Comparison of Filgrastim and Its Biosimilars in Cancer Chemotherapy

Ruoyu Ning

China Pharmaceutical University, Nanjing, Jiangsu Province, China

2020220457@stu.cpu.edu.cn

Abstract. Chemotherapy-induced neutropenia (CIN) is a common and serious complication in cancer patients, potentially leading to febrile neutropenia (FN), increased risk of infection, and delayed chemotherapy, severely impacting treatment efficacy and patient prognosis. Filgrastim (FIL), a granulocyte colony-stimulating factor (G-CSF) drug, significantly reduces the incidence of FN by stimulating neutrophil proliferation and differentiation. This article systematically reviews the molecular structure, mechanism of action, pharmacokinetic characteristics, and efficacy of FIL in cancer chemotherapy. This article also provides an in-depth comparative analysis of the structural consistency and clinical efficacy of various FIL biosimilars. Numerous clinical studies and data demonstrate that these biosimilars are equivalent to the original drug, Neupogen®, in terms of efficacy and safety, while significantly reducing treatment costs and improving patient accessibility and compliance. Although additional follow-up data are needed for some biosimilars regarding immunogenicity and long-term interchangeability, current evidence suggests their potential for broad clinical application. Future efforts should strengthen monitoring of the long-term effects of biosimilars and optimize their structural properties to further enhance their quality consistency and global accessibility.

Keywords: Filgrastim, biosimilar, cancer chemotherapy, chemotherapy-induced neutropenia.

1. Introduction

Cancer is one of the leading causes of death worldwide, with its morbidity and mortality rates continuing to rise, with an estimated 2.3 million new cases in 2022. It remains a major global public health concern (Filho et al., 2025). Although emerging treatments such as targeted therapies and immunotherapies have made progress in prolonging patient survival, chemotherapy remains a key clinical treatment for many malignancies. However, while chemotherapeutic drugs kill tumor cells, they also suppress bone marrow hematopoiesis, potentially leading to chemotherapy-induced neutropenia (CIN), resulting in severe consequences such as febrile neutropenia (FN) and severe infections. Statistics show that the incidence of neutropenia in patients receiving high-intensity chemotherapy regimens can exceed 50%. Effective prevention and management of chemotherapy-induced neutropenia has become a key clinical concern.

Granulocyte colony-stimulating factor (G-CSF) stimulates the proliferation and differentiation of neutrophil progenitor cells and promotes the release of neutrophils from the bone marrow into the blood. Filgrastim (FIL, Neupogen®) is the original short-acting recombinant G-CSF (rhG-CSF), first approved in 1991. It has been shown in multiple clinical studies to significantly reduce the incidence of FN. A clinical trial in patients with small cell lung cancer (SCLC) in which the control group received a placebo and the experimental group received FIL (G-CSF) demonstrated a significant reduction in the incidence of FN in the G-CSF group (40%) compared to the experimental group (77%). The study also evaluated the drug's safety, and while 20% of patients experienced the indication, the indication was well tolerated (Crawford, 1994).

Several biosimilars of FIL are available, such as Zarxio® (Sandoz), Nivestim® (Pfizer), and Grastofil® (Apotex), which reduce the financial burden on patients. Studies have shown that the use of biosimilars can reduce the cost of G-CSF treatment by 20–30%. Furthermore, these generic drugs have been validated as equivalent to the brand-name drug, Neupogen® (FIL), in terms of structure and pharmacokinetics. In a Phase III randomized, double-blind, controlled trial, Zarxio demonstrated

no significant differences in neutrophil nadir (nadir) and FN incidence compared with the brand-name drug (Blackwell et al., 2016).

Some physicians and patients still have concerns about the immunogenicity and interchangeability of biosimilars, and further long-term follow-up is needed to confirm their feasibility as a viable alternative to the brand-name drug. Therefore, this article will comprehensively evaluate the efficacy and safety of FIL and its generic counterparts in the prevention and intervention of CIN. Further comparison and analysis will be conducted to provide a sound basis for rational clinical use and future research.

