Education and Research Center for Clinical Pharmacy, Osaka University of Pharmaceutical Sciences, Takatsuki, Osaka, Japan

Evaluation of adverse events associated with filgrastim originator and biosimilar using a spontaneous reporting system database

I. Niinomi, K. Hosohata*, S. Oyama, A. Inada, T. Wakabayashi, K. Iwanaga

Received November 17, 2019, accepted January 10, 2020

**Corresponding author: Keiko Hosohata, Ph.D. Education and Research Center for Clinical Pharmacy, Osaka University of Pharmaceutical Sciences, 4-20-1 Nasahara, Takatsuki, Osaka 569-1094, Japan*
hosohata@gly.oups.ac.jp

Pharmazie 75: 151-153 (2020) *doi: 10.1691/ph.2020.9189*

Biosimilar products of filgrastim have become available for improved sustainability of cancer care; however, the real-world safety profile remains unknown. The purpose of this study was to clarify the adverse events associated with filgrastim originator and its biosimilar using the Japanese Adverse Drug Event Report (JADER) database. Adverse event reports submitted to the Pharmaceuticals and Medical Devices Agency between 2014-2018 were extracted. We calculated the reporting odds ratio and 95% confidence interval for each adverse event. We obtained 584 reports of adverse events associated with filgrastim originator and 102 reports with its biosimilar. Signals were detected for bone marrow failure and febrile neutropenia with both filgrastim originator and its biosimilar; whereas those for drug resistance and hypoxia only involved filgrastim originator, and those for interstitial lung disease only involved its biosimilar. The safety profiles of filgrastim originator and its biosimilar were partly different. Further studies are needed to confirm these findings.

1. Introduction

Filgrastim is a recombinant human granulocyte colony-stimulating factor (G-CSF) that acts in the same manner as endogenous G-CSFs, which promote the proliferation, differentiation, and maturation of neutrophil progenitor cells and survival and functional stimulation of mature neutrophils (Bennett et al. 2013). Filgrastim is widely used for the treatment of patients with aplastic anemia (Bacigalupo et al. 2000; Teramura et al. 2007) as well as for prophylaxis of febrile neutropenia in patients receiving chemotherapy (Lyman et al. 2002; Kuderer et al. 2007; Cooper et al. 2011) and hematopoietic cell transplantation (Duong et al. 2014). Filgrastim has been used clinically for over a decade in Japan, and a significant amount of evidence supports the long-term safety, efficacy, and value of the products.

The development of biosimilars may improve access to reliable treatments including G-CSFs with the expiry of patent protection. Biosimilars are biological medicinal products containing a version of the active substance of an already authorized original biological medicinal product, for which they are required to have similar efficacy, safety, and immunogenicity. Randomized controlled clinical studies demonstrated that biosimilars of filgrastim have efficacy and safety comparable to the filgrastim originator (del Giglio et al. 2008; Gascon et al. 2010; Waller et al. 2010; Blackwell et al. 2015). However, its real-world safety profile remains unknown.

Recently, spontaneous reporting systems have been used as a source of post-marketing drug safety surveillance for the detection of adverse drug events (Mendes et al. 2014; Mahe et al. 2018). The Japanese Adverse Drug Event Report (JADER) database is a large published database managed by the Pharmaceuticals and Medical Devices Agency for pharmacovigilance (Hosohata et al. 2018, 2019 a,b). The objective of this study was to assess adverse events associated with filgrastim originator and its biosimilar using the JADER database.

2. Investigations and results

During the study period, the total number of co-occurrences with filgrastim originator was 584 (199 different events) and 102 (31 different events) with its biosimilar. The demographics of those who experienced adverse events are described in Table 1, with the most frequent age in the 70s (26.9%) for filgrastim originator and the 60s (33.3%) for its biosimilar, and the proportion of females was 42.7% for filgrastim originator and 56.9% for its biosimilar.

