Expanded access to cancer treatments from conversion to neutropenia prophylaxis with biosimilar filgrastim-sndz

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Aim: Biosimilar medicines offer significant cost-savings potential over their reference products, which can be re-allocated to provide access to other cancer treatments on a budget-neutral basis. **Methods:** Simulation study using cost data for the USA under consideration of several prophylaxis patterns. **Results:** Potential savings from conversion from reference filgrastim to biosimilar filgrastim-sndz are significant. These savings expand budget-neutral access to novel immunotherapies (obinituzumab; pembrolizumab) or supportive care (filgrastim-sndz). **Conclusion:** The combination of biosimilar savings and expanded access increases the value of cancer care as the same supportive care is provided at lower cost, additional cancer care is enabled at no additional cost, and more patients will have access to cancer care.

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Cancer patients undergoing myelosuppressive chemotherapy are at significant risk for developing severe and often febrile neutropenia [1]. Recombinant G-CSF are biological growth factors that stimulate the production of neutrophils in the bone marrow and are indicated in the prophylaxis of chemotherapy-induced (febrile) neutropenia (CIN/FN) [2]. For instance, the NCCN [3] and EORTC [4] best practice guidelines recommend that prophylaxis be initiated in patients undergoing chemotherapy with regimens having an FN risk >20% or with FN risk between 10 and 20% in the presence of risk factors. The G-CSF filgrastim (Neupogen®, Amgen, CA, USA) is administered as a daily injection for a maximum of 14 days, while its pegylated form (Neulasta®, Amgen) requires only a single injection. Neulasta Onpro®, an on-body injector which is applied on the day of chemotherapy to administer pegfilgrastim approximately 27 h later, was introduced recently. Following the patent expiration for reference filgrastim, biosimilar filgrastim-sndz was approved in Europe in 2009 (where it is marketed as Zarzio®) and in the USA in 2015 (where it is marketed as Zarxio®).

We recently completed a comparative cost-minimization study for the US formulations of reference filgrastim, pegfilgrastim and filgrastim-sndz for prophylaxis periods ranging in duration from 1 (1d) to 14 days (14d) [5]. Relevant to the simulation study reported here, when considering only the cost of medicines, savings from conversion from reference filgrastim to filgrastim-sndz

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ranged from USD\$65 (1d) to USD\$916 (14d) and savings from conversion from pegfilgrastim ranged from USD\$834 (14d) to USD\$3666 (1d; note the inverse direction of the savings due to single injections of pegfilgrastim vs daily filgrastim injections). Under no condition was filgrastim-sndz prophylaxis more expensive than the reference products.

From a payer perspective, extrapolating the savings from treating one patient with biosimilar growth factor to, at the population level, panels of patients translates into significant potential aggregate savings. As we showed initially for biosimilar epoetin α , an erythropoiesis-stimulating agent, for the EU G5 countries (Germany, France, UK, Italy, Spain), these potential savings from supportive cancer care can create significant expanded access to more expensive primary cancer treatments with expensive monoclonal antibody agents [6]; an analysis we also replicated for biosimilar filgrastim [7].

With filgrastim-sndz now commercially available in the USA, we sought to replicate and extend the GCSF simulation study with a cost-of-medicines-based analysis for the USA from the payer perspective. The European simulation focused on how conversion from reference filgrastim and pegfilgrastim to the biosimilar filgrastim marketed by Sandoz Inc. (Sandoz, Holzkirchen, Germany) can create, on a budget-neutral basis, expanded access to rituximab and trastuzumab. As biosimilar versions of these agents have become or soon will be available, we instead focused our simulation study for the USA on the expanded access enabled by converting a hypothetical panel of 20,000 cancer patients receiving GCSF support with either reference filgrastim or pegfilgrastim to prophylaxis with filgrastim-sndz to two novel expensive immunotherapy agents: obinutuzumab (Gazyva®, Roche, Basel, Switzerland) in combination with bendamustine for patients with relapsing/refractory follicular lymphoma, and pembrolizumab (Keytruda®, Merck, NJ, USA) as a single agent for patients with metastatic non-small-cell lung cancer (NSCLC). We also performed simulation analyses for expanded access to filgrastim-sndz. In addition to cost and volume analyses of potential savings translating into expanded access, we also estimated the number of patients receiving prophylaxis with reference filgrastim or, alternately, with pegfilgrastim who need to be converted to filgrastim-sndz (number-needed-to-convert) [7] to treat one additional patient with

these agents. One ethical assumption underlying the analyses reported here is that cost-savings from using biosimilars should be re-allocated on a budget-neutral basis to provide more patients with access to either therapeutic or supportive cancer care. Another ethical assumption is that the tandem of biosimilar savings and expanded access increases the value of cancer care as the same supportive care is provided at lower cost and additional therapeutic care is enabled at no additional cost.

