A REVIEW ON THE USE OF BIOSIMILARS IN THE TREATMENT OF RHEUMATOID ARTHRITIS

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Honors)

Department of Pharmacy
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December 2020

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "A Review on the Use of Biosimilars in the Treatment of Rheumatoid Arthritis" submitted by Md. Abul Bashar (16346026) of Summer, 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This study does not involve any human or animal trial.

Abstract

Biosimilars are biological agents that are very similar to their reference product but follow a separate regulatory framework and marketing strategy and usually include interferons, interleukins, growth factors, hormones and monoclonal antibodies. The implementation of biologics as targeted treatment strategy, significantly improved health condition of patients with rheumatoid arthritis compared to other conventional therapies. In this study, the biosimilars that can be used in the management of rheumatoid arthritis have been highlighted and an insight on its importance in terms of patient accessibility and affordability provided. The treatment algorithm of biosimilars and the guidelines followed for it to be prescribed to such patients have also been mentioned in this study. Moreover, the role of molecular docking and drug repurposing in discovering biosimilars and minimizing the development task of a lead molecule considering the growing demand for these biological agents worldwide have been discussed in this study.

Keywords: Biosimilars, Biologics, Rheumatoid arthritis, Molecular docking, Drug repurposing.

Dedication

I want to dedicate this project to my loving parents for their constant encouragement and support.

Acknowledgment

First of all, I would like to praise the Almighty for being the source of our knowledge and having an arsenal of strength ready for us to keep us motivated. This ample number of blessings has allowed me to complete this project with full perseverance.

Secondly, I would like to showcase my deepest and most sincere gratitude to my project supervisor, Dr. Eva Rahman Kabir (Professor and Chairperson, Department of Pharmacy, BRAC University), whose expertise, constant guidance, sincere monitoring and motivational approaches in every sphere have inspired me to conduct this project efficiently. I sincerely proffer my appreciation and admiration for her patience and provided sense of direction whenever I encountered complications throughout this phase.

Thirdly, I would like to express my deepest gratitude and appreciation to my project supervisor, Tanisha Tabassum Sayka Khan (Lecturer, Department of Pharmacy, Brac University), whose consistent guidance in every step have helped me to accomplish this project efficiently. I would like to thank her for her great advice and patient behavior throughout this phase whenever I encountered difficulty.

I would also like to thank Nashrah apa and Nahid apa for their continuous support throughout my project work.

Lastly, I would like to thank my parents for their constant support and encouragement that further pushed me to work harder and face the difficulties during this time frame.

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List of Acronyms

ACF	Anti-citrullinated fibrinogen
ACPA	Anti-citrullinated protein antibodies
ACR	American College of Rheumatology
ADAM	A disintegrin and metalloproteinase
ADAs	Antidrug antibodies
AS	Ankylosing spondylitis
bDMARDs	Biological DMARDs
BGTD	Biologics and Genetic Therapies Directorate
BLA	Biologics license application
bsDMARD	Biosimilar DMARDs
CarP	Carbamylated protein
CCP	Cyclic citrullinated peptide
CEP1	Citrullinated α-enolase peptide 1
Cit-HPV47	Citrullinated human papilloma virus-47
CRP	C-reactive protein
csDMARDs	Conventional synthetic DMARDs
CTGF	Connective tissue growth factor

cTNC5	Citrullinated tenascin-C 5
DMARDs	Disease-modifying antirheumatic drugs
EMA	European Medicines Agency
ESR	Erythrocyte sedimentation rate
EU	European union
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FGF-2	Fibroblast growth factor-2
IA	Inflammatory arthritis
IBD	Inflammatory bowel disease
IFN	Interferon
IL	Interleukin
ILD	Interstitial lung disease
INN	International Nonproprietary Names
IRRs	Infusion-related reactions
JAK	Janus kinase
JRA	Juvenile rheumatoid arthritis
MCV	Mutated citrullinated vimentin

MMP	Matrix metalloproteinase
MOA	Mechanism of action
MRI	Magnetic resonance imaging
NN	Nonproprietary Name
NSAIDs	Nonsteroidal anti-inflammatory drugs
PAD	Peptidylarginine deiminase
PMDA	Pharmaceuticals and Medical Devices Agency
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RCTs	Randomized clinical trials
RF	Rheumatoid factor
RMDs	Rheumatic and musculoskeletal diseases
STATs	Signal transducers and activators of transcription
TGA	Therapeutic Goods Administration
TNFi	Tumor necrosis factor inhibitors
tsDMARDs	Targeted synthetic DMARDs
US FDA	United States Food & Drug Administration
VEGF	Vascular endothelial growth factor

WHO	World Health Organization

Chapter 1 Introduction

Rheumatoid arthritis (RA) is one of the most widely known autoimmune disorders and its prevalence ranges from 0.4% to 1.3% worldwide. In the United states, it has been estimated that among the 1.3 million adults suffering from RA, approximately 60 percent are women. More recent data have shown that the incidence of RA in women is increasing and it is believed that environmental variables such as obesity rates, declining protective effects (such as those from oral contraception and breastfeeding), and financial and economic status in the society trigger the onset of rheumatoid arthritis (Littlejohn, 2020). In this disorder, mainly small joints are damaged due to inflammation and other features that can be observed include swelling and pain that later leads to chronic progressive destruction of the joint. Consequently, the physical function and working capacity of an individual are hampered which ultimately deteriorates the standard of living. In addition, the pathogenesis of rheumatoid arthritis is greatly dependent on the imbalance between proinflammatory cytokine levels that includes tumor necrosis factor (TNF), interleukin 5 (IL-5) and interleukin 6 (IL-6), and anti-inflammatory cytokine levels (Furst & Emery, 2014).

New clinical techniques including early diagnosis of RA, the treatment-to-target theory and disease-modifying anti-inflammatory drugs or DMARDs, which avoid or decrease the progression of systemic joint injury and decrease the risk of mortality, have dramatically strengthened RA management over the past few years (Smolen et al., 2018). A number of biological DMARDs (bDMARDs) and more recently, the first biosimilar DMARDs (bsDMARDs) and targeted synthetic DMARDs (tsDMARDs) are now available in addition to conventional synthetic DMARDs (csDMARDs) for the treatment of RA (Smolen et al., 2017). While bDMARDs and tsDMARDs were effective in alleviating the characteristic symptoms in many RA patients, they

are expensive and should be used in an evidence-based manner ensuring local healthcare system availability and affordability (Nam et al., 2017).

Targeted biological DMARDs are known to positively alter the treatment strategies in rheumatoid arthritis. Examples such as adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab which are tumor necrosis factor inhibitors or TNFi; anakinra which is an interleukin 1 receptor antagonist; and tocilizumab which is an anti-interleukin 6 receptor antibody are some of the effective cytokine targeting bDMARDs approved for RA treatment. Furthermore, some other bDMARDs are used to treat RA include abatacept and rituximab, which modulate activation of T cells and B cells, respectively (Braun & Kay, 2017).

1.1 Objectives of the study

This study aims to provide an overview of the biosimilar agents that are currently available in the treatment of rheumatic diseases or are in the development process. The study will explore the current algorithms involved in the treatment of rheumatic disease and the potential use of biosimilars in this auto-immune disease. Moreover, the role of molecular docking and drug repurposing in discovering biosimilars and minimizing the development task of a lead molecule will be discussed in the current study.

1.2 Rationale of the study

Rheumatic disease has been prominent globally in the adult population for decades. Although the advances in therapies is noticeable, the employment of biologic agents in the treatment algorithms brought about a remarkable progress in the mitigation of this type of disease. Biosimilars portraying very close quality and efficacy profile to that of biologics also come with a benefit of lower cost. With that acceptable lower cost, biosimilars as antirheumatic drugs can be affordable

to most patients. Keeping the above points in mind, the current biosimilars used in the treatment of rheumatoid arthritis will be discussed, as well as the potential of these biologics in current treatment algorithms. To discover novel biosimilars in future, the use of molecular docking and drug repurposing methods will also be discussed.

Chapter 2 Literature Review

The current study involved a review on the use of biosimilars as a promising treatment option for rheumatoid arthritis. Information was collected in a systematic manner from secondary research articles indexed in PubMed, Elsevier, Nature, SpringerLink, BMJ journals etc. Most of the articles cited in the study have been published in the last ten years and therefore up-to-date information has been included in this study. The use of published articles validates the review, and thus the current study can be claimed as reliable. Although it was not possible to actively participate with the rheumatoid arthritis treatment related to biosimilars, the use of published article gave the work a reliable compilation.

Chapter 3 Biologics and Biosimilars

Biosimilars are biologics that are very similar to its reference biologic product but not identical, and are considered for launching in the market after the reference product patent expires (Combe, Tredree, & Schellekens, 2005). Agents that are acknowledged as DMARDs enhance the symptoms and signs of RA and minimize the advancement of damage. DMARDs can either be synthetic small molecules or biologics (Table 1) (Pisetsky, 2017). Two of the most widely used DMARDs are methotrexate and TNF blockers. Many other such drug molecules are in the development stage, targeting new mediators and pathways (Burmester & Pope, 2017).

Table 1: List of Classes of DMARDs *(Pisetsky, 2017)*.

