



Efficacy and safety of biosimilar Peg-filgrastim after autologous stem cell transplant in myeloma and lymphoma patients: a comparative study with biosimilar Filgrastim, Lenograstim, and originator Peg-filgrastim

Francesco Marchesi¹ · Irene Terrenato² · Elena Papa¹ · Martina Tomassi¹ · Paolo Falcucci¹ · Svitlana Gumenyuk¹ · Francesca Palombi¹ · Francesco Pisani¹ · Daniela Renzi¹ · Atelda Romano¹ · Antonio Spadea¹ · Giulia Regazzo³ · Maria Giulia Rizzo³ · Mafalda De Rienzo⁴ · Claudio Ripellino⁵ · Simona Sgromo¹ · Caterina Viggiani¹ · Eleonora Ponte⁶ · Ramy Kayal⁷ · Iole Cordone⁸ · Maria Laura Foddai⁴ · Andrea Mengarelli¹

Received: 17 November 2023 / Accepted: 21 December 2023 / Published online: 8 January 2024
© The Author(s) 2024

Abstract

Data about biosimilar Peg-filgrastim (bioPEG) in autologous stem cell transplant (ASCT) are still scarce. The aim of this study has been to assess efficacy and safety of bioPEG among lymphoma and myeloma patients undergoing ASCT, comparing these data with historical controls receiving other G-CSFs. Furthermore, an economic evaluation has been included to estimate the savings by using bioPEG. This is a prospective cohort study comparing lymphoma and myeloma patients undergoing ASCT and receiving bioPEG ($n = 73$) with three historical consecutive cohorts collected retrospectively who received other G-CSFs (Lenograstim — Leno — $n = 101$, biosimilar Filgrastim — bioFIL $n = 392$, and originator Peg-filgrastim — oriPEG $n = 60$). We observed a significantly shorter time to neutrophils and platelet engraftment ($p < 0.001$) in patients treated with bioPEG and oriPEG. Moreover, patients who received bioPEG showed a shorter hospitalization time ($p < 0.001$) and a lower transfusion need ($p < 0.001$). We did not observe any significant difference in terms of transplant-related mortality, mucositis, and diarrhea among the four groups. No serious adverse events were associated with bioPEG. Similar data were obtained after running a stratified analysis for lymphomas and myeloma separately conducted by using a propensity score matching. The average total cost per patient of bioPEG was € 18218.9 compared to € 23707.8, € 20677.3 and € 19754.9 of Leno, oriPEG, and bioFIL, respectively. In conclusion, bioPEG seems to be as effective as the originator and more effective than short-acting G-CSFs in terms of post-transplant engraftment in myeloma and lymphoma patients undergoing ASCT. Moreover, bioPEG was cost-effective when compared with the other G-CSFs.

Keywords Autologous stem cell transplant · Biosimilars · Granulocyte colony-stimulating factors · Myeloma · Lymphoma · Peg-filgrastim

✉ Francesco Marchesi
francesco.marchesi@ifo.it

¹ Hematology Unit, IRCCS Regina Elena National Cancer Institute, Via Elio Chianesi 55, 00144 Rome, Italy

² Department of Research, Advanced Diagnostics and Technological Innovation, Clinical Trial Center, Biostatistics and Bioinformatics Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy

³ Department of Research, Advanced Diagnostics and Technological Innovation, Genomic and Epigenetic Unit, Translational Research Area, IRCCS Regina Elena National Cancer Institute, Rome, Italy

⁴ Immuno-Transfusional Medicine Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy

⁵ Health Economics & Real-World Evidence Freelance, Milan, Italy

⁶ Leukapheresis and Cellular Therapy Unit, S. Camillo-Forlanini Hospital, Rome, Italy

⁷ Radiology Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy

⁸ Clinical Pathology Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy

Background

Autologous hematopoietic stem cell transplant (ASCT) is performed after administration of high dose chemotherapy, called conditioning regimen, typically determining a detrimental effect on bone marrow and causing severe neutropenia, thrombocytopenia, and anemia [1]. The most widely used conditioning regimens around the globe are MEL200 (melphalan 200 mg/sqm) for multiple myeloma patients, BEAM (carmustine, etoposide, cytarabine, and melphalan) or BEAC (carmustine, etoposide, cytarabine, and cyclophosphamide) for lymphoma patients and BU-CY2 (busulfan and cyclophosphamide) for acute leukemia patients [2]. Nowadays, after the approval of novel cellular therapy approaches (i.e., CAR-T), the right placement of ASCT in the therapeutic algorithm of some hematologic malignancies is under debate, but so far still remains the standard of care in several settings [2]. ASCT can be associated with several side effects and potentially death (transplant-related mortality, TRM) mainly due to infections and hemorrhages. However, in the last years, TRM has constantly dropped given the improvement of our knowledge of supportive measures [3]. In particular, the administration of granulocyte colony stimulating factors (G-CSF) after stem cell infusion permitted a faster neutrophil number recovery and consequent drop in febrile neutropenia events, infection occurrence, antibiotic use, and hospital stay days [4]. Several G-CSF have been so far approved for febrile neutropenia prophylaxis in patients undergoing high-dose chemotherapy, divided in short-acting and long-acting. The first ones are characterized by a daily administration until neutrophil engraftment and are Filgrastim, biosimilar Filgrastim, and Lenograstim. On the contrary, long-acting G-CSFs (Peg-filgrastim, biosimilar Peg-Filgrastim, and Lipofilgrastim) are given as one-shot post-chemo administration as a consequence of their long lasting action [5]. Since the implementation of a biosimilar approval pathway in 2005, several biosimilars including somatotropins, filgrastim, epoietins, and infliximab have been approved in Europe, on the basis of demonstrating comparable quality, safety, and efficacy to the originator products [6]. Biosimilars are biological drugs whose target and mechanisms of action are the same as those of an originator biological drug. A “biosimilar” is correctly defined as a drug that has been approved in highly regulated markets and that meets stringent criteria of quality and comparability to its respective originator biologic product. The development of biosimilars is achieved by applying the same evidence-based regulatory standards as originator products, where cost limitations do not reflect lower quality, efficacy, and safety, or worsening of patient outcomes [6, 7]. Biosimilar G-CSFs are substantially identical to the originators and the only small differences in the microheterogeneity pattern

