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Granulocyte colony-stimulating factor-associated aortitis in the Japanese Adverse Drug Event Report database

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ABSTRACT

Background: Granulocyte colony-stimulating factor (G-CSF) is the standard-of-care therapy for chemotherapy-associated neutropenia in patients with malignancies. Recent case reports have implied that G-CSF treatment may be associated with the development of aortitis, but the precise nature of the relationship is unclear. We investigated the association between G-CSF and risk for aortitis in patients with various malignancies.
Methods: We performed an observational study of 102,014 subjects with malignant neoplasms documented in the Japanese Adverse Drug Event Report (JADER) database between April 2004 and February 2018. The adjusted odds ratio (OR) and 95% confidence interval (CI) for aortitis in patients treated and not treated with G-CSF were estimated using multivariate logistic regression with R software.
Results: Among the 102,014 subjects, 25 developed aortitis. Of the 3409 and 98,630 subjects treated and not treated with G-CSF, 16 (0.47% [95% CI; 0.27, 0.76]) and 9 (0.01% [0.00, 0.02]) developed aortitis, respectively. Multivariate logistic regression indicated an association between G-CSF and aortitis (adjusted OR 45.87 [19.16, 109.8], $p < 0.001$). The values for filgrastim, pegfilgrastim, and lenograstim were 0.25% (0.07, 0.63), 1.58% (0.79, 2.81), and 0.24% (0.05, 0.69), respectively.
Conclusion: G-CSF treatment was associated with a signal of increased risk for aortitis among patients with malignant neoplasms. Three different G-CSF agents were associated with such risk, implying that it is a class effect. However, we do not recommend changing G-CSF prescriptions, because our results may have been influenced by the limitations of the JADER database and because the benefit of G-CSF treatment outweighs the potential risk.

1. Introduction

Granulocyte colony-stimulating factor (G-CSF) is the standard-of-care therapy for chemotherapy-associated neutropenia in patients with malignancies, including hematological malignancies and solid tumors. There are a few case reports of the development of aortitis after G-CSF treatment [1–4]. However, no study has quantitatively evaluated the risk for G-CSF-associated aortitis. Thus, we analyzed the risk for aortitis associated with G-CSF treatment using the Japanese Adverse Drug Event Report (JADER) adverse drug reaction (ADR) database.

The JADER is maintained by the Japan Pharmaceuticals Medical Devices Agency (PMDA). The database collects ADRs from throughout Japan, and is available at the PMDA website (http://www.pmda.go.jp/). The most recent version of JADER (June 2018) contains 513,764 ADRs registered between April 2004 and February 2018. We hypothesized that if aortitis was incidental, the frequency of ADRs would be similar irrespective of G–CSF use.

2. Subjects and methods

2.1. Database and data handling

The JADER (513,764 ADRs) was obtained from the PMDA website (https://www.pmda.go.jp/). We extracted information on patients with various malignant solid tumors or hematological malignancies, including malignant lymphoma and leukemia. As of June 2018, three

Abbreviations: G-CSF, granulocyte colony-stimulating factor; JADER, Japanese Adverse Drug Event Report; PMDA, Pharmaceuticals Medical Devices Agency; AE, adverse event; RWE, real-world evidence; ADR, adverse drug reaction; EPO, erythropoietin; BCPNN, Bayesian confidence propagation neural network; MAH, marketing authorization holder; EPPV, early post-marketing phase risk minimization and vigilance; DUI, drug use investigation; RMP, risk management plan

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wild-type human recombinant G-CSF agents are approved for use in Japan: filgrastim, lenograstim, and pegfilgrastim. Aortitis events were identified based on the MedDRA PT code.

2.2. Software and data manipulation

We used multivariate logistic regression to compare the frequency of aortitis between those treated and not treated with G-CSF, and calculated the crude and adjusted odds ratios (ORs) using R software (R Core Team [2016]; R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. G-CSF and aortitis

Of the 102,014 patients with malignant neoplasms (8422 breast cancer, 6473 colon cancer, 5516 prostate cancer, and 5358 lung adenocarcinoma), 3409 were treated with G-CSF. The mean (standard deviation) ages of those treated and not treated with G-CSF were 53.98 (17.50) and 60.38 (14.36) years, respectively. The percentages of females treated and not treated with G-CSF were 46.7% and 40.9%, respectively (Table 1). The numbers of patients with aortitis among those treated and not treated with G-CSF were 16 (0.47% [95%CI 0.27, 0.76]) and 9 (0.01% [0.00–0.02]), respectively (Table 2) (crude OR, 49.5 [95%CI 21.86, 112.11]; adjusted OR, 45.87 [19.16, 109.8]; $p < 0.01$ by Wald's test). The adjusted OR for males was 0.01 (95%CI 0.03, 0.33; $p = 0.001$).

