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BIOSIMILARS: REVOLUTIONIZING TREATMENT FOR SERIOUS ILLNESSES

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Abstract

A biosimilar is a biological medical product highly similar to another already approved biological medicine it has introduced many new treatments to life-threatening and rare illnesses. The first generation of biopharmaceutical products manufactured using recombinant technologies was launched in the 1980s and they are now on the way to patent expiration.
Vascular endothelial growth factor receptors (VEGFRs) are a family of receptor protein tyrosine kinases that play an important role in the regulation of tumor-induced angiogenesis. Currently, VEGFR inhibitors have been widely used in the treatment of various tumors. However, current VEGFR inhibitors are limited to a certain extent due to limited clinical efficacy and potential toxicity, which hinder their clinical application. Thus, the development of new strategies to improve the clinical outcomes and minimize the toxic effects of VEGFR inhibitors is required.

Keyword: Biosimilar, Rheumatoid Arthritis, Vascular Endothelial Growth Factor ReceptorsInflammatory bowel disease.

1.INTRODUCTION

Biosimilar drugs are pharmaceuticals that are structurally and functionally similar to FDA-approved biologic drugs, commonly referred to as reference products [1]. They are produced after the original drug's patent has expired and can have the same treatment effects, method of administration, strengths, doses, and safety profiles as the biologic pharmaceuticals they replicate [2]. Biologics are complex compounds created from living organisms such as yeast, bacteria, or animal cells that differ somewhat from batch to batch. These variations cause differences between original biologics and biosimilars [3].

In the United State (US), biosimilars include monoclonal antibodies, insulin, vaccines, and allergens [4]. Biologics are expensive due to their complicated research and manufacturing processes, which limits patient access [2]. The Biologics Price Competition and Innovation Act implemented an accelerated FDA approval procedure for biosimilars, which might reduce the cost of biologics and improve accessibility if enough biosimilars are approved and used [5]. A biosimilar must acquire first FDA approval before being used, but it must also receive separate, specialized FDA permission to be considered equivalent with a brand name biologic [6].

Biosimilars are complex proteins generated from natural sources that are intended to resemble brand-name biologics. Generic drugs, on the other hand, are chemically similar to their brand-name counterparts [7]. The FDA approval process for biosimilars differs from that for generic drugs, and biosimilars must receive additional permission to be considered compatible [8]. The primary difference between them is the complexity and variety of the active ingredients in biosimilars, compared to the smaller, simpler parts of generic drugs [9].

Biosimilars are increasingly being used to treat a variety of diseases, including cancer, autoimmune disorders, and chronic inflammatory ailments, giving patients cheaper therapy alternatives. Biologics used in cancer treatment work by increasing the immune system to fight cancer cells, targeting specific proteins on cancer cells to inhibit their growth or stimulating the production of blood cells to neutralize the effects of other cancer therapies [3]. The FDA thoroughly examines additional clinical trial findings proving that

the biosimilar is equally effective and secure as the original biologic medicine are required for compatibility [10].

Biosimilars can help more people get the medicines they need because they are usually cheaper than the original biologics [5]. Biosimilars use for different diseases could make healthcare more accessible for everyone, which is really important.

History:

Biosimilars are developed by biotech or pharmaceutical companies once the patent of the original product expires [2]. As they do not require the same level of research expenditure that the reference biologic product did, their production costs are lower.
The European Medicines Agency (EMA) established biosimilar guidelines in 2003. The first biosimilar, Omnitrope, was approved by EMA in 2006, followed by several others including Valtropin and somatropin biosimilars in Japan. The U.S. saw its first FDA-approved biosimilar, Zarxio, in 2015 and later approved Mvasi for cancer treatment in 2017 [11,12,13]. As of January 2024, the EU has approved 79 biosimilars, the US FDA has approved 45, and India has approved 98 as of September 2019 [14].