CLASSES OF DMARDS	EXAMPLES
CONVENTIONAL SYNTHETIC	Sulfasalazine, methotrexate, leflunomide, hydroxychloroquine, azathioprine
BIOLOGIC	T cell co-stimulatory blocker (abatacept); TNF blockers (infliximab, golimumab, certolizumab, etanercept, adalimumab); anti-CD20 (rituximab); anti-interleukin-6 receptor (tocilizumab)
TARGETED SYNTHETIC	Tofacitinib

The emergence of targeted biologics transformed the treatment of many acute and long-term diseases. These medications are produced via living systems and are considered complex macromolecular drugs. The ability of these drugs in providing targeted therapeutic intervention against autoimmune disorders, anemia (erythropoietin substitutes), cancer (monoclonal

antibodies), Crohn's disease, ulcerative colitis, diabetes (human insulin) and some other diseases has led to an increase in the demand and growth of biologics (Espiritu, Collier, & Bingham, 2014). Biological therapy extends the scope of medicaments not limiting the research and development of small molecule drugs and are expected to demonstrate continuous expansion. However, considering the high costs of these biologics, the necessity for low-cost products are now a concern for the mass population (Kabir, Moreino, & Siam, 2019).

In terms of safety, potency and purity, biosimilars can be considered closely identical to the reference products but may have slight variations and are meant to be used in the same way as the reference product. A variety of biosimilar DMARDs (bsDMARDs) such as infliximab, etanercept, rituximab and adalimumab have been indicated in rheumatic diseases, and several more bsDMARDs are being developed (Smolen, Goncalves, Quinn, Benedetti, & Lee, 2019). Diseases that previously were difficult to treat are now easily managed due to the arrival of biologic therapies, adopted for the treatment of immune-mediated rheumatic, skin and gastrointestinal diseases and the therapies are considered to bring about noticeable development in therapeutic strategies. Voiced by 83% of Industry Experts, 80% of Academicians, and 67% of Clinicians, assurance of possible healthcare cost lowering can aid the accessibility and affordability of biosimilars, particularly from the perspective of a developing country. With agreement of 44% of Industry Experts, 35% of Academicians and 44% of Clinicians, the biosimilars are assured to treat the same indications as those treated with reference biologic. However, the concept of possible advantages of a lower therapeutic dose or usage of an administration route different from the original biologic were less favored by the surveyed candidates (Kabir, Moreino, & Siam, 2018), which necessitates the immediate requirement of awareness to the different stakeholders. Several biosimilars of patent expired bio-originator DMARDs are being developed which have

demonstrated comparable effectiveness and safety when used in the initial treatment as biologic in patients and the effects are same as their bio-originators (Fleischmann, 2017). European Union (EU) along with other countries approved three biosimilars that are being utilized for the treatment of patients with rheumatoid arthritis, while several others are in the pipeline. Infusion-related reactions (IRRs) and immunogenicity projected with some other indications in which the knowledge is limited and pharmacovigilance remain the subjects of discussion on safety issues related to biosimilars (Reinisch & Smolen, 2015). In contrast, a biomimic or intended copy is an imitation of a biopharmaceutical product that has not been developed, analyzed or authorized by following biosimilar regulations and the mimic action to the intended copy has not been illustrated via extensive comparability studies (Castañeda-Hernández, González-Ramírez, Kay, & Scheinberg, 2015). Biomimics may differ in formulation, primary structure, dosage/dosing regimen, safety, efficacy, and immunogenicity from the bio-originator, all of which could have clinical significant difference in the result (Braun & Kay, 2017).

Several pharmaceutical companies have been found to be interested to enter the biologics market, aiming in the commercialization of monoclonal antibodies and recombinant proteins. The variety of biotherapeutics have also expanded and include soluble receptors, nanobodies, immuno-therapies, fusion proteins, immunoconjugates, synthetic vaccines, modified proteins (glycosylated and pegylated), etc. The contribution of evolving technology and an increased knowledge of cell line production, identification of protein, engineering and expression has led to the emergence of these therapies (Bannas, Hambach, & Koch-Nolte, 2017). Biologics are capable of binding to receptors that appear to be out of reach to small molecule drugs (Wan, 2016). Therefore, protein-protein interactions affecting flat surfaces with lower number of areas that are charged can be considered.

There is a rising interest in the approval and further development of biologics and biosimilars. Pharmaceutical companies have attempted to replicate existing products and ensure a constant supply of the biosimilars because of the high expenditure in replicating new lead and tedious processes involved in developing novel biotech products (Kabir et al., 2018). The World Health Organization (WHO) describes biosimilars to be similar in terms of efficacy, safety and quality to those of an already authorized reference biopharmaceutical product. Exhibiting a potential or long-term remedial property, this group of drug is similar to that of the bio-originator, by demonstrating small yet acceptable differences in the potency, safety, purity and efficacy (Markus et al., 2017). The timeline of biosimilars approved till 2020 has been provided in Table 2.

Table 2: Biosimilars approved till 2020 by United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA) ("Medicines | European Medicines Agency," n.d.); ("Biosimilar Product Information | FDA," n.d.).

NAME OF BIOSIMILAR PRODUCT	MANUFACTURER	APPROVED BY	DATE OF APPROVAL
RIABNI	Amgen	United States Food and Drug Administration	December 2020
EQUIDACENT	Centus	European Medicines Agency	September 2020
LIVOGIVA	Theramex	European Medicines Agency	August 2020
AYBINTIO	Samsung Bioepis	European Medicines Agency	August 2020
HULIO	Mylan	United States Food and Drug Administration	July 2020
NIVESTYM	Hospira Inc.	United States Food and Drug Administration	July 2020
BLITZIMA	Celltrion	European Medicines Agency	July 2020
ZERCEPAC	Shanghai Henlius Biotech	European Medicines Agency	July 2020
NYVEPRIA	Hospira Inc.	United States Food and Drug Administration	June 2020
NEPEXTO	Mylan NV	European Medicines Agency	May 2020

AMSPARITY	Pfizer Europe	European Medicines Agency	February 2020
AVSOLA	Amgen	United States Food and Drug Administration	December 2019
ABRILADA	Pfizer Inc.	United States Food and Drug Administration	November 2019
ZIEXTENZO	Sandoz	United States Food and Drug Administration	November 2019
HADLIMA	Samsung Bioepis	United States Food and Drug Administration	July 2019
RUXIENCE	Pfizer Inc.	United States Food and Drug Administration	July 2019
ZIRABEV	Pfizer Inc.	United States Food and Drug Administration	June 2019
KANJINTI	Amgen	United States Food and Drug Administration	June 2019
GRASUSTEK	USV Ltd.	European Medicines Agency	June 2019
ETICOVO	Samsung Bioepis	United States Food and Drug Administration	April 2019
IDACIO	Fresenius Kabi	European Medicines Agency	April 2019
KROMEYA	Fresenius Kabi	European Medicines Agency	April 2019
TRAZIMERA	Pfizer Inc.	United States Food and Drug Administration	March 2019
ONTRUZANT	Samsung Bioepis	United States Food and Drug Administration	January 2019
HERZUMA	Celltrion	United States Food and Drug Administration	December 2018
UDENYCA	Coherus	United States Food and Drug Administration	November 2018
HYRIMOZ	Sandoz	United States Food and Drug Administration	October 2018
FULPHILA	Mylan NV	United States Food and Drug Administration	June 2018
RETACRIT	Pfizer Hospira	United States Food and Drug Administration	May 2018
IXIFI	Pfizer Inc.	United States Food and Drug Administration	December 2017
OGIVRI	Mylan	United States Food and Drug Administration	December 2017
MVASI	Genentech	United States Food and Drug Administration	September 2017
TRUXIMA	Celltrion	European Medicines Agency	August 2017

CYLTEZO	Boehringer Ingelheim	United States Food and Drug Administration	April 2017
RENFLEXIS	Merck & Co. Inc.	United States Food and Drug Administration	April 2017
SOLYMBIC	Amgen	European Medicines Agency	March 2017
AMGEVITA	Amgen	European Medicines Agency	January 2017
TERROSA	Gedeon Richter	European Medicines Agency	November 2016
MOVYMIA	Stada	European Medicines Agency	November 2016
AMJEVITA	Amgen	United States Food and Drug Administration	September 2016
ERELZI	Sandoz	United States Food and Drug Administration	August 2016
THORINANE	Pharmathen S.A	European Medicines Agency	July 2016
INHIXA	Techdow Europe AB	European Medicines Agency	July 2016
FLIXABI	Samsung Bioepis	European Medicines Agency	May 2016
INFLECTRA	Celltrion	United States Food and Drug Administration	April 2016
BENEPALI	Samsung Bioepis	European Medicines Agency	January 2016
BASAGLAR	Eli Lilly	United States Food and Drug Administration	December 2015
ZARXIO	Sandoz	United States Food and Drug Administration	March 2015
ABASAGLAR	Eli Lilly	European Medicines Agency	September 2014
ACCOFIL	Accord	European Medicines Agency	July 2014
BEMFOLA	Finox Biotech	European Medicines Agency	March 2014
GRASTOFIL	Apobiologix	European Medicines Agency	October 2013
OVALEAP	Teva	European Medicines Agency	September 2013
REMSIMA	Celltrion	European Medicines Agency	September 2013
NIVESTIM	Hospital UK	European Medicines Agency	June 2010
ZARZIO	Sandoz	European Medicines Agency	February 2009
FILGRASTIM HEXAL	Hexal	European Medicines Agency	February 2009

FILGRASTIM RATIOPHARM	Ratiopharm	European Medicines Agency	September 2008
BIOGRASTIM	CT Arzneimittel	European Medicines Agency	September 2008
TEVAGRASTIM	Teva	European Medicines Agency	September 2008
RATIOGRASTIM	Ratiopharm	European Medicines Agency	September 2008
RETACRIT	Hospira UK	European Medicines Agency	December 2007
SILAPO	Stada	European Medicines Agency	December 2007
ABSEAMED	Medice	European Medicines Agency	August 2007
EPOETIN ALFA HEXAL	Hexal	European Medicines Agency	August 2007
BINOCRIT	Sandoz	European Medicines Agency	August 2007
OMNITROPE	Sandoz	European Medicines Agency	April 2006

Manufacturers are being motivated to promote biosimilars by the increase of their sales, such as Remicade. However, biosimilar acceptance comes with challenges, in particular linked to production, regulatory and marketing concerns. Such barriers require strategical planning, adequate connection between stakeholders of biosimilar industry, time and monetary investment to be overcome. Table 3 show some of the challenges that have been faced by the manufacturers when introducing biosimilars with probable solutions to the problem (Kabir et al., 2018).

