Use of Biologics and Biosimilars in Rheumatology

Shefali Khanna Sharma

Abstract

Prior to the availability of biologics, synthetic DMARDs (Disease modifying anti-rheumatic drugs) were the mainstay of the treatment in rheumatology. With the introduction of biologics, the scenario is changing to become more promising. These drugs have innovative mechanism of action, based on the targeted inhibition of specific molecular or cellular targets directly involved in disease pathogenesis. The biosimilars are highly similar copies of originator biologics approved through pre-defined, stringent regulatory processes after rigorous physicochemical, non-clinical, and clinical evaluations. Low cost and resulting wider patient access as compared to innovators goes in favor of biosimilars. Regulatory guidelines for biosimilar development and approval are rigorous and undergoing constant refinement. Approval of several biosimilars in across the world in last few years bears testimony to the increased regulatory acceptance of these agents. This article addresses development of biosimilars, regulatory process, benefits and concerns about their usage in rheumatologic practice.

Introduction

Conventionally, autoimmune diseases managed using disease modifying anti-rheumatic drugs (DMARDS), which including methotrexate, sulphasalazine, hydroxychloroquine and leflunomide along with corticosteroids and NSAID's.[1] Occasionally used immunosuppressants include azathioprine, cyclophosphamide, cyclosporine and mycophenolate mofetil. Main adverse drug reactions include infections, liver dysfunction, cytopenias and multiple organ system damage. But some patients do not respond to synthetic DMARDs completely. Either because of high disease activity or that they are not able to tolerate the oral therapy. Biologics are another powerful tool in the bag of a rheumatologist.[2] These biologics are developed by biological processes such as recombinant DNA technologies. These biologics usually are monoclonal antibodies or fusion proteins counteracting or blocking a substance in the body or targeting any specific cell type. Selected cells or molecules in the cascade of events involved in autoimmunity are targeted by these cells. Efficacy and safety of several biologics like Infliximab, Adalimumab, Etanercept, Tocilizumab, Rituximab has been well established in rheumatologic patients. After patent expiry, these biologics are facing stiff competition from biosimilars. However, long term safety and immunogenicity of these biosimilars is a matter of concern for rheumatologists. The following article gives an overview of biologics in rheumatology, their regulatory process and their place in rheumatology practice.

What is a Biologic Drug?

The story of biological drugs began in 1975, when Köhler and Milstein developed the method for isolating monoclonal antibodies (mAbs) from hybridoma cells. A biologic medicine is a large molecule derived from living cells and typically produced by recombinant DNA, hybridoma, or other technologies. The first step in the production of antibodies against specific molecules was the cloning of murine genes of variable heavy (VH) and variable light (VL) chains. It was then possible to synthetize chimeric antibodies, containing the murine VH and VL chains fused with the constant region of human origin.[3] More specifically, antibodies obtained by this technology show approximately one-third murine and two thirds human sequences. However, the efficacy of murine derived immunoglobulin preparations could be limited by the induction of anti-mouse immune responses, with consequent impairment of the therapeutic efficacy. Hence, recent antibodies of are as human as possible.

Biologics are used in the treatment, diagnosis, or prevention of several non-communicable and some communicable diseases and conditions and include hormones, small proteins, vaccines, monoclonal antibodies, and fusion proteins. The introduction of biologics (e.g., etanercept, adalimumab, infliximab, rituximab, abatacept, and tocilizumab) revolutionized treatment algorithms in rheumatological patients.[4]

How are Biological Drugs Manufactured?

A biologic is manufactured in a living system such as a microorganism, or plant or animal cells. Most biologics are very large, complex molecules or mixtures of molecules. Many biologics are