Use of Biosimilars instead of Biologics:

Biosimilar drugs have the potential to save the US healthcare system up to $133 billion by 2025, helping treatment for 1.2 million more patients and improving access and affordability [15]. Biosimilars provide a less expensive alternative to reference biologics, increasing access to cancer treatment [16]. They, also offer patients and doctors more personalized cancer treatment options because of increased competition [17]. The use of biosimilars promotes innovation in the pharmaceutical industry. Because biosimilars pose a challenge to established biologic drugs, manufacturers must innovate in R&D, cost management, and manufacturing processes [18]. Biosimilars are being manufactured more efficiently as biotechnological processes advance, resulting in their widespread use in cancer therapy. Aside from significant cost savings, biosimilars increase patient access and competition [19].

Biosimilars use in various diseases:

Biotherapeutic agents, or biosimilars, are similar to their original biologic substance. The purpose of this activity is to draw attention to the adverse event profile, mechanism of action, and other crucial elements for interprofessional team members [20].
Biosimilars can now treat a number of ailments with FDA approval. Rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), psoriatic arthritis (PA), glioblastoma, recurrent or metastatic cervical cancer, inflammatory bowel disease (IBD) such as adult Crohn's disease (CD) and ulcerative colitis (UC), granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), type 1 diabetes mellitus (DM), non-squamous non-small cell lung cancer, metastatic colorectal cancer, metastatic renal cell carcinoma, glioblastoma, recurrent or metastatic cervical cancer, HER2 (human epidermal growth factor receptor-2) associated breast cancer, and HER2 associated gastric (metastatic) or gastroesophageal junction adenocarcinoma, chronic lymphocytic leukaemia (CLL), and non-Hodgkin lymphoma (NHL) [21].

1) Rheumatoid Arthritis:

Rheumatoid arthritis (RA) is a chronic inflammatory disease with joint swelling and pain [22]. Biologic disease-modifying anti-rheumatic drugs (DMARDs) are widely used, targeting TNF-alpha, IL-1, IL-6 receptors, T-cells, and B-cells. However, high costs make optimal disease management inaccessible [23,24]. Biosimilar DMARDs have been developed to reduce costs and increase access to biologic therapy. The EU and USA have approved seven ADL biosimilars, while seven more are presently undergoing clinical trials evaluation [25].

2) Inflammatory bowel disease (IBD):

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is projected to be 4-6 times higher in 2030 compared to 2003, placing a significant economic burden on healthcare systems [26]. Treatment involves medication, particularly biologics, which are becoming more affordable. Biosimilars, which closely resemble the original biologic, are being developed to reduce the inflammatory response and alleviate symptoms. The main goal of IBD treatment is

to manage acute flare-ups, maintain remission, address complications, and monitor for potential malignancy [27].

3) Cancer:

Introduction:

Cancer treatment has changed drastically with the development of numerous biologic treatments, including immunotherapy therapies [28]. Furthermore, biosimilar copies of these drugs have entered the market. Notably, certain biosimilars have been approved for the treatment of certain cancer types, while others have been cleared to help manage treatment-induced side effects. Oncology biological products are among the most expensive pharmaceuticals on the market, posing a significant financial burden on patients and healthcare systems [29].
Monoclonal antibodies (mAbs) and protein kinase inhibitors are the two most rapidly increasing kinds of oncology therapy [30]. As novel medicines are introduced, mAbs account for 35% of cancer spending. Global spending on oncology and supportive care medications hit $100 billion in 2014, with targeted therapy accounting for nearly half of total cost [31]. In 2015, the United States spent $39.1 billion on oncology drugs, an increase of 18.0% from 2014. In 2015, the United States sold $6.2 billion of bevacizumab and $5.6 billion of trastuzumab, two of the world's top 20 products [32]. By 2020, many main biological cancer treatments will lose their patent protection, allowing biosimilar competitors to enter the market [33].

Essentiality:

Cancer is a few of the major causes of death across the globe. Cancer kills roughly one per six people around the globe, more than HIV, tuberculosis, and malaria combined [34]. In 2020, there are expected to be 19.3 million new cases and 10 million cancer-related deaths worldwide. The global cancer burden is expected to rise to 27.5 million cases and 16.3 million deaths by 2040, as the population ages and grows [35]. The National Cancer Institute predicts that the direct medical expenditures associated with cancer treatment in the United States were $183 billion in 2015 and will rise to $246 billion by 2030, a 34% increase [36].

