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Mini Review

Role of biosimilar pegfilgrastim in the treatment of febrile neutropenia: A Mini Review

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Biologics have no true generics due to their complex nature but biosimilars offer a hopeful alternative. Biosimilars are similar to biologics as tested with comparable safety and efficacy profiles to the reference product. With more cancer patients needing extensive chemotherapy, life threatening complications like febrile neutropenia (FN) can be fatal. FN is a medical condition characterized by fever and a dangerously low count of neutrophils; a type of white blood cell crucial for fighting infections. Pegfilgrastim, a modified long-lasting form of the medication filgrastim, has helped patients recover without comprising their active chemotherapy regimens. Yet, for many cancer patients, the expenses associated with essential treatments persist as a significant challenge, leaving limited resources available to address the accompanying adverse effects. Biosimilars to pegfilgrastim can contribute to cost-savings, increase in accessibility and variability. This article delves into the fundamental advantages of biosimilars comparing financial benefits and availability with special reference to biochemistry, pharmacology, and therapeutic roles of pegfilgrastim in FN. It also undertakes the task of evaluating and synthesizing the safety and efficacy profiles of pegfilgrastim biosimilars, encompassing those both available and pending approval from the U.S. Food and Drug Administration. It provides hope and benefits for patients, clinicians, and healthcare organizations in the treatment of FN. Thus, we conclude that biosimilars to pegfilgrastim are by-and-large comparable in regard to pharmacodynamic and pharmacokinetic profiles to the reference products with no significant differences in safety and efficacy while treating FN.

Keywords: Adverse events, Biosimilars, Chemotherapy-induced, Cost-effectiveness, Febrile neutropenia, GCSFs, Pegfilgrastim, Pharmacodynamic and pharmacokinetic profiles, Regulatory approvals, Savings, Therapeutics

Introduction

Febrile neutropenia (FN) refers to the event of fever in individuals with an abnormally low level of neutrophils, a type of leukocyte responsible for fighting off bacterial infections. It is a serious medical condition commonly experienced by chemotherapy patients or hematopoietic stem cell transplantation (HSCT), where the immune system is compromised[1]. FN requires immediate medical attention due to the increased risk of life-threatening infections.

FN usually occurs as a result of the suppression of bone marrow activity, leading to a downfall in neutrophil production[1]. Chemotherapy agents, specifically those with myelosuppressive properties, are the primary cause of FN in cancer patients[2]. Moreover, HSCT recipients are also susceptible due to the conditioning regimen received prior to transplantation, which disrupts the bone marrow[3]. Other causes may include medications, radiation therapy, and underlying hematologic disorders. Additionally, the absolute neutrophil count (ANC) at the time of chemotherapy initiation serves as a key predictor of FN risk. ANC of less than 1500 cells/mm^3 is defined as mild neutropenia, less than 1,000 cells/mm^3 is moderate and less than 500 cells/mm^3 leads to a severe account of neutropenia[1]. FN is characterized as neutropenia with fever greater than or equal to 100.4°F (38°C)[3].

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Abbreviations: ADA, Anti-drug antibody; ANC, Absolute neutrophil count; ASP, Average sales price; AUC, Area under the curve; BGTD, Biologics and Genetics Therapies Directorate; BLA, Biologics License Application; CD, Cluster of differentiation; CDSCO, Central Drugs Standard Control Organization; C/EBPβ, CCAAT/enhancer-binding protein beta; CIN, Chemotherapy-induced neutropenia; C_{max}, Maximum serum concentration; EMA, European Medicines Agency; ER, Emergency room; FDA, Food and Drug Administration; FN, Febrile neutropenia; GSCF, Granulocyte colony-stimulating factor; HSCT, Hematopoietic stem cell transplantation; IBM, International Business Machines Corporation; JAK-STAT, Janus kinase - signal transducer of activation pathway; LLC, Limited liability company; MAPK, Mitogen activated protein kinase; NCT, National Clinical Trial; OOP, Out-of-pocket; PD, Pharmacodynamics; PEG, Polyethylene glycol molecule; PI3K, Phosphoinositide 3-kinase; PK, Pharmacokinetics; PPPC, Per-patient per-cycle; TAC, Neoadjuvant chemotherapy with docetaxel, doxorubicin, and cyclophosphamide