2. Pharmacological Properties of FIL

2.1. Molecular Structure and Source

FIL is a non-glycosylated form of rhG-CSF, consisting of 175 amino acid residues with a total molecular weight of approximately 18.8 kDa. It is produced using recombinant E. coli expression technology. At the molecular level, the amino acid sequence of FIL is essentially identical to endogenous human G-CSF, with the exception of an additional methionine residue at the N-terminus, which is introduced during expression in prokaryotic systems (E. coli) to facilitate translation initiation. Despite lacking the glycosylation found in native G-CSF, FIL's function is unaffected. Its native conformation is a four-helix bundle, as shown in Figure 1. This maintains similar functionality to native G-CSF and allows it to effectively bind to the G-CSF receptor and activate downstream signaling pathways. Compared to some glycosylated G-CSFs expressed in mammalian cells (such as lenograstim), FIL's non-glycosylated nature makes its production process more stable and relatively low-cost, providing a technical foundation for the subsequent development of a large number of biosimilars.

Neupogen® was the first marketed original FIL product, developed by Amgen and approved by the Food and Drug Administration (FDA) in 1991. Following the expiration of its patent protection, several biosimilars have been launched. For structural comparison, the Protein Data Bank (PDB) already has multiple G-CSF structure entries, such as the G-CSF-receptor complex with PDB IDs 1CD9 and 1PGR, as well as the Amgen original structure 1RHG. The crystal structure of Eurofarma's (Fiprima®) shows that the protein is in monomeric form. By superimposing the structure with the existing model, the α-carbon RMSD value is in the range of 0.93–1.2Å, further verifying that FIL from different sources all present a highly consistent tertiary conformation.

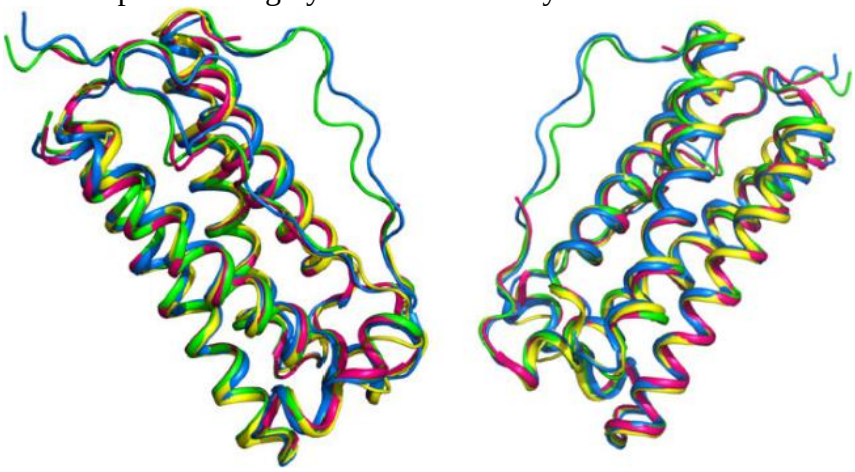

Figure 1: The crystal structure model of the human FIL protein (green, pink, and yellow) published by the PBD is compared with the tertiary structure of its analog Fiprima® (blue) (Mantovani et al., 2016).

2.2. Mechanism of Action

FIL's mechanism of action is primarily through binding to the G-CSF receptor (G-CSF-R) on the surface of bone marrow hematopoietic progenitor cells, activating a series of intracellular signaling pathways, thereby promoting neutrophil proliferation, differentiation, and maturation. The G-CSF receptor belongs to the class I cytokine receptor family and is primarily expressed on granulocyte progenitor cells and some monocytes. When FIL binds to this receptor, it induces receptor dimerization, which in turn activates members of the Janus kinase (JAK) family, triggering a phosphorylation cascade of the signal transducer and activator of transcription (STAT) pathway. Activation of the JAK/STAT pathway regulates the expression of multiple genes involved in cell proliferation and differentiation, thereby promoting neutrophil migration from the bone marrow to the peripheral blood.