Current Impact:

Supportive cancer therapy is the use of medications to alleviate cancer treatment side effects. In 2007, the European Union (EU) approved its first biosimilars, filgrastim and epoetin alfa, for supportive care therapy. Since then, other biosimilar development projects have been initiated, including those for rituximab, trastuzumab, and bevacizumab [37]. Poland, Finland, Denmark, and the Netherlands have already created national plans to transition to biosimilars. Nine of the world's top ten best-selling pharmaceuticals will lose patent protection during the next five years, with combined sales of more than USD 50 billion in 2011 [38]. The approval of filgrastim biosimilars in countries such as the EU, the United States, and Japan, as well as the patent expiration and anticipated arrival of trastuzumab and rituximab biosimilars, has allowed all three medications to be added to the most recent WHO essential pharmaceutical list [39].

Pharmacoeconomics:

The increase in tumors necessitates earlier cancer medication prescriptions and longer treatment times, increasing financial costs [40]. Cancer expenses rose by 15-22% between 2018 and 2019, and the sector is expected to grow by 105% by 2024. Biosimilars could save USD 54 billion over ten years [41]. Biosimilars, which accounted for less than 2% of the US biologics market in 2018, experienced a significant increase in FDA approvals and use in 2019 [42]. The top three biosimilars introduced in 2019 were bevacizumab, trastuzumab, and rituximab. The financial impact of biosimilars is frequently compared to European procedures. The cost-effectiveness ratio varies by country, with Canada, England, the Netherlands, New Zealand, and the United States having higher thresholds [39].

First biosimilar for cancer:

Mvasi (bevacizumab-awwb), a biosimilar to Avastin (bevacizumab), was authorized by the US Food and Drug Administration today for the treatment of different types of cancer [43]. Mvasi is the first biosimilar licensed in the United States for the treatment of cancer. Mvasi is licensed to treat adult patients with specific colorectal,

lung, brain, kidney, and cervical malignancies [44]. The accepted indications for bevacizumab include intravenous 5-fluorouracil-based chemotherapy for metastatic colorectal cancer, fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin-based chemotherapy for patients advanced from a first-line bevacizumab regimen, a combination of carboplatin and paclitaxel for unresectable lung cancer, glioblastoma with progressing disease after prior therapy, interferon alfa for metastatic renal cell cancer, and paclitaxel and cisplatin [45]. The FDA approved Mvasi for Amgen, Inc., citing its biosimilarity to Avastin. Common side effects include nose bleeds, headaches, hypertension, rhinitis, proteinuria, taste changes, dry skin, and back pain. Avastin was approved in 2004 by Genentech, Inc [46].

Types of Biosimilars used to treat cancer:

In the United States, FDA-approved biosimilars are used to treat breast cancer, stomach cancer, colorectal cancer, and other malignancies [47]. They can also be used to manage the negative effects of cancer therapy. The FDA-approved biosimilars are [48]:

Biosimilar Product Information | FDA			
Biosimilar Name	**Approval Date**	**Reference Product**	**More Information**
Hercessi (trastuzumab-strf)	April 2024	Herceptin (trastuzumab)	Hercessi Information
Selarsdi (ustekinumab-aekn)	April 2024	Stelara (ustekinumab)	Selarsdi Information
Tyenne (tocilizumab-aazg)	March 2024	Actemra (tocilizumab)	Tyenne Information
Jubbonti and Wyost (denosumab-bbdz)	March 2024	Prolia and Xgeva (denosumab)	Jubbonti and Wyost Information
Simlandi (adalimumab-ryvk)	February 2024	Humira (adalimumab)	Simlandi Information
Avzivi (bevacizumab-tnjn)	December 2023	Avastin (bevacizumab)	Avzivi Information
Wezlana (ustekinumab-auub)	October 2023	Stelara (ustekinumab)	Wezlana Information
Tofidence (tocilizumab-bavi)	September 2023	Actemra (tocilizumab)	Tofidence Information
Tyruko (natalizumab-sztn)	August 2023	Tysabri (natalizumab)	Tyruko Information
Yuflyma (adalimumab-aaty)	May 2023	Humira (adalimumab)	Yuflyma Information
Idacio (adalimumab-aacf)	December 2022	Humira (adalimumab)	Idacio Information
Vegzelma (bevacizumab-adcd)	September 2022	Avastin (bevacizumab)	Vegelma Information
Stimufend (pegfilgrastim-fpgk)	September 2022	Neulasta (pegfilgrastim)	Stimufend Information
Cimerli (ranibizumab-eqrn)	August 2022	Lucentis (ranibizumab)	Cimerli Information
Fylnetra (pegfilgrastim-pbbk)	May 2022	Neulasta (pegfilgrastim)	Fylnetra Information
Alymsys (bevacizumab-maly)	April 2022	Avastin (bevacizumab)	Alymsys Information
Releuko (filgrastim-ayow)	February 2022	Neupogen (filgrastim)	