PGIMER, Chandigarh

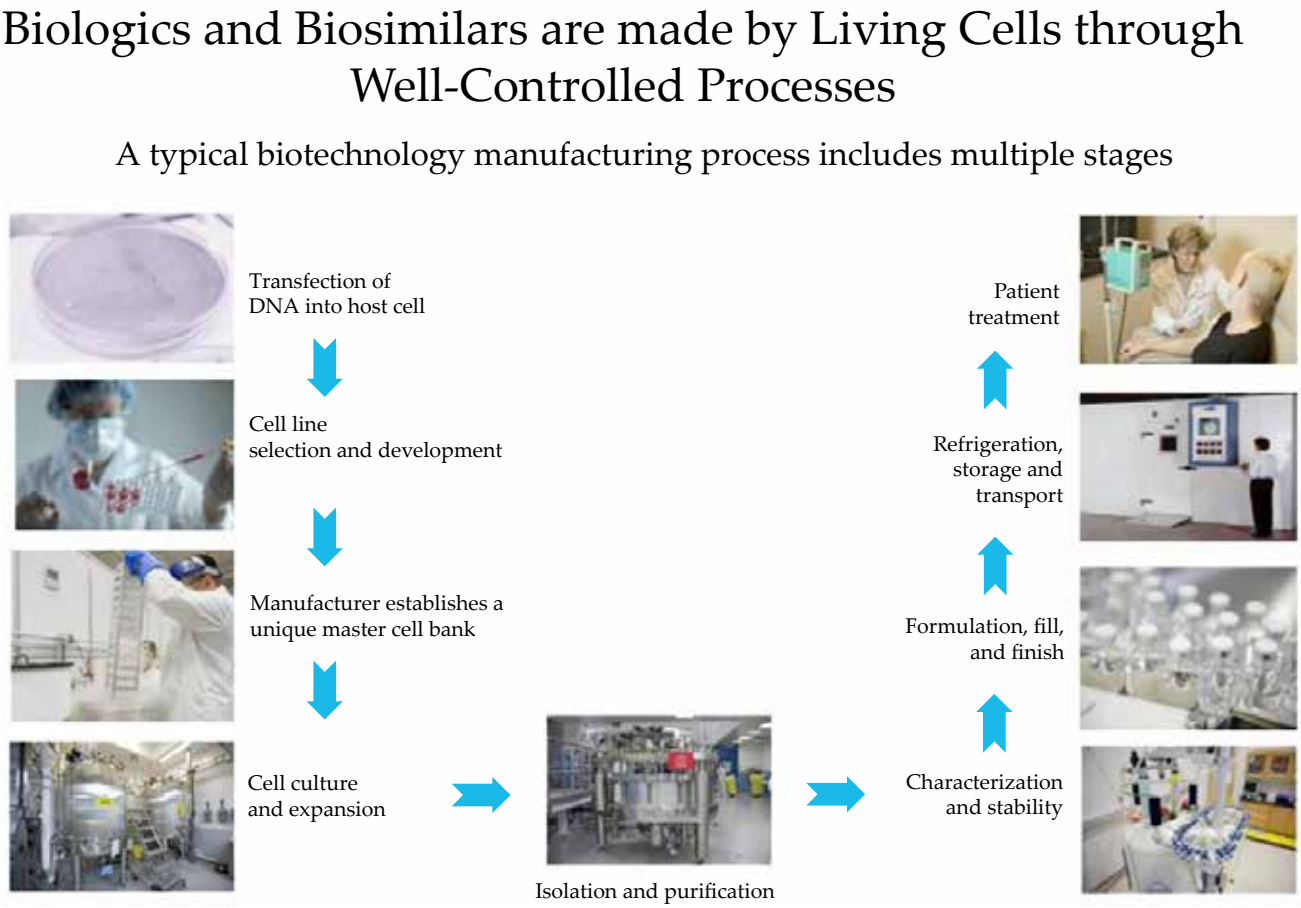

Fig. 1: A typical biologic manufacturing process includes multiple stages

Table 1: Biosimilar terminologies across the world

Term	Agency	Definition
Similar biotherapeutic products	WHO	A Biotherapeutic product to an already licensed reference. Biotherapeutic product in terms of quality, safety and efficacy
Follow on protein products or follow on biologics	US-FDA JAPAN	A product highly similar to the reference product without clinically meaningful differences in safety, purity and potency
Subsequent entry Biologics	Canada	A biologic drug that enters the market subsequent to a version previously authorized in Canada with demonstrated similarity to a reference biologic drug
Biosimilars	Europe Korea India China Australia	Biological products which demonstrated its equivalence to an already approved reference product with regard to quality, safety, and efficacy.

produced using recombinant DNA technology, whereas a drug is typically manufactured through chemical synthesis, which means that it is made by combining specific chemical ingredients in an ordered process. The Biologics and Biosimilars are made by living cells through well controlled processes as shown in Figure 1.