Table 3: Recent challenges faced when introducing biosimilars and their potential solution (Kabir et al., 2018)

Challenges	**Solutions**
Hesitation in drug substitution	By promoting clinician and patient knowledge of biosimilars, provision of sufficient clinical data to raise assurance and better clinical acceptance can avoid the problem.

Complex manufacturing process	Approval of regulatory authorities that are related, in even minor variation in the production process and the investment in advanced production techniques as well as in outsourcing of biosimilar technology can overcome the challenge.
Regulatory complications and lack of clarity	Maintaining a liaison between regulatory authorities and connected stakeholder, allowing open platforms to dialogue between all parties can be a potential solution.
Intellectual property rights	The problem can be solved by designing strong unified and unitary patent litigation systems.
Reach of biosimilar manufacturers to patients	The challenge can be solved by encouraging the manufacturers to compare their product from other service offerings and deliver necessary evidence of cost effectiveness, quality, safety, etc.

Biosimilars tend to have matching amino acid sequence as their bio-originator brand (Zelenetz et al., 2011). In other words, biosimilars can be introduced as the ‘‘generic versions’’ of the bio-originator drugs. However, it is essential to mention that they are not truly ‘‘generics’’ when compared to small molecule drugs (Gravel, Naik, & Le Cotonnec, 2012). Even in the same batch of biologics manufactured, exists variety, and therefore, all biosimilars would not be exactly counterparts of the respective biologics. (Patel, King, & Feldman, 2015).

These biopharmaceutical products are large complex proteins produced by inserting a gene encoding for the protein of interest into a DNA vector and introducing the resulting recombinant DNA in a living organism or cell line for gene expression. These transfected cells are grown in suitable culture media to get the biological substance, followed by recovery, purification and packaging of the final product. The complex structure of a biopharmaceutical product and its post-translational modifications make the production of same protein virtually impossible, unlike a

generic drug for which the active ingredient can be accurately replicated in such a way that the generic drug is similar in chemical structure to the reference product. Thus, replicas of biopharmaceutical products are typically similar to their reference products, but not exactly the same. (Cohen & Kay, 2017).

Biosimilars have been defined by different regulatory bodies. According to the United States Food and Drug Administration (US FDA), biosimilar products are referred as the biological products that are authorized on the basis that the product is very analogous to a previously authorized biological product, known as a reference product, where there are hardly any clinical differences among the reference and the biologic product in terms of potency, purity and safety. Hence suggesting, the products have no new indications or clinical target, route of administration or regimen other than its originator biologics. After having gone through meticulous non-clinical and clinical comparative evaluations, immunogenicity, analytical evaluations in a defined and stringent regulatory process, these products are manufactured. Several regulatory bodies like the United States Food & Drug Administration (US FDA), Therapeutic Goods Administration (TGA) of Australia, the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, the Biologics and Genetic Therapies Directorate (BGTD) of Canada, the World Health Organization (WHO), and the European Medicines Agency (EMA) set definition of biosimilars that have been highlighted in Table 4 (Kabir, Moreino, & Siam, 2019b).

Table 4: Biosimilars definition set by several regulatory authorities (Kabir et al., 2019b).

Regulatory Guideline	**DEFINITION**
United States Food & Drug Administration (US FDA)	A biologic product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components and

	that there are no clinically meaningful differences between the biologic product and the reference product in terms of safety, purity and potency of the product
Therapeutic Goods Administration (TGA)	A version of an already registered biologic medicine that has a demonstrable similarity in physicochemical, biologic, and immunological characteristics, efficacy, and safety, based on comprehensive comparability studies
Pharmaceuticals and Medical Devices Agency (PMDA)	A biotechnological drug product developed by a different company, which is comparable with an approved biotechnology-derived product
Biologics and Genetic Therapies Directorate (BGTD)	A biologic drug that enters the market subsequent to a version previously authorized in Canada, with demonstrated similarity to a reference product
World Health Organization (WHO)	A biotherapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product
European Medicines Agency (EMA)	A biologic medicinal product similar to another biologic medicine that has already been authorized for use

Biologic targets are receptors or specific proteins involved in the pathogenesis of a disease (Dos Reis, Teixo, Mendes, & Cruz, 2016). Biologics incorporate a large diversity of molecules in structural complexity and size (molecular mass fluctuate from 5 kDa for insulin to greater than 150 kDa for monoclonal antibodies). Examples of such molecules include monoclonal antibodies, interleukins, growth factors, hormones, etc. The production process for biologics also is much more complex in comparison to chemically synthesized drug molecules resulting in higher production cost (Ingrasciotta et al., 2018). In Table 5, the differences between biologic and biosimilar have been pointed out with respect to some parameters (Khanna Sharma, 2017).

Table 5: Difference between Biologic and Biosimilar (Khanna Sharma, 2017).

	Biologic	**Biosimilar**

Definition	A therapeutic serum, vaccine, blood, blood component or derivative, toxin, antitoxin, allergenic product, virus, protein (except any synthetic polypeptide), or arsphenamine or derivative of arsphenamine (or any other organic arsenic compound having valence of three), or analogous component, contributing to treating disease or condition of human beings are mentioned as the innovator biologic, pioneer or reference.	Biologic product is very analogous to reference product not withstanding small dissimilarities in clinically inactive components and there is hardly any clinical differences between the reference and biological product in terms of potency, purity and safety.
Properties	Extracted from living sources like 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 extraction or purification processes, protein source and manufacturing processes.
Approval process	Submitted through the BLA process Requirements: • Applicant information: Includes name and addresses of manufacturing facilities • Manufacturing/product information: Raw material/source material; control and process of manufacturing; formulation; facility information; contamination/cross-contamination information; environment assessment or categorical exclusion • Pre-clinical studies: Safety, efficacy, and use • Labelling: Use, efficacy and safety • Clinical studies: efficacy, use and safety	2012 FDA Draft Guidance allows a step-by-step process to display biosimilarity, submitted through an abbreviated BLA. Requirements (unless FDA deems unnecessary): **Structural analyses:** Determining the structural features of the post-translational modification and or other potential variants of the protein **Functional assays:** Evaluate the pharmacologic activity of the protein (e.g., potency and MOA) **Animal studies:** Comprise of pharmacokinetics and pharmacodynamics measures, immunogenicity and toxicity **Clinical studies:** Clinical immunogenicity assessment, human pharmacology data, and clinical safety and efficacy data acquired to demonstrate potency, safety and purity for the conditions(s) the reference product is licensed to be used for.

Safety data	Generally, need to have post marketing safety monitoring that consist of understanding, assessment, detection and prevention of adverse effects after the release of biologic into the market	In the post marketing phase, biosimilars should include surveillance system to detect and record potential rare adverse effects and immunogenicity when seeking approval

A biologic product that is manufactured from a living system, are different to the mechanism or chemistry of conventional chemical synthesis. The plotting of complicated step-by-step processes that utilizes mammalian and microbial cell cultures is necessary for manufacturing biologics and biosimilars to mass-produce therapeutic proteins (Vulto & Jaquez, 2017). One long existing ideology for the biologic production process is "The process is the product", which suggests that the safety and efficacy outline of the product can be affected dramatically if any variation in the production process randomly occurs. Both analytical and process development methods are merged in the existing biologic manufacturing facilities. This enables the scale-up process to be assessed at the same time confirming that the necessary yield of a quality product is maintained. The regulatory agency and business panel progress to sending feedback as soon as the biologic product display acceptable safety and efficacy. Finally, the product is ready to get a license and approval from authorities. The step-by-step preparation process of a typical biologic is shown in Figure 1 (Kabir et al., 2019b).