Methods

• Assumptions

In line with our prior economic analyses of biosimilar filgrastim [5,7–8], the following assumptions applied. Considering the evidence from the pivotal pegfilgrastim versus (reference) standard filgrastim noninferiority trials [9,10], prophylaxis with standard and pegylated filgrastim were considered to be similar to each other in efficacy. By triangulation, as filgrastim-sndz and reference filgrastim have been shown to be similar in efficacy, we assumed pegfilgrastim and filgrastim-sndz to be noninferior to each other as well [11–13]. Analogously, the safety profile of filgrastim-sndz was assumed to be the same as that of reference filgrastim [14]. As reference filgrastim and pegfilgrastim are similar in safety [9,10], we assumed filgrastim-sndz and pegfilgrastim to be similar in safety as well. Hence, we did not adjust our cost estimates for differential efficacy or safety. No adjustments were made for discounting of products in the procurement process. Prophylaxis was assumed to be initiated in the 24–72 h time window following the completion of chemotherapy. The Neulasta Onpro on-body injector was not considered separately as its price is identical to single-injection pegfilgrastim.

• Model

We developed a model to determine how the potential savings accrued within a hypothetical panel of 20,000 patients converted from febrile neutropenia prophylaxis with either reference filgrastim or pegfilgrastim to filgrastim-sndz can be used to purchase, on a budget-neutral basis, additional supportive and therapeutic cancer care and thus expand patient access to such treatments. We assumed a hypothetical panel of 20,000 cancer patients receiving one cycle of a myelotoxic chemotherapy that puts them at risk for (febrile) neutropenia and therefore necessitates prophylaxis. We expressed this prophylaxis need in terms of the number of daily injections

with standard filgrastim that a clinician might prescribe (denoted here as X , as the number may vary across scenarios). We used fixed numbers of days of filgrastim support (i.e., X of 5, 7, 11 and 14 daily injections) in our base-case analyses and complemented this with duration averages (X of 4.3, 5.4, 6.1 and 6.5 days) reported in the literature in subsequent sensitivity analyses [15,16]. This resulted in a total of eight prophylaxis durations. Reconciling the respective costs of X administrations of reference filgrastim or one treatment with pegfilgrastim relative to the corresponding cost of X filgrastim-sndz administrations, we took the conversion-related potential cost-savings accrued from the conversion from X reference filgrastim to X filgrastim-sndz injections, and from the conversion from one treatment with pegfilgrastim to X injections with filgrastim-sndz [5], for a total of 16 potential cost-savings calculations.

This provided the basis for subsequent calculations to determine how much additional supportive cancer care with biosimilar filgrastim-sndz could be purchased for patients at risk for (febrile) neutropenia; and how many additional therapeutic treatments with obinutuzumab could be procured for relapsing/refractory follicular lymphoma or with pembrolizumab for metastatic NSCLC. With 16 potential cost-savings estimates (see above), one supportive and two therapeutic treatments, a total of 48 expanded estimates were calculated.

Note that this was a simulation study. Therefore, all estimated savings are potential, not actual, savings.

• Expanded access treatments

We specified the expanded access treatments to be purchased from accrued biosimilar conversions as follows. For supportive care with filgrastim-sndz, we considered six cycles of prophylaxis with five biosimilar filgrastim injections each (30 total), the latter being the median number of injections recorded in the European MONITOR-GCSF study, the first large postapproval study of the Sandoz biosimilar filgrastim (marketed commercially in Europe as Zarzio) [17–20]. For obinutuzumab in patients with relapsing/refractory follicular lymphoma, we used the longest possible treatment regimen specified in the US label [21]: three administrations in cycle 1, one administration in cycles 2–6, followed by one administration every 2 months for 2 years. Likewise,

for pembrolizumab in patients with metastatic NSCLC, we used the longest label-specified regimen of one administration every 3 weeks for 2 years [22].

