WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 8, Issue 2, 1370-1378 Review Article ISSN 2278 – 4357

REVIEW OF BIOSIMILARS FOR CANCER, ULCERATIVE COLITIS AND IT'S CURRENT STATUS WITH ONGOING CHALLENGES

Dr. Sunita Ogale*, Mahadev Tate, Shreya Parkar

India.

Article Received on
18 December 2018,

Revised on 08 Jan. 2019,
Accepted on 29 Jan. 2019

DOI: 10.20959/wjpps20192-13200

***Corresponding Author**
Dr. Sunita Ogale
India.

ABSTRACT

A biosimilar is a biological product that is highly similar to licensed biologic (originator) such that there are no clinically meaningful differences in potency and safety between the biosimilars and originator i.e. manufactured by different company. It can be manufactured when the original products patent expires. The Food and Drug Administration has approved ten different biosimilars, and the European Medicines Agency has approved 40.[23] The goal of this article is to describe the chemical and clinical nature of biosimilars, review focus areas of interest for biosimilar development in oncology and ulcerative colitis. Biosimilars can not be viewed as generics because generics must be identical to the reference product.

INTRODUCTION

Biopharmaceuticals (biologics) represent one of the fastest growing sectors of cancer treatment and ulcerative colitis. As the costs of biologics are high, biosimilars offer the potential of greater choice and value, increased patient access to treatment, and the potential for improved outcomes. Biosimilars are evaluated using rigorous and through analyses of the potential Biosimilars verses the originator biological to confirm similarity in function, structure and safety. The biosimilar must have the same dosage form, concentration, and route of administration as the reference biologic agent. The manufacturing facility must pass rigorous inspections and review by the FDA. An increased level of inspection and scrutiny of manufacturing processes is therefore necessary to ensure patient safety and clinician trust of biosimilar development.[2] Due to the complexity involved in creating biologics, heterogeneity in the final product may occur. Heterogeneity refers to minor variations in the biologic agent that can occur both naturally or through the production process. These

differences can contribute to batch-to-batch variations that are expected in the development of complex biologics.

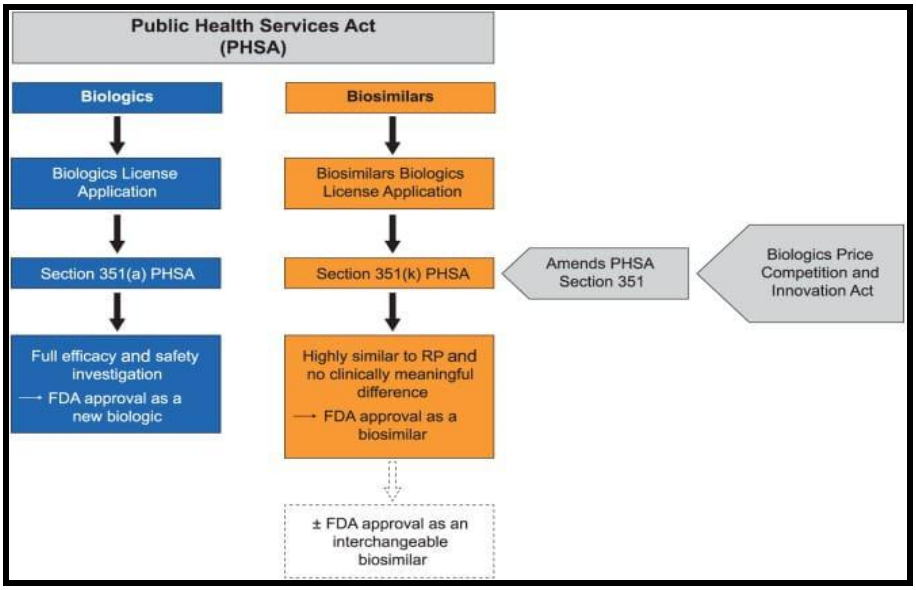
The analytical, nonclinical, and clinical data requirements for approval of a potential biosimilar are specific and scientifically rigorous. In some countries, products are available that have not met the stringent criteria for biosimilars; they are usually referred to as "intended copies".[9] The extrapolation of safety and efficacy data from one clinical indication to another is a scientific principle that may be utilized in certain situations during biologic drug development of similar biologic medicinal products or Biosimilars.

