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A Systematic Review to Compare Costs and Outcomes of Pharmacoeconomic Evaluations of Conventional and Biosimilars G-CSFs

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***Abstract*— Introduction:** The presence of biosimilars in the field of oncology is regarded as a key approach to attain sustainable healthcare. Granulocyte colony-stimulating factor (G-CSF) is a drug mostly prescribed after chemotherapy to avoid neutropenia. There are several G-CSF biosimilars approved to help reduce the significant economic burden on healthcare stakeholders through cost saving and to increase patient access. To date, no systematic assessment of the pharmacoeconomic evaluation of G-CSF biosimilars has been performed. The aim of this study is to synthesize evidence from economic evaluations (EEs) of G-CSF biosimilars published articles to provide essential data for involved stakeholders and policy makers. **Materials and methods:** PRISMA-guided systematic searches of PubMed, Scopus and EMBASE databases were conducted. Search was done up to April 2023 using predefined keywords. Articles were screened for relevant publications about EEs of G-CSF biosimilars that were used as prophylactic and or as a treatment for chemotherapy-induced neutropenia (CIN). We included articles for cost-effectiveness analysis (CEA) and budget impact analysis (BIA) Exclusion criteria were case reports, abstracts, letters to the editor, conference presentations, editorials, and studies written in languages other than English and articles of other types of pharmacoeconomic analysis. Risk of bias assessments were undertaken to assess data strength and validity. **Results:** We identified a total of six EEs studies (one cost-effectiveness analysis, two studies reporting both cost-effectiveness and cost-utility analysis and three budget impact analyses. Three studies were from the US, two from France and one from Singapore. The six studies met > 80% of the JBI quality assessment criteria. The primary prophylaxis with filgrastim biosimilar in breast cancer, non-small cell lung cancer, and non-Hodgkin lymphoma provided an additional 0.102-0.118 FN event avoided, 0.065-0.144 Lys, 0.057-0.13 QALYs at an incremental cost of 651 US$-2463 US$. The incremental cost effectiveness ratio (ICER) ranged from 5660 US$-20806 US$ per FN event avoided, 5123 US$ - 31077 US$ per LY gained, and 7213 US$ - 35563 US$ per QALY gained. The NSCLC has the lowest ICERs. **Conclusions:** studies showed that G-CSF biosimilars are cost effective compared to the references as primary and secondary prophylaxis for chemotherapy induced FN among oncology patients.

Keywords: Systematic Review, Pharmacoeconomic Evaluations, Biosimilars, G-CSFs, Cost-Effectiveness Analysis (CEA), Budget Impact Analysis (BIA)

1. Introduction

As originator biologics' patents and exclusivity rights have expired worldwide, biosimilars have experienced significant growth over the past decade. Biosimilars are considered a great solution to combat the substantially increasing cost of cancer treatment and expand sustainable affordability to patients [1]. Chemotherapy-induced neutropenia (CIN) is a potentially fatal and common complication in myelosuppressive chemotherapy. The timing and grade of CIN may play prognostic and predictive roles in cancer therapy [2]. According to the National Comprehensive Care Network (NCCN) clinical practice guidelines, chemotherapy regimens with high febrile neutropenia (FN) risk ≥20% are recommended to receive primary prophylaxis using a granulocyte colony-stimulating factor (G-CSF). If a chemotherapy regimen FN risk is intermediate, additional risk factors including prior chemotherapy or radiation therapy, persistent neutropenia, bone marrow involvement, recent surgical procedure, liver or renal dysfunction and older age ≥65 years are considered to determine the need for G-CSF use [3].

Neupogen® (Filgrastim) is the first biopharmaceutical human recombinant G-CSF products to be commercialized and the reference drug upon which all biosimilar G-CSF have

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Table 1: Filgrastim and pegfilgrastim biosimilars approved by FDA/EMA

Name	Regulatory designation	Company name	Approval
Reference product: Neulasta (pegfilgrastim)			
Stimufend (pegfilgrastim-fpgk)	Biosimilar	Fresenius Kabi USA, LLC	September 1, 2022
Fylnetra (pegfilgrastim-pbbk)	Biosimilar	Amneal Pharmaceuticals, Inc.	May 26, 2022
Nyvepria (pegfilgrastim-apgf)	Biosimilar	Pfizer Inc.	June 10, 2020
Ziextenzo (pegfilgrastim-bmez)	Biosimilar	Sandoz Inc.	November 4, 2019
Udenyca (pegfilgrastim-cbqv)	Biosimilar	Coherus BioSciences, Inc.	November 2, 2018
Fulphila (pegfilgrastim-jmdb)	Biosimilar	Mylan N.V.	June 4, 2018
Pelgraz (Apo-Peg)	Biosimilar	Intas Biopharmaceuticals	September 2018
Reference product: Neupogen (filgrastim)			
Releuko (filgrastim-ayow)	Biosimilar	Kashiv BioSciences, LLC	February 25, 2022
Nivestym (filgrastim-aafi)	Biosimilar	Pfizer Inc.	July 20, 2018
Zarxio (filgrastim-sndz)	Biosimilar	Sandoz Inc.	March 6, 2015

to be compared [4]. Several biosimilar G-CSF have been approved by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA), as presented in Table 1. They have comparable safety, efficacy and quality to the comparable [5-7].

