

The Safety Profile of Filgrastim and Pegfilgrastim

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1 Introduction

The discovery of endogenous proteins that regulate hematopoiesis led to the identification of human granulocyte colony-stimulating factor (G-CSF). With the advent of recombinant DNA technology, it became possible to manufacture bioactive recombinant proteins for medicinal use. Since the approval of recombinant human G-CSF (rHuG-CSF), such as filgrastim in 1991 and pegfilgrastim in 2002, millions of patients at risk for severe myelosuppression have received these products. Overall, filgrastim and pegfilgrastim have a high margin of safety for short-term use; however, rare severe adverse events have emerged and questions remain regarding the long-term safety and consequences of use of these products. This chapter primarily focuses on the safety and adverse event profile of the most widely used commercially available rHuG-CSF, Neupogen (filgrastim) and Neulasta [a modified (pegylated) filgrastim, pegfilgrastim]. As safety information can change rapidly, we suggest readers consult the latest package inserts for any changes that have occurred from the time of this writing. Other chapters in this volume discuss key studies in specific disease settings in greater detail than is the purview of this chapter, and we encourage the interested reader to reference them for further information.

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2 Filgrastim

Filgrastim is a 175-amino acid recombinant protein expressed in *Escherichia coli*. The filgrastim peptide has the same amino acid sequence as endogenous human G-CSF with the exception that the backbone of the molecule is not glycosylated and the *N*-terminus is a methionine. Endogenous human G-CSF is a lineage-specific glycoprotein and is responsible for regulation of neutrophil production in bone marrow. The lineage specificity is an important aspect of filgrastim's safety profile in that it has been shown to have a relatively consistent safety profile. Both in vivo and ex vivo studies have demonstrated the molecule acts by binding to the G-CSF receptor (G-CSFR) and it plays a key role in neutrophil regulation and differentiation and in neutrophil functions (i.e., respiratory burst, antibody-dependent killing, and phagocytosis) [1–3]. Exogenous rHG-CSF administration has been shown to mobilize stem cells from the marrow into the peripheral system [4–6]. Techniques have been developed to isolate and harvest stem cells from the blood in a process known as peripheral blood progenitor cell (PBPC) collection.

2.1 Overview

The clinical utility of filgrastim in correcting and reversing low neutrophil counts and in improving the function of neutrophils led to evaluation of the molecule in the setting of cancer chemotherapy, bone marrow transplantation, systemic infections, and congenital neutropenia. As a result of extensive investigations, filgrastim is approved for prevention and treatment of severe neutropenia in patients receiving myelosuppressive chemotherapy. It is also approved for use in adult patients with acute myeloid leukemia (AML) who are undergoing induction or consolidation chemotherapy, and in patients who are receiving myeloablative chemotherapy followed by bone marrow transplantation. Filgrastim is also approved, used to treat patients with chronic forms of neutropenia such as idiopathic neutropenia, congenital neutropenia, and cyclic neutropenia.

The adverse event profile of filgrastim includes bone pain, headache, allergic reactions, rash, and splenomegaly, with bone pain the only adverse event that has been consistently reported across all patient populations. Increases in lactate dehydrogenase, alkaline phosphatase, and uric acid have been reported and may be related to increased cell turnover in chemotherapy [7, 8]. These changes are transient and not associated with any clinical sequelae. Incidental reports suggest that some patients believe that bone pain is an indication that filgrastim is “working” and do not mind the pain. Obviously, pain is not necessarily indication of filgrastim's activity.

Unlike other human proteins, filgrastim is devoid of side effects such as fever, malaise, autoimmune reactions, and fluid retention. The lack of these side effects makes filgrastim an ideal product to address bone-marrow recovery after cytotoxic chemotherapy. Of note, filgrastim is used primarily to address short-term loss of

neutrophils after 6–8 cycles of chemotherapy for advanced cancer. Long-term use of filgrastim, defined as >1 year, has only been characterized in a smaller subset of patients with severe chronic neutropenia (SCN).

What is important to note is what adverse events are not reported. Filgrastim does not produce dose-limiting side effects even at 115 µg/kg, a dose that can cause marked leukocytosis ($50 \times 10^9/L$) [9]. Unlike rHu granulocyte-macrophage colony-stimulating factor (rHuGM-CSF), indicated for use in many of the same patient populations as filgrastim, treatment with filgrastim does not appear to produce fever [3, 10–12], capillary-leak syndrome [13–19], or first-dose reaction [11, 14, 18, 20].

