

Safety and tolerability of Peg-grafeel™, a pegfilgrastim, for the prophylactic treatment of chemotherapy-induced neutropenia and febrile neutropenia: A prospective, observational, postmarketing surveillance study in India

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Abstract

Background: A granulocyte colony-stimulating factor, pegfilgrastim, is efficacious though expensive for prophylactic treatment of chemotherapy-induced neutropenia and febrile neutropenia. Biologics available and accessible today, having acceptable safety-efficacy profiles, require postapproval studies for better understanding of such drugs in clinical settings. **Aim:** This postmarketing surveillance study evaluated the safety of prophylactic Peg-grafeel™ (pegfilgrastim) in cancer patients with chemotherapy-induced neutropenia. **Settings and Design:** This prospective, noninterventive, single-arm, open-label study was conducted at 10 study sites in India. **Methods:** Patients received subcutaneous 6 mg Peg-grafeel™ approximately 24 h following chemotherapy as part of routine patient care. **Statistical Analysis:** Data were summarized descriptively. **Results:** The study included 250 patients (male:female = 36.4%:63.6%; median age, 54 [16–80] years). Most patients had Stage III (33.2%) or IV (41.6%) cancers and received cyclophosphamide (37.2%) and doxorubicin (31.6%) as chemotherapy. On an average, 4 Peg-grafeel™ doses were administered per patient. Treatment-emergent adverse events (AEs) were reported in 115 (46%) patients, the most common being vomiting (11.6%), pain (11.2%), nausea (8.4%), and constipation (8.4%). Peg-grafeel™-related AEs included pain (3.2%), asthenia (2.4%), and arthralgia (1.2%). Bone pain (0.4%) and extremity pain (1.2%) were rare. Grade 3/4 neutropenia and febrile neutropenia occurred in 4 (1.6%) and 3 (1.2%) patients, respectively. Serious AEs included vomiting (2.8%) and pyrexia (2%). No new safety concerns were identified. None of the five deaths was considered related to Peg-grafeel™. **Conclusion:** The overall safety profile of Peg-grafeel™ was consistent with the expected safety profile of pegfilgrastim in patients with advanced malignancies in a clinical setting.

Key words: Chemotherapy-induced neutropenia, febrile neutropenia, granulocyte colony-stimulating factor, myelosuppressive chemotherapy, pegfilgrastim, Peg-grafeel™, postmarketing surveillance study

Introduction

Granulocyte colony-stimulating factor (G-CSF) significantly reduces the incidence of neutropenia and/or hospital stays resulting from febrile neutropenia.^[1] Long-acting pegylated G-CSF, such as pegfilgrastim, provides similar benefit in fewer doses.^[2]

High cost often impedes patient access to such products. Therefore, an affordable biologic, similar to the innovator product in terms of safety, efficacy, and structural and physicochemical properties, is required. Postmarketing surveillance (PMS) studies of biologics guide clinicians' choice of treatment for their patients. This observational study evaluated the safety/tolerability of Peg-grafeel™ (Dr. Reddy's Laboratories Ltd., India), a pegfilgrastim approved for prophylactic treatment of chemotherapy-induced neutropenia and febrile neutropenia.^[3]

Methods

This was a prospective, observational, multicenter, noninterventive, single-arm, open-label, PMS study conducted at 10 sites in India between May 2012 and November 2013. Patients with nonmyeloid malignancies undergoing chemotherapy, and who were prescribed Peg-grafeel™ as part of patient care, were eligible for this study. All eligible patients providing a written informed consent were enrolled in the study. Those patients who were on other investigational products, or had known hypersensitivity or contraindications to Peg-grafeel™, or were not eligible clinically were excluded from the study. The study was approved by an Institutional Review Board or an Independent Ethics Committee at each study site and was conducted in accordance with the Declaration of

Helsinki, local regulations, and the International Conference on Harmonization Good Clinical Practices guidelines.

Patients received a standard dose of 6 mg Peg-grafeel™ in a prefilled syringe subcutaneously, approximately 24 h following their cancer-specific chemotherapy. As this was an observational study, there were no specific restrictions on the use of prior and concomitant medications. The duration of treatment with Peg-grafeel™ was at the physicians' discretion based on the clinical need of each patient. Patients were discontinued from the study if they experienced a serious adverse event (SAE) or withdrew their consent.

The primary/key objective of this study was to observe the incidence of treatment-related adverse events (AEs) and SAEs in patients receiving Peg-grafeel™ for cancer chemotherapy-induced neutropenia and febrile neutropenia. The safety and tolerability data were recorded by the study investigators, which included treatment, treatment duration, outcomes, and causal relationship with Peg-grafeel™ or other suspect drugs for the observed AEs.

