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ORIGINAL RESEARCH

Budget Saving Potential of Pegfilgrastim Biosimilar for the Treatment of Chemotherapy-Induced Febrile Neutropenia, in Italy

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ABSTRACT

INTRODUCTION: Current Italian guidelines recommend prophylaxis with granulocyte colony-stimulating factors (G-CSFs) to reduce the risk of chemotherapy-induced febrile neutropenia (FN). The availability of G-CSF biosimilars represents an opportunity for savings in the Italian National Healthcare Service (NHS) delivery of care.
OBJECTIVE: To assess the cost saving potential associated with the introduction of pegfilgrastim biosimilars to local formularies, compared to the current G-CSF standard practice in Italy.
METHODS: A budget impact model was developed to compare the current standard practice of long-acting (LA) and short-acting (SA) G-CSFs use, with a future scenario in which the market share of LA G-CSFs grows due to the more advantageous administration schedule and price of pegfilgrastim biosimilar. The analysis included G-CSF treatment schedules, drug acquisition costs and costs of patient management including hospitalization and ambulatory care.
RESULTS: The introduction of pegfilgrastim biosimilar resulted in cumulative 3-year cost savings of € 59,650 and € 41,539 for FN prophylaxis in a potential cohort of 1000 patients with solid tumors and lymphomas, respectively.
CONCLUSIONS: The results indicate that the introduction of pegfilgrastim biosimilar is potentially associated with substantial cost savings for the Italian healthcare system.

Keywords

Biosimilars; Budget Impact Analysis; Cost saving; Febrile neutropenia; Granulocyte colony stimulating factor (G-CSF)

INTRODUCTION

Febrile neutropenia (FN) is a potentially fatal hematologic toxicity of myelosuppressive cancer chemotherapy that may lead to severe infections, sepsis, and death [1]. FN is defined as an oral temperature >38.3 °C or 2 consecutive readings of >38.0 °C for 2 h and an absolute neutrophil count (ANC) of <0.5 x 10^9/L [2]. The incidence of FN has been estimated to be as high as 117 cases per 1000 cancer patients [1]. FN causes a significant burden to the healthcare system, often requiring dose reductions, imposing treatment delays, and/or treatment interruptions, which can consequently reduce the efficacy of chemotherapy, resulting in worse survival outcomes and with mortality rates up to 21% [2-4].

One of the primary treatment strategies to reduce the risk of FN is the prophylactic use of granulocyte colony stimulating factor (G-CSF). G-CSF is a biological growth factor that supports the proliferation, differentiation, and activation of hematopoietic cells [5,6]. Current national and international guidelines support the use of G-CSFs as primary prophylaxis alongside chemotherapy administration, when the risk of FN is >20% [2,7,8].

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Treatment with G-CSFs is associated with reduced risk of FN, shorter FN-related hospitalization, and lower mortality rate due to infection [9,10]. In addition, patients treated with G-CSFs are associated with increased probability of receiving full doses of chemotherapy [9] as well as use of highly myelosuppressive dose-dense regimens at shorter intervals than would be possible without G-CSF support [9,11].

Two types of G-CSF are available: short-acting (SA) (e.g. lenograstim and filgrastim) and long-acting (LA) (e.g. pegfilgrastim and lipegfilgrastim). SA G-CSFs are administered as a daily subcutaneous injection (for a recommended ≥10 days per cycle), while LA G-CSFs are given as a subcutaneous injection once per chemotherapy cycle [12].

Although, there are no differences in efficacy between LA G-CSF and SA G-CSF, when correctly used [7,13], LA G-CSFs are less burdensome to administer (once per cycle with long-acting vs. up to 11 injections with short-acting G-CSFs) with better compliance, and decreased burden for healthcare professionals and patients in solid tumors or non-Hodgkin's lymphomas (NHL) [14]. In clinical practice the use of LA G-CSF improved adherence to G-CSF guidelines [15] and consequently maximized the preventive effect in terms of reduction of chemotoxic events, delays and interruptions of chemotherapy treatment. Additionally, Rosti et al., reported that the long-lasting G-CSF pegfilgrastim, represents an optimal prophylaxis strategy for FN providing, in addition to the clinical benefit for the patient, important savings to the Italian National Health Service (NHS) [16].