2.2 Patients Receiving Myelosuppressive Chemotherapy

Filgrastim is typically given 24 h after chemotherapy, an important consideration to avoid stimulation of bone marrow cell division during peak systemic cytotoxic chemotherapy levels that could accentuate bone-marrow damage. The most frequently reported adverse events attributed to filgrastim are bone pain, injection-site reaction, rash, acute neutrophilic dermatoses, allergic reaction, worsening of inflammatory conditions, and splenic enlargement. The most common adverse event associated with patients receiving filgrastim relative to patients receiving placebo appears to be bone pain. This event is dose-related and commences shortly after beginning treatment with filgrastim and may reoccur or worsen shortly before neutrophilic recovery in patients who have received chemotherapy [21].

Early in the use of filgrastim in the setting of chemotherapy, reports of possible pulmonary toxicity associated with filgrastim and bleomycin surfaced. Critical review of several randomized and nonrandomized studies suggested no increase in the known pulmonary toxicity. The studies were done in the settings of non-Hodgkin's lymphoma (NHL) [22–26], and in metastatic teratoma [27], germ-cell tumors [28], and advanced testicular cancer [29].

In a pivotal randomized, placebo-controlled, double-blind phase 3 study, 210 patients with nonsmall-cell lung cancer (NSCLC) received chemotherapy with or without filgrastim [30]. The most commonly reported adverse event was mild-to-moderate medullary bone pain that was treated with non-narcotic analgesics. A total of 6% of patients given filgrastim reported allergic reactions. None of the expected side effects of human protein administration such as fever, fluid retention, arthralgia, and malaise were reported in this double-blind study.

2.3 Patients Receiving Chemotherapy with Concomitant Thoracic Radiotherapy

The use of rHuG-CSF before chemotherapy and during thoracic radiation is not recommended due to the risk of more marrow damage. A small number of studies

have shown that use of growth factors, primarily studies with rHuGM-CSF, during concomitant radiation will increase the risk of thrombocytopenia [31–33].

The use of concomitant filgrastim was evaluated in 38 patients with small-cell lung cancer (SCLC) receiving cyclical chemotherapy with concurrent mediastinal irradiation, and the authors reported no increase in pulmonary toxicity associated with concomitant use of filgrastim during thoracic radiation [34]; however, thrombocytopenia did occur and it is unclear if this side effect outweighs the use of filgrastim in this setting.

2.4 Patients with AML Receiving Induction or Consolidation Chemotherapy

Induction and consolidation therapy for treatment of acute myeloid leukemia (AML) has a high mortality rate associated with a high risk of prolonged severe neutropenia, an ideal setting for intervention with filgrastim. A randomized, placebo-controlled phase 3 study evaluated the clinical utility of adjunctive filgrastim in patients with AML receiving remission induction and consolidation chemotherapy [35]. Adverse events including allergic reactions and bone pain were slightly higher in the filgrastim group compared with the placebo group. Long-term outcome of this study confirms the earlier result that filgrastim does not have any untoward impact on survival of patients with AML and is not associated with any secondary malignancies [36]. The issue may not be fully resolved, however, as the perceived relationship between the use of any hematopoietic growth factor and the risk of developing leukemia remains controversial in some patient populations [37].

2.5 Patients with NHL Receiving Stem Cell Transplantation

Studies have been reported for patients with NHL who received stem cell transplantation – either bone marrow or PBPC. Some of the earliest work in stem cell transplantation, specifically bone marrow, included patients with NHL who were receiving filgrastim support for marrow recovery [38]. In this study, no significant toxicity was noted beyond localized erythema at 2/88 infusion sites, and no significant difference was reported in veno-occlusive disease of the liver or interstitial pneumonia between the filgrastim and placebo groups.

Several early, generally small, studies in the setting of PBPC mobilization, collection, and reinfusion enrolled patients with NHL [39–42]. No untoward adverse events were reported in these studies. A comparison of filgrastim-mobilized PBPC versus autologous bone marrow transplant was evaluated in 58 patients with NHL [43]. The group receiving filgrastim-mobilized PBPC had a lower number of platelet transfusions and a shorter duration to platelet recovery and neutrophil

recovery, which led to fewer days of hospitalization compared with patients who received bone marrow. No adverse events were attributed to the filgrastim-mobilized PBPC procedure.

