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Biologics and Biosimilars: Differences and Clinical Implications

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Authors' contributions

This work was carried out in collaboration between all authors. Authors CJG and GR designed the protocol for the review, performed the literature search, data acquisition, data analysis and wrote the first draft of the manuscript. Author URKR edited the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Biologics or biopharmaceuticals are drugs derived from living organisms by recombinant technology. Biologics have made a significant contribution to the management of certain chronic diseases such as cancer, rheumatoid, arthritis, ankylosing spondylitis, psoriasis and other immune mediated disorders. Biologics are produced by genetically modifying cells and, are highly complex and expensive to manufacture. Many of them are now facing patent expiry which has paved the way for the development of biosimilars. Biosimilars are biologic medicine that is similar in terms of quality, safety and efficacy but not the same as a registered innovator biologic. The manufacturing of biosimilars has many complexities, such as consistency of manufacturing process, conformation of manufacturing standards and demonstration of product consistency Also, powered clinical trials have to be executed to demonstrate similarity to the innovator biologic. Registration of biosimilars requires a more stringent evaluation than that is required for conventional generics. Biosimilars have the potential to be the molecules of the future as long as they are developed strictly in

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accordance with comparative procedures mandated by regulatory authorities such as EMA and USFDA. It is believed that the advent of biosimilars will improve patient access to expensive biologics for chronic illnesses. However, it is important that clinicians distinguish between innovator biologics and biosimilars. Physicians should avoid substituting biosimilars for innovators as well as avoid interchangeability as biosimilars are not generics. In addition, pharmacovigilance will be the need of the hour to track down any safety and efficacy problems arising from the use of biosimilars.

Keywords: Biologics; biosimilars; interchangeability.

ABBREVIATIONS

Ab - Antibody
DNA - Deoxyribo Nucleic Acid.
EMA - European Medicines Agency.
EPO - Erythropoietin
FDA - Food and Drug Administration.
G-CSF - Granulocyte Colony Stimulating Factor.
PRCA - Pure Red Cell Aplasia.
rHuEPO - recombinant Human Eythropoetin.
USFDA - United States Food and Drug Administration.
WHO - World Health Organisation.

1. INTRODUCTION

The era of 1970s and 1980s, heralded a new drug development pathway known as the Recombinant DNA technology. This technology enabled scientists to manipulate genes and cells to produce structurally complex drugs [1]. These drugs were later categorized as biological products, biologics or biopharmaceuticals [2]. Biologics are derived from living organisms (plant and animal cells, bacteria, viruses and yeast); for example - proteins monoclonal antibodies, vaccines, cell and tissue based therapies [2]. (Refer Table 1). Over the years, biologics that had novelty in mechanisms of action and/or design were produced and collectively called as "innovative biologics."

A deeper understanding of disease mechanisms coupled with the newly established ability to make a variety of innovative biologic drugs helped in improving prognosis in areas where there were unmet medical needs. Biologics for management of many life-threatening and chronic illnesses such as cancer, diabetes, anemia, rheumatoid arthritis and multiple sclerosis, Crohn's disease, Gaucher's disease, macular degeneration, psoriatic skin diseases, retinal vein occlusions etc. were introduced. [1-4]. Biologics thus brought about a revolution in management of many diseases in recent times and enabled millions of patients to improve their quality of life.

2. BIOLOGICS – WHAT NEXT?

Biologics are highly complex to manufacture, and therefore they remain expensive and beyond the scope of many patients who could otherwise benefit. [5] Hence, the idea of follow-on biologics i.e. to make a molecule that is as similar to the innovator as far possible was born and the follow-on molecules in the biologic space were termed biosimilars (rather than biogenerics). When patents on biologics expire, biosimilars will want to be approved as cost-effective options just as generics wait for loss of exclusivity of small chemical molecules [6,7].