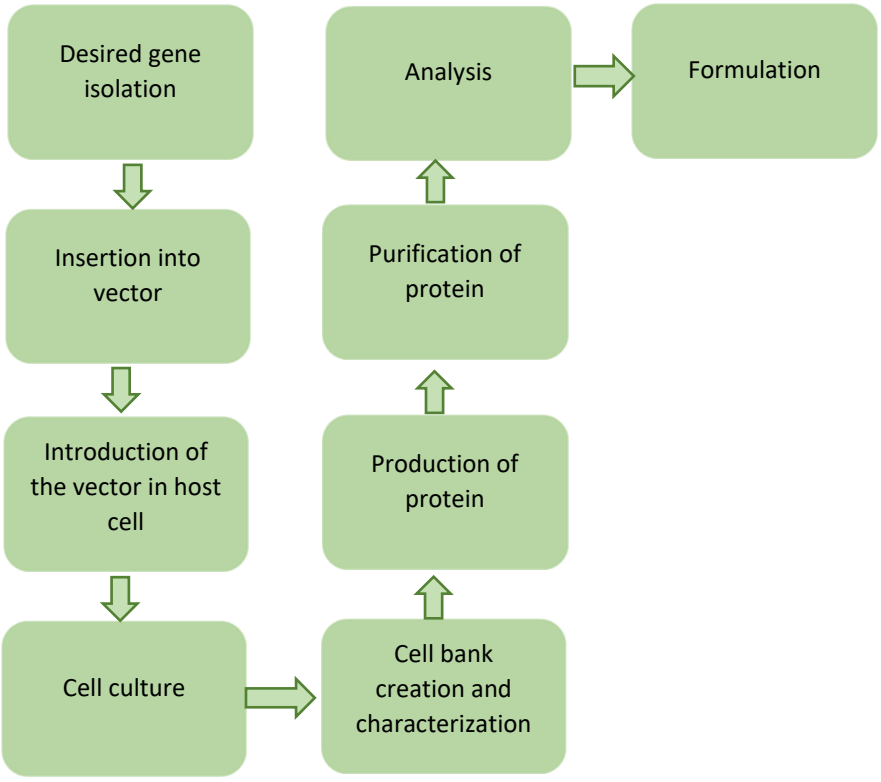

Figure 1: Flowchart for the conventional preparation process of biologics (Kabir et al., 2019b)

The concept of a separate biosimilar approval system particularly in third world nations, remains unfamiliar or ambiguous to many remaining countries. The process of adapting to the new systems is quite tedious for the third world nations. In certain countries, the affordability of healthcare products is narrow which indicates that these countries are in need of introducing cost-effective products. In addition, the necessity to introduce a pharmacovigilance system to regulate the safety profiles of already authorized biosimilars for therapeutic purpose has made the whole concept more extensive for developing countries. Table 6 gives a list of the biosimilars that were approved by US FDA and EMA till 2019 (Kabir et al., 2019b).

Table 6: List of biosimilars approved by United Stated Food & Drug Administration and European Medicines Agency (Kabir et al., 2019b).

BIOSIMILAR PRODUCT	CLASS OF BIOLOGICAL MEDICINE	INN	NN	REFERENCE PRODUCT
ZARZIO ZARXIO	Granulocyte Colony Stimulating Factor (G-CSF)	Filgrastim	X filgrastim-sndz	Nepogen
REMSIMA INFLECTRA	Tumour Necrosis Factor (TNF) alpha blocker	Infliximab	X infliximab-dyyb	Remicade
ERELZI	Tumour Necrosis Factor (TNF) Žalpha blocker	Etanercept	etanercept-szzs	Enbrel
AMGEVITA AMJEVITA	Tumour Necrosis Factor (TNF) alpha blocker	Adalimumab	X adalimumab-atto	Humira
RENFLEXIS FLIXABI	Tumour Necrosis Factor (TNF) alpha blocker	Infliximab	infliximab-abda X	Remicade
CYLTEZO	Tumour Necrosis Factor (TNF) alpha blocker	Adalimumab	adalimumab-adbm	Humira
MVASI	Monoclonal Antibody (Mab)	Bevacizumab	bevacizumab-awwb	Avastin
OMNITROPE	Growth Hormone (GH)	Somatotropin		Genotropin
BINOCRIT	Erythropoietin (EPO)	Epoetin alpha		Eprex
EPOETIN ALFA HEXAL	Erythropoietin (EPO)	Epoetin alpha		Eprex
ABSEAMED	Erythropoietin (EPO)	Epoetin alpha		Eprex
SILAPO	Erythropoietin (EPO)	Epoetin alpha		Eprex
RETACRIT	Erythropoietin (EPO)	Epoetin alpha		Eprex
RETIOGRASTIM	Granulocyte Colony Stimulating Factor (G-CSF)	Filgrastim		Neupogen
TEVAGRASTIM	Granulocyte Colony Stimulating Factor (G-CSF)	Filgrastim		Neupogen
BIOGRASTIM	Granulocyte Colony Stimulating Factor (G-CSF)	Filgrastim		Neupogen

FILGRASTIM RATIOPHARM	Granulocyte Colony Stimulating Factor (G-CSF)	Filgrastim		Neupogen
FILGRASTIM HEXAL	Granulocyte Colony Stimulating Factor (G-CSF)	Filgrastim		Neupogen
ACCOFIL	Granulocyte Colony Stimulating Factor (G-CSF)	Filgrastim		Neupogen
NIVESTIM	Granulocyte Colony Stimulating Factor (G-CSF)	Filgrastim		Neupogen
OVALEAP	Follicle Stimulating Hormone (FSH)	Follitropin alpha		Gonal-f
GRASTOFIL	Granulocyte Colony Stimulating Factor (G-CSF)	Filgrastim		Neupogen
BEMFOLA	Follicle Stimulating Hormone (FSH)	Follitropin alpha		Gonal-f
ABASAGLAR BASAGLAR	Human Insulin Hormone	Insulin glargine		Lantus
BENEPALI	Tumour Necrosis Factor (TNF) alpha blocker	Etanercept		Enbrel
INHIXA	Low molecular weight heparin (anticoagulant)	Enoxaparin Sodium		Clexane
THORINANE	Low molecular weight heparin (anticoagulant)	Enoxaparin Sodium		Clexane
SOLYMBIC	Tumour Necrosis Factor (TNF) alpha blocker	Adalimumab		Humira
TRUXIMA	Monoclonal Antibody (MAb)	Rituximab		MabThera
MOVYMIA	Para-Thyroid Hormone (PTH)	Teriparatide		Forsteo
TERROSA	Para-Thyroid Hormone (PTH)	Teriparatide		Forsteo
OGIVRI	Monoclonal Antibody (MAb)	Trastuzumab	trastuzumab-dkst	Herceptin
IXIFI	Tumor Necrosis Factor (TNF) blocker	Infliximab	infliximab-gbtx	Remicade
FULPHILA	Leukocyte Growth Factor	Pegfilgrastim	pegfilgrastim-imdb	Neulasta
NIVESTYM	Granulocyte Colony Stimulating Hormone (G-CSF)	Filgrastim	filgrastim-aafi	Neupogen
HYRIMOZ	Monoclonal Antibody (MAb)	Adalimumab	adalimumab-adaz	Humira
UDENYCA	Leukocyte Growth Factor	Pegfilgrastim	Pegfilgrastim-cbqv	Neulasta
HERZUMA	Monoclonal Antibody (MAb)	Trastuzumab	trastuzumab-pkrb	Herceptin
ONTRUZANT	Monoclonal Antibody (MAb	Trastuzumab	trastuzumab-dttb	Herceptin
TRAZIMERA	Monoclonal Antibody (MAb	Trastuzumab	trastuzumab-qyyq	Herceptin
ETICOVO	Tumor Necrosis Factor (TNF) alpha blocker	Etanercept	etanercept-ykro	Enbrel

3.1 Biologics and biosimilars in the treatment of rheumatoid arthritis

Introduction of biologics has brought revolution in the treatment algorithm of patients diagnosed with rheumatic and musculoskeletal diseases (RMDs), including long-term autoimmune inflammatory diseases like juvenile idiopathic arthritis, ankylosing spondylitis (AS), psoriasis arthritis (PsA) and rheumatoid arthritis. Having to diagnose with such rheumatic and musculoskeletal diseases increase the economic burden of the patient and lowers the quality of life (Strand et al., 2012). Biologics seem to be a promising treatment option in the remission of such disorders or at minimum in reducing disease activity in every patient (Smolen et al., 2014). However, access to biologics is limited by variation in national health care system, rising burden of chronic diseases, and worldwide crisis of rheumatologists amid cost constraints. Despite the prominent therapeutic outcome of biologics, the need of such treatment for rheumatic disease remains unmet for most population around the globe (Mysler et al., 2016).

The selection of a biologic agent for a particular patient depend on some key factors, such as the candidate drug's safety or adverse event profile, prevalence of comorbidities, route and mode of administration and frequency of dosing (Gartlehner, Hansen, Jonas, Thieda, & Lohr, 2006). For this reason, the guidelines and recommendations stringently considers the use of any of these biologic agents, in particular, anti-TNF agents prior to considering the key factors related to the candidate drug and patient's medical history (Nikiphorou et al., 2015). Although these agents are considered to be extremely useful in the treatment of rheumatic diseases and perhaps cost-efficient for patients who do not react appropriately to conventional therapy, these agents are not always used as the first-line treatment in patients. It is also possible that these agents could exhibit obstacles in their application. This partially reflects the regulatory constraints and high price issues related to such agents (Gulácsi et al., 2015). Furthermore, a large number of patients undergoing

biologic treatment lose responsiveness or stop responding to initial treatment strategy, and greater than 1 out of 10 patients stops the treatment as they experience side effects (Vincent et al., 2013). To improve the treatment strategy and ultimately improve the therapeutic outcome for patients with rheumatic diseases, a broad range of alternative biologic agents should be accessible to most patients. A novel strategy to attain this goal is to introduce biosimilars that are very highly comparable to the reference product (Schulze-Koops & Skapenko, 2017).

Patients with rheumatoid arthritis and other inflammatory diseases have however started to show great response to biologic agents such as tocilizumab, secukinumab, rituximab, infliximab, golimumab, etanercept, certolizumab pegol, anakinra, adalimumab and abatacept (Scheinberg & Azevedo, 2014). These therapies target key modulators of inflammatory response, such as cell surface receptors, T-cells or B-cells (lymphocytes), and proinflammatory cytokines (Quan, Thiele, Tian, & Wang, 2008). Regardless of its target specific activity, the patient outcomes are greatly influenced by accessibility and availability of candidate drug to the patients, and clinical efficacy of these biologic therapies (Desai et al., 2014). The disease outcomes and patient accessibility problems can be solved, if the regulatory agencies can implement stringent laws and guidelines for the development and approval of biosimilars. Along with few regulatory agencies of several countries, US FDA and EMA have approved the first biosimilars for the treatment of inflammatory diseases in 2016 (Table 7). In future, many more biosimilars that can be used for inflammatory diseases are expected to emerge in the market as the patents and data protection period of drugs expire (Markenson, Alvarez, Jacobs, & Kirchhoff, 2017).