2.6 Peripheral Blood Progenitor Cell Collection and Therapy in Cancer Patients

While use of high-dose chemotherapy has been an important advance in the treatment of patients with cancer, the consequence of this high-dose therapy is often a temporary or permanent ablation of hematopoietic activity and an increased morbidity and mortality. The focus of research turned to discovery of ways to abrogate the neutropenia, as well as anemia and thrombocytopenia, of high-dose chemotherapy. Bone marrow transplantations, both autologous and allogeneic, were first steps, but with the advent of hematopoietic growth factors, the utility of filgrastim in mobilizing PBPC for reinfusion after ablative therapy became apparent. Collection of PBPC is inherently less hazardous than harvesting of bone marrow and there was hope that reinfusion of PBPC would be without tumor contamination.

In studies with a total of 126 patients undergoing PBPC collection, filgrastim treatment was associated with a 44% incidence of mild-to-moderate muscle or bone pain with a 7% rate of headache [44]. Reversible increases in serum alkaline phosphatase occurred in 21% of patients. All patients had an increase in neutrophil counts, with two patients experiencing significant counts $>100 \times 10^9/L$ with no associated clinical sequelae. Mild-to-moderate anemia and thrombocytopenia did occur in most patients, suggesting that treatment with filgrastim for mobilization can lead to lineage steal and a temporary decrease in erythrocyte and thrombocyte production.

2.7 Patients with Severe Chronic Neutropenia

Patients with idiopathic or genetic abnormalities in neutrophil production and regulation suffer with susceptibility to chronic infections, another ideal setting for the utility of filgrastim. As filgrastim was originally approved only for short-term use, the safety of the product in chronic use in children was a serious question that needed to be answered. In a phase 3 study, 123 patients with documented severe chronic neutropenia (SCN) and an absolute neutrophil count (ANC) $<0.5 \times 10^9/L$ were randomly assigned to receive filgrastim or to undergo a 4-month observation period followed by treatment with filgrastim [45]. Filgrastim treatment resulted in a correction in the ANC and reduction in infection rate. The safety profile was characterized by a 30% incidence in mild and transient headache, bone pain, skin rash and manageable thrombocytopenia. Asymptomatic splenomegaly did occur in more

than half of the patients but did not result in splenectomies or significant clinical sequelae. The enlargement of the spleen in response to filgrastim is attributed to extramedullary hematopoiesis which has been observed in animal models.

Safety data of long-term use of filgrastim have been collected in the Severe Chronic Neutropenia International Registry (SCNIR) and a subset of patients receiving filgrastim for congenital neutropenia has been monitored for any emergent adverse events. Case reports suggest a possible association between long-term filgrastim and splenomegaly, osteopenia, osteoporosis, vasculitis, retarded growth, and development. With treatment of 7 years or more, there is an increased risk of malignant myeloid transformation which is associated with filgrastim given for years [46, 47]. The underlying disease of chronic neutropenia, however, can also put these patients at risk of myeloid transformation.

2.8 Patients with Active Infection

Nonclinical studies suggested that filgrastim regulated the survival, proliferation, and differentiation of precursor cells of neutrophilic granulocytes, and functionally activated mature neutrophils [1]. The functional properties of neutrophils that are enhanced by filgrastim are those related to host defenses and the concentration of endogenous G-CSF has been shown to increase in a variety of infections [48]. Taken together, these observations suggested a role for filgrastim in patients with infectious diseases.

Adjunctive filgrastim in combination with antibiotics was evaluated in a phase 1 study of non-neutropenic patients with pneumonia [49]. A total of 30 patients with community-acquired pneumonia received daily filgrastim subcutaneous doses ranging from 75 to 600 μg for 10 days or until their ANC reached or exceeded $0.75 \times 10^9/\text{L}$. Safety evaluation included vital signs, pulse oximetry, arterial blood gases, daily complete blood counts with differential, serum chemistries, coagulation profiles, electrocardiograms, and chest radiographs. The results of the study indicated no evidence of pulmonary toxicity or exacerbation of the infection. Two large, randomized phase 3 studies of patients with pneumonia compared standard antibiotics with or without the addition of filgrastim and the results confirmed the safety of filgrastim in this population and demonstrated an improved resolution of chest infection based on radiographic evidence [50, 51].