Different pharmacoeconomic evaluations were conducted to assess the economic impact of using biosimilar G-CSF for CIN and concluded that it is cost-effective and may provide opportunities to optimize FN management in cancer patients with less cost that led to sustainable patient access [8-10]. To date, no systematic assessment of the pharmacoeconomic evaluation of G-CSF biosimilars has been performed. This study aimed to conduct a systematic review of published EEs of G-CSF biosimilars and to evaluate them using related tools. We further aimed to analyze and compare the evaluation results, which may provide relevant guidance to stakeholders in other countries of comparable economic status.

2. Materials & methods

Data sources and search strategy: We conducted a computerized search using the electronic databases of PubMed, Scopus and Embase up to April 2023 using the following keywords: "Neutropenia" AND "neoplasm" or "neoplasms" or "cancer" or "cancers" or "carcinoma" or "carcinomas" AND "filgrastim biosimilars" AND "cost-effectiveness analysis" OR "budget impact analysis". Articles were screened based on the inclusion and exclusion criteria. Only articles published in the English language were evaluated.

Selection of studies: An independent extraction of the data from eligible studies was performed by 2 reviewers. Any discrepancies in extracted data were resolved by mutual consensus. Data that was extracted from the eligible studies included setting, first author name, publication year, biosimilar(s) used, comparator name, type of the economic evaluation, outcomes measured, perspective and time horizon. These data were further collected and arranged into a table. Final data was then reported in the text of the review article.

Eligibility criteria: Studies were eligible and included if they were original economic evaluations (EEs) limited to cost-effectiveness analysis (CEA) or budget impact analysis (BIA), cost-utility analysis of G-CSF biosimilars that was used as prophylactic and or as a treatment for CIN from payer perspective in the English language. We excluded 1) other types of pharmacoeconomic analysis such as cost-saving and cost-efficiency studies, 2) editorials, letters to the editor, review articles, non-payer perspectives and indications other than CIN. Full text of eligible studies was obtained and reviewed independently. Any disagreements were resolved with the third reviewer (K.S).

Data extraction and quality assessment: DH and NI independently extracted information on the research question, methods, and other general study characteristics using standard data extraction forms. The reviewers compared and validated data extraction tables for accuracy and completeness. The data extraction was guided by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [11]. Extracted study characteristics included author name, publication year, country, target population, type of prophylaxis, type of economic evaluations, study perspective, analytical approach (model type), time horizon, comparator, discount rate, year of valuation, study outcome measures (incremental cost-effectiveness ratio (ICER), FN averted, life years gained, mortality rates, medication cost, drug effectiveness), influential parameters, type of sensitivity analysis and funding score. We assessed the methodological quality of each reviewed study using the Joanna Briggs Institute (JBI) checklist for economic evaluations [12]. Studies were considered as high quality if they met > 80% of the applicable JBI checklist criteria. Table 2 represents the details of JBI checklist criteria for the included studies. Table 3 summarizes the results of CHEERS scoring per reporting domain.

The included studies were appraised in three domains: methodological variations, adequacy, and transparency of reporting and quality of data input parameters. A standard extraction tool was used to provide a general overview of the study characteristics, in terms of study setting, first author name, affiliation and funding source. Data used to assess methodological variations were the type of EE, type of modeling used, study perspective, time horizon, cycle length, discounting and uncertainty analysis.

Table 2: JBI checklist criteria for the included studies

	Questions	Li et al 2021	Cornes et al 2022	Wang et al 2016	Trautman et al 2018	J. Yang et al 2021	Tilleul et al 2020
1	Is there a well-defined question?	Yes	Yes	Yes	Yes	Yes	Yes
2	Is there a comprehensive description of alternatives?	Yes	Yes	Yes	Yes	Yes	Yes
3	Are all important and relevant costs and outcomes for each alternative identified?	Yes	Yes	Yes	Yes	Yes	Yes
4	Has clinical effectiveness been established?	Yes	Yes	Yes	Yes	Yes	Yes
5	Are costs and outcomes measured accurately?	Yes	Yes	Yes	Yes	Yes	Yes
6	Are costs and outcomes valued credibly?	Yes	Yes	Yes	Yes	Yes	Yes
7	Are costs and outcomes adjusted for differential timing?	Yes	Yes	Yes	NA	NA	NA
8	Is there an incremental analysis of costs and consequences?	Yes	Yes	Yes	NA	NA	NA
9	Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?	Yes	Yes	Yes	Yes	No	Yes
10	Do the study results include all issues of concern to users?	Yes	Yes	Yes	Yes	Yes	Yes
11	Are the results generalizable to the setting of interest in the review?	Yes	Yes	Yes	Yes	Yes	Yes

3. RESULTS

General results: The initial search yielded five hundred articles, out of which three hundred and sixty-seven were from EMBASE, one hundred and nine from Scopus and twenty-four from PubMed. Fifty-three articles were identified as duplicates and excluded. Screening of all remaining articles for eligibility was performed by assessing the title and the abstract. The results of the four hundred and forty-seven screened articles were as follows: (1) two hundred and sixty-one were irrelevant, (2) eighty-one conference abstracts, (3) twenty-one editorials, letters and notes, (4) sixty-seven reviews. Out of the relevant hundred and eighty-six articles, the total excluded studies in the first screening were one hundred and seventy-one studies. The remaining fifteen articles were assessed. Eleven articles were further excluded, five studies of cost efficiency analysis, three cost-saving studies, two abstracts, one study with different indication and one illustrative paper.

The total number of articles included in this systematic review was six articles. Three studies were cost-effectiveness analysis and three studies were budget impact analysis. Figure 1 demonstrates the PRISMA flow diagram with the conducted search strategy of our systematic review. The summary of the general eligible studies information and methodologies used in the included EEs are presented in Table 4.