Chemical drugs have well defined structure and a final drug product can be analysed to determine its components, while it is extremely difficult to assess a biologic by available laboratory methods. It can safely be said that for a biologic the process determines the final product. Even very minor changes in the manufacturing process can alter the living systems used in manufacturing a biologic. Nature and ultimately, the function of a biologic can be affected by only a minute change in the process. Tight control over the source and nature of starting materials is required and manufacturers have to employ hundreds of process controls for assuring predictable manufacturing outcomes which is not the case with chemical drugs. These process controls for biologics are not applicable to a manufacturing process/product created by another manufacturer as these are established separately for each unique manufacturing product. As process controls may also confidential it would be difficult or impossible for a second manufacturer to replicate the innovator without intimate knowledge of the innovator's process.[5]

What is a Biosimilar?

Biosimilar a biologic product considered 'highly similar' but not identical to its reference biologic product. The FDA further defines a biosimilar as highly similar

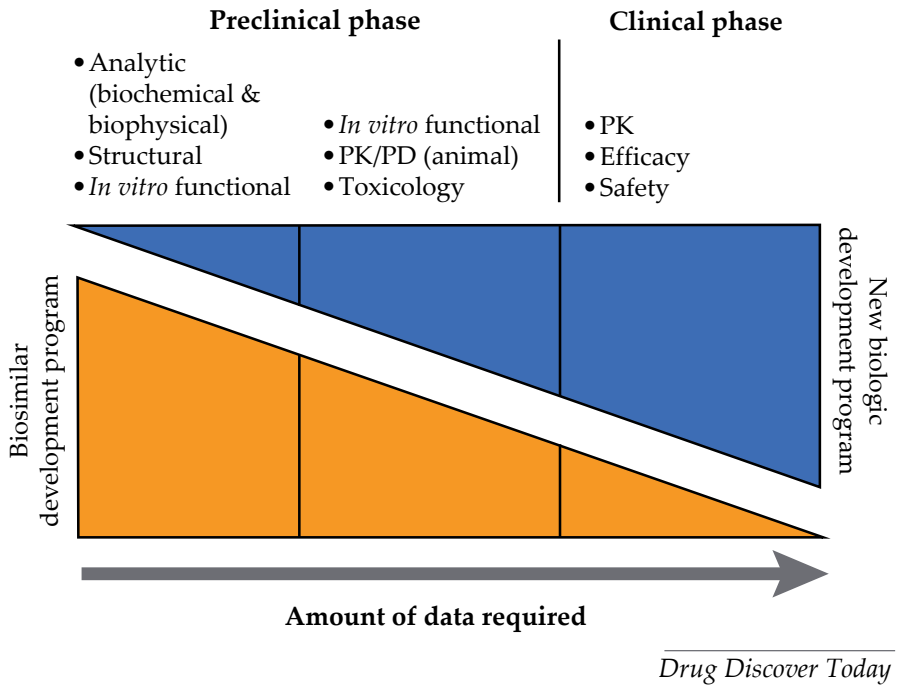

Fig. 2: Biosimilars vs original biologics development pathway

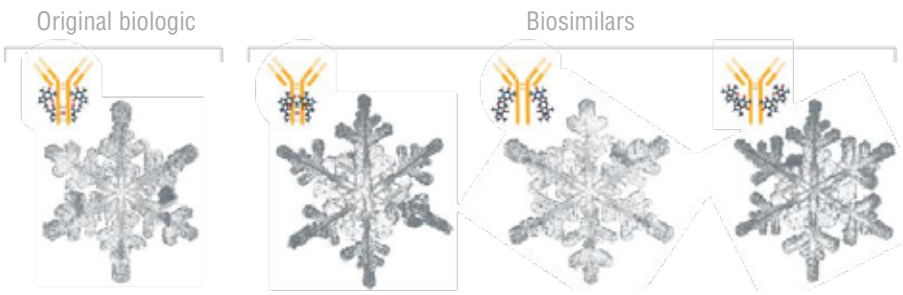

Fig. 3: How biosimilars differ from original or Innovator Biologics (Figure adapted from amgem biosimilar report)

'notwithstanding minor differences in clinically inactive components', and having 'no clinically meaningful differences between the biologic product and the reference product in terms of the safety, purity, and potency of the product.[6]

These biologic proteins or peptides have been developed using recombinant DNA technology in living systems via complex purification techniques.[7] These biologics require proprietary knowledge which precludes duplication, while small-molecule products have simpler manufacturing processes. However, some pharmaceutical companies have been able to replicate the patented production process facilitating development of generic versions identical copies of the originator called as biosimilar. Different countries use different terminologies for Biosimilars as mentioned here[8] in Table 1.