• Cost inputs

The method used for estimating the direct medication cost of febrile neutropenia prophylaxis with reference filgrastim, pegfilgrastim and filgrastim-sndz is described in detail in our prior paper [5]. Summarized, the cost estimate of interest is the direct cost, based on the average selling price (ASP) in US dollars (USD\$) for 3Q2016 (Table 1), that a payer or buyer would incur to cover or purchase prophylaxis with any of these agents in one patient during one cycle of chemotherapy. The ASPs for 3Q2016 were derived from the CMS 1Q2017 payment limits [23] using the Centers for Medicare and Medicaid Services' (CMS) methodology [24]. Thus, for reference filgrastim and pegfilgrastim the 3Q2016 ASP equals the CMS 1Q2017 payment limit minus 6%; whereas for filgrastim-sndz, being a biosimilar, the ASP equals the payment limit for the biosimilar minus the 6% of the ASP of the reference product [23,24]. The costs of preparation and administration were excluded, as were any indirect costs.

We estimated the costs of prophylaxis with filgrastim 300 µg and filgrastim-sndz 300 µg when used from 1 to 14 days by multiplying the ASP-based cost of each of these agents by the number of days across 14 days. Being single-administration, the cost of pegfilgrastim was fixed. We did not consider the Neulasta Onpro on-body injector, as its ASP is the same as that of pegfilgrastim. Filgrastim is also available in 480 µg, however the 300 µg dose has been the unit of reference in several economic evaluations of GCSF prophylaxis [5,8,25]. The medication costs for the expanded access treatments with filgrastim-sndz, obinutuzumab and pembrolizumab were determined by multiplying the required number of doses with the number of administrations (Table 1).

• Number-needed-to-convert

The number-needed-to-convert (NNC) refers to the number of patients that need to be converted onto filgrastim-sndz prophylaxis to purchase supportive cancer care with filgrastim-sndz or therapeutic cancer care with obinutuzumab or pembrolizumab. For a given scenario, the NNC is calculated by dividing the cost of providing

Table 1. Treatment costs (average selling price 3Q2016).

Dose costs			
Supportive care	Dose	Cost (USD\$)/dose	Savings from filgrastim-sndz (USD\$)
Filgrastim-sndz	300 mcg	217.90	
Reference filgrastim	300 mcg	283.30	65.40
Pegfilgrastim	6 mg	3,884.18	3,666.28
Therapeutic care			
Obinutuzumab	1000 mg	5,417.45	
Pembrolizumab	200 mg	8,781.32	
Treatment costs			
Supportive care	Dose	Cost (USD\$)/dose	Total treatment cost (USD\$)
Filgrastim-sndz	300 mcg	217.90	6,537.00
Therapeutic care			
Obinutuzumab	1000 mg	5,417.45	108,349.00
Pembrolizumab	200 mg	8,781.32	307,346.20

Pegfilgrastim also covers Neulasta Onpro® as the costs are identical.
Treatment regimens:
Filgrastim-sndz: six cycles of prophylaxis with five injections each (30 injections).
Obinutuzumab: three administrations in cycle 1, one administration in cycles 2-6, followed by one administration every 2 months for 2 years.
Pembrolizumab: one administration every 3 weeks for 2 years.

one patient with expanded access to a given treatment (filgrastim-sndz, obinutuzumab or pembrolizumab) by the potential savings achieved from biosimilar conversion under that scenario [7].

Results

• Potential savings from biosimilar conversion per 20,000 patients

As shown in Table 2, in the base-case analyses, the cumulative potential savings of converting a panel of 20,000 patients from prophylaxis with reference filgrastim to filgrastim-sndz rose from USD\$6,450,000 if all these patients were treated for 5 days to USD\$18,312,000 if the prophylaxis duration extended to 14 days, based on potential per-patient conversion savings of USD\$327.00 for 5 days to USD\$915.60 for 14 days of prophylaxis. The potential savings benefit of converting patients from single-injection pegfilgrastim to filgrastim-sndz declines as the number of days of prophylaxis increases as more filgrastim-sndz injections are needed. Base-case analyses yielded estimated potential cumulative savings of converting 20,000 patients of USD\$55,893,600 when the prophylaxis duration is 5 days, declining to USD\$16,671,600 if the duration is 14 days. In the sensitivity analyses of likely clinical scenarios, potential cumulative savings across 20,000 patients converted from reference filgrastim ranged between USD\$5,624,400 (4.3 days) and USD\$8,502,000

(6.5 days). Potential cumulative savings across 20,000 patients converted from pegfilgrastim ranged between USD\$58,944,200 (4.3 days) and USD\$49,356,600 (6.5 days).

