Antineoplastic Drug-induced Aortitis: An Unraveled Adverse Effect Using the World Health Organization Pharmacovigilance Database

To the Editor:

Aortitis is a rare inflammatory disease ranging from asymptomatic aortic thickening to life-threatening manifestations, especially aortic dissection or stenosis. Aortitis mainly occurs during systemic inflammatory diseases (giant cell arteritis, Takayasu arteritis, IgG4-related disease) and less frequently in patients with syphilis or tuberculosis[1]. Aortitis is rarely suspected to be induced by drugs and its causality is hardly assessable. The aim of our study is to identify drugs associated with aortitis occurrence using a data- mining approach.

We used VigiBase, the World Health Organization (WHO) global Individual Case Safety Report (ICSR) database, which contains reports of suspected adverse drug reactions (ADR) collected by national drug authorities in more than 130 countries. The database is automatically deduplicated by VigiBase; further, a case-by-case review has been performed to exclude possible duplicates. This makes it powerful for the conduct of disproportionality analyses. This pharmacovigilance statistical method, based on a case/non-case approach, estimates whether an adverse event is differentially reported for a drug compared to other drugs. The association can be expressed using the reporting OR (ROR) and its CI for each drug adverse event combination. This approach has proven its interest for the detection of safety signals[2]. To identify drugs associated with aortitis occurrence, we extracted ICSR recorded in VigiBase from inception in 1967 until June 30, 2019, with the ADR "aortitis." According to the European Medicines Agency, threshold for signal detection is defined as an ROR lower boundary 95% CI ≥ 1 and a number of cases ≥ 3[3]. Drugs not reported in at least 3 ICSR and 2 different countries have been excluded. To limit reporting bias, comparators were all drugs of the Anatomical Therapeutic Chemical (ATC) class L (antineoplastic and immunomodulating agents).

VigiBase is a fully anonymized database of spontaneous reports from WHO; access is granted for national or regional pharmacovigilance centers, such as our team. The information within VigiBase, a global pharmacovigilance database, comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. According to French law, ethics board approval is not mandatory for studies on an anonymous pharmacovigilance database. The present analysis does not represent the opinion of the University Medical Center (UMC) or the WHO, and reflects only the authors' opinions.

Of the 19,834,180 ICSR in VigiBase, 162 aortitis cases have been identified, reported with 95 different suspected drugs. After exclusion of ICSR reported in only 1 country (n = 58) and suspected drugs reported in less than 3 different ICSR (n = 2), we retained 102 ICSR corresponding to 18 suspected drugs. Aortitis ICSR were reported by physicians in 62.7%, other health professionals in 22.5%, consumers in 6.9%, and pharmacists in 3.9%; reporter qualification was unknown in 3.9%. Mean age at the onset of aortitis was 58 ± 13 years; 70% of patients were female. Reports originate mainly from Japan (31%), United States (27%), Canada, and Sweden (7% each). Figure 1 indicates for each suspected drug the number of cases and corresponding ROR for aortitis. Of the 18 suspected drugs, 9 are associated with a significant ROR for aortitis, meaning a possible pharmacovigilance signal. Strikingly, all these drugs were antineoplastic and immunomodulating agents (ATC L class): granulocyte colony-stimulating factor (G-CSF) drugs (lipegfilgrastim, lenograstim, filgrastim, pegfilgrastim), epirubicin, nivolumab, tocilizumab (TCZ), trastuzumab, and rituximab (RTX).

Our analysis identified certain antineoplastic and immunomodulating agents as being strongly associated with the occurrence of aortitis, the strongest signal being for G-CSF drugs. This association has already been

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Substance	Aortitis cases	Non cases	Number of countries	ROR (95% CI)
Etanercept	7	490 582	3	0.5 (0.2-1.0)
Influenza vaccine	4	217 405	4	0.7 (0.2-1.9)
Cisplatin	3	76 997	3	1.4 (0.5-4.5)
Paclitaxel	4	89 140	3	1.6 (0.6-4.5)
Cyclophosphamide	4	88 568	3	1.7 (0.6-4.5)
Infliximab	7	149 235	6	1.7 (0.8-3.7)
Docetaxel	5	100 139	3	1.8 (0.8-4.5)
Tacrolimus	3	52 733	2	2.1 (0.7-6.6)
Gemcitabine	3	47 956	3	2.3 (0.7-7.2)
Rituximab	7	72 243	4	3.7 (1.7-7.8)
Trastuzumab	5	30 128	3	6.2 (2.5-15.2)
Tocilizumab	6	36 123	3	6.3 (2.8-14.2)
Nivolumab	6	34 811	3	6.5 (2.9-14.7)
Epirubicin	4	17 233	2	8.6 (3.2-23.4)
Pegfilgrastim	25	35 773	6	31.1 (20.1-48.1)
Filgrastim	17	13 248	6	53.4 (32.0-88.9)
Lenograstim	3	2 129	2	52.3 (16.6-164.4)
Lipegfilgrastim	3	1 451	3	76.8 (24.4-241.5)

