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A Review

Effectiveness of bevacizumab biosimilars in the treatment of pulmonary diseases

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Biosimilars have emerged as viable cost-effective therapeutic alternatives to the original high-cost biologics in oncology. This research focuses on biosimilars' roles in pulmonology, diving into non-small cell lung cancer. Central to this is bevacizumab, a monoclonal antibody biosimilar that works by targeting the root cause of tumor spread by vascular metastasis through inhibiting vascular endothelial growth factor, suppressing angiogenesis. The FDA-approved biosimilars (bevacizumab-awwb and bevacizumab-bvzr) demonstrate similar efficacy, safety, and immunogenic profiles modeled after their well-worked predecessors when compared to the original therapeutic agents. Our review also aimed to explain the role of tumor necrosis factor-inhibitor biosimilars such as etanercept, which are used to counteract autoimmune conditions regarding inflammation, and are studied for their inherent properties in treating cancers. Clinical trials show that these agents play supportive roles in inflammation, a central symptom amongst patients with cancer. Survival and placebo data support the success of these biosimilars in desirable medical outcomes. Although adverse effects of the use of biosimilars arise, such as interstitial lung disease, these issues are examined by case studies and comparisons. By integrating clinical evidence, regulatory mechanisms, and pharmacologic/immunogenic profiles, this review expands on the role of biosimilars towards their increased acceptance as viable therapeutic agents.

Keywords: Biologics, Biosimilars, Chronic obstructive pulmonary disease, Cost-effectiveness, Interstitial Lung disease, Lung cancer, Patient outcomes, Safety, Sarcoidosis, Tumor necrosis factor, Vascular endothelial growth factor

Introduction

Biosimilars are highly crafted medical products made from already living organisms that are built to resemble the real approved biologics equivalents. These medicines are meant to serve the same purpose that the U.S. Food and Drug Administration (FDA) approved drugs can often do to save cost or make it easier to obtain[1]. Developing these "biosimilars" aids in providing therapies to people who could not before, while assuring safety, dosage, and purity.

These substances account for about 37% of all US drug costs but 2% of all prescriptions that are written for patients[2]. Thus, biosimilars undergo clinical research trials to demonstrate effectiveness compared to biologics and offer an alternative opportunity for certain populations.

Pulmonary diseases such as interstitial lung disease (ILD) and chronic obstructive pulmonary disease (COPD) pose significant health challenges across the world. ILD is characterized by inflammation of the lungs and scar tissue around the lesion. These groups of diseases are usually accompanied by other problems such as asthma, rheumatoid arthritis (RA), and non-small cell lung cancer (NSCLC), which can make breathing increasingly difficult.

Related to pulmonary disease, lung cancer, specifically the NSCLC, accounts for about 90% of all lung cancers and is the third leading cause of death globally[3]. Even though there are no top-notch

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Abbreviations: AAM, Association for Accessible Medicines; ACA, Affordable Care Act; AEC, Absolute Blood Eosinophil Count; BLA, Biologics License Application; BPCI, Biologics Price Competition and Innovation; CI, Confidence Interval; CIP, Chronic Interstitial Pneumonia; COPD, Chronic Obstructive Pulmonary Disease; CT, Computed Tomography; CTD, Connective Tissue Disorders; DLL3, Delta-like Ligand 3; DM, Dermatomiositis; EGFR, Epidermal Growth Factor Receptor; EMA, European Medicines Agency; FADD, Fas-Associated Death Domain; FDA, Food and Drug Administration; FVC, Forced Vital Capacity; GINA, Global Initiative for Asthma; HCP, Health Care Providers; IPF, Idiopathic Pulmonary Fibrosis; KDR, Kinase-insert Domain Receptor; LABA, Long-Acting Beta Antagonist; NSCLC, Non-Small Cell Lung Cancer; OR, Odds Ratio; ORR, Overall Response Rate; OS, Overall Survival; PCP, Primary Care Physicians; PFS, Progression-Free Survival; PK, Pharmacokinetics; QALI, Quality-Adjusted Life Year; QoL, Quality of Life; RA, Rheumatoid Arthritis; RCT, Randomized Controlled Trial; SCLC, Small Cell Lung Cancer; SSc-ILD, Small-scale Studies Interstitial Lung Disease; TKI, Tyrosine Kinase Inhibitor; US, United States; VEGF, Vascular Endothelial Growth Factor; WHO, World Health Organization

universal treatments for advanced lung cancer, there is a biosimilar offered to help treat a variety of tumor levels targeting non-squamous NSCLC[4].

Despite further advancements in technology and treatment of lung disease, the prevalence of lung disease is still high. These terminal diseases have seen an increase in the quality and longevity of life within the past few years with early detection and targeted therapies[5]. But they still pose an immense threat due to the affordability and hard-to-grasp nature of such medicinal routes. The advancements in biosimilars have helped treat vast pulmonary diseases and improve the quality-of-life (QoL).

Asthma is an inflammatory disorder characterized by hyper-responsiveness of the bronchus, limiting airflow into the lungs. A biosimilar may help target the inflammatory modulator endotypes in patients with severe asthma. Examples include targeting the endotypes T-helper cells or T2 high-level and T2 low-level cells[6].