It is well-recognized that chemotherapy agents exert their cytotoxic effects on promptly dividing cells, including hematopoietic progenitor cells, leading to myelosuppression and a decrease in neutrophil production[2]. While molecular pathways may vary depending on the chemotherapy drug usedfor eachpatient, the general mechanisms involve DNA damage, cell cycle arrest, and apoptosis[2]. Alkylating agents like cyclophosphamide and platinum compounds form covalent adducts with DNA, leading to DNA strand breaks and cross-linking, which can result in cell death or cell cycle arrest[2]. Some chemotherapy drugs, such as vinca alkaloids (*e.g.*, vincristine, vinblastine), taxanes (*e.g.*, paclitaxel, docetaxel), and epothilones (*e.g.*, ixabepilone), damage microtubule function[4]. By interfering with microtubules, these drugs misguide mitosis and cell division, affecting the production of blood cells, including neutrophils[4].

Chemotherapy-induced neutropenia (CIN) is declared as an oncologic emergency given the trends of mortality and prevalence which leads to FN. The febrile response is sometimes not detectable due to decreased circulating leukocytes producing interleukin (IL) 1, IL-6, and tumor necrosis factor (TNF) in some immunosuppressed cancer patients[5]. The onset of CIN is induced byolder age, lower body mass index (BMI), and a history of various multiple cytotoxic chemotherapy regimens[2]. FN patients with lung cancer have the highest hospitalization and mortality compared to breast, non-Hodgkin lymphoma, colorectal, and ovarian cancers[5]. Hospitalization and mortality rate of patients with breast cancer is the lowest[5]. Overall risk of mortality for cancer patients with FN was minimum 15% higher than matched patients without FN[5].

The treatment of FN in cancer patients typically involves a multidisciplinary approach aimed at addressing the underlying infection, providing supportive care, and managing complications. Prompt initiation of broad-spectrum antibiotics is crucial in the management of FN[6]. Commonly used antibiotic regimens include combinations of beta-lactam antibiotics (such as cephalosporins or carbapenems) with or without an aminoglycoside or fluoroquinolone[6]. Granulocyte colony-stimulating factors (GCSFs), such as filgrastim or pegfilgrastim, are sometimes administered to stimulate the production and maturation of neutrophils[6]. GCSFs can be used as prophylaxis in patients developing FN or as adjunctive therapy in patients with established FN to potentially shorten the duration and severity of neutropenia[7]. With the administration of GCSFs, dose-dense, and dose-intense chemotherapy regimens can be supported[7]. The lack of GCSFs given can delay or reduce dose of subsequent cycles of chemotherapy[7]. The decision to use GCSFs is based on various factors, including the underlying cancer, treatment regimen, and individual patient characteristics.

Therefore, in this mini-review, we sought to highlight the emerging roles of pegfilgrastim biosimilars in the treatment of FN with special reference to biochemistry, pharmacology, therapeutic potentials, and safety profiles.

Overview of Biosimilars

Biosimilars, which are biological products highly similar to an active ingredient of an approved reference biologic with no clinically significant changes, offer several advantages in oncology[8]. Biologic drugs (or biologics) are intricate and specialized medications typically sourced from living organisms including animal cells and microorganisms[9]. Due to this, biologics are some of the costliest prescription medications ranging from US$10,000 to exceeding $500,000 per year[9]. With their complex nature and expensive production, biologics do not have true generics but biosimilars offer hope. The biosimilar has a similar route of administration, strength, and dosage as the reference biologic. Unlike small-molecule generic drugs, which are chemically synthesized to have identical structures to brand-name drugs, biosimilars are produced in living systems[10]. Therefore, biosimilars are not identical to the reference biologics, distinguishing them from generic drugs[10].