The data set comprised 250 patients, as defined by the inclusion criteria. The "all patients enrolled set" (ENR) comprised all patients who qualified for study inclusion, whereas the safety analysis set (SAS) comprised all patients in the ENR set who received at least one dose of Peg-grafeel™. The overall safety profile, based on the SAS, was summarized descriptively. AEs and SAEs were listed based on the seriousness/severity and relationship to Peg-grafeel™ using the World Health Organization - Uppsala Monitoring Centre causality assessment system. All AEs were recorded with terminologies based on the Medical Dictionary for Regulatory Activities system organ

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A total of 68 SAEs were reported, with 29 (11.6%) patients reporting at least one SAE. None of the reported SAEs was considered to be related to Peg-grafeel™. The most commonly reported SAEs were vomiting in 7 (2.8%), pyrexia in 5 (2%),

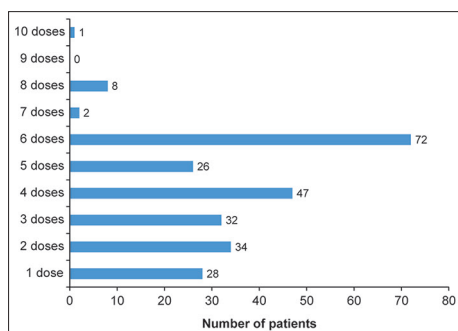


Figure 3: Summary of exposure to Peg-grafeel™

Table 2: Overview of adverse events

Events	n=250
Patients with at least one AE	115 (46)
Patients with at least one nonserious AE	98 (39.2)
Patients with at least one SAE	29 (11.6)
Patients with at least one Peg-grafeel™-related AE	13 (5.2)
Patients with at least one Peg-grafeel™-related SAE	0 (0.0)
Patients who discontinued the study due to an SAE	4 (1.6)
Patients who died due to an SAE	5 (2.0)
Patients with drug withdrawn due to an AE	4 (1.6)
Patients with drug withdrawn due to an SAE	4 (1.6)

Except for the number of AEs, patients experiencing multiple events were counted only once. If the same AEs were captured in different visits, the last visit AE was considered. Responses "certain," "possible," and "probable," were considered as Peg-grafeel™-related AEs. All values are n (%) unless indicated. AEs=Adverse events, SAE=Serious adverse event

Table 3: Incidence of treatment-emergent adverse events occurring in ≥1% of patients by preferred term and severity

Preferred term	n=250					
	All	Mild	Moderate	Severe (Grade 3)	Life-threatening (Grade 4)	Death
Number of patients with at least one AE	115 (46)	53 (21.2)	32 (12.8)	22 (8.8)	3 (1.2)	5 (2.0)
Pain	28 (11.2)	17 (6.8)	8 (3.2)	3 (1.2)	0	0
Vomiting	29 (11.6)	16 (6.4)	8 (3.2)	4 (1.6)	0	1 (0.4)
Pyrexia	16 (6.4)	12 (4.8)	1 (0.4)	3 (1.2)	0	0
Cough	14 (5.6)	9 (3.6)	3 (1.2)	2 (0.8)	0	0
Diarrhea	16 (6.4)	7 (2.8)	5 (2)	4 (1.6)	0	0
Nausea	21 (8.4)	7 (2.8)	13 (5.2)	1 (0.4)	0	0
Arthralgia	9 (3.6)	7 (2.8)	1 (0.4)	1 (0.4)	0	0
Constipation	21 (8.4)	6 (2.4)	15 (6)	0	0	0
Asthenia*	20 (8.0)	6 (2.4)	13 (5.2)	0	0	0
Insomnia	10 (4.0)	6 (2.4)	4 (1.6)	0	0	0
Anemia	11 (4.4)	4 (1.6)	5 (2.0)	2 (0.8)	0	0
Abdominal pain	11 (4.4)	4 (1.6)	3 (1.2)	2 (0.8)	0	2 (0.8)
Upper abdominal pain	3 (1.2)	3 (1.2)	0	0	0	0
Decreased appetite	6 (2.4)	2 (0.8)	4 (1.6)	0	0	0
Febrile neutropenia	5 (2.0)	1 (0.4)	1 (0.4)	2 (0.8)	1 (0.4)	0
Neutropenia*	6 (2.4)	1 (0.4)	0	2 (0.8)	2 (0.8)	0
Thrombocytopenia*	6 (2.4)	1 (0.4)	1 (0.4)	0	3 (1.2)	0
Back pain	7 (2.8)	1 (0.4)	4 (1.6)	2 (0.8)	0	0
Dyspnea	6 (2.4)	1 (0.4)	4 (1.6)	1 (0.4)	0	0
Cardio-respiratory arrest	3 (2.1)	0	0	0	0	3 (1.2)
Fatigue	6 (2.4)	0	2 (0.8)	4 (1.6)	0	0

