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 health-care 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].

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)
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 lipogfilgrastim). 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, Rosi 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 scenario”

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**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.

### Table I. Duration of treatment with G-CSFs

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

Table I. Duration of treatment with G-CSFs

CT = computer tomography; G-CSF = granulocyte colony stimulating factor; LA = long-acting; SA = short-acting

### Table II. Drug Regional price and DPC price

| Region    | DPC (€) | 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    | 4.59       | 75.80         | 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, weighted 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 Filgrastim | LA G-CSF Pegfilgrastim | Lipegfilgrastim | Reference |
|-------------------|---------------------|------------------------|-----------------|-----------|
| **Solid tumors**  |                     |                        |                 |           |
| FN incidence      | 13.30               | 6.70                   | 3.66¹           | 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                  | 15.65¹          | 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 assumption² 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-

| Year | Annual increase of pegfilgrastim market share (%) | Market share (%) | G-CSF | Market share (%) |
|------|-----------------------------------------------|------------------|-------|------------------|
|      |                                               |                  | Solid tumors | Lymphomas        |
|      |                                               |                  | SA (filgrastim) | LA G-CSF |
| Solid tumors |                                          |                  | 67.67 | 65.32 |
| I     | 2                                             |                  | 32.33 | 34.68 |
| II    | 2                                             |                  | 17.00 | 17.00 |
| III   | 2                                             |                  | 5.50  | 5.50  |

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 (%) | G-CSF | Market share (%) |
|------|-----------------------------------------------|------------------|-------|------------------|
|      |                                               |                  | Solid tumors | Lymphomas        |
|      |                                               |                  | Filgrastim | Pegfilgrastim | Lipegfilgrastim |
| Solid tumors |                                          |                  | 67.67 | 26.84 | 5.50  |
| I     | 2                                             |                  | 65.82 | 28.64 | 5.35  |
| II    | 4                                             |                  | 63.97 | 30.84 | 5.20  |
| III   | 6                                             |                  | 63.32 | 28.79 | 5.90  |

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 (%) | G-CSF | Market share (%) |
|------|-----------------------------------------------|------------------|-------|------------------|
|      |                                               |                  | Solid tumors | Lymphomas        |
|      |                                               |                  | Filgrastim | Pegfilgrastim | Lipegfilgrastim |
| Solid tumors |                                          |                  | 65.82 | 28.64 | 5.35  |
| I     | 2                                             |                  | 62.12 | 32.84 | 5.05  |
| II    | 4                                             |                  | 56.57 | 38.84 | 4.60  |
| III   | 6                                             |                  | 63.48 | 30.79 | 5.73  |

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

| Year | Patients (n) | G-CSF | Market share (%) |
|------|--------------|-------|------------------|
|      |              | Filgrastim | Pegfilgrastim | Lipegfilgrastim |
| Solid tumors |              | 677   | 268 | 56  |
| I     |              | 668   | 288 | 52  |
| II    |              | 640   | 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
Budget Saving Potential of Pegfilgrastim Biosimilar for the Treatment of Chemotherapy-Induced Febrile Neutropenia, in Italy

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 cumulative total of €41,539.

Table IX. Budget Impact – Lymphomas
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 – 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    | -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 VIII. Patients by treatment in the future scenario
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].

**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].

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 Filgrastim (€) | LA G-CSF Pegfilgrastim (€) | LA G-CSF Lipegfilgrastim (€) | Budget impact – future vs. current scenario (€) |
|------|------------------------|---------------------------|-----------------------------|-----------------------------------------------|
| 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
Budget Saving Potential of Pegfilgrastim Biosimilar for the Treatment of Chemotherapy-Induced Febrile Neutropenia, in Italy

The introduction and increased use of pegfilgrastim biosimilars could improve potential advantages of LA G-CSFs treatment, increasing patient self-efficacy, feelings of independence, adherence to medications and, ultimately, saving healthcare and social costs [49-51].

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.
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PLC acts as Medical Consultant for Accord Healthcare Italy

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