• Expanded access afforded by biosimilar conversion

Therapeutic care with obinutuzumab
Expanded access

An additional 60 patients with relapsing/refractory follicular lymphoma could be treated with obinutuzumab under the 5 day reference filgrastim to filgrastim-sndz scenario, increasing to an additional 169 patients under the 14-day prophylaxis scenario (Table 3). Under pegfilgrastim to filgrastim-sndz conversion, an incremental 516 patients could be treated with obinutuzumab if the duration of prophylaxis is 5 days declining to 154 if 14 days of prophylaxis is indicated. In the sensitivity analyses of likely clinical scenarios, the expanded access yield from reference filgrastim to filgrastim-sndz conversion was between 52 (4.3 days) and 78 (6.5 days) additional patients; and the yield from pegfilgrastim to filgrastim-sndz conversion between 544 and 456 patients.

Numbers-needed-to-convert

Base-case analyses under the reference filgrastim to filgrastim-sndz scenarios yielded an NNC of 331 patients to provide one additional patient with obinutuzumab treatment under the 5-day

Table 2. Savings in USD\$ from conversion to filgrastim-sndz in a panel of 20,000 converted patients.

Base-case analysis					
Days of prophylaxis		5	7	11	14
– Per patient	Reference filgrastim to filgrastim-sndz	327.00	457.80	719.40	915.60
	Pegfilgrastim to filgrastim-sndz	2,794.68	2,358.88	1,487.28	833.58
– Per 20,000 patients	Reference filgrastim to filgrastim-sndz	6,540,000	9,156,000	14,388,000	18,312,000
	Pegfilgrastim to filgrastim-sndz	55,893,600	47,177,600	29,745,600	16,671,600
Sensitivity analysis					
Days of prophylaxis		4.3	5.4	6.1	6.5
– Per patient	Reference filgrastim to filgrastim-sndz	281.22	353.16	398.94	425.10
	Pegfilgrastim to filgrastim-sndz	2,947.21	2,707.52	2,554.99	2,467.83
– Per 20,000 patients	Reference filgrastim to filgrastim-sndz	5,624,400	7,063,200	7,978,800	8,502,000
	Pegfilgrastim to filgrastim-sndz	58,944,200	54,150,400	51,099,800	49,356,600

scenario, declining to 118 if 14 days of prophylaxis is needed (Table 4). In the sensitivity analyses, the NNC declined from 385 (4.3 days) to 255 (6.5 days) patients. Under the pegfilgrastim to filgrastim-sndz conversion scenarios, the NNC was 39 patients for one additional patient to be treated with obinutuzumab under the 5-day scenario increasing to 130 patients under the 14-day scenario. In the sensitivity analyses, the NNC was 37 patients under 4.3 days and 44 patients under 6.5 days of prophylaxis.

Therapeutic care with pembrolizumab Expanded access

An incremental 21 patients with metastatic NSCLC could be treated with pembrolizumab under the 5-day reference filgrastim to filgrastim-sndz scenario, increasing to an additional 60 patients under the 14-day prophylaxis scenario (Table 3). Under pegfilgrastim to filgrastim-sndz conversion, an additional 182 patients could be treated with pembrolizumab if the duration of prophylaxis is 5 days declining to 54 if 14 days of prophylaxis is required. In the sensitivity analyses of likely clinical scenarios, the expanded access yield from reference filgrastim to filgrastim-sndz conversion was between 18 (4.3 days) and 28 (6.5 days) additional patients; and the yield from pegfilgrastim to filgrastim-sndz conversion between 192 and 161 patients.

