The evolution of value with filgrastim in oncology

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The recombinant G-CSF filgrastim was first approved in 1991, and its value has been evolving ever since. Initial health technology assessments suggested low value due to high drug cost and no evidence for significant gain in overall survival. However, more recent meta-analyses of placebo-controlled randomized trial data show falling costs due to biosimilar competition and absolute overall survival gains of 3.2% (95% CI: 2.1–4.2%) from filgrastim support of cytotoxic chemotherapy. The launch of biosimilar alternatives merits a re-evaluation of decisions by health technology assessments and explains the first inclusion of filgrastim in the WHO Essential Drug List for cancer >20 years after its original approval in 1991, thus demonstrating the power of biosimilar medicines in transforming healthcare.

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The value of drugs evolves over time as new evidence for risks and benefits emerge and the price of a drug changes. The G-CSF filgrastim was first approved in 1991 and its value has been evolving ever since. Filgrastim is indicated for the amelioration of neutropenia in patients receiving cytotoxic chemotherapy [1–4], and since 2015, has been included on the WHO Model List of Essential Medicines: a list of minimum medicine needs for a basic healthcare system that includes the most efficacious, safe and cost-effective medicines for priority conditions [5].

Neutropenia is a commonly reported adverse event associated with cytotoxic chemotherapy, defined as a neutrophil count of $<0.5 \times 10^9/l$. The duration of neutropenia determines the risk of infection, with the shorter the period of neutropenia, the lower the risk. Signs of infection in patients with neutropenia include fever and febrile neutropenia (FN). FN is defined as an oral body temperature of $\geq 38.3^\circ\text{C}$ or two consecutive readings of $>38.0^\circ\text{C}$ for 2 h in a patient with an absolute neutrophil count (ANC) $<0.5 \times 10^9/l$ [4]. The risk of FN increases sharply as the duration of neutropenia increases [6], and to keep the risk of FN $<10\%$, the duration of neutropenia should be shortened to <2 days. Each year in the USA, 60,000 cancer patients are hospitalized because their low neutrophil count led to a serious infection and one in 14 of these patients dies [7]. The administration of G-CSF treatment in cancer patients depends on several factors such as type of chemotherapy regimen, comorbidities, performance status, patient age and complicating factors such as renal or hepatic dysfunction [4,8,9]. There is also a cost implication since estimates suggest that each patient with neutropenic fever costs almost US\$28,000 to treat [10]. A recent study showed that among 3314 breast cancer patients undergoing chemotherapy, 14% experienced FN that required hospitalization for a mean of 4 days, at a mean cost of US\$20,462 [11]. Neutropenia also means that anticancer chemotherapy treatment may be delayed and doses are reduced if infection occurs or the patient does not recover their blood counts in time for the next treatment cycle [7,12–14]. Once chemotherapy dose delays and dose reductions reach 15%, cancer cure rates fall [13]; this was reported in half of breast cancer patients prior to the introduction of G-CSF treatment to prevent neutropenia [14]. Thus, prevention is better than cure. WHO recommendations on essential medicines for cancer recognize the need for improved control of infection and improved cancer control [15], supporting the use of filgrastim in patients receiving myelosuppressive chemotherapy.

Economic evaluation of filgrastim

We performed a search with the term ‘filgrastim’ through the Evidence Search Portal of the UK National Institute for Health and Care Excellence (NICE) [16]. This search, on 28 August 2018, revealed 25 systematic reviews and 55 economic evaluations of filgrastim, up to the NICE Key-Topic Report 15 on biosimilar medicines for drug optimization that was updated in February 2018 [17]. These were read to find evidence for either the clinical value or the economic value of filgrastim during chemotherapy. Key papers have been summarized in Table 1.

Some early economic evaluations suggested low value due to high drug cost and no evidence for significant gain in overall survival (OS) [22,39]. However, this may be due to the types of patients included in these studies. For example, one study included elderly patients with aggressive non-Hodgkin’s lymphoma; survival benefits may be less likely in this cohort, compared with less frail patients with less aggressive disease [39]. As a consequence of the high cost of a biologic drug and the low benefits, the cost–effectiveness of G-CSF was considered to be very poor. One study estimated its impact at more than 5 million Canadian Dollars (almost 4 million Euros) for each Quality Adjusted Life Year (QALY) gained [33,34].

