

Pegfilgrastim Biosimilars: Where Are We Now?

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Abstract

In 1991, the U.S. Food & Drug Administration (FDA) approved rmetHuG-CSF for human use. This recombinant methionyl human granulocyte colony-stimulating factor, or filgrastim, saw use in over 1 million patients in its first 5 years on the market. In 2002, the FDA approved a version of filgrastim with covalent linkage to a monomethoxypolyethylene glycol, increasing the molecular size and half-life to replace multiple days of dosing with a single injection. These medications remained standard of care for neutropenia until the Biologics Price Competition and Innovation Act of 2009 created an abbreviated pathway to licensure for biologic products. Practitioners now have their pick of numerous and expanding options for pegfilgrastim biosimilars.

Chemotherapy-induced neutropenia is one of the major dose-limiting toxicities of many cancer treatments. Neutropenia is defined as an absolute neutrophil count (ANC) of < 500 cells/mm³ or an expected decrease to < 500 cells/mm³ during the next 48 hours. This, combined with a single oral temperature measurement of $> 38.3^{\circ}\text{C}$ (101°F) or a temperature of $\geq 38.0^{\circ}\text{C}$ (100.4°F) sustained over a 1-hour period, defines febrile neutropenia (FN; National Comprehensive Cancer Network [NCCN], 2020; Smith et al., 2015; Taplitz et al., 2018). A reduced ANC predisposes patients to potentially serious and life-threatening infections. In patients receiving chemotherapy, neutropenia can result in dose reduction, treatment delays, and/or treatment discontinuation, which can negatively impact overall disease control. Major complications of FN, such as hypotension, acute heart, renal and/or respiratory failure, have been reported to occur in 25% to 30% of patients with a mortality rate upwards of 11% (Taplitz et al., 2018). A study by Tai and colleagues (2017) estimated that in 2012, there were 108,419 cancer-related neutropenia hospitalizations in the United States at a total cost of \$2.7 billion, accounting for 8.3% of all cancer-related hospitalization costs. Thus, neutropenia prophylaxis is vital to prevent infectious complications and treatment interruptions from both a

personal and public health perspective (Smith et al., 2015).

Hematopoietic colony-stimulating factors (CSFs) have been shown to reduce the duration and severity of neutropenia and the risk of febrile neutropenia. Current cancer therapy guidelines recommend using granulocyte colony-stimulating factors (G-CSF) for primary prophylaxis in chemotherapy regimens with $\geq 20\%$ risk of febrile neutropenia or for secondary prophylaxis to allow more intensive or dose-dense chemotherapy when appropriately indicated (NCCN, 2020; Smith et al., 2015; Taplitz et al., 2018). Until recently, provider options were limited to filgrastim (Neupogen) and pegfilgrastim (Neulasta). Now, patients and providers have more choices in the matter thanks to the Biologics Price Competition and Innovation Act (BPCI Act) of 2009 (FDA, 2017).

Biosimilar products are not generics in that they are not exact copies. Due to the complex physical nature of proteins, the products are instead similar, hence the term “biosimilar.” The biosimilar has no clinically meaningful differences from the reference product in terms of safety, purity, and potency of the product (FDA, 2017). They are required to maintain the primary amino acid structure but may differ in terms of deamination, glycosylation, oxidation, or within the layout of their three-dimensional structure (Aronson & Ferner, 2016). This slight difference requires clinical testing to ensure that the biosimilar functions similarly to its reference product, typically through bioequivalence testing. To test for bioequivalence, a biosimilar is compared with its reference product in terms of pharmacokinetic and pharmacodynamic endpoints and must fall within 80% to 125% of the reference product. In terms of finding bioequivalence for G-CSF products, pharmacodynamic endpoints focus on the medication concentrations such as area under the curve (AUC) and peak levels (C_{max}), while pharmacodynamic endpoints tend to be response measurements like ANC_{max} , ANC AUC, ANC responses including time to ANC nadir, depth of ANC nadir, or time to ANC recovery (Blackwell et al., 2016; Gladkov et al., 2016; Glaspy et al., 2017).

With medications like pegfilgrastim (Neulasta) serving as the reference product, other manufacturers now have a pathway to getting competing products to market. With more of these new products

rapidly gaining approval and pharmacy benefit manager preferences changing just as quickly, providers are struggling to keep up. This article is intended to compare and contrast the currently available biosimilars for the reference product of pegfilgrastim.

