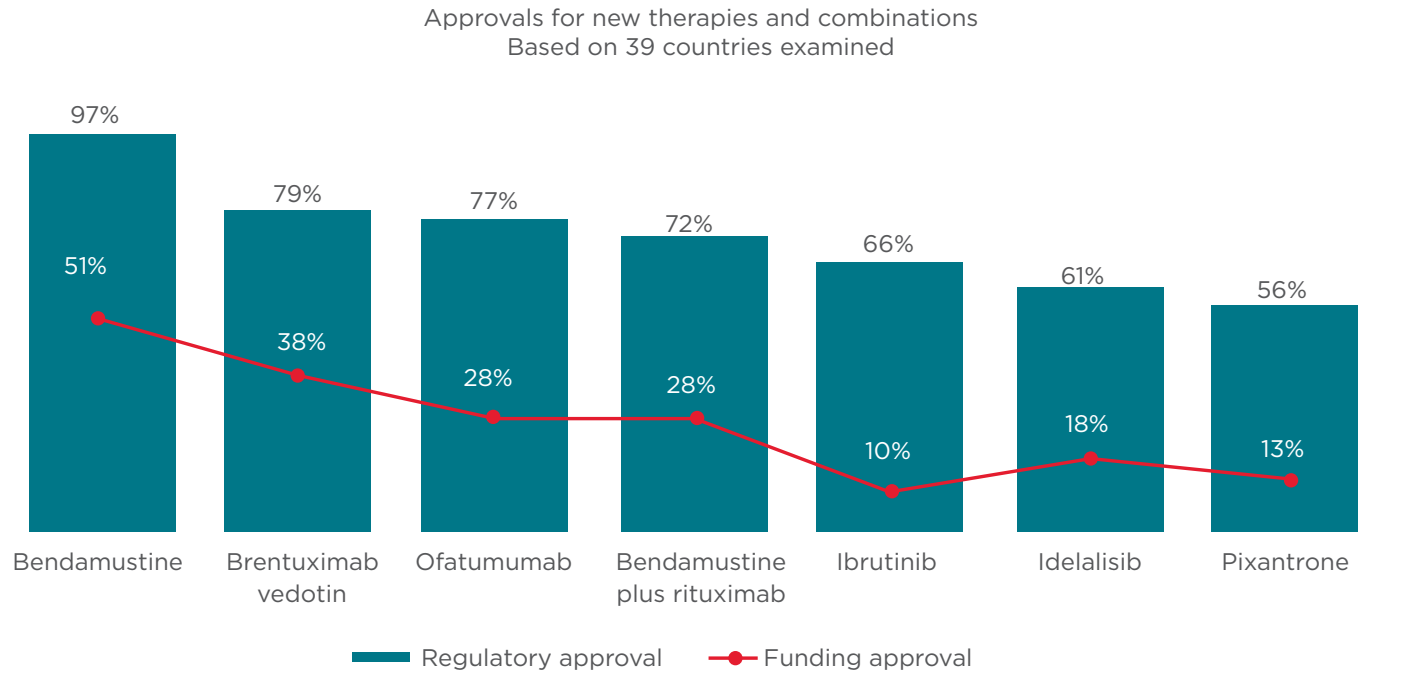

Figure 2: Therapy availability.

The established pathway for biosimilar development ensures quality. Biosimilars may provide increased patient access to medication in a time when global healthcare costs are increasing. RTX biosimilars development may encourage further trials that focus on personalised anti-CD20 treatment in lymphoma. Post-approval surveillance and extrapolation of efficacy to other indications of the reference product remain critical and challenging topics in haematology.