of the molecule do not translate in meaningful clinical differences in terms of both efficacy and safety [8]. The key driver for uptake of biosimilars is cost reduction relative to the originator biologics; in fact, biosimilars are at least 15–45% less expensive than the originator biologics [9]. A variety of incentives and policies have been implemented in Europe to promote market access and uptake of biosimilars. The main reason for this favorable market is that countries wish to capture the savings resulting from the lower cost of biosimilars in an era of limited healthcare budgets, increasing burden of life-threatening diseases, earlier detection of diseases, and increasing aging population [10]. As a consequence, economic assessments that offer a comprehensive estimate of savings represent important decision-making tools for the payer. In 2019, the Food and Drug Administration (FDA) approved the first biosimilar Peg-filgrastim with the same indications of its originator. Even though the use of biosimilar Peg-filgrastim is progressively increasing in oncohematology field, there are still few data about its efficacy and safety in patients undergoing ASCT and allogeneic hematopoietic stem cell transplant. As for ASCT, a recent study from an Italian transplant center have explored the use of biosimilar Peg-filgrastim among multiple myeloma patients undergoing ASCT suggesting a substantial superimposable efficacy and safety compared to other G-CSFs (originator Peg-filgrastim and biosimilar short-acting filgrastim) [11]. The aim of this study has been to assess the efficacy and the safety of biosimilar Peg-Filgrastim among a lymphoma and myeloma patient population undergoing ASCT, comparing these data with those derived by our historical control groups of patients receiving other G-CSFs for febrile neutropenia prophylaxis (i.e., biosimilar Filgrastim, originator Peg-filgrastim, and Lenograstim). Furthermore, an economic evaluation has been included to estimate the savings associated with the use of biosimilar Peg-Filgrastim compared to other therapeutic options.

Methods

Study design and patients

This is a prospective cohort study comparing lymphoma and myeloma patients undergoing ASCT at Hematology Unit of Regina Elena National Cancer Institute and receiving biosimilar Peg-filgrastim with three historical consecutive patient cohorts collected retrospectively who received other G-CSF formulations at the same institution. The main study patient cohort included 73 patients affected by multiple myeloma or lymphoma who consecutively underwent ASCT at our institution between June 2021 and May 2023. Inclusion criteria were age above 18 years, eligibility for ASCT and

availability of a post-transplant 3 month-long follow-up for collecting data. Patients in all disease phases (i.e., complete remission — CR, very good partial remission — VGPR, partial remission — PR, stable disease — SD, or progressive disease — PD) were included.

Procedures

For all patients, we collected the following data: sex, age, diagnosis, induction treatment before ASCT, and number of chemotherapeutic lines, disease status at ASCT, number of CD34+ $\times 10^6$ /kg collected and actually infused, conditioning regimens, days to neutrophil and platelet engraftment, febrile and infectious episodes, other side effects, antibiotic and transfusion needing, days of hospitalization, and TRM. In all enrolled patients, a single administration of Peg-filgrastim at 6 mg was subcutaneously given at day 3 after stem cell infusion. This cohort of patients was compared with three historical cohorts (Table 1): (a) 392 consecutive adult patients treated with biosimilar Filgrastim at dosage of 5 mcg/kg daily given from day 3 after infusion until neutrophil engraftment from March 2013 to May 2021; (b) 101 consecutive adult patients treated with Lenograstim at a dosage of 5 mcg/kg daily given from day 3 after infusion until neutrophil engraftment from January 2009 to February

2013; (c) 60 consecutive adult patients treated with originator Peg-filgrastim at a dosage of 6 mg single dose at day 3 after infusion from March 2006 to December 2008. All multiple myeloma patients younger than 65 years received a MEL200 conditioning regimen, whereas patients aged above 65 years received a reduced intensity conditioning regimen with melphalan 140 mg/sq m (MEL140). All but 60 lymphoma patients received BEAM conditioning regimen; those 60 patients received FEAM conditioning regimen between September 2011 and August 2015 due to difficult supply of carmustine.

All patients received the same institutional standard procedures. In particular, oral Valacyclovir was given at the dosage of 1 g/day from the day of stem cell infusion to 6 months after transplant for herpes viruses prophylaxis. *Pneumocystis jirovecii* pneumonia prophylaxis was administered with Trimethoprim/Sulfamethoxazole 1 double strength tablet twice a week from the day of stem cell infusion to 6 months after transplant. No anti-microbial prophylaxis was given. Red blood cell (RBC) and platelet transfusion were administered for hemoglobin level < 8 g/dL and platelet count $< 10 \times 10^9$ /L or in patients with symptomatic anemia or hemorrhagic syndrome. Intravenous hydration and electrolyte support was given according the good clinical practice and the institutional standard protocols.