In addition to the JAK/STAT pathway, FIL can also activate the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway and the mitogen-activated protein kinase (MAPK) pathway. The PI3K/AKT pathway is mainly involved in cell survival and anti-apoptosis processes, while the MAPK pathway plays a key role in cell cycle progression and functional maturation. Through the coordinated regulation of multiple pathways, FIL can effectively increase the proliferation rate of granulocyte progenitor cells in the bone marrow and accelerate their differentiation process, allowing them to be released into the peripheral blood earlier. FIL not only promotes the recovery of neutrophil numbers, but also enhances their functions, such as chemotaxis, phagocytosis, and antibacterial ability, so that patients still have a certain degree of anti-infection ability during the immunosuppression period after chemotherapy. Rastogi et al., (2021) found in a meta-analysis that of the 21 included studies, 11 (a total of 2,553 patients) clearly reported the incidence of FN. The results showed that the average incidence of FN in the FIL treatment group was 23% (95% CI: 16–30%), significantly lower than the 42% (95% CI: 32–52%) in the control group, with a relative risk (RR) of 0.58 (95% CI: 0.50–0.67), indicating that FIL can effectively reduce the risk of FN. This further confirms the clinical advantage of FIL in the management of CIN.

2.3. Pharmacokinetic Characteristics

The pharmacokinetics of FIL exhibit distinct linear kinetics, and its distribution and clearance patterns are closely related to the biological properties of G-CSF. FIL is typically administered by subcutaneous (SC) or intravenous (IV) injection. In healthy volunteers and neutropenic patients, the bioavailability after SC injection is approximately 62%, significantly superior to that of some other protein-based drugs. The drug significantly increases peripheral blood neutrophil counts within 24 hours of administration, reaching a peak around 72 hours.

The primary clearance mechanisms of FIL in vivo include renal filtration and receptor-mediated endocytosis. Due to its relatively small molecular weight, some FIL unbound to the receptor can be excreted directly in the urine via glomerular filtration. Once bound to the G-CSF receptor, however, it is primarily enzymatically degraded within target cells, participating in the regulation of neutrophil proliferation and function. FIL has a short plasma half-life of approximately 3.5 to 4 hours, necessitating daily dosing in clinical practice until neutrophil counts return to normal.

FIL clearance is regulated by neutrophil count. When a patient is neutropenic, drug clearance decreases due to a decrease in target cell numbers, maintaining high concentrations in the body. Conversely, when neutrophil counts increase, receptor expression levels rise, and FIL is rapidly cleared, resulting in a self-limiting pharmacokinetic profile. This property also explains the need for individualized dose adjustments during treatment. Polyethylene glycol modification (PEG-FIL) can extend its half-life (up to 15–80 hours), a fundamental difference from FIL's approximately 3.5–4 hours. Comparing the incidence of FN, the results showed that PegFIL and FIL have comparable overall efficacy in reducing FN, and some studies even suggest that PegFIL may be slightly superior (Marjoncu et al., 2023).

3. Applications of FIL in Cancer Chemotherapy

3.1. Effectiveness Evaluation

FIL's important role in supportive cancer chemotherapy is widely recognized. Chemotherapy drugs significantly suppress the bone marrow hematopoietic system, particularly the granulocyte lineage. This damage often leads to severe neutropenia in patients, increasing the risk of infection and even leading to chemotherapy delays or dose reductions, thus compromising the overall efficacy of cancer treatment. FIL specifically stimulates the proliferation and differentiation of neutrophil progenitor cells in the bone marrow and accelerates their release into the peripheral blood, effectively shortening the duration of neutropenia and reducing the incidence of infection.

FIL is used in patients with solid tumors and hematologic malignancies at various stages of treatment, including prevention of neutropenia after high-intensity chemotherapy, promotion of granulocyte recovery after hematopoietic stem cell transplantation, and management of neutropenia associated with antiviral medications. Real-world data (RWD) from patients with diffuse large B-cell lymphoma (DLBCL) receiving R-CHOP (rituximab + CHOP) chemotherapy without G-CSF prophylaxis showed a high incidence of FN in the first cycle of 20.4%. This was particularly high in patients with risk factors such as age ≥ 65 years, bone marrow involvement, low albumin levels, or a relative dose intensity ≥ 80% (mean incidence of 20.4%, range 17–22%; high-risk group as high as 61.9%), suggesting that R-CHOP itself is often classified as a high-risk FN regimen in real-world clinical settings. In contrast, when FIL was administered three times prophylactically on days 7, 11, and 14 in patients ≥ 65 years, the FN hospitalization rate was reduced to 6.35% (8/126 cycles), significantly lower than the expected 10–20% range (typically associated with FN rates in studies without G-CSF). Comprehensive evidence, including real-world retrospective cohorts and hospital practice audits, indicates that without FIL prophylaxis during R-CHOP chemotherapy, the incidence of FN can exceed 20%. However, with FIL prophylaxis, the incidence of FN can often be reduced to approximately 6–10%, significantly improving chemotherapy safety and completion rates (El-Shakankery et al., 2019).