2.9 Patients with HIV Infection

The hallmark of human immunodeficiency virus (HIV) infection is defects in the production and function of CD4⁺ helper cells; anemia, neutropenia, and thrombocytopenia are major clinical problems. Patients with HIV infection have poor hematopoietic reserves [52, 53]. Recurrent bacterial infections are recognized as criteria for the diagnosis of AIDS [54]. In clinical studies of patients with HIV

infection receiving filgrastim, the incidence of adverse events was similar to that reported in cancer patients and consisted of musculoskeletal pain, predominantly mild-to-moderate bone pain and myalgia [55, 56]. Splenic enlargement has been reported to be related to filgrastim therapy in <3% of patients with HIV infection/AIDS, but the splenomegaly is mild or moderate and does not result in splenectomy [57]. As the finding of splenic enlargement is common in patients with HIV infection and also common in large number of patients with AIDS, the relationship to filgrastim treatment is unclear.

2.10 Patients with Renal or Hepatic Impairment

Studies of filgrastim in patients with severe impairment of renal or hepatic function demonstrate that it exhibits a similar pharmacokinetic and pharmacodynamic profile to that seen in normal individuals, and the safety profile is similar to that seen in patients with normal renal and hepatic function [57]. No dose adjustments are required for these special populations.

3 Pegfilgrastim

Pegfilgrastim is a chemically modified derivative of filgrastim in which a polyethylene glycol (PEG) molecule is covalently attached to the *N* terminus of the peptide. This polyethylene glycol tail has no intrinsic biologic activity but does alter the pharmacokinetics and pharmacodynamic profiles enabling the half-life to be extended from 3 h to approximately 80 h and subsequently reduced clearance from the systemic circulation [58]. This extended half-life can support one injection per cycle of chemotherapy rather than daily dosing that is required with filgrastim. Pegylation of filgrastim is advantageous in that a single injection is sufficient to produce neutrophil recovery. Pegylation of proteins is also useful for reduction in immunogenicity of the native protein; however, filgrastim has not been shown to be highly immunogenic in which neutralizing antibodies that cross-react with endogenous G-CSF have been detected. The effect of pegylation of filgrastim to reduce immunogenicity has not been evaluated as filgrastim is not highly immunogenic. Unlike filgrastim, pegfilgrastim is only approved for the prevention and treatment of febrile neutropenia and unlike the short-acting filgrastim, pegfilgrastim is not approved for peripheral stem cell mobilization for transplantation or for use in patients with myeloid cancers.

3.1 Overview

Pegylation is a process by which a polyethylene glycol molecule is attached to a native protein in order to stabilize the protein, reduce degradation of the protein, and reduce the immunogenic potential [59]. Polyethylene glycol is categorized by

the US Food and Drug Administration (FDA) as “Generally Recognized As Safe” (i.e., the GRAS List). However, attachment of a polyethylene glycol molecule to an active molecule may reduce the potency of the therapeutic molecule due to steric hindrance but is offset by a longer circulating half-life [60].

While single-dose per cycle pegfilgrastim has comparable efficacy compared to daily injections of filgrastim, the side-effect profile has been shown to differ from filgrastim with a greater number of warning labels. Postmarketing safety studies indicate that use of pegfilgrastim is associated with severe allergic reactions such as anaphylaxis, angioedema, or urticaria, and splenic rupture, including fatal cases, has been reported with pegfilgrastim [57]. In addition to fatal splenic rupture, rare cases of acute respiratory distress syndrome (ARDS) have occurred in patients receiving pegfilgrastim [57]. The exact mechanism of the ARDS is unknown but with a longer half-life and enhanced neutrophil function may play a role.

3.2 Patients Receiving Myelosuppressive Chemotherapy

In a phase 2 randomized study of 154 patients comparing filgrastim to pegfilgrastim, the most frequently reported adverse event was mild-to-moderate medullary bone pain [61]. Despite the pegylation and longer-acting filgrastim, the duration and severity of the bone pain were similar with an overall incidence of bone pain of 35% in pegfilgrastim patients and 36% in filgrastim patients; most incidences were mild to moderate in severity. In the 30-, 60-, and 100-g/kg pegfilgrastim dose groups, the incidence of bone pain was 16%, 34% and 45%, respectively. Treatment for the bone pain included the use of non-narcotic analgesics but a few patients (7% pegfilgrastim and 12% filgrastim) did require narcotics. The safety and efficacy of pegfilgrastim compared to filgrastim has been evaluated in two phase 3 trials [61, 62]. The results show equivalent efficacy and safety with approximately 25% of patients reporting mild-to-moderate bone pain.

In one of the largest randomized study to evaluate the safety of pegfilgrastim, 928 patients with breast cancer receiving chemotherapy were randomly assigned to receive pegfilgrastim or placebo [63]. The addition of pegfilgrastim reduced the febrile neutropenia rate by 94% and the side-effect profile was consistent with other large randomized studies.