3.2. Subgroup analyses

Patients with malignant lymphoma, breast cancer, and ovarian cancer had higher ORs for aortitis ($p < 0.01$) (Table 3). The wide CIs indicate imprecision due to the low frequencies of events. Thus, treatment with G-CSF did not increase the risk for aortitis in patients with some types of malignancy.

3.3. Quality of the model

No evidence of multicollinearity was detected by multivariate logistic regression because the variance inflation factor for independent variables in the model was < 4.0. The multivariate logistic regression model and the full model (Table 2) had up to six variables for 25 events; this is too many variables and may have caused over-fitting of the model [5]. To overcome this, we tested the following models with fewer variables:

- Additional model 1: Sex and G-CSF. Age, carboplatin, bevacizumab, and paclitaxel were removed.
- Additional model 2: Sex, G-CSF, and carboplatin.
- Additional model 3: Sex, G-CSF, carboplatin, and paclitaxel.

The adjusted ORs for additional models 1, 2, and 3 were 46.5 (20.52, 105.4), 39.49 (17.21, 90.6), and 41.3 (17.9, 95.3), respectively.

Table 1
Demographical characteristics of subjects (n = 102014).

Variables	G-CSF (+) (n = 3409)	G-CSF (−) (n = 98605)
Age (mean (sd))	53.98 (17.50)	60.38 (14.36)
Sex		
Female	1591 (46.7)	40,299 (40.9)
Male	1793 (52.6)	55,413 (56.2)
Unknown	25 (0.7)	2893 (2.9)

Abbreviations: G-CSF, granulocyte colony-stimulating factor.

The ORs by univariate logistic regression for G-CSF and the full model were 51.66 (22.81, 116.99) and 45.87 (19.16, 109.9); both indicate an association between aortitis and G-CSF. Thus, over–fitting of the full model did not influence the association between aortitis and G-CSF.

3.4. Aortitis cases

We analyzed 16 patients (15 females) with G-CSF-associated aortitis (Table 4). Their underlying malignancies included breast cancer and malignant lymphoma. All 16 patients recovered or improved; none died due to aortitis. Fifteen of the sixteen cases were reported after January 2016, despite the fact that the JADER contains ADRs from April 2004 and that lenograstim and filgrastim were approved in 1991 in Japan.

3.5. Concomitant use of G-CSF and EPO

The EPO agents epoetin alfa, epoetin beta, epoetin beta pegol, epoetin kappa, and darbepoetin alfa are approved for use in Japan. Of 102,014 subjects with malignant diseases, 234 were treated with EPO; none of them developed aortitis. Of the 234 EPO-treated subjects, 5 also received G-CSF; this small number precluded evaluation of the effects of combination treatment with EPO and G-CSF.

4. Discussion

4.1. G-CSF and aortitis

We investigated potential factors associated with aortitis in patients with malignant disease. We hypothesized that if aortitis was incidental, the frequency of ADRs would be similar irrespective of G–CSF use. The frequencies of aortitis in patients treated and not treated with G–CSF were 0.47 (95%CI 0.27, 0.76) and 0.01 (95% CI 0.00, 0.02), respectively (OR 49.50 [95% CI 21.86, 112.11]; $p < 0.001$) (Table 2). These data imply an association between G-CSF and aortitis.

We evaluated subjects with malignancies registered between the first quarter of 2013 and the third quarter of 2018 in the United States Food and Drug Administration Adverse Event Reporting System (FAERS; https://www.fda.gov/). The FAERS contains data on the following G-CSF agents: balugrastim, filgrastim, lenograstim, lipegfilgrastim, nartograstim, and pegfilgrastim. The frequencies of aortitis per 10^5 subjects treated and not treated with G-CSF were 1.44 (95%CI 0.36, 80.22) and 0.31 (95% CI 0.01, 1.75), respectively (OR 45.94 [95% CI 0.59, 3482.53]; $p = 0.042$ by Fisher's exact test). The wide CIs indicate imprecision due to the low frequency of events.