Lymphoma Coalition: Worldwide Network of Lymphoma Patient Groups

Ms Karen Van Rassel

The Lymphoma Coalition was founded in 2002 and has 63 member organisations based across 44 countries. They are managed by a global Board of Directors and have an international Medical Advisory Board. In addition, many of the member patient organisations also have Scientific Advisory Boards that the Lymphoma Coalition are able to access in order to obtain the relevant advice and an understanding of the current clinical situation. This provides an opportunity for patients all around the world to come together to obtain information and share best practice. The goal of the Lymphoma Coalition is to: (1) be a global source of information for lymphoma patients, with considerable statistics and facts; (2) improve awareness and understanding of lymphomas; and (3) build capacity for new and existing lymphoma groups. Information is provided in the context of an algorithm of care, is gathered based around the subtype of lymphoma that patients are diagnosed with, and is broken down into areas such as guidelines for diagnosis, therapies, clinical trials, incidence, mortality, and quality of life (QoL). One of the Lymphoma Coalition's goals is to advise that non-Hodgkin lymphoma is not one disease, rather it is made up of many different subtypes. Information regarding subtypes of non-Hodgkin lymphoma is compiled into case studies that can be used to advise and lobby governments regarding patient needs. This is important as patients need specific information on their illness, which is often difficult to obtain when the umbrella category of non-Hodgkin lymphoma is used.

The Lymphoma Coalition gathers information on each of the categories in the algorithm of care and also on clinical trials for lymphoma and chronic lymphocytic leukaemia, and keeps this information in a global database. The information is also available by country and may be used to build a picture of the disease landscape. For instance, of the 119 approved therapies available for the seven subtypes of lymphoma that the Lymphoma Coalition tracks, 96 are approved in the USA, 72 in the EU, but only 6 in Venezuela. RTX has

regulatory approval in 40 of the Lymphoma Coalition member countries, and is reimbursed or insured in 33, yet it is a component of 40 lymphoma chemotherapy regimenns. Reimbursement is a more accurate measure of patient access to medication compared with regulatory approval (Figure 2). It is still not clear if biosimilars will help funding approvals, however patients do not currently have access to the medications that are available.

There are many clinical trials ongoing, however it is very difficult to find biosimilar clinical trials online. The Lymphoma Coalition identifies trials to give patients the knowledge of where trials (including biosimilar trials) are available. The group also conducts a bi-annual patient survey focussing on specific topics, but designed in general to gain a better understanding of the questions patients with lymphoma from around the world may have, and to answer those questions. It covers topics such as patient and physician understanding of the signs and symptoms of lymphoma, clinical trials, barriers to treatment, QoL issues, and the role of patient support groups. Interestingly, of the >3,500 respondents from the 2014 survey, only 19% reported that they were approached to enter a clinical trial; yet, of those who were approached, 71% agreed to participate. Of those who were not approached, 27% said that they would likely have participated in a clinical trial and only 9% of patients said it was unlikely. The majority of patients who were approached had been approached by a healthcare professional (82%) and, of these, most (63%) fully understood their options. Therefore it is important to discuss clinical trial options with patients. Most patients (65%) said that they had reported QoL issues to their doctor, but only 38% felt that their doctor was able to help. Approximately half of patients were newly diagnosed, and these patients really need support. Outside of their doctor, many patients receive information through the internet, other patients and friends, and patient support groups/organisations. Therefore patient groups play a vital role in supporting physicians in providing information.

When providing guidance to patients, physicians should be mindful that they understand their options, use plain language to explain, direct them to further information or provide it for them, take the time to explain the options fully, and to offer support through patient organisations. The Lymphoma Coalition is learning about developments in biosimilar approvals and is sharing the information with patients. Patients have the right to know about their options and to be assisted in making their choices. The greater understanding of lymphoma biology is leading to the development of new biological molecules and markers. It is important that everyone learns about all new therapies including biosimilars so that they can provide the best information to patients.

During the question and answer session, Ms Van Rassel highlighted that the Lymphoma Coalition provides practical information on entering clinical trials, rather than analysing the trials themselves. She also commented on the utility of internet research but emphasised the importance of physicians helping patients to find the most reliable information.

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