Current technology can characterize accurately chemical structure of a generic small-molecule drug guaranteeing that it is identical to the reference product. In contrast, biologics are much larger and more complex than small-molecule drugs typically requiring living systems, such as bacteria, yeast, or mammalian cells.[9] Hence, manufacturing process of biosimilars is generally more complex than manufacturing small molecule generics. Additionally, the regulatory process for biosimilar approval is very different from the approval process for small-molecule generic medicines. Biosimilars must demonstrate pharmacokinetic bioequivalence and also high similarity to the originator product; however, small-molecule generics only require proof of quality.[10] Biosimilars, thus, should have similar complexity, manufacturing method, storage techniques and transport technology as compared to innovators.[11] Approximate timeline for the development of biosimilars, includes host cell copying, making cell banks, development process, scale up and comparability testing, taking about 8 years (Figure 2).

What is the Difference between Biologic and a Biosimilar?

As they are biologics, biosimilars should be considered as generic medicines; however, unlike small-molecule generics cannot be manufactured to be identical to the originator biologic. They have certain differences (Figure 3).

The summary of these differences between biologics and biosimilars[5,6] is given in Table 2.

Biosimilars Approval Process in US, Europe and India

FDA and EMA Approval process

Biologics, a new class of chemotherapeutic agents came to picture in mid-nineties. After their patent expiry, the generic versions of innovator biologics appeared. By 2007, the biologics market had already grown noticeably with a double-digit growth of 20%. Biosimilar monoclonal antibodies (mAbs) and insulin will account for 57% of the global biosimilars market.[12]

Biosimilars were first approved in the European Union (EU) in 2006 and were first approved in the U.S. in 2015. In US the Biologics Price Competition and Innovation Act of 2009 (BPCIA) permits the licensing of biological products which have proven biosimilarity to previously licensed innovators. The

Table 2: Difference between Biologic and Bisomilar

	Biologic	Biosimilar
Definition	A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings Referred to as the reference, pioneer, or innovator biologic	The biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product Referred to as follow-on biologic
Properties	Derived from living sources such as cells Complex mixtures whose active ingredients (usually proteins) are hundreds of times larger than the compounds found in most pills Mostly given by injection due to unstable environ- mental conditions	The active ingredient of biosimilars closely resemble the reference biologic However, they are not identical, generic equivalents due to differences in manufacturing processes, protein source, and extraction/purification processes
Approval Process	Submitted through the BLA process Requirements: • Applicant information: Includes name and addresses of manufacturing facilities • Product/Manufacturing information: Source material/raw material; manufacturing process and controls; formulation; facility information; contamination/cross-contamination information; environment assessment or categorical exclusion • Pre-clinical studies: Safety, efficacy, and use • Clinical studies: Safety, efficacy, and use • Labeling: Safety, efficacy, and use	2012 FDA Draft Guidance recommends a stepwise approach to demonstrate biosimilarity, submitted through an abbreviated BLA. Requirements *(unless FDA deems unnecessary)*: **Structural analyses**: Determine structural characteristics of the protein, post-translational modifications, and/or other potential variants **Functional assays**: Evaluate the pharmacologic activity of the protein (eg, potency and MOA) **Animal studies:** Include toxicity, PK and PD measures, and immunogenicity **Clinical studies:** Human pharmacology data, clinical immunogenicity assessment, and clinical safety and efficacy data to demonstrate safety, purity, and potency for the condition(s) the reference product is licensed to be used for.
Safety data	Typically required to have postmarketing safety monitoring Includes the detection, assessment, understanding and prevention of adverse effects after the launch of the biologic onto the market	Biosimilars should include postmarketing surveillance to address immunogenicity and potential rare adverse events when seeking approval May undergo more strict monitoring due to limitations of clinical data compared to the reference product

BLA = biologics license application; MOA = mechanism of action; PD = pharmacodynamic; PK = pharmacokinetic

Table 3: EMA and FDA guidance on approval of Biosimilars [9,29]

