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Biologicals and Biosimilars in Hematology: The Case of Rituximab

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Biological medicines have been a game-changer in medicine

Biological medicines have shaped dramatic advances in the treatment of serious acute and chronic diseases like rheumatoid arthritis, inflammatory bowel disease, cancer, and hematological malignancies. However, this success has come at a price. Biological medicines can cost 10,000 euros or more per year, causing 'financial toxicity' for the patients concerned.[1] As a consequence, many countries in the world struggle with their drug budget as use of pharmaceuticals increases and new drugs, in particular biologicals, are very expensive.[2] The total spend on biological drugs in many countries is increasing by 5% to 10% per year. This situation is unsustainable in healthcare systems. After expiration of market exclusivity, alternative versions of innovative medicines introduce competition and this will drive prices down, increase access to formerly (too) expensive medicines and create headroom for innovation. For generic medicines this has been a very successful strategy. When it comes to biosimilars–equally effective and safe alternatives for innovative biological medicines–barriers appear to exist for prescribers and patients. The main reason is lack of knowledge of the essentials of biological medicines on the one hand and the new drug development paradigm for biosimilars on the other hand. This creates uncertainty among prescribers and patients alike,[3] and hence reluctance to accept biosimilars. That is a pity, as the competition made possible by biosimilars is the single most effective way to drive down the overall costs of medicines, improve patient access and create headroom for new innovative therapies.

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Three classes of therapeutic biological medicines[4]

From a clinical point of view it may help to look at biological medicines from the perspective of observability of the effect the drug has on patients. It is reasoned that if the observability is high (the prescriber can observe whether the drug "works" or not) that the acceptance of biosimilars will also be higher. When the observability is low (eg, in cancer) it requires more trust in the development paradigm and the scientific and statistical principles behind the pharmaceutical.

The *first class* of therapeutic biological medicines was substitution products: they were replacing or augmenting the body's own hormones (like growth hormone) or growth factors (like epoetin and filgrastim). These products, once injected, result in an almost universal therapeutic effect, measurable in a relatively short time, for example, as an increase in white or red blood cells. For this reason, these biosimilars were accepted relatively easily. With the advent of hybridoma techniques it became possible to produce monoclonal antibodies on a large scale, making it possible to treat patients with these agents. One of the first monoclonals was muronomab (OKT3), a murine antibody used in the treatment of transplant rejection. It was a major breakthrough in therapeutic possibilities. However, due to the murine residues in the molecule, the drug became notorious for allergic reactions. Hence, the fear of immune reactions became connected with biological therapies. One of the greatest successes in antibody development – both therapeutically and commercially - was the anti-TNF antibodies infliximab and adalimumab. This *second class* of biosimilars changed the fate of millions of patients with rheumatic diseases, inflammatory bowel diseases and psoriasis. It is not easy to observe efficacy in an individual patient: the therapeutic effect is delayed, and not all patients go into remission. As a result, this group has achieved fewer acceptances than class one. For many prescribers the absence of clinical trials for certain indications (as a result of the principle of indication extrapolation) was another reason not to prescribe a biosimilar instead of the originator drug. Then the *third class* of biological therapeutics became available, for example, rituximab and trastuzumab, compounds to be used in hematology (e.g, lymphoma treatment) and oncology (Her-2 receptor positive breast cancer). These molecules have - on a population level - revolutionized the therapy of diseases hitherto with a very poor prognosis. However, clinical effectiveness for an individual patient can only be seen at some point in the future, for example, an average increase in survival of 20% after 5 years. This implies that an individual prescriber cannot observe a

clinical effect directly: he must rely on clinical trial data for each indication. Trials of biosimilars when tested in the most sensitive indication *have the intention to illicit a difference* – if such a difference between reference product and biosimilar is present. But this "most sensitive indication" might not be the most clinically relevant indication. So far, the acceptance of rituximab biosimilars by hematologists is better than that of trastuzumab biosimilars by medical oncologists. One reason could be that hematology relies more on laboratory results then solid tissue oncology. In addition, hematologists already had experience with filgrastim and epoetin biosimilars, available since 2008.

