SHORT COMMUNICATION

Patient Characteristics and Utilization Patterns of Short-Acting Recombinant Granulocyte Colony-Stimulating Factor (G-CSF) Biosimilars Compared to Their Reference Product

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Abstract

Background Data on short-acting recombinant granulocyte colony-stimulating factor (G-CSF) biosimilar utilization from claims data in the USA are limited.

Objective To evaluate patient baseline characteristics and utilization patterns for short-acting G-CSF products with particular focus on the assessment of filgrastim biosimilar usage relative to the originator product.

Patients and methods We examined filgrastim, filgrastim-sndz, and tbo-filgrastim use among adult patients between January 2012 and March 2019 across the five health-plan research partners in the BBCIC Distributed Research Network. The publicly available Sentinel System analytic toolkit was used to perform the distributed analyses.

Results We evaluated over 38 million eligible health-plan members representing more than 88 million person-years of data. We identified 45,204 incident treatment episodes, including 33,118 episodes with filgrastim, 6525 episodes with filgrastim-sndz, and 5,561 episodes with tbo-filgrastim. We observed that the demographic and clinical characteristics of users were comparable across products. While total use of all filgrastim products remained consistent, the proportion of incident episodes of the originator filgrastim steadily decreased since 2014, with filgrastim-sndz and tbo-filgrastim making up the difference. Utilization for the G-CSF biosimilar, filgrastim-sndz, increased from 40 (1%) of 6823 total filgrastim product episodes in 2015, to 2486 (44%) of a total 5668 episodes of filgrastim products in 2018 (partial data for 2018).

Conclusion New episodes of short-acting biosimilar filgrastim products have increased over time while the overall number of new users remained flat. Although barriers to biosimilar use in oncology have been noted, uptake has begun and continues to grow.

Key Points
Filgrastim biosimilar utilization is on the rise and represents a growing share of total short-acting G-CSF use.
Real-world evidence on clinical outcomes for the short-acting G-CSF biosimilar versus the originator product is important as biosimilar use continues to increase in the coming years.

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1 Introduction

Short-acting recombinant granulocyte colony stimulating factors (G-CSFs; filgrastim (Neupogen®), tbo-filgrastim (Granix®)) are used as both prophylaxis and treatment of severe or febrile neutropenia caused by myelosuppressive chemotherapy [1–4]. In 2015, the US Food and Drug Administration (FDA) approved the first filgrastim biosimilar, filgrastim-sndz (Zarxio®), for prophylaxis and treatment of chemotherapy-induced neutropenia, with a second biosimilar, filgrastim-aafi (Nivestym®) being approved in 2018 [5]. Biosimilars have the potential to reduce treatment costs [6]. The available data on G-CSF biosimilar utilization through the analysis of claims data in the USA have been limited, though studies have suggested increased filgrastim biosimilar uptake over time [7, 8]. Additional data from diverse sources can help quantify variation in biosimilar use.

The Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) is a non-profit, multi-stakeholder, research consortium dedicated to investigating the real-world safety and effectiveness of biologic drugs, including biosimilars, in the USA [9]. The BBCIC Distributed Research Network (DRN) provides administrative claims data for approximately 95 million patient years across five research partners including two large national health insurers (Healthagen (Aetna), HealthCore (Anthem)) and three regional health plans or integrated delivery networks (Harvard Pilgrim Health Care, HealthPartners, Kaiser Permanente of Washington). The BBCIC DRN Research Partners participate in the FDA Sentinel System, enabling the consortium to leverage the Sentinel System's infrastructure, including the Sentinel Common Data Model and curated data resources for data standardization, and analytic tools for conducting distributed analyses [10, 11]. Periodic queries are conducted in the BBCIC DRN to monitor utilization of medications of interest. In this report, we provide a high-level summary of utilization and patient characteristics of short-acting G-CSF users in the BBCIC DRN.

2 Methods

Adult patients receiving any short-acting G-CSF between 1 January 2012 and as recent as 31 March 2019 were identified across the five health-plan Research Partners in the BBCIC DRN. Some Research Partners provided data through part of 2018; this was accounted for in the denominator of our calculations. Medications of interest included filgrastim, filgrastim-sndz, and tbo-filgrastim. We did not include filgrastim-aafi in these analyses as the

product was only recently made available toward the end of the study period. Additionally, given the low utilization of sargramostim (Leukine®) in the USA [12] and that a biosimilar for sargramostim is not available in the USA, we did not include this product in our study.