Furthermore, tumor necrosis factor (TNF) plays an essential signaling factor in diseases of the human body, such diseases include RA, an autoimmune disease that affects the body's joints. This relates to biosimilars, in which these medications employ blockers on the TNF, causing inflammation and targeting the joints related to RA[7]. TNF relates to pulmonary diseases, which develop into further-stage ILD and other autoimmune complications and are treated by targeting *via* biosimilars. These endotypes vary based on cytokine levels secreted by lymphocytes, which play a role in the initiation and progression of asthma.

Cytokines refer to a class of proteins released by the immune system that act as signaling molecules released when antibodies bind to antigens[8]. These signals include monitoring inflammation, blood flow, and overall immunity of the human body. These cytokines play roles in the inflammation of the lungs in COPD, in which the cytokine TNF-α is related to inflammation levels[9]. These delve further into metastatic growth, as observed with NSCLC.

Vascular endothelial growth factor (VEGF) is another cytokine that promotes angiogenesis, which is the creation of new blood vessels in the body, spreading the cancer to various parts of the body in a detrimental manner. Cytokines also contribute to airway regulation with varying airflow of oxygen buffered by these proteins[10].

Biosimilars offer an alternative treatment route for people while maintaining minimal risks, effectively minimizing potential adverse patient risks. There has been increased recognition of biosimilars offered by primary care physicians (PCPs), sub-specialists, and the FDA[10]. For example, biosimilars such as Bevacizumab-awwb[11] are offered to treat NSCLC and are replicated after the bevacizumab (Avastin) drug[12].

The biosimilars are created from reference products' biologics and chemical analysis[1]. Such reference products are derived from the sequence of amino acids and their primary structure. However, even though this alternative route is created, there are still minor clinical differences in the product[13]. Herein, we sought to critically review the emerging treatment options with bevacizumab biosimilars in treating pulmonary diseases like COPD and NSCLC. Biosimilars highlight the main benefits, such as the fact that these biosimilars have always been in the supply and are cost-effective for certain patients seeking an alternative treatment path[14].

Biosimilar interventions

Targeted bevacizumab (Avastin®) for NSCLC

Bevacizumab, a monoclonal antibody that targets VEGF, has shown immense potential for treating NSCLC[4]. The way that bevacizumab works is by targeting those new blood vessels that these potent tumors use for metastasis, which is the spread of cancer to a different part of the body than where it originated[15]. A study involved the addition of bevacizumab with paclitaxel and carboplatin, which are chemotherapy drugs that work to damage certain DNA in cancer cells in an attempt to prevent cell division and metastasis. This treatment worked and overall showed that the combination of biosimilars and targeted chemotherapy drugs can have remarkable results in the progression and outcome of NSCLC patients in Sandler's study.

Furthermore, comparison of the different therapies is also an important distinction in the pursuit of biosimilars and their effect on lung diseases. The AVAiL trial worked to study the effectiveness of the lone use of chemotherapy along with rates when bevacizumab is combined[12]. The addition of bevacizumab to chemotherapy has demonstrated substantial improvements in patient outcomes, especially in NSCLC. The combination showed enhanced progression-free survival (PFS) and overall survival (OS) compared to simply using chemotherapy alone. These findings underscore the importance of incorporating these therapies, such as bevacizumab, along with other regimens, such as chemotherapy.

When compared to immunotherapies such as programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors[16]. These proteins also play a role in the immune system's ability to deal with cancer. These proteins bind to cancer cells to turn them off, which are similar to bevacizumab, VEGF which blocks the formation of new blood vessels to prevent spread and has been proven to improve OS in patients with high expression[17]. This bevacizumab incorporated with chemotherapy remains a crucial treatment for the broader population of patients with NSCLC. People without the biomarkers for PD-L1 or EGFR mutations rely on bevacizumab as an alternative pathway for treatment and do not qualify for other newer therapies[16]. Globally, the role of bevacizumab biosimilars in managing pulmonary disease plays an important therapeutic role. Below, we summarize key biosimilars of bevacizumab concerning pulmonary disease and therapeutic outcomes.

Bevacizumab (Zirabev) targeted therapies

Bevacizumab biosimilars, such as Zirabev, have emerged in the context of treatment as an effective alternative for Avastin in the effort to treat NSCLC. Zirabev functions similarly to bevacizumab by inhibiting VEGF. Incorporating Zirabev and targeting VEGF significantly limits the amount of proliferation by this tumor, preventing angiogenesis.

Angiogenesis, for reference, is the formation of new blood vessels as it relates to NSCLC and metastasis[18]. Clinical effectiveness of bevacizumab biosimilars was demonstrated in a phase III trial of Zirabev to bevacizumab in patients with NSCLC. This randomized study established the equivalence in 18-week induction therapy, and it was found that the overall response rate (ORR) was 54% in the Zirabev group and 63.1% in the bevacizumab group. Even though the difference between the treatments showed that Zirabev was slightly less effective than bevacizumab, the 90% confidence interval (CI) showed us that the two treatments fell within the equivalence region, making them clinically equivalent in the ability to treat tumors such as NSCLS[19].

This study not only supports the clinical application of Zirabev as a biosimilar to bevacizumab but also highlights the roles that these biosimilars have in treatments without compromising their outcomes. Additionally, clinical studies have shown that Zirabev offers similar PFS and OS in patients affected with NSCLC. Also, in addition to large cost savings, Zirabev acts as an accessible treatment option for patients and also combines with chemotherapy as an option for patients who do not have other biologics[19].