Table 1 Baseline features of patients according to the received G-CSF formulation

Parameter	Biosimilar Peg-filgrastim, <i>N</i> = 73 <i>N</i> (%)	Biosimilar Filgrastim <i>N</i> = 392 <i>N</i> (%)	Lenograstim, <i>N</i> = 101 <i>N</i> (%)	Originator Peg-filgrastim, <i>N</i> = 60 <i>N</i> (%)	<i>p</i> -value
Sex, M/F, <i>N</i> (%)	33/40 (45/55)	24/181 (54/46)	64/37 (63/37)	36/24 (60/40)	0.089*
Median age, years (range)	60 (31–70)	57 (19–72)	55 (19–72)	56 (18–71)	< 0.001**
Diagnosis					0.004*
MM	57 (78)	227 (58)	66 (65)	26 (43)	
NHL/HD	16 (22)	165 (42)	35 (35)	34 (57)	
Median chemotherapy lines prior ASCT (range)	1 (1–2)	1 (1–5)	2 (1–4)	2 (1–4)	< 0.001**
Disease status at ASCT					0.071*
CR	39 (53)	205 (52)	64 (63)	38 (63)	
PR	34 (47)	166 (42)	35 (35)	21 (35)	
SD/PD	-	21 (6)	2 (2)	1 (2)	
Conditioning chemotherapy					0.004*
MEL200/MEL140	57 (78)	227 (58)	66 (65)	26 (43)	
BEAM/FEAM	16 (22)	165 (42)	35 (35)	34 (57)	
Median infused CD34+ cells $\times 10^6$ /kg (range)	4.83 (2.92–10.36)	5.62 (3.37–16.68)	5.53 (3.31–14.50)	5.42 (2.93–14.4)	< 0.001**

Bold values are those statistically significant

MM multiple myeloma; NHL non-Hodgkin's lymphoma; HD Hodgkin's disease; ASCT autologous stem cell transplantation; CR complete remission; PR partial remission; SD stable disease; PD progressive disease; MEL200 melphalan 200 mg/sq m; MEL 140 melphalan 140 mg/sq m; BEAM carmustine, etoposide, cytarabine, melphalan; FEAM fotemustine, etoposide, cytarabine, melphalan

* Pearson's chi-square test ** Kruskal-Wallis test

Febrile neutropenia was homogenously managed according to the institutional protocols in all patients. In particular, empirical broad-spectrum anti-microbial treatment was promptly started at the onset of fever (defined as body temperature ≥ 38 °C in two consecutive determinations) during neutropenia (defined as $ANC \leq 0.5 \times 10^9/L$) with a combination of Piperacillin-tazobactam plus Amikacin, following the local protocols and the international guidelines [12, 13]. Hematologic engraftment after ASCT was defined as an absolute neutrophil count upper than $0.5 \times 10^9/L$ and a platelet count upper than $20 \times 10^9/L$ in three consecutive checks. Other adverse events were collected and graded according to the Common Toxicity Criteria of the National Cancer Institute.

Ethical approval

The study was approved by the local institutional review board and ethical committee (approval protocol number: 36/IRE/23–2866) and conducted in accordance to the Helsinki Declaration and the International Conference on Harmonization Guidelines for Good Clinical Practice.

Study objectives

The primary objective of the study was to evaluate the efficacy in terms of ANC engraftment after stem cell infusion in our patient population receiving a single dose of biosimilar Peg-filgrastim after ASCT. Secondary objectives of the study included platelet engraftment after stem cell infusion, febrile neutropenia, documented infections, and antibiotic use, transfusion and hospitalization days, safety, and TRM. For all these objectives, we also performed a comparison of patients receiving biosimilar Peg-filgrastim with those receiving other G-CSF formulations.

Statistical analysis

Descriptive statistics were calculated for all variables of interest. Categorical variables were summarized through frequencies and percentage values while continuous variables through median or mean values and their relative variability index (standard deviation or range, respectively). All distributions were tested for normality by Shapiro–Wilk test, and the most suitable test was applied to compare groups: Pearson’s chi-square test or Fisher for categorical variables and the Mann–Whitney test or Kruskal–Wallis test for continuous variables. Bonferroni correction for multiple comparisons was applied, when appropriate. Stratified analyses for lymphoma and myeloma patients were conducted. In this specific sub-group, in order to control for potential confounders that could affect the outcomes of interest when we compared the

different G-CSFs, propensity score matching (PSM) was employed to generate two different pair wise groups with balanced distribution of specific baseline features [14]. The dependent variable was the choice of specific G-CSF: biosimilar Peg-filgrastim was considered the experimental drug, while Lenograstim, biosimilar Filgrastim and Peg-filgrastim were considered the control group for each sub-analysis. Patients were matched one-to-one with a tolerance of 0.5 for age at diagnosis, gender, and number of CD34 infused cells. A p -value < 0.05 was considered statistically significant. All statistical analyses were carried out with IBM SPSS v 29.0.

Costs analysis

A cost analysis in terms of average total and saved cost per person between the groups was conducted. G-CSF treatment, intravenous empirical broad-spectrum antibiotic needing (piperacillin-tazobactam 4.5 g every 6 h plus 20 mg/kg/daily for an average duration of 8 days), RBC and PLT transfusions, and days of hospitalization, which clinical and resource utilization data derive from the main study, were considered for the economic evaluation. Treatment costs were calculated considering the lowest ex-factory prices (October 2023); the costs of blood components and related processes, inclusive for all costs incurred for self-donation by the transfusion service, were estimated by using the tariffs of interregional agreement for the compensation of healthcare mobility [15], and the average cost of hospitalization per day was estimated in the 2004 by the Italian Ministry of Economy and Finance [16], and it was revalued to 2022 based on the ISTAT consumer price index (Table 2).

Table 2 Unit costs

	Euro (€)
Biosimilar peg-filgrastim 6 mg	390.00 €
Lenograstim 34 MUI/mL *	87.96 €
Originator Peg-filgrastim 6 mg	1000 €
Biosimilar Filgrastim 30 MU *	63.90 €
Piperacillin-Tazobactam 4 + 0.5 g 10 units	83.77 €
Amikacin 500 mg 10 units	18.31 €
Cost of blood components and related processes (RBC)	181.00 €
Cost of blood components and related processes (PLT)	418.00 €
Average cost of hospitalization per day	905.86 €

RBC red blood cells, *PLT* platelets

* 1 vial per day was considered for an assumed patient with a median body weight of 70 kg

