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Underreporting of Major Cardiac Adverse Events With Immune Checkpoint Inhibitors in Clinical Trials: Importance of Postmarketing Pharmacovigilance Surveys

TO THE EDITOR:

Naqash et al¹ reported major adverse cardiac events (MACEs) with immune checkpoint inhibitors (ICI) through the clinical trial database of the National Cancer Institute (NCI). As underlined by the authors, ICI-related myocarditis is a rare but life-threatening immune-related adverse event, with little data about predictors of outcome. Importantly, if myocarditis accounted for 45% of ICI-related MACEs, ICI may be responsible for acute coronary syndrome, congestive heart failure, pericardial disease, dysrhythmia, and cardiac arrest. In this work, the report of non-myocarditis MACE is of particular interest since previous studies mostly focused on ICI-related myocarditis. Furthermore, the authors noted that nonmyocarditis MACEs were more commonly reported when ICI were associated with targeted therapies, questioning the impact of these associations on microvasculature and atherosclerosis progression, as recently reported by others.² These observations

TABLE 1. Characteristics of All MACE Cases Reported With Anti-PD-(L)-1 in VigiBase

Characteristic	All MACEs (n = 5,195)
Age, years; median (P25-P75; n = 3,916)	65.3; 67 (59–74)
Sex, No. (%)	
Male	3,166 (60.9)
Female	1,698 (32.7)
Unknown	331 (6.4)
Reporter type, No. (%)	
Health professional	4,757 (91.6)
Others	899 (17.3)
Unknown	110 (2.1)
MACE reported, No. (%)	
Cardiac arrhythmias (HLGT)	1,993 (38.4)
Pericardial disorders (HLGT)	638 (12.3)
Coronary artery disorders (HLGT)	1,598 (30.8)
Cardiomyopathies (HLT)	203 (3.9)
Noninfectious myocarditis (HLT)	1,241 (23.9)

(continued in next column)

TABLE 1. Characteristics of All MACE Cases Reported With Anti-PD-(L)-1 in VigiBase (continued)

Characteristic	All MACEs (n = 5,195)
Anti-PD-(L)-1 reported, No. (%)	
Atezolizumab	558 (10.7)
Avelumab	118 (2.3)
Cemiplimab	58 (1.1)
Durvalumab	233 (4.5)
Nivolumab	2,735 (52.6)
Pembrolizumab	1,551 (29.9)
Time to onset, days, No. (%)	82 (1.6)
Mean	44
Median	30
Min	0
Max	228
Single suspect (%)	60.5
Serious, No. (%)	
Yes	4,731 (91.1)
No	411 (7.9)
Unknown	53 (1.0)
Fatal, No. (%)	
Yes	1,446 (27.8)
No	3,749 (72.2)
Coreported preferred terms of interest	
Tumor progression	416 (8.0)
Myositis	234 (4.5)
Myasthenia gravis	144 (2.8)
Coreported active ingredient of interest, No. (%)	
Ipilimumab (anti-CTLA-4)	840 (16.2)
Carboplatin	293 (5.6)
Paclitaxel	169 (3.3)
Pemetrexed	156 (3.0)
Bevacizumab	98 (1.9)
Cisplatin	91 (1.8)
Axitinib	76 (1.5)
Rechallenge, No. (%)	1,423 (27.4)
No recurrence	89 (6.3)
Recurrence	15 (1.1)
Unknown	1,319 (92.7)

Abbreviations: CTLA-4, cytotoxic T-cell lymphocyte-4; HLGT, high-level grouped term (MedDRA 25.0); HLT, high-level term (MedDRA 25.0); MACEs, major adverse cardiac events; PD-(L)-1, programmed death-(ligand)-1.

undoubtedly warrant further awareness both in the short and long term.