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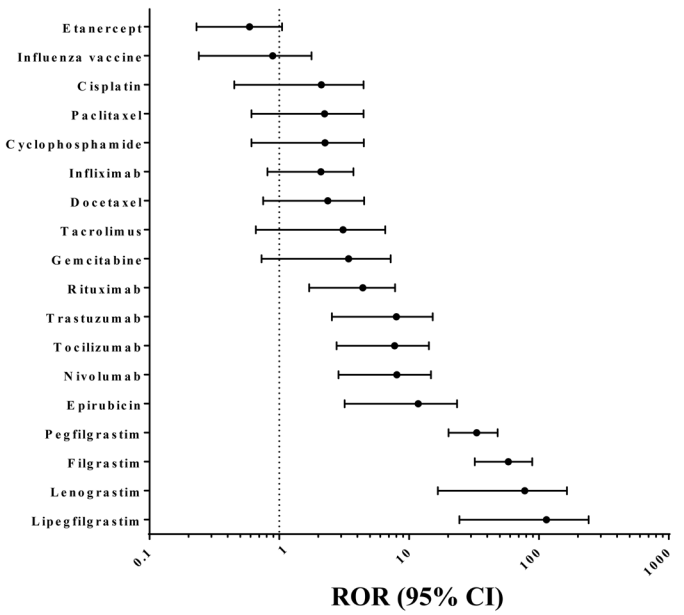

Figure 1. Drugs associated with aortitis reporting within the WHO pharmacovigilance database, and ROR. Left panel shows the number of cases and ROR of aortitis ICSR and right panel shows the forest plot of ROR and their 95% CI. Of note, 1 ICSR can include more than 1 suspected drug. ROR (95% CI) are calculated as ad/bc (e ^(± 1.96 √(1/a+1/b+1/c+1/d))), where a is the number of aortitis cases reported for the suspected drug, b is the number of other ADR cases reported for the suspected drug, c is the number of aortitis cases reported with the comparator drugs, and d is the number of other ADR cases reported for the comparator drugs. If the CI does not include 1, the ROR is considered significant and is interpreted as indicating an association between the drug and the occurrence of aortitis. WHO: World Health Organization; ROR: reporting OR; ICSR: Individual Case Safety Report; ADR: adverse drug reaction.

Table 1. Detailed description of aortitis cases reported with epirubicin, nivolumab, RTX, TCZ, or trastuzumab.

Suspected Drug	Sex	Age, yrs	Country	Reporter Qualification	Indication of Suspected Drug	Concomitant Drug	Reported Reactions
Epirubicin	Female	55	Japan	Physician	Breast cancer	Unknown drug	Aortitis
Epirubicin	Female	55	Japan	Physician	Breast cancer	Aprepitant, CYC (S), dexamethasone, palonosetron	Aortitis
Epirubicin	Female	55	Japan	OHP	Breast cancer	Unknown drug	Aortitis
Epirubicin	Female	55	Germany	OHP	Breast cancer	Erythropoietin human, paclitaxel (S)	Aortitis, polyserositis
Nivolumab	Female	NA	Spain	OHP	Malignant melanoma	—	Aortitis
Nivolumab	Male	57	USA	OHP	Lung cancer	—	Aortitis
Nivolumab	Male	NA	Greece	C/NHP	Unknown indication	—	Aortitis
Nivolumab	Male	57	USA	OHP	Lung cancer	Methylprednisolone	Aortitis, back pain
RTX	Female	46	Canada	Physician	Takayasu arteritis	Acetylsalicylic acid, alendronic acid, amlodipine, atenolol, calcium carbonate, clopidogrel, levothyroxine, prednisone, ranitidine	Aortitis, carotid artery stenosis, increased CRP, vascular pain
RTX	NA	NA	NA	Physician	Granulomatosis with polyangiitis	—	Abdominal pain, Aortitis, drug ineffective, granulomatosis with polyangiitis, IgG4-related disease, treatment failure
RTX	NA	NA	USA	Physician	ANCA vasculitis	—	Aortitis, IgG4-related disease
RTX	NA	NA	USA	C/NHP	IgG4-related disease	—	Aortitis
RTX	Male	78	UK	Physician	Rheumatoid arthritis	Methotrexate	Acute kidney injury, Aortitis, pneumonia
RTX	Male	48	Canada	OHP	Non-Hodgkin lymphoma	Cisplatin (S), dexamethasone, gemcitabine (S)	Aortitis, ALT and AST increased, atelectasis, anemia, headache, pleural effusion, pyrexia, vasculitis
RTX	Male	68	Austria	Physician	Chronic polyarthritis	—	Aortitis, splenitis, stent placement
TCZ	Female	44	Canada	C/NHP	Rheumatoid aortitis	Alprazolam, amlodipine, asenapine, atorvastatin, clopidogrel, folic acid, hydrochlorothiazide, hydroxyquinoline, lorazepam, MTX, metoprolol, naproxen, pantoprazole, ramipril, sertraline, valproic acid	Abdominal discomfort, anxiety, Aortitis, arthralgia, blood creatinine increased, bursitis, calcinosis, drug ineffective, gait inability, gastric disorder, abnormal glomerular filtration rate, gout, granuloma, hyperhidrosis, injection site pain, joint swelling, memory impairment, middle insomnia, multiple sclerosis, nausea, pain, peripheral swelling, rash, red cell distribution width increased, taste disorder, tremor, vomiting
TCZ	Female	51	Japan	Physician	Aortitis	Alendronic acid, folic acid, MTX, omeprazole, prednisolone, tacrolimus (S)	Aortitis
TCZ	Female	47	Canada	Physician	Relapsing polychondritis	Atenolol, enalapril, folic acid, indapamide, iron, MTX, pantoprazole, prednisone, risedronic acid	Aortitis, dysphonia, polychondritis
TCZ	Female	NA	USA	Physician	Temporal arteritis	—	Aortitis, blindness, temporal arteritis
TCZ	Female	NA	USA	Physician	Temporal arteritis	—	Aortitis
TCZ	Female	16	Canada	Physician	Takayasu arteritis	Acetylsalicylic acid, clonazepam, clonidine, folic acid, MTX, pantoprazole, prednisone	Aneurysm, Aortitis, cardiac disorder, device related infection, graft infection, hypotension, pneumonia, vasculitis
Trastuzumab	Female	70	Sweden	OHP	Breast cancer	Docetaxel (S), filgrastim (S), pertuzumab, piperacillin-tazobactam	Aortitis, febrile neutropenia
Trastuzumab	Female	70	Sweden	OHP	Breast cancer	Docetaxel (S), pertuzumab	Aortitis, dehydratation, diarrhea, febrile neutropenia, gastric ulcer hemorrhage, syncope
Trastuzumab	Female	60	Sweden	OHP	Breast cancer	Docetaxel (S), G-CSF	Aortitis, pyrexia, vasculitis
Trastuzumab	Female	72	Japan	Physician	Breast cancer	CYC (S), unknown drug, pegfilgrastim (S)	Aortitis
Trastuzumab	Female	NA	USA	Physician	Breast cancer	Docetaxel, carboplatin	Aortitis

