

Provider Barriers in Uptake of Biosimilars: Case Study on Filgrastim

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Filgrastim-sndz (Zarxio), a granulocyte colony-stimulating factor (G-CSF) used to prevent and treat neutropenia, was the first biosimilar drug to receive FDA approval, launching in September 2015 as a biosimilar to the originator product, Neupogen. Before the biosimilar pathway was available, tbo-filgrastim (Granix) was approved under a full Biologics License Application in 2012 and launched in November 2013. Uptake of biosimilars in the United States has been modest vs in Europe despite the lower prices of biologics compared with originators.^{1,2} As more biosimilars enter the market, understanding hospital variation in uptake will be important to allow policy makers to improve policies to encourage use of lower-cost versions of these often very expensive drugs.³ Because 340B-participating hospitals, rural hospitals, and hospitals with rural service lines disproportionately treat vulnerable patient populations with known health disparities, higher poverty rates, and lower incomes, it is important to identify factors associated with variation in uptake of lower-cost drugs.⁴ In this study, we examined the association between hospital characteristics and uptake of biosimilar filgrastim and tbo-filgrastim among Medicare Advantage (MA) enrollees.

METHODS

We identified episodes of use of short-acting filgrastim (originator, biosimilar, and tbo-filgrastim) among MA enrollees between September 2015 and May 2020 from the OptumLabs Data Warehouse, which contains longitudinal, deidentified pharmacy and medical claims data for enrollees across the United States.⁵ We used claims information to classify each episode as a chemotherapy regimen with a high risk of neutropenia (classified by National Comprehensive Cancer Network guidelines),⁶ stem cell transplant, or other. We limited the cohort to individuals with 6 or more months of continuous enrollment in medical and pharmacy benefits prior to the index date. Patient demographic information assessed as of the index date included age, sex, and Charlson comorbidities assessed as binary flags for each condition measured over the 6 months prior to the episode start. We excluded episodes with multiple filgrastim

ABSTRACT

In this article, we used administrative claims data from the OptumLabs Data Warehouse and American Hospital Association Annual Survey data to examine associations between hospital characteristics and uptake of biosimilar granulocyte colony-stimulating factor treatments. We found that 340B-participating hospitals and non-rural referral center (RRC) hospitals that reported owning rural health clinics were less likely to administer the lower-cost biosimilars, whereas the opposite was true for hospitals that are RRCs. To our knowledge, our study offers a first look at an underappreciated source of disparities in access to lower-cost medications such as biosimilars. Results from our study reveal opportunities for targeted policies to encourage adoption of lower-cost treatments, particularly among hospitals that serve rural communities where patients often have fewer choices in care site.

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TAKEAWAY POINTS

Biosimilars are intended to increase competition, reduce prices, and improve patient access to important treatments. The first FDA-approved biosimilar was launched in 2015: Filgrastim-sndz [Zarxio], a biosimilar for the reference drug filgrastim (Neupogen), is a granulocyte colony-stimulating factor used to prevent and treat neutropenia.

- ▶ Rural and 340B-participating hospitals were less likely to use biosimilar filgrastim than urban and non-340B hospitals, respectively.
- ▶ Patients seen in rural and 340B hospitals may have fewer choices for receiving care close to home, limiting their ability to choose lower-cost treatment options.

products or unknown patient sex. We constructed patient covariates such as Charlson comorbidity flags based on claims prior to the filgrastim use episode and likely reason for filgrastim use, such as high-risk chemotherapy, stem cell transplant, or other. We ascertained hospital characteristics with data from the American Hospital Association survey and the Health Resources and Services Administration, including bed counts, 340B program participation, and CMS rural facility designations. We created a measure of the relative intensity of the use of biologic drugs for each hospital. We constructed a ratio of the number of patient-service dates that included the use of any biologic drug to the total number of patient-service dates observed for each hospital. The biologic intensity variable is a binary variable indicating whether the hospital was at or above the 90th percentile on that measure.

We used 2 separate measures to identify rurality. The first was whether a hospital is designated as a rural referral center (RRC), which is a rural hospital that serves a high share of complex patients. The second measure was whether a hospital is not an RRC but owns a CMS-certified rural health clinic (RHC), which is paid by Medicare under a different reimbursement schedule for clinics that provide primary care services to rural communities. We classified hospitals into 3 categories: RRC hospitals, non-RRC hospitals that own an RHC, and nonrural hospitals (that is, non-RRC hospitals that do not own an RHC). RRCs that are not owned by for-profit corporations and that serve low-income patients (ie, a disproportionate share adjustment percentage of at least 8%) are eligible to participate in the 340B program.