Cost-effectiveness analysis results: Xiao Jun Wang et al. [15] employed a cost-effectiveness analysis model to compare seven prophylaxis strategies with Granulocyte colony-stimulating factors (G-CSF) to reduce the risk of chemotherapy-induced febrile neutropenia, the seven prophylaxis strategies were 1) primary prophylaxis (PP) with nivestim (biosimilar filgrastim) throughout all cycles of chemotherapy; 2) PP with nivestim during the first two cycles of chemotherapy; 3) secondary prophylaxis (SP) with nivestim; 4) PP with pegfilgrastim throughout all cycles of chemotherapy; 5) PP with pegfilgrastim during the first two cycles of chemotherapy; 6) SP with pegfilgrastim; and 7) no prophylaxis (NP). The target population in the study was a hypothetical cohort of patients with Non-Hodgkin Lymphoma (NHL) with a mean age of 55 years receiving R-CHOP as treatment. The proposed Markov model used in the analysis includes five health states: 1) no FN or history of FN; 2) FN with severe complications; 3) FN without complications; 4) no FN, but a history of FN; and 5) death of FN. The time horizon of this Markov model was equivalent to the period of six chemotherapy cycles (Cycle length = 1 Week), which is 18 weeks. The outcome measured in the study was the incremental cost per episode of FN prevented.

Stating a hospital perspective, Xiao Jun Wang et al. [15] used direct medical costs in which the drug acquisition costs of nivestim and pegfilgrastim, and the cost of hospitalization for febrile neutropenia with and without complications were obtained from the National Cancer Center Singapore (NCCS), as in local practice the patient usually self-inject the G-CSF drug and as chemotherapy costs were assumed to be the same in all patients so both the cost of drug administration and the cost of chemotherapy were not included in the study.

The primary outcome of the study was incremental cost per episode of FN avoided, the costs of strategies 4,1,5 and 2 were 5331 US$, 4545 US$, 4056 US$ and 3813 US$ respectively, while strategies 3,6 and 7 were dominated by strategy 5. The ICER for strategies 4 vs. 1, strategy 1 vs. 5, and strategy 5 vs. 2 were 30452 US$, 22565 US$, and 13532 US$ respectively, strategy 2 was the dominant strategy with the highest probability of being cost-effective when the threshold of the

Table 3: Summary results of CHEERS scoring per reporting domain (n=6)

Reporting domain	Number of studies (out of 6)	%
Introduction:		
Title	6	100
Abstract	6	100
Methods:		
Background & objectives	6	100
Target population & subgroups	6	100
Setting & location	6	100
Study perspective	6	100
Intervention	6	100
Comparator	6	100
Time horizon	6	100
Discount rate	4	66.6
Choice of health outcomes	6	100
Measurement of effectiveness	3	50
Measurement & valuation of preference-based outcomes	2	33.3
Estimating costs & resources	6	100
Currency, price date & conversion	5	83.3
Choice of model	6	100
Assumptions	6	100
Analytical methods	5	83.3
Results:		
Study parameters	6	100
Incremental costs & outcomes	5	83.3
Characterizing uncertainty	6	100
Characterizing heterogenicity	1	16.6
Discussion:		
Study findings, limitations, generalizability, and current knowledge	6	100
Others:		
Source of funding	6	100
Conflicts of interest	6	100

willingness to pay is less than 10000 US$ per FN episode avoided. The author also used the quality-adjusted life year (QALY) as an outcome to project the cost per QALY gained, however, due to the short time horizon of the study (18 weeks) which wouldn't be suitable to capture all the benefits of reducing FN related mortality, it wasn't included as a primary outcome and the author opt to use the ICER per episode of FN avoided. Probabilistic sensitivity analysis was performed, and it showed that strategy 2 had the highest probability of being cost-effective when the threshold of the willingness to pay is less than 10,000 US$ per FN episode avoided. If the willingness to pay threshold is higher than 20,000 US$, strategies 1 and 4 would have the highest probabilities of being cost-effective.

Cost-utility analysis results: Edward Li et al. [13] employed a cost-utility analysis model to compare two G-CSF prophylaxis strategies for intermediate to high-risk chemotherapy-induced febrile neutropenia. The prophylaxis strategies were 1) primary prophylaxis and 2) secondary prophylaxis, both strategies use a biosimilar filgrastim (filgrastim-sndz) in patients with breast cancer, non–small cell lung cancer (NSCLC), and non-Hodgkin lymphoma (NHL). The target population of the study was a cohort of patients receiving intermediate to high-risk curative chemotherapy for breast cancer receiving (adjuvant docetaxel), non–small cell lung cancer (NSCLC) receiving (adjuvant carboplatin and paclitaxel), and non-Hodgkin lymphoma (NHL) receiving (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)). The population age varied according to the cancer type. The proposed Markov cycle tree-based model was constructed as follows: the first cycle of each regimen was represented as a decision tree in which the patients were categorized to follow either a primary prophylaxis or a secondary prophylaxis and then patients would either develop febrile neutropenia or complete the cycle without developing febrile neutropenia based on the risk during the first cycle. Then the patients would be tracked through the remainder of chemotherapy by a Markov cycle model. The time horizon used in the model was a lifetime. The outcomes measured in the study were incremental costs per FN avoided, incremental cost per life year (LY) gained, and incremental cost per quality-adjusted life year (QALY) gained.