A reason for the low rate of G-CSF prophylaxis use, is the historically high acquisition cost of G-CSFs, causing health systems to be mindful about the potential impact on overall drug-related costs [17]. However, with the introduction of biosimilar G-CSFs, significant cost savings with the same quality of care may be achieved. In Italy, pegfilgrastim biosimilars, available since 2019, offer clinical and economic benefits in FN management [18-21].

We report the results of a budget impact model (BIM) that was developed to understand the economic impact for the Italian NHS of introducing pegylated LA G-CSFs in local formularies.

MATERIALS AND METHODS

Model overview

A budget impact model was developed in Microsoft Excel™ to estimate the cost impact of G-CSFs from the perspective of the Italian healthcare system. The model was developed in accordance with the Principles of Good Practice for Budget Impact Analysis from the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) [22]. To identify suitable references for the model, a targeted review of the relevant literature was undertaken through the PubMed/Medline database, supplemented by additional, local language and grey literature studies identified by the authors. A "current (reference) scenario" was compared with a "future

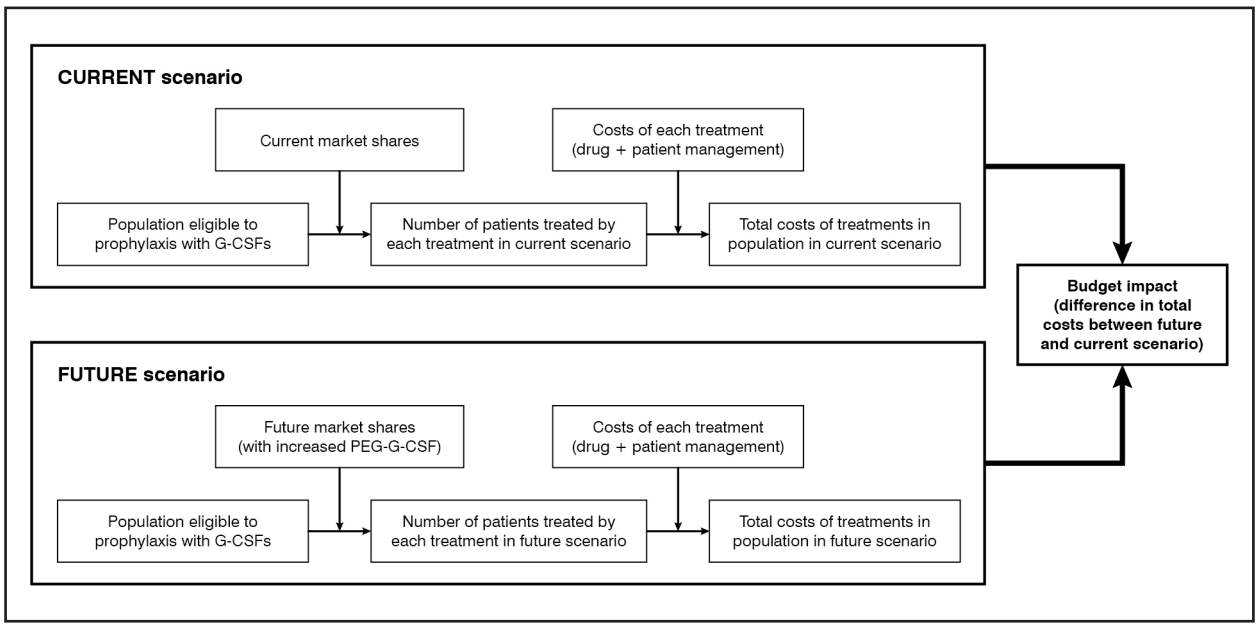

Figure 1. *Flow of the model*

(hypothetical) scenario", in which the shares of patients (number of chemotherapy cycles) were redistributed favouring LA G-CSFs, due to the driving effect of increasing use of pegfilgrastim biosimilar. The model calculated for each year of simulation the resources consumed by a cohort of target patients treated with G-CSFs for FN prophylaxis. The costs of drug acquisition, hospitalization and outpatient management for FN were calculated for each type of G-CSF: SA and LA, to provide a per-patient cost. The per-patient costs, specific for each G-CSF, were multiplied by the number of annual patients in both the current and future scenarios over a 3-year timeframe. The difference between the two scenarios provided the budget impact (Figure 1).