The first NICE evidence with data to suggest any clinically and statistically significant survival benefit was published in 2013, more than 20 years after the first approval of filgrastim in 1991 [36,40]. This 2013 meta-analysis of placebo-controlled randomized trial data showed absolute OS gains of 3.2% (95% CI: 2.1–4.2%) from filgrastim support of cytotoxic chemotherapy [36] and decreased costs due to biosimilar competition. This systematic review and meta-analysis of 61 randomized controlled trials evaluated the impact of filgrastim on chemotherapy dose intensity and cancer survival [36]. The risk reduction (RR) with G-CSF support for all-cause mortality was 0.93 (95% CI: 0.90–0.96; $p < 0.001$). A greater RR was observed in studies with a longer follow-up ($p = 0.02$), where treatment was for curative intent (RR = 0.91; $p < 0.001$), where survival was the primary outcome (RR = 0.91; $p < 0.001$) and where dose-dense chemotherapy was used [36].

The 3.2% absolute increase in OS is particularly of note when it is considered that patients with early-stage node-negative breast cancer are treated with adjuvant chemotherapy for a 2.3% absolute survival benefit [41]. There are two probable explanations as to why filgrastim could impact on improved survival. The first is that G-CSF can improve control of infection by reducing the risk of FN, hospitalization and death during chemotherapy. The second could be that G-CSF can also meet the need for improved cancer control by allowing more chemotherapy to be given on time and without the need for dose reductions, making it more effective. We suggest that the delay of two decades to discover this survival benefit is probably explained by the lack of published data with long-term outcomes from the earlier era of research.

It is this long delay that probably explains why G-CSF was not included in the WHO Model List of Essential Medicines until 2015, 24 years after its first approval [5]. WHO reports that, “Only those medicines should be selected for which sound and adequate data on efficacy and safety are available from clinical studies, and for which evidence of performance in general use in a variety of medical settings has been obtained” [42]. Inclusion in an essential drug list mandates that G-CSF is available to all citizens, either free or for an affordable price [1]. However, since filgrastim is a recombinant biologic drug costing between US\$42,000 and US\$50,000 (USA 2012 pricing) for a typical patient having one cycle of chemotherapy, this has implications for affordability in many regions [43,44].

The value of a treatment, in terms of cost–effectiveness, is determined by both its clinical effect and its financial cost. While more than two decades were needed to report the general impact of G-CSF on OS to the satisfaction of WHO, this period also spanned a change in the cost of treatment. Surveys of drug costs over time suggest that branded medicines under patent protection show pharmaceutical price inflation at rates above the general consumer price inflation [45]. This cost inflation is later checked by patent expiry and the advent of competition from other manufacturers. For traditional medicines, competition has been from ‘generic’ medicines [46]. The 2010 WHO report, ‘More Health for the Money’, cited underuse of generics and higher than necessary prices for medicines as leading causes of inefficiency in global healthcare [46]. Reasons for this inefficiency included lower perceived efficacy and safety of generic medicines, and historical prescribing patterns. The report provided clear guidance on how to address inefficiency, including improving prescribing guidance, information, training and practice; requiring, offering or permitting incentives for generic substitution, and purchasing based on assessment of costs and benefits of alternatives [47].

The structural complexity of biologic medicines, such as G-CSF, means that generic versions are insufficient to ensure a similar quality, safety and efficacy as the original patented ‘reference drug’ [48]. Instead the economic role

Table 1. Timeline of key economic studies of filgrastim prophylaxis during cancer chemotherapy.