Yusimry (adalimumab-aqvh)	December 2021	Humira (adalimumab)	Yusimry Information
Rezvoglar (insulin glargine-aglr)	December 2021	Lantus (insulin glargine)	Rezvoglar
Byooviz (ranibizumab-nuna)	September 2021	Lucentis (ranibizumab)	Byooviz Information Press Release: FDA Approves First Biosimilar to Treat Macular Degeneration Disease and Other Eye Conditions
Semglee (Insulin glargine-yfgn)	July 2021	Lantus (Insulin glargine)	Semglee Information Press Release: FDA Approves First Interchangeable Biosimilar Insulin Product for Treatment of Diabetes
Riabni (rituximab-arrx)	December 2020	Rituxan (rituximab)	Riabni Information
Hulio (adalimumab-fkjp)	July 2020	Humira (adalimumab)	Hulio Information
Nyvepria (pegfilgrastim-apgf)	June 2020	Neulasta (pegfilgrastim)	Nyvepria Information
Avsola (infliximab-axxq)	December 2019	Remicade (infliximab)	Avsola Information
Abrilada (adalimumab-afzb)	November 2019	Humira (adalimumab)	Abrilada Information
Ziextenzo (pegfilgrastim-bmez)	November 2019	Neulasta (pegfilgrastim)	Ziextenzo Information
Hadlima (adalimumab-bwwd)	July 2019	Humira (adalimumab)	Hadlima Information
Ruxience (rituximab-pvvr)	July 2019	Rituxan (rituximab)	Ruxience Information
Zirabev (bevacizumab-bvzr)	June 2019	Avastin (bevacizumab)	Zirabev Information
Kanjinti (trastuzumab-anns)	June 2019	Herceptin (trastuzumab)	Kanjinti Information
Eticovo (etanercept-ykro)	April 2019	Enbrel (etanercept)	Eticovo Information
Trazimera (trastuzumab-qyyp)	March 2019	Herceptin (trastuzumab)	Trazimera Information
Ontruzant (trastuzumab-dttb)	January 2019	Herceptin (trastuzumab)	Ontruzant Information
Herzuma (trastuzumab-pkrb)	December 2018	Herceptin (trastuzumab)	Herzuma Information

Truxima (rituximab-abbs)	November 2018	Rituxan (rituximab)	Truxima Information Press Release: FDA approves first biosimilar for treatment of adult patients with non-Hodgkin's lymphoma
Udenyca (pegfilgrastim-cbqv)	November 2018	Neulasta (pegfilgrastim)	Udenyca Information
Hyrimoz (adalimumab-adaz)	October 2018	Humira (adalimumab)	Hyrimoz Information
Nivestym (filgrastim-aafi)	July 2018	Neupogen (filgrastim)	Nivestym Information
Fulphila (pegfilgrastim-jmdb)	June 2018	Neluasta (pegfilgrastim)	Fulphila Information Press Release: FDA approves first biosimilar to Neulasta to help reduce the risk of infection during cancer treatment
Retacrit (epoetin alfa-epbx)	May 2018	Epogen (epoetin-alfa)	Retacrit information Press Release: FDA approves first epoetin alfa biosimilar for the treatment of anemia
Ixifi (infliximab-qbtx)	December 2017	Remicade (infliximab)	Ixifi information
Ogivri (trastuzumab-dkst)	December 2017	Herceptin (trastuzumab)	Ogivri information Press Release: FDA approves first biosimilar for the treatment of certain breast and stomach cancers
Mvasi (Bevacizumab-awwb)	September 2017	Avastin (bevacizumab)	Mvasi information Press Release: FDA approves first biosimilar for the treatment of cancer

