Granulocyte-Colony Stimulating Factor (G-CSF) Reference and Biosimilar Products using Real-World Data to Assess Data Variability Across Different Sources to Evaluate its Potential Utility in Regulatory Assessment: A Study by the Biologics and Biosimilars Collective Intelligence Consortium

8888

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OBJECTIVE

To assess the potential of real-world data (RWD) and real-world evidence (RWE) to streamline the pre-market regulatory approval process of biosimilars, and interchangeable biosimilars

INTRODUCTION

- Using real-world data (RWD) and real-world evidence (RWE) for regulatory review could support regulatory assessment of biosimilars
- Since enactment of the 20th Century Cures Act FDA has expressed growing interested in understanding RWD fitness for purpose and how to apply it for regulatory purposes.

RESULTS

Table 1. Demographic Characteristics by Study Site

Characteristic	Site A (n=8,890)	Site B (n=8218)	Site C (n=856)
Age at Index Date (years), mean (SD)	58.1 (12.3)	56.3 (12.5)	53.8 (10.8)
Female Sex, n (%)	8805 (99.0)	8119 (98.8)	848 (99.1)
G-CSF Initial Product Receipt, n (%)			
Pegfilgrastim reference	7695 (86.6)	6263 (76.2)	685 (80.0)
Pegfilgrastim biosimilar (any)	1195 (13.4)	1955 (23.8)	171 (20.0)

- Overall, 17,964 patients with breast cancer receiving chemotherapy and prophylactic pegfilgrastim were identified (Table 1)
- Most initiated reference pegfilgrastim
- All sources readily identified patients, treatment, and demographics

Table 2. Outcome Measures by Study Site

Outcomes	Site A (n=8,890)	Site B (n=8218)	Site C (n=856)
Cycle 1, Febrile Neutropenia, n(%)	113 (1.3)	96 (1.2)	<11 (***)
Cycle 1 Severe Neutropenia, n (%)	562 (6.3)	2050 (24.9)	75 (8.8)

- FN event rates were low (1.2%-1.3%), Table 2
- Severe FN rates varied (6.3% - 24.9%)

- Chemotherapy administration was consistent across sites, but variability in regimens was observed (e.g., doxorubicin and cyclophosphamide 3.5%-49%)

Table 3. Chemotherapy Regimen Utilization by Study Site

Chemotherapy regimen receipt, Cycle 1, n (%)	Site A	Site B	Site C
Dose-dense AC (doxorubicin, cyclophosphamide) + paclitaxel	21 (0.2)	<11 (***)	0 (0)
TAC (docetaxel, doxorubicin, cyclophosphamide)	<11(***)	52 (0.6)	0 (0)
AC (doxorubicin, cyclophosphamide) + docetaxel	311 (3.5)	3537 (43.0)	419 (49.0)
TC (docetaxel, cyclophosphamide)	50 (0.6)	2095 (25.5)	207 (24.2)
TCH (docetaxel, carboplatin, trastuzumab)	326 (3.7)	19 (0.2)	28 (3.3)
TCHP (docetaxel, carboplatin, trastuzumab, pertuzumab)	1594 (17.9)	<11 (***)	170 (19.9)
CMF (cyclophosphamide, methotrexate, fluorouracil)	<11 (***)	65 (0.8)	0 (0)
FEC (fluorouracil, epirubicin, cyclophosphamide)	0 (0)	<11 (***)	0 (0)
EC (epirubicin, cyclophosphamide)	0 (0)	<11 (***)	0 (0)
Docetaxel	3362 (37.8)	2059 (25.0)	<11 (***)
Paclitaxel	3220 (36.2)	127 (1.5)	<11 (***)
Other	0 (0)	246 (3.0)	29 (3.4)

- Overall, 555 (3.1%) switched between reference pegfilgrastim and a biosimilar

Table 4. Characteristics of Pegfilgrastim Switching

Characteristic	Site A (n=220)	Site B (n=311)	Site C (n=24)
Age <65 years, n (%)	169 (76.8)	229 (73.6)	>11 (***)
Age >/=65 years, n (%)	51 (23.2)	82 (26.4)	<11 (***)
Metastatic cancer, n (%)	116 (52.7)	141 (45.3)	<11(***)
NCI Comorbidity Score, mean (SD)	1.21 (1.36)	0.27 (0.43)	0.05 (0.17)
Number of follow-up days to pegfilgrastim product switch or censor, mean (SD)	51.3 (180.4)	69.9 (159.4)	38.9 (19.4)

Table 5. Availability of Laboratory Results and Vital Signs

Laboratory Results	Site C (n=856)
CD34+ count, n (%)	N/A
Hemoglobin (Hgb), n (%)	332 (38.8)
Serum creatinine (SCr), n (%)	323 (37.7)
Aspartate aminotransferase (AST), n (%)	270 (31.5)
Alanine aminotransferase (ALT), n (%)	241 (28.2)
Alkaline phosphatase (AP), n (%)	265 (31.0)
Vital Signs	**Site C (n=856)**
Height, n (%)	381 (44.5)
Weight, n (%)	396 (46.3)
Body mass index, n (%)	393 (45.9)
Pulse, n (%)	401 (46.9)
Blood pressure, n (%)	397 (46.4)
ECOG Performance Status, n (%)	118 (13.8)