Biosimilars provide an opportunity to expand patient access to critical oncology treatments. By offering alternative treatment options, biosimilars increase competition in the market and can help address affordability and availability shortages. The availability of biosimilars can encourage manufacturers of reference biologics to develop improved therapies, invest in research and development to explore new treatment initiations. The European Medicines Agency (EMA) and other regulatory bodies around the world have over 50 approved biosimilars[11-14] (Fig. 1). This competition benefits both patients and the healthcare system by fostering innovation and potentially driving down costs. This is particularly important in oncology, where the cost of biological therapies can be a significant burden for patients and healthcare systems.

Extensive analytical, pre-clinical, and clinical studies are conducted to establish similarity, ensuring that biosimilars perform comparably to the reference biologics in terms of safety and efficacy. This regulatory scrutiny provides confidence in the use of biosimilars in oncology practice. Biosimilars allow for broader access to effective treatments, potentially improving outcomes for cancer patients. They are generally priced lower than the reference biologics, offering cost savings for patients, healthcare providers, and payers[15-17] (Table 1).

One of the key advantages of biosimilars is the significant cost reduction of approximately 20% to 30% compared to the corresponding biologic medications[18]. With the use of biosimilars instead of biologics, an estimated $38.4 billion saving between the years 2021 to 2025 can be realized9. In the United States, pharmaceutical prices are 2.56 times higher compared to 32 similar countries[9]. However, when accounting for rebates and other discounts, the prices are still 1.90 times higher[9].

Due to these marketed down prices, health professionals and patients may be weary of using biosimilars, but efficacy and outcomes are assured by the FDA just as reference products would be[19]. It is essential to take into account the administration and nursing labor costs when evaluating the cost conversion from reference products to biosimilars. It was estimated that $5.80 M is needed to manage 121 cancer patients with prophylaxis of febrile neutropenia using reference pegfilgrastim[19]. With Ziextenzo®, a pegfilgrastim biosimilar, that cost was significantly reduced to roughly half or $2.85 M[19]. When patients can save money through the use of biosimilars, it enables them to allocate those funds toward other crucial primary treatment expenses. Patients would no longer have to choose whether to treat their current complications or better their chances at their quality of life. With data from 17 studies about cost savings associated with biosimilars across different cancer types, the findings indicated that cancer therapy biosimilars are pharmacoeconomically favorable[20]. In comparison to the reference products, all the assessed biosimilars demonstrated dominance. The cost ratios for GCSF biosimilars ranged from 21% to 76.9%, for erythropoietin biosimilars ranged from 51% to 86.2%, and for monoclonal antibody biosimilars ranged from 59.4% to 86%[20].

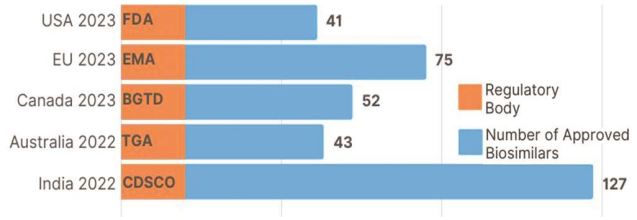

Fig. 1 — Number of approved biosimilars in regulatory bodies around the world in 2022-2023
Abbreviations: FDA: Food and Drug Administration, EMA: European Medicines Agency, BGTD: Biologics and Genetics Therapies Directorate, TGA: Therapeutic Goods Administration, CDSCO: Central Drugs Standard Control Organization

Properties of Pegfilgrastim

To consider primary prophylaxis with pegfilgrastim (Neulasta®, Amgen, Thousands Oak, CA) for FN, certain criteria should be met: i) the patient should have a risk of developing FN that is 20% or higher, and ii) there should be no alternative regimen that is both safer and equally effective[21]. Pegfilgrastim is a long-acting form of filgrastim with 20 kD polyethylene glycol molecule (PEG), GCSF,