Year of publication	Country of origin	Value assessment of filgrastim	Refs.
1991	USA	Clinical value recognized. First RCT reports filgrastim reduces FN during cancer chemotherapy for small cell lung cancer	[18]
1991	USA/Europe	Filgrastim first approved USA and Europe	[19]
1996	Italy	Prophylactic filgrastim clinically effective but not cost-effective in the Italian hospital setting. The ICER assumes no tumor control or OS advantage from filgrastim	[20]
2000	Multinational	Filgrastim cost-effectiveness decreased by identifying low-risk FN patients who do not require hospital admission and so save costs using the Multinational Association for Supportive Care in Cancer Risk Index	[21]
2004	The Netherlands	Prophylactic filgrastim clinically effective but not cost effective to payers for elderly patients with diffuse B-cell non-Hodgkin's Lymphoma. The ICER assumes no tumor control or OS advantage	[22]
2004	UK	Prophylactic filgrastim cost saving only in patients likely to have two episodes of FN and if drug price is reduced by $\geq 85\%$. The ICER assumes no tumor control or OS advantage from filgrastim	[23]
2004	USA	Prophylactic filgrastim may not be cost-effective from a payers' perspective; however, it is cost-effective at FN risk $\geq 18\%$ when indirect patient costs are included (e.g., loss of earnings)	[24]
2006	The Netherlands	Filgrastim is cost saving to payers only when FN risk $\geq 84\%$. The ICER assumes no tumor control or OS advantage from filgrastim	[25]
2006	USA	Widespread underdosing of filgrastim saves drug costs but leads to increased FN admissions reported from large US patient outcomes database. Each additional day of filgrastim prophylaxis reduced this risk between 8 and 23%, depending on tumor type	[16]
2007	Canada	Filgrastim offers no OS benefit in meta-analysis of RCTs	[26]
2008	Europe	First biosimilar filgrastim approved Europe	[27]
2009	Europe	Price competition promoted in Europe with five competing brands of biosimilar filgrastim approved	[27]
2011	USA	Majority of filgrastim use in multiregional population-based cohort patients shown to be outside guidelines. Restricting use would increase cost-effectiveness	[28]
2011	UK	Filgrastim price discount of 60% could make primary prophylaxis cost-effective for UK payer thresholds of £30,000 per QALY if OS impact of reduced chemotherapy intensity following FN is considered. At list prices, only secondary prophylaxis cost-effective at UK thresholds	[29]
2012	UK	Filgrastim prophylaxis ICER estimated at £1.0–4.1 million per QALY – assuming no OS gains. NICE advises reimbursement only as an integral part of the chemotherapy regimen or in order to maintain chemotherapy dose intensity in curative patients	[12,30,31]
2012	UK	Patient access increases fivefold with budget-saving through price competition by biosimilars for London NHS	
2012	Canada	Filgrastim prophylaxis ICER estimated at CAD 700,500 per QALY in diffuse B-cell non-Hodgkin's Lymphoma	[33]
2013	Canada	Filgrastim prophylaxis ICER estimated at CAD 5,796,000 per QALY in diffuse B-cell non-Hodgkin's Lymphoma	[34]
2013	Europe	Price competition promoted in Europe with seven competing brands of biosimilar filgrastim approved	[27]
2013	Sweden	Patient access increases fivefold with budget-saving through price competition by biosimilars in southern Sweden	[35]
2013	USA	Filgrastim prophylaxis for trials reporting at least 2 years of follow-up show overall mortality reduced 3.2% absolute (95% CI: -2.1 to -4.2%). Improved OS seen across cancer types and dose and schedule categories. Greater reductions in risk for all-cause mortality were observed in studies with longer follow-up	[36]
2014	USA	Filgrastim prophylaxis ICER estimated at <US\$50,000 per QALY using a whole life calculation in non-small cell lung cancer	[37]
2014	Europe	Price competition promoted in Europe with eight competing brands of biosimilar filgrastim approved	[27]
2015	USA	First biosimilar filgrastim approved USA	[19]
2015	Canada	First biosimilar filgrastim approved Canada	[38]
2015	World	Filgrastim given WHO essential drug status for oncology	[5]

These papers defined either the clinical or economic value of filgrastim prophylaxis to prevent FN, chemotherapy delay, or treatment dose reduction and led to the change in perception of the value of this treatment. Papers were identified from the NICE evidence database for filgrastim up to 1 September 2017 [11].
 FN: Febrile neutropenia; ICER: Incremental cost-effectiveness ratio; NICE: UK National Institute for Health and Care Excellence; OS: Overall survival; QALY: Quality-adjusted life-year; RCT: randomized controlled trial.

of generic medicines for biologics is taken by 'biosimilar' drugs [49]. As with generic medicines, competition from biosimilars drives price reductions [50,51].