Stating a payer perspective, Edward Li et al. used direct medical costs in which the drug acquisition costs were based on the average sales price of filgrastim-sndz, also used drug administration costs, inpatient and outpatient febrile neutropenia management costs. Both costs of chemotherapy and post-chemotherapy were excluded from the study. The primary outcomes of the study were incremental costs per FN avoided, incremental cost per life year (LY) gained, and incremental cost per quality-adjusted life year (QALY) gained. Across all three types of cancer primary prophylaxis has a higher cost than secondary prophylaxis however, primary prophylaxis provides an additional 0.102-0.118 FN event avoided, 0.065-0.144 Lys, 0.057-0.13 QALYs at an incremental cost of 651 US$-2463 US$. The incremental cost effectiveness ratio (ICER) ranged from 5660 US$-20806 US$ per FN event avoided, 5123 US$ - 31077 US$ per LY gained, and 7213 US$ - 35563 US$ per QALY gained. The NSCLC has the lowest ICERs.

Both one-way sensitivity analysis and probabilistic sensitivity analysis were performed on cost per QALYs gained to address the uncertainty across all three cancer types. The one-way sensitivity analysis showed that for breast cancer, the model was sensitive to changes in baseline risk for FN, mortality hazard ratio for low relative dose intensity, and the relative risk of FN with filgrastim versus no filgrastim. As for both NSCLC and NHL, the model was sensitive to changes in baseline risk for FN, mean length of stay for hospitalization, and the cost of FN events requiring hospitalization. Probabilistic sensitivity analysis showed that the cost-effectiveness per QALY gained at willingness to pay threshold of 50,000 US$ for Breast cancer, NSCLC, and NHL have the probability of 73.6%, 99.4% and 91.8% respectively.

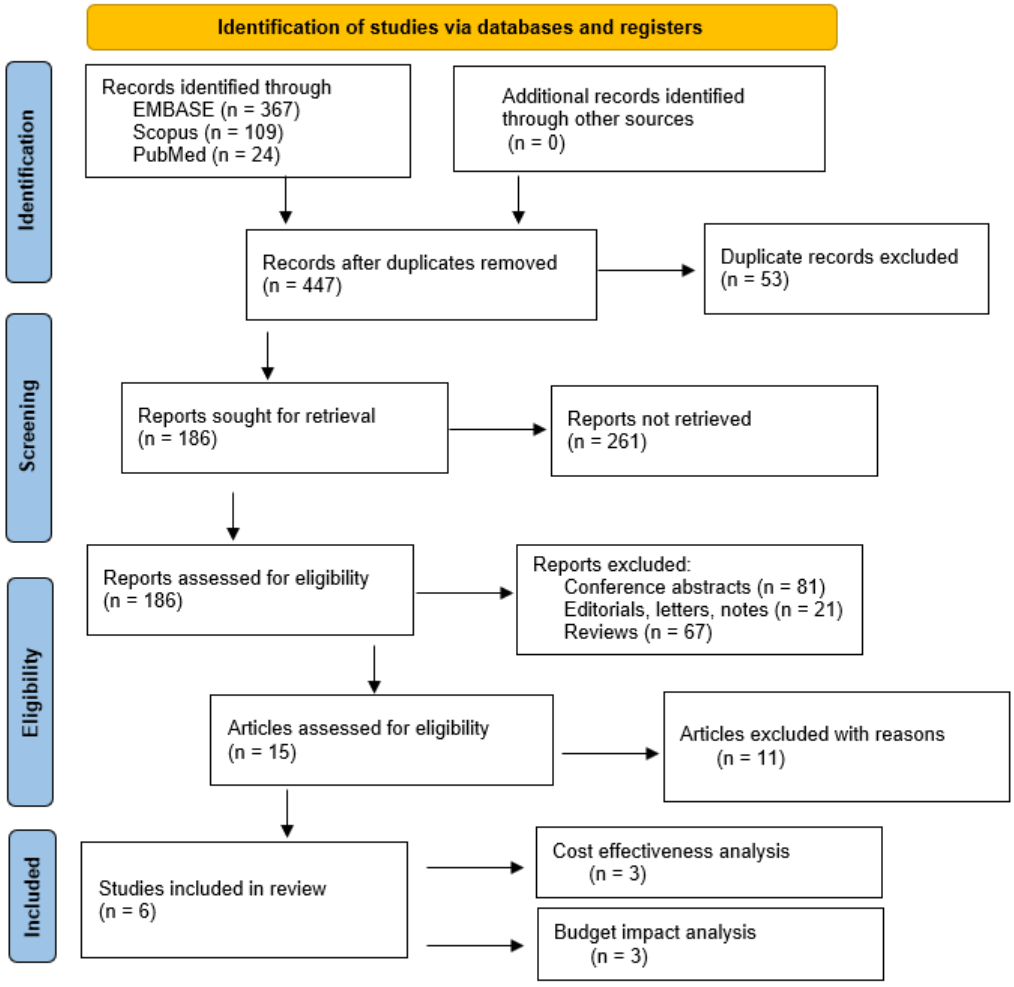

Figure 1: The PRISMA flow diagram for the search and selection processes of this systematic review.