Table 7: Approved biosimilars for inflammatory diseases in 2016 (Markenson et al., 2017)

BIOLOGIC	BIOSIMILAR BRAND NAME (MANUFACTURER)	ORIGINATOR BRAND NAME (MANUFACTURER)
ETANERCEPT	Flixabi (Samsung Bioepis, Chertsey, UK) Benepali (Samsung Bioepis, Chertsey, UK)	Enbrel (Amgen Inc., Thousand Oaks, CA, USA, and Pfizer Inc, Sandwich, UK [EU])
INFLIXIMAB	Remsima (Celltrion Healthcare Hungary Kft, Budapest, Hungary)	Remicade (Janssen Biotech, Horsham, PA, USA, and Janssen Biologics B.V., Leiden, the Netherlands)
NOTE: REMSIMA IS ALSO MARKETED AS INFLECTRA (HOSPIRA, MAIDENHEAD, UK) IN THE EU.		

In the United States, two biosimilars of the reference product infliximab were approved by FDA for rheumatoid arthritis treatment (Mahajan & Mikuls, 2018). Among these two biosimilars, the first one to be approved was inflectra, also known as CT-P13, in 2016. This biosimilar was approved on the basis of extremely comparable results between inflectra and infliximab from two 52-week, multinational, randomized double-blind, parallel group studies (Yoo et al., 2013). Later to demonstrate the effect on safety, immunogenicity and efficacy from switching to inflectra in patients who were already being treated with the reference product and to assess the safety and efficacy of inflectra from its long-term use (more than 2 years), an open-label extension study of 102 weeks was performed. No significant changes in safety, immunogenicity and efficacy were found in patients switching to inflectra during that study. Moreover, consistent efficacy and tolerability to this biosimilar were observed in patients with the passage of time (Yoo et al., 2017). One of the most recent infliximab biosimilar to be authorized in the United States is Renflexis or SB2. The other biosimilar of infliximab is renflexis, also called SB2 which was approved in 2017 based on similar experimental design and purpose as performed for inflectra (Choe et al., 2017). SB4, HD203 AND GD2015 are the biosimilars of etanercept and has met prespecified biosimilarity criteria demonstrated through a robust trial evidence and are considered non-inferior

to the reference product for rheumatoid arthritis. The continuous development of etanercept and authorization of other biosimilar drugs offer potential accessibility and treatment opportunities for RA worldwide (Chadwick, Zhao, Mysler, & Moots, 2018).

3.2 Guidelines

The decision of when biologics can be prescribed for patients with rheumatic and musculoskeletal diseases (RMDs) is made by the physicians by following certain guidelines. Usually, biologics are not considered as first-line treatment. The anti-TNF bio-originator products infliximab and etanercept and their biosimilars are approved to be used only in patients who did not respond well or has shown intolerance to conventional treatments. However, as an exception it can be referred for first-line use in patients with severe active and progressive rheumatoid arthritis. A similar treatment algorithm for rheumatoid arthritis using bDMARDs has also been recommended in the current European guidelines, which were updated in 2016. Moreover, if alternative strategies like use of combination csDMARDs or treat-to-target approach with combination csDMARDs in RA patients on whom first-line therapy did not work fails, or if the patients experience unacceptable toxicity within the 6 months of the initial treatment, a bDMARD or Jak inhibitor should be used as indicated for Phase I and Phase II in Figure 2. If the first trial of biologic therapy fails, Jak inhibitor or a substitute bDMARD should be considered. Despite following the current rheumatic disease treatment algorithm, a significant number of patients treated with bDMARDs are anticipated to encounter intolerable side effects or be unresponsive to treatment with bDMARDs leading to withdrawal of the biologics (Schulze-Koops & Skapenko, 2017).

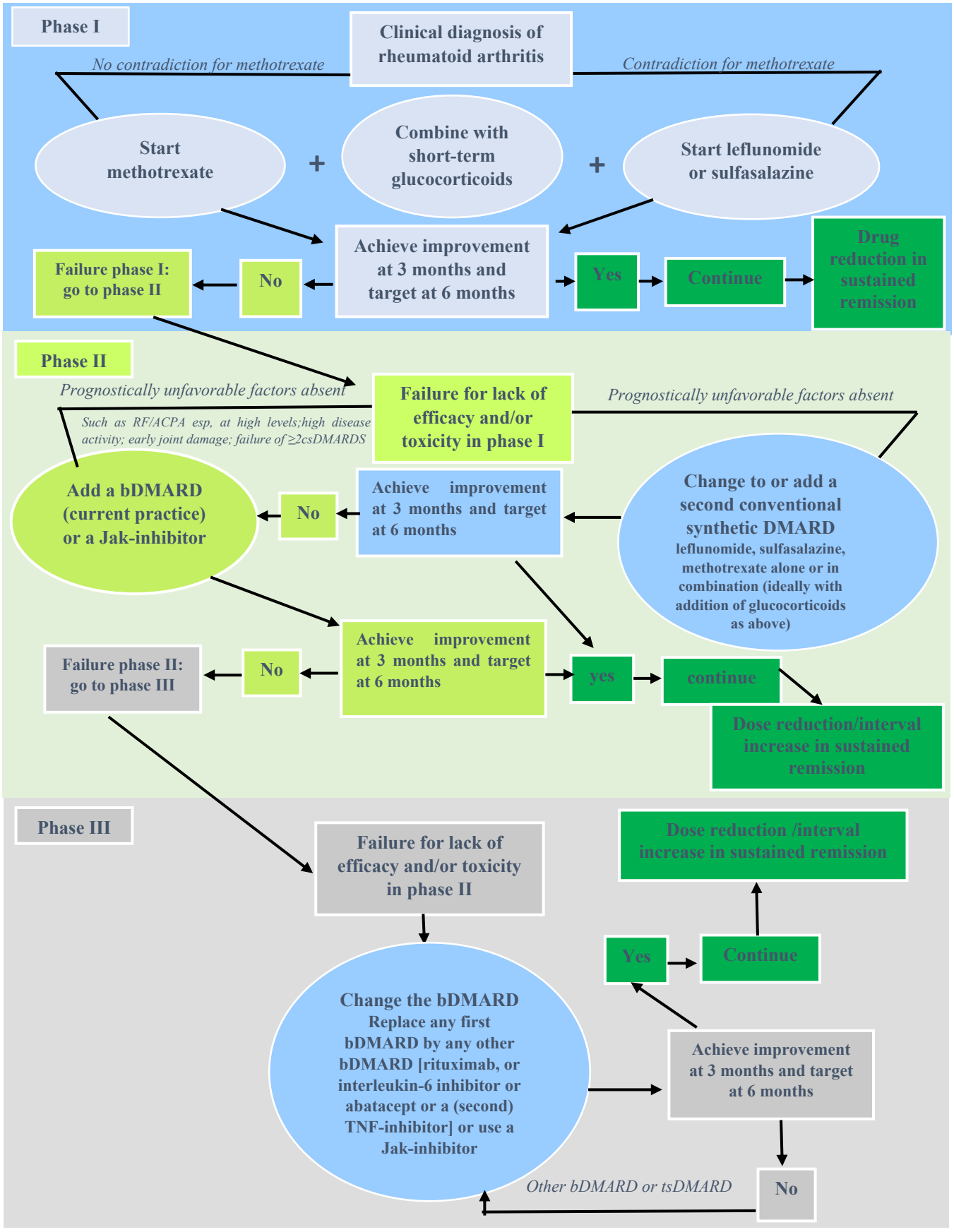

Figure 2: Algorithm based on the 2016 EULAR recommendations on rheumatoid arthritis management (Smolen et al., 2017)

The issue of efficacy and safety associated with the use of intended copies in patients with rheumatic and musculoskeletal diseases (RMDs) and other conditions has been reported in Asia and Latin America. 10% of patients treated with etanar, which is an intended copy of etanercept that is marketed in Columbia, reported side effects in a non-comparative observational study with 110 patients suffering from RA. Heart failure, nausea, dizziness, pneumonia and asthma were the side effects along with lack of efficacy which caused the etanar therapy to be ceased. On the contrary, infections and reactions in the injection site were the side effects of the originator Etanercept (Mysler et al., 2016). At least one treatment related adverse event was observed in a second observational report of patients with rheumatic diseases from four hospitals in Mexico and Columbia where 101 out of 205 patients were treated with kikuzubam, an intended copy of rituximab and 10 out of 14 patients were treated with etanar or infinitam, both of which are intended copies of etanercept. Grade 3 and 4 adverse effects were reported by 14.3% of patients who receive these intended copies. Other safety issues were reported in Chile with recombinant insulin and Thailand with epoetin alpha and beta. It is hard to observe if any of the adverse effects missed detection due to the absence of rigorous pharmacovigilance for these drugs, including periodic safety update reports (Mysler et al., 2016).