Target population

The analysis evaluated the resource consumption of a cohort of patients for whom G-CSF prophylaxis was indicated, more specifically: patients with high (≥20%) FN risk and patients with intermediate (10-20%) risk of FN, with unfavourable multifactorial assessment, as recommended by AIOM Guidelines [7].

The analysis was carried out on a hypothetical cohort of 1000 patients' population affected by either haematological tumors, in particular lymphomas (Hodgkin's lymphoma, HL; non-Hodgkin's lymphoma, NHL), or solid tumors. The model also returned the overall budget impact for a mixed population, with both haematological and solid tumors: the result was weighted by type of neoplasm either with a 50/50% ratio or, with a 33/67% ratio (lymphomas: 33%; solid tumors: 67%) as reported by Almenar-Cubells et al. [23], assuming this distribution may apply to the current Italian context.

	Solid tumors		Lymphomas	
	SA G-CSF	LA G-CSF	SA G-CSF	LA G-CSF
Number of CT cycle per-patient	4.72	4.72	6.06	6.06
Days of cycle per-patient	5.09	1	5.65	1

Table I. *Duration of treatment with G-CSFs*
CT = computer tomography; G-CSF = granulocyte colony stimulating factor; LA = long-acting; SA = short-acting

Region	DPC (€)	Price per dose unit (€)		
		SA G-CSF	LA G-CSF	
		Filgrastim	Pegfilgrastim	Lipegfilgrastim
Abruzzo	7.44	4.06	73.27	566.06
Basilicata	4.00	5.40	75.00	566.06
Calabria	4.60	3.94	73.00	566.06
Campania	6.00	5.23	67.85	566.06
Emilia Romagna	3.20	4.08	100.00	566.06
Friuli Venezia Giulia	6.50	3.91	71.19	566.06
Lazio	1.50	3.94	71.80	566.06
Liguria	3.90	4.18	125.00	566.06
Lombardia	7.00	4.05	75.09	566.06
Marche	3.50	5.98	91.45	566.06
Molise	5.00	6.99	73.00	566.06
Piemonte	5.00	4.44	73.00	566.06
PA Trento	6.30	4.18	125.00	566.06
PA Bolzano	5.10	4.18	125.00	566.06
Puglia	5.10	4.50	72.60	566.06
Sardegna	5.90	4.18	91.45	566.06
Sicilia	4.30	4.29	78.00	566.06
Toscana	4.68	5.70	78.00	566.06
Umbria	4.50	4.71	NA	566.06
Valle d'Aosta	7.00	4.44	73.00	566.06
Veneto	5.20	5.81	75.00	566.06
ITALY	4.93 [1]	4.59 [2]	75.80 [2]	566.06

Table II. *Drug Regional price and DPC price*
[1] Average value weighted by the size of the regional population
[2] Weighted average value for the expected regional annual consumption
DPC = distribution on behalf of the Local Health Authority; G-CSF = granulocyte colony stimulating factor; LA = long-acting; NA = information not available; PA = autonomous province; SA = short-acting

Drug acquisition costs

The cost of therapy for SA and LA G-CSFs was calculated from the unit price and the number of doses required to complete each therapeutic cycle. The recommended dose of LA G-CSF is one vial per chemotherapy course [24] and, the daily dose of filgrastim which depends on patient's weight is one or two vials for patients with body weight <60 Kg and ≥60 Kg, respectively [25-27]. The duration of treatment with G-CSFs per chemotherapy cycle was taken from the literature (Supplementary Tables I-IV) and the mean value is reported in Table I.