Another study reviewed was by Paul Cornes et al. [14] which employed cost-utility analysis to compare between pegfilgrastim and filgrastim in primary prophylaxis in cancer patients receiving intermediate to high-risk chemotherapy with five different treatment strategies. The prophylaxis treatment strategies were as follows: 1) Pegfilgrastim biosimilars. 2) Pegfilgrastim reference product (prefilled syringe (PFS)); 3) Pegfilgrastim reference product (on-body injector (OBI)); 4) Filgrastim biosimilars; and 5) Filgrastim reference product. The target population was two cohorts of patients receiving intermediate-risk and high-risk chemotherapy with a mean age of approximately 60 years. The proposed Markov cycle tree-based model was constructed in the form of four stages as follows: Stage A, initial chemotherapy, cycle 1 (cycle length = 3 weeks); Stage B, chemotherapy cycles 2–6 (cycle length = 3 weeks); stage C, post-chemotherapy (first 5 years; cycle length = 6 months); and stage D, post-chemotherapy (after 5 years; cycle length = 6 months). All patients with intermediate- or high-risk of FN would receive Primary Prophylaxis with any of the five G-CSFs. Patients would expect to have an episode of FN and it would require management either inpatient or outpatient. Then the patients would be tracked through the remainder of chemotherapy by a Markov cycle model. The time horizon used in the model was a lifetime. The outcomes measured in the study were incremental costs per FN avoided, incremental cost per life year (LY) gained, and incremental cost per quality-adjusted life year (QALY) gained.

Stating a payer perspective, Paul Cornes et al. [14] used direct medical costs in which the drug acquisition costs were obtained as the average sales price in the Centers for Medicare & Medicaid Services price list, the administration costs derived from Physical Fee Schedule, and FN management costs. The costs of chemotherapy, post-chemotherapy, and the non-FN related costs were assumed to be the same between patients and were excluded from the study.

The primary outcomes of the study were incremental costs per FN avoided, incremental cost per life year (LY) gained, and incremental cost per quality-adjusted life year (QALY) gained. In both intermediate and high-risk groups, pegfilgrastim and filgrastim biosimilars have lower total costs and approximately the same number of FN avoided, LY gained and QALYs gained when compared with their associated reference products. Thus, both pegfilgrastim and filgrastim biosimilars dominated their reference products respectively.

In comparing pegfilgrastim biosimilar with filgrastim biosimilar in high-risk group, pegfilgrastim provided 8.015 QALYs, 9.52 LYs, and 0.732 FN event at a total cost of 102576 US$, while filgrastim biosimilar provided 7.733 QALYs, 9.196 LYs, and 1.163 FN event at a total cost of 108279 US$ which resulted in 0.28 QALYs gained, 0.32 LYs gained, and 0.43 FN event avoided at a cost saving of 5703 US$. Thus, pegfilgrastim biosimilar was the dominant prophylaxis strategy in the high-risk group. While in the intermediate-risk group pegfilgrastim provided 8.609 QALYs, 10.213 LYs, and 1.024 FN event at a total cost of 106811 US$, while filgrastim biosimilar provided 8.488 QALYs, 10.074 LYs, and 1.206 FN event at a total cost of 105059 US$ which resulted in 0.12 QALYs gained, 0.13 LYs gained, and 0.18 FN event avoided at an incremental cost of 1752 US$. The incremental cost effectiveness ratio (ICER) was 14502 US$ per QALYs gained, 12583 US$ per LYs gained, and 9674 US$ per FN avoided.

Both one way sensitivity analysis and probabilistic sensitivity analysis were performed on cost per QALYs gained to address the uncertainty in both intermediate and high-risk groups. The one-way sensitivity analysis showed that in the high-risk group pegfilgrastim biosimilar was always dominant on the filgrastim biosimilar, while in the intermediate risk group the model was sensitive to changes in the drug cost of pegfilgrastim. Probabilistic sensitivity analysis showed that the cost effectiveness per QALY gained, per LY gained, and per FN avoided at willingness to pay threshold of 100,000 US$ have a probability of 100, 100, and 100% respectively.

Budget impact analysis results: Three budget impact analysis studies were reviewed, the first study reviewed was Holly Trautman et al. [16] in which a budget impact model was employed to assess the impact of increasing the use of patient-administered tbo-filgrastim and filgrastim-sndz at home in patients receiving myelosuppressive chemotherapy. The time horizon for the study was 1 year. The treatment strategies in both the current treatment mix and future treatment mix were the same reference filgrastim, tbo-filgrastim, and filgrastim-sndz but with different market shares. The current treatment mix was as follows: 84.7% reference filgrastim, 4.9% tbo-filgrastim, and 10.4% filgrastim-sndz while the future treatment mix were projected with an increase in the market share of both tbo-filgrastim and filgrastim-sndz by 5% and 2% respectively, so the future treatment mix market share would be as follows: 77.7% reference filgrastim, 9.9% tbo-filgrastim, and 12.4% filgrastim-sndz.

Stating a payer perspective, Holly Trautman et al. [16] used direct medical costs in which drug acquisition costs were obtained as wholesale acquisition (WAC) costs as the study evaluated the patient-administered G-CSF at home. The primary outcome of the study was the annual drug cost and its impact on the total budget in which the current treatment mix annual drug costs for reference filgrastim, tbo-filgrastim, and filgrastim-sndz were 46,037,202 US$, 2,311,211 US$, and 4,949,804 US$ respectively with a total annual drug cost of 53,298,217 US$. Upon increasing the market share of both tbo-filgrastim and filgrastim-sndz by 5% and 2% respectively and subsequent decrease in the market share of reference filgrastim, the annual drug costs in the future treatment mix for reference filgrastim, tbo-filgrastim, and filgrastim-sndz were 42,260,349 US$, 4,703,546 US$, and 5,864,937 US$, respectively with a total annual drug cost of 52,828,832 US$ resulting in a total annual cost saving of 469,385 US$. One-way sensitivity analysis was performed to address the uncertainties, it showed that the model was sensitive to variations in the percentage of patients who are self-administering at home and to variations in the WAC of filgrastim.