Variability: inherent to biological medicines

Traditional chemical medicines are produced on a large scale with a very predictable outcome. The purity is close to 100% and batch to batch variations are within narrow limits. Biological medicines are produced by living cells, and are consequently affected by subtle variations in the behavior of these cells when growing. In addition, these cells do not produce just one unique molecule, but a mixture of closely related isoforms. The molecular backbone (amino acid sequence) is the same, but subtle variations occur in sugar-like moieties in the molecule. In general these variations have little effect on the molecular action of the molecule (binding of a targeted protein). It should be realized that such variations actually occur from batch to batch. However, it is possible that these subtle changes induce an immunological response or other side effects, and therefore changes in the manufacturing of these medicines – which often occur - are tightly controlled by the manufacturing companies and the regulating authorities. In 2011, Schiestl et al published a letter in *Nature Biotechnology* showing that manufacturing changes at originator companies also affect parts of the molecule deemed critical for the clinical action, apparently still to the satisfaction of the regulators.[5] This led to the paradigm: variability is everywhere in biological molecules and not all variation may compromise efficacy and safety. Nevertheless, in several biosimilar trials it became clear that such variations in originator molecules do matter, and may show up in clinical trials optimized to detect even small differences between biological molecules.[6]

Biological medicines: affordability and accessibility.

Both development and manufacture of biological medicines were quite costly last century. Hence, these products got a high price tag, in general unaffordable for an individual patient. Due to their therapeutic success, healthcare systems looked for ways to provide access by including these expensive medicines in reimbursement schemes. But even with a limited co-payment, treatment with these medicines spells financial ruin for some families. As the number of these costly medicines increased, governments faced an unsustainable situation. Total worldwide sales of the top 10 biologicals increased from 77 to 82 billion dollars in 2018, an increase of 6% in 1 year (See Table 1). Global spending on therapeutic antibodies used in oncology amounted to $50 billion in 2018, in increase of 15% compared to 2017. Sales of oncology products like Opdivo and Neulasta increased by 25%. There are 3 options for governments to curb these costs: firstly to limit access, which from a societal perspective is very undesirable. Second, to negotiate lower prices, which in general is unsuccessful when products have market exclusivity, or thirdly stimulate competition with alternative versions once market exclusivity has expired.[7] This option is the most realistic, as market exclusivity has expired for 7 of the top 10 products and the alternative versions, biosimilars, have been licensed. As of January 2019, more than 50 biosimilars of high quality from 15 originator molecules have been licensed and are available on the European market and in several other continents (see Table 2).

Development of biological medicines: originators and biosimilars

However, before such products are accepted by prescribers and patients, there has to be a proper understanding of the essentials of biological medicines, and how subsequently, biosimilars can be developed. It is this lack of understanding that creates uncertainty among prescribers, and hence reluctance to prescribe. Understanding biosimilars has to start with the basics of biological medicines: how they are developed and manufactured, with all the variability inherent to biological medicines. Only then, can one understand the exact meaning of a biosimilar: a version of the innovator molecule, with essentially the same clinical properties: equally safe and efficacious.

Biological medicines are complex molecules that are produced in living cells, so manufacturing conditions are critical for the outcome of the culture and purification of the therapeutic protein. One has to realize that the resulting product does not contain a single molecule, but a mixture of closely related isoforms. When a new batch is produced, there will be another mixture of closely related isoforms, however with in general the same clinical properties. In the lifetime of a biological product, manufacturers are often changing the process for a variety of reasons: to make

Table 1

Cost Development Globally of Top-10 Biologic Blockbusters

Rank 2018 (2017)	Brand	INN	Global sales 2018	Global sales 2017	Difference 2018 - 2017	Relative difference (%)
1 (1)	Humira	adalimumab	20.470	18.973	1.497	7.9%
2 (9)	Opdivo	nivolumab	7.573	5.799	1.774	30.6%
3 (2)	Enbrel	etanercept	7.447	8.345	−898	−10.8%
4 (12)	Keytruda	pembrolizumab	7.171	3.809	3.362	88.3%
5 (5)	Herceptin	trastuzumab	7.015	7.392	−377	−5.1%
6 (6)	Avastin	bevacizumab	6.881	7.042	−161	−2.3%
7 (3)	Rituxan/MabThera	rituximab	6.783	7.783	−1.000	−12.8%
8 (8)	Eyla ophthalmic	aflibercept	6.746	5.929	817	13.8%
9 (4)	Remicade	infliximab	6.446	7.772	−1.326	−17.1%
10 (10)	Stelara	ustekinumab	5.252	4.011	1.241	30.9%
Total			81.784	76.855	−4.929	−6,4%

LaMerie Publishing Global Sales in Billion US$ (Source: www.lamerie.com, Accessed April 29, 2019.)