Study	EMA and FDA Guidance
Non-clinical studies	• Head-to-head comparative approach evaluates biosimilars on a case-by-case basis • Physicochemical characterization; PK, PD studies • In vivo animal studies, biologic testing, and toxicology
Clinical studies	
Human PK and PD Studies	• PK comparability in a sufficiently sensitive and homogenous population, PD studies if possible: dose-concentration response curve
Efficacy studies	Similar efficacy and safety in adequately powered, randomised, parallel-group comparative trials
Extrapolation	Yes if biosimilarity is confirmed in the comparability studies, there is adequate justification, and
Safety and immunogenicity	• Comparable safety (type, frequency, and severity of AEs) including immunogenicity
Pharmacovigilance	• Pharmacovigilance and risk management plan for the post authorization phase (safety in extrapolated indications; rare and SAEs described for reference product; detection of novel safety signals, long-term immunogenicity and safety) • Traceability – recording the brand name used by physician

FDA has recently approved three Biosimilars Amjevita (Adalimumab), Inflectra (Infliximab) and Erelzi (Etanercept).[13] European Union (EU) has been a pioneer in the development of a regulatory system for biosimilars. Formal consideration of scientific issues presented by biosimilar products was considered by European Medicines Agency (EMA) in 2001, which was further amended in 2003. Subsequently, EMA issued a general guideline in 2005, on similar biological medicinal products. EMA requires that the biosimilar and innovator should be same in terms of the active substance, the pharmaceutical form, strength, route of administration. Other unregulated markets of the world follow less stringent regulatory guidelines.[14] Given in the Table 3 is the FDA and EMA guidance on approval of biosimilars.

India regulatory approval process

The first biosimilar in rheumatology to come to India market was Rituximab in 2007 subsequently many biosimilars have made it to the Indian market (Table 4). In June 2012, guidelines for an abbreviated pathway for biosimilar

Table 4: Biosimilar agents used in Rheumatology in India

Biosimilar (year)	Therapeutic area	Company
Infliximab (2014)	RA, AS, PsA, JIA	Sun/Ranbaxy(Epirus)
Etanercept (2013)	RA, AS, PsA, JIA	Cipla
Adalimumab (2014)	RA, AS, PsA, JIA	Zydus
Rituximab (2007)	RA	Dr. Reddy's

RA=Rheumatoid arthritis, AS= Ankylosing Spondylitis; PsA: Psoriatic Arthritis; JIA: Juvenile Inflammatory Arthritis; UC= Ulcerative Colitis; CD= Crohn's Disease