Building on the success of the treatment of NSCLC, Zirabev has shown promising capability in other pulmonary diseases as well, such as idiopathic pulmonary fibrosis (IPF) as well as chronic obstructive pulmonary disease (COPD)[20]. In these diseases, angiogenesis plays a crucial role in the spread of cancer[18], which is also targeted by the use of these biosimilars. Detection, inflammation, and lung function can be managed by targeting VEGF, and the disease spread can be slowed. Real-world data from clinical studies have shown and supported using Zirabev and other treatments to improve the QoL in patients diagnosed with severe pulmonary diseases[19]. There is ongoing research on the combination of Zirabev with targeted immunotherapies to enhance the treatment and offer opportunities that do not create barriers to available treatments for pulmonary cancers.

Survival rate vs placebo trial for non-squamous NSCLC

The AVAiL trial was a phase III, double-blinded, and placebo-controlled study aimed to determine the efficacy as well as the safety of bevacizumab as a treatment. This trial provided key details about the survivability of patients with advanced NSCLC, and the procedure was combined with cisplatin-gemcitabine chemotherapy[12]. Cisplatin is a widely used chemotherapy drug known for its cytotoxic as well as anti-neoplastic (anti-growth forming) effects on cancer cells. This drug's mechanism is by entering the cell and binding to DNA to form intra-strand DNA adducts, all interfering with DNA in cancer cells, preventing uncontrolled cell growth by hindering transcription[21] (Fig. 1).

Gemcitabine, a pyrimidine anti-metabolite with recently known activity in the treatment of solid tumors, is useful and exerts its effects aided by its low toxicity profile. Like cisplatin, it is another chemotherapy drug that similarly targets the replication of DNA growth[21,22] (Fig. 2). Together, these two therapeutic agents provided essential use in the target of reducing the growth of NSCLC, providing a viable therapeutic option for patients with advanced stages of the disease. Nearing the endpoint of the trial, there was a significant improvement in PFS, noting a 25% reduction in the risk of disease progression. This comparison was struck between the

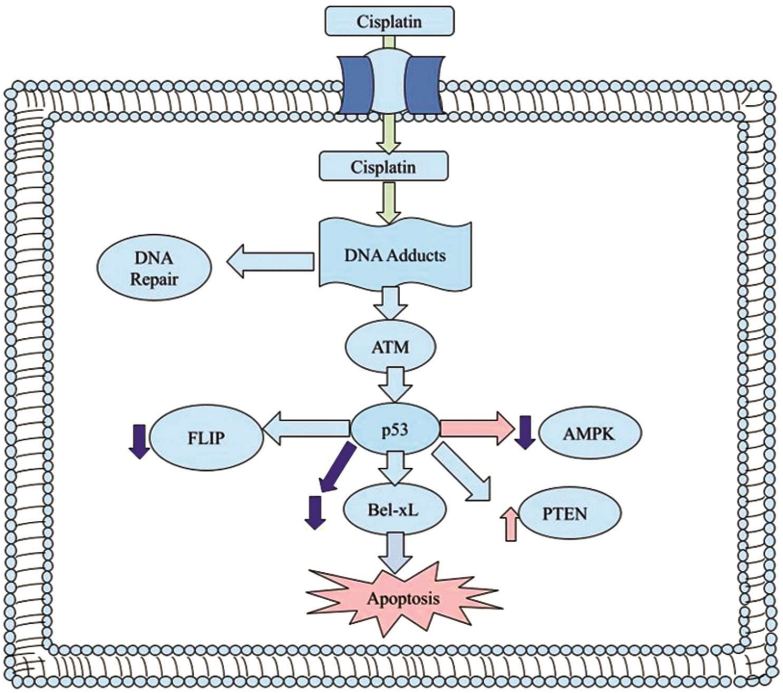

Fig. 1 — A schematic diagram of the molecular mechanisms of cisplatin cytotoxicity. It illustrates how the cisplatin chemotherapy agent works - cisplatin enters cancer cells, forming DNA adducts which lead to aggregations of DNA damage. The pathway is shown by ATM protein kinase and how the activation of p53 directs the signaling of apoptosis in cancer cells[21]. *Abbreviations:* ATM: Ataxia telangiectasia mutated; FLIP: FLICE-like inhibitory protein; FLICE: FADD (Fas-associated death domain)-like IL-1β–converting enzyme; AMPK: 5'-adenosine monophosphate-activated protein kinase; p53: Tumor protein p53; Bcl-xL: B-cell lymphoma-extra-large; PTEN: Phosphatase and tensin homolog

7.5 mg/kg and the 15 mg/kg group, which had a 25% and 15% reduction in the risk of disease progression[12]. However, upon analysis of the OS data, there was no statistical significance dictating improvement and similarities in the median OS due to a small sample size.

These findings highlight a common hurdle in NSCLC trials, in the pursuit of determining the efficacy of the trials and experimentation, this one includes the skewing of results due to alternative treatments. To expand more on this, the use of alternative therapies after the initial treatment makes it harder to measure the true impact of the first one's actual effects. In the AVAiL trial, about 62% of the patients received post-study alternative therapies after the first trial, this explains why there was likely no great improvement in the OS with bevacizumab when compared to the placebo[4].