PHARMACOLOGY AND MECHANISM OF ACTION

Typically, healthy individuals have a low circulating level of endogenous G-CSF, which is upregulated in the presence of potential infection. This is known as demand-driven granulopoiesis (Panopoulos & Watowich, 2008). G-CSF in circulation will bind to the G-CSF receptor (G-CSFR), leading to the increased production of granulocytic precursors, decrease in granulocyte maturation time, and increased survival of mature granulocytes. This receptor is located primarily on granulocytes and is present throughout their life cycle, from myeloblast to mature neutrophil, but is not found on any megakaryocyte or erythrocyte cell lines (Demetri & Griffin, 1991).

Recombinant G-CSF, administered exogenously, leads to the same changes in endogenous G-CSF. By binding to the G-CSFR, G-CSF starts a process that involves the phosphorylation and/or activation of multiple intracellular kinase pathways, including the JAK/stat and the RAS/RAF/MEK/ERK/MAP pathways. Cyclin-dependent kinase 3 is also necessary to achieve granulopoiesis, illustrating how complex this process can be (Panopoulos & Watowich, 2008).

CLINICAL TRIALS

In clinical studies, biosimilar products were compared with either a European pegfilgrastim product, United States pegfilgrastim product, or both. The FDA considers biosimilar pharmacokinetic/pharmacodynamic studies the most useful information for detecting clinically meaningful differences between a biosimilar and its reference.

Pegfilgrastim-jmdb (Fulphila)

Pegfilgrastim-jmdb demonstrated comparability to pegfilgrastim in terms of pharmacokinetics, pharmacodynamics, and safety in a phase I clinical trial (Waller et al., 2018). It has also proven to have a similar immunogenic profile compared with pegfilgrastim (Waller et al., 2017). In a phase

III, multicenter, randomized, double-blind, parallel group trial, the safety and efficacy of pegfilgrastim-jmdb was compared with the European reference pegfilgrastim. This trial was conducted in 194 newly diagnosed breast cancer patients who were randomized in a 2:1 ratio to receive pegfilgrastim-jmdb vs. reference pegfilgrastim 24 hours after completion of neoadjuvant chemotherapy for 6 cycles. There was no difference in number of days of severe neutropenia (1.2 ± 0.93 and 1.2 ± 1.10 ; 95% confidence interval [CI] for difference = $-0.285-0.298$) for pegfilgrastim-jmdb and reference pegfilgrastim, respectively. Time to ANC nadir, duration of post-nadir recovery, and treatment-related adverse events were also similar between the two treatment groups (Waller et al., 2019)

Pegfilgrastim-cbqv (Udenyca)

Pegfilgrastim-cbqv bioequivalence was studied in a multicenter, randomized, single-blind, crossover study in 122 healthy subjects, ages 18 to 45. Patients received one single 6-mg dose of pegfilgrastim-cbqv and two 6-mg doses of pegfilgrastim in random sequence. Each administration was separated by at least 28 days. Bioequivalence was achieved for the pharmacokinetic endpoints of C_{max} (geometric mean ratio [GMR] = 105; 90% CI = 95.5–115.4), $AUC_{0-\infty}$ (GMR = 97.5; 90% CI = 88.6–107.2), and for the pharmacodynamic endpoints of ANC $_{max}$ (GMR = 99.6; 90% CI = 96.2–103.2) and ANC AUC_{0-t} (GMR = 96.7; 90% CI = 92.2–101.4; Glaspy et al., 2017).

Pegfilgrastim-bmez (Ziextenzo)

Pegfilgrastim-bmez has shown equivalence to pharmacokinetic and pharmacodynamic properties of pegfilgrastim, with no difference in safety (Nakov et al., 2018). It has also demonstrated equivalent efficacy and safety in two phase III clinical trials. In PROTECT-1, 316 breast cancer patients receiving neoadjuvant or adjuvant treatment were randomized 1:1 to receive pegfilgrastim-bmez (n = 159) or reference pegfilgrastim (n = 157) 24 hours after completion of chemotherapy. Pegfilgrastim-bmez was equivalent to reference pegfilgrastim for the primary endpoint of mean duration of severe neutropenia during cycle 1 of chemotherapy (difference: 0.07 days; 95% CI = $-0.12-0.26$). There were no clinically meaningful differences found regarding secondary endpoints for either treat-

ment arm (Harbeck et al., 2016). Secondary endpoints included depth of ANC nadir, time to ANC recovery during cycle 1, incidence of FN across all cycles, and mortality due to infection.

These findings were confirmed in the PROTECT-2 trial. 308 breast cancer patients receiving neoadjuvant or adjuvant treatment were randomized 1:1 to receive pegfilgrastim-bmez (n = 155) or reference pegfilgrastim (n = 153) 24 hours after completion of chemotherapy. Primary endpoint of mean duration of severe neutropenia was equivalent between groups, with a treatment difference of 0.16 days (95% CI = $-0.40-0.08$). Secondary efficacy parameters, the same endpoints as PROTECT-1, and safety profiles were similar between the two groups (Blackwell et al., 2016).