4.2. Clinical presentation of aortitis cases

Patients with G-CSF-associated aortitis report nonspecific mild to moderate symptoms such as fever, epigastric pain, and general malaise (Table 5). They also exhibit abnormal results of laboratory tests indicating inflammation, as well as thickening of the walls of major arteries, including the aorta, carotid artery, and iliac artery. Aortitis has various causes, including infections (e.g., syphilis and salmonella) and connective-tissue disorders, or can be idiopathic [6,7]. Bacterial culture of patients' blood, urine, and sputum yielded negative results. Serological tests for syphilis and Rickettsia were performed in the case of one patient and proved negative. Because biopsy of the aortic wall is risky, no previous study has included histological analyses. In summary, the clinical characteristics of G-CSF-associated aortitis in four patients were similar to those of Takayasu arteritis. The proportions of female patients with G-CSF-associated and non-G–CSF-associated aortitis were 15 of 16 (93.8% [95%CI 69.8, 99.8]) (Table 4) and 22 of 25 (88% [95%CI 68.8, 97.5]), respectively (Table 2). This female bias is similar to that of Takayasu arteritis [8–10]. The mean age of the patients with aortitis was 56.9 (10.4) years, which is older than is typical for Takayasu arteritis in Japan (35 and 43.5 years in females and males,

Table 2
Proportion and odds ratio of aortitis (n = 102014).

Variables	Aortitis (n = 25)	All (n = 102014)	Proportion (%) (95% CI)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	P value (Wald's test)
Age (mean (sd))	56.0 (10.4)	60.2 (14.5)		0.98 (0.96–1.01)	1.00 (0.97–1.03)[§]	0.935
Sex						
Female	22	41,890	0.05 (0.03–0.08)	reference for Male		
Male	3	57,206	0.01 (0.00–0.02)	0.10 (0.03–0.33)	0.13 (0.04–0.46)	0.001
Unknown	0	2918	0.00 (0.00–0.13)			
G-CSF	16	3409	0.47 (0.27–0.76)	49.50 (21.86–112.11)	45.87 (19.16–109.8)	< 0.001
Filgrastim	4	1617	0.25 (0.07–0.63)			
Pegfilgrastim	11	696	1.58 (0.79–2.81)			
Lenograstim	3	1274	0.24 (0.05–0.69)			
No G-CSF	9	98,630	0.01 (0.00–0.02)	reference for G-CSF		
Other Medical Products						
Carboplatin	8	5234	0.15 (0.07–0.30)	8.86 (3.82–20.55)	2.55 (0.79–8.25)	0.117
Bevacizumab	4	8220	0.05 (0.01–0.12)	2.20 (0.75–6.41)	2.61 (0.81–8.45)	0.109
Paclitaxel	8	7345	0.11 (0.05–0.21)	6.03 (2.6–13.97)	1.98 (0.61–6.45)	0.257

Abbreviations: G-CSF, granulocyte colony-stimulating factor.
[§] Age increment is per year for odds ratio of logistic regressions.

respectively). However, these data may be affected by the age distribution of the malignant diseases for which the drugs were administered.

4.3. Recent increase in the incidence of aortitis

Although G-CSF has been available for more than 27 years and the JADER database contains data from the last 14 years, most of the aortitis cases were reported after 2015. We considered this from the following viewpoints:

4.3.1. Does the ADR result from a specific lot with a quality issue?

Lenograstim, filgrastim, and pegfilgrastim are marketed and distributed by different market authorization holders (MAHs). Thus, aortitis is not likely due to a quality issue with a specific lot.

4.3.2. Does the ADR result from interactions with newly approved and marketed drugs?

Screening for ADRs in the JADER database using a Bayesian confidence propagation neural network (BCPNN) [11,12] resulted in identification of carboplatin, bevacizumab, and paclitaxel ADRs in patients with malignancies. In a multivariate logistic regression, although the crude ORs for these agents indicated an association with aortitis, this was lost after adjustment. Moreover, bevacizumab was approved in 2007. Thus, concomitant use of drugs does not explain the recent increase in the prevalence of G-CSF-associated aortitis.

4.3.3. Does the ADR result from newly approved and marketed biosimilars of G-CSF?

Although 104 patients were treated with G-CSF biosimilars, none developed aortitis.

4.3.4. Does the ADR result from newly approved and marketed PEGylated G-CSF?

Of the 16 patients with G-CSF-associated aortitis, 11 were treated with PEGylated G-CSF. PEGylated G-CSF was first approved and marketed in 2014, so the recent increase in the prevalence of G-CSF-associated aortitis may be due to its delayed use in clinical practice after approval.

The frequency of aortitis was higher in patients treated with PEGylated G-CSF than in those administered other G-CSF agents. However, the development of aortitis in some patients who received filgrastim and lenograstim means that the condition is not specific to pegfilgrastim.