Results

Analysis on the overall population

From June 2021 to May 2023, 73 consecutive patients with multiple myeloma (57) and lymphoma (16) underwent ASCT and received biosimilar Peg-filgrastim after stem cell infusion. Baseline demographic and clinical characteristics of these patients and of the three historical control groups (as above defined) are resumed in Table 1. As shown, patients who received biosimilar Peg-filgrastim were significantly older ($p < 0.001$), more frequently affected by myeloma and then treated with melphalan-based conditioning regimens ($p = 0.004$) and were infused with a significantly lower number of CD34+ cells ($p < 0.001$). On the contrary, no significant differences as for sex distribution and disease status at transplant were observed among the four patient cohorts ($p = 0.089$ and 0.071 , respectively). Table 3 shows the post-transplant clinical outcomes by the received G-CSF formulation. We observed a shorter time to neutrophil engraftment in the cohort of patients treated with both biosimilar and originator Peg-filgrastim ($p < 0.001$), with a median time of 10 days among those patients, compared with 11 days achieved in the cohort of patients receiving short-acting G-CSFs, as biosimilar Filgrastim and Lenograstim. The same result was observed for PLT engraftment, significantly faster in Peg-filgrastim groups (biosimilar 11 days and originator 12 days) than in the other two groups (biosimilar Filgrastim 13 days, Lenograstim 14 days; $p < 0.001$). As for the other analyzed parameters, we did observe a similar incidence of febrile neutropenia

episodes, microbiologically documented infections and intravenous antibiotic needing among the four patient cohorts ($p = 0.770$, $p = 0.493$, and $p = 0.770$, respectively). In contrast, our data showed a significant lower RBC and platelet transfusion rate in patients receiving both biosimilar and originator Peg-filgrastim, when compared with the other two groups ($p < 0.001$). In addition, a shorter median duration of the hospitalization was observed in the patient cohort treated with biosimilar Peg-filgrastim (19 days; $p < 0.001$). In particular, the advantage was statistically significant when compared with Lenograstim group ($p = 0.001$) and did not reach the statistical significance when compared with the other two groups (originator Peg-filgrastim and biosimilar Filgrastim). Finally, we did not observe any significant difference in terms of TRM among the four groups of patients. No significant differences in terms of mucositis and diarrhea were observed among the four groups of patients. No grade 3–4 adverse events were associated with the biosimilar Peg-filgrastim administration.

Sub-analysis for lymphoma and myeloma patients

A stratified analysis for lymphoma and myeloma patients only was conducted by using PSM to generate different pair wise groups with balanced distribution of specific baseline features. Setting the tolerance at 0.5 allowed creating different sub-groups in terms of sample size. As shown in Table 4, lymphoma patients who received biosimilar Peg-filgrastim have a shorter median time to neutrophil engraftment than patients receiving Lenograstim (10 vs 11 days; $p < 0.001$) and biosimilar Filgrastim (10 vs

Table 3 Post-transplant clinical outcomes by the received G-CSF formulation

Results	Biosimilar Peg-filgrastim, $N = 73$	Biosimilar Filgrastim, $N = 392$	Lenograstim, $N = 101$	Originator Peg-filgrastim, $N = 60$	p -value
Engraftment					
Median days (range) at $ANC > 0.5 \times 10^9/L$	10 (9–12)	11 (5–30)	11 (9–29)	10 (8–18)	< 0.001**
Median days (range) $PLTs > 20 \times 10^9/L$	11 (9–16)	13 (5–120)	14 (10–35)	12 (9–23)	< 0.001**
Median days (range) G-CSF injections		8 (4–26)	9 (4–26)		< 0.001°
Febrile neutropenia episodes (%)	34 (47%)	208 (53%)	54 (63%)	32 (53%)	0.770*
Microbiologically documented infections (%)	24 (33%)	153 (39%)	43 (43%)	20 (33%)	0.493*
Intravenous antibiotics needing (%)	34 (47%)	208 (53%)	54 (63%)	32 (53%)	0.770*
Mean number (SD) RBC transfusions	0.3 (1.4)	0.7 (1.9)	0.8 (1.5)	0.4 (0.9)	0.004**
Median number PLT transfusions (range)	1 (0–15)	2 (0–18)	2 (0–12)	1 (0–6)	< 0.001**
Median hospitalization duration, days (range)	19 (14–59)	20 (13–66)	24 (15–68)	21 (6–29)	< 0.001**
TRM (%)	1 (1%)	8 (2%)	4 (4%)	1 (2%)	0.619*

Bold values are those statistically significant

RBC red blood cells, PLT platelets, ANC absolute neutrophils count, TRM transplant-related mortality, SD standard deviation

* Pearson's chi-square test; ** Kruskal–Wallis test

° Mann–Whitney test

Table 4 Post-transplant clinical outcomes by the received G-CSF formulation. Pairwise propensity score matching analysis in lymphoma patients

Results	Biosimilar Peg-filgrastim, N=13	Lenograstim, N=13	p-value	Biosimilar Peg-filgrastim, N=16	Originator Peg-filgrastim, N=16	p-value	Biosimilar Peg-filgrastim, N=16	Biosimilar Filgrastim, N=16	p-value
Engraftment									
Median days (range) at ANC > 0.5 × 10 ⁹ /L	10 (9–10)	11 (10–16)	<0.001°	10 (9–11)	9 (8–10)	0.009°	10 (9–11)	11 (9–15)	<0.001°
Median days (range) PLTs > 20 × 10 ⁹ /L	12.5 (9–15)	12 (10–26)	0.802°	12 (9–15)	13 (9–17)	0.561°	12 (9–15)	14 (10–45)	0.016°
Febrile neutropenia episodes (%)	10 (77%)	10 (77%)	1.000**	12 (75%)	13 (81%)	1.000**	12 (75%)	9 (56%)	0.458**
Microbiologically documented infections (%)	5 (38%)	8 (62%)	0.239*	7 (44%)	6 (37%)	0.719*	7 (44%)	8 (50%)	0.723*
Intravenous antibiotics needing (%)	10 (77%)	10 (77%)	1.000**	12 (75%)	13 (81%)	1.000**	12 (75%)	9 (56%)	0.458**
Mean number (SD) RBC transfusions	0.9 (3.3)	1.6 (2.0)	0.012°	0.8 (3.0)	0.7 (1.3)	0.085°	0.8 (3.0)	1.8 (4.9)	0.024°
Median number PLT transfusions (range)	2 (0–15)	3 (1–7)	0.012°	2 (0–15)	2 (1–4)	0.750°	2 (0–15)	2 (1–10)	0.421°
Median hospitalization duration, days (range)	21 (18–59)	28 (17–48)	0.022°	22 (18–59)	23 (6–29)	0.354°	22 (18–59)	22 (18–66)	0.894°