The price per unit dose of each G-CSFs corresponds to the tender price negotiated between the winning manufacturer and the regional purchasing centre, as outlined in Table II. An average price was calculated for the Italian scenario, based on regional population weights. The so-called distribution on behalf of the Local Health Authority (DPC) (i.e. an additional cost, paid by the NHS for distribution via retail pharmacy stores) is determined by regional authorities and applied to every drug unit supplied; the Model is based on the assumption that all doses are supplied through retail pharmacies (DPC = 100%). At the national level, DPC cost was calculated as the average of the tariffs for each region, weighed by regional populations (Table II).

Trento and Bolzano took part in the same tender as Liguria for pegfilgrastim and filgrastim. Valle d'Aosta and Molise took part in the same tender as Piemonte for pegfilgrastim. Valle d'Aosta took part in the same tender as Piemonte for filgrastim. The tender prices for lipegfilgrastim are the same for all regions. Umbria: lack of sufficient information, only the price of filgrastim and lipegfilgrastim for this region is considered. Emilia Romagna, price for pegfilgrastim set out of tender: 100 €.

Clinical inputs

Consumption of resources for management of FN, included grade 3-4 severity events (based on the Common Terminology Criteria for Adverse Events version 5—CTCAE). FN incidence rate and FN hospitalization rates specific for SA and LA G-CSF were taken from the literature (Table III). The difference between incidence of FN and incidence of hospitalization for FN was used as a proxy for FN events managed in the outpatient setting.

Cost per event was valued assuming the perspective of the third payer, and considering the tariffs by Diagnosis Related Group (DRG) for FN management in the hospital setting (€ 2,387.75), cost per outpatient visit (€ 20.66) and for toxicity management (€ 1,312.44) [33,34]. As to the occurrence of FN in the outpatient setting, a course of therapy with filgrastim with a standard duration of 11 days (average cost of treatment, € 197.48, and cost per outpatient visit, € 20.66), is considered [1].

Clinical Input (%)	SA G-CSF	LA G-CSF		Reference
	Filgrastim	Pegfilgrastim	Lipegfilgrastim	
Solid tumors				
FN incidence	13.30	6.70	3.66[1]	Filgrastim and pegfilgrastim:[28] Lipegfilgrastim:[29]
FN hospitalization incidence	10.90	2.80	1.53	[28]
FN outpatient incidence	2.40	3.90	2.13	Difference between incidence of FN and incidence of hospitalizations for FN
Toxicity	5.40	1.30	1.30	[23]
Lymphomas				
FN incidence	17.30	15.65	15.65[1]	Filgrastim and pegfilgrastim: mean value [30] and [31] Lipegfilgrastim:[32]
FN hospitalization incidence	10.71	15.65	15.65	Filgrastim and pegfilgrastim: mean value [31] and assumption[2] Pegfilgrastim and lipegfilgrastim: [32]
FN outpatient incidence	6.59	0.00	0.00	Difference between incidence and incidence of hospitalizations for FN
Toxicity	5.40	1.30	1.30	[23]

Table III. *Clinical inputs for solid tumors and lymphomas*

[1] Based on relative risk (RR)

[2] In the absence of the hospitalization data in Chan 2011, the same ratio is maintained between hospitalization for FN and the FN rate observed in Bozzoli 2015

FN = febrile neutropenia; G-CSF = granulocyte colony stimulating factor; LA = long-acting; SA = short-acting

Analysis

The budget impact was assessed by comparing the "current (reference) scenario", in which the market share of G-CSFs follows what has been observed in recent years, with a "future (hypothetical) scenario", in which the market share of LA G-CSF grows due to the more advantageous treatment schedule and price of biosimilars. The distribution of G-CSFs market shares in year 1 was com-

G-CSF	Market share (%)	
	Solid tumors	Lymphomas
SA (filgrastim)	67.67	65.32
LA	32.33	34.68
• Pegfilgrastim	83.00	83.00
• Lipegfilgrastim	17.00	17.00