However, when considering bevacizumab, this did indeed show a clear benefit in PFS, aiding in the risk of the disease getting worse over time shown by the 15 mg/kg group, marked with a statistically significant p-value of 0.0456. These findings are essential in understanding the role of bevacizumab as well as other biosimilars in the treatment of NSCLC. The results further work to reinforce the rationale of utilizing PFS as a valid tool in NSCLC and cancer trials, especially when evaluating popular biosimilars such as Zirabev, as the use of other alternative studies skews the data and increases difficulty in interpretation.

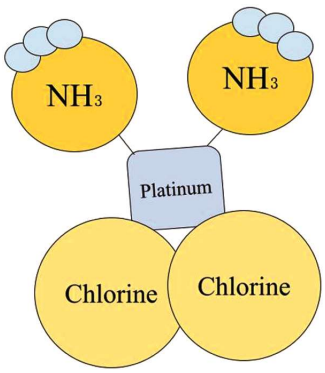

Fig. 2 — Molecular structure of cisplatin, a well-known chemotherapeutic agent utilized in the treatment of non-small cell lung cancer (NSCLC). The figure represents the structure of cisplatin with a central platinum atom surrounded by ammonia (NH_3) and chlorine groups, which aids in the prevention of DNA replication, inhibiting cancer-related uncontrolled cell growth[21]

Tarlatamab and other biosimilars

Tarlatamab is a T-cell engager that was developed for the treatment of recurring small-cell lung cancer (SCLC). This is a bispecific T-cell engager and a type of biologic drug that has its mechanism by binding to two different targets simultaneously. Tarlatamab works by targeting DLL3 (Delta-like ligand 3), which is present on the cell surface of cancer cells and T-cells, which are what comprise the immune system of the human body[23]. When these two proteins bind, Tarlatamab moves T-cells into close contact, and it effectively allows the human immune system to destroy cancer cells. The way that this biosimilar differs from the traditional chemotherapy used to treat cancer with radiation is that it has a side effect of attacking both cancer and healthy cells in the body.

DLL3 is a protein that is on the surface of SCLC cells, which makes it a primary target for cancer treatment to discriminate from the healthy cells of the human body. Tarlatamab brings a revolutionary treatment to spare healthy tissues and reduce the side effects of traditional methods. In a recent phase I clinical trial, promising results showed effective treatment in the case of recurring SCLC. This type of lung cancer (*i.e*., SCLC), is most commonly known to be extremely aggressive with fast metastasis, which is the colonization of neoplastic cells from the primary tumor in other areas of the body[24]. In this trial, Tarlatamab showed a response rate of 23.4%, meaning that almost a quarter of the enrolled patients saw a significant tumor shrinkage in their disease[23]. Furthermore, the median OS for the given patients was around 13.2 months, which marked a significant improvement for a population that is usually represented with restricted and reduced modes of treatment. An important feature to note, however, was the relatively small sample size of the study; while this research was encouraging, further results are desirable to further validate the effectiveness of this treatment.

Along with Tarlatamab, other biosimilars are starting to become prominently used around the globe. All these biosimilars aid in providing affordable treatment options and increasing access to therapies that are usually quite expensive for the general population. These are therapies that provide superior treatment to the original chemotherapy used, which comes with many side effects[24]. Traditional chemotherapy, while being a cornerstone of cancer treatment, can also worsen a patient's condition[10].

Chemotherapy includes potent and toxic agents such as bleomycin, methotrexate, as well as gemcitabine, that are associated with pulmonary toxicity in interstitial disease (a type of lung inflammation) and increasing alveolar damage (damage to the miniscule air sacs in the lung) in addition to the original complication[10,20,25] (Table 1). These complications arise due to immunosuppression, characterized by a weakened immune system. When chemotherapy is given to patients, it can leave them more vulnerable to bacteria and viruses that could affect the lungs. Additionally, biosimilars such as bevacizumab, as discussed above, can block the vessel growth of tumors but still contribute to alveolar hemorrhage or bleeding pooling up in the lungs of the human body[26]. This effectively demonstrates how chemotherapy, while aiding in the treatment of cancer, can also harm patients, making it important to monitor treatments properly regarding pulmonary and related diseases.

Table 1 — A summary of pulmonary drug toxicity, radio-pathological findings, and their respective commonly impacted drugs. This table represents the pulmonary complications that arise because of chemotherapy, as well as the drugs responsible for them. As example, Tarlatamab, a targeted biosimilar, works by reducing the pulmonary side effects that are present when patients utilize chemotherapy as a treatment[10]

Radio-pathological findings	Prevalently involved drugs
Interstitial infiltrates	Bleomycin, methotrexate, taxanes, platins, rituximab, gemcitabine, bortezomib, everolimus, temsorilimus, and gefitinib
Alveolar damage	Bleomycin, busulfan, carmustine, melphalan, mitomycin, cyclophosphamide
Nonspecific interstitial pneumonia	Methotrexate, bleomycin, carmustine, or chlorambucil
Pulmonary hemorrhage	High-dose cyclophosphamide, cytarabine (ara-C), mitomycin, bevacizumab, platins
Capillary leak syndrome	Gemcitabine and immune-mediated therapies such as interleukin-2 and interferon
Eosinophilic pneumonia	Methotrexate, bleomycin
Cryptogenic organizing pneumonia	Bleomycin, cyclophosphamide, everolimus, and methotrexate
Hypersensitivity pneumonitis	Methotrexate