Table 1. Examples of available biologics

Trade Name	Generic name	Indications	Developed by
Epogen [31]	Epoetin alfa	Anemia	Amgen
Rituxan [32]	Rituximab	Lymphoma, Rheumatoid Arthritis	Biogen Idec & Roche
Humulin [33]	Human Insulin	Diabetes	Eli Lilly
Lantus [34]			Sanofi Aventis
Levemir [35]			Novo Nordisk
Avonex [36]	Interferon beta-1a	Multiple Sclerosis	Biogen Idec
Betaseron [37]			Bayer
Rebif [38]			Merck Serano
Enbrel [39]	Etanercept	Rheumatoid Arthritis, Psoriasis	Amgen/Wyeth
Remicade [40]	Infliximab	Crohn's disease, Rheumatoid arthritis	Janssen

3. WHAT ARE BIOSIMILARS?

A biosimilar is a biological medicine that is similar, but not the same as an already registered innovator biologic (reference product). Biosimilars are licensed on the basis of prior information obtained from the reference product, and detailed comprehensive product characterization, including comparative analytical, pre-clinical and clinical studies with the reference product [6,8]. Examples of biosimilars include: (Refer Table 2). Biosimilars should also be developed strictly in accordance with comparative procedures used for reference products [7,8]. A recent example of an approved biosimilar is CT-P13 - an infliximab biosimilar with demonstrated therapeutic equivalence to reference infliximab. Such biosimilars can be a useful alternative to reference infliximab in patients requiring infliximab therapy [9]. However, in the developing and under-developed world; biosimilars are getting approved without stringent efficacy and safety testing. This is a serious issue as these biosimilars are now applying for approvals in other parts of the world.

Table 2. Biosimilars currently being marketed in various countries across the world

International nonproprietary name	Trade name reference product	Trade name biosimilar
Somatotropin	Genotropin	Omnitrope [41]
Epoetin alfa	Eprex	Abseamed [42], Binocrit [43], Epoetin alfa Hexal [44]
Epoetin zeta	Eprex	Retacrit [45]
Etanercept	Enbrel	Etacept [46]
Filgrastim	Neupogen	Biograstim [47], Ratiopharm [48]

4. BASIC SCIENTIFIC CONSIDERATIONS FOR APPROVAL OF BIOSIMILARS

In case of biologics, it is the manufacturing process that defines the product [10]. The process of introducing a biosimilar of an innovative biologic is highly complex. This is because

- Biologics are produced by cells in culture or whole organism
- Production is complex – this is due to the size and complexity of protein structure [11].

Conventional pharmaceutical agents are small-molecule chemicals. Hence comparatively the manufacturing of biologics requires a greater number of batch testing [12].

- Even small and seemingly insignificant manufacturing changes would result in significant differences in the safety and efficacy of the therapeutic molecule. Cellular and physiological events like post–translational modifications and heterogeneity in product characterization and the possibility of altered pharmacokinetics or increased immunogenicity can result in altered clinical impact. So even when biosimilars are produced from the same genetic construct, using the same technique, formulation and packaging; they may not be comparable with the reference product [13].

5. REGULATORY HURDLES

There are many regulatory complexities associated with the approval of a biosimilar such as:

- Evidence of integrity and consistency in the manufacturing process,
- Demonstration of product consistency with appropriate innovator biologic or comparators using assays that should be relevant and most of all standardized; pharmacokinetic and pharmacodynamic data and powered comparative clinical experience data with the approved product [14] and implementation of tailored pharmacovigilance plans [15]
- Issues like post-translation modification and immunogenicity [15].

6. WHY BIOSIMILARS ARE NOT GENERICS

It is important to remember that biosimilars are not generics. These are rather unique molecules which are supported by only limited clinical data at the time of approval [16].

Conventional drugs have fewer molecular ingredients, and most small molecules can be completely identified with a limited set of

analytical assays. On the other hand, biotechnology products have many molecular ingredients and are often not fully characterized by using evaluative tools but need a number of analytical techniques to characterize the structure or functions of proteins [17,18]. Due to these unique characteristics of biologics in comparison to the small molecule; the generic drug paradigm cannot be applied to biosimilars [12].

7. IMPACT ON HEALTH CARE

It is a noted fact that a biosimilar must undergo an extensive, and a highly regulated (EMA and USFDA) comparability exercise, which includes demonstrating similar pharmacokinetics, efficacy and safety in randomized controlled trials [7,8]. However, for products which have not undergone stringent efficacy and safety testing, several issues may arise such as efficacy and variability issues, patient safety issues and interchangeability and hence such products should not be considered biosimilars.