Table IV. *Market share of G-CSFs*
G-CSF = granulocyte colony stimulating factor; LA = long-acting; SA = short-acting

Year	Annual increase of pegfilgrastim market share (%)	Market share (%)		
		SA G-CSF	LA G-CSF	
		Filgrastim	Pegfilgrastim	Lipegfilgrastim
Solid tumors				
I		67.67	26.84	5.50
II	2	65.82	28.84	5.35
III	2	63.97	30.84	5.20
Lymphomas				
I		65.32	28.79	5.90
II	2	63.48	30.79	5.73
III	2	61.65	32.79	5.56

Table V. *Annual distribution for current scenario*
G-CSF = granulocyte colony stimulating factor; LA = long-acting; SA = short-acting

Year	Annual increase of pegfilgrastim market share (%)	Market share (%)		
		SA G-CSF	LA G-CSF	
		Filgrastim	Pegfilgrastim	Lipegfilgrastim
Solid tumors				
I	2	65.82	28.84	5.35
II	4	62.12	32.84	5.05
III	6	56.57	38.84	4.60
Lymphomas				
I	2	63.48	30.79	5.73
II	4	59.82	34.79	5.40
III	6	54.31	40.79	4.90

Table VI. *Annual distribution for future scenario*
G-CSF = granulocyte colony stimulating factor; LA = long-acting; SA = short-acting

Year	Patients (n)		
	SA G-CSF	LA G-CSF	
	Filgrastim	Pegfilgrastim	Lipegfilgrastim
Solid tumors			
I	677	268	55
II	658	288	53
III	640	308	52
Lymphomas			
I	653	288	59
II	635	308	57
III	617	328	56

Table VII. *Patients by treatment in the current scenario*
G-CSF = granulocyte colony stimulating factor; LA = long-acting; SA = short-acting

Year	Patients (n)		
	SA G-CSF	LA G-CSF	
	Filgrastim	Pegfilgrastim	Lipegfilgrastim
Solid tumors			
I	658	288	53
II	621	328	50
III	566	388	46
Lymphomas			
I	635	308	57
II	598	348	54
III	543	408	49

Table VIII. *Patients by treatment in the future scenario*
G-CSF = granulocyte colony stimulating factor; LA = long-acting; SA = short-acting

puted by dividing the consumption of G-CSFs [35] by the product of G-CSF daily dose (from the respective SmPCs) and the average duration of chemotherapy cycle (Table IV).

For the following years, a steady growth of pegfilgrastim market share was assumed due to the driving effect of biosimilar drugs, to the disadvantage of SA and lipegfilgrastim (Table V).

For the future scenario, higher growth was assumed for pegfilgrastim market share, against lipegfilgrastim and filgrastim (Table VI).

Table VII and VIII report the distribution of patients by treatment in the current and future scenario, calculated on market assumptions, assuming a target population of 1000 patients per cancer type.

RESULTS

The results of the budget impact were calculated as the difference between current and future scenario costs. The introduction of pegfilgrastim biosimilars in the treatment of FN results in substantial cost savings, with different biosimilar penetration over 3 years.

The budget impact analysis estimated that by introducing LA G-CSFs in particular pegfilgrastim biosimilars, in place of SA G-CSF treatments, € 59,650 could be saved over 3 years (€ 8,521 in year 1, € 17,043 in year 2, € 34,086 in year 3) for every 1000 patients affected by solid tumors and treated with G-CSFs (Table IX).

