More biosimilars reach the market in efforts to improve access and cut costs

Biosimilars are copies of FDA-approved biologic drugs (those generally derived from a living organism) that cannot be identical to the reference drug but demonstrate a high similarity to it. As patents on the reference drugs expire, biosimilars are being developed to increase competition in the marketplace to reduce costs and improve patient access to therapy. Although the US Food and Drug Administration (FDA) has no regulatory power over drug prices, it recently announced efforts to streamline the biosimilar approval process to facilitate access to therapies and curb the associated skyrocketing costs.

Several biosimilars have been approved by the agency in recent years, and earlier this year they were joined by 2 more: the approval in May of epoetin alfa-epbx (Retacrit; Hospira, a Pfizer company) for all indications of the reference product (epoetin alfa; Epogen/Procrit, Amgen), including the treatment of anemia caused by myelosuppressive chemotherapy, when there is a minimum of 2 additional months of planned chemotherapy;[1] and the June approval of pegfilgrastim-jmdb (Fulphila, Mylan and Biocon) for the treatment of patients undergoing myelosuppressive chemotherapy to help reduce the chance of infection as suggested by febrile neutropenia (fever, often with other signs of infection, associated with an abnormally low number of infection-fighting white blood cells).[2] The reference product for pegfilgrastim-jmdb is pegfilgrastim (Neulasta, Amgen).

The approval of both biosimilars was based on a review of a body of evidence that included structural and functional characterization, animal study data, human pharmacokinetic (PK) and pharmacodynamic (PD) data, clinical immunogenicity data, and other clinical safety and efficacy data. This evidence established that the biosimilars were highly similar to the already FDA-approved reference products, with no clinically relevant differences.

Biocon and Mylan-GmBH, which jointly developed pegfilgrastim-jmdb, originally filed for approval in 2017; and Hospira Inc, a Pfizer company that developed epoetin alfa-epbx, filed for the first time in 2015. They subsequently received complete response letters from the FDA, twice in the case of the epoetin alfa biosimilar, rejecting their approval. For pegfilgrastim-jmdb, the complete response letter was related to a pending update of the Biologic License Application as the result of requalification activities taken because of modifications at their manufacturing plant. For epoetin alfa-epbx, the FDA expressed concerns relating to a manufacturing facility. The companies addressed the concerns in the complete response letters and submitted corrective and preventive action plans.[3,4]

What's new, what's important

A number of biosimilars have been approved in recent years by the FDA, which plans to streamline the approval process to improve access to these cheaper therapies. Two recent biosimilar approvals were for epoetin alfa-epbx (Retacrit) for the treatment of CIA, and pegfilgrastim-jmdb (Fulphila) for reducing the risk of infection from febrile neutropenia. The approvals were based on a review of evidence that established that the biosimilars were highly similar to the FDA-approved reference products, with no clinically relevant differences.

The recommended dose of pegfilgrastim-jmdb is a 6 mg/0.6 mL injection, administered subcutaneously once per chemotherapy cycle. It should not be administered between 14 days before and 24 hours after administration of chemotherapy. Among the warnings in the prescribing information are splenic rupture, ARDS, allergic reactions, risk for sickle cell crises in patients with sickle cell disorders, and potential for tumor growth or recurrence.

The recommended dose of epoetin alfa-epbx is 40,000 Units weekly or 150 U/kg 3 times weekly in adults and 600 U/kg IV weekly in patients aged 5 years or younger. It comes with a boxed warning about increased risks of death, heart problems, stroke, and tumor growth, or recurrence. There are warnings in the prescribing information relating to hypertension, seizures, lack or loss of hemoglobin response, pure red cell aplasia, serious allergic reactions, and severe cutaneous reactions. There are also recommendations for lack or loss of hemoglobin response to epoetin alfa-epbx. Treatment should be discontinued for serious allergic reactions or severe cutaneous reactions.

— Jame Abraham, MD, FACP (abrahaj5@ccf.org)

Pegfilgrastim-jmdb

The results from a phase 3, multicenter, randomized, double-blind parallel-group trial of pegfilgrastim-jmdb compared with European Union-approved pegfilgrastim were published in 2016. Chemotherapy and radiation-naïve

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Mechanism of action: pegfilgrastim-jmdb and epoetin alfa-epbx

Biosimilars exploit CSF family. Pegfilgrastim and epoetin alfa are FDA-approved drugs indicated for the treatment of febrile neutropenia and anemia, respectively, in patients receiving myelosuppressive chemotherapy. As the lawful intellectual property on these drugs expires, other pharmaceutical companies are seeking to develop their own versions, and it is hoped that the increased competition could improve access and drive down costs.

Since both drugs are biological products, derived from living organisms, it is impossible to produce an identical copy. Instead other companies can produce biosimilars that have high similarity and display no clinically meaningful differences in terms of their safety, purity, potency, and other criteria. Several biosimilars have been approved in recent years, including a non-pegylated version of filgrastim (Zarxio).