Patients experiencing multiple events within the same system organ class or preferred term were counted only once under those categories. Patients experiencing the same event with different severity level were counted under the most severe occurrence. Four AEs (alopecia, malaise, pain in extremity, and peripheral neuropathy) with an event rate of ≥1% of patients, are not included in the table above as their severity grading were not reported. *Severity grading was not reported for all treatment-emergent adverse events. All values are n (%) unless indicated. AE=Adverse event

and febrile neutropenia in 5 (2.0%) patients. Neutropenia was reported as an SAE in 3 (1.2%) patients. Grade 4 thrombocytopenia was reported in 3 (1.2%) patients. SAEs led to study discontinuation in four patients (neutropenic sepsis in 1 patient, neutropenia and thrombocytopenia in 2 patients each, and pyrexia and multiorgan failure in 1 patient). A total of 5 (2%) deaths were reported during the study, none of which were related to Peg-grafeel™ treatment (cardiorespiratory arrest in 3 [1.2%] patients, abdominal pain with progression of cancer in 1 [0.4%] patient, and multiorgan failure in 1 [0.4%] patient). A list of treatment-emergent SAEs by preferred term and severity is presented in Table 5.

Discussion

Patients undergoing cancer chemotherapy frequently experience hematological toxicities, neutropenia and febrile neutropenia being the most common and often most serious. Pegfilgrastim, a long-acting form of filgrastim administered as a single fixed-dose injection per chemotherapy cycle, was approved by the US Food and Drug Administration in 2002 to lower the incidence of infections manifesting as febrile neutropenia following chemotherapy for nonmyeloid malignancies.^[4] The high cost of pegfilgrastim has led to limited patient accessibility and underutilization in the appropriate patient population despite its advantages.^[5]

Peg-grafeel™ is a pegfilgrastim that has been approved and prescribed in India and Vietnam for reducing the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancies.^[3] The use of prophylactic Peg-grafeel™ in this study was associated with

Table 4: Incidence of Peg-grafeel™-related adverse events (safety population)

Preferred term	n=250	Severity				
		Mild	Moderate	Severe (Grade 3)	Life-threatening (Grade 4)	Death
Number of patients with at least one AE related to study medication	13 (5.2)					
Pain	8 (3.2)	0	5	3	0	0
Asthenia	6 (2.4)	1	5	0	0	0
Arthralgia	3 (1.2)	0	2	1	0	0
Malaise	2 (0.8)	0	2	0	0	0
Back pain	2 (0.8)	0	1	1	0	0
Leukocytosis	1 (0.4)	1	0	0	0	0
Neutrophilia	1 (0.4)	0	1	0	0	0
Fatigue	1 (0.4)	0	1	0	0	0
Pain in extremity	1 (0.4)	0	1	0	0	0

Patients experiencing multiple events within the same system organ class or preferred term were counted only once under those categories. Responses “certain,” “possible,” and “probable” were considered as Peg-grafeel™-related AEs. If the same adverse events were captured in different visits, the last visit AE was considered. All values are n (%) unless indicated. AEs=Adverse events

Table 5: Treatment-emergent serious adverse events by preferred term (≥1% of patients) and severity (≥0.5% of patients)

Preferred term	Total	Mild	Moderate	Severe (Grade 3)	Life-threatening (Grade 4)	Death
Number of patients with at least one SAE	29 (11.6)	3 (1.2)	4 (1.6)	14 (5.6)	3 (1.2)	5 (2.0)
Cardio-respiratory arrest	3 (1.2)	0	0	0	0	3 (1.2)
Abdominal pain	4 (1.6)	0	0	2 (0.8)	0	2 (0.8)
Vomiting	7 (2.8)	0	2 (0.8)	4 (1.6)	0	1 (0.4)
Disease progression	1 (0.4)	0	0	0	0	1 (0.4)
Multiorgan failure	1 (0.4)	0	0	0	0	1 (0.4)
Febrile neutropenia	5 (2.0)	1 (0.4)	1 (0.4)	2 (0.8)	1 (0.4)	0
Neutropenia	3 (1.2)	0	0	1 (0.4)	2 (0.8)	0
Thrombocytopenia	3 (1.2)	0	0	0	3 (1.2)	0
Diarrhea	3 (1.2)	0	1 (0.4)	2 (0.8)	0	0
Fatigue	4 (1.6)	0	0	4 (1.6)	0	0
Pyrexia	5 (2.0)	1 (0.4)	1 (0.4)	3 (1.2)	0	0
Cough	2 (0.8)	0	0	2 (0.8)	0	0