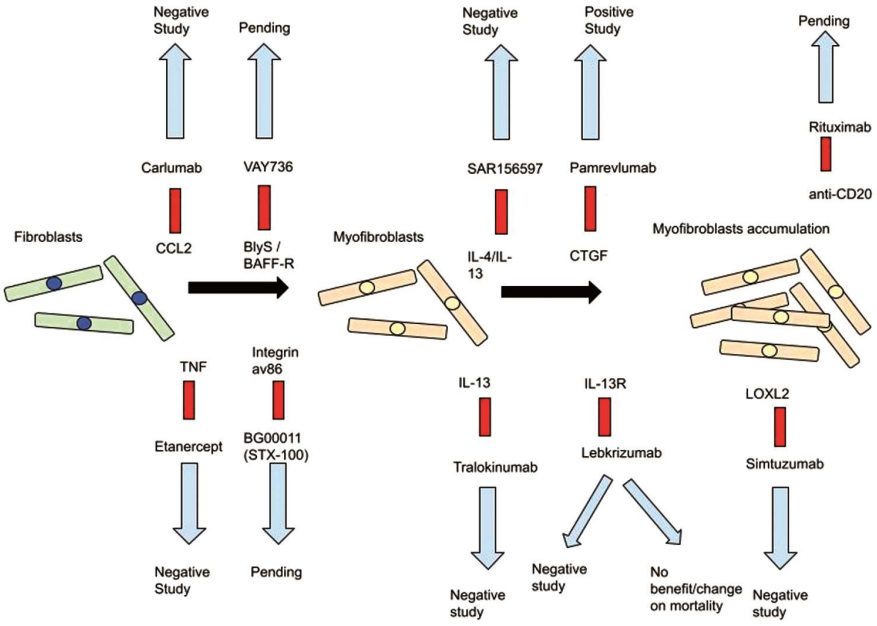

Fig. 3 — Illustration of the various inflammatory signaling pathways involved in fibroblasts. This figure shows the microenvironment of tumors and their respective cytokine targets, TNF and IL-13. These pathways intersect with the angiogenic pathways involved in biosimilars, such as bevacizumab used to treat NSCLC[29]. *Abbreviations:* CCL2: Chemokine (C-C motif) ligand 2; IL: interleukin; BAFF-R: B-cell activating factor receptor; BlyS: B Lymphocyte stimulator; TNF: Tumor necrosis factor; CD: Cluster of differentiation; LOXL2: Lysyl oxidase-like 2; CTGF: Connective tissue growth factor

NSCLC targeted TNF inhibitors

TNF is a cytokine, which is a small protein that is released when antibodies bind to the antigen and is involved in the immune system[27]. TNF works by allowing the progression of the tumor, increasing cell proliferation, and leading to chronic inflammation. The use of TNF inhibitors allows for specially designed agents to block TNF's normal biological activity, reducing inflammation as well as decreasing the prevalence of disease advancement. A prominent biosimilar example of a TNF-inhibitor would be the biosimilar etanercept-szzs, which functions to bind to TNF-α as well as TNF-β to inactivate these molecules biologically and limit inflammatory responses[1].

Biosimilars of TNF inhibitors are designed in a way to mimic the original structure and function of the original biologics and are strictly regulated by regulatory agencies. The FDA evaluates the biosimilars produced, one of which is under the established Biologics Price Competition and Innovation (BPCI) Act of 2009. An example: The pathway is contingent on biosimilars that are produced to be competitive in treatment, as well as meeting criteria in the broad field of immunogenicity and pharmacology. These biosimilars also exhibit similar outcomes and progression as patients treated with other therapeutic agents.

An example would be in a retrospective analysis of patients receiving bevacizumab biosimilars simultaneously with chemotherapy or epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs). These patients experienced PFS outcomes similar to the same results as if the patients had just used the original bevacizumab treatment[1]. Under the provision of NSCLC, with great regard to patients with underlying autoimmune diseases such as RA or sarcoidosis, these TNF inhibitors, while not directly decreasing cancer, can still manage to serve a great need in reducing the chronic inflammation and prevention of tumor exacerbation in patients afflicted.

Etanercept biosimilars, specifically the etanercept-szzs and -ykro, are fusion proteins that act as decoy receptors for TNF-α and TNF-β[28]. These work by effectively limiting the biological activity of these cytokines, and like infliximab, these are approved by the FDA for managing inflammatory diseases one such as RA or diseases associated with a high immunological response and activation. These biosimilars aim to replicate the etanercept drug, which is composed of a p75 TNF receptor, both dimeric and soluble, which resists the binding of TNF to its original receptor, preventing any oncoming immune effects[29] (Fig. 3).

An important notice in the use of biosimilars is their efficacy, and it was noted that biosimilars overall do not

report any clinically significant differences regarding safety or toxicity when compared to original biologics as they are used[30]. Although no direct clinical trials were made around the use of etanercept in lung cancer, the rationale for the mechanism of these TNF inhibitors remains a valid point. TNF-α is often elevated in the environment of NSCLC, with the body making itself much more prone to inflammation, supporting the rationale of the targeted use of the biosimilar for counteracting inflammation[7].