Furthermore, FIL is crucial in the "dose-dense" strategy of cancer treatment. Dose-dense chemotherapy requires maintaining high doses at shorter intervals, which carries a greater risk of myelosuppression. Results from the CALGB 9741 study showed that the use of a FIL-supported dose-dense regimen in breast cancer patients not only did not increase the incidence of serious infections but also improved disease-free survival (DFS) and overall survival (OS). This strategy is increasingly being validated for some aggressive tumor types, demonstrating greater therapeutic potential.

Overall, the use of FIL not only improves treatment continuity for cancer patients but also significantly improves safety and prognostic indicators during chemotherapy. With the addition of biosimilars, FIL has also expanded its clinical application.

3.2. Safety Assessment

Although FIL has demonstrated significant clinical benefits in cancer patients, its use is associated with certain adverse reactions, the most common of which is bone and muscle pain, particularly in the sternum, pelvis, and back regions. According to statistics, approximately 20%–30% of patients report moderate to severe bone pain after FIL treatment (Dimitrijevic et al., 2022). This side effect is primarily due to FIL stimulating bone marrow proliferation, leading to increased periosteal tension. Other relatively uncommon adverse events include injection site reactions, mild fever, headache, and fatigue. In rare cases, splenomegaly, splenic rupture, hyperleukocytosis, allergic reactions, or ARDS (acute respiratory distress syndrome) may occur, but the overall incidence is low.

To alleviate these side effects, clinical practice typically employs symptomatic treatment strategies, such as NSAIDs or acetaminophen to relieve bone pain. Injections are recommended at fixed times to reduce the risk of diurnal fluctuations in response. Research is also exploring the use of PEG-based FIL to reduce injection frequency and discomfort and improve patient compliance. Optimizing the FIL molecular structure or developing biosimilars are also key approaches to

improving safety and reducing costs. For example, some generic drugs utilize advanced expression systems and purification technologies to reduce aggregate formation, potentially reducing the incidence of immune-related adverse reactions. Furthermore, the high cost of FIL contributes significantly to the global burden of cancer treatment, prompting several countries to accelerate the development and launch of biosimilars.

4. Biosimilars

As the patents for Neupogen® (the original FIL drug) gradually expired, regulatory agencies in various countries and regions approved numerous biosimilar FIL products for clinical use. The first approved product was Sandoz's Zarzio® (FIL-sndz), which received approval from the European Medicines Agency (EMA) in 2009 and the FDA in 2015, and are widely used for the prevention and treatment of FN associated with cancer chemotherapy. Other approved generic drugs in the EU market include Biograstim®, FIL Hexal®, Ratiograstim®, and Grastofil®, all of which were approved by the EMA between 2008 and 2009. These products are gradually replacing or supplementing Neupogen®'s market share in multiple countries.

Fiprima®, developed by the Brazilian company Eurofarma in collaboration with the National Health System Biomanguinhos, received ANVISA approval in 2015, becoming the first fully domestically developed and manufactured FIL biologic in Latin America, marking a significant milestone in local pharmaceutical independence. Structural and functional comparative studies demonstrated that Fiprima is highly consistent with Roche's commercial product, Granulokine®, in terms of mass spectrometry, chromatography, electrophoresis, circular dichroism, ligand binding capacity, and in vitro cell proliferation potency, meeting EMA/FDA risk assessment and equivalence criteria. In clinical practice, Zarzio and Nivestym have been widely used in over 40 countries worldwide, accumulating a wealth of real-world evidence. For example, a large cohort study in supportive care settings demonstrated that Zarzio has become the most commonly used brand of daily G-CSF medication in Europe, surpassing Neupogen® in market share. Although limited clinical research on Fiprima has been published in international journals, its use is relatively mature within the Brazilian National Cancer Institute (INCA) and the health system. It has been produced and promoted within the Unified Health System (SUS) through technology transfer, resulting in cumulative savings of millions of dollars. In summary, currently approved biosimilars of FIL come from several major global pharmaceutical manufacturers and follow regulatory pathways in multiple countries. All are supported by structural and functional consistency studies and clinical data, and their practical applications include supporting cancer chemotherapy and preventing and treating related neutropenia (Table 1).

