JACC: CARDIOONCOLOGY VOL. 4, NO. 5, 2022

EDITORIAL COMMENT

A New Risk Factor for Cardiovascular Events in Patients Receiving Immune Checkpoint Inhibitor Therapy?*

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Immune checkpoint inhibitor (ICI) therapy has become an important pillar of cancer treatment. The use of ICIs has provided substantial improvement in cancer outcomes and overall survival in several cancers.[1,2] The clinical indication of ICIs continues to expand beyond the metastatic setting to early-stage cancers with hundreds of ongoing clinical trials.[3] In patients receiving ICI therapy there has been a growing recognition of the development of cardiovascular events (CVEs) many of which are felt to be due to immune activation.[4] The spectrum of reported CVEs has included myocarditis, pericarditis, vasculitis, cardiomyopathy, acute coronary syndromes, arrhythmias, and conduction abnormalities with a reported overall incidence ranging from 3.7 to 5.8%.[5-7]

Some of the potential mechanisms hypothesized to contribute to CVEs among those receiving ICIs include: 1) similar antigen/common epitopes between tumor and cardiovascular tissue; 2) decreased self-tolerance; 3) up-regulation of pre-existing autoantibodies; and 4) dysregulation of myocardial metabolism by smoldering inflammation.[8] As the use of ICIs broaden, there has been significant concern about the safety of ICI therapy in patients with pre-existing autoimmune disease, given that these patients are predisposed to pathological anti-self-immune responses. Thus, it is possible that the incidence of immune-related adverse events (irAEs) and overall CVEs may be higher in patients with autoimmune disease, given their known predisposition to CVEs. This is particularly relevant, given that 31 million Americans live with autoimmune disease, and there is a significant overlap between pre-existing autoimmune disease and certain malignancies where ICIs are indicated. For example, 14% to 25% of patients with lung cancer and 28.3% with metastatic melanoma have concomitant autoimmune disease.[9,10]

Prior literature addressing the cardiovascular safety of ICI use in patients with autoimmune disease is limited. Clinical trials of ICI have usually excluded these patients. A recent systematic review of 17 retrospective studies constituting 805 patients with pre-existing autoimmune disease receiving ICIs[11] concluded that the efficacy of ICIs in these patients was similar to that seen historically in those without autoimmune disease. However, the observed incidence of all irAEs was higher, ranging from 16% to 50%. Specific data about CVEs and comparison to matched cohorts were not provided.

In this issue of *JACC: CardioOncology*, Lee et al[12] address the aforementioned knowledge gap by presenting data on the incidence of CVEs in patients receiving ICI therapy with pre-existing autoimmune disease, using a retrospective analysis employing a case-control design. Patients receiving ICI therapy (multiple cancers) were matched 1:1 with patients without pre-existing autoimmune disease (n = 251 in each group) for sex, history of coronary artery disease, heart failure, diabetes mellitus, and age. Approximately 41% of the patients had significant autoimmune disease as determined by the concomitant use of immunosuppressive drugs at the start of ICI therapy. The primary composite outcome was

*Editorials published in *JACC: CardioOncology* reflect the views of the authors and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2022.11.010

myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, cerebrovascular events, deep venous thrombus, pulmonary embolism, and myocarditis. Over a median follow-up of 205 days, 67 CVEs occurred (45 and 22 in those with and without autoimmune disease, respectively). The adjusted HR for CVEs in those with pre-existing autoimmune disease was 1.77 (95% CI: 1.04-3.03). The composite of any noncardiovascular irAEs was not higher in those with pre-existing autoimmune disease, although the incidence of psoriasis and colitis individually was higher.

Lee et al[12] have made an important contribution to the field of immuno-oncology by providing compelling evidence of increased CVEs in patients with autoimmune disease receiving ICI therapy. The lack of significant difference in overall noncardiovascular iRAEs was different from a recent systematic review,[11] however, a matched comparison group was not presented in the review. Limitations of the study are well discussed by the investigators. However, a few other limitations should be considered. The lack of established markers of autoimmune disease severity is important because those with more severe disease were likely underrepresented. Therefore, larger studies that can provide CVE information based on autoimmune disease subtype, autoimmune disease severity, and the specific subtype of ICI (anti PD-1, PD-L1, CTLA-4) are needed. Despite best efforts, an unaddressed mismatch existed in baseline clinical risk factors between the 2 groups. Hence the HRs should be interpreted in this context. Another limitation was the lack of a control group of patients with autoimmune disease but not receiving ICI therapy. Therefore, the *incremental* contribution of ICIs to CVEs in patients with autoimmune disease (who are intrinsically at higher risk of CVEs) remains unknown. Furthermore, the primary driver of CVEs in this study was deep vein thrombosis and pulmonary embolism (common in autoimmune disease as well), as opposed to classic irAEs, such as myocarditis, that are more biologically associated with ICI therapy and associated with poor prognosis. Therefore, defining the prognostic significance of the various CVEs seen would be important to guide clinicians on the use of ICIs in patients with autoimmune disease.

Despite these limitations, the study by Lee at al[12] has clinical implications. First, the study demonstrates that among patients about to start ICI therapy those with pre-existing autoimmune disease should be considered at elevated risk for CVEs and possibly cardiovascular iRAEs. The current European Society of Cardiology (ESC) guidelines[13] recommend comprehensive cardiovascular history in patients before ICI therapy, and based on the current study, a history of autoimmune disease should also be obtained. However, given retrospective data on the efficacy of ICI therapy in patients with autoimmune disease,[11] a history of autoimmune disease itself should not be a reason to avoid ICI therapy. Consistent with this heightened risk during ICI therapy and possibly pre-existing cardiovascular disease from autoimmune disease, consideration should be given to performing baseline electrocardiogram (ECG), transthoracic echocardiogram, measurement of troponin, and B-type natriuretic peptides, especially in the highest risk patients (Class I, Level of Evidence: B recommendation[13]). Patients with autoimmune disease should be informed upfront regarding the higher risk of CVEs compared with patients without autoimmune disease. Studies of routine screening for myocarditis with troponin during ICI therapy have not yielded consistent results,[14,15] however, there are currently no data in those with autoimmune disease. The study by Lee et al[12] was not powered to show differences in myocarditis; in our view, it may nonetheless be reasonable to consider repeated ECG and troponin during initial treatment cycles when irAEs most commonly occur, given the 4-fold higher incidence of myocarditis in the study (1 vs 4 patients). Consideration may also be given to repeating tests such as ECG and troponin should a noncardiovascular iRAE develop later during treatment.

There remains much to be learned about the optimal care of patients with pre-existing autoimmune disease receiving ICI therapy. The study highlights the challenges of studying low frequency CVEs and iRAEs in patients receiving ICI therapy. Advancement in this area will require a concerted effort and collaboration between various medical specialties with standardized approach to data collection and long-term follow-up.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr. Thavendiranathan is supported by a Canada Research Chair in Cardiooncology; and has received speakers honoraria from Amgen, Boehringer Ingelheim, and Takeda. Dr. Sacher has served on advisory boards for Amgen, AstraZeneca, and Genetech-Roche; and has received research funding from Genetech-Roche, AstraZeneca, and Bristol Myers Squibb.

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JACC: CARDIOONCOLOGY, VOL. 4, NO. 5, 2022
DECEMBER 2022:670–672

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KEY WORDS autoimmune disease, cardiovascular events, immune check point inhibitors, immune related adverse events, myocarditis