RBC red blood cells, PLT platelets, ANC absolute neutrophils count, SD standard deviation

* Pearson's chi square test; ** Fisher's exact test

° Mann–Whitney test

11 days; $p < 0.001$), whereas the better performance was observed in patients treated with originator Peg-filgrastim (9 vs 10 days; $p = 0.009$). As for the other analyzed parameters, we did not observe significant differences among the four patient cohorts, except for a better time to PLT engraftment and a lower needing for RBC transfusions in the biosimilar Peg-filgrastim group compared with biosimilar Filgrastim ($p = 0.016$ and $p = 0.024$, respectively); a lower number of RBC and platelet transfusions and a lower hospitalization time in the biosimilar Peg-filgrastim group compared with Lenograstim ($p = 0.012$, $p = 0.012$, and $p = 0.022$, respectively). Similar results are carried out from myeloma sub-analysis, as shown in Table 5.

Costs analysis

The average total cost per patient of biosimilar Peg-filgrastim was € 18218.9 compared to € 23707.8, € 20677.3, and € 19754.9 of Lenograstim, originator Peg-filgrastim and biosimilar Filgrastim, respectively (Table 6). The main driver of the cost resulted to be the hospitalization followed by PLT transfusion and G-CSF treatments. The average cost savings per patient in favor of biosimilar Peg-filgrastim were € 5488.9, € 2458.4, and € 1536.0 for Lenograstim, originator Peg-filgrastim, and biosimilar Filgrastim, respectively (Table 6).

Discussion

Our study showed the efficacy and safety of biosimilar Peg-filgrastim in post-transplant engraftment among myeloma and lymphoma patients undergoing ASCT. The median time to neutrophil and platelet engraftment was 10 and 11 days, similarly to that observed in our historical cohorts of patients receiving originator Peg-filgrastim and significantly shorter than those receiving short-acting G-CSFs (i.e., Lenograstim or biosimilar Filgrastim). Pegylated G-CSF was associated with a significantly faster neutrophil engraftment in ASCT in other studies, substantially conducted by using the originator [17–19]. However, several previous reports suggested the comparability for both pharmacokinetic and pharmacodynamic properties between biosimilar Peg-filgrastim and its originator [20]. Indeed, our study confirmed in the setting of autologous transplant the equivalence in terms of clinical efficacy of both biosimilar and originator Peg-filgrastim, being significantly superior to biosimilar Filgrastim and Lenograstim in terms of neutrophil and platelet engraftment. Data about biosimilar Peg-Filgrastim are still scarce in this context. Recently, some studies have been published, all together showing a slightly superiority of biosimilar pegylated formulations over the short-acting G-CSFs in myeloma and lymphoma patients undergoing ASCT [11, 21]. The physiological reason for the better

Table 5 Post-transplant clinical outcomes by the received G-CSF formulation. Pairwise propensity score matching analysis in myeloma patients

Results	Biosimilar Peg-filgrastim, N=45	Lenograstim, N=45	p-value	Biosimilar Peg-filgrastim, N=22	Originator Peg-filgrastim, N=22	p-value	Biosimilar Peg-filgrastim, N=57	Biosimilar Filgrastim N=57	p-value
Engraftment									
Median days (range) at ANC > 0.5 × 10 ⁹ /L	10 (9–12)	12 (9–22)	<0.001°	10 (9–12)	10 (9–10)	0.015°	10 (9–12)	11 (5–15)	<0.001°
Median days (range) PLTs > 20 × 10 ⁹ /L	11 (9–15)	15 (10–35)	<0.001°	11 (9–16)	11 (9–18)	0.798°	11 (9–16)	12 (5–40)	<0.001°
Febrile neutropenia episodes (%)	5 (11%)	5 (11%)	1.000*	0 (%)	1 (4%)	1.000**	5 (9%)	3 (5%)	0.463**
Microbiologically documented infections (%)	14 (31%)	14 (31%)	1.000*	10 (45%)	8 (36%)	0.540*	17 (30%)	19 (33%)	0.687*
Intravenous antibiotics needing (%)	19 (42%)	19 (42%)	1.000*	10 (45%)	9 (41%)	0.761*	22 (39%)	22 (39%)	1.000*
Mean number (SD) RBC transfusions	0.1 (0.4)	0.6 (1.5)	0.042°	0.2 (0.5)	0.2 (0.5)	1.000°	0.1 (0.4)	0.4 (0.9)	0.229°
Median number PLT transfusions (range)	1 (0–3)	2 (0–12)	<0.001°	1 (0–5)	1 (0–2)	0.960°	1 (0–5)	1 (0–5)	0.008°
Median hospitalization duration, days (range)	18 (14–34)	21 (15–27)	<0.001°	18 (15–24)	18 (15–25)	1.000°	18 (14–30)	18 (14–30)	0.679°

Bold values are those statistically significant

RBC red blood cells, PLT platelets, ANC absolute neutrophils count, FUO fever of unknown origin, SD standard deviation