Table 1 — Summary of pegfilgrastim biosimilar savings in the treatment of febrile neutropenia

Biosimilar	Reference	Patient Sample	Costs (US$)	Limitations
MYL-1401H	Wang *et al* (2022)[15]	1,930 chemotherapy patients in 2019	PPPC OOP $299 v. $182 MYL-1401H	67%-83% had zero OOP for the originator pegfilgrastim
Q5111	Wang *et al* (2022)[15]	1,930 chemotherapy patients in 2019	PPPC OOP $299 v. $159 Q5111	67%-83% had zero OOP for the originator pegfilgrastim
LA-EP2006	McBride *et al* (2020)[16]	20,000 cancer patients receiving CIN/FN prophylaxis	PPPC payer cost savings $637 LA-EP2006	Simulation model from payer perspective for 2019
PF-06881894	Singer *et al* (2022)[17]	44 patients who received at least 1 dose of filgrastim	ASP per mg $262.83 v. $342.76 PF-06881894	Patients had variety of hematologic and oncologic conditions, excluded FN patients and rapid chemotherapy patients
Q5130 and MSB11455	Singer *et al* (2022)[17]	ASP not available due to recent FDA approval	Not applicable	Not applicable

Abbreviations: PPPC: per-patient per-cycle, OOP: out-of-pocket, ASP: average sales price, CIN: chemotherapy induced neutropenia, FN: febrile neutropenia, FDA: U.S. food and drug administration

and exhibits several properties with a specific mechanism of action in treating FN[22]. Unlike filgrastim's daily administration, pegfilgrastim is administered once-per-chemotherapy cycle due to reduced renal clearance and increased plasma half-life[22].

In response to inflammatory signals, such as IL-1, TNF-α, and other pro-inflammatory cytokines, various cell types within the bone marrow and peripheral tissues produce higher levels of GCSF[23]. GCSF is a vital regulator of neutrophil production and maturation, playing a critical role in maintaining an adequate supply of these immune cells (Fig. 2)[23]. Upon GCSF binding, the GCSF receptor initiates downstream signaling events, including activation of the Janus kinase - signal transducer of activation (JAK-STAT) pathway, mitogen activated protein kinase (MAPK), and phosphoinositide 3-kinase (PI3K) pathways[23]. These signaling pathways are essential for transmitting the GCSF signal into the cell and regulating gene expression necessary for hematopoiesis[23]. The transcription factor C/EBPβ (CCAAT/enhancer-binding protein beta) is highlighted as a key regulator of neutrophil lineage commitment and maturation[23][23]. It is induced by GCSF signaling and coordinates the expression of genes involved in neutrophil development and function[23] (Fig. 2).

Biosimilars of Pegfilgrastim Approved by the FDA

Pegfilgrastim, including biosimilars, is sold under the US brand names: Neulasta®, Fulphila®, Fylnetra®, Nyvepria®, Stimufend®, Udenyca®, and Ziextenzo®[24]. Pegfilgrastim was approved for subcutaneous use by the FDA and EMA in the year 2002 for FN in patients receiving myelosuppressive anti-cancer drugs and hematopoietic syndrome of acute radiation syndrome[24]. As summarized in Table 2, there are several approved biosimilars to pegfilgrastim, below we focus on the biochemical and clinical properties of these key biosimilars that are increasingly being utilized for the treatment of FN with improved cost-effectiveness.