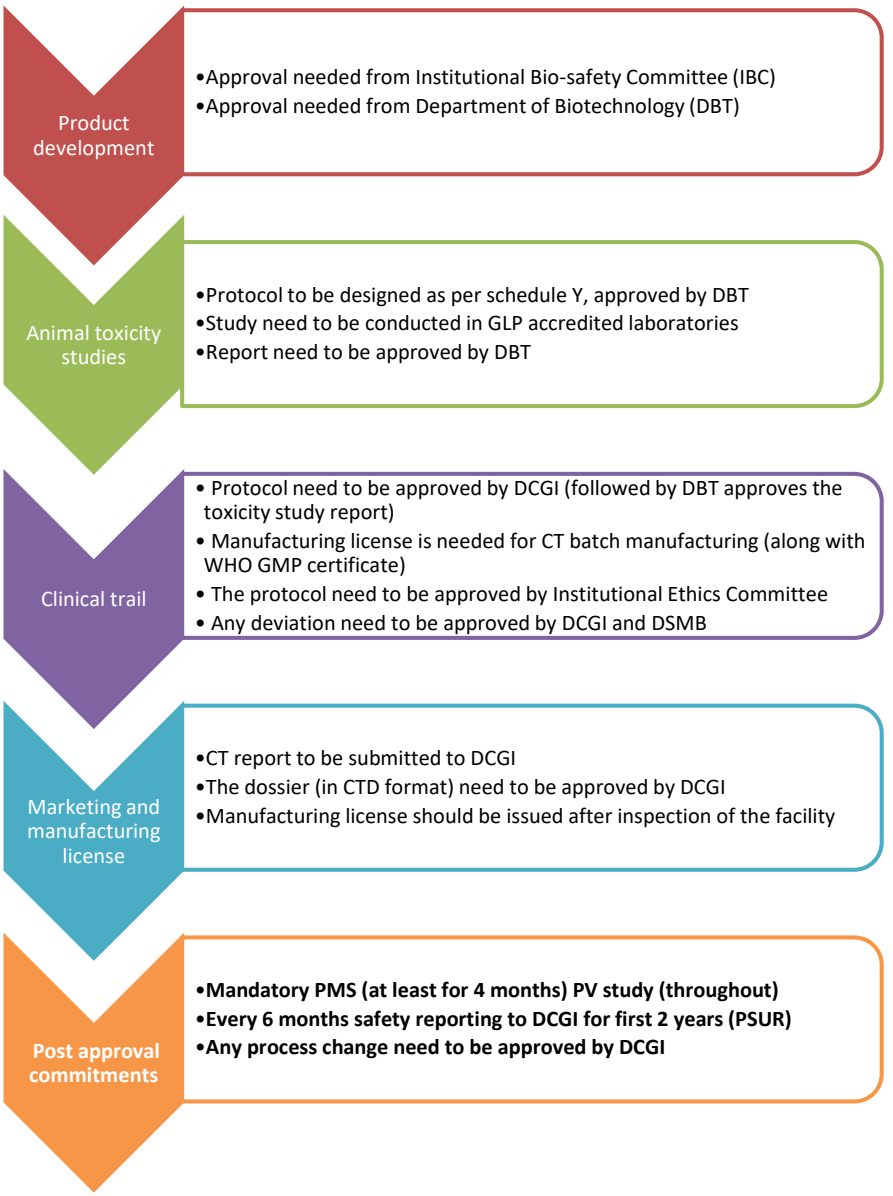

Fig. 4: The regulatory pathway for approval of biosimilars in India

registration were published by the government of India, Department of Biotechnology (DBT) and the Central Drugs Standard Control Organization (CDSCO) DBT is responsible oversees the development and preclinical evaluation of recombinant biologics. In India the following process is required for approval of a "similar biologic" in India (Figure 4).[15]

Opportunities and Challenges with Biosimilars

Most important driver for prescribing biosimilar is pricing as some biosimilars have been marketed at a lower price as compared to their innovator (Table 5).[16] Trivial investigational cost and absence of comparative studies can be the reason for such a low pricing. Also in absence of proper comparative studies efficacy and safety of such drugs are questionable. Many regulatory agencies hesitate to use biosimilars for lack of scientific data on safety. For a practicing physician to prescribe a biosimilar, recognition and authorization from legal entities is crucial. One of the major factors that can influence the prescriber is the patient. Innovator can be substituted for a biosimilar where patient is the payer for markets like India. For example, rituximab (Mabthera™) has been in use in India since 2000 and its biosimilar molecule of rituximab (Reditux™) was approved in India in 2007 considering no change in efficacy or safety parameters. It has been widely accepted by clinicians and turned out to be significant milestone bringing down the cost of biologics by using a biosimilar.[17]

Table 5: Cost comparison of Biologic vs Biosimilar

Molecule	Innovator company price (INR) (6 months treatment)	Biosimilar price (INR) (6 months treatment)
Rituximab	4,80,000	2,40,000
Infliximab	4,80,000	2,40,000
Adalimumab	Nai	1,32,000
Etarnacept	108,000	84, 000

NAI= Not Available in India

Since 2006, 21 biosimilars have been approved by EMA, 4 biosimilars by FDA and around 250 biosimilars are in the pipeline globally. In spite of an effort to reduce healthcare cost globally, this market is expected to grow tremendously in the next five years.[18]

Physician implications

Except for drugs for compassionate use and in clinical trials, a physician should prescribe a drug based on demonstrated quality, safety, and efficacy. Proper analytical tools and sensitive tests are used to establish

similarity between a biosimilar and an innovator, with more and more biologicals being used in treatment of various diseases, one can expect the market to be flooded with biosimilars in the future. Hence, as a physician proper understanding of a biosimilar concept is very essential.[19] As far as safety is concerned it should be understood that a biosimilar and an innovator are similar but not identical. Differences in their manufacturing process should also be taken into consideration. A well-known example being epoetin antibody-induced pure red cell aplasia which ocurred due to a major change in the manufacturing process used for an originator epoetin, and not with a biosimilar.[20] Human immunogenicity data are also required as such seemingly minor changes can have major effects on immunity. Proper scrutiny and regulatory oversight and scrutiny are a must in case of biological to ensure their safe use, in particular, post marketing surveillance. In view of this a proper documentation on the part of physicians is required to establish which biological is used for an individual patient. This might be helpful in identifying an ADR caused by a specific biosimilar. This further establishes and confirms the role of a well informed and vigilant physician in overall concept of regulatory control of patients' health. Lastly, complete information about existing guidelines and access to unbiased information on biosimilars regarding the clinical utility should be done.