We modeled the association between uptake characteristics and drug choice at the patient-episode level, using multinomial logit regression with clustered SEs (at the patient level), adjusting for patient and hospital characteristics. We calculated predictive margins (ie, adjusted proportions of patients receiving each drug) to ease interpretation of model results.

RESULTS

Our study included 17,637 episodes, of which 83.6% were seen in nonrural hospitals and 70.8% were seen in 340B hospitals (Table⁷). We found no clinically significant differences by patient characteristics (eg, comorbidities, sex) in the choice of filgrastim originator, biosimilar, and tbo-filgrastim, which accounted for 38.9%,

34.0%, and 27.1% of all episodes, respectively. Hospital characteristics such as bed count were associated with differences in filgrastim choice, with hospitals with 400 or more beds being 70% more likely to administer biosimilar filgrastim and about half as likely to administer tbo-filgrastim compared with those with less than 200 beds. Complete results from the multinomial logit model are presented in the eAppendix (available at ajmc.com).

Based on the adjusted proportions from the multinomial logit model, patients seen in 340B-participating hospitals were 9.8 percentage points less likely than those seen in non-340B hospitals to receive potentially lower-priced alternatives such as biosimilar filgrastim and tbo-filgrastim (rate of nonoriginator filgrastim use in 340B-participating hospitals vs non-340B-participating hospitals: 58.1% vs 67.9%; $P < .001$) (Figure, panel A).

Among episodes of nonoriginator filgrastim use, 340B hospitals were more likely to use biosimilar filgrastim than tbo-filgrastim (biosimilar was used in 59.7% of nonoriginator episodes in 340B hospitals vs 48.2% in non-340B hospitals; $P < .001$).

Patients treated at non-RRC hospitals that own an RHC were the least likely to receive biosimilar or tbo-filgrastim (40.6%), whereas those treated at RRC hospitals (65.2%) and nonrural hospitals (63.6%) had similar rates of biosimilar or tbo-filgrastim receipt ($P = .61$ for comparison of RRC vs nonrural hospitals; $P < .001$ for comparison of non-RRC hospitals that own an RHC vs RRC hospitals) (Figure, panel B).

DISCUSSION

Results from our study on G-CSF episodes found that 340B hospitals were less likely to administer the lower-cost biosimilar or tbo-filgrastim. Certain rural hospitals were also less likely to administer lower-cost versions of filgrastim; episodes of care at non-RRC hospitals that own RHCs were more than 20 percentage points less likely to include the use of biosimilar or tbo-filgrastim than larger RRC hospitals or nonrural hospitals. Rural hospitals' small size and relatively low volume compared with their urban counterparts may give them less flexibility to offer both originator and biosimilar drugs to patients. Reimbursement policies for 340B and other hospitals may incentivize use of more expensive originator drugs. For example, Medicaid classifies biosimilars as a single-source drug under the mandatory manufacturer rebate, which makes the value of the originator rebate higher than for the biosimilar, reducing incentives to switch to a biosimilar for those patients and creating a spillover effect for other patients.⁸

Limitations

This study is limited to individuals with MA insurance and may not represent the experience of those with Medicaid or traditional