The second study reviewed was by Jingyan Yang et al. [17] in which a budget impact model was employed to assess the impact of introducing a new pegfilgrastim biosimilar (NYVEPRIA) to the French market in patients receiving myelosuppressive chemotherapy. The time horizon for the study was 5 years. The current treatment mix was reference pegfilgrastim with a market share of 9.4%, 8.8%, 6.8%, 6.8%, and 6.4% from year 1 to year 5 respectively, other existing pegfilgrastim biosimilars with a market share of 28.5%, 31.7%, 33.7%, 33.7%, and 34.1% from year 1 to year 5 respectively, reference filgrastim with a market share of 1.7% in the first year and then 1.5% from year 2 to year 5, other existing filgrastim biosimilars with a market share of 48% across the five years, and lenograstim with a market share of 12.4% in the first year and then 10% from year 2 to year 5. The future treatment mix would be the same with the addition of the new pegfilgrastim biosimilar (NYVEPRIA). Since the study assumed that only patients receiving reference or biosimilar pegfilgrastim would be eligible for switching to the new pegfilgrastim biosimilar (NYVEPRIA), the market share of reference or biosimilar filgrastim and lenograstim will remain the same while the market share of reference, existing biosimilar pegfilgrastim and new pegfilgrastim biosimilar would change across the five years. The future market share of reference pegfilgrastim is 9.4%, 7%, 5%, 5%, and 4.5% from year 1 to year 5 respectively, other pegfilgrastim biosimilars is 26.5%, 29.5%, 30.9%, 30.8%, and 30.9% from year 1 to year 5 respectively, while the market share of the new pegfilgrastim biosimilar (NYVEPRIA) is 2%, 4%, 4.6%, 4.7%, and 5.1% from year 1 to year 5 respectively.

Stating a payer perspective, Jingyan Yang et al. [17] used direct medical costs in which the drug acquisition costs were manufacturing prices obtained from L'Assurance Maladie and drug administration costs. It was proposed that the manufacturing prices of reference, existing biosimilar pegfilgrastim would decrease in the year after the introduction of the new pegfilgrastim biosimilar (NYVEPRIA), while the manufacturing prices of reference and biosimilar filgrastim and lenograstim will remain the same across the 5 years.

The primary outcome of the study was the annual drug cost and its impact on the total budget in which the current treatment mix total annual drug costs were 120,757,615 €, 114,973,828 €, 114,008,831 €, 114,008,831 € and 113,815,831 from year 1 to year 5 respectively, and the cumulative cost of 577,564,936 €. While the future treatment mix total annual drug costs were 120,748,995 €, 114,105,331 €, 113,140,333 €, 113,194,729 €, 112,856,880 from year 1 to year 5 respectively, and the cumulative cost of 574,046,267 €, with a subsequent cost savings in the drug acquisition costs of 8,535

Table 4: Study characteristics table

Study	Setting	Type of EE	Intervention	Comparator	Outcomes measured	Perspective	Time horizon	Sensitivity analysis	Model type	Discount rate %	Funding
Li et al 2021[13]	US	CEA/ CUA	Filgrastim-sndz as PP	Filgrastim-sndz as SP	incremental costs per FN event avoided, per LY gained, and per QALY gained	US Payer	Life time	Probabilistic & deterministic	Markov	3% (range 1.0% - 5.0%)	Sandoz
Cornes et al 2022 [14]	US	CEA/ CUA	Pegfilgrastim & filgrastim biosimilar as PP	Pegfilgrastim & filgrastim reference as PP	incremental cost per QALY gained, incremental cost per LY gained and incremental cost per FN event prevented	US payer	Life time	Probabilistic & deterministic	Markov	3%	Pfizer
Wang et al. 2016 [15]	Singapore	CEA	Biosimilar filgrastim (nivestim) as PP & SP	Pegfilgrastim reference as PP & SP	The incremental cost per episode of FN prevented	Hospital	18 weeks	Probabilistic	Markov	NA	Not funded
Trautman et al 2018 [16]	US	BIA	tbo-filgrastim & filgrastim-sndz	Filgrastim reference	Annual Drug Cost WAC (PMPM and PMPY)	US Payer	1 year	One way	Budget impact	No discounting	Teva
J. Yang et al 2021 [17]	France	BIA	Pegfilgrastim biosimilar (NYVEPRIA)	Long acting & short acting filgrastim reference & biosimilar	Annual Drug acquisition and administration cost	French healthcare system	5 years	Not clear	Budget impact	No discounting	Pfizer
Tilleul et al 2020 [18]	France	BIA	Pegfilgrastim biosimilar	Long acting & short acting filgrastim reference & biosimilar	Annual Drug acquisition, ambulatory care, and hospital costs associated with FN episodes	French healthcare system	5 years	Not clear	Budget impact	NA	Accord

€, 868,498 €, 868,498 €, 814,688 €, and 958,497 € from year 1 to year 5 respectively, and the cumulative cost saving of 3,518,716 €.

Scenario analysis was performed to address the uncertainties, it showed that the model was sensitive to variations in the drug acquisition cost of new and other pegfilgrastim biosimilars and to the variations in the market share of new pegfilgrastim biosimilars.

The third reviewed study was Patrick R Tilleul et al. [18] in which a budget impact model was employed to assess the impact of introducing a new pegfilgrastim biosimilar to the French market in patients receiving myelosuppressive chemotherapy. The time horizon for the study was 5 years. The current treatment mix was short acting G-CSF with a market share of 67% and existing long-acting G-CSF with a market share of 33% across the five years. Since the study assumed that only patients receiving long-acting G-CSF would be eligible for switching to the new pegfilgrastim biosimilar, the market share of short acting G-CSF will remain the same while the market share of long-acting G-CSF and new pegfilgrastim biosimilar would change across the five years. The future market share of the existing long-acting G-CSF is 28%, 26%, 23%, 21%, and 19% from year 1 to year 5 respectively, while the new pegfilgrastim biosimilar market share is 5%, 7%, 10%, 12%, and 14% from year 1 to year 5 respectively.