Chapter 4 Drug Repurposing

Drug repositioning methods have been enhanced with the development of computer sciences, and research has also been accelerated. Data mining and molecular modeling approaches are some of the application of information technologies that help in proposing many effective drug repurposing methods. To inspect the nature of binding of a drug to a target and the amount of energy present between them, molecular docking methods are incorporated (Yuniwati et al., 2018). To cope up with the evolving technologies, several software application is launched to fulfil the needs and master the techniques (Pagadala, Syed, & Tuszynski, 2017). Data-mining techniques help to decipher the relationships between the targets and the drugs (Munir, Elahi, & Masood, 2018). As a result, the acquired information is used to identify drugs that can target a specific biological site. The techniques used to discover the drugs can be categorized into three groups. First of all, raw data of different sources are mined for extracting information using efficient algorithms, categorized as text mining. Secondly, machines generate a model, such as a decision tree, support vector machine, or an artificial neural network, etc. that can be utilized to predict drug-target interaction, categorized as the machine-learning. Finally, protein-protein interactions, drug-target interactions, metabolic pathways are studied for acquiring novel data and discovering new therapeutic properties of drugs, categorized as the network-based approaches. To discover novel therapeutic benefits of conventional drugs by forecasting drug-target interactions, databases like MalaCards and DisGeNET can be used, where information associated with the genes and diseases is available (Masoudi-Sobhanzadeh, Omidi, Amanlou, & Masoudi-Nejad, 2020).

The drug discovery process begins from discovering a molecule of interest to implementing the molecule into the market. Being a tedious process of around 15 years, repurposing became widely successful as a strategy to resolve this tedious process and accelerate the drug development process

to a great extent. The present repurposing techniques includes methods such as *in silico* method to identify the good binding target and statistical screening method for the authorized drug (Kumar et al., 2019). Drug repositioning, reprofiling, re-tasking or more commonly termed as drug repurposing is a strategy that discovers new therapeutic indications of investigational or approved drugs (Ashburn & Thor, 2004). This strategy is advantageous over developing a novel drug for a particular indication. The most important aspect of the strategy is that it provides lower risk of failure as the repurposed drug appear to be already safe enough in preclinical models if early-stage trials is passed. Therefore, it is less likely that the drug will fail in the process of efficacy trials from the safety point of view. Since most of the safety assessment test, preclinical tests and the development of formulations have already been approved, drug repurposing technique creates a window to shorten the drug development time frame. Also, the investment required for this strategy is estimated to be low, but it can change depending on the process of development an on the stage of the candidate that is being repurposed (Breckenridge & Jacob, 2018). For a repurposed drug, preclinical, phase I and phase II clinical trial costs will cause sufficient saving, but the phase III and regulatory costs will be similar to a new drug of the same indication. The mentioned advantages in repurposed drug development process promotes minimum risk and a better return on investment with a lower average and holds the potential to offer lower average associated costs after failures have been accounted for (the estimated cost of introducing a repurposed drug to the market is around 300 million US dollars on average, compared with an estimated ~2-3 billion dollars for a new chemical entity) (Nosengo, 2016). New pathways and targets can be further discovered and explored as the repurposed drugs may reveal the way (Pushpakom et al., 2018). The process for approval of a new drug is costly and can take around 10-15 years. During this

prolonged discovery process, drug repurposing (repositioning) can be used as an alternative way to shorten the time required to develop a drug.

To conduct virtual screening campaigns based on structure similar to when it was first developed and to aid in rationalizing the activity of ligands in contrast to a target of interest, molecular docking can be considered. In addition to these applications, identification of targets and their ligands having reasonable complementarity (target fishing and profiling) is possible, some of which can possibly be behind unexpected adverse drug reactions (off-target prediction). Also, docking is being used for discovering new uses for chemical compounds readily having optimized safety profiles (drug repositioning) and for the identification of ligands that binds to a range of selected target of interest simultaneously (polypharmacology) as shown in Figure 3 (Anighoro, Bajorath, & Rastelli, 2014).

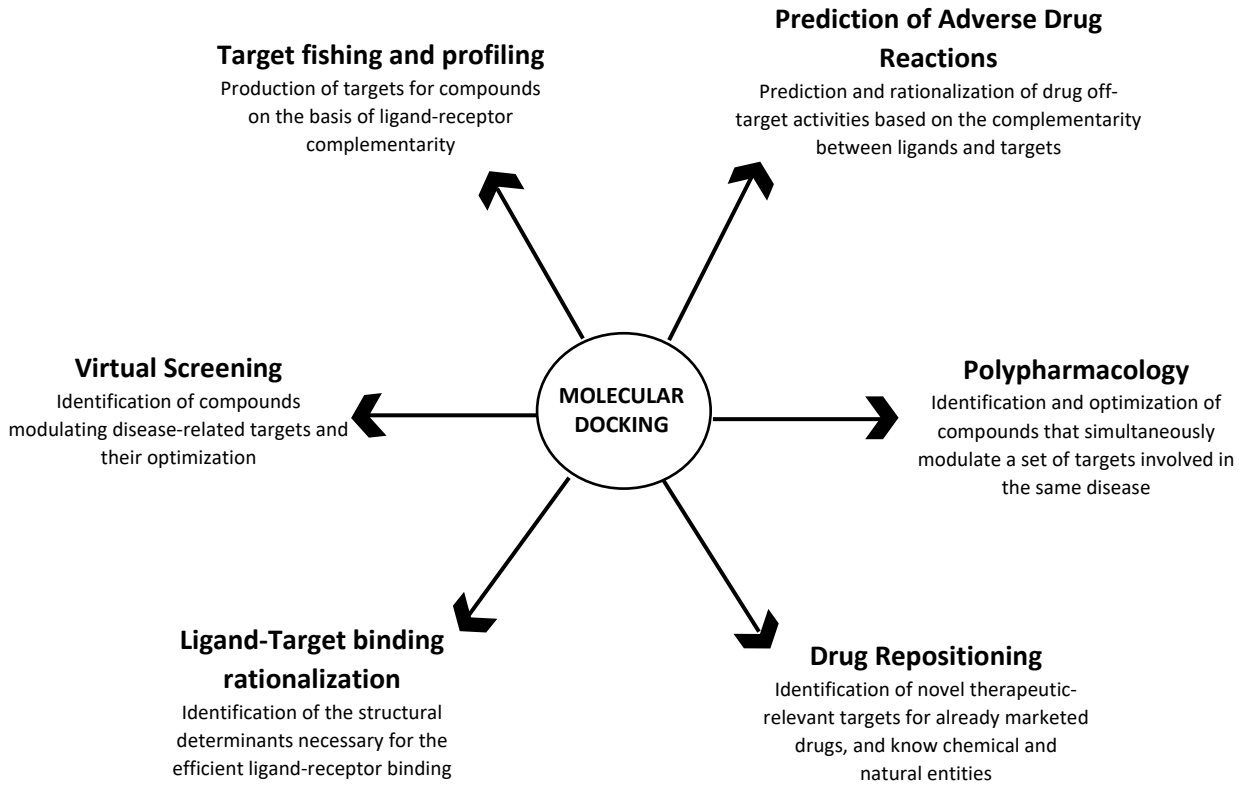

Figure 3: Molecular docking applications in current drug discovery and development (Pinzi & Rastelli, 2019)

In the field of drug discovery and development to better understand the interaction between chemical compounds and their molecular targets, docking has proven to be a significant technique in drug repurposing since its first introduction in the mid-1970s. Since the emergence of this technique, the number of studies reporting the employment of molecular docking to identify structural determinants required for efficient ligand-receptor binding and the development of more accurate docking technique have greatly increased (Pinzi & Rastelli, 2019). In the 1980s, while performing studies using the docking technique, a computational method to analyze geometrically feasible ligand-receptor alignments for the known structures of prealbumin/thyroxin and metmyoglobin/heme-myoglobin was developed (Kuntz, Blaney, Oatley, Langridge, & Ferrin, 1982). However, this study was not the first one to describe docking for predicting possible conformations of molecular complexes (Levinthal, Wodak, Kahn, & Dadivanian, 1975). The use of simplified function consisting 'hard sphere repulsion' and 'hydrogen bonding' in order to explain the interaction between protein-ligand interactions reported for the first time, strongly differed from previous studies. Moreover, several studies were done where receptors were considered as a solid rigid body, whose binding site is constituted by 'pockets'. It was possible to predict structures that are close to those of X-ray complexes by using the method in this study. Apart from the prediction of structures, it was able to discover protein conformations that can be used to refine energy and sooner or later develop new ligands. Due to that achievement, molecular docking went through remarkable advancement, for example, employing flexible algorithms in the calculations (Pinzi & Rastelli, 2019).

Chapter 5 Rheumatoid Arthritis

A popular systemic inflammatory autoimmune disease, rheumatoid arthritis (RA), is distinguished by sore, swollen joints which severely affect bodily function and deteriorate the quality of life. In clinical practice, the signs of musculoskeletal discomfort, swelling, and constraint are normal, so familiarity with the diagnosis and treatment of RA is necessary. RA patients are more susceptible to severe infection, osteoporosis, respiratory diseases, cardiovascular diseases, mortality and cancer, compared to a healthy individual. Early diagnosis, intensive therapy, and increased treatment opportunities for DMARDs have greatly strengthened the long-term prognosis and the management of RA in recent years (Sparks, 2019). In this disease, the joints are often impaired and tendons or ligaments are weakened (Lee, Kim, Cho, & Lee, 2017). All this damage to the joints, normally very painful for a patient, produces deformities and bone erosion. Most common RA signs include tender, swollen and warm joints followed by greater than thirty minutes of morning stiffness of the affected joints, fever, fatigue, under-skin rheumatoid nodules and weight loss. The onset of this disease, with remission and exacerbation, typically occurs from the age of 35 to 60 years and young children below the age of 16 can also be affected, referred to as juvenile RA (JRA), which is same as RA, omitting that no rheumatoid factor is present (Bullock et al., 2019).