Pegfilgrastim-apgf (Nyvepria)

Pegfilgrastim-apgf, the newest approved biosimilar, has been evaluated in two phase I studies that resulted in its recent FDA approval. The first phase I trial was a three-way study that compared pegfilgrastim-apgf to both the US and EU pegfilgrastim reference products. Pegfilgrastim-apgf achieved both pharmacodynamic endpoints and pharmacokinetic variables within the predefined guidelines for noninferiority to both the US and EU reference products. In the second phase I study, patients were randomized to assess immunogenicity and safety of pegfilgrastim-apgf vs. US pegfilgrastim. Pegfilgrastim-apgf was shown to be noninferior to US pegfilgrastim, and there was no clinically meaningful difference in safety between the two study groups (Moosavi et al., 2020).

ADVERSE EVENTS

The most common adverse reactions of pegfilgrastim, occurring in $\geq 5\%$ difference in incidence compared to placebo, are bone pain and pain in the extremity (Amgen Inc., 2020; Coherus Biosciences, Inc., 2018; Mylan Pharmaceuticals Inc., 2018; Pfizer Inc., 2020; Sandoz Inc., 2019). The mechanism of bone pain secondary to G-CSFs is not fully understood, but the following pathophysiological processes are thought to be involved: expansion of bone marrow, direct stimulation of afferent nerves, immune function changes, and direct stimulation of osteoclasts and osteoblasts. Furthermore, histamine release has been suggested as a mediator of

bone pain due to causing inflammation of the bone marrow, leaving antihistamines as promising, low-risk treatment agents (Romeo et al., 2015). Additional treatment options for G-CSF-induced bone pain include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids.

In direct comparison to reference pegfilgrastim, there was no statistically significant difference in the rate of treatment-emergent adverse events for the biosimilar or reference product (Glaspy et al., 2017; Nakov et al., 2018; Waller et al., 2019), suggesting that the reference products are well within the predefined FDA guidelines for safety of a biosimilar product.

All four biosimilar products plus the reference product carry a set of warnings for rare but serious side effects. Table 1 contains a list of these warnings and information about them.

FUTURE DIRECTIONS

It appears that the market will continue to grow in the number of biosimilar products available. As of June 2021, there are at least eight biosimilar pegfilgrastim products currently under review by the FDA or similar medical agency, or that have previously been approved outside of the US (see Table 2 for a concise listing of these medications). There are currently four FDA-approved biosimilars in the United States, with one other currently under FDA review (Biosimilars Review and Report, 2020; Hagen, 2020). When combined with reference pegfilgrastim (Neulasta) and pegfilgrastim on-body injector (Neulasta Onpro), the number of long-acting G-CSF products available in the US could soon reach seven. With safety and efficacy considered similar across products, this should lead to lower costs for patients and the health-

Table 1. Rare but Serious Adverse Events of Pegfilgrastim Products

Warning	Description
Splenic rupture	Patients with shoulder or left upper abdominal pain after receiving pegfilgrastim products should be evaluated for an enlarged spleen/splenic rupture.
Acute respiratory distress syndrome (ARDS)	Patients developing fever and lung infiltrates or respiratory distress after receiving pegfilgrastim products should be evaluated for ARDS.
Serious allergic reactions	Serious allergic reactions, including anaphylaxis, can occur in patients receiving pegfilgrastim products. The majority of reported events occurred upon initial exposure. Permanently discontinue pegfilgrastim products in patients with serious allergic reactions. Do not attempt to use a different pegfilgrastim product in the case of an allergic reaction. Neulasta Onpro also has reported allergic reactions to the acrylic adhesive that is used to adhere this product to the patient's body.
Use in patients with sickle cell disorders	Severe and potentially fatal sickle cell crises have been reported in patients with sickle cell disorders who have received pegfilgrastim products.
Glomerulonephritis	Glomerulonephritis has occurred in patients receiving pegfilgrastim. If glomerulonephritis is suspected, evaluate for causality.
Leukocytosis	White blood cell counts of $100 \times \geq 10^9/L$ have been observed in patients receiving pegfilgrastim products. Monitoring of complete blood count during therapy is recommended.
Capillary leak syndrome	Capillary leak syndrome has been reported after pegfilgrastim product use. This syndrome can be characterized by hypotension, hypoalbuminemia, and edema. Episodes vary in severity and may be life threatening. Treatment should not be delayed.
Potential for tumor growth stimulatory effects on malignant cells	The G-CSFR has been found on tumor cell lines. Therefore, the possibility of any contribution of pegfilgrastim products to tumor growth cannot be ruled out. This includes myeloid disease for which no pegfilgrastim product is currently indicated.
Aortitis	Aortitis occurring as early as the first week of therapy has been reported in patients receiving pegfilgrastim products. Signs and symptoms may include fever, abdominal pain, malaise, back pain, and increased inflammatory markers. Consider aortitis in patients who develop these signs and symptoms with no other known etiology.
Nuclear imaging	Increased bone marrow activity post growth factor use has been associated with transient positive bone imaging changes. This may affect the interpretation of bone imaging results.