3.3 Use of Pegfilgrastim in Special Populations

3.3.1 Pediatric

To obtain marketing approval by health authorities, drug sponsors must submit clinical data in the form of results from randomized controlled trials, most often conducted in adults. Many medicines that receive marketing approval can be used

and often are used in the pediatric population off-label; however, a study suggests that some physicians are unaware that they are prescribing medicines off-label [64]. Off-label use of medications to treat children may produce no therapeutic benefit, but expose the child to all potential risks [65]. By virtue of its off-label status, the pharmacokinetics and pharmacodynamics of the medicine have not been studied in the pediatric population, and inherent metabolic differences between adults and children may not be detected by extrapolation methods [65]. Off-label use may produce, years later, serious, debilitating, or fatal results. Pediatric studies are mandated by the FDA and other health authorities.

Small nonrandomized studies have been conducted to evaluate pegfilgrastim in children. A total of 28 pediatric patients were given 126 injections of pegfilgrastim [66]. Adverse events included four patients with bone pain and two patients with headache.

A randomized study comparing filgrastim to pegfilgrastim was evaluated in 44 pediatric patients undergoing myelosuppressive chemotherapy for sarcoma [67]. No differences with adverse event incidence were detected across the two treatment groups, with bone pain being the most commonly reported adverse event.

3.3.2 Geriatric

The FDA also encourages drug sponsors to include elderly patients in studies of new drugs or new indications. Elderly patients are major consumers of drug products and to neglect to study the effects of drugs in this population does not provide a complete safety profile of the product.

A total of 852 elderly patients with either solid tumor or NHL who were eligible for treatment with myelosuppressive chemotherapy were randomly assigned to receive either prophylactic pegfilgrastim or physician's choice for reactive use of pegfilgrastim [68]. Severe arthralgia was a commonly reported adverse event and was considered to be related to treatment with pegfilgrastim. Relative to other populations, the reported incidence of bone pain was low with the overall incidence ranging from 9 to 12% across all groups.

3.3.3 Renal Impairment

A phase 1 study in 30 nonneutropenic patients with varying degrees of renal function was conducted to determine if renal clearance is an important determinant in the pharmacokinetics and pharmacodynamic profiles of pegfilgrastim [69]. Patients with normal, mildly impaired, moderately impaired, severely impaired, and end-stage renal disease received a single subcutaneous injection of pegfilgrastim. The results indicate no difference in pharmacokinetics and pharmacodynamic relationships, and suggest renal impairment does not impact clearance of pegfilgrastim and therefore is not a consideration from a safety perspective.

4 Biosimilar rHuG-CSF and Next Generation of rHuG-CSF

Recently, a new filgrastim biosimilar was approved in the European Union. Nivestim is a new filgrastim available in three strengths in prefilled syringes with a needle-safe device enabling self-administration at home. In a randomized phase 3 study, Nivestim demonstrated comparable efficacy to Neupogen (the original filgrastim) in the prevention of febrile neutropenia, and was as well tolerated, with a similar adverse event profile and no unexpected or untoward side effects [70, 71].

Other drug delivery formulations of rHuG-CSF are in development. To date, no new formulation has been approved by regulatory authorities. As G-CSF is a protein and can be digested through the oral route, administration of rHuG-CSF necessitates that the product be injected. Mimetics of G-CSF are currently in early discovery development but have yet to reach the clinic [72]. The next decade will see the introduction of next generation biosimilars and new delivery modalities which will further add to the body of literature regarding the safety of short- and long-term use of rHuG-CSF.

5 Conclusion

Filgrastim and pegfilgrastim were approved initially for clinical use to address the myelosuppression in patients undergoing chemotherapy. Such a drug product must itself have a reasonably high margin of safety so as not to further add to the adverse event profile of chemotherapy. Use of rHuG-CSF for acute neutropenia and reducing duration of neutropenia has resulted in reductions in infections and hospitalizations. In rare cases, the use of these drugs has caused fatal splenic rupture and other rare but serious side effects but overall the benefit of these products has clearly outweighed the risks and has contributed to the survival of millions of cancer patients. The success of these products is an important contribution in the overall supportive care of patients receiving chemotherapy for life-threatening cancers. Long-term use of filgrastim for chronic neutropenia has also been acceptable but another decade will reveal additional data on the safety of these important products.

Acknowledgement Dedicated to the memory of Jean Willisie-Chirino, colleague and friend.

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