Of 584 adverse events associated with filgrastim originator and 102 with its biosimilar, the top 10 adverse events are listed in Table 2. For both filgrastim originator and its biosimilar, bone marrow failure was the most frequently reported adverse event, with 33 reports (5.7%) for filgrastim originator and 20 reports (19.6%) for its biosimilar. The next most common reported adverse events were febrile neutropenia (24 reports) and drug resistance (24 reports) for filgrastim originator, and interstitial lung disease (18 reports) for

Table 1: Patient characteristics

Variables		Filgrastim originator	filgrastim biosimilar
		n (%)	n (%)
Sex			
	Men	329 (56.3)	42 (41.2)
	Women	249 (42.7)	58 (56.9)
	Unknown	6 (1.0)	2 (1.9)
Age			
	<10	76 (13.0)	0 (0)
	10s	15 (2.6)	0 (0)
	20s	16 (2.7)	2 (2.0)
	30s	33 (5.7)	0 (0)
	40s	54 (9.2)	10 (9.8)
	50s	108 (18.5)	18 (17.6)
	60s	94 (16.1)	34 (33.3)
	70s	157 (26.9)	33 (32.4)
	80s	8 (1.4)	3 (2.9)
	Unknown	23 (3.9)	2 (2.0)

n, number; 10s, 10-19 years; 20s, 20-29 years; 30s, 30-39 years; 40s, 40-49 years; 50s, 50-59 years; 60s, 60-69 years; 70s, 70-79 years; 80s, 80-89 years.

Table 2: Disproportionality analysis of adverse events of filgrastim originator and biosimilar

Drug	Adverse event	n	ROR	95%CI
Filgrastim originator				
	Bone marrow failure	33	9.06	6.37-12.9*
	Febrile neutropenia	24	2.82	1.87-4.24*
	Drug resistance	24	112	73.3-170*
	Hypoxia	23	39.1	25.6-59.6*
	Platelet count decreased	19	1.35	0.85-2.13
	Interstitial lung disease	18	1.31	0.82-2.1
	Neutropenia	16	2.04	1.24-3.36*
	Hypokalemia	14	8.04	4.72-13.7*
	White blood cell count decreased	14	1.78	1.04-3.02*
	Pneumonia	13	1.36	0.78-2.35
Filgrastim biosimilar				
	Bone marrow failure	20	36.9	22.6-60.1*
	Interstitial lung disease	18	8.84	5.31-14.7*
	Febrile neutropenia	9	6.36	3.21-12.6*
	Hemophagocytic lymphohistiocytosis	6	63	27.5-144*
	Back pain	6	75.4	33-173*
	Peritonitis	6	38.5	16.9-88*
	Blast cell count increased	4	193	70.3-529*
	Acute myeloid leukaemia	3	25.1	7.94-79.2*
	Netrophil count decreased	3	1.25	0.4-3.95
	Pyrexia	3	2.2	0.7-6.94

CI, confidence interval; ROR, Reporting odds ratio. *, signal detected.

its biosimilar. Of note, adverse events induced by filgrastim originator that were not reported for its biosimilar were drug resistance (24 reports) and hypoxia (23 reports).

Disproportionality analyses revealed positive signals for bone marrow failure, febrile neutropenia, drug resistance, hypoxia, neutropenia, hypokalemia, and a decreased white blood cell count for filgrastim originator (Table 2). As for filgrastim biosimilar, signals were detected for bone marrow failure, interstitial lung disease, febrile neutropenia, hemophagocytic lymphohistiocytosis, back pain, peritonitis, a blast cell count increase, and acute myeloid leukaemia. Especially, the association with the blast cell count increase, which was tested by calculating the reporting odds ratio (ROR) and 95% confidence interval (CI), was noteworthy (ROR, 193; 95%CI, 70.3-529). This adverse event was not reported for filgrastim originator.