Cyltezo (Adalimumab-adbm)	August 2017	Humira (adalimumab)	Cyltezo information
Renflexis (Infliximab-abda)	May 2017	Remicade (infliximab)	Renflexis information
Amjevita (Adalimumab -atto)	September 2016	Humira (adalimumab)	Amjevita information Press Release: FDA approves Amjevita
Erelzi (Etanercept-szzs)	August 2016	Enbrel (etanercept)	Erelzi information Press Release: FDA approves Erelzi
Inflectra (Infliximab-dyyb)	April 2016	Remicade (infliximab)	Inflectra information Press Release: FDA approves Inflectra
Zarxio (Filgrastim-sndz)	March 2015	Neupogen (filgrastim)	Zarxio information

The FDA has approved several biosimilars to treat cancer, including bevacizumab-awwb, trastuzumab-dkst, pegfilgrastim, and rituximab-abbs [49]. Filgrastim-sndz is the first licensed biosimilar that stimulates the body's production of white blood cells, which can be low in cancer patients receiving chemotherapy or bone marrow transplants [13]. Trastuzumab-dkst treats specific cancers, whereas trastuzumab-anns treats breast and stomach cancer. From 2018 to 2019, pegfilgrastim was used to treat non-myeloid cancer patients undergoing chemotherapy. Rituximab-abbs was approved in November 2018 for the treatment of non-Hodgkin lymphoma [50].

Biosimilar monoclonal antibodies for cancer treatment:

Many biosimilar mAbs are now being developed for the treatment of cancer. The EMA guidelines for biosimilar mAbs approved for cancer indications state that the most sensitive patient population and clinical endpoints should be used to discover differences in efficacy and safety between a biosimilar and a reference product [51]. Oncologists should be aware that in some countries, several non-comparable copies of biological products (also known as 'intended copies') have been introduced without the proper demonstration of biosimilarity to a licensed reference product and without approval through a regulatory pathway aligned with EMA, FDA, or WHO guidelines [52].

Exploring the Therapeutic Potential and Market Impact of VEGFR Biosimilars in Cancer Treatment:

The therapeutic potential of VEGFR biosimilars in cancer treatment is intricately linked to the mechanisms through which they combat disease progression. For instance, bevacizumab and its biosimilars bind to Vascular Endothelial Growth Factor (VEGF), effectively inhibiting the interactions that promote tumor growth and metastasis [53]. The VEGF pathway, which includes factors like VEGF-C and VEGF-D, plays a pivotal role in encouraging tumor advancement through processes such as lymphangiogenesis and lymphatic metastasis, mediated by VEGFR-3 [54]. This activation of the VEGF pathway extends beyond cancer and has implications in various disease processes, encompassing autoimmunity, retinopathy, and more [55]. Notably, the overexpression of VEGF has been strongly correlated with tumor progression and poor prognosis across different cancer types, such as colorectal carcinoma and gastric carcinoma [56]. VEGF-A, a key player in the VEGF family, exerts significant effects on both cancer cells and immune cells, making it a crucial target for therapeutic interventions through anti-angiogenic agents and combinational therapies [57]. Moreover, the overexpression of VEGFR-2, particularly observed in breast cancer, underscores its significance as a target for

both biologics and small molecule inhibitors, further emphasizing its role in cancer treatment [58]. Interestingly, the VEGF-VEGFR system emerges as a vital target for anti-angiogenic therapy in cancer treatment while also showing promise for pro-angiogenic therapy in specific contexts. The expression of VEGF has been closely associated with poorer prognosis and aggressive disease in various cancers such as non-small cell lung cancer, colorectal carcinoma, glioblastoma, and ovarian cancer, highlighting the prognostic implications of targeting the VEGF pathway in cancer management [59].