There are also other positive aspects for the use of TNF inhibitors, one being in the progression of cachexia. Cachexia, also known as "wasting syndrome", is a metabolic syndrome characterized by a loss of muscle mass, simultaneously or not with loss of fat mass[31]. This syndrome also induces metabolic disturbances and is associated with cancer, as it can lead to an increased wasting of muscle and changes in body composition that can result in death of the person afflicted with this syndrome. This metabolic syndrome, prevalent in up to 50% of cancer patients, remains an important factor to consider in the treatment of cancers with biosimilars. TNF inhibition successfully showed a decrease in the prevalence of cachexia and showed an improvement in appetite in patients with an advanced level of cancer[32].

However, despite the rise in emerging benefits of these biosimilars, they remain suppressed by the FDA for treatment of NSCLC largely due to the need for more clinical trials regarding the subject matter, with more targeted studies in patients with advanced lung cancer. This overlapping link in the immune system and cancer-related effects is an important note in patients who have advanced cancer afflicted with immune defects. Additionally, etanercept can also manage lung conditions with coexisting symptoms of immune system problems and from the disease itself, which are often present, especially in the disease progression of older patients.

Mechanism of biosimilars in pulmonology

Biosimilars are biologic agents that are specially engineered to closely mimic the structure and function of already approved reference products available in the medical field. The mechanism of action for these biosimilars is very contingent on what reference product they are modeled over, thus also providing the same effects and treatment. In the context of pulmonology, biosimilars such as bevacizumab-awwb and related function *via* inhibiting VEGF. A way that these biosimilars function would be by binding to the VEGF-A and thus preventing the interaction of the subsequent Flt-1 and kinase-insert domain receptors (KDR) present on endothelial cells.

Analogously, TNF-inhibitors such as infliximab-dyyb as well as adalimumab-abdm reduce inflammation *via* the binding and subsequent neutralization of TNF-α (a cytokine involved in the activation of the immune response by the body's system), worsening the lung disease. Similar to other biosimilars, this one prevents TNF from binding to TNFR1 and TNFR2, which blocks the downstream inflammatory immune pathway cascade[1]. These pathways, in general, are very essential and relevant in lung conditions exacerbated by an underlying autoimmune disease in the patient. These biosimilars can help the inflammatory and angiogenesis-related problems that are commonly associated with NSCLC.

Biosimilars that are used in the treatment of asthma, such as omalizumab and dupilumab, for example, work by the selective targeting of key inflammatory pathways that are involved in type 2 (T2) asthma, which are properly replicated. An example would be with omalizumab, a monoclonal antibody (made from one cell) against IgE blocks the interaction with receptors on mast cells and basophils[25]. Mast cells and basophils are immune cells responsible for allergic reactions and inflammation, and when decreased, they result in reduced inflammation of the body, counteracting the effects of the tumor[6] (Table 2).

Analogously, mepolizumab works by binding to IL-5, inhibiting downstream cascade, and preventing the activation of other immune cells responsible for inflammation and immune responses, such as eosinophils. The biosimilar benralizumab, however, goes even further, by selectively targeting the IL-5 receptor alpha present on eosinophils, which instead leads to apoptosis (programmed cell death) through cell-mediated toxicity with the use of antibodies[33]. In the case of dupilumab, the IL-4 as well as the IL-13 signaling downstream immune cascade is inhibited, reducing eosinophil inflammation[29] (Fig. 3).

Furthermore, recent studies have begun to research the scope of application of biosimilars in the treatment of COPD, specifically in patients marked by higher inflammation levels. Notably, COPD is a lung disease characterized by an obstruction of air flow by exposure to harmful substances and is a prevalent cause of death worldwide[34]. Associated with the disease, inflammation is quite prevalent in COPD,

Table 2 — A summary of key biosimilar/biologics therapies that are offered to treat asthma[6]. This table provides an account of respiratory changes, pulmonary functions and related considerations while using biosimilars/biologics as therapeutics

Therapy	Respiratory change	Function of lungs	Prognosis of corticosteroid	Considerations
Omalizumab	- 25%	Equivalent or minimal improvement	Reports less usage of ICS	This biosimilar was approved for the younger population of 6-11 years old
Mepolizumab	- 50%	Inconsistent results were found	Decreased use of OCS was found	Standard dosing is not correlated with a decrease; a higher dosage is approved
Reslizumab	- 50/60%	An improved function of the lungs	Unevaluated	Weight-related dosing for asthma approved biosimilar.
Benralizumab	- 25/60%	An improved function of the lungs	Decreased use of OCS was found	8-Week cycles employed
Dupilumab	- 50/70%	An improved function of the lung	Decreased use of OCS was found	Self-used biosimilar

Abbreviations: ICS = inhaled corticosteroid; OCS = oral corticosteroid

with up to 40% of patients afflicted with the disease being affected. Biosimilars such as mepolizumab, benralizumab, and dupilumab, which target type 2 inflammation mediators like IL-5, IL-4, and related, all have varying results in the efficacy of their downstream cascade inhibition.

However, a specialized focused trial, namely the BOREAS trial, showed that the duplimab biosimilar significantly reduced the extreme inflammation responses and showed improved lung function, demonstrating up to 18-20% reduction of IL-5α target inhibition. These findings show the role that varying biologics have in the therapeutic resolution of COPD, as shown by the biomarkers of these patients afflicted with the disease. The understanding of the mechanism of how these biosimilars work is essential, and mediators such as IL-5 targeting and other biologics are making a rise in treatment.