REQUIRED DOCUMENTATION FOR EVALUATION

The WHO guidelines for evaluation of a biosimilar require submission of the following documentation[9]-

1) Physicochemical and biological characterization and a head-to-head preclinical comparison to the reference product.
2) Manufacturing follows Good Manufacturing Practices; documentation includes the known process information for the reference product.
3) A plan for conducting pharmacovigilance.
4) Phase III head-to-head clinical efficacy studies with the reference product.
5) A repeat-dose preclinical toxicity study in an appropriate animal species.
6) Clinical studies evaluating immunogenicity.
7) A single-dose head-to-head clinical pharmacokinetic study with the reference product.

FDA APPROVAL PATHWAY OF BIOSIMILARS



DEVELOPMENT OF BIOSIMILARS

Number of biologics are nearing expiration/ have already expired and regulatory pathways have been established to allow the development and approval of products called Biosimilars. They are produced using same gene.

Initial animal and human studies must be performed to assess toxicities and pharmacokinetics/ pharmacodynamics. In order to achieve a better knowledge on safety and efficacy of biosimilar drugs the clinical trials data should be collected and therapeutic drug monitoring, patient compliance should be evaluate. Through legislation, the US Food and Drug Administration (FDA) approved the Biologics Price Competition and Innovation (BCPI) Act in 2009.[2] This law implemented a framework for development and regulation of biosimilars for manufacturers and provided guidance for the key submission components necessary to achieve final FDA approval. The objective of BPCI are conceptually similar to those of the Hatch-Waxman Act for generic drugs in that BPCI allows the entry of less expensive biologic medicines and thereby increases competition and availability.

The European Medicines Agency(EMA) has approved more than 20 Biosimilars, including biosimilars of Monoclonal antibodies adalimumab, etanercept and Rituximab. The US-FDA approved the first US biosimilar in 2015 (filgrastim) and first biosimilar mAb (infliximab) in April 2016.

The development of biosimilars is different from the process applied to a new biologic. Pharmaceutical company producing a potential biosimilars must analyze the originator extensively and use reverse engineering to develop a biologic entity with highly similar structure and function. A small molecule drug can be fully defined structurally and therefore, a generic equivalent can be reproduced with an identical chemical structure via a defined chemical synthesis. However, biologics are usally larger, complex proteins produced using a biologic process requiring production in living cells that are more difficult to characterized fully. Clinical performance of biologic drugs may affected by minor post-translational structural modification due to the manufacturing process. Thus the process of developing a potential biosimilars requires substantial knowledge and expertise regarding the development and manufacturing of biologics.

BIOSIMILARS FOR CANCER

The first FDA-approved biosimilar for cancer treatment is bevacizumab-aww. Rituximab is a chimeric mouse/human monoclonal antibody (mAb) therapy with binding specificity to CD20. It was the first therapeutic antibody approved for oncology patients.[3] Immunotherapies represent a broad and rapidly growing group of therapies having a substantial impact on cancer outcomes. Trastuzumab improves survival outcomes for patients with HER2-positive (HER2+) breast cancer, yet not all such women receive this important therapy.

For the patients HER-2 +ve breast cancer an anti-human epidermal growth factor receptor-2 (HER-2) monoclonal antibodies, trastuzumab based therapy has become the standard of care, but the treatment cost is high therefore many patients do not receive trastuzumab therapy.[7] Currently used Biosimilars in Breast cancer include hematopoietic growth factor and Monoclonal antibodies (mAbs). e.g. GF-erythropoietin and Rilgrastim.

Types of Monoclonal Antibodies:

1) Naked Monoclonal Antibodies -

Naked mAbs are antibodies that work by themselves. There is no drug or radioactive material attached to them. These are the most common type.

e.g. For chronic lymphocytic leukemia- Alemtuzumab

Action: Alemtuzumab binds to the CD52 antigen, which is found on cells called lymphocyte (which include leukemia cells). Once attached, the antibody attracts immune cells to destroy these cells.