* Pearson's chi-square test; ** Fisher's exact test

° Mann–Whitney test

Table 6 Cost analysis results

	Biosimilar Peg-filgrastim	Biosimilar Filgrastim	Lenograstim	Originator Peg-filgrastim
G-CSF treatments	390.0 €	511.2 €	791.6 €	1000.0 €
Intravenous antibiotics	145.3 €	163.8 €	194.7 €	163.8 €
RBC transfusions	54.3 €	126.7 €	144.8 €	72.4 €
PLT transfusions	418.0 €	836.0 €	836.0 €	418.0 €
Hospitalization	17211.3 €	18117.2 €	21740.6 €	19023.1 €
Total	18218.9 €	19754.9 €	23707.8 €	20677.3 €
<i>Savings</i>	-	1536.0 €	5488.9 €	2458.4 €

G-CSF granulocyte colony stimulating factor, RBC red blood cells, PLT platelets

performance of pegylated G-CSF formulation can be found looking at the pharmacokinetics of Peg-filgrastim. Indeed, its pharmacological profile allows the same powerful effect on myeloid progenitors with the advantage of a single and fixed-dose injection given per cycle, thanks to reduced renal clearance and extended half-life [22, 23]; the only pathway of Peg-filgrastim elimination is the neutrophil-mediated clearance [24]. However, in some studies this biological advantage did not translate in a meaningful better time to neutrophil recovery, mainly because several confounding factors basically due to patient's selection biases and variability were present in those studies, including population age, CD34+ -infused cells, disease stage, and prior exposure

to chemotherapy or radiotherapy. Several factors, other than G-CSFs, are indeed known as able to significantly affect the neutrophil and platelet engraftment after ASCT [25]. The most relevant are age at transplant, number of CD34+ -infused cells, disease stage, and previous radiant treatment [25]. In our study, at least two of those factors were able to negatively influence the post-transplant engraftment in biosimilar Peg-Filgrastim patient cohort, since the median age of these patients was significantly higher and they received a significantly lower number of CD34+. On the contrary, no significant differences were found in terms of previous chemotherapeutic lines and previous radiotherapy. In addition, we carried out a sub-analysis on lymphoma and myeloma

patients separately by PSM to generate different pair wise groups with balanced distribution of specific baseline features (age, gender, and number of infused CD34+). Even in this “unbiased” model, we observed a significant advantage at least in terms of neutrophil engraftment for pegylated G-CSF formulations compared to short-acting ones, confirming the better performance observed in the overall patient population. In our study, we observed a slightly lower incidence of febrile neutropenia episodes and documented infections with consequent lower broad-spectrum antibiotic consumption in patients who received biosimilar Peg-filgrastim; however, it is not statistically significant. This trend is consistent with that reported in the study of Martino et al. [11] and other groups [19, 26–28], where it however reached the statistical significance. Our data about febrile neutropenia episodes and documented infections could be however potentially influenced by the higher number of myeloma patients observed in the biosimilar Peg-filgrastim group. Indeed, taking a look at lymphoma sub-analysis, we can easily understand that the number of febrile episodes and antibiotic needing was quite similar among all the patient’s cohorts, suggesting that febrile neutropenia was more rarely detected in myeloma patients, irrespective to the received G-CSF formulation, in accordance with our previous published data [29]. Further studies are warranted to better clarify whether the G-CSF formulation can potentially influence the occurrence of post-transplant febrile neutropenia, documented infections and antibiotic needing in ASCT. As a consequence of a shorter engraftment time, from our study, we observed a significantly lower transfusion needing and a shorter hospitalization time among patients receiving biosimilar and originator Peg-filgrastim. In particular, this difference was statistically significant compared to Lenograstim patient cohort, and less evident if compared to biosimilar Filgrastim. Even if hospitalization duration could be potentially affected by several confounding factors, this datum seems to be relevant in our opinion, since less hospitalization time means a better management of health resources in terms of both organization and costs. In general, it has already been widely discussed and demonstrated in the literature how the lower cost of biosimilar drugs and the consequent savings derived from their use can lift the financial burden of health care systems and increase patient access to drugs [30–32]. Over the past decade, the biosimilar Filgrastim transformed patient access, with clear evidence of clinical benefits in preventing febrile neutropenia at reduced costs (savings conservatively estimated at 39% in Europe) and in 2019 the licensing in Europe of the biosimilar Peg-filgrastim provided the opportunity to offer the additional benefits of long-acting G-CSF over short-acting G-CSF at a reduced cost [33–35]. Our study showed that potential cost savings per patient range from approximately € 1500 to approximately € 5500 by adopting the biosimilar Peg-filgrastim in place of biosimilar

Filgrastim, originator Peg-filgrastim or Lenograstim. These benefits could be more substantial at a population level. For example, the economic impact of introducing biosimilar Peg-filgrastim compared to the current standard G-CSF practice in France was estimated to generate a cost saving from € 51007531 to € 287344835 over 5 years switching from the current standard practice to biosimilar Peg-filgrastim [36]. In Germany, the health-economic impact of biosimilar Peg-filgrastim in the real world for healthcare system would generate a potential annual savings of up to € 56.4 million, with a saving of up to € 4199 per patient compared to originator product [37]. Most economic evaluations of biosimilars consider only the cost of the drug, but it is fundamental in economic evaluations to estimate the real savings beyond the cost of the drug, especially in the case of differences in the form of administration or in adherence, differences in use of healthcare resources, or to consider value-added services. Our study showed that cost savings of biosimilar Peg-filgrastim were in fact mainly attributable at the inpatient management. A real-world data study on primary prophylaxis with Peg-filgrastim vs Filgrastim in cancer patients at intermediate-to-high risk of febrile neutropenia showed that biosimilar Peg-filgrastim was dominant (with a cost saving of \$ 5703 and a gain of 0.28 quality-adjusted life year (QALY)) compared with biosimilar Filgrastim for the high-risk group and a cost/QALY of \$ 14502 for the intermediate-risk group [38]. In line with our study, the main saving of biosimilar Peg-filgrastim vs biosimilar Filgrastim was primarily driven by a lower cost of inpatient febrile neutropenia management for patients receiving biosimilar Peg-filgrastim [38]. The savings arising from the cost containment using biosimilar Peg-filgrastim could be reallocated to increase patient access to innovative therapies, to move therapy to an earlier line of treatment, to increase the number of healthcare staff thus resulting in a better health outcome for more patients. Peg-filgrastim administration was safe, with no reported grade 3–4 adverse events and the safety profile was similar to that seen for the other G-CSF formulations. At the same time, we observed a superimposable rate of mucositis and diarrhea among the four patient cohorts and the TRM was quite similar, overall ranging between 1 and 4%. This is quite in contrast to some previous report [11, 39] in which the authors showed a lower incidence of mucositis and grade 2–3 diarrhea in patients who received pegylated G-CSFs both in myeloma patients undergoing ASCT and in breast cancer patients, respectively. Multiple factors can potentially explain this difference, keeping in mind that post-transplant gastrointestinal toxicities are usually related to several variables not always easy to predict and control. The present study has some limitations, basically due to the study design, including the use of historical controls. The differences detected in the baseline demographic and clinical characteristics among the four patient cohorts can potentially