Adverse effects of bevacizumab: Interstitial lung disease

Side effects from the use of bevacizumab can arise, and one prominent side effect of the biosimilar includes the exacerbation or inducing of interstitial lung disease[35]. This is especially prevalent in patients who already suffer from chronic interstitial pneumonia (CIP), which is a disease characterized by respiratory distress, afflicted with many bilateral air-ground glass opacities shown in the lungs in respective medical scans[6]. Interstitial lung disease (ILD) is a disease characterized by scarring and inflammation of the lungs, with scar tissue, which is important as inflammation is what is targeted in biosimilars (such as bevacizumab). Although a rare inducement by bevacizumab, which is an anti-angiogenic and noninflammatory drug, these reports of induced toxicity remain relatively rare. However, a recent study involving the incidence of CIP due to bevacizumab was done during bevacizumab monotherapy along with chemotherapy[29] (Table 3). There was a case of a 62-year-old man of Asian descent with NSCLC who developed dyspnea, shortness of breath, as well as ground-glass opacities in high-resolution computed tomography (CT) scans[1]. These ground glass opacities signaled signs of interstitial dysfunction and prompted further investigation. This patient had only undergone chemotherapy with bevacizumab, and laboratory findings showed elevated levels of fibrosis markers, confirming this diagnosis[36]. Following up, this patient's overall condition improved after a dose of corticosteroid therapy, highlighting the risk of a side effect of immune dysfunction.

Table 3 — Radiologic findings associated with biologic treatments. This table helps conceptualize the pulmonary complications exhibited with biosimilars, such as in ILD. These facts highlight rare, but still evidently possible adverse effects induced by bevacizumab therapy against cancers[29]

Biologic Treatment	Radiologic Findings
Anti-TNF-α	Aseptic granulomatous pulmonary nodules, Interstitial lung infiltrates (0.5-3%)
Rituximab	Organizing pneumonia ARDS
Tocilizumab	Organizing pneumonia Increase inflammation of ILD Pneumonitis
Abatacept	Rarely caused/induced ILD

Abbreviations: TNF: Tumor necrosis factor; ARDS: Acute respiratory distress syndrome; ILD: Interstitial lung disease

Overall, while bevacizumab is generally considered a low risk for adverse effects on the lung, the notable case mentioned highlights the importance of monitoring pulmonary conditions. This is quite essential in times when symptoms arise in patients showing dyspnea, which is the shortness of breath, or in abnormal findings in medical scans, especially when no other inducing agents are involved[37]. In a

2022 meta-analysis of 13 randomized clinical trials (n=7, 201) with solid tumors, scientists studied the incidence of ILD in patients treated with bevacizumab. Surprisingly, the results showed us that the incidence of this inflammation-related disease was significantly lower odds ratio (OR) 0.62 95% CI: 0.42-0.92; p=0.02) than the control. These findings highlight the case reports of bevacizumab-induced ILD, and this data demonstrates that, instead, the risk of inflammation is reduced in the setting of this treatment[1]. The overall findings also suggest that, rather than isolated reports of ILD, bevacizumab with a complex profile can play a protective role instead.

Cost-effectiveness of biosimilars

Biosimilars have become particularly useful in the economic context of treating chronic and high-burden diseases like NSCLC and COPD. The greatest selling point of biosimilars remains their cost association, especially when dealing with complex and chronic conditions with long-term therapeutic interventions. Innovation in medicine using biologics is associated with a very high cost, which is a burden to both the health systems as well as the patients. Clinically equivalent biosimilars are available at a lower cost, without compromising safety, efficacy, or quality represented by biosimilars ending up being below what patients were willing to pay in a study assessing infliximab and leflunomide biosimilars[38]. Due to abbreviated regulatory pathways, biosimilars need less development and production work, which directly reduces their costs for payers and patients alike.

For example, Mvasi and Zirabev biosimilars, which were incorporated into oncology treatment bevacizumab-awwb. The biosimilars have a fraction of the price of the original drug, Avastin[39]. They undergo rigorous clinical trials, including equivalence studies, to ensure that no meaningful differences in PFS or OS exist, in order to support therapeutic interchangeability. This fact is leading more institutions to incorporate biosimilars into their formularies and treatment guidelines, allowing a reduced cost without compromise to the clinical outcomes achieved. The Association for Accessible Medicines (AAM) reported in 2023 that biosimilars alone saved the U.S. over $23.6 billion, including a large portion from pulmonary-related conditions like COPD[5].

Furthermore, it was represented that a huge topic of concern lies in the co-pay provided by insurance, along with savings that biosimilars provide, offering

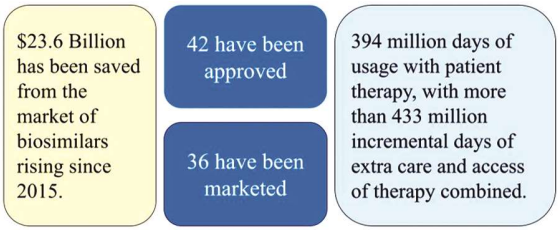

Fig. 4 — Key indicators of cost-effectiveness and access to biosimilars in the United States healthcare system. Summary of biosimilar cost savings since 2015 and expanded treatment. These indicators represent the impact of biosimilars and their integration in the healthcare system[5]

an ever-increasing market for the treatment in the field of oncology[5] (Fig. 4). This broadens the scope of patient care services, especially for the underinsured, while enabling healthcare practitioners to start treatment earlier in the disease progression. In NSCLC, prognosis and long-term hospitalization costs greatly benefit from early intervention with therapeutic biosimilars.