5.1 Disease pathway

Due to the increased emigration and adherence of activated immune and nonimmune cells induced by increased release of different chemokines and adhesion proteins the normal single membrane synovium becomes hyperplastic in synovial joints. A significant rise in the release of proinflammatory cytokines including tumor necrosis factor-α (TNF-α), IL-1ß, IL-6, IL-7, IL-8, IL-12/IL-23. IL-15, IL-17, IL-18, IL-32, and interferon-γ (INF- γ), as well as growth factors, for

example, fibroblast growth factor-2 (FGF-2) and vascular endothelial growth factor (VEGF) are highly responsible for the disease progression, thereby, leading to impaired articular cartilage and erosion of subchondral bone, eventually followed by synovial joint failure (Fox, Gizinski, Morgan, & Lundy, 2010). In response to these factors, repression of cartilage-derived extracellular matrix production, high recurrency of apoptotic chondrocytes, 'apoptosis resistance' of synovial tissue and elevated level of matrix metalloproteinase (MMP) gene expression as well as the class of enzymes known as a disintegrin and metalloproteinase (ADAM) gene expression are the changes that takes place in RA synovial joints, which are considered as the critical components of the RA development process (Malemud, 2018). A class of molecules known as Janus kinase/ signal transducers and transcription activators (JAK/STATs) are linked with a key pathway by which several cytokines operate and integrate and are popularly recognized for playing a major part in the pathogenesis of RA and several other immune mediated diseases (Fragoulis, Mcinnes, & Siebert, 2019). The JAK/STAT pathway is an evolutionary preserved pathway that mediates the influence of several molecules such as interferons, interleukins, colony-stimulating factors, growth factors, hormones resembling cytokines, to bring about responses by binding with cytokine receptors of type I and type II. Many interleukins, hormones such as growth hormone, and colony-stimulating factors use type I cytokine receptors, in contrast, interferons and cytokines such as interleukin-10, interleukin-19, interleukin-20, interleukin-22 and interleukin-26 bind with type II cytokine receptors (O'Shea, Kontzias, Yamaoka, Tanaka, & Laurence, 2013). These receptors are made up of different subunits and every single one is associated with a Janus kinase molecule. When ligation occurs between the effector protein and its receptor, the receptor is oligomerized that leads to the activation of the relevant Janus kinase. Later, the Janus kinase is auto phosphorylated and it pass on a phosphate to a tyrosine residue in the receptor's subunit. Phosphate

transfer ultimately creates a docking site for a STAT molecule in the receptor and the STAT molecule is phosphorylated by the Janus kinase. In due course, STATs are dimerized and it is translocated from the cytosol to the nucleus that functions in regulating gene expression (Baker & Isaacs, 2018).

5.2 Etiology

Joint swelling in rheumatoid arthritis indicates inflammation of the synovial membrane due to immune activation and is characterized by leukocyte intrusion into the synovial cavity that is usually sparsely inhabited. In rheumatoid arthritis, the cellular content of synovitis consists of innate immune cells (for example, innate lymphoid cells, monocytes, dendritic cells and mast cells) and adaptive immune cells (for example, plasmablasts, plasma cells, B cells, T-helper-1 and T-helper-17 cells). Articular destruction is promoted by synovial fibroblasts that exhibits an aggressive inflammatory, matrix regulatory and invasive phenotype, and trigger chondrocyte catabolism and synovial osteoclastogenesis. Data from ultrasound-guided small joint biopsies and comprehensive molecular (particularly transcriptomic) studies indicate that there could be lymphocytic-dominant, myeloid-dominant and fibroid-dominant synovial subtypes that may be targeted for therapeutic intervention (Smolen, Aletaha, & McInnes, 2016).

The development of RA is guided by several hereditary and environmental factors. A comprehensive study related to these factors has contributed significantly in the advent of the framework of RA development and in particular, seropositive RA development, where there is usually a phase with circulating autoantibody elevations that can sustain for several years before the first occurrence of inflammatory arthritis (Deane & El-Gabalawy, 2014). This duration can be called as ‘Preclinical RA’, and its existence has raised the topic that a portion of hereditary and environmental factors that regulate RA are likely acting years prior to the first emergence of

inflammatory arthritis (IA). Although the disease progression mechanism may not be the same in all population, as few research detected limited percentage of patients with IA prior to the presence of circulating autoantibodies (Barra, Pope, Bessette, Haraoui, & Bykerk, 2011). There is a preclinical stage for most of the cases of seropositive RA which are practically detected by the existence of circulating rheumatoid arthritis-related autoantibodies including rheumatoid factor and anti-citrullinated protein antibodies (ACPAs), as well as other autoantibodies such as carbamylated protein antibodies (Shi et al., 2014). To a great extent, the emphasis of perceiving the hereditary, and environmental factors that plays a key role in the progression of rheumatoid arthritis, particularly in preclinical RA has increased due to several pharmacologic prevention trials. Also, the above-mentioned factors may be considered for anticipating models for rheumatoid arthritis in future, as well as to identify targets for prevention (Deane et al., 2017).

5.3 Symptoms

Patients with joint problems or with a family history of inflammatory arthritis, inflammatory bowel disease or psoriasis, are more likely to be diagnosed with IA. The patients with inflammatory arthritis experience pain, swelling, stiffness, heat and tenderness on certain joint areas. Symptoms may be severe and can either develop over a period of days or weeks or can also progress very gradually, without noticeable basic swelling of the joint (arthralgia). Systemic attributes like lethargy are predominant. Further indicators of IA include a rapid onset of disability and acute pain in the joints which increases rapidly and progressively (Ledingham, Snowden, & Ide, 2017).

5.4 Diagnosis

Modern technologies including transcriptomics, proteomics, metabolomics, genomics and epigenomics have surfaced as an efficient appliance that detect molecular biomarkers for prognosis, diagnosis and treatment of rheumatoid arthritis over the last ten years. These techniques

permit large-scale analyses to detect a variety of promising biomarkers of the disease in the synovial fluid, sera or in other tissues. For example, using proteomics approaches, detection of five serum proteins have been done which can be used as applicant biomarkers for early diagnosis of rheumatoid arthritis. Apart from these serological biomarkers, imaging techniques are also considered effective in identifying subclinical synovitis and radiographically non-detectable bone erosions. Examples of such imaging techniques include ultrasound and magnetic resonance imaging. These approaches facilitate early diagnosis of RA, particularly in sero-negative patients. In Table 8, the biomarkers used for diagnosing rheumatoid arthritis have been included. These biomarkers may not be found in all RA patients, in spite of the clinical utility of these biomarkers. New biomarkers need to be identified, especially in sero-negative patients, for diagnosis of early rheumatoid arthritis in a better way. Researchers have recently developed a novel approach for the detection of trace sulfated immunoglobulin G N-glycans as biomarkers for both seropositive and sero-negative RA (Zhao & Li, 2018).

Table 8: Biomarkers used for the diagnosis of rheumatoid arthritis (RA) (Zhao & Li, 2018).

Biomarkers	**Features**	**Ligand specificity (%)**	**Sensitivity of low-abundance acidic N-glycans and glycoproteins (%)**
RF	Related to disease activity	50-95	50-70
Anti-CCP	Related to erosive disease	95	60-70
ACF	Predictor of radiographic progression	92.6	55.8
Anti-cit-HPV47	Related to disease activity and radiographic progression	92.3	41.2
Anti-CEP1	Biomarker for rheumatoid arthritis-associated Interstitial lung disease (ILD) and erosive disease	98	44

Anti-MCV	Related to bone erosion	94.2	68.6
Anti-cTNC5	Detected in 18% of pre-rheumatoid arthritis	98	57-51
Anti-CarP	Related to radiographic progression	89	44
Anti-PAD4	Related to radiographic progression	96	38
14-3-3η protein	Useful in early rheumatoid arthritis	93	77
CTGF	Useful in rheumatoid arthritis	92	86

Existence of autoantibodies like rheumatoid factor (RA) and anti-citrullinated protein antibodies (ACPAs), and inclusion of acute phase reactants consisting of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are an important criterion for the new American College of Rheumatology (ACR) – European League Against Rheumatism (EULAR) classification benchmark of rheumatoid arthritis. Ultrasound and MRI (Magnetic resonance imaging) scans serve as useful techniques by which synovitis and vascularity of joints are detected and evaluation of the degree of joint involvement is done. In several clinical settings, American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 criteria has been approved where it offers a certain percentage of sensitivity (82%) and specificity (61%) that is higher than ACR 1987 criteria 105 by 11%. The classification system was especially developed for patients exhibiting at least one clinically diagnosed swollen joint that cannot be related with any of the other disorders. Designing of an efficient disease-suppressing therapy for an improved result in the late-stage sequelae of rheumatoid arthritis is done by ACR/EULAR 2010 criterion by focusing on earlier diagnosis (Zamanpoor, 2019).