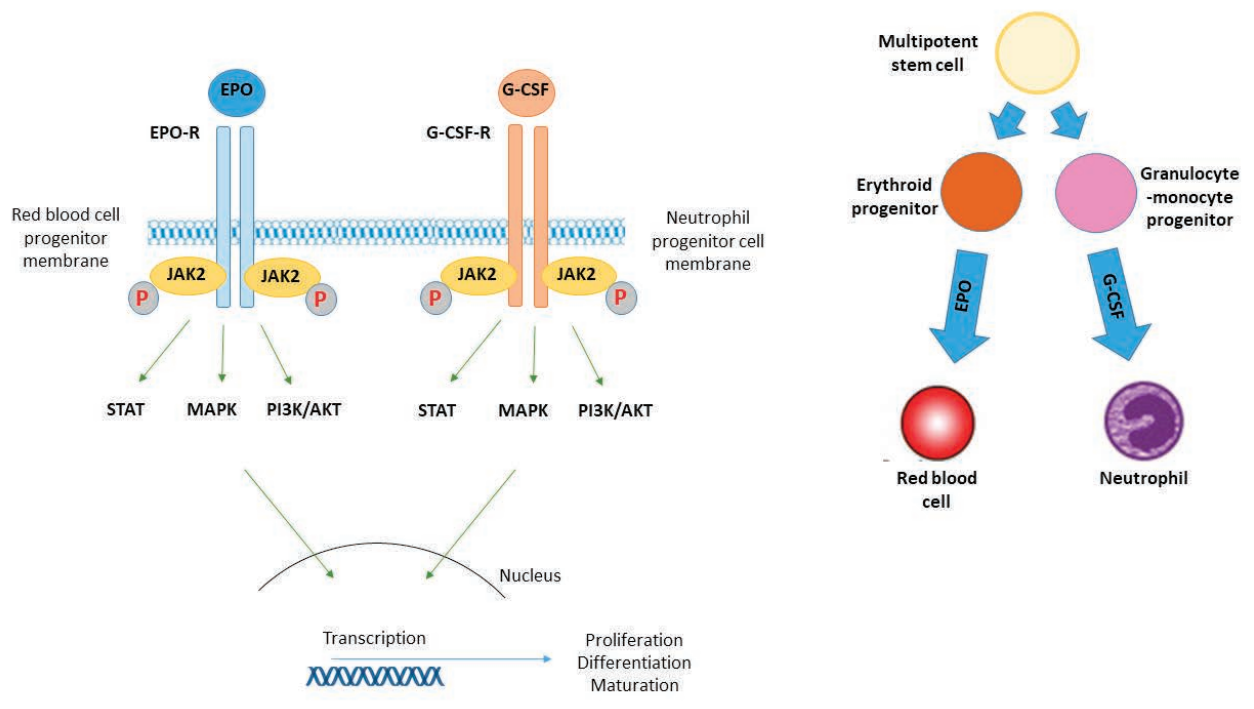
Pegfilgrastim-jmdb (Fulphila) is the first FDA-approved biosimilar to pegfilgrastim, a form of filgrastim that has been modified by the addition of polyethylene glycol (PEG) polymer chains that help to increase its time in the circulation by reducing renal clearance. Filgrastim is a recombinant human analog of granulocyte-colony stimulating factor (G-CSF), a cytokine that binds to its receptor – G-CSFR – on the surface of precursor cells in the bone marrow, including granulocyte-monocyte progenitors.

Epoetin alfa-epbx (Neupogen) is a biosimilar of epoetin alfa, a recombinant analog of another member of the colony-stimulating factor family, erythropoietin (EPO). EPO binds to EPO receptors on the surface of other types of precursor cells in the bone marrow, mostly erythroid progenitors.

Binding of the these CSF family cytokines to their respective receptors triggers intracellular signaling networks that include the Janus kinase (JAK)-signal transducer and activator of transcription (STAT), mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI3K)/AKT pathways. Ultimately, these pathways trigger the transcription of genes in the nucleus that drive the proliferation, differentiation, and maturation of the target cells.

In the case of EPO, this drives the production of red blood cells; EPO stimulates the daily production of about 200 billion new cells. G-CSFR, meanwhile, stimulates the production of neutrophils, a type of white blood cell characterized by little sacs of digestive enzymes in their cytoplasm that they use in their phagocytic role in the immune system.

Thus, treating patients who are undergoing myelosuppressive chemotherapy with pegfilgrastim-jmdb or epoetin alfa-epbx can help to boost the production of neutrophils and red blood cells, respectively, to overcome the neutropenia and anemia that are often associated with the use of this type of cancer therapy.