Table 2

EU Approved Biosimilars by Molecule, November 2019 (not available in all EU-countries) (status November 29, 2019; 55 products)

Molecule	Reference	Biosimilar(s)
Adalimumab	Humira	Amgevita, Halimatoz, Hefiya, Hulio, Hyrimoz, Idacio, Imraldi, Kromeya
bevacizumab	Avastin	MVasi, Zirabev
Enoxaparine	Clexane	Inhixa, Thorinane
Epoetine alfa	Eprex	Absaemed, Binocrit, Epoetin alfa Hexal, Retacrit, Silapo
Etanercept	Enbrel	Benepali, Erelzi
Filgrastim	Neupogen	Accofil, Filgrastim Hexal, Grastofil, Nivestim, Ratiograstim, Tevagrastim, Zarzio
Follitropin alfa	Gonal-f	Bemfola, Ovaleap
Infliximab	Remicade	Flixabi, Inflectra, Remsima, Zessly
Insulin glargine	Lantus	Abasaglar, Semglee
Insulin Lispro	Humalog	Insulin Lispro Sanofi
Pegfilgrastim	Neulasta	Fulphila, Grasustek, Pegfilgrastim Mundipharma Pelgraz, Pelmeg, Udenyca, Ziextenzo
Rituximab	Mabthera IV	Blitzima, Ritemvia, Rixathon, Riximyo, Truxima
Somatropine	Genotropin	Omnitrope
Teriparatide	Forsteo	Movymia, Terrosa
Trastuzumab	Herceptin IV	Herzuma, Kanjinti, Ogivri, Ontruzant, Trazimera

Source: EMA website. https://www.ema.europa.eu/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_medicine/field_ema_med_status/authorised36/ema_medicine_types/field_ema_med_biosimilar/search_api_aggregation_ema_medicine_types/field_ema_med_biosimilar. Accessed April 29, 2019.

In addition: 15 Biosimilar molecules in the licensing pipeline at EMA (Status 4/11/2019).

Adalimumab (1x), bevacizumab (2x), etanercept (1x), insulin aspart (2x), pegfilgrastim (1x), rituximab (3x), teriparatide (3x), trastuzumab (2x).

the process more efficient, to get a more pure or more stable product, or just because a raw materials supplier changes. Any change of the manufacturing process leads to a new version of the active substance, and for the average biological this happens twice a year or more often.[8] The manufacturer has to demonstrate the comparability of the resulting versions from the old and the new manufacturing process in a carefully designed comparability exercise. The rules for this are laid down in the ICH Q5E guidelines, standard for all countries with a well-established medicines regulatory system. Regulators have thus extensive experience in comparing different versions of a biological regarding quality, efficacy and safety. So both EMA and FDA recognize that biosimilars are just new versions of an existing biological.

What makes biosimilars similar?

It was Schiestl and coworkers who reported for the first time how large the actual differences may be after such manufacturing changes, while remaining acceptable to the regulators.[5] In their paper they showed for a number of biologicals, among them rituximab, how critical quality attributes, those properties of a molecule that play a critical role in efficacy and safety, actually might vary. The significance of that paper is twofold. As the originator varies over time, it is not possible to make an exact copy of such a moving target. And second, it shows that properties of a biological can apparently vary between rather wide boundaries without affecting efficacy and safety. From this we can draw 2 conclusions. One is, the fact that a biosimilar cannot be an exact copy of an originator molecule is not a biosimilar problem, but lies in the variability of the originator. And secondly, as long as the biosimilar variability is within the limits of variation of the originator, we may expect the biosimilar to display the same efficacy and safety. Based on these principles EMA and FDA build a regulatory framework for assessing candidate biosimilars. By carefully establishing the chemical, pharmacological, immunological and other pre-clinical properties of such a candidate, a fingerprint can be made for the critical attributes of the biosimilar.[9] Once established, the validity of the fingerprint can be tested in a clinical trial optimized to elicit any possible differences in efficacy or safety. Such a trial is not to prove efficacy, because we know that already from the originator, but to confirm that the biosimilar does not behave differently from the originator in patients. Traditional clinical trials in a normal drug development process are notoriously insensitive to eliciting small differences between versions of a molecule, and asking for such trials shows poor understanding of clinical trial methodology.