Numbers-needed-to-convert

Under the reference filgrastim to filgrastim-sndz scenarios, base-case analyses generated an NNC of 940 patients to provide one additional patient with pembrolizumab treatment under the 5-day scenario, decreasing to 336 under 14 days of prophylaxis (Table 4). In the sensitivity analyses,

the NNC declined from 1093 (4.3 days) to 723 (6.5 days) patients. Under the pegfilgrastim to filgrastim-sndz conversion scenarios, the NNC was 110 patients for one additional patient to be treated with pembrolizumab under the 5-day scenario increasing to 369 under the 14-day scenario. In the sensitivity analyses, the NNC was 104 patients under 4.3 days and 125 patients under 6.5 days of prophylaxis.

Supportive care with filgrastim-sndz Expanded access

In line with the increase in potential savings as the duration of prophylaxis with standard filgrastim in one cycle extends, an additional 1000 patients could receive 5 days of prophylaxis with filgrastim-sndz over six chemotherapy cycles under the 5-day reference filgrastim to filgrastim-sndz scenario, rising to an additional 2801 patients under the corresponding 14-day scenario (Table 5). Conversely, with the decline in potential savings from pegfilgrastim to filgrastim-sndz conversion as the duration of prophylaxis increases, an incremental 8550 patients could be treated for a 6-cycle line of chemotherapy if the prophylaxis duration is 5 days, compared with 2550 if 14 days of prophylaxis is needed. In the sensitivity analyses of likely clinical scenarios, the expanded access yield from reference filgrastim to filgrastim-sndz conversion was between 860 (4.3 days) and 1301 (6.5 days) additional patients; and the yield from pegfilgrastim to filgrastim-sndz conversion between 9017 and 7550 patients.

Numbers-needed-to-convert

Base-case analyses under the reference filgrastim to filgrastim-sndz conversion scenarios yielded an NNC of 20 patients to provide one

Table 3. Expanded access to therapeutic cancer care (obinutuzumab; pembrolizumab) achieved from converting 20,000 patients to filgrastim-sndz.					
Reference filgrastim to filgrastim-sndz					
Base-case analysis					
Days of prophylaxis in one converted cycle		5	7	11	14
Patients with expanded access to:	Obinutuzumab	60	85	133	169
	Pembrolizumab	21	30	47	60
Sensitivity analysis					
Days of prophylaxis in one converted cycle		4.3	5.4	6.1	6.5
Patients with expanded access to:	Obinutuzumab	52	65	74	78
	Pembrolizumab	18	23	26	28
Pegfilgrastim to filgrastim-sndz					
Base-case analysis					
Days of prophylaxis in one converted cycle		5	7	11	14
Patients with expanded access to:	Obinutuzumab	516	435	275	154
	Pembrolizumab	182	153	97	54
Sensitivity analysis					
Days of prophylaxis in one converted cycle		4.3	5.4	6.1	6.5
Patients with expanded access to:	Obinutuzumab	544	500	472	456
	Pembrolizumab	192	176	166	161
Expanded access to treatment regimens: Obinutuzumab: three administrations in cycle 1, one administration in cycles 2–6, followed by one administration every 2 months for 2 years. Pembrolizumab: one administration every 3 weeks for 2 years.					

additional patient with supportive care with filgrastim-sndz (30 injections over six cycles of chemotherapy) under the 5-day scenario, declining to seven patients if 14 days of prophylaxis is needed (Table 4). In the sensitivity analyses of likely clinical scenarios, the NNC declined from 23 (4.3 days) to 15 (6.5 days) patients. Under the pegfilgrastim to filgrastim-sndz conversion scenarios, the NNC was two patients for one additional patient to receive supportive care with filgrastim-sndz under the 5-day scenario increasing to eight patients under the 14-day scenario. In the sensitivity analyses, the NNC was two patients under 4.3 days and three patients under 6.5 days of prophylaxis.