7.1 Efficacy and Variability Issues

Combe et al. [19] found that analytical studies for non-innovator epoetins failed the test of comparability to the reference biologic. Products differed in composition and there was a variation between batches. Additional compounds were detected in 3 of 11 biosimilar products analyzed, when compared with the reference product, and additional epoetin isoforms were detected in 9 of 11 cases.

7.2 Patient Safety Issues

The primary safety concern for biosimilars is their potential immunogenicity [20]. In fact, all biologics, in comparison to conventional drugs, demonstrate a greater capacity to induce antibodies and to elicit immune reactions [21]. Although these proteins are designed to closely mimic human proteins; when administered as multiple doses over prolonged periods they can evoke an immune response [22]. In many patients, such a response does not lead to any clinical consequence. But in some patients, it can produce allergy, serum sickness, anaphylaxis, decrease the efficacy of the drug or in rare instances enhance its activity [23].

Neutralization of endogenous proteins responsible for essential biological activity can result in major clinical consequences. For example, Ab-mediated pure red cell aplasia (PRCA) has known to be caused due to neutralizing endogenous EPO. One common example on biological product safety is the large increase in the incidence of Antibody-mediated PRCA occurring between 1998 and 2003 in chronic kidney disease patients with anemia treated with a formulation of epoetin alfa, marketed by Johnson & Johnson [21,24-26]. The PRCA cases were associated with a breakdown of immune tolerance to subcutaneous treatment with rHuEPO, resulting in neutralizing Ab formation against both recombinant and endogenous EPO [27].

7.3 Interchangeability

An interchangeable biological product is one that may be substituted for the reference product without the consultation of the health care provider who prescribed the reference product in the first place.

A biological product is considered interchangeable with a reference biological product if [28]

- It meets the criteria for being a biosimilar to the reference biological
- It produces the same clinical result as the reference product in any given patient, and
- Switching may have to be conducted more than once during the clinical trial to ensure that the risk in terms of safety or efficacy is not greater with the interchangeable product than with the use of reference product alone Switching or substitutions between innovator products and biosimilars should be viewed as a change in clinical management [10].

8. CONCLUSIONS

- Biologics are complex molecules, produced with complex manufacturing processes that have changed many fields of medicine.
- Because of these manufacturing complexities, it is extremely difficult to produce exact replicas (generic versions) of originator biologics post patent expiry
- Biosimilars are similar (but not identical) to the reference biologic.
- In order to be called a biosimilar; the required comparability qualification in

accordance with EMA or USFDA guidelines must be fulfilled.

- Success of an individual biosimilar will ultimately depend on the clinical data generated to support the product
- Patient safety and interchangeability of biosimilars will depend on establishment of stringent regulatory processes that best manage the potential benefits and risks associated with this newer drug category.
- Guidelines have been developed for regulating approval of biosimilars in major developed countries, taking into account the relative vagaries of biosimilars.
- Every country in the process of introducing biosimilars needs a science-driven regulatory framework and guidelines to ensure that such products approved are of good quality and demonstrate significant efficacy, safety and immunogenicity to the original reference product. The WHO guidelines further provide a good basis for developing countries to draw upon and adapt [29].

9. FUTURE PROSPECTS

Biosimilars are recent entrants in the field of medicine. Despite the similarities of biosimilars with the innovator product, clinicians and health care workers should be made aware of some of the issues that have emerged during the development and approval of these products. These will highlight the challenges of biosimilars [30] and that they should be adopted more cautiously than generics. Physicians should avoid substituting biosimilars for innovators and avoid interchangeability as it is essentially a change in clinical management [10]. As biosimilars are not generics, the possible implications for clinical outcomes of switching products, should be considered. Additionally, pharmacovigilance will be required to track down any safety and efficacy problems that may arise from the use of biosimilars will help ensure safety of patients. Finally the question is not whether you can afford an original biologic but whether you can afford not to use the original!

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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