Table 3
Proportion and odds ratio of aortitis by underlying malignancy.

Underlying Malignancy	G-CSF (+) Aortitis (+)	Aortitis (−)	G-CSF (−) Aortitis (+)	Aortitis (−)	odds ratio point estimate (95% CI)		p-value
Lung Cancer	1	432	0	16,971	Inf	(1.00, Inf)	0.025
Colorectal Cancer	0	97	1	13,603	0.00	(0.00, 5039.07)	1.000
Breast Cancer	4	369	5	11,411	24.71	(4.88, 115.54)	0.000
Renal Cancer	0	94	0	6898	0.00	(0.00, Inf)	1.000
Prostate Cancer	1	215	0	6825	Inf	(0.81, Inf)	0.031
Gastric Cancer	0	42	0	6583	0.00	(0.00, Inf)	1.000
Hepatic Cancer	0	16	0	5911	0.00	(0.00, Inf)	1.000
Malignant Lymphoma	3	671	0	4953	Inf	(3.04, Inf)	0.002
Chronic Myeloid Leukemia	0	27	0	4596	0.00	(0.00, Inf)	1.000
Acute Myeloid Leukemia	0	412	1	2972	0.00	(0.00, 280.20)	1.000
Pancreatic Cancer	0	30	0	2898	0.00	(0.00, Inf)	1.000
Ovarian Cancer	4	270	2	2666	19.70	(2.81, 218.18)	0.001
Acute Lymphoid Leukemia	0	291	0	2212	0.00	(0.00, Inf)	1.000
Bladder Cancer	0	15	0	1727	0.00	(0.00, Inf)	1.000
Esophageal Cancer	1	30	0	1675	Inf	(1.39, Inf)	0.018
Uterine Cancer	2	116	0	808	Inf	(1.29, Inf)	0.016
Cervical Cancer	0	12	0	750	0.00	(0.00, Inf)	1.000
Adult T-cell Leukemia/Lymphoma	0	85	0	624	0.00	(0.00, Inf)	1.000
Chronic Lymphoid Leukemia	0	22	0	321	0.00	(0.00, Inf)	1.000
others	0	284	0	8635	0.00	(0.00, Inf)	1.000

Abbreviations: Inf = infinity.

Table 4
Aortitis case treated with G-CSF.

Case ID	Reported Year-Quarter	Age	Gender	Height	Body weight	Outcome	G-CSF	Underlying Malignancy
#1	2013.Apr-Jun	60	F	150 cm	40 kg	improved	Lenograstim	B-cell lymphoma
#2	2016.Jan-Mar	50	F	160 cm	50 kg	recovered	Pegfilgrastim	Ovarian cancer
#3	2016.Jan-Mar	70	F	140 cm	40 kg	recovered	Filgrastim	Fallopian tube cancer
#4	2016.Jul-Sep	40	F	150 cm	60 kg	recovered	Filgrastim	Uterine cancer
#5	2016.Oct-Dec	60	F			recovered	Pegfilgrastim	Breast cancer
#6	2016.Oct-Dec	70	F	150 cm	60 kg	improved	Pegfilgrastim	Uterine cancer
#7	2017.Apr-Jun	40	F		50 kg	recovered	Lenograstim	Ovarian cancer
#8	2017.Apr-Jun	60	F	150 cm	60 kg	recovered	Pegfilgrastim	Oesophageal carcinoma
#9	2017.Apr-Jun	40	F		50 kg	improved	Lenograstim	Ovarian cancer
#10	2017.Jul-Sep	60	M	160 cm	50 kg	recovered	Pegfilgrastim	Hormone-refractory prostate cancer
#11	2017.Jul-Sep	70	F	150 cm	50 kg	improved	Pegfilgrastim Filgrastim	Lymphoma
#12	2017.Oct-Dec	60	F	140 cm	40 kg	improved	Pegfilgrastim	Breast cancer
#13	2017.Oct-Dec	60	F			improved	Pegfilgrastim	Lung adenocarcinoma
#14	2017.Oct-Dec	60	F	150 cm	40 kg	improved	Pegfilgrastim	Lymphoma
#15	2017.Oct-Dec	60	F	140 cm	40 kg	improved	Pegfilgrastim	Breast cancer
#16	2018.Jan-Feb	60	F			improved	Filgrastim Pegfilgrastim	Breast cancer recurrent

Ages, height, body weight are shown as rounded by truncation.