In addition, the introduction of biosimilars fosters competition among healthcare providers, further improving system sustainability, and even leads to retail price drops on originator biologics. In a bundled or value-based payment model, this becomes helpful when lowering the healthcare costs while aiming to improve patient outcomes and QoL. Biosimilars have traditionally been associated with chemotherapy adverse events, directly harmful from traditional chemotherapy, while providing an indirect economic benefit and reducing their incidence. For instance, biosimilars targeting inflammatory cytokines and angiogenesis pathways help reduce disease exacerbation and associated healthcare utilization. Moreover, these have reduced inpatient care needs and improved quality-adjusted life years (QALY) when combined with chemotherapy, bolstering their favorable cost-effectiveness profile.

With ever-changing healthcare systems focused on precision medicine and outcome-based reimbursement frameworks, biosimilars continue to reflect a “middle ground” for cost containment and quality of care. Their active management, including additional research and market surveillance, still reinforces their role as cost and clinically effective treatment options for pulmonary diseases.

The FDA approval process

The FDA has a special policy system for assessing and authorizing biosimilars under the framework of the BPCI Act of 2009[40]. This form of licensure

subsidization enables biosimilars to gain access to the market without going through all the steps of original drug development as long as they prove high similarity to the reference biologic product concerning clinical safety, purity, and potency.

The approval process is stepwise. It starts with comprehensive analytical studies that confirm molecular similarity within the scope of the structure, glycosylation patterns, and binding activity. These assessments guarantee that the biosimilar is "highly similar" to its reference product without any clinically meaningful differences. After analytical similarity is established, non-clinical studies assess the toxicity and pharmacological behavior of the drug in animal models. Then, the biosimilar undergoes clinical evaluation, including pharmacokinetic and pharmacodynamic studies in humans. These are followed by clinical immunogenicity studies and at least one comparative clinical trial that assesses the biosimilar's efficacy and safety in a sensitive patient population. For instance, bevacizumab biosimilars were subject to head-to-head trials against Avastin in NSCLC populations to confirm therapeutic equivalence[41].

Moreover, biosimilars can apply for an "interchangeability" designation, which allows for substitution at the pharmacy level. This designation is granted after more studies are conducted to confirm that patients can switch between the biosimilar and the reference biologic without decreased efficacy or increased risk. The FDA requires post-marketing surveillance, or phase IV studies, to track long-term safety and adverse event outcomes. This is critical safety monitoring, especially for biosimilars used in chronic or life-threatening conditions such as NSCLC and COPD. The framework set by the FDA for biosimilars addresses innovation, cost, and safety of the pulmonary biologic therapies, thus widening access while upholding strict regulatory oversight.

Future considerations and innovations

Unprecedented research breakthroughs, new regulations, and wider clinical applications are ushering biosimilars into a new era. A prominent example is the creation of biosimilars for complex biologics like monoclonal antibodies and fusion proteins utilized in oncology and immunology[29]. To ensure safety and efficacy, next generation biosimilars will require more advanced scientific analytics, prompting manufacturers to strengthen structural and functional efficacy assessments.

Regulatory agencies, like the FDA, are also moving towards more streamlined approval models. For instance, there is increasing advocacy for the removal of the separate "interchangeable" biosimilar designations, which would simplify market access and substitution[24]. This change would promote greater accessibility for biosimilars to healthcare providers and patients, particularly in under-resourced regions[42]. Digital integration stands out as another promising frontier. Pharmacovigilance and post-market safety monitoring are beginning to be augmented by artificial intelligence and machine learning. These technologies can process real-world data efficiently to identify adverse effects more precisely and earlier, enhancing reliance on biosimilars.

In addition, worldwide collaboration between the regulatory agencies is creating consolidated policies, which are likely to decrease duplication in the international approval processes and enable swifter worldwide access to biosimilars. With the rising prominence of biologics in the management of chronic diseases and cancers, biosimilars are anticipated not merely serve as alternatives, but rather become foundational therapeutic options[24].

Conclusion

The integration of biosimilars into the field and treatment of pulmonology, particularly diseases such as NSCLC and COPD, offers significant advancements in targeted therapy. Biosimilars such as bevacizumab work as TNF-inhibitors, reducing the downstream cascade of inflammation, along with etanercept-szzs show efficacy in comparison to the reference products they are modeled after. These biological therapeutic agents disrupt key inflammatory pathways that are implicated in advanced cancer. These biosimilars inhibit VEGF, which works to disrupt the nutrient supply and spread of cancer by limiting the prominent metastasis associated with the mechanism of NSCLC.

The increasing shift to the usage of biosimilars in medicine shows precision in the treatment of cancers and pulmonary diseases. These benefits, while important, still come with some adverse side effects such as CIP and ILD. As the regulatory agencies relying on NSCLC trials increase and support for biosimilars rises, clinical confidence and the immunogenic efficacy of these agents remain critical. Understanding of the mechanism and results of biosimilars work to improve pharmacodynamics, which empowers oncologists as

well as pulmonologists in the integration with patients. The broader acceptance and use of biosimilars will depend on the development of continued trials centered around patients and monitoring longevity, resulting in improved clinical outcomes and QoL.

Conflicts of interest

All authors declare no conflicts of interest.

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