The reduction of consumption of SA in favour of LA G-CSFs would result in total cost savings of € 5,934 in year 1, € 11,868 in year 2, € 23,737 in year 3, leading to a cumula-

Year	SA G-CSF	LA G-CSF		Budget impact – future vs. current scenario (€)
	Filgrastim (€)	Pegfilgrastim (€)	Lipegfilgrastim (€)	
I	-14,160	10,179	-4,540	-8,521
II	-28,320	20,358	-9,081	-17,043
III	-56,640	40,716	-18,162	-34,086
Cumulative	-99,120	71,253	-31,783	-59,650

Table IX. *Budget Impact – Solid tumors*
G-CSF = granulocyte colony stimulating factor; LA = long-acting; SA = short-acting

Year	SA G-CSF	LA G-CSF		Budget impact – future vs. current scenario (€)
	Filgrastim (€)	Pegfilgrastim (€)	Lipegfilgrastim (€)	
I	-17,499	18,511	-6,945	-5,934
II	-34,999	37,021	-13,891	-11,868
III	-69,998	74,043	-27,782	-23,737
Cumulative	-122,496	129,575	-48,618	-41,539

Table X. *Budget Impact – Lymphomas*
G-CSF = granulocyte colony stimulating factor; LA = long-acting; SA = short-acting

tive 3-year cost savings of € 41,539 for every 1000 patients affected by lymphomas and treated with G-CSFs (Table X).

Figure 2 and Figure 3 show the annual budget impact compared with the expenditure for pegfilgrastim in patients affected by solid tumors and lymphomas, respectively. Indeed, this budget impact model shows that increasing the NHS' expenditure for pegfilgrastim biosimilars over 3-years, would increase savings for the Italian NHS.

Table XI shows the results of the budget impact analysis on a patient population affected by both solid and haematological tumors: the expected savings are approximately € 50,000 for every 1000 patients treated, considering a population distribution from the literature [23].

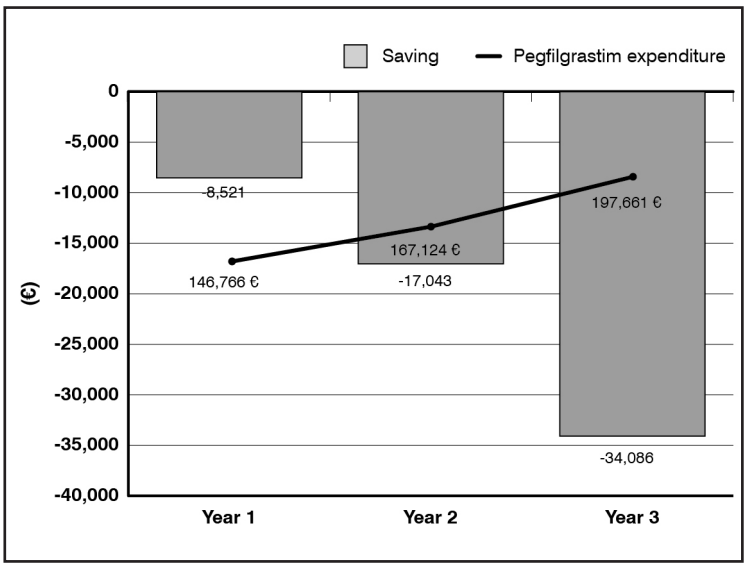

Figure 2. *Budget Impact over 3 years – Solid tumor*

DISCUSSION

The recent patent expiration of several biological drugs led to the commercialisation of biosimilar products, nowadays representing an important segment of the global pharmaceutical market. Biosimilar penetration has been observed across the five major European Union (EU) markets and Italy has registered a high and increasing biosimilars up-take, albeit not uniform across the Italian regions [36,37].

The recent licensing in Europe of biosimilar pegfilgrastim-containing products offers the opportunity to deliver the additional advantages of long-over short-acting G-CSF at a reduced cost. For countries currently using reference pegfilgrastim, evident cost savings are reported by switching to biosimilar pegfilgrastim [18,20,21].