All patients were required to have medical and pharmacy coverage and be enrolled for a minimum 183 days prior to the first observed short-acting G-CSF utilization date (index date) during the period noted above. An enrollment gap of 45 days was permitted. Incident use was defined as having no exposure to a given medication in the 183 days before the index date. We examined the number of incident use episodes for each medication of interest, overall and according to patient demographic and clinical characteristics (e.g., comorbid conditions). Patients could contribute multiple "incident" episodes for the same or different drugs if they met the eligibility criteria, including the 183-day washout period, each time. Demographic characteristics were measured on the index date, and clinical characteristics were assessed during the 183-day period before the index date ("baseline period"). The publicly available Sentinel System analytic toolkit (Cohort ID and Descriptive Analysis (CIDA v8.1.0)) was used to perform the distributed analyses [13]. Products of interest were identified using J-codes from Healthcare Common Procedure Coding System or National Drug Codes (NDCs). The complete list of codes used in this analysis can be found at https://www.bbcic.org/research/completed-research.

Distributed analyses were conducted by each Research Partner, with results aggregated for final analysis. Cells with counts < 10 are not presented to protect the anonymity of patients, per standard BBCIC practice. Institutional Review Boards for the participating Research Partners determined that this work does not meet the definition of human subjects research.

3 Results

Over 38 million eligible health plan members representing more than 88 million person-years of data were evaluated from the BBCIC DRN. A total of 45,204 incident treatment episodes were identified, including 33,118 episodes with filgrastim, 6525 episodes with filgrastim-sndz, and 5561 episodes with tbo-filgrastim (Table 1). The age distribution was similar across treatments, and females accounted for 58.2% of filgrastim patients, 61.1% of filgrastim-sndz, and 58.5% of tbo-filgrastim patients. The mean combined comorbidity index score [14] was 5.4 (SD = 3.3) for originator filgrastim episodes and 6.0 (SD = 3.5) for filgrastim-sndz. Other clinical characteristics were comparable across the filgrastim products.

Table 1 Patient baseline characteristics for incident use of filgrastim products. The Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) Distributed Research Network, January 2012–March 2019