This table shows aortitis cases with a doubtful causality regarding the suspected drug, because these cases also include G-CSF as concomitant drugs, which are strongly associated with aortitis. A case-by-case review has been performed to exclude possible duplicates, on the basis of the following data: sex, age, country, date of introduction of treatment, and date of onset of sign. RTX: rituximab; TCZ: tocilizumab; C/NHP: consumer/non-health professional; NA: not available; OHP: other health professional; S: another suspected drug; MTX: methotrexate; CYC: cyclophosphamide; CRP: C-reactive protein; ANCA: antineutrophil cytoplasmic antibodies; ALT: alanine aminotransferase; AST: aspartate aminotransferase; G-CSF: granulocyte colony-stimulating factor.

reported in case series and using pharmacovigilance databases[4,5,6]. However, some authors pointed out that aortitis was a rare adverse event of G-CSF and it was therefore difficult to assess the drug causality[7]. Our data strongly support the role of G-CSF drugs in the onset of aortitis. ICSR reported with epirubicin or trastuzumab also included G-CSF drugs as concomitant medications. The causal relationship of epirubicin or trastuzumab and aortitis is therefore questionable (Table 1). Aortitis ICSR reported with TCZ and RTX involved patients treated for aortitis or inflammatory diseases associated with aortitis, suggesting treatment failure. In contrast, patients treated with nivolumab were not receiving any concomitant medication, especially G-CSF, strengthening a causal relationship with aortitis. Of note, of the 6 aortitis ICSR associated with nivolumab and reported in VigiBase, 2 had also been reported in the literature[8,9]. For the 2 drugs likely to induce aortitis, G-CSF and nivolumab, time to onset was available in 12 and 3 patients, respectively[8,9]. In these patients, median time to aortitis onset was 8 days (range 3–34 days) and 285 days (range 275–305 days) after initial exposure to G-CSF and nivolumab, respectively. Intrinsic limitations of this analysis, as in other studies based on pharmacovigilance database, include underreporting and a heterogeneous causality assessment among ICSR due to different pharmacovigilance practices. However, aortitis is an expert physician diagnosis that is trustworthy, and that limits the reporting bias. Finally, although our study design cannot estimate the extent of drug-induced aortitis risk, it is powerful to find out unidentified ADR.

Our study shows a likely safety signal for aortitis with G-CSF and nivolumab. Physicians should consider aortitis in case of abdominal and/or chest pain and increased acute-phase reactants in patients receiving these drugs. These findings also support roles for G-CSF and programmed cell death protein 1 in the pathophysiology of large vessel inflammation. They need to be confirmed in further studies, especially experimental studies.

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