Stating a payer perspective, Patrick R Tilleul et al. [18] used direct medical costs in which the drug acquisition cost, ambulatory care costs including medical fees, pharmacy fees, ambulatory cancer treatment, nursing care, laboratory tests, medical devices, and transport were obtained from the French national insurance database, The cost of switching to pegfilgrastim biosimilar, within a pharmacy setting, and the cost of hospitalization associated with FN episode.

The primary outcome of the study was the annual drug cost and its impact on the total budget. The current treatment mix cumulative cost over 5 years was 894,529,203 € while the future treatment mix cumulative cost over 5 years was 843,521,671 €. Resulting in cost savings with the future mix that is equal to 51,007,531 € over the 5 years which can be used to expand access to more patients by switching them from short-acting G-CSF and long-acting G-CSF to the new pegfilgrastim biosimilar. Sensitivity analysis was performed to address the uncertainties, it showed that the model was sensitive to variations in the market share of new pegfilgrastim biosimilar.

4. Discussion

This systematic review, encompassing six studies [13-18], has provided substantial insights focusing on the economic impact, cost-effectiveness and clinical efficacy of various G-CSF biosimilars and biologic filgrastim, particularly in the context of FN management in patients undergoing chemotherapy in different types of cancer.

The included studies conducted in different healthcare systems and contexts, offer a broad perspective on the use of

G-CSF biosimilars, to manage FN induced by chemotherapy, including cost-effectiveness and budget impact analysis. These studies, ranging from Xiao Jun Wang et al.'s [15] comprehensive evaluation of seven prophylaxis strategies to Edward Li et al.'s [13] and Paul Cornes et al.'s [14] assessments of biosimilar filgrastim and pegfilgrastim, respectively, collectively underscore the nuanced economic implications of FN management in cancer care.

The reviewed studies consistently demonstrated that primary prophylaxis with G-CSG biosimilars, particularly pegfilgrastim, offers a cost-effective strategy for reducing the incidence of FN. Most notably, Xiao Jun Wang et al study [15] highlighted the cost-effectiveness of pegfilgrastim in the initial cycles of chemotherapy. Concurrently, Edward Li et al and Paul Corners et al [13,14] provided evidence supporting the broader use of biosimilar filgrastim and pegfilgrastim in various chemotherapy regimens. Collectively, these findings suggest a potential paradigm shift in FN management, favoring early and routine use of biosimilars.

Xiao Jun Wang et al [15] presented a thorough analysis comparing multiple prophylaxis strategies, concluding that primary prophylaxis with nivestim in the initial chemotherapy cycles was the most cost-effective. This finding aligns with Edward Li et al.'s and Paul Cornes et al.'s studies, which demonstrated the economic and clinical benefits of G-CSFs biosimilars in diverse cancer types, including breast cancer, NSCLC, and NHL. Particularly, Paul Cornes et al.'s [14] study highlighted the dominance of pegfilgrastim biosimilar in high-risk chemotherapy patients, emphasizing its cost-effectiveness over a lifetime horizon.

Budget impact analyses by Holly Trautman et al., Jingyan Yang et al. and Patrick R. Tilleul et al. [16-18], further elucidate the financial implications of integrating G-CSF biosimilars into healthcare systems. Holy Trautman et al. [16] demonstrated significant cost saving by increasing the use of patient-administered tbo-filgrastim and filgrastim-sndz. Meanwhile, Jingyan Yang et al. and Patrick R Tilleul et al. [17,18] highlighted the substantial savings achieved by introducing pegfilgrastim biosimilar into the French healthcare market, with Tilleul et al. [18] specifically advocating for expanding access to this biosimilar.

Economic evaluations in decision-making often encounter uncertainties related to factors like model structure and parameter choices. To assess the impact of these uncertainties, sensitivity analysis is essential. It determines how changes in input variables might influence the outcomes of the economic evaluations. The studies under consideration employed both deterministic and probabilistic sensitivity analyses. Deterministic analysis examined the effects of variations in aspects such as drug acquisition costs (referenced in Cornes et al. [14], Trautman et al. [16], Yang et al. [17]), market share alterations (Yang et al. [17], Tilleul et al. [18]), and other factors like the baseline risk for FN, mortality hazard ratio, hospital stay duration, and FN event hospitalization costs (Li et al. [13]). On the other hand, probabilistic analysis looked at different willingness-to-pay thresholds, which varied from 10,000 USD (Wang et al. [15]), through 50,000 USD (Li et al. [13]), to 100,000 USD (Cornes et al. [14]). This analysis showed that changing willingness-to-pay thresholds can significantly affect the perceived cost-effectiveness of a technology. We suggest that future studies incorporate both deterministic and probabilistic sensitivity analyses to fully address uncertainties and recommend applying varying willingness-to-pay thresholds based on disease type and severity.

The implications of these findings are significant for clinical practice. They advocate for the re-evaluation of current treatment guidelines to incorporate biosimilars G-CSFs more prominently. Such a shift could not only enhance patient care by reducing FN incidence but also contribute to healthcare cost savings. However, the varying healthcare systems and reimbursement policies across different countries, as evident in studies like that of Jingyan Yang et al and Holly Trautman et al [17,16], indicate the need for context-specific guidelines.