5.5 Treatment

In the last 30 years, exponential rise have been observed over the amount of clinical services available which also includes the treatment of rheumatoid arthritis (Burmester, Bijlsma, Cutolo, & McInnes, 2017). At present, drugs available for the treatment of rheumatoid arthritis comprise of glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs) and DMARDs of synthetic origin or from biological origin (Chatzidionysiou et al., 2017). The diagnostic procedure and treatment strategies of rheumatoid arthritis have been outlined in Figure 4. Both the ACR and EULAR have revised their recommendations and guidance on rheumatoid arthritis management to develop treatment algorithms (Burmester & Pope, 2017). The first-line treatment of rheumatoid arthritis includes corticosteroids and non-steroidal anti-inflammatory drugs. The gross objective of the first-line treatment is to mitigate joint pain and reduce swelling. Medicaments that are considered to be rapid-acting are NSAIDs which comprise naproxen (Naprosyn), etodolac (Lodine), acetylsalicylate (Aspirin) and ibuprofen (Advil and Motrin). When used at high doses, aspirin works as an efficient anti-inflammatory drug for RA due to its ability to inhibit prostaglandin synthesis. It is one of the oldest NSAIDs used to treat pain in the joint (Bullock et al., 2019). Corticosteroids are anti-inflammatory medications that are more potent in comparison to NSAIDs. However, corticosteroids exhibit more side effects compared to NSAIDs. As a result, they are indicated only for a shorter duration of time and at low doses, during exacerbation of rheumatoid arthritis. Intra-articular injections of corticosteroids are known to be used for local symptoms of inflammation. Methotrexate (MTX), an analog of folic acid, is the initial second-line drug (also considered an anchor drug). This immunosuppressive drug needs daily blood testing because of its side effects, such as liver complications, cirrhosis, and weakening of the bone marrow. However, supplementation with folic acid is known to minimize the risk of side effects.

It is an effective DMARD due to its lower frequency of side effects than other DMARDs, and has flexibility in dosing that ensures that doses can be changed if needed (Bullock et al., 2019). Tocilizumab is approved by regulatory agencies in treating adult rheumatoid arthritis patients that failed the treatment with csDMARDs and/or bDMARDs. In 2017, tocilizumab (TCZ) has also been approved for giant cell arteritis, polyarticular and systemic juvenile idiopathic arthritis. It has received approval for Castleman disease in Japan and for the treatment of CAR T Cell-induced Cytokine Release Syndrome in the USA (Sanmartí, Ruiz-Esquide, Bastida, & Soy, 2018).

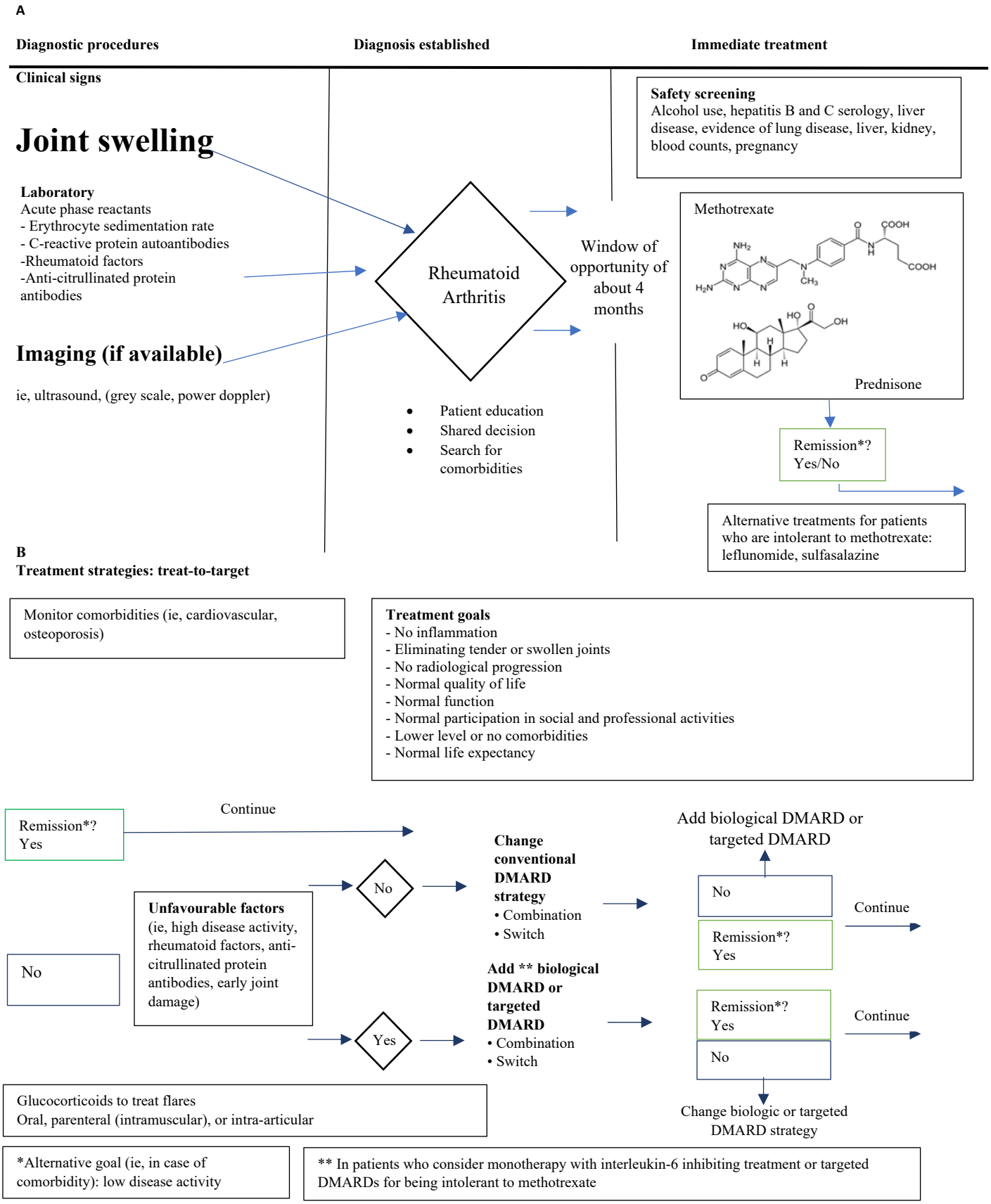

Figure 4: Diagnosis and treatment of rheumatoid arthritis (Burmester & Pope, 2017)

Chapter 6 Discussion and Conclusion

At the end of the nineteenth century, a paradigm shift has been noticed in the treatment of inflammatory and other rheumatic diseases, with the introduction of targeted biologic therapies and the availability of biosimilars in the clinical practice. With time the patent protection of many of the drugs expired and opened the portal for biosimilars to emerge as an alternative but effective treatment option. Biosimilars, also like biologics are sensitive to changes in manufacturing process and both the inherent variability of the protein production, or expression system (Kabir et al., 2019b). Biosimilars for rheumatoid arthritis and other inflammatory conditions are now available worldwide. The limited, but growing, 'real world' experience to date suggests that biosimilars and their bio-originators have similar efficacy and safety. If the cost of biosimilars is lower, a rapid increase in their use to treat patients with inflammatory diseases can be expected. Concern about 'nonmedical switching' and 'interchangeability' persists but will not be resolved until there is greater experience using biosimilars and appropriate post marketing surveillance, both to assess efficacy and to detect potential safety signals. If the cost efficiency of biosimilars are realized, these should allow more patients to access effective biologic therapies and reduce the morbidity and mortality associated to rheumatoid arthritis and other inflammatory diseases (Cohen & Kay, 2017).

The design of a biosimilar using molecular docking and virtual screening is of increasing interest. For example, drugs that target Janus Kinase 3 are considered appropriate in the treatment of RA using molecular docking with Molegro Virtual Docker to design suitable inhibitors for JAK3 dimers. The selective inhibition of JAK3 is recognized as a major intervention for the treatment of autoimmune disorders (Jain et al., 2019). When docked in the cavity 1 of the JAK3 protein

structure, the docking results show that tofacitinib (CP 690,550) displayed in the Table 9 as Cmpd5 portraits the best interaction among all the pre-established drugs (Jain et al., 2019).

Table 9: Established drug docking result (Jain et al., 2019).

NAME	LIGAND	MW	H-BOND	MOLDOCK SCORE	RERANK SCORE	INTERACTION
[00] CMPD5	Cmpd5	312.37	-5.00779	-139.109	-118.575	-150.279
[01] CMPD4	Cmpd4	356.381	-1.8916	-137.471	-116.71	-157.659
[00] 9926791	9926791	312.37	-5.01012	-132.532	-115.618	-149.689
[02] CMPD4_1	Cmpd4_1	357.389	-2.44973	-134.428	-114.697	-157.149
[01] 59422203	59422203	392.378	-6.40297	-144.113	-112.997	-157.552
[00] 59422203	59422203	392.378	-0.05029	-138.499	-112.487	-157.141
[00] CMPD4	Cmpd4	356.381	-1.64215	-141.412	-110.582	-166.422
[02] CMPD5	Cmpd5	312.37	-2.58482	-128.311	-109.219	-141.045
[00] CMPD6_2	Cmpd6_2	310.345	-5.49497	-129.514	-109.036	-138.288
[00] CMPD6_1	Cmpd6_1	309.338	-5	-129.111	-109.026	-138.179

Future Directions

Biosimilars have been found to transform the treatment of several diseases such as cancer, diabetes, and immune-mediated inflammatory diseases, such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). Despite exhibiting high similarity profile with the reference biologics in terms of quality, safety and efficacy, there are several aspects of biosimilars which still require stringent monitoring and strategic planning to increase its positioning in the market. To acknowledge those concerns, some future work to maximize the benefits associated with biosimilars could include:

1. Clear guidelines for switching biosimilars in the treatment.

2. A stringent pharmacovigilance system and risk management plan to ensure the clinical safety of biosimilars.

3. High degree of collaboration between multiple stakeholders who hold a distinct role in the regulatory pathway to improve efficiency of the approval process and promote commercialization of biosimilars.

4. Pharmacoeconomic evaluations following biosimilar market entry to minimize the risk of imposing nonmedical barriers to biologic treatment.

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