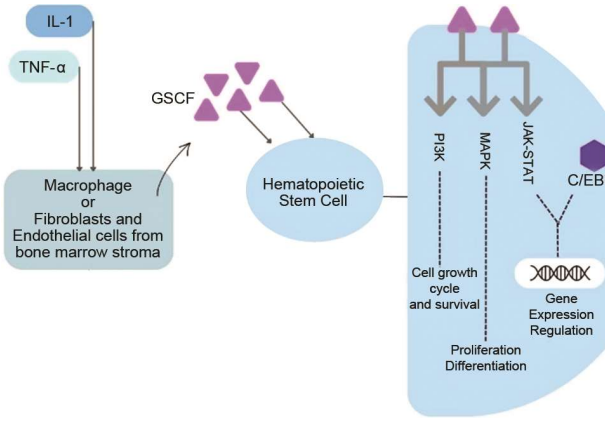

Fig. 2 — Mechanism of granulocyte colony-stimulating factor signaling for expression and development of neutrophils *Abbreviations:* IL-1: interleukin 1, TNF-α: tumor necrosis factor alpha, GSCF: granulocyte colony-stimulating factor, JAK-STAT: Janus kinase - signal transducer of activation pathway, MAPK: mitogen activated protein kinase, PI3K: phosphoinositide 3-kinase, C/EBPβ: CCAAT/enhancer-binding protein beta

MYL-1401H (pegfilgrastim-jmdb)

Made by Mylan (Hyderabad, India), MYL-1401H or Fulphila® is the first pegfilgrastim biosimilar to be approved by the FDA in June 2018[25]. The approved dosing regimen is 6mg/0.6 mL[25]. Results of a phase III study demonstrated that MYL-1401H was comparable to the reference pegfilgrastim in terms of efficacy and safety[26]. The primary endpoint of the study, which was the duration of severe neutropenia in the first chemotherapy cycle, showed no statistically significant difference between MYL-1401H and the reference pegfilgrastim. Secondary endpoints, including the incidence of FN, duration of severe neutropenia across all chemotherapy cycles, time to ANC recovery, and adverse events, were also similar between MYL-1401H and the reference product. The incidence of grade 4 neutropenia throughout all therapeutic cycles was observed in only 7% of patients receiving MYL-1401H and 9% of patients receiving the reference pegfilgrastim[26].

A retrospective cohort study investigated the cost savings for reference pegfilgrastim and Fulphila® in the first cycle among those commercially insured. The results indicated patients using pegfilgrastim biosimilar (Fulphila® and Udenyca®) for primary prophylaxis allocated 47%-57% lower costs than patients using the originator[15]. Another study found the FN incidence ranged from 1.8% to 3.83% for MYL-1401H whereas pegfilgrastim originator ranged from 1.35% to 2.59%[27].

Q5111 (pegfilgrastim-cbqv)

Q5111 or Udenyca®, made by Coherus BioSciences, Inc. (Redwood City, CA), was approved by the FDA in November 2018[28]. A retrospective cohort study compared the effectiveness of Q5111 and pegfilgrastim originator in the prevention of FN[27]. The results of the study indicated that there were no significant differences in the incidence of FN between the patients treated with pegfilgrastim biosimilars and those treated with the originator product[27].

Table 2 — Summary of the approved pegfilgrastim biosimilars for the treatment of febrile neutropenia