Some unique features of biosimilars

Thus, the development of a biosimilar follows a novel drug development paradigm, resulting in a drug with the same quality, efficacy, and safety as any other drug. What makes a biosimilar unique? From biosimilars we know a lot more about quality and mode of action than of the average originator biologicals. This is the result of accumulating a decade of knowledge on an originator drug, in these aspects of molecular design. As a result many biosimilars are more pure and more stable than their originator counterparts, as they follow a more sophisticated optimization pathway. In general, there should be no difference in efficacy and safety but it has been reported that in some cases a biosimilar may seem to be more potent, as originators due to all the manufacturing changes over time may have drifted away from their original potency.[6] This then leads to extensive discussion with the regulators, reflected in the EPAR after licensing. A second unique feature is, that biosimilars have been defined so accurately in the pre-clinical phase, that more clinical trials in other indications have become redundant, even unethical. This is called extrapolation of indications and has been defined as extending information and conclusions from studies in one or more subgroups of the source patient population.[10] Based on these findings inferences can be made for other indications in patients, thus reducing the need to do additional trials. For companies striving for this, extrapolation is not a free ride: it requires solid scientific justification. Such evidence can be a similar mode of action / same receptor target. Relevant is also that in another subgroup of patients the safety risks must be the same. To explore potential differences between anti-TNF biologicals, psoriasis appears to be the most sensitive model. More sensitive

than, for example, inflammatory bowel disease which shows so much variation in course of the disease and drug reaction, that proving biosimilarity is virtually impossible. In the case of rituximab rheumatoid arthritis is a very sensitive disease model, as it is based on the same receptor model and cell killing properties (ADCC) as hematologic malignancies. Again, if prescribers have no knowledge of these scientifically based principles,[10] they will find it difficult to accept and prescribe a biosimilar in extrapolated indications.

Europe, the world leader for biosimilars since 2000[11]

There has been a strong political will in Europe to develop a biosimilar approval pathway to encourage competition in the biologicals market. The European Medicines Agency subsequently developed an extensive set of guidelines for the industry and set up a transparent assessment model. By November 2019 this had resulted in 55 licensed biosimilars of 15 originator molecules (see Table 2). On each approved biosimilar, the EMA publishes an extensive European Public Assessment Report (EPAR), which includes all relevant raw quality data, research results and a critical appraisal of these data by the regulators. This means that at the time of marketing approval there is in the EPAR an abundance of critically assessed information available on each biosimilar, which may not show up in scientific journals. This information is much more valuable than scattered and selective publications in scientific journals, which usually come too late. Expressing an opinion on the intrinsic value of a new biosimilar without having read the EPAR is not possible and by definition flawed.

European research has shown the way to set up an implementation program for biosimilars, based on "The Rule of Four".[12] The following 4 principles work together to create a successful biosimilars policy in the hospital.

- Multi-stakeholder approach: involve everybody from top to bottom in your healthcare setting and educate about biosimilars;
- One-voice principle: the whole team should talk about biosimilars in a positive way, and as leaders avoid sending confusing mixed messages. This will greatly reduce any nocebo effect.
- Shared decision making: inform the patient that the treatment is initiated/continued with a biosimilar, an equally effective and safe alternative.
- Gain sharing: introduction of biosimilars requires extra effort (= time) from busy healthcare professionals. A part of the savings from biosimilars should benefit the clinical department that generates the savings.

As a result, market competition is strongly developed, and the cost of biologicals decreases by billions of Euros (See Table 2). Biosimilars offer 5 wins for a typical solidarity-based European healthcare system:

1. Biosimilars offer greater value, lower cost for equal or better quality.
2. Biosimilars encourage competition, with subsequent lower innovator cost extending possibly to a whole therapeutic category.
3. Patients can get earlier access to costly advanced medicines, with a significant health gain
4. More patients can get treatment for less budget
5. Biosimilars create headroom in the budget for new (costly) medicines.