Notwithstanding, we were taken aback by the very low incidence of ICI-related MACE in this pooled analysis of trials (0.6% of patients treated), with an incidence of myocarditis as low as 0.26%, whereas myocarditis may occur in more than 1% of patients³ with a recent report of a 3% incidence through a prospective study in patients with lung cancer.⁴ Additionally, a recent retrospective study reported an incidence of 10.3% of nonmyocarditis MACEs (acute coronary syndrome, heart failure, stroke, and transient ischemic attack) through a median follow-up of 13 months.⁵

This underestimation of ICI-related MACE found in the NCI trials database may stem from numerous facts. First, clinical trials mostly include patients with few coexistent medical conditions, whereas nonmyocarditis MACE is associated with cardiac comorbidity (ie, heart failure and valvular heart disease⁵). It reminds us that the extrapolation of clinical trials data to real-life setting may always be uncertain because of this selection bias.

Second, the pooled analysis by Naqash et al¹ included clinical trials conducted between 2015 and 2019. It is noteworthy that the first description of ICI-related myocarditis by Johnson et al dates back to 2016⁶ while the first definition proposed by Bonaca et al for this emerging syndrome dates to 2019⁷ with a very recent update by the International Cardio-Oncology Society.⁸ Herein, only four patients were reported with definite myocarditis according to these criteria since systematic workup using angiography, cardiac magnetic resonance, and endomyocardial biopsies was not set up at the time of these trials. Hence, the precise incidence of ICI-related MACE remains uncertain here because of this potential classification bias.

Third, since clinical trials are usually designed to focus on survival and response rates through limited sample size and over short follow-up periods, they are not completely reliable for the detection of rare or delayed immune-related adverse events. Conversely, postmarketing pharmacovigilance surveys aim at a detection of all AEs in real-life settings. Using VigiBase, the WHO's pharmacovigilance database, we searched all serious adverse drug reactions reported with anti-programmed death-(ligand)-1 (PD-[L]-1) agents through a selection of broad MedDRA terms (Medical Dictionary of Regulatory Activities): cardiac arrhythmias, pericardial disorders, coronary artery disorders, cardiomyopathies, and noninfectious myocarditis. Over 31,429,918 reported drug AEs, we found 5,195 ICI-related MACEs with 1,241 myocarditis where anti-PD-(L)-1 was the single suspected drug in 61% of cases (Tables 1 and 2). The overall reporting of myocarditis with anti-PD-(L)-1 was more than 30-fold higher than with other antineoplastic agents

TABLE 2. Characteristics of Myocarditis Cases Reported With Anti-PD-(L)-1 in VigiBase

Characteristic	Myocarditis MACE (n = 1,241)
Age, years; median (P25-P75; n = 954)	67.4; 70 (62-75.3)
Sex, No. (%)	
Male	737 (59.4)
Female	407 (32.8)
Unknown	97 (7.8)
Reporter type, No. (%) ^a	
Health professional	1,216 (98.0)
Others	899 (10.4)
Unknown	20 (1.6)
Type of myocarditis reported (HLT), No. (%)	
Myocarditis (PT)	987 (79.5)
Immune-mediated myocarditis (PT)	162 (13.1)
Autoimmune myocarditis (PT)	70 (5.6)
Myopericarditis (PT)	19 (1.5)
Hypersensitivity myocarditis (PT)	2 (0.2)
Eosinophilic myocarditis (PT)	1 (0.1)
Giant cell myocarditis (PT)	1 (0.1)
Anti-PD-(L)-1 reported, No. (%)	
Atezolizumab	84 (6.8)
Avelumab	28 (2.3)
Cemiplimab	23 (1.9)
Durvalumab	55 (4.4)
Nivolumab	667 (53.7)
Pembrolizumab	415 (33.4)
Time to onset, days, No. (%)	153 (12.3)
Mean	36
Median	32
Min	0
Max	117
Single suspect (%)	61.3
Serious, No. (%)	
Yes	1,224 (98.6)
No	6 (0.5)
Unknown	11 (0.9)
Fatal, No. (%)	
Yes	359 (28.9)
Unknown	882 (71.1)
First coreported preferred terms, No. (%)	
Myositis	198 (16.0)
Myasthenia gravis	111 (8.9)
Coreported active ingredient of interest, No. (%)	
Ipilimumab (anti-CTLA-4)	293 (23.6)
Carboplatin	52 (4.2)

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TABLE 2. Characteristics of Myocarditis Cases Reported With Anti-PD-(L)-1 in VigiBase (continued)