Biosimilar	Reference	Therapy	Patient Sample	Phase	Cohort	Results	AEs/SAEs
MYL- 1401H	Waller *et al* (2019)[26]	Neoadjuvant chemotherapy with docetaxel/doxorubicin/ cyclophosphamide (TAC) every 3 weeks for 6 cycles with MYL-1401H	Adult patients with newly diagnosed stage II/III BC	III	194	Incidence ofneutropenia 7% MYL-1401H *vs.* 9%	TEAEs 90% MYL-1401H v. 87%
Q5111	Wang *et al* (2023)[27]	Retrospective cohort study using 2019 IBM MarketScan database	Adult patients with cancer (BC, lung, colorectal, esophageal, gastric, pancreatic, prostate, ovarian or non-Hodgkin lymphomas) who received myelosuppressive chemotherapy	N/A	2,045	Incidence of neutropenia 1.10%-2.53% Q5111 *vs.* 1.35%-2.59%	No TEAEs reported
LA-EP2006	Harbeck *et al* (2016)[32]	Neoadjuvant TAC regimen chemotherapy on day 1 of each chemotherapy cycle and every 3 weeks for 6 weeks with LA-EP2006	Adult women receiving chemotherapy for BC	III	316	Incidence of neutropenia 5.7% LA-EP2006 v. 7.6%	Similar TEAEs 88.1% LA-EP2006 *vs*. 82.8%
PF-06881894	Yao *et al* (2021)[36]	TAC chemotherapy after definitive breast surgery for 4 consecutive 21-day cycles with PF-06881894	Adult women with non-distantly metastatic (non-stage IV) BC	I, II	25	Incidence of neutropenia 15% in phase II PF-06881894	98.2% TEAEs during Phase I/II
Q5130	FDA (2022)[38]	Doxorubicin 60 mg/m²and docetaxel 75 mg/m² administered every 21 days for up to 4 cycles for the treatment of metastatic BC	Patients with cancer receiving myelosuppressive chemotherapy	N/A	157	Mean days of severe neutropenia 1.8 in peg v. 1.6 in filgrastim arm	Similar TEAEs and SAEs
MSB11455	Lickliter *et al* (2020)[42]	6 mg/0.6 mL MSB11455 day 1 with 42-day washout between doses	Healthy adult men and women	I	292	Immunogenicity rate 8.9% MSB11455 v. 9.5%	TEAE 93.3% MSB11455 v. 97%

Abbreviations: BC: breast cancer, ANC: absolute neutrophil recovery, TEAE: Treatment Emergent Adverse Events, AE: Adverse Events, SAE: Serious Adverse Events, IBM: International Business Machines Corporation, ECOG: Eastern Cooperative Oncology Group, BMI: Body Mass Index, TAC: neoadjuvant chemotherapy with docetaxel, doxorubicin and cyclophosphamide

Additionally, no significant differences were observed in the rates of hospitalizations or emergency room (ER) visits related to FN between the two groups[27]. Specifically, the incidence of neutropenia was 1.1%-2.53% for Q5111 versus 1.35%- 3.59% for the originator[27]. The efficacy endpoint of a matched cohort analysis of breast cancer patients receiving Q5111 versus reference pegfilgrastim was the neutropenia rate. This study concluded Q5111 neutropenia rate at 28.6% and reference pegfilgrastim neutropenia rate at 29.1%[29].

The application of Q5111 has expanded to not just novel therapeutic agents but to folfirinox[30]. The study suggests that converting to the biosimilar Q5111 can provide budget-neutral access to folfirinox treatment for patients with metastatic pancreatic cancer. Results showed that using biosimilar Q5111 for one cycle can provide enough savings to purchase an additional month (two cycles) of folfirinox for one patient. Over 12-cycles, the patient saved $6,907.41 with the conversion from reference to biosimilar Q5111. By using biosimilar Q5111, it enables the patient to use savings towards better access to pivotal anti-cancer treatment.

LA-EP2006 (pegfilgrastim-bmez)

LA-EP2006 or Ziextenzo®, was made by Sandoz International (Basel, Switzerland) and approved by the FDA in November 2019[31]. In a two-part trial investigation, PROTECT-1 trial concluded LA-EP2006 to be therapeutically equivalent to the reference pegfilgrastim in terms of effectiveness and safety for breast cancer patients undergoing

chemotherapy[32]. The recorded incidence of FN in cycle-1 for LA-EP2006 and reference pegfilgrastim was 3.8% and 7%, respectively. The recorded incidence of FN in all cycles for LA-EP2006 and reference pegfilgrastim was 5.7% and 7.6%, respectively. Subsequently, PROTECT-2 trial confirmed the results of PROTECT-1 and further implied that patients have the possibility of receiving prophylactic biologic treatments instead of waiting until complications arise[33].