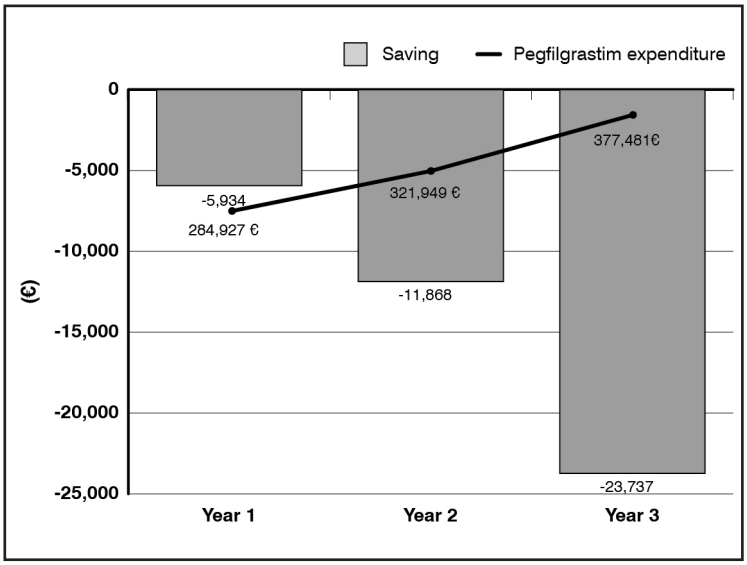

Figure 3. *Budget Impact over 3 years – Lymphomas*

In the past 10 years, the introduction of SA G-CSF biosimilars favoured their adoption due to their cost-efficiency in reducing the incidence of FN in chemotherapy-treated patients than SA G-CSF originator and LA G-CSFs [38,39]; hence, a similar pattern is expected for the LA G-CSFs category.

These results are consistent with our findings which showed that the introduction of pegfilgrastim biosimilars in place of SA G-CSF treatments, have a substantial cost-saving potential for the Italian NHS. The budget impact was sensitive to pegfilgrastim biosimilar market uptake rate and greater savings are observed whenever the expenditure for pegfilgrastim biosimilar is higher.

The analysis highlighted the economic advantage of using pegfilgrastim biosimilars in place of SA G-CSF treatments in the FN treatment setting, providing a substantial cumulative

Year	SA G-CSF	LA G-CSF		Budget impact – future vs. current scenario (€)
	Filgrastim (€)	Pegfilgrastim (€)	Lipegfilgrastim (€)	
I	-15,262	12,928	-5,334	-7,668
II	-30,524	25,857	-10,668	-15,335
III	-61,048	51,714	-21,336	-30,671
Cumulative	-106,834	90,499	-37,339	-53,674

Table XI. *Budget Impact – All tumors*
G-CSF = granulocyte colony stimulating factor; LA = long-acting; SA = short-acting

cost saving of € 59,650 and € 41,539 respectively for a 1000 patients' population with solid tumors and lymphomas over a 3-years' timeframe.

A confirmation of our analysis comes from the results of a budget impact model built by Ravasio et al. [21] in order to assess the economic impact generated in Italy from the use of the pegfilgrastim biosimilar compared to the originator. These authors showed that the availability of the biosimilar could (in five years) generate cumulated savings as high as € 6.4 million for the whole Italian NHS [21]. However, this analysis did not calculate the potential savings of the introduction of pegfilgrastim biosimilar to the local formulary, compared to SA and LA G-CSFs currently used for FN prophylaxis. Additionally, the budget impact built by Ravasio et al. did not consider the effect that any regional or local tenders could exercise on the price of biosimilar and originator pegfilgrastim and costs of patient management including hospitalization and ambulatory care.

Our findings are in line with the cost savings observed across EU markets and the US switching from the reference product to pegfilgrastim biosimilar [18-20]. Tilleul et al. revealed that extending pegfilgrastim biosimilar to patients on both LA G-CSF and SA G-CSF could provide substantial mean cost savings to the French healthcare system over 5 years [20].

A meta-analysis found that in randomized clinical trials (RCTs), there was no statistically significant difference in the incidence of FN and FN-related complications between short and long-acting G-CSFs, whereas in non-RCTs, the overall risk of FN was lower within long-acting G-CSF than with short-acting G-CSF [12]. Mitchell et al. conducted a review of comparative effectiveness of long vs. short-acting G-CSFs in real-world clinical settings and also found that risks of FN and FN-related complications were generally lower for prophylaxis with pegfilgrastim versus prophylaxis with short acting G-CSFs, which might be attributed to under-dosing of short-acting G-CSFs per chemo-cycle in routine clinical practice [13].