Patients experiencing multiple events within the same system organ class or preferred term were counted only once under those categories. Patients experiencing the same event with different severity level were counted under the most severe occurrence. Only those events with <1% incidence were included which led to death. SAE=Serious adverse event

neutropenia and febrile neutropenia incidence rates of 2.4% and 2%, respectively. These rates are much lower than those reported in similar patient populations with or without prophylactic G-CSF support in India (febrile neutropenia, 15%; Grade 0–2 neutropenia, 58%; Grade 3–4 neutropenia, 42%).^[6] Studies conducted in other countries have shown good response to pegfilgrastim (i.e. a study in the US [neutropenia, 2.6%; febrile neutropenia, 3.4%]^[7] and Austria [neutropenia and febrile neutropenia, 5.7%])^[8] Other studies have reported greater variations in rates of febrile neutropenia (17%^[9] and 68.8%^[10]) in placebo-treated groups, largely due to differences in chemotherapeutic regimens. However, the rates of neutropenia and febrile neutropenia in this study are similar to those reported in observational studies in similar patient populations receiving pegfilgrastim prophylaxis.^[7,8,11] In one preapproval study from Dr. Reddy’s Laboratories Ltd., CDP-03-07,^[12] prophylactic Peg-grafeel™ significantly reduced the duration and frequency of incidents of severe neutropenia (Grade 3 and 4) in patients with advanced nonsmall cell lung carcinoma and breast cancer; rates were comparable with Grafeel® and published literature on pegfilgrastim, and distinctly different than the no-prophylaxis arm.^[13]

Peg-grafeel™ therapy was well-tolerated by a majority of patients in this study. Peg-grafeel™-related AEs were reported in approximately 5% patients, whereas none of the SAEs were related to the study drug. In general, the treatment-related AEs observed in this study were similar to those reported in the literature for myelosuppressive chemotherapy.^[7,8,11,14]

Bone pain was reported in approximately 6–10% of patients as an AE associated with pegfilgrastim in several clinical trials.^[10,14] A multicenter, retrospective, observational study using pegfilgrastim reported bone and muscle pain in only 1.7% of patients.^[11] The latter is supported by our findings, i.e. 1 (0.4%) patient reported bone pain, while 3 (1.2%) patients reported pain in the extremities. Pain was of mild or moderate severity, transient, and could be controlled with standard analgesics.

Allergic reactions/hypersensitivity including anaphylaxis, skin rash, and urticaria; generalized erythema; and flushing are listed as the side effects of pegfilgrastim.^[15] Treatment-emergent skin and subcutaneous tissue disorders were noted as treatment-related hypersensitivity reactions in 3.2% patients in the current PMS study. Other AEs reported in observational studies have been asthenia (2.2%), fever (0.6%), dyspnea (1.1%), anorexia (1.1%), and diarrhea (1.1%).^[11] In the current PMS study, <2% patients had AEs possibly related to pegfilgrastim, such as arthralgia, malaise, back pain, leukocytosis, neutrophilia, fatigue, and pain in the extremities. None of the rare AEs associated with pegfilgrastim, such as splenic rupture, acute respiratory distress syndrome, and sickle cell crisis, were observed in the current study. None of the deaths were attributed to Peg-grafeel™, and no new safety concerns were identified for Peg-grafeel™. The safety events observed in this study are in line with the known safety profile of the originator compound pegfilgrastim.^[4]

There were a few limitations in this study, such as, small sample size and nonavailability of longitudinal data. Also, like all observational studies, the patients in this study had different types of cancer, and thus received varied chemotherapeutic regimens. Hence, additional studies are necessary to study the drug in larger patient populations across geographies.

Overall, this PMS study evaluated the safety and tolerability of prophylactic Peg-grafeel™ in patients with advanced stages of nonmyeloid malignancies in India. The safety profile of Peg-grafeel™ was found to be similar with that reported in the globally available literature on pegfilgrastim. It was safe and well-tolerated in patients with chemotherapy-induced neutropenia, with a low incidence of Peg-grafeel™-related TEAEs, no Peg-grafeel™-related SAEs, and no unexpected safety concerns. Thus, the potential of effective, safe, and affordable pegfilgrastim such as Peg-grafeel™ needs to be considered, not just to provide better accessibility to patients, but to facilitate uninterrupted cancer chemotherapy and enhance overall response, leading to a better quality of life.

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Conflicts of interest

Ramkumar Anupama received consultancy fees from Dr. Reddy's Laboratories Ltd. Sinha Nitu is an employee of the study sponsor company, Dr. Reddy's Laboratories Ltd. Nirni Sharanabasappa, Talwar Vineet and Mallavarapu Krishna Mohan have no conflicts to declare.

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