2) Chemolabeled Antibodies-

These mAbs have powerful chemotherapy drug attached to them. They are also known as Antibody-Drug conjugates.

e.g. Brentuximab, Ado-trastuzumab

One year treatment with adjuent trastuzumab with chemotherapy results in statistically significant reduction in the risk of disease recurrence by as much 48% in some trials.

CASE STUDY OF TRASTUZUMAB TREATMENT AS ANTICANCER AGENTS

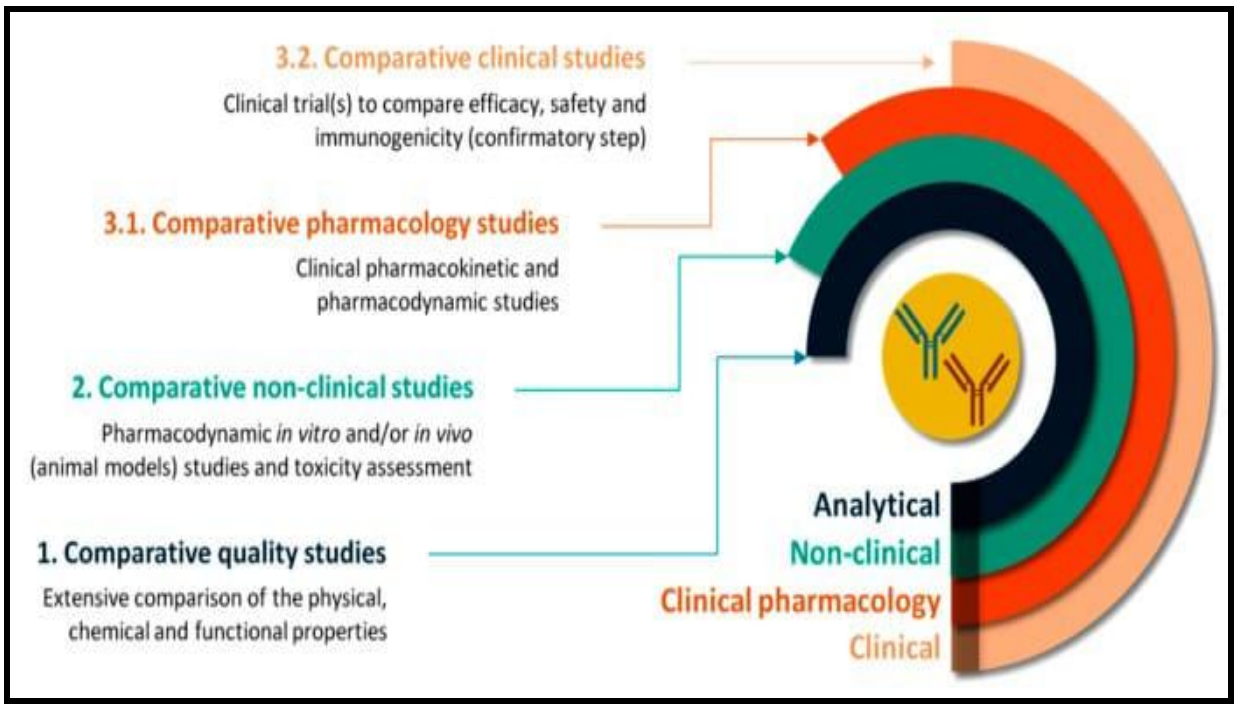
Trastuzumab increases several among women with HER-2 receptor positive metastatic breast cancer but maternal and fetal risk are associated with advanced disease and it's treatment in pregnancy.[7] we represent a case of HER-2 positive metastatic breast cancer who received trastuzumab throughout pregnancy. She presented with cerebral metastases requiring surgical

decompression and resection. Reversible oligohydramnios developed during pregnancy. Oligohydramnios is the state of deficiency of amniotic fluid results in causing intrauterine mechanical compression of the fetus and prevention of intrauterine expansion, causes growth restriction and may death also (i.e. fetal toxicity).

One case described oligohydramnios in pregnant women who receive Herceptin either alone or in combination with chemotherapy. In some case reports amniotic fluid index increased after Herceptin was stopped.[7]

No teratogenic effects were observed in offspring from reproduction studies in cynomolgus monkeys at doses up to 25 times the recommended weekly human dose of 2 mg/kg trastuzumab.