Table 1: Comparison of Neupogen® and major generic drugs.

Comparison Item	Neupogen® (Originator)	Zarzio®/Zarzio (Sandoz)	Nivestym®/Nivestim® (Pfizer)	Fiprima® (Eurofarma, Brazil)
Molecular Structure	Identical to endogenous G-CSF	Highly consistent with Neupogen®	Highly consistent with Neupogen®	High structural similarity to Granulokine® (Roche)
Clinical Efficacy	Validated through years of clinical use	Equivalence supported by RCTs and RWD	Equivalence supported by RCTs and RWD	Pharmacodynamic efficacy comparable to Neupogen®
Safety	Good, with manageable risk of bone pain	Consistent with originator	Consistent with originator	Similar adverse event profile to the originator
Immunogenicity	Very low	No significant difference	No reports of severe immunogenicity	No significant difference compared to natural product
Cost Advantage	Relatively high	Approximately 60–70% lower than originator	Comparable, with slight competitive edge	More cost-effective than imported products
Policy Support	No specific support	Included in national insurance of multiple countries; prioritized procurement in some cases	Included in reimbursement list with strong substitution support	Prioritized by Brazil's SUS system; supported by national tech transfer initiatives

5. Optimization Directions for Generic Drugs

In the development of biosimilars, future optimization focuses primarily on reducing immunogenicity and enhancing drug stability. Host cell line optimization is one such approach. Taking CHO cell optimization as an example, host cell genetic stability and protein expression efficiency can help improve the yield and quality consistency of biosimilars. A study indicates that remodeling metabolic pathways in CHO cells through genetic engineering can increase recombinant protein production by over 30% (Zhao et al., 2021).

Reducing immunogenicity is another key optimization focus. Sandoz's R&D team conducted a systematic purification and structural comparison of EP2006 (Zarzio®), a biosimilar to FIL, with the original drug Neupogen®. Analysis showed that EP2006's levels of impurities, including oxidation, deamination, and aggregates, were identical to those of Neupogen®. Quantitative results showed impurity levels of only 1.7%–2.0%, significantly lower than the 4.5%–5.8% for the innovator (Gascon et al., 2015). While the innovator exhibited an approximately 3% incidence of antibodies in patients expected to develop non-neutralizing ADA, no anti-G-CSF antibodies were detected in the EP2006 trial population. This result demonstrates that through rigorous control of impurities and purification steps, the immunogenicity of biosimilars can match or even exceed that of the innovator (Harris & Cohen, 2024).

6. Conclusion

This article systematically reviews the pharmacological mechanisms, pharmacokinetic characteristics, clinical efficacy, and safety of FIL and its biosimilars in the prevention and intervention of CIN. It also comprehensively compares the equivalence of Neupogen® with several marketed generic drugs. The results demonstrate that FIL effectively promotes neutrophil proliferation and release by activating multiple signaling pathways, including JAK/STAT and PI3K/AKT, significantly reducing the incidence of FN. Multiple studies have also confirmed that generic drugs (such as Zarzio® and Nivestym®) are highly consistent with the original drugs in terms of structure, efficacy, and safety, and offer significant advantages in price and accessibility.

Despite this, some physicians and patients remain concerned about the long-term immunogenicity and interchangeability of generic drugs. Current studies primarily focus on short-term efficacy assessments and lack large-scale, long-term follow-up data. Future efforts should strengthen multicenter clinical studies, continuously accumulate real-world data, and further mitigate immunogenic risks through host cell optimization and impurity control technologies to promote the widespread global use of biosimilars.

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