Discussion

This simulation study for a hypothetical panel of 20,000 cancer patients receiving myelotoxic chemotherapy showed how the potential savings from converting patients receiving CIN/FN prophylaxis with either standard daily (reference filgrastim) or single-administration pegylated filgrastim (pegfilgrastim) to prophylaxis with the biosimilar filgrastim-sndz, now available in the USA, may not only yield significant savings but, importantly, how these savings can be applied to procure additional therapeutic or supportive cancer care on a budget-neutral

basis. Specifically, we showed how savings potentially ranging from (rounded) USD\$7 million to USD\$56 million in base-case analyses with fixed prophylaxis durations, and ranging from (rounded) USD\$6 million to USD\$59 million in sensitivity analyses based on likely clinical regimens could provide significant expanded access to recently introduced immunotherapy regimens. Between 52 and 544 patients with relapsing/refractory follicular lymphoma could be treated budget-neutrally with obinutuzumab and between 18 and 192 patients with metastatic NSCLC with pembrolizumab. Similarly, these potential savings could provide significant expanded access to supportive care with filgrastim-sndz to between 860 and 9017 patients with 5 days of filgrastim-sndz prophylaxis in each of the cycles of a 6-cycle chemotherapy regimen. Conversely, we also calculated the number of patients that would need to be converted (NNC) to filgrastim-sndz to provide one patient with therapeutic or supportive cancer care budget-neutrally under the 16 scenarios analyzed for each expanded access agent. Treating one additional patient with obinutuzumab is possible from converting as few as 37 patients from pegfilgrastim and as few as 118 from reference filgrastim to filgrastim-sndz. Providing one

Table 4. Number of patients needed to convert to filgrastim-sndz to purchase one therapeutic or supportive cancer treatment.

Reference filgrastim to filgrastim-sndz					
Base-case analysis					
Days of prophylaxis in one converted cycle		5	7	11	14
Number needed to convert for treatment with:	Obinutuzumab	331	237	151	118
	Pembrolizumab	940	671	427	336
	Filgrastim-sndz	20	14	9	7
Sensitivity analysis					
Days of prophylaxis in one converted cycle		4.3	5.4	6.1	6.5
Number needed to convert for treatment with:	Obinutuzumab	385	307	272	255
	Pembrolizumab	1093	870	770	723
	Filgrastim-sndz	23	19	16	15
Pegfilgrastim to filgrastim-sndz					
Base-case analysis					
Days of prophylaxis in one converted cycle		5	7	11	14
Number needed to convert for treatment with:	Obinutuzumab	39	46	73	130
	Pembrolizumab	110	130	207	369
	Filgrastim-sndz	2	3	4	8
Sensitivity analysis					
Days of prophylaxis in one converted cycle		4.3	5.4	6.1	6.5
Number needed to convert for treatment with:	Obinutuzumab	37	40	42	44
	Pembrolizumab	104	114	120	125
	Filgrastim-sndz	2	2	3	3
Expanded access to treatment regimens:					
Filgrastim-sndz: six cycles of prophylaxis with five injections each (30 injections).					
Obinutuzumab: three administrations in cycle 1, one administration in cycles 2–6, followed by one administration every 2 months for 2 years.					
Pembrolizumab: one administration every 3 weeks for 2 years.					

additional patient with access to pembrolizumab requires as few as 104 patients to be converted to filgrastim-sndz from pegfilgrastim and as few as 336 from reference filgrastim. Providing one additional patient with filgrastim-sndz support during a 6-cycle course of chemotherapy, could be achieved with as few as 2 out of 20,000 patients converted from pegfilgrastim and only seven patients converted from reference filgrastim to filgrastim-sndz. The incremental number of patients who can be provided with expanded access to therapeutic or supportive cancer provides the result of conversion to biosimilars. The NNC metric, as originally proposed by Sun *et al.* [7], provides a measure of efficiency to achieve a given result.

It is not surprising that the greatest efficiencies and the highest expanded access rates are achieved with converting patients from pegfilgrastim to filgrastim-sndz, as pegfilgrastim is the more expensive agent. This is important because of the anecdotal evidence of US payers declining prophylaxis with pegfilgrastim and instead authorizing up to 7 days of prophylaxis with daily filgrastim. At the ASP costs in our simulation, the potential savings generated

by 7 days of filgrastim-sndz instead of single-administration pegfilgrastim for 20,000 patients in, notably, only one cycle of chemotherapy totals USD\$47,177,600. These savings would provide an additional 7217 patients with CIN/FN prophylaxis over a six-cycle course of chemotherapy, an additional 435 patients with treatment with obinutuzumab, or an additional 153 patients with access to pembrolizumab, and this on a budget-neutral basis without any further cash demand. It is not unlikely that, in the future, payers will negotiate panel-level access targets to increasingly expensive cancer treatments based on drug cost-efficiencies achieved in other areas of cancer care.