The case of rituximab in Europe

In the context of this article we will discuss the example of rituximab in more detail. Rituximab (RTX) is a monoclonal antibody that binds to a CD20 cell surface protein, present on B lymphocytes. When RTX binds to CD20, it causes B-lymphocyte death, which helps in lymphoma and chronic lymphocytic leukemia (where B lymphocytes have become cancerous). It is also used in rheumatoid arthritis, where B lymphocytes are involved in joint inflammation. In granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), destroying the B lymphocytes lowers the production of antibodies thought to play an important role in attacking the blood vessels and causing inflammation.

There are 4 possible mechanisms of action by which anti CD20 antibodies kill B cells: (i) antibody-dependent cellular cytotoxicity (ADCC) through binding of the Fc portion of rituximab to Fc-gamma-III receptor bearing effector cells; (ii) complement-dependent cytotoxicity (CDC) through binding of C1qA to the Fc domain of rituximab and subsequent lytic cascade; (iii) activation of signaling cascades that results in programmed cell death (apoptosis) and (iv) phagocytosis of malignant B cells by macrophages (antibody-dependent cellular phagocytosis (ADCP). Indirect evidence suggests that in vivo, dominance might differ by indication. These mechanisms thus need to be tested in the pre-clinical development phase once a candidate molecule has passed the elaborate physicochemical testing.[11] For this, companies have set up carefully validated in-vitro assays, and all the results have been published in the public domain.[13–15]

There are maybe 20 or more rituximab biosimilars in development, but by early 2019, 7 rituximab-biosimilar brands were licensed in the EU. These involve essentially only 2 different products: GP2013 from Sandoz (Rixathon, Riximyo) and CT-P10 from Celltrion (Blitzima, Ritemvia, Truxima). Different brands of the same molecule were licensed to circumvent patent issues in some countries around certain indications. November 2019, there were 3 more rituximab biosimilars were under review at the EMA.

The candidate biosimilars were tested in a variety of clinical indications, but in the end they got all reference product indications extrapolated by the EMA. The patient trials, performed in rheumatoid arthritis and advanced follicular lymphoma, were discussed critically by Mielke et al[16] and also by Wörmann and Sinn.[17]

Licensing of biological medicines is centralized in Europe, as it allows free trade of licensed medicines between EU countries. Implementation of use and reimbursement for patients however is a national issue. Acceptance of the rituximab biosimilars by prescribers was relatively smooth in Europe after the earlier introduction of TNF-alfa inhibitors infliximab and etanercept. This positive experience led in The Netherlands, for instance, within 3 months after launch to 90% of patients being switched to biosimilars (personal communication). There was even a back-switch from SC rituximab to IV biosimilars, because this was deemed cost effective by many due to the large price difference between biosimilar and reference product.

Hematologists were already familiar with biosimilars, and hematology is a more heavily laboratory-science driven specialty than many others.

Outlook and recommendations

There are unfortunately confusing differences between the situations in the US and Europe.[18] Many countries see FDA as a leading agency for drug approval. In the case of biosimilars this is not true. Due to political lobbying and constraints in legislation (induced again by political lobby) the FDA was hardly able to develop a flourishing biosimilar pathway.[12] The predominantly profit-driven healthcare market is very biosimilar unfriendly. Of the 17 US-licensed biosimilars, only 7 are available on the market, and only 2 are more or less a commercial success. The atmosphere around biosimilars in the US is so poisoned by misinformation and political turmoil, that US prescribers have little confidence in biosimilars.[19]

As explained before, in Europe the situation is completely different. In 2016 there were 700 million patient biosimilar treatment days without complications. Some 173 switch trials have almost universally shown biosimilars to be equally safe and efficacious as originators.[20,21] The argument of immunogenicity has been spelled out in detail, and there is now positive evidence that biosimilars bear no additional risks to immune response than originators.[22,23] Responsible health care professionals like doctors and pharmacists who work in a solidarity-based healthcare system cannot deny the nation the immense advantages and savings brought about by biosimilars. Refusal to improve healthcare sustainability with biosimilars is actually a sign of distrust in the drug regulatory system as a whole. There is no single scientific argument left not to use them. No country can any longer afford NOT to use biosimilars.

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