Conclusion

Biologics and biosimilars offer good alternate treatment options in patients who cannot be treated with synthetic DMARDs. Not all biologics are created equal, hence it is important to distinguish between biosimilars, biobetters, and other biologics, as these products may have clinically significant differences in quality, efficacy and safety from their reference products. These products have opened up additional therapeutic choices for health care providers and patients and with biosimilars, competition may increase access to biologic products for appropriate patients.

However, some challenges in rheumatology like the–biological registry, substitution of biological with a biosimilar and lack of long term safety data do remain. This article aimed to provide information about biological and biosimilar drugs, the approval processes, clinical indications, benefits and physician implications.

References

1. Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol* 1997; 84:223-43.
2. Bakker MF, Jacobs JW, Verstappen SM, Bijlsma JW. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. *Ann Rheum Dis* 2007; 66 Suppl 3: iii56-60.
3. Köhler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 1975; 256:495-7
4. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010; 69:631–637.
5. https://www.bio.org/articles/how-do-drugs-and-biologics-differ. Last accessed on 28th March 2017.
6. U.S. Food and Drug Administration. Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product–Draft Guidance. U.S. Food and Drug Administration. [Online] February 2012. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed March 20, 2017.
7. Epstein MS, Ehrenpreis ED, Kulkarni PM. Biosimilars: the need, the challenge, the future: the FDA perspective. *Am J Gastroenterol* 2014;109:1856–1859.
8. Hurley P, Boren J, Congiatu C. Challenges in global biosimilar development: A regulatory perspective. *Contract Pharma* 2015.
9. Klotz U, Teml A, Schwab M. Clinical pharmacokinetics and use of infliximab. *Clin Pharmacokinet* 2007; 46:645–60.
10. Ramanan S, Grampp G. Drift, evolution, and divergence in biologics and biosimilars manufacturing. *Bio Drugs* 2014; 28:363–72.
11. European Medicines Agency. Guideline on similar biological medicinal products. EMA/CHMP/437/04 Rev 1. Committee for Medicinal Products for Human Use (CHMP). 2014.
12. Thulasi LK, Reddy S, Alagusundaram M, Reddy J. Regulatory approval of biosimilars: indian market perspective. *International Journal of Advanced Pharmaceutics* 2014; 4:245-8
13. http://rheumnow.com/content/biosimilar-reports-%E2%80%93-october-2016. Last accessed on 25th March 2017
14. Khraishi M, Stead D, Lukas M, Scotte F, Schmid H. Biosimilars: A Multidisciplinary Perspective. 2-16. *Clinical Therapeutics* 2016; 5:2-16.
15. Guidelines on Similar Biologic: Regulatory Requirements for Marketing Authorization in India. http://cdsco.nic.in/writereaddata/Proposed%20Guidelines%20for%20Similar%20Biologic%202016.pdf
16. DATA based on website http://www.medguideindia.com/ (2017)
17. Mysler E, Pineda C, Horiuchi T, Singh E etal. Clinical and regulatory perspectives on biosimilar therapies and intended copies of biologics in rheumatology. *Rheumatol Int* 2016; 36:613–625.
18. Deloitte (2015) Winning with biosimilars Opportunities in global markets. http://www2.deloitte.com/content/dam/Deloitte/us/Documents/lifesciences- health-care/us-lshc-biosimilars-whitepaper-final.pdf. Accessed 17 Mar 2017.
19. Schneider CK, Kalinke U. Toward biosimilar monoclonal antibodies. *Nat Biotechnol* 2008; 26:985-990.
20. McKoy JM, Stonecash RE, Cournoyer D, et al. Epoetin-associated pure red cell aplasia: past,\ present, and future considerations. *Transfusion* 2008; 48:1754-1762.