Limitations: The generalizability of these studies findings is subject to certain limitations. First, the majority of these studies were concentrated on specific cancer types as breast cancer, lung cancer, and non-Hodgkin lymphoma, which may not represent the full spectrum of chemotherapy-induced FN risk. Secondly, the time horizons and discount rates varied across studies or were often not mentioned, which might impact the long-term cost effectiveness analysis. Moreover, some studies did not explicitly discuss the methods for characterizing uncertainty and heterogeneity, which are crucial for understanding the scope of the results.

Future studies should aim to address these limitations by including a broader range of cancer types and more comprehensive demographic profiles. Additionally, long-term studies are needed to fully capture the cost-effectiveness and clinical benefits of G-CSF biosimilars over the entire course of cancer treatment. Exploring the real-world effectiveness of these interventions across diverse healthcare settings would also be valuable. Lastly, more detailed analyses of the cost structures, including potential discounts or rebates and varying healthcare policies, would provide a more nuanced understanding of the economic impact of these biosimilars.

Key insights summary:

1- Diverse study focuses: these studies vary in focus, from PP in patients with different cancer types to BIA from a healthcare system perspective. This diversity highlights the multifaceted nature of economic evaluation in healthcare.

2- Comparative analysis: the studies compare different interventions like PP with biosimilar filgrastim against SP or existing treatments. Such comparisons are crucial in determining the most cost-effective strategies in cancer care.

3- Health outcomes: while all studies are centered around economic outcomes, some like Edward Li et al and Cornes et al [13,14] also considered clinical outcomes like life years (Lys) and quality-adjusted life years (QALYs) gained. These metrics are essential for a holistic understanding or treatment value.

4- Cost efficiency: the studies generally conclude that biosimilar G-CSFs are cost-effective. For instance, Edward Li et al and Xiao Jun Wang et al [13,15] highlight

the cost-effectiveness of biosimilar filgrastim in specific cancer treatments.

5- Generalizability: findings are often specific to the healthcare system under study, as seen in Jingyan Yang et al, Patrick R. Tilleul et al [17,18], focusing on the French healthcare system. This limits the generalizability of conclusions to other healthcare contexts.
6- Heterogeneity: these studies are diverse in terms of methodologies, populations, and healthcare systems, which suggests significant heterogeneity. This diversity can impact the ability to combine data effectively.
7- Statistical analysis: given the varying nature and reporting styles of economic outcomes in these studies, the future traditional quantitative meta-analysis might be challenging and not visible. Instead, a qualitative synthesis or narrative review approach might be more suitable.
8- Funding and potential biases: the source of funding and declared conflicts of interest, like those in studies sponsored by pharmaceutical companies can influence study outcomes and interpretations.
9- Economic analysis focus: the studies predominantly focus on the economic aspect. Such as budget impact and cost savings, rather than clinical efficacy.
10- Varied incremental costs: the incremental costs vary widely across studies, with some like Holly Trautman et al [16], showing specific cost savings, while others provide more general conclusions on economic benefits.
11- Methodological approaches: the absence of ICER calculations in some studies, like in those by Holly Trautman et al and Jingyan Yang et al [16,17], indicates a focus on budget impact rather than cost-effectiveness, which could influence healthcare policy decisions differently.
12- Recommendations for practice: studies like those by Edward Li et al [13] recommend the expanded use of biosimilar filgrastim, underlining its cost-effectiveness and potential clinical benefits. Such recommendations can guide treatment guidelines and policy formulations.
13- Country-specific economic implications: studies focusing on specific countries, like France [17,18], indicate the potential for significant healthcare savings through the adoption of biosimilar G-CSF, but also highlight the need for country-specific economic evaluations.
14- Interpretation: based on the available data, we could infer that biosimilar G-CSF generally leads to cost savings in various healthcare systems. However, due to the lack of uniformity in reporting incremental costs and effects, as well as ICERs, drawing a firm quantitative conclusion is challenging.

Overall implications:

1- Healthcare policy and decision-making: the integration of economic evaluations into healthcare policy and decision-making is essential. It aids in selecting treatments that are both effective and financially sustainable, given the limited healthcare budgets. The cost savings highlighted in various studies offer the possibility of extending treatment access to more patients or reallocating funds to introduce innovative technologies. Furthermore, these evaluations are instrumental in refining clinical guidelines. However, it's important to note that these measures may lead to an increase in overall healthcare costs. Our review underscores the value of incorporating biosimilar filgrastim in cancer treatment, providing healthcare policymakers and practitioners with insights into its economic benefits and practical viability.
2- Need for further research: there's a notable need for further research, particularly in expanding the generalizability of findings to other healthcare systems and exploring long-term clinical outcomes.
3- Potential shift in treatment practices: the economic benefits highlighted in these studies suggest a potential shift towards more widespread adoption of biosimilar G-CSFs in oncology, aligning with cost-containment efforts and value-based care initiatives.
4- In summary: the analysis of these studies underscores the importance of comprehensive economic evaluations in healthcare, particularly in oncology, where treatment costs are a significant concern. The findings support the growing role of biosimilars in achieving cost-effective healthcare solutions [19-21].

5. Conclusions

This systematic review supports the cost-effective use of G-CSF biosimilars, particularly in the primary prophylaxis of FN among chemotherapy patients with high risk. These findings encourage a paradigm shift in FN management, emphasizing the need to incorporate biosimilars into clinical guidelines and policy-making decisions for more effective and economical cancer care.

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