3. Discussion

This is the first report on safety profiles of adverse events due to filgrastim originator and its biosimilars according to a spontaneous reporting system. Despite the similarity in physicochemical structure and biological function between the biosimilar and originator biologic, there may be minor differences due to their complex nature and production methods. As for efficacy, any variability and differences between the biosimilar and its reference medicine were shown not to reduce effectiveness (Blackwell et al. 2015). Indeed, a retrospective study by Sivgin et al. (2013) revealed that filgrastim biosimilar (Leucostim®) has a potency comparable to filgrastim originator (Neupogen®) on peripheral blood stem cell collection. As for safety, a phase III study revealed that the adverse event profile was similar between Neupogen® and XM02, but there was a difference in the incidence of drug-related adverse events across all cycles (Neupogen® group, 39.7% of patients vs. XM02 group, 25.7% of patients)(del Giglio et al. 2008). However, the real-world safety profile is unknown and so pharmacovigilance such as through the JADER database is considered important.

Our results revealed that signals were commonly detected for bone marrow failure and febrile neutropenia with filgrastim originator and its biosimilar. On the other hand, signals were detected for drug resistance and hypoxia, neutropenia, hypokalemia, and a decrease in the white blood cell count with filgrastim originator, but not its biosimilar. Hematologic events, including febrile neutropenia, neutropenia, and a decrease in the white blood cell count are likely attributable to chemotherapy treatment or underlying disease. Of note, interstitial lung disease was significantly correlated with filgrastim biosimilar, but not its originator. One explanation for the difference in the safety profile may be the differences in patient background between both groups. Indeed, some differences were observed in sex and age distribution (Table 1). Another is immunogenicity. Immunogenicity is associated with a reduced response and various adverse events. The degree of immunogenicity is not the same for all biologics, and only minor differences in the formulation, purity, or packaging of a biological drug can affect the immunogenicity profile. However, the difference in this study may be due to factors other than immunogenicity. Adverse event reports were limited for the biosimilar compared with originator. If the number of reports increases in the future, the general consensus may change.

This pharmacovigilance study using the JADER database had several limitations. First, as with all pharmacovigilance studies, we were unable to calculate the true incidence rates, notably because there are no data on the total number of patients receiving the drugs of interest and under-reporting. Second, the ROR does not provide a robust indication of the signal strength. In spontaneous reporting systems such as JADER, control populations are not included, so the ROR is different from the "odds ratio" that is commonly used in epidemiological studies. In real terms, the ROR indicates an increased risk of adverse event reporting, and not the risk of adverse events itself. Third, there may be a reporting bias between filgrastim originator and its biosimilar. It is expected that adverse events associated with filgrastim biosimilar may be more positively reported than filgrastim originator because the biosimilar was more recently introduced. Fourth, the present method did not provide us with detailed clinical information on the patients (Franciotta et al. 2009). Finally, we could not consider the variability of quality among "filgrastim biosimilar 1", "filgrastim biosimilar 2", and "filgrastim biosimilar 3".

In conclusion, the safety profiles of filgrastim originator and its biosimilar were partly different. Further studies are needed to confirm these findings.

4. Experimental

4.1. Data

Data were extracted from the public release of the JADER database of PMDA, covering the period between the third quarter of 2014 and the fourth quarter of 2018. The main reason for limiting our research to this period is that the latest filgrastim biosimilar was launched in November 2014 in Japan. The data structure of JADER consists of 4 datasets: patient demographic information (DEMO), drug information (DRUG), adverse events (REAC), and medical history (HISTO). Preferred terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA) serve as the terminology for registration of adverse events in the REAC table. After we removed duplicate data from each table because the same case report will be received from different sources (Bate et al. 2009), the DEMO table was linked to the REAC and DRUG tables using the ID number.