Biosimilars

Biosimilars are defined by WHO as, “A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product” [52]. The expiry of patents for biological drugs presents opportunities for the development of biosimilars with the rationale of cost savings and consequent improved access to biological medicines [49,53–55]. Biosimilars are a key component of the biologics market which was worth US\$277 billion in sales worldwide in 2017, and are predicted to offer savings of over €10 billion from 2016 to 2020 in the European Union Five countries (EU5: France, Germany, Italy, Spain, UK) alone [56]. Cost-saving is not the sole determinant for biosimilar uptake in Europe; local guidelines and policies are influential too [56]. In the USA, geographical differences in regulatory frameworks have led to delays in the approval and clinical uptake of biosimilar oncology drugs compared with the EU [57]. Perceived safety concerns and discounting of reference filgrastim may also have had a negative impact on the rate of approval and clinical uptake of biosimilars in the USA [57,58]. In the EU, formal postapproval risk management plans, which detail measures taken in order to ensure that new biosimilar drugs are used as safely as possible, have been set up to address these concerns [59,60].

Biosimilar filgrastim

Following approval of the first biosimilar filgrastim in 2008, several biosimilar G-CSF products are now available, offering potential for increased treatment access for patients. Biosimilars of filgrastim have been approved in Canada (one filgrastim biosimilar), USA (two filgrastim biosimilars), Europe (nine filgrastim biosimilars, one withdrawn postapproval) and Japan (three filgrastim biosimilars) and clinical and pharmacoeconomic experience is thus emerging. Current ESMO and EORTC guidelines consider biosimilar filgrastim as an alternative to reference filgrastim [4,60] and the 2017 JSCO, 2016 ASCO Guideline Update and the 2018 ASCO Statement: Biosimilars in Oncology recommend either biosimilar or reference filgrastim for FN prevention [62–64].

In the EU, where postapproval experience of biosimilar G-CSF is the longest, barriers and facilitators of adoption of the five available biosimilar filgrastims have been identified [65]. For example, data from London hospitals show that switching from reference G-CSF to biosimilar G-CSF was associated with an annual saving of £1 million [32,35]. UK guidelines were also updated to reflect the improved cost-effectiveness of biosimilar G-CSF. G-CSF was recommended as first-line cancer treatment and uptake of both reference and biosimilar filgrastim increased by 104% [63,66]. Data from Sweden show that in the southern healthcare region (population 1.7 million), biosimilar G-CSF was associated with net savings of €2 million and allowed a fivefold increase in daily G-CSF usage [35]. This represented a saving of around 4 to 5% of the total drug budget. It is important to note that this region previously had restrictions regarding the use of G-CSF which were reduced since the introduction of biosimilar G-CSF [35,67]. Cost estimates from 17 European countries suggested that total savings from switching from the reference to the biosimilar were €85 million across the region [35,67]. A cost-effectiveness study from the European G5 countries also showed that biosimilar G-CSF was the most cost-effective approach, compared with reference, regardless of the treatment regimen [68]. These data highlight the importance of biosimilars in making treatments available for reimbursement when they may otherwise be unaffordable [69]. However, in the USA, the introduction of biosimilars has yet to deliver significant cost savings, which may be achievable through changes to current legislation and policies concerning patent litigation, naming of biosimilars, and the interchangeability, formulary listing and rebate schemes of biological reference drugs and their biosimilar counterparts [58,65,70–73].