Note. G-CSFR = granulocyte colony-stimulating factor receptor. Information from Amgen Inc. (2020); Coherus Biosciences, Inc. (2018); Mylan Pharmaceuticals Inc. (2018); Pfizer Inc. (2020); Sandoz Inc. (2019).

care system as a whole. However, this will require providers to be flexible and responsive to changes in a patient's insurance coverage and payors' preferred agents, as this could change frequently. Obtaining prior authorizations for G-CSF products as early as possible should minimize impact on the patient.

The BPCI Act allows for interchangeable biologic products. However, no products have been approved by the FDA for use in this manner. Interchangeable products are different from biosimilars in that they must undergo further testing to demonstrate that they will produce the same clinical response as the reference product and data regarding the safety and efficacy of switching between the interchangeable and reference product. In this way, any interchangeable product is thought to be more alike to its reference product than a biosimilar.

As there are no FDA-approved interchangeable biologic products, no biosimilar biologic product may be substituted for the reference product without prescriber approval. However, it should be noted that hospitals and health systems may enact policies allowing for substitution at a local level that also serves as prescriber notification. Now that the FDA provides a pathway for interchangeable products, individual state laws will begin to govern the dispensation of interchangeable products (Liu et al., 2020). A total of 49 states in the US have considered specific legislation on interchangeable biologic product substitution (Cauchi, 2019). These state laws provide guidance for pharmacists and providers in terms of what substitutions are allowed and how the pharmacist must notify or communicate to the provider of the substitution. The best resource for providers regarding biological product status in the US is the FDA's Purple Book, which provides the FDA's definitive stance on whether a biologic product is considered interchangeable or not. This is a companion to the FDA's Orange Book for nonbiologic drug products.

IMPLICATIONS FOR THE ADVANCED PRACTITIONER

Due to the strict requirements that the FDA sets for determining bioequivalence, the biggest difference with currently approved biosimilars and their

Table 2. Non-US Pegfilgrastim Products

Name	Company	Approval location
Lapelga	Apotex	Canada
Pelmeg	Cinfa Biotech/ Mundipharma	European Union
MSB11455	Fresenius Kabi	N/A
Peg-neutropine	Gema Biotech	Argentina
Cegfila	Mundipharma	European Union
Efgratin (RGB-02)	Gedeon Richter	Withdrawn
Grasustek	Juta Pharma	European Union
Pelgraz	Accord Healthcare	European Union
TPI-120	Adello Biologics	N/A
Lupifil P	Lupin	India
Peg-grafeel	Dr. Reddy's	N/A

Note. Information from Davio (2019a, 2019b, 2019c, 2019d); European Medicines Agency (2020); GaBI Online (2021); Hagen (2020); The Center for Biosimilars Staff (2019, 2020).

reference product is the possibility for significant cost savings. An economic analysis performed by McBride and colleagues (2020) demonstrated that conversion of pegfilgrastim to biosimilar pegfilgrastim could provide cost savings ranging from \$702.27 to \$1,638.63 per cycle per patient, depending on the discount percentage offered. For 20,000 patients, this yields a potential savings of over \$14 million (using a 15% discount) to \$32 million (based on a 35% discount) at 100% conversion rate to the biosimilar product. Building upon this, the authors state that with 100% conversion rate and the lower 15% discount, an additional 3,529 patients could be treated with G-CSF utilizing the savings generated from product conversion (McBride et al., 2020).

SUMMARY

New biosimilar products pegfilgrastim-bmez, pegfilgrastim-cbqv, pegfilgrastim-jmdb, and pegfilgrastim-apgf offer providers and patients more options in the single-dose, long-acting G-CSF class. Due to the FDA approval process, as described in the BPCI, and appropriate pharmacokinetic and pharmacodynamic data from clinical tri-

als, these products are considered to be as safe and effective as their reference biologic product. However, due to their abbreviated research and approval processes, these biosimilar manufacturers are typically willing and able to offer these products at a lower cost than the available reference product. This equivalent safety and efficacy data, combined with a potentially lower price point, offers clinicians and patients expanded access to medications and hopefully a decrease in potential dose-limiting adverse effects of cancer therapy. ●

Disclosure

The authors have no conflicts of interest to disclose.

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