The contribution of the medication to adverse events was classified into three categories: "suspected medicine," "concomitant medicine," and "interaction," as described previously (Oyama et al. 2018; Hosohata et al. 2019a, b, c; Inada et al. 2019). Briefly, a "suspected medicine" is defined as a pharmaceutical product suspected to be associated with an adverse reaction. A "concomitant medicine" is defined as another pharmaceutical product used at the time of the adverse reaction. When the reporter suspects an interaction, he/she reports it as an "interaction." In order to exclude the masking effect, defined as the condition whereby the effect of a given drug-event pair might be hidden by the presence of another product (Maignen et al. 2014), we extracted cases that were classified as "suspected medicine." Of the filgrastim biosimilars in Japan, "filgrastim biosimilar 1", "filgrastim biosimilar 2", and "filgrastim biosimilar 3" were approved in 2013, 2013, and 2014, respectively. In this study, we included the reports of "filgrastim biosimilar 1" (n = 59), "filgrastim biosimilar 2" (n = 21), and "filgrastim biosimilar 3" (n = 22) for analysis as filgrastim biosimilar.

4.2. Data analysis

Next, we calculated the ROR. The ROR is the rate of reporting a specific adverse reaction caused by a particular drug divided by the rate of the same adverse events caused by all other drugs present in the database. A signal was considered to be present when the lower limit of the 95% CI of the ROR was >1.

In this database, age, height, and weight information are indicated in the form of age in decades, height in centimeter-denominated ranges, and weight in kilogram-denominated ranges. Because these data are not continuous variables, we could not conduct multiple analyses using them. All analyses were performed with JMP Pro 12 (SAS Institute Inc., Cary, NC, USA.).

Funding: K. Hosohata received research support from the Science Research Promotion Fund.

Competing interests: The authors report no conflicts of interest in this work.

References

Bacigalupo A, Bruno B, Saracco P, Di Bona E, Locasciulli A, Locatelli F, Gabbas A, Dufour C, Arcese W, Testi G, Broccia G, Carotenuto M, Coser P, Barbui T, Leoni P and Ferster A (2000) Antilymphocyte globulin, cyclosporine, prednisolone, and granulocyte colony-stimulating factor for severe aplastic anemia: an update of the GITMO/EBMT study on 100 patients. European Group for Blood and Marrow Transplantation (EBMT) Working Party on Severe Aplastic Anemia and the Gruppo Italiano Trapianti di Midolio Osseo (GITMO) Blood 95: 1931-1934.

Bate A, Evans SJ (2009) Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf 18: 427-436.

Bennett CL, Djulbegovic B, Norris LB, Armitage JO (2013) Colony-stimulating factors for febrile neutropenia during cancer therapy. N Engl J Med 368: 1131-1139.

Blackwell K, Semiglazov V, Krasnozhon D, Davidenko I, Nelyubina L, Nakov R, Stiegler G, Singh P, Schwebig A, Kramer S, Harbeck N (2015) Comparison of EP2006, a filgrastim biosimilar, to the reference: a phase III, randomized, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy. Ann Oncol 26: 1948-1953.

Cooper KL, Madan J, Whyte S, Stevenson MD, Akehurst RL (2011) Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis. BMC Cancer 11: 404.

del Giglio A, Eniu A, Ganea-Motan D, Topuzov E, Lubenau H (2008) XM02 is superior to placebo and equivalent to Neupogen in reducing the duration of severe neutropenia and the incidence of febrile neutropenia in cycle 1 in breast cancer patients receiving docetaxel/doxorubicin chemotherapy. BMC Cancer 8: 332.

Duong HK, Savani BN, Copelan E, Devine S, Costa LJ, Wingard JR, Shaughnessy P, Majhail N, Perales MA, Cutler CS, Bensinger W, Litzow MR, Mohty M, Champlin RE, Leather H, Giralt S, Carpenter PA (2014) Peripheral blood progenitor cell mobilization for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 20: 1262-1273.

Franciotta D, Kwan P, Perucca E (2009) Genetic basis for idiosyncratic reactions to antiepileptic drugs. Curr Opin Neurol 22: 144-149.

Gascon P, Fuhr U, Sorgel F, Kinzig-Schippers M, Makhson A, Balser S, Einmahl S, Muenzberg M (2010) Development of a new G-CSF product based on biosimilarity assessment. Ann Oncol 21: 1419-1429.