Epoetin alfa-epbx and pegfilgrastim-jmdb are biosimilars of FDA-approved recombinant analogs of the human colony-stimulating factors erythropoietin (EPO) and granulocyte colony-stimulating factor (G-CSF) analogs, respectively. EPO and G-CSF bind to their respective receptors on the surface of particular types of hematopoietic cells in the bone marrow and, through activation of intracellular signaling pathways stimulate their proliferation, differentiation and maturation, thereby replenishing the loss of red blood cells and neutrophils that occur as a result of anemia and neutropenia, respectively. Figure created by Jane de Lartigue.

patients with newly diagnosed breast cancer (n = 194) received the biosimilar or reference product every 3 weeks for 6 cycles. The primary endpoint was duration of severe neutropenia in cycle 1, defined as days with absolute neutrophil count <0.5 x 10^9/L. The mean standard deviation was 1.2 [0.93] in the pegfilgrastim-jmdb arm and 1.2 [1.10] in the EU-pegfilgrastim arm, and the 95% confidence interval of least squares means differences was within the -1 day, +1 day range, indicating equivalency.[5]

A characterization and similarity assessment of pegfilgrastim-jmdb compared with US- and EU-approved pegfilgrastim was presented at the 2018 Annual Meeting of the American Society of Clinical Oncology. G-CSF receptor (G-CSFR) binding was assessed by surface plasmon resonance and potency was measured by in vitro stimulated proliferation in a mouse myelogenous leukemia cell line. In vivo rodent studies were also performed and included a PD study with a single dose of up to 3 mg/kg.[6]

There was high similarity in the structure, molecular mass, impurities and functional activity of the biosimilar and reference products, as well as similar G-CSFR binding and equivalent relative potency. Neutrophil and leukocyte counts were increased to a similar degree, and toxicology and drug kinetics were also comparable.

The recommended dose of pegfilgrastim-jmdb is a 6 mg/0.6 ml injection in a single-dose prefilled syringe for manual use only, administered subcutaneously once per chemotherapy cycle. The prescribing information also has dosing guidelines for administration in pediatric patients who weigh less than 45 kg. Pegfilgrastim-jmdb should not be administered between 14 days before and 24 hours after administration of chemotherapy.

The prescribing information details warnings and precautions relating to splenic rupture, acute respiratory distress syndrome (ARDS), serious allergic reactions, potential for severe/fatal sickle cell crises in patients with sickle cell disorders, glomerulonephritis, leukocytosis, capillary leak syndrome, and the potential for tumor growth or recurrence.[7]

Patients should be evaluated for an enlarged spleen or splenic rupture if they report upper left abdominal or shoulder pain. Patients who develop fever and lung infiltrates or respiratory distress should be evaluated for ARDS and treatment discontinued if a diagnosis is confirmed. Pegfilgrastim-jmdb should be permanently discontinued in patients who develop serious allergic reactions and should not be used in patients with a history of serious allergic reactions to pegfilgrastim or filgrastim products.

Dose-reduction or interruption should be considered in patients who develop glomerulonephritis. Complete blood counts should be monitored throughout treatment. Patients should be monitored closely for capillary leak syndrome and treated with standard therapy. Pegfilgrastim-jmdb is marketed as Fulphila.

Epoetin alfa-epbx

Epoetin alfa-epbx was evaluated in 2 clinical trials in healthy individuals. The EPOE-12-02 trial established the PK and PD following a single subcutaneous dose of 100 U/kg in 81 participants. The EPOE-14-1 study was designed to determine the PK and PD of multiple doses of subcutaneous 100 U/kg 3 times weekly for 3 weeks in 129 participants. Both studies met prespecified criteria for PK and PD similarity to US-approved epoetin alfa, including geometric mean of area under the curve (AUC)0-120h, AUC0-inf, C_{max} (maximum serum concentration achieved by a drug in a specified area of the body) and E_{max} (maximum response achievable for a drug dose).

Evidence of efficacy and safety were also evaluated using pooled data from EPOE-10-13 and EPOE-10-01, conducted in patients with chronic kidney disease, which was considered the most sensitive population in which to evaluate clinically meaningful differences between the biosimilar and reference product.[8,9]

There were no clinically meaningful differences in efficacy and a similar adverse event profile. The most common side effects include high blood pressure, joint pain, muscle spasm, fever, dizziness, respiratory infection, and cough, among others.

The recommended dose of epoetin alfa-epbx, which is marketed as Retacrit, is 40,000 Units weekly or 150 U/kg 3 times weekly in adults and 600 U/kg intravenously weekly in pediatric patients aged 5 years or younger. Epoetin alfa-epbx comes with a boxed warning to alert health care providers to the increased risks of death, heart problems, stroke, and tumor growth, or recurrence. The prescribing information also details warnings and precautions relating to these risks, as well as hypertension, seizures, lack or loss of hemoglobin response, pure red cell aplasia, serious allergic reactions, and severe cutaneous reactions.[9]

Blood pressure should be appropriately controlled before treatment initiation, treatment should be reduced or withheld if it becomes uncontrollable, and patients should be advised of the importance of compliance with anti-hypertensive medication and dietary restrictions. Patients should be monitored closely for premonitory neurologic symptoms and advised to contact their provider in the event of new-onset seizures, premonitory symptoms, or change in seizure frequency.

The prescribing information has dosing recommendations for lack or loss of hemoglobin response to epoetin alfa-epbx. If severe anemia or low reticulocyte count occur, treatment should be withheld and patients evaluated for neutralizing antibodies to erythropoietin and, in the event that PRCA is confirmed, treatment should be permanently discontinued. Treatment should be immediately and permanently discontinued for serious allergic reactions or severe cutaneous reactions.

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