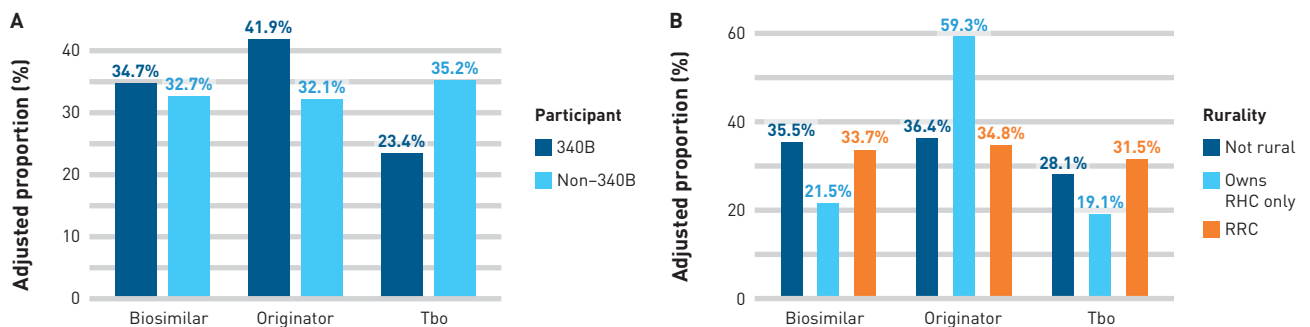
TABLE. Episode Characteristics⁷

Characteristics	Originator filgrastim		Biosimilar filgrastim		Tbo-filgrastim		Total		P
	n	%	n	%	n	%	n	%	
340B participation	5273	76.9%	4455	74.3%	2764	57.8%	12,492	70.8%	<.001
Hospital bed size category									<.001
0-49 beds	489	7.1%	274	4.6%	338	7.1%	1101	6.2%	
50-199 beds	1565	22.8%	937	15.6%	1514	31.6%	4016	22.8%	
200-399 beds	1280	18.7%	1338	22.3%	1446	30.2%	4064	23.0%	
≥400 beds	3524	51.4%	3444	57.5%	1488	31.1%	8456	47.9%	
Rurality indicator									<.001
Not rural	5376	78.4%	5314	88.7%	4048	84.6%	14,738	83.6%	
Owns rural health clinic	1164	17.0%	380	6.3%	421	8.8%	1965	11.1%	
Rural referral center	318	4.6%	299	5.0%	317	6.6%	934	5.3%	
Biologic intensity ^a	414	6.0%	326	5.4%	244	5.1%	984	5.6%	.080
Group purchasing ^b	6049	88.2%	5017	83.7%	4260	89.0%	15,326	86.9%	<.001
Male gender	2919	42.6%	2630	43.9%	2031	42.4%	7580	43.0%	.216
Cohort flag									<.001
High-risk chemotherapy	255	3.7%	247	4.1%	178	3.7%	680	3.9%	
Other	6248	91.1%	5529	92.3%	4423	92.4%	16,200	91.9%	
Stem cell transplant	355	5.2%	217	3.6%	185	3.9%	757	4.3%	
Charlson comorbidity flags ⁷									
Myocardial infarction	425	6.2%	453	7.6%	382	8.0%	1260	7.1%	<.001
Congestive heart failure	948	13.8%	889	14.8%	809	16.9%	2646	15.0%	<.001
Peripheral vascular disease	1482	21.6%	1407	23.5%	1022	21.4%	3911	22.2%	.011
Cardiovascular disease	742	10.8%	686	11.4%	564	11.8%	1992	11.3%	.203
Chronic obstructive pulmonary disease	2046	29.8%	1683	28.1%	1629	34.0%	5358	30.4%	<.001
Mild liver disease	1428	20.8%	1273	21.2%	1099	23.0%	3800	21.5%	.017
Diabetes without complication	1982	28.9%	1924	32.1%	1640	34.3%	5546	31.4%	<.001
Diabetes with complication	738	10.8%	887	14.8%	751	15.7%	2376	13.5%	<.001
Renal disease	1393	20.3%	1420	23.7%	1022	21.4%	3835	21.7%	<.001
Metastatic solid tumor	3560	51.9%	3129	52.2%	2577	53.8%	9266	52.5%	.099

^aBiological intensity indicates whether the treating provider has a biologic treatment rate (defined as ratio of patient-service dates with any biologic drug to total patient-service dates) above the 90th percentile.

^bGroup purchasing indicates whether facility is part of a group purchasing agreement (from American Hospital Association Annual Survey).

FIGURE. Filgrastim Formulation Share by Hospital Characteristics^a



RHC, rural health clinic; RRC, rural referral center.

^aPercentages are within hospital type. For example, in 340B-participating hospitals, 34.7% of filgrastim episodes are biosimilar, 41.9% are originator filgrastim, and 23.4% are tbo-filgrastim.

TRENDS FROM THE FIELD

Medicare seen in the same hospitals. We do not observe the prices that hospitals pay to acquire drugs, which may be lower for originator biologics than for biosimilars at some hospitals; however, in prior work we identified lower insurer- and patient-paid amounts for biosimilar compared with originator filgrastim.¹

CONCLUSIONS

In this study, we offer a first look at an underappreciated source of disparities in access to lower-cost biologic drugs. Individuals living in rural areas, including a significant proportion of Americans 65 years and older,⁹ may have fewer choices of hospitals than those living in urban areas, and they typically seek care in hospitals with RRC or RHC designations. Without access to lower-cost biosimilars, they may end up paying more for some high-cost treatments. As more biosimilars enter the market, results of our study reveal opportunities for targeted policies to encourage adoption of lower-cost treatments, particularly among hospitals treating older patients with fewer choices in care site. ■

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eAppendix. Episode sample selection

Sample selection:

1. Identified all claims with any short-acting filgrastim with the following HCPCS code between September 2015 and December 2019

Type	HCPCS code
Originator filgrastim	J1440, J1441, J1442
Tbo-filgrastim	J1447, J1446
Biosimilar filgrastim	Q5101, Q5110