PF-06881894 (pegfilgrastim-apgf)

The FDA approved PF-06881894 or Nyvepria® made by Pfizer, Inc. (New York, NY) in June 2020[34,35]. A study involving a phase I/II design, evaluated single ascending doses as well as multiple subcutaneous doses of PF-06881894[36]. The results of the study demonstrated that PF-06881894 exhibited a pharmacokinetic profile and safety profile similar to the reference pegfilgrastim. The pharmacokinetic parameters, such as area under the curve (AUC) and maximum serum concentration (C_{max}) were comparable between PF-06881894 and the reference product. The incidence of FN was 15% in phase II, and when compared with literature values, was consistent with the reference pegfilgrastim.

Findings of a single-dose (C1221001) and multiple-dose (C1221005) phase I study indicated that PF-06881894 demonstrated similar pharmacodynamic effects, pharmacokinetic profiles, and immunogenicity compared to the reference products[37]. The study also showed that PF-06881894 had a comparable safety profile to the reference products, with no significant differences in the incidence of adverse events. The most common treatment-emergent adverse events (TEAEs) were musculoskeletal pain, headache, and back pain.

Q5130 (pegfilgrastim-pbbk)

Made by Kashiv BioSciences, LLC (Piscataway, NJ), Q5130 or Fylnetra® was approved in May 2022 by the FDA[35,38,39]. Cancer patients (n=157) receiving myelosuppressive chemotherapy employed doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 every 21-days for up to four cycles for the treatment of metastatic breast cancer. The mean days of severe neutropenia for Q5130 were 1.8 and 1.6 in the reference drug, respectively[40].

A placebo-controlled study randomized 928 breast cancer patients to receive either pegfilgrastim (6 mg) or place on day 2 of chemotherapy. The incidence of FN and hospitalizations was lower in the pegfilgrastim-treated patients. Clinically significant adverse reactions when receiving pegfilgrastim products included acute respiratory distress syndrome, splenic rupture, and serious allergic reactions[40].

The efficacy, safety, and pharmacokinetics (PK) properties in pediatric and young adult patients were established (n=43). The patients were randomized to receive single dose pegfilgrastim or filgrastim. The recovery of neutrophil counts and common adverse reactions were similar in both groups. Bone pain was the most common adverse reaction[40].

MSB11455 (pegfilgrastim-fpgk)

Made by Fresenius Kabi (Bad Homburg, Germany), MSB11455 or Stimufend® was approved by the FDA in September 2022[41]. In a phase I study, findings indicate that MSB11455 is bioequivalent to reference pegfilgrastim in terms of pharmacokinetics and pharmacodynamics in healthy subjects[42]. The results of the study showed that MSB11455 exhibited pharmacokinetic parameters, such as the C_{max} and AUC, that were comparable to the reference product. Furthermore, the pharmacodynamic effects, including the ANC and duration of severe neutropenia, were also similar between MSB11455 and reference pegfilgrastim. The data recorded an immunogenicity rate of 8.9% and 9.5% for the MSB11455 and reference product, respectively[42].

Assessment of tolerability and safety of MSB11455 supports biosimilarity to reference pegfilgrastim products[43]. The primary objective of the study was to compare the immunogenicity. The secondary objective was to establish and compare safety and tolerability of MSB11455 and reference pegfilgrastim. The study of 336 patients showed no significant differences in the anti-drug antibody (ADA) titers among the subjects with an ADA-positive sample in the two treatment groups. The TEAE like increased white blood cell count ($\geq 50.0 \times 10^9$/L) occurred in 9.5% of MSB11455 cohort and 11.9% in the reference pegfilgrastim cohort. Headache, bone pain, and spinal pain were the most common TEAE reported among both groups.

Additional pegfilgrastim biosimilar launches for the US-FDA

Cardinal Health's list of *"New and upcoming biosimilar launches"* lists two pegfilgrastim biosimilars pending the FDA approval (updated February 2023): Lupifil-P® and Lapelga®[44]. Below we

describe biochemical and clinical properties of these additional/key pegfilgrastim biosimilars launches by the FDA for the treatment of FN.