Characteristic	Myocarditis MACE (n = 1,241)
Pemetrexed	32 (2.6)
Axitinib	19 (1.5)
Bevacizumab	17 (1.4)
Paclitaxel	17 (1.4)
Cisplatin	11 (0.9)
Rechallenge, No. (%)	346 (27.9)
No recurrence	8 (2.3)
Recurrence	3 (0.9)
Unknown	335 (96.8)

Abbreviations: CTLA-4, cytotoxic T-cell lymphocyte-4; HLT, high-level term (MedDRA 25.0); MACE, major adverse cardiac event; PD-(L)-1, programmed death-(ligand)-1; PT, preferred term (MedDRA 25.0).

^aThe same report can be reported with more than one reporter qualification.

(reporting odds ratio, 31.7; 95% CI, 28.9 to 34.8, using disproportionality analysis). Unexpectedly, anti-vascular endothelial growth factor agents were rarely reported in association with anti-PD-(L)-1 therapy (1.9%).

Finally, the fatality rate reported by Naqash et al¹ is lower than early reports (22.5% v 50%) but close to recent publications including our own series of 29 ICI-related myocarditis⁹ and data from VigiBase. Beyond progresses made in early detection of ICI-related MACE, there also may be smoldering cases who benefit from early steroid treatment, the main prognostic factor of outcome to date.¹⁰ This questions the possibility of ICI rechallenge in some cases, although scarce data have been reported to date, even in VigiBase. In our experience, six patients were successfully rechallenged after ICI-related MACE, with only one myocarditis relapse with favorable outcome.⁹

Altogether, the study by Naqash et al,¹ on the basis of the analysis of the NCI clinical trials database, found a lower incidence of ICI-related MACE than what may be observed in real-life settings. However, it sheds light on the necessity of an early and appropriate detection of myocarditis and nonmyocarditis MACEs under ICI treatment and on the urge of prospective studies to evaluate recent diagnostic criteria, novel immunomodulatory drugs for refractory cases, and assess the possibility of ICI rechallenge.

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REFERENCES

1. Naqash AR, Moey MYY, Cherie Tan X-W, et al: Major adverse cardiac events with immune checkpoint inhibitors: A pooled analysis of trials sponsored by the National Cancer Institute—Cancer Therapy Evaluation Program. *J Clin Oncol* 40:3439-3452, 2022
2. Drobni ZD, Alvi RM, Taron J, et al: Association between immune checkpoint inhibitors with cardiovascular events and atherosclerotic plaque. *Circulation* 142:2299-2311, 2020
3. Nardi Agmon I, Itzhaki Ben Zadok O, Kornowski R: The potential cardiotoxicity of immune checkpoint inhibitors. *J Clin Med* 11:865, 2022
4. Faubry C, Faure M, Toublanc A-C, et al: A prospective study to detect immune checkpoint inhibitors associated with myocarditis among patients treated for lung cancer. *Front Cardiovasc Med* 9:878211, 2022
5. Laenens D, Yu Y, Santens B, et al: Incidence of cardiovascular events in patients treated with immune checkpoint inhibitors. *J Clin Oncol* 40:3430-3438, 2022
6. Johnson DB, Balko JM, Compton ML, et al: Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med* 375:1749-1755, 2016
7. Bonaca MP, Olenchock BA, Salem J-E, et al: Myocarditis in the setting of cancer therapeutics: Proposed case definitions for emerging clinical syndromes in cardio-oncology. *Circulation* 140:80-91, 2019
8. Herrmann J, Lenihan D, Armenian S, et al: Defining cardiovascular toxicities of cancer therapies: An International Cardio-Oncology Society (IC-OS) consensus statement. *Eur Heart J* 43:280-299, 2022
9. Coustal C, Vanovershelde J, Quantin X, et al: Prognosis of immune checkpoint inhibitors-induced myocarditis: A case series. *J Immunother Cancer* (in press)
10. Zhang L, Zlotoff DA, Awadalla M, et al: Major adverse cardiovascular events and the timing and dose of corticosteroids in immune checkpoint inhibitor-associated myocarditis. *Circulation* 141:2031-2034, 2020