In our simulation, we used fixed durations of filgrastim prophylaxis (5, 7, 11 and 14 days) in the base-case analyses and variable durations obtained from the literature in the sensitivity analyses. Weycker *et al.* [15] reported mean durations of filgrastim prophylaxis of 4.3 days for lung cancer patients, 6.1 days for breast cancer patients and 6.5 days for non-Hodgkins lymphoma patients. In the MONITOR-GCSF [19] study, patients initiated within the recommended 24–72 h postchemotherapy window

Table 5. Expanded access to supportive cancer care with biosimilar filgrastim-sndz achieved from converting 20,000 patients to filgrastim-sndz.

Reference filgrastim to filgrastim-sndz				
Base-case analysis				
Days of prophylaxis in one converted cycle	5	7	11	14
Patients with expanded access to filgrastim-sndz	1000	1401	2201	2801
Sensitivity analysis				
Days of prophylaxis in one converted cycle	4.3	5.4	6.1	6.5
Patients with expanded access to filgrastim-sndz	860	1080	1221	1301
Pegfilgrastim to filgrastim-sndz				
Base-case analysis				
Days of prophylaxis in one converted cycle	5	7	11	14
Patients with expanded access to filgrastim-sndz	8550	7217	4550	2550
Sensitivity analysis				
Days of prophylaxis in one converted cycle	4.3	5.4	6.1	6.5
Patients with expanded access to filgrastim-sndz	9017	8284	7817	7550
Expanded access to treatment regimen: filgrastim-sndz: six cycles of prophylaxis with five injections each (30 injections).				

received on average 5.4 days of prophylaxis, with a median of 5 days. In a parallel French study, the average number of days of prophylaxis was between 4.5 and 4.7 days depending on the cycle, also with cycle medians of 5 days [26]. Though, arguably, the approved label should serve as standard, almost two decades of clinical experience with filgrastim has indeed revealed clinical patterns of shorter durations of filgrastim prophylaxis – in addition to a trend away from normative, guideline-specified treatment patterns.

Our findings specific to GCSFs may contribute to the broader cost, value and policy debates in cancer care. It is evident that biosimilars offer a significant cost alternative to the reference products. As the biosimilar market is beginning to transition from supportive to therapeutic cancer care and several biosimilar versions of monoclonal antibody agents are on the horizon, biosimilar conversion will afford savings that, based on market dynamics, may range from modest to significant. This reduces the overall cost of common biological treatments but, importantly, as our simulation shows enables the purchase of additional novel but expensive treatments for more patients on a budget-neutral basis. Further, the combination of biosimilar treatment and expanded access affects two aspects of the value equation. The first is the cost-to-outcome ratio; that is, the health outcomes achieved per dollar spent or conversely, how much it costs to achieve 1 unit of outcome, such as a CIN/FN episode or a CIN/FN-related hospitalization averted [27,28].

The second is the cost-to-access ratio, or how much it costs to provide one patient with access to therapeutic cancer treatment. Additionally, clinicians are increasingly sensitive about and responsive to cost considerations in cancer. They may have had patients who could not afford or were denied coverage for cancer treatment, or they may have concerns about the benefits achieved relative to the cost of treatment. Thus, clinicians may see in biosimilars a cost-responsible alternative and this may increase their adoption of biosimilars – especially as past apprehensions about biosimilars may no longer apply [29].

Our study has limitations. It is a simulation based on assumptions and needs to be validated with actual treatment cost and conversion data. Our model considered only one cycle of chemotherapy cycle of GCSF support, independent of time, and was not structured to simulate financial streams over a full year or over several years. The emphasis being on the cost of medications and potential savings from biosimilar conversion, it did not consider the cost of administration, though this is known to be minimal [4]. As it is a follow-on simulation to a biosimilar conversion cost-efficiency study, the primary focus was on the budget impact and therefore did not consider any clinical or patient-related indirect costs. Our simulation was limited to one biosimilar filgrastim as filgrastim-sndz is the only US-approved GCSF, even though another GCSF, tbo-filgrastim (Teva), is approved in Europe as a biosimilar but in the USA as biological.