Aortitis usually manifests as nonspecific symptoms such as fever, epigastric pain, and general malaise, as well as laboratory findings suggestive of inflammation (Table 5). It is diagnosed based on detection of thickening of the walls of major arteries by computed tomography, magnetic resonance imaging, or ultrasonography. In April 2018, positron emission tomography was approved for diagnosis of aortitis in Japan; this will likely have improved the diagnosis of aortitis.

Pegfilgrastim was approved under different regulatory conditions than filgrastim and lenograstim. The MAH of pegfilgrastim conducted early post-marketing phase risk minimization and vigilance (EPPV) and is performing a drug use investigation (DUI) based on a risk management plan (RMP) prepared based on regulatory requirements. In April 2012 the Risk Management Guidance and Formulation of Drug Risk Management Plan was issued in Japan. An RMP is required for all newly approved drugs and biosimilars for which the application was filed after April 2013. The DUI and EPPV were introduced in Japan in 1997 and 2000, respectively. Because filgrastim and lenograstim were approved in 1991, they do not require pharmacovigilance. Thus, data on pegfilgrastim ADRs were obtained post-marketing. Any study based on an ADR database should consider the fact that pegfilgrastim and conventional G-CSFs were approved under different regulatory conditions. Thus, pegfilgrastim may not be associated with an increased incidence of aortitis compared to conventional G-CSFs.

5. Conclusions

G-CSF treatment is associated with a signal of an increased risk for aortitis, irrespective of the G-CSF agent used. Due to the limitations of the JADER database, we do not recommend that clinicians alter their prescribing of G-CSFs, although appropriate monitoring should be considered.

6. Limitations

There are limitations to using ADR databases; for example, they do not contain information on persons who did not develop an ADR or (in the version available to the public) their locations. The latter prevented analyses of the geographic distribution of aortitis. The data may also be subject to reporting bias and the lack of a research protocol means that ADR reports are not collected systematically. Finally, data on possible confounding factors (e.g., background information, underlying conditions, and environmental factors) are not collected systematically.

Disclaimers

The findings and views expressed in the submitted article are his or her own and not an official position of the institution.

Table 5
G-CSF associated aortitis cases reported in medical literatures.

Case Report ID	Literature Case #1	Liteature Case #2	Literature Case #3	Literature Case #4
Reporter	Darie C [1]	Adiga G [4]	Miller E [3]	Sato Y [2]
Age	55	54	52	67
Gender	Female	Male	Male	Female
Underlying disease	None (PBSC donor)	lung squamous cell carcinoma	None (PBSC donor)	lung adenocarcinoma
G-CSF	filgrastim	not specified	filgrastim	pegfilgrastim
therapy duration (day)	5	8	4	1
Time to onset	2 days	8 days	6 months	8 days
Symptoms	Epigastric pain, fever	Epigastric pain, fever	Back pain, constipation	General malaise, high fever, hypotension
Physical findings	Abdominal tenderness, murmur	Abdominal tenderness	None	unremarkable
ESR	108	113	39	not reported
Other abnormal labs	Hematuria, CRP, ANA, LFTs	CRP	CRP	CRP, WBC, D-dimer
Diagnostic imaging	CT/MRI	CT/MRI	CT	CT
Response to corticosteroids	Rapid, complete	Rapid, complete	Rapid, complete	Shortly, complete
Complications	None	None	Aneurysm	None

Abbreviations: LFT's liver function tests.

Declaration of interests

Dr. Oshima reports personal fees from Novartis Pharma K.K., personal fees from sanofi K.K., outside the submitted work; Dr. Tani reports grants from Neo Pharma Japan Co.,Ltd, grants from Shinnihonseiyaku Co., Ltd, outside the submitted work; Dr. Tojo reports grants from Bristol-Myers, grants from Pfizer, grants from Chugai Pharmaceutical, grants from Daiichi Sankyo, grants from Sumitomo Dainippon-pharma, personal fees from Taiho Pharmaceutical, personal fees from Rohto Pharmaceutical, personal fees from Celgene, personal fees from Novartis, personal fees from Ohtsuka Pharmaceutical, personal fees from Sysmex, outside the submitted work; Dr. Takahashi has nothing to disclose.

CRediT authorship contribution statement

Yasuo Oshima: Conceptualization, Software, Writing - original draft. **Satoshi Takahashi:** Investigation, Data curation, Writing - original draft. **Kenzaburo Tani:** Methodology, Validation, Visualization, Writing - review & editing, Supervision. **Arinobu Tojo:** Supervision, Writing - review & editing.

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