- Data availability varied across sites for some variables (e.g., laboratory results: confirmation of lab test vs. presence of results), and some disease measures (e.g., cancer diagnosis vs. cancer stage and disease progression)
- Only Site C had laboratory and vital sign records, but only for a subset of patients

METHODS

Table 7. Products Included

pegfilgrastim reference (Neulasta)
pegfilgrastim-apgf (Nyvepria)
pegfilgrastim-bmez (Ziextenxo)
pegfilgrastim-cbqv (Udenyca)
pegfilgrastim-jmdb (Fulphila)

- A target trial emulation was conducted in patients with breast cancer across three research partners (Table 6)
- A hypothetical trial (Table 8) was designed to assess pegfilgrastim product use (Table 7) for febrile neutropenia (FN) prophylaxis and adverse events (AEs) within the first 6 chemotherapy cycles from 1/1/2016-12/31/2023
- Outcome measures assessed: chemotherapy administration, pegfilgrastim utilization and switching across reference and biosimilar products, AEs, and laboratory results
- Sites independently examined data availability and reliability of cohort identification, exposures, and outcomes among switchers compared with non-switchers
- Adverse outcomes for switching and non-switching were compared following inverse probability of treatment weighting
- Index Date: First receipt of pegfilgrastim following the first receipt of chemotherapy

Table 6. Database Characteristics at each Study Site

Data Source	Site A	Site B	Site C
Description	Administrative claims data from multiple payer types, including commercial, Medicaid, Medicare, employer, self-pay	Administrative claims (medical, pharmacy) and enrollment data from a large, national, commercial health plan. Possible to obtain medical record data for ~70 of patients	Administrative claims (medical, pharmacy) linked to electronic health records from a regional health system and insurance plan
Date Range	January 2010 - April 2023	Jan 2008 – Feb 2024	Jan 2000 – Apr 2024
Population Size	>170 million patient-lives	>44 million patient-lives	>4 million patient-lives
Average Follow-Up	9 years	2 years	5 years
Geographic Region	All 50 states	All 50 states + territories	Midwestern U.S.

Table 8. Target Trial and Emulation Study Design

	Target Trial	Emulation
Inclusion Criteria	• Women aged >=18 years with histologically proven breast cancer • Eastern Cooperative Oncology Group (ECOG) performance status<=2 • Adequate bone marrow function on day 1 of cycle 1 before chemotherapy.	• Adults aged >=18 years with breast cancer diagnosis • Pegfilgrastim receipt within 7 days of the first chemotherapy administration (cycle 1) • Medical and pharmacy insurance coverage
Exclusion Criteria	• History of myelogenous leukemia, myelodysplastic syndrome or concomitant sickle cell disease • Concurrent or prior radiotherapy within 4 weeks of randomization • Use of prophylactic antibiotics • Prior chemotherapy or anticancer treatment of breast cancer • Previous G-CSF therapy	• Prior cancer or confounding conditions* • Radiation therapy within 28 days prior or after the index date • Prior G-CSF or chemotherapy therapy in the 365 days prior to the index date • Receipt of prophylactic antibiotics during chemotherapy cycles
Treatment Strategy	Two non-switching arms with only one product (biosimilar or reference), and two switching arms with alternating treatments every other cycle over six cycles	Two arms: **non-switchers** (using same pegfilgrastim product at each chemotherapy cycle) and **switchers** (receiving a different pegfilgrastim product at any non-index chemotherapy cycle).
Randomization	Randomized 1:1:1:1 into four arms: no treatment, switched treatment from reference to biosimilar, reference treatment only, and biosimilar treatment only.	Emulation randomization by adjusting for baseline covariates such as patient age, sex, comorbidity score, year of administration, and chemotherapy-induced FN risk.
Follow-Up Period	Chemotherapy cycle 2 through cycle 6	Chemotherapy cycle 2 through Cycle 6
Outcomes	Febrile neutropenia (FN), infections, hospitalizations due to FN, time and depth of absolute neutrophil count (ANC) nadir, time to ANC recovery, adverse events (AEs)	Febrile neutropenia (FN), infections, hospitalizations due to FN, time and depth of absolute neutrophil count (ANC) nadir, time to ANC recovery, adverse events (AEs)

*bone marrow or stem cell transplant, a diagnosis of HIV/AIDS, severe hepatic disease, chronic kidney disease, myeloid leukemia, myelodysplastic syndrome, sickle cell disease, or any non-oncology related FN, skilled nursing facility or hospice care in the 365 days prior to the index date

Index Date: First receipt of pegfilgrastim following the first receipt of chemotherapy

CONCLUSIONS

Three independent real-world data sources successfully assessed data availability, cohort identification, exposures, and outcomes.

Differences in data availability were identified; however, all sites conducted the emulation study and demonstrated similar results.

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