Vascular Endothelial Growth Factor Receptors:

Vascular Endothelial Growth Factor Receptor (VEGFR) is a crucial player in the field of biology and medicine due to its role in regulating angiogenesis, vascular permeability, and endothelial cell survival [60]. VEGFR belongs to the receptor tyrosine kinase family and exists in three main isoforms: VEGFR-1, VEGFR-2, and VEGFR-3 [61]. Structurally, VEGFR belongs to the receptor tyrosine kinase family and consists of three main subtypes: VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flk-1), and VEGFR-3 (Flt-4). Among these subtypes, VEGFR-2 is considered the primary mediator of vascular permeability and endothelial cell proliferation [62]. Activation of VEGFR occurs upon binding with its ligands - primarily vascular endothelial growth factor (VEGF) proteins. The downstream signaling pathways triggered by activated VEGFR include Ras-Raf-MEK-MAPK pathway, PI3K-Akt-mTOR pathway, and PLCγ-PKC pathway. These pathways collectively regulate processes like cell survival, proliferation, migration, and angiogenesis under normal physiological conditions [63].

Role of VEGFR in cancer:

Vascular Endothelial Growth Factor Receptor (VEGFR) regulates vascular permeability by controlling the integrity of blood vessels [64]. However, dysregulation of VEGFR signaling can lead to pathological conditions such as cancer, diabetic retinopathy, and inflammatory disorders. In cancer, overexpression of VEGF leads to excessive angiogenesis promoting tumor growth and metastasis [65].

Vascular Endothelial Growth Factor Receptor (VEGFR) plays a crucial role in cancer progression by promoting angiogenesis, the formation of new blood vessels that supply nutrients and oxygen to tumors [66]. VEGFR is a key player in cancer progression due to its involvement in angiogenesis, the process through which tumors acquire the blood supply necessary for their growth and metastasis [67]. VEGFR interacts with Vascular Endothelial Growth Factor (VEGF) ligands, such as VEGF-A, VEGF-B, and VEGF-C, to promote tumor vascularization. The binding of VEGF ligands to VEGFR triggers downstream signaling pathways, including the phosphoinositide 3-kinase (PI3K) [68].

VEGFR inhibitors:

In the realm of targeted cancer therapy, Vascular Endothelial Growth Factor Receptor (VEGFR) inhibitors have emerged as a potent class of drugs with promising therapeutic potential [57]. By specifically targeting the VEGF signaling pathway, these inhibitors have shown efficacy in various cancers and other conditions characterized by abnormal angiogenesis [69]. VEGFR inhibitors exert their pharmacological effects by disrupting the intricate VEGF-VEGFR axis. By inhibiting the binding of VEGF ligands to their receptors, VEGFR inhibitors impede the activation of downstream signaling pathways involved in angiogenesis and tumor growth [70]. For instance, drugs like bevacizumab and sunitinib have been shown to block the VEGF-mediated signaling cascades, leading to reduced vascular permeability and tumor vascularization [71].

Clinical utility of VEGFR inhibitors:

The clinical utility of VEGFR inhibitors in cancer treatment has been demonstrated through numerous studies and clinical trials [72]. These inhibitors have shown promising results in various malignancies, including colorectal cancer, renal cell carcinoma, and non-small cell lung cancer, among others [73]. Clinical outcomes have highlighted the ability of VEGFR inhibitors to prolong progression-free survival and improve overall survival rates in patients with advanced or metastatic disease [74]. However, the use of VEGFR inhibitors is not without limitations, as they are associated with a spectrum of side effects ranging from hypertension and proteinuria to gastrointestinal disturbances. Despite these adverse events, the overall safety profile of VEGFR inhibitors is manageable, and

ongoing research aims to optimize their use in cancer therapy through combination strategies and personalized treatment approaches [75].