The opportunity to switch more patients to LA G-CSF may have the potential to improve patient outcomes [37,40,41]. No requirement for daily self-administration, hospital visits, or regular tests to evaluate absolute neutrophil count levels, may also provide improved compliance with LA over SA G-CSF [42,43], thus reducing indirect costs, such as patients' and caregivers' time and costs, as well as productivity losses or reductions. Worth mentioning is that the current clinical practice for SA G-CSFs does not observe the recommended posology of at least 11 days of administration per cycle, essential to achieve comparable efficacy to LA G-CSFs [1], but rather falls within the 4 to 6 range [44-46]. The main determinant in favour of a switch to LA G-CSFs, when feasible, is, thus, their facilitated administration management—especially in the instance of FN or adverse events occurrence—as therapeutic continuity can be assured, nevertheless. Furthermore, the introduction of auto-injection devices, which allows to automatically insert the needle and deliver a controlled dose of drug, has demonstrated that it may increase treatment adherence and, consequently, reduce costs by decreasing the frequency of hospital visits [47].

Overall, the auto-injection improves the injection experience by mitigating fear and anxiety, overcomes the challenges resulting from hand dexterity problems, and empowers patients to take control of their treatment journey [48].

In a recent publication, the HCPs identified multiple major HCP benefits in administering subcutaneous injections via auto-injector including ease of use, fewer needle-stick injuries, more consistent dosing, and faster administration. HCPs also thought that use of an autoinjector would provide major benefits to patients facilitating therapeutic adherence [48].

Additionally, the introduction of auto-injectors as an alternative route of administration for pegfilgrastim biosimilar could improve the quality of life of oncology patients, increasing patient self-efficacy, feelings of independence, adherence to medications and, ultimately, saving healthcare and social costs [49-51].

Therefore, the potential cost savings due to the introduction and increased use of pegfilgrastim biosimilars could improve potential advantages of LA G-CSFs treatment, increasing rate of G-CSF prophylaxis and leading to clinical improvements in key areas such as FN hospitalization, chemotherapy delivery and response rates.

Although the results of this budget impact model further highlight the relevance of biosimilar uptake in clinical practice to reduce total costs, some limitations of this study are associated with the economic model itself. This model represents a simplification of the complex utilization patterns of G-CSF prophylaxis within a hypothetical oncology practice population plan. In fact, the generalizability of the model results is limited to clinical input assumptions and distribution of patients based on published literature data.

In conclusion, our study demonstrates that the introduction and increased use of pegfilgrastim biosimilars has the potential to reduce healthcare costs in Italy for prophylaxis of FN

among patients with cancer who are undergoing myelosuppressive chemotherapy. Pegfilgrastim biosimilars offer a fresh opportunity to rethink neutropenia management and value of G-CSF, based on the significant potential for both clinical and economic benefits, thus providing to payers, physicians and patients a life-saving strategy.

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Conflicts of interest

PB and MDS are consultants of Regulatory Pharma Net srl.
MB and AS are employees of AdRes.
DG reports Honoraria from Novartis, Roche and Lilly, Research Funding from Novartis, LILT and AstraZeneca, outside of the submitted work.
CP reports personal fees for advisory role, speaker engagements and travel and accommodation expenses from Amgen, Astellas, AstraZeneca, Bayer, Bristol Meyer Squibb, Celgene, Clovis Oncology, Eisai, Ipsen, Janssen, Incyte, Merck-Serono, Merck Sharp and Dohme, Novartis, Roche, Sandoz, Sanofi, and Servier, outside the submitted work.
MM declares Honoraria from Novartis, Kite/Gilead, BMS, MSD, JAZZ, Jansenn, Tillomed, outside of the submitted work.
PLC acts as Medical Consultant for Accord Healthcare Italy

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