Lupifil-P

Lupifil-P® is a pegfilgrastim biosimilar being developed by Lupin Limited, headquartered in Mumbai, India[45]. As of 2021, the FDA has accepted the Biologics License Application (BLA) of Lupin's pegfilgrastim biosimilar. This biosimilar was filed under a biosimilar 351 (k) application. In early 2022, Lupin licensed Axantia Holding, a pharmaceutical company, to register, distribute, and market Lupifil-P®. Axantia Holding (Amman, Jordan) will supply to countries like Saudi Arabia, Jordan, Lebanon, Iraq, Sudan, Libya, and Algeria[46].

INTP5

INTP5 or Lapelga®, made by Apotex, Inc. (Toronto, Ontario, Canada), was approved by Health Canada in 2018[47]. A study (of early breast cancer with adjuvant chemotherapy, n=201) recorded 3.48% incidence of FN across three different types of chemotherapy regimens[48,49]. Another study (of breast cancer with neoadjuvant chemotherapy, 129 patients) findings agreed with these results as theFN occurrence was 2.4% for Neulasta® and 5.1% for Lapelga®[50].

Intas Pharmaceutical Ltd. (Ahmedabad, India) is currently assessing the pharmacodynamics (PD), PK, and safety of INTP5 (EudraCT2021-004792-14). The study will include pediatric patients under 6-years of age diagnosed with rhabdomyosarcoma or Wilms' tumor who are on myelosuppressive chemotherapy regimen[51]. The primary endpoint will look at ANC, incidence of febrile neutropenia and AUC of ANC. The secondary endpoint will establish the PK, PD, safety, and tolerability of single versus daily dose administrations.

In a phase I study (n=66), Apotex's biosimilar pegfilgrastim showed bioequivalence for primary and secondary end points with that of the reference pegfilgrastim[52]. There were no significant differences in the serious adverse events reported (SAE). Increased white blood cells, bone pain and headache were the three most common adverse events (AE). ANC and cluster of differentiation (CD)34^+ were well within the 90% confidence intervals with relative mean ratios near 100%. This goes to further solidify the pharmacodynamic similarity between the pegfilgrastim biosimilar and reference product.

Conclusion

FN is characterized by fever with a dangerously low count of neutrophils crucial for fighting infections. This condition is commonly experienced by chemotherapy patients or hematopoietic stem cell transplantation, where the immune system is compromised[53]. Other causes for FN may include medications, radiation therapy, and underlying hematologic disorders.

Biosimilars facilitate advancement in modern medicine by not only providing cost effective alternatives but increasing accessibility and variability. As regulatory pathways for biosimilars continue to evolve and gain acceptance in various regions, the market penetration of biosimilars is expected to increase. Regulatory agencies worldwide are working to streamline and harmonize biosimilar approval processes in efforts of a global collaboration. This global alignment will lead to more efficient and consistent evaluation and approval of biosimilars, accelerating their entry into the market. Interchangeability status means a biosimilar can be substituted for the reference product without the intervention of a healthcare provider. As more biosimilars meet interchangeability criteria, patient access and market adoption could further increase[54,55].

Biosimilars empower patients and healthcare providers to make informed treatment choices based on cost-effectiveness and individual patient needs[54,55]. Pegfilgrastim, a modified long-lasting form of the medication filgrastim, has helped patients recover without comprising their active chemotherapy regimens. Pegfilgrastim is commonly used in oncology and hematology settings and used to treat a number of complications including FN. With the introduction of pegfilgrastim biosimilars, the outcomes of many diseases and their treatment success rates can be greatly improved. Biosimilars to pegfilgrastim have showed comparable pharmacodynamic and pharmacokinetic profiles with no significant differences in safety and efficacy while treating FN. As noted above, as more biosimilars are being approved and launched, biomedical technologic innovations are on the rise. An active study is researching patient preference of a prefilled pegfilgrastim pen device in hopes of teaching the patient to self-administer at home or rural area emergencies (NCT05910164)[53]. This pushes for effective treatment that contributes to the sustainability of healthcare worldwide.

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