Conclusion

Biosimilars may generate sizeable cost-savings at a time of significant advances in cancer treatments and the introduction of expensive novel treatment options. This simulation study demonstrated how the significant potential cost-savings from converting to biosimilar filgrastim-sndz can be reallocated on a budget-neutral basis to increase the access to both therapeutic and supportive cancer care, especially if the conversion is from pegfilgrastim to filgrastim-sndz. In a panel of 20,000 patients, converting (febrile) neutropenia prophylaxis in one chemotherapy cycle from pegfilgrastim to filgrastim-sndz can provide up to an additional 192 patients with NSCLC with a full regimen of pembrolizumab, up to an additional 544 patients with relapsing/refractory follicular lymphoma with a complete regimen of obinutuzumab, or up to an additional 9017 patients with (febrile) neutropenia prophylaxis with filgrastim-sndz. It

would require converting as few as 104 patients from pegfilgrastim to filgrastim-sndz to provide one additional patient with access to pembrolizumab, as few as 37 patients to treat one additional patient with obinutuzumab, as few as two patients to provide one patient with five injections of filgrastim-sndz over six cycles of chemotherapy. The combination of biosimilar savings and expanded access increases the value of cancer care as the same supportive care is provided at lower cost, additional therapeutic care is enabled at no additional cost and more patients will have access to cancer care.

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SUMMARY POINTS

- Advances in our understandings of the biology of cancer and the ensuing innovation of targeted and precise pharmacological treatments have led to a marked increase in the cost of cancer treatments.
- Beginning with growth factors, biological therapeutic and supportive cancer treatments at the vanguard of innovation two decades ago are losing patent protection and biosimilar versions are being approved.
- Biosimilars offer significant cost advantages over reference products. Payers might be inclined to view savings accrued from treating patients with biosimilars as such. We have proposed to use these savings to expand access to expensive novel cancer treatments on a budget-neutral basis. We have previously demonstrated this in a simulation study for the EU G5 countries.
- With filgrastim-sndz being the first biosimilar agent approved in the USA for the prophylaxis of chemotherapy-induced (febrile) neutropenia, we replicated and extended our European simulation for the US market. We used obinutuzumab in the setting of relapsing/refractory follicular lymphoma and pembrolizumab in the setting of metastatic non-small-cell lung cancer as examples of therapeutic cancer care, and filgrastim-sndz as example of supportive cancer care. We used four fixed prophylaxis durations in the base-case analyses, and supplemented this with sensitivity analyses based on four literature-reported real-world prophylaxis durations in common solid and hematological tumor settings.
- In addition to calculating the number of patients who would benefit from such budget-neutral expanded access, we also calculated the number of patients needed to be converted onto biosimilar granulocyte-colony stimulating factors support to enable treatment for one additional patient.
- Our findings contribute to the broader cost, value and policy debates in cancer care – certainly in the USA but also in other major markets.
- The combination of biosimilar conversion and expanded access affects the cost-to-outcome ratio in the value of cancer care: the health outcomes per monetary unit spent or, conversely, how much it costs to achieve one unit of outcome (e.g., chemotherapy-induced [febrile] neutropenia episode and hospitalization averted; life year gained; ...).
- This combination also impacts the cost-to-access ratio, or how much it costs to provide one patient with access to therapeutic cancer treatment – either nominally at the patient level or as part of a pool at the population level.

Author contributions

Study concept: I Abraham, S Balu, K Campbell, K MacDonald, M Bikkina; *study design:* I Abraham, S Balu, K Campbell, K MacDonald, A McBride, M Bikkina; *model development and simulations:* I Abraham, K MacDonald; *review and interpretation of results:* I Abraham, S Balu, K Campbell, K MacDonald, A McBride, M Bikkina; *development of manuscript:* I Abraham, K MacDonald, A McBride; *review of the manuscript for intellectual content:* S Balu, K Campbell, M Bikkina.

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simulations. By company policy, Matrix45 employees are prohibited from owning equity in client organizations (except through mutual funds or other independently administered collective investment instruments) or contracting independently with client organizations. Matrix45 provides similar services to those described in this article to other biopharmaceutical companies on a nonexclusivity basis. 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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