Conclusion

Value changes over time; physicians and payers need to be aware that decisions regarding the use of medicines need constant re-evaluation, especially following the launch of biosimilar alternatives. Although not yet significant in the USA, evidence from different European countries shows the cost savings and increased access to treatment permitted by use of biosimilar filgrastim, which explains the first inclusion of filgrastim in the WHO Essential Drug List for cancer more than 20 years after its original approval in 1991 [5] and demonstrates the power of biosimilar medicines in transforming healthcare. However, affordable cancer treatment is a global challenge, with 8.2 million deaths reported due to cancer worldwide in 2012 [73]. Around 65% of cancer-related deaths are reported in developing countries and trends suggest that the incidence of cancer in the Middle East is expected to increase more than any other part of the world over the next decade [73]. Adoption of biosimilars, including biosimilar filgrastim, has the potential to improve sustainability of healthcare in oncology, which is particularly important as the incidence of cancer increases worldwide.

Future perspective

The values of drugs are not fixed: value evolves over time as new evidence for risks and benefits emerge and the price of a drug changes. The G-CSF filgrastim was first approved in 1991 and was rejected by all initial health technology assessments as both poor clinical and economic value. Since 2015, filgrastim has been included in the WHO Model List of Essential Medicines: a list of minimum medicine needs for a basic healthcare system [5].

Value is a measure of cost and effect. Changes to either parameter should prompt a reappraisal of the value of a medicine, and hence, its reimbursement status. Filgrastim is a drug where both parameters have changed significantly over the last three decades. Cost changes, driven by biosimilar approval, clearly influenced decisions of the value of filgrastim – evidenced by the significant increase in access to the drug in all European markets – with increases up to fivefold recorded. Effect changes were driven by the realization that the effect of filgrastim influenced long-term cancer cures and not just short-term outcomes, such as hospitalization for neutropenic fever. This is evidenced by the first inclusion of filgrastim in the WHO Essential Drug List for cancer, more than 20 year after its original approval in 1991.

Health technology assessments are not static documents. The appreciation of clinical benefits evolves over time with incremental research. Cost changes are driven by near universal price rises over the period of patent protection followed by reductions due to competition on patent expiry. The high acquisition cost of biologic medicines means that biosimilar versions have the potential to transform healthcare by delivering similar outcomes at a reduced price, offering two major opportunities to increase the number of patients treated and to save money from current drug budgets to reinvest into innovative treatment programmes, providing sustainability in healthcare.

Executive summary

Background

- The G-CSF filgrastim was first approved in 1991 and its value has been evolving ever since.

Economic evaluation of filgrastim

- Some early economic evaluations suggested low value of filgrastim due to high drug cost and no evidence for significant gain in overall survival (OS).
- The first UK National Institute for Health and Care Excellence (NICE) evidence with data to suggest any clinically and statistically significant survival benefit was published in 2013, more than 20 year after the first approval of filgrastim in 1991.
- It is this long delay that probably explains why G-CSF was not included in the WHO Model List of Essential Medicines until 2015; 24 years after its first approval [5].

Biosimilars

- Biosimilars are defined by the WHO as “a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product” [52].
- The expiry of patents for biological drugs presents opportunities for the development of biosimilars with the rationale of cost savings and consequent improved access to biological medicines [49,53,55].

Biosimilar filgrastim

- Following approval of the first biosimilar G-CSF in 2008, several biosimilar G-CSF products are now available.
- Cost estimates from 17 European countries suggested that total savings from switching from the reference to the biosimilar were €85 million across the region [35,67].

Summary

- Evidence from different European countries shows the cost savings and increased access to treatment permitted by use of biosimilar filgrastim.
- This explains the first inclusion of filgrastim in the WHO Essential Drug List for cancer more than 20 year after its original approval in 1991 [5].
- This demonstrates the power of biosimilar medicines in transforming healthcare.

Author contributions

P Cornes and A Krendyukov conceived and designed this review, developed the search strategy, completed the searches, reviewed the included studies, prepared the manuscript, edited the manuscript and read and approved the final version prior to submission.

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A Krendyukov is a former employee of Hexal AG. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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