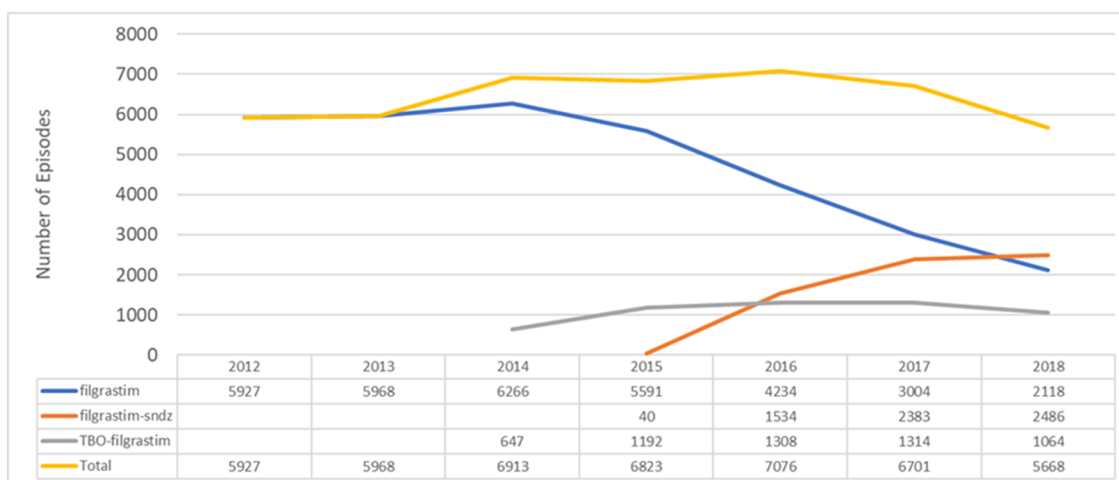| Total number of episodes	$N = 45{,}204$		
	Filgrastim (Neupogen®)	Filgrastim-sndz (Zarxio®)	tbo-Filgrastim (Granix®)
G-CSF exposure episodes			
Patients contributing to cohort[a], n	31,023	6305	5325
GCSF episodes[a], n	33,118	6525	5561
Patient characteristics			
Mean (SD) age, years	59.8 (13.6)	59.8 (13.2)	60.5 (13.1)
Female, %	58.2	61.1	58.5
Age groups[b], n (%)			
18–49 years	6758 (20.4)	1409 (21.6)	1023 (18.4)
50–64 years	14,734 (44.5)	2869 (44.0)	2524 (45.4)
65–79 years	9690 (29.3)	1896 (29.1)	1709 (30.7)
80+ years	1936 (5.8)	351 (5.4)	305 (5.5)
Clinical characteristics by exposure episode[c], n (%)			
Combined Comorbidity Index, mean (SD)	5.4 (3.3)	6.0 (3.5)	6.1 (3.5)
Breast cancer	7038 (21.3)	1669 (25.6)	1153 (20.7)
Lung cancer	4343 (13.1)	692 (10.6)	769 (13.8)
Breast chemotherapy—GCSF prophylaxis	4052 (12.2)	891 (13.7)	740 (13.3)
Lung chemotherapy—GCSF prophylaxis	88 (0.3)	18 (0.3)	26 (0.5)
Breast chemotherapy—GCSF treatment	6608 (20.0)	1374 (21.1)	1168 (21.0)
Lung chemotherapy—GCSF treatment	134 (0.4)	26 (0.4)	33 (0.6)
Other chemotherapy	21,613 (65.3)	4248 (65.1)	3673 (66.0)
Bone/stem cell transplant	339 (1.0)	73 (1.1)	100 (1.8)
Cancer radiation	5845 (17.6)	1115 (17.1)	1051 (18.9)
HIV/AIDS	241 (0.7)	40 (0.6)	36 (0.6)
Neutropenia	11,368 (34.3)	2513 (38.5)	2397 (43.1)
Anaphylaxis	3515 (10.6)	1656 (25.4)	1204 (21.7)
Anemia	17,295 (52.2)	3319 (50.9)	3106 (55.9)
Arthritis	1578 (4.8)	319 (4.9)	290 (5.2)
Bone pain	6642 (20.1)	1401 (21.5)	1179 (21.2)
Capillary leak syndrome	51 (0.2)	< 10 (NC)	< 10 (NC)
Chronic obstructive pulmonary disease	6755 (20.4)	1261 (19.3)	1212 (21.8)
Congestive heart failure	2352 (7.1)	445 (6.8)	456 (8.2)
Glomerulonephritis	145 (0.4)	20 (0.3)	27 (0.5)
Hyperleukocytosis	3223 (9.7)	676 (10.4)	560 (10.1)
Kidney disorder	1594 (4.8)	389 (6.0)	388 (7.0)
Lumpectomy/mastectomy	2510 (7.6)	608 (9.3)	355 (6.4)
Metastatic bone cancer	4572 (13.8)	910 (13.9)	810 (14.6)
Metastatic brain cancer	1288 (3.9)	222 (3.4)	230 (4.1)
Metastatic disease	11,237 (33.9)	2761 (42.3)	2179 (39.2)
Metastatic liver cancer	3987 (12.0)	870 (13.3)	715 (12.9)
Metastatic lung cancer	2818 (8.5)	541 (8.3)	497 (8.9)
Peptic ulcer disease	763 (2.3)	172 (2.6)	164 (2.9)
Poor nutritional status	5530 (16.7)	1351 (20.7)	1095 (19.7)
Any cancer diagnosis (except breast cancer)	23,312 (70.4)	4449 (68.2)	3921 (70.5)
Severe liver impairment	3937 (11.9)	774 (11.9)	745 (13.4)
Splenic rupture	63 (0.2)	15 (0.2)	< 10 (NC)
Thyroid disorder	5994 (18.1)	1250 (19.2)	1061 (19.1)
Antibiotics	19,727 (59.6)	3724 (57.1)	3271 (58.8)
Endocrine drug products	3183 (9.6)	620 (9.5)	534 (9.6)