affect the reliability of our findings. In addition, we analyzed only a small amount of lymphoma patients who received biosimilar Peg-filgrastim after ASCT. Even in this last group, although we used a PSM to generate different pair-wise groups with balanced distribution of specific baseline features in order to maximize the comparability among the different patient cohorts, our results should be read carefully particularly if we consider the limited sample size. In conclusion, being aware of the limitations discussed above, from our study biosimilar Peg-filgrastim seems to be as effective as the originator and more effective than short-acting G-CSF formulations (Lenograstim and biosimilar Filgrastim) in terms of post-transplant engraftment in myeloma and lymphoma patients undergoing ASCT. In addition, pegylated formulations seem to be associated to a better patient clinical management in terms of transfusion needing, febrile neutropenia, and hospitalization duration. Finally, from our pharmacoeconomic evaluation, biosimilar Peg-filgrastim was cost-effective when compared with the other G-CSF formulations and savings derived from its use may contribute to an expansion of medical treatment options for patients, hence concomitantly contributing to the long-term sustainability of the healthcare system. We believe that our findings could help clinicians and healthcare decision-makers in the better management of febrile neutropenia prophylaxis of myeloma and lymphoma patients undergoing ASCT.

Acknowledgements The authors would like to thank Dr. Federica Falconi (Scientific Direction of IRCCS Regina Elena National Cancer Institute) for the technical study support.

Author contribution Study concept and design: MF, TI, and MA. Statistical analysis: MF and TI. Protocol approval and technical support: PE and TM. Patient's data collection: MF, FP, GS, PaF, PiF, RD, RA, SA, RG, RMG, DRM, SS, VC, PE, KR, CI, and FML. Economic analysis: RC. Manuscript writing: MF and RC. Final review and supervision: MA. All the authors have read and approved the final version of the manuscript. All listed authors have made substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data; have drafted the work or revised it critically for important intellectual content; have approved the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability The datasets are available from the corresponding author on reasonable request.

Declarations

Ethical approval The study was approved by the local institutional review board and ethical committee (approval protocol number: 36/IRE/23–2866) and conducted in accordance to the Helsinki Declaration and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients had signed a specific informed consent for conditioning chemotherapy, for transplant and for data analysis for scientific purposes.

Competing interests The authors declare no competing interests.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. Auletta JJ, Kou J, Chen M, Shaw BE (2021) Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides. <https://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/pages/index.aspx>. Assessed Aug 31 2023
2. Snowden JA, Sánchez-Ortega I, Corbacioglu S et al (2022) Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022. *Bone Marrow Transplant* 57:1217–1239
3. Bhatt VR, Loberiza FR Jr, Jing H et al (2015) Mortality patterns among recipients of autologous hematopoietic stem cell transplantation for lymphoma and myeloma in the past three decades. *Clin Lymphoma Myeloma Leuk* 15:409–415.e1
4. Lalami Y, Klastersky J (2017) Impact of chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN) on cancer treatment outcomes: an overview about well-established and recently emerging clinical data. *Crit Rev Oncol Hematol* 120:163–179
5. Marchesi F, Mengarelli A (2016) Biosimilar filgrastim in autologous peripheral blood hematopoietic stem cell mobilization and post-transplant hematologic recovery. *Curr Med Chem* 23:2217–2229
6. Weise M, Bielsky MC, De Smet K et al (2012) Biosimilars: what clinicians should know. *Blood* 120:5111–5117
7. McCamish M, Woollett G (2012) The state of art in the development of biosimilars. *Clin Pharmacol Ther* 91:405–417
8. U.S. Food and Drug Administration (2017) Biosimilar and interchangeable products. <https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products>
9. Heredia E, Ribeiro A (2018) Discount offered by first and subsequent biosimilars in the US, EU and LATAM: impact trends of originator starting price, market dynamics and regulations. *Value Health* 21(Suppl. 1):S103–S104
10. Dutta B, Huys I, Vulto AG et al (2020) Identifying key benefits in European off-patent biologics and biosimilar markets: it is not only about price! *BioDrugs* 34:159–170
11. Martino M, Gori M, Porto G et al (2023) Effectiveness of biosimilar pegfilgrastim in patients with multiple myeloma after high-dose melphalan and autologous stem cell transplantation. *Ann Hematol* 102:1915–1925
12. Averbuch D, Orasch C, Cordonnier C et al (2013) ECIL4, a joint venture of EBMT, EORTC, ICHS, ESGICH/ESCMID and ELN. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European conference on infections in leukemia. *Haematologica* 98:1826–1835
13. Baden LR, Swaminathan S, Angarone M et al (2016) Prevention and treatment of cancer-related infections, version 2.2016, NCCN

- clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 14:882–913
14. Austin PC (2011) Comparing paired vs non-paired statistical methods of analyses when making inference about absolute risk reduction in propensity score matched samples. *Stat Med* 30:1292–1301
 15. Accordo interregionale per la compensazione della mobilità sanitaria (2020) Emocomponenti ad uso trasfusionale (1 unità), Italy, cod. 99758, 99766
 16. Italia Ministero dell'Economia e delle Finanze; Commissione Tecnica per la Finanza Pubblica. Libro Verde Sulla Spesa Pubblica. Spendere Meglio: Alcune Prime Indicazioni; Ministero dell'Economia e delle Finanze (2007) Roma, Italy, pp 36–57.
 17. Wannesson L, Luthi F, Zucca E et al (2011) Pegfilgrastim to accelerate neutrophil engraftment following peripheral blood stem cell transplant and reduce the duration of neutropenia, hospitalization, and use of intravenous antibiotics: a phase II study in multiple myeloma and lymphoma and comparison with filgrastim-treated matched controls. *Leuk Lymphoma* 52:436–443
 18. Marchesi F, Cerchiara E, Dessanti ML et al (2015) Comparison between biosimilar vs other granulocyte-colony stimulating factor formulations (originator filgrastim, peg-filgrastim and lenograstim) after autologous stem cell transplantation: a retrospective survey from the Rome Transplant Network. *Br J Haematol* 169:293–296
 19. Vanstraelen G, Frere P, Ngirabacu MC et al (2006) Pegfilgrastim compared with filgrastim after autologous hematopoietic peripheral blood stem cell transplantation. *Exp Hematol* 34:382–388
 20. Bellon A, Wang J, Skerjanec A et al (2020) A large multicenter, randomized, double-blind, cross-over study in healthy volunteers to compare pharmacokinetics, pharmacodynamics and safety of a pegfilgrastim biosimilar with its US- and EU-reference biologics. *Br J Clin Pharmacol* 86:1139–1149
 21. Wang X, Ren J, Liang X, He P (2021) Efficacy and cost of G-CSF derivatives for prophylaxis of febrile neutropenia in lymphoma and multiple myeloma patients underwent autologous hematopoietic stem cell transplantation. *Hematology* 26:950–955
 22. Allen RC (2002) Ex vivo half-life of neutrophils from healthy human subjects pre and post treatment with daily filgrastim or single-dose pegfilgrastim. *Blood* 100:A918
 23. Molineux G (2004) The design and development of pegfilgrastim (PEG-rmetHuG-CSF, Neulasta). *Curr Pharm Des* 10:1235–1244
 24. Yang BB, Kido A (2011) Pharmacokinetics and pharmacodynamics of pegfilgrastim. *Clin Pharmacokinet* 50:295–306
 25. Hassan MN, Fauzi HM, Husin A et al (2019) Autologous peripheral blood stem cell transplantation among lymphoproliferative disease patients: factors influencing engraftment. *Oman Med J* 34:34–43
 26. Cooper KL, Madan J, Whyte S et al (2011) Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis. *BMC Cancer* 11:404
 27. Pfeil AM, Allcott K, Pettengell R et al (2015) Efficacy, effectiveness and safety of long-acting granulocyte colony-stimulating factors for prophylaxis of chemotherapy-induced neutropenia in patients with cancer: a systematic review. *Sup Care Cancer* 23:525–545
 28. Castagna L, Bramanti S, Levis A et al (2010) Pegfilgrastim versus filgrastim after high-dose chemotherapy and autologous peripheral blood stem cell support. *Ann Oncol* 21:1482–1485
 29. Marchesi F, Tendas A, Giannarelli D et al (2017) Cryotherapy reduces oral mucositis and febrile episodes in myeloma patients treated with high-dose melphalan and autologous stem cell transplant: a prospective, randomized study. *Bone Marrow Transplant* 52:154–156
 30. Kvien TK, Patel K, Strand V (2022) The cost savings of biosimilars can help increase patient access and lift the financial burden of health care systems. *Semin Arthritis Rheum* 52:151939
 31. Singh SC, Bagnato KM (2015) The economic implications of biosimilars. *Am J Manag Care* 21(16 Suppl):s331–340
 32. Moorkens E, Broux H, Huys I et al (2020) Economic evaluation of biosimilars for reimbursement purposes - what, when, how? *J Mark Access Health Policy* 8:1739509
 33. Gascón P, Tesch H, Verpoort K et al (2013) Clinical experience with Zarzio® in Europe: what have we learned? *Support Care Cancer* 21:2925–2932
 34. Schwartzberg LS, Lal LS, Balu S et al (2018) Clinical outcomes of treatment with filgrastim versus a filgrastim biosimilar and febrile neutropenia-associated costs among patients with nonmyeloid cancer undergoing chemotherapy. *J Manag Care Spec Pharm* 24:976–984
 35. Cornes P, Gascon P, Vulto AG et al (2020) Biosimilar pegfilgrastim: improving access and optimising practice to supportive care that enables cure. *BioDrugs* 34:255–263
 36. Tilleul PR, Rodgers-Gray BS, Edwards JO (2021) Introduction of biosimilar pegfilgrastim in France: economic analysis of switching from originator. *J Oncol Pharm Pract* 27:1604–1615
 37. Hübel K, Kron F, Lux MP (2020) Biosimilars in oncology: effects on economy and therapeutic innovations. *Eur J Cancer* 139:10–19
 38. Cornes P, Kelton J, Liu R et al (2022) Real-world cost-effectiveness of primary prophylaxis with G-CSF biosimilars in patients at intermediate/high risk of febrile neutropenia. *Future Oncol*. <https://doi.org/10.2217/fon-2022-0095>
 39. Blackwell K, Gascon P, Jones CM et al (2017) Pooled analysis of two randomized, double blind trials comparing proposed biosimilar LA-EP2006 with reference pegfilgrastim in breast cancer. *Ann Oncol* 28:2272–2277

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.