Hosohata K, Matsuoka E, Inada A, Oyama S, Niinomi I, Mori Y, Yamaguchi Y, Uchida M, Iwanaga K (2018) Differential profiles of adverse events associated with mycophenolate mofetil between adult and pediatric renal transplant patients. J Int Med Res 46: 4617-4623.

Hosohata K, Inada A, Oyama S, Furushima D, Yamada H, Iwanaga K (2019a) Surveillance of drugs that most frequently induce acute kidney injury: A pharmacovigilance approach. J Clin Pharm Ther 44: 49-53.

Hosohata K, Inada A, Oyama S, Niinomi I, Wakabayashi T and Iwanaga K (2019b) Adverse cutaneous drug reactions associated with old- and new-generation antiepileptic drugs using the Japanese Pharmacovigilance Database. Clin Drug Investig 39: 363-368.

Hosohata K, Oyama S, Niinomi I, Wakabayashi T, Inada A, Iwanaga K (2019c) Comparison of safety profiles of new oral anticoagulants with warfarin using the Japanese spontaneous reporting database. Clin Drug Investig 39: 665-670.

Inada A, Oyama S, Niinomi I, Wakabayashi T, Iwanaga K, Hosohata K (2019) Association of Stevens-Johnson syndrome and toxic epidermal necrolysis with antiepileptic drugs in pediatric patients: Subgroup analysis based on a Japanese spontaneous database. J Clin Pharm Ther 44: 775-779.

Kuderer NM, Dale DC, Crawford J, Lyman GH (2007) Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol 25: 3158-3167.

Lyman GH, Kuderer NM (2002) Filgrastim in patients with neutropenia: potential effects on quality of life. Drugs 62 Suppl 1: 65-78.

Mahe J, de Campaigno EP, Chene AL, Montastruc JL, Despas F, Jolliet P (2018) Pleural adverse drugs reactions and protein kinase inhibitors: Identification of suspicious targets by disproportionality analysis from VigiBase. Br J Clin Pharmacol: 2373-2383.

Maignen F, Hauben M, Hung E, Van Holle L, Dogne JM (2014) Assessing the extent and impact of the masking effect of disproportionality analyses on two spontaneous reporting systems databases. Pharmacoepidemiol Drug Saf 23: 195-207.

Mendes D, Alves C, Batel-Marques F (2014) Safety profiles of adalimumab, etanercept and infliximab: a pharmacovigilance study using a measure of disproportionality in a database of spontaneously reported adverse events. J Clin Pharm Ther 39: 307-313.

Oyama S, Hosohata K, Inada A, Niinomi I, Mori Y, Yamaguchi Y, Uchida M, Iwanaga K (2018) Drug-induced tubulointerstitial nephritis in a retrospective study using spontaneous reporting system database. Ther Clin Risk Manag 14: 1599-1604.

Sivgin S, Karakus E, Kaynar L, Kurnaz F, Pala C, Keklik M, Zararsiz G, Solmaz M, Eser B, Cetin M, Unal A (2013) The comparison of Filgrastim (Neupogen(R)), biosimilar filgrastim (Leucostim(R)) and Lenograstim (Granocyte(R)) as a first line peripheral blood stem cell mobilization strategy in autologous hematopoieitic stem cell transplantation: a single center experience from Turkey. Transfus Apher Sci 48: 315-320.

Teramura M, Kimura A, Iwase S, Yonemura Y, Nakao S, Urabe A, Omine M, Mizoguchi H (2007) Treatment of severe aplastic anemia with antithymocyte globulin and cyclosporin A with or without G-CSF in adults: a multicenter randomized study in Japan. Blood 110: 1756-1761.

Waller CF, Semiglazov VF, Tjulandin S, Bentsion D, Chan S, Challand R (2010) A phase III randomized equivalence study of biosimilar filgrastim versus Amgen filgrastim in patients receiving myelosuppressive chemotherapy for breast cancer. Onkologie 33: 504-511.