Table 1 (continued)	Total number of episodes	$N = 45,204$		
		Filgrastim (Neupogen®)	Filgrastim-sndz (Zarxio®)	tbo-Filgrastim (Granix®)
	Anti-osteoporosis medications	715 (2.2)	111 (1.7)	85 (1.5)

AIDS acquired immunodeficiency syndrome, *GCSF* granulocyte colony-stimulating factor, *HIV* human immunodeficiency virus, *NC* not calculated (for considerations of patient privacy counts less than 10 are specified as < 10 and a percentage is unable to be calculated), *SD* standard deviation

[a]Number of episodes is not equal to number of patients due to the relatively short (183-day) lookback period, so the same patient could contribute a second episode if the time between the last exposure and the new dispensing is > 183 days, which would then be considered incident

[b]Number of episodes observed for patients in each age category contributing time to the exposure category

[c]Counts are based on the number of episodes in which a clinical characteristic of interest was observed in any care setting (e.g., inpatient, outpatient) in the 183-day lookback period prior to the episode index date

	2012	2013	2014	2015	2016	2017	2018
filgrastim	5927	5968	6266	5591	4234	3004	2118
filgrastim-sndz				40	1534	2383	2486
TBO-filgrastim			647	1192	1308	1314	1064
Total	5927	5968	6913	6823	7076	6701	5668

[a] Two Research Partners (of five total) had data through the end of 2018.

Fig. 1 Incident granulocyte colony-stimulating factor (filgrastim products) use over time. The Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) Distributed Research Network, January 2012–March 2019

Total use of all filgrastim products remained consistent at about 6,500 incident episodes annually (Fig. 1); however, the proportion of incident episodes of filgrastim steadily decreased since 2014, with filgrastim-sndz and tbo-filgrastim making up the difference. Specifically, in the BBCIC DRN, tbo-filgrastim was available beginning in 2014 and accounted for 647 (9%) of a total 6913 episodes of filgrastim products in that year. Utilization of tbo-filgrastim rose to 1314 (20%) of 6701 total episodes in 2017. Utilization for filgrastim-sndz increased from 40 (1%) of 6823 total filgrastim product episodes in 2015 to 2486 (44%) of a total 5668 episodes of filgrastim products in 2018 (partial data for 2018).

4 Discussion

This systematic, longitudinal surveillance on short-acting G-CSF utilization patterns in the USA showed that new episodes of biosimilar filgrastim products have increased over time. Our study provides data demonstrating that although barriers to biosimilar use in oncology have been noted [15], uptake has begun and continues to grow. As more biosimilar products enter the market, we will be watching closely to evaluate whether or not biosimilar utilization distributes further among available options. The implications of biosimilar utilization in the USA are

uncertain until greater overall utilization is observed, but, as noted, there is a potential for decreased cost of treatment with biosimilar products [6].

There are some limitations that need to be considered in interpreting these results. The BBCIC DRN data are generally representative of commercially insured individuals in the USA. These findings may not be applicable to other populations, for example, Medicare patients. Also, we were not able to fully evaluate trends in utilization for the later years of the study period given partial data for 2018 and 2019. Finally, there is the possibility of misclassification in identifying drug exposures and clinical characteristics through administrative claims data.

Given that the focus of this analysis was on biosimilar versus originator products, and that there were insufficient pegfilgrastim biosimilar data at the time of this study, our analysis was limited to short-acting filgrastim only. We previously found that pegfilgrastim represents approximately two-thirds of total incident G-CSF use in the BBCIC DRN [16] compared with short-acting filgrastim. We intend to perform similar analyses to the present study comparing utilization and patient characteristics among the pegfilgrastim products when sufficient data are available.

In sum, gaining additional real-world evidence on the clinical outcomes and comparative effectiveness of biosimilars compared to reference products is important as shorting-acting G-CSF biosimilar use grows in the coming years.

Declarations

Conflict of interest All authors declare that they have no conflicts of interest.

Ethics approval Institutional Review Boards for the participating Research Partners in the BBCIC Distributed Research Network (DRN) determined that this work does not meet the definition of human subjects research.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The data analyzed for this study are available from the corresponding author on reasonable request.

Code availability Not applicable.

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