VEGFR biosimilars:

VEGFR biosimilars, a class of intravitreally injected biologic medications, target vascular endothelial growth factor (VEGF) to address various retinal disorders such as macular edema associated with wet Age-related Macular Degeneration (AMD) [76]. These biosimilars are evaluated for their effectiveness and safety compared to the reference product for neovascular AMD treatment, with the first FDA-approved biosimilar being for ranibizumab [77]. Notably, the introduction of prefilled syringe (PFS) biosimilar options can potentially reduce costs by saving the excess drug volume left in the vial, offering a more cost-effective alternative. In certain regions, like India, ophthalmic biosimilars of ranibizumab have been approved for clinical use since 2015, further expanding the accessibility of these treatments [78]. Despite the cost-saving potential of biosimilars, challenges exist in the pricing strategies, as evidenced by the dilemma of setting the price for an intraocular bevacizumab biosimilar to avoid increasing Medicare costs significantly [79]. Additionally, the off-label use of bevacizumab, an anti-VEGF agent originally approved for oncology indications, as a compounded drug for retinal disorders adds complexity to the landscape of VEGF-targeting treatments in ophthalmology [80]. The role of VEGF, a signaling protein promoting abnormal blood vessel growth, is crucial in both AMD and macular edema, highlighting the significance of biosimilars in managing these conditions effectively [76]. Despite the cost reduction and increased accessibility that biosimilars bring, the field of retina presents unique challenges compared to other medical specialties, which necessitate tailored approaches for the successful integration of these innovative treatments [81].

VEGFR biosimilars compare to the original VEGFR drugs:

The introduction of biosimilars targeting vascular endothelial growth factor (VEGF) has presented a potential shift in the treatment landscape for various retinal disorders [82]. Specifically, the approval of biosimilars such as ranibizumab-nuna (SB11, Byooviz) and Razumab has offered alternatives to the original VEGF drugs like ranibizumab, showing comparable efficacy and safety profiles in treating conditions like neovascular age-related macular degeneration (AMD) [83]. These biosimilars have the advantage of potentially reducing costs, as seen with the option of prefilled syringe (PFS) biosimilars, which can help save on drug wastage and overall treatment expenses [84]. However, challenges persist in the ophthalmic biosimilar market, particularly in the retina specialty, where unique obstacles hinder the widespread adoption of these cost-effective alternatives compared to other medical fields [85]. Despite these challenges, the availability and utilization of VEGF biosimilars like bevacizumab offer promising opportunities for enhancing access to effective treatments for retinal disorders, ultimately benefiting patients and healthcare systems alike [86].

Challenges and opportunities in the development and market acceptance of VEGFR biosimilars:

The development and market acceptance of VEGFR biosimilars present a unique set of challenges and opportunities in the medical field [87]. One significant opportunity lies in the potential cost reduction that biosimilars offer, especially when considering the use of pre-filled syringes (PFS) which can help save on drug wastage and ultimately reduce overall treatment expenses [88]. Additionally, biosimilars have been instrumental in increasing access to essential medications, thereby improving healthcare outcomes for patients in need [89]. However, despite these advantages, the journey towards market acceptance is not without hurdles. For instance, the pricing of intraocular bevacizumab biosimilars must be carefully considered to avoid unintended consequences on healthcare costs, as evidenced by the potential 15.2% increase in Medicare costs with a $500 per injection price tag [90]. Furthermore, the off-label use of bevacizumab compounds for ocular conditions, even though it is not FDA-approved for such indications, poses regulatory challenges that biosimilar developers must navigate [91]. These challenges underscore the importance of addressing regulatory, pricing, and access issues to ensure the successful development and market acceptance of VEGFR biosimilars in the medical landscape [85].

2. CONCLUSION:

Biotechnological medicines will become an important part of the future healthcare landscape. Biologics and properly regulated biosimilars will increasingly become available, will provide patients and doctors with alternative treatment options and most likely will make it possible to decrease the direct costs of therapies and increase their availability to the patients. Physicians should be aware that quality, safety and efficacy issues in the case of biotechnological medicines and biosimilars are key and much more complex than with traditional generics. Substitution rules between originator and biosimilar products must be different than in the case of generic substitutions as such products are never identical. Awareness of the differences between original biotechnological medicines and biosimilars is essential for the safety of the patients.

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