2. Created episode of GCSF use, defined as filgrastim use separated by at least 7 days
3. Limit to episodes of patients who were continuously enrolled at least 183 days prior to start of GCSF episode

To classify chemotherapy regimen (Source: National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections. v2.2020. 2020):

- a. Lookback period of medical and pharmacy claims by 14 days and identifying chemotherapy of interest

Chemotherapy agents	CPT/HCPCS/NDC code
Alemtuzumab	J9010, J0202
Bleomycin	J9040
Carboplatin	J9045
Cisplatin	J9060
Cyclophosphamide	J9070, J9171, J8630
Cytarabine	J9098
Dacarabazine	J9130
Decitabine	J0984
Dexamethasone	J1094
Docetaxel	J9171
Doxorubicin	J9000, Q2050, Q2049
Etoposide	J9181, J8560
Fludarabine	J9185
Fluorouracil	J9185
Gemcitabine	J9201
Ifosfamide	J9208
Mesna	J9209
Methotrexate	J9260, J9250, J8610
Methylprednisolone	J2930, J1030, J1040, J1020, J7509

Paclitaxel	J9267, J9264, J9265
Prednisone	J7506, J7512
Rituximab	J9310, J9312, J9311
Topotecan	J9351
Trastuzumab	J9355
Vinblastine	J9360
Vincristine	J9370, J9371, J9375

4. Identified the high-risk chemotherapy regimen of interest

Chemotherapy regimen of interest	Chemotherapy agents
MVAC	Methotrexate, Vinblastine, Doxorubicin, Cisplatin
DT	Docetaxel, Trastuzumab
ACT	Doxorubicin, Cyclophosphamide, Paclitaxel
DP	Doxorubicin, Paclitaxel
DD	Doxorubicin, Docetaxel
TAC	Docetaxel, Doxorubicin, Cyclophosphamide
DCF	Docetaxel, Cisplatin, Fluorouracil
DG	Doxorubicin, Gemcitabine
CFAR	Cyclophosphamide, Fludarabine, Alemtuzumab, Rituximab
ICE	Ifosfamide, Carboplatin, Etoposide
RICE	Rituximab, Ifosfamide, Carboplatin, Etoposide
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
DHAP	Dexamethasone, Cisplatin, Cytarabine
ESHAP	Etoposide, Methylprednisolone, Cisplatin, Cytarabine
HYPERCVAD	Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone
DCV	Dacarbazine, Cisplatin, Vinblastine
DECIT	Decitabine
TOP	Topotecan
PAC	Paclitaxel
DOCE	Docetaxel
MAID	Mesna, Doxorubicin, Ifosfamide, Dacarbazine
DOXO	Doxorubicin
VEIP	Vinblastine, Ifosfamide, Cisplatin
VIP	Etoposide, Ifosfamide, Cisplatin
BEP	Bleomycin, Etoposide, Cisplatin
TIP	Paclitaxel, Ifosfamide, Cisplatin

5. Identifying specific types of cancer

Cancer Site	ICD diagnosis codes
Bladder	C67x, C68x, 188x
Breast	D50x, 174x, 175x, C50x
Esophageal	C15x, C16x, 150x, 151x
Kidney	C64x, 189x
Non-Hodgkin Lymphoma	202x, C85x
Melanoma	C43x, 172x
Ovarian	183x, C56x
Small-cell lung cancer	C34x, 162x
Testicular	186x, C62x
MDS	D46x, 238.72, 238.73, 238.74, 238.75

6. Identified stem cell transplants with the following CPT codes: 38205-38232, 38207-38215, 38240-38243 or ICD procedure codes: 410x, 30233Y1, 30253G1, 30243G4, 30243G1, 30243G3, 30260X1, 30233X0, 30240G3, 30263X0, 30230Y0
 - a. Lookback period of medical and pharmacy claims by 14 days and identifying chemotherapy of interest
7. Dropped episodes of treatment if rendered at multiple providers, multiple/conflicting demographics (insurance, age, sex, or state)

Comorbidity ascertainment:

We identified Charlson comorbidities in the cohort using ICD9 and 10 diagnosis codes from any diagnosis position found in facility or physician claims prior to the G-CSF episodes

Other covariates:

Group purchasing: Derived from AHA annual survey to indicate if facility is part of a group purchasing agreement

Biologic intensity: Binary variable set to 1 if treating provider has a biologic treatment rate (defined as ratio patient-service dates with any biologic drug to total patient-service dates) above the 90th percentile.

Rural designation status: Derived from AHA annual survey

Bed size code: Derived from AHA annual survey