The stepwise process of the comparability exercise required to demonstrate the biosimilarity of trastuzumab Biosimilars to it's reference product:



BIOSIMILARS FOR ULCERATIVE COLITIS

Ulcerative colitis is characterized by chronic inflammation, which may lead to the accumulation, of high level of cytokines within colonic mucosa. Ulcerative colitis patients have higher risk of colorectal cancer compared to other. Ulcerative proctitis is defined as mucosal inflammation limited to rectum. Data are currently available for azathioprin, topical

tacralimus and anti-TNF monoclonal antibodies are use as treatment for ulcerative proctitis. Approximately 50% US patients develop an acute attack of severe colitis and 30% of these patients require colectomy. IL-23 and IL-12 reduce the severity or inflammation in colitis. They are more safer and show efficacy also.

A retrospective multicenter study evaluating the clinical efficacy and safety of CT-P13 in 32 anti-TNF CD patients and 42 anti-TNF UC patients. In Anti-TNF CD patients, clinical responces rates at week 8,30 & 54 were 90.6%, 95.5% & 87.5% respectively and clinical remission rates at week 8,30 & 54 were 84.4%, 77.3%, 25%.

For anti-TNF UC patients clinical responses rate at week 8,30 & 64 were 81%, 91.3% & 100% and clinical remission rates at 8,30,54 were 38.1%, 47.8% & 50%.[8]

A recent study using 125-IBD Patients and controls sera demonstrated that Anti-Remicade antibodies in IBD patients recognize and functionally inhibit remsima to a similar degree, suggesting similar immunogenicity profile. All 69 positive Anti-Remicade cross reactive with remsima. Antibody to infliximab titers against remicade or remsima were strongly co-related. Anti-remicade antibodies of IBD patients exerted Similar functional inhibition on Remsima TNF-alpha binding capacity.

The induction of apoptosis in monocyte and lymphocytes by infliximab is a significant action because of the diminished cytokine release, which leads to blockade of inflammatory responses.

ADVANTAGES

1) The main advantage offered by Biosimilar is the enlarged patient access to biological medicines with proven pharmaceutical quality.

2) Biosimilars are biologics highly similar in terms of quality, characteristics, biological activity and safety.

3) The key advantage of biosimilar is that the cost is 20-25% less than originator product due to reduced clinical trials.

CHALLENGES

1) As the number of biosimilars is continuously growing, patients may switch between two or more biosimilars whose interchangeability has not been assessed. The importance of additional data to support interchangeability has been issued in draft guidance on

interchangeability emitted by the FDA. On the other hand, specific interchangeability studies could be very complex and time-consuming.

2) The safety and efficacy of biosimilars are rigorously tested through the comparability exercise, but still require continuous monitoring once the biosimilar is approved.

INCOMING WAVE OF BIOSIMILARS

The rate of arrival of biosimilars on the market is accelerating with approval of 14 new molecules in 2017 alone, compared with no more than 5 annual approvals since 2005.[7] Economic advantages with biosimilar use can be expected within a relatively short term period.

Recently on 18 January 2019, FDA has approved Samsung Bioepis 'Ontruzant' (trastuzumab-dttb), a biosimilar trastuzumab referencing Herceptin, for the treatment of HER2-positive breast cancer and HER2 overexpressing gastric cancer. The drug was first approved by the European Medicines Agency in November 2017, making it first biosimilar trastuzumab to be approved in the European Union. Since the approval, Europe has also seen the entry of 3 additional versions of biosimilar trastuzumab, Herzuma, Kanjinti, and Ogivri.

Ontruzant will now compete in the United States with the reference product, Herceptin, which in the third quarter of 2018 had earned developer Roche an estimated $5,332,998 globally.

CONCLUSION

In the last several years, the evidence supporting the use of biosimilars has grown significantly. The cost saving generated with the introduction of biosimilars is estimated to be 20–30% lower compared to the cost of the reference product. The extent to which biosimilars will contribute to the reduction of health care budgets and will be integrated into the management of cancer treatment depends on their level of acceptance by regulators, prescribers, pharmacists and patients. To date, no clinically meaningful differences in safety, efficacy, and immunogenicity have been reported after switching a reference product to its biosimilar version.

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