Journal of Nuclear Medicine, published on December 2, 2021 as doi:10.2967/jnumed.121.262301

Imaging the inflammatory response in checkpoint inhibition myocarditis

Rischpler Christoph MD[1], Rassaf Tienush MD[2], Umutlu Lale[3], Herrmann Ken MD[1], Schlosser Thomas-Wilfried[3], Totzeck Matthias MD[2]

[1] Department of Nuclear Medicine, University Hospital Essen, University of Duisburg-Essen, Essen, Germany
[2] Department of Cardiology and Vascular Medicine, West German Heart and Vascular Center, University Hospital Essen, University of Duisburg-Essen, Essen, Germany
[3] Institute for Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, Essen, Germany

Corresponding author:
Christoph Rischpler, MD
Department of Nuclear Medicine, University Hospital Essen
University of Duisburg-Essen, Essen, Germany
Tel.: +49 (0) 201 / 723 – 2032

Word count: 1732

Running title: Imaging of ICI-induced myocarditis

Immune checkpoint inhibitor (ICI) therapy is a novel therapy that directs the immune system to recognise cancer cells and promotes their elimination. Briefly, T-cells are activated by antigen-presenting cells (APCs) or tumor cells primarily via the interactions of the major histocompatibility complex with T-cell receptors and of CD80 (APCs) with CD28 (T-cells). An inactivating co-receptor on T-cells, which has a higher affinity for CD80, is CTLA-4 and leads to inactivation of T-cells. Another inactivating receptor on T-cells is PD1 (programmed death 1), that interacts with PD-L1 (programmed death-ligand 1), which in turn is induced by inflammatory signals and is thought to preserve collateral damage in healthy tissue. Monoclonal antibodies that block CTLA-4 (e.g. Ipilimumab), PD1 (e.g. Nivolumab and Pembrolizumab) or PD-L1 (Atezolizumab) result in T-cell reactivation, which in turn increases the antitumor response, but also causes immune-related adverse events (irAEs). ICI is based on the knowledge of these processes and ~~This therapy~~ is undoubtedly one of the most significant and promising developments in cancer therapy in recent years and is increasingly being used for various tumours (*1*). As impressive as the results may seem for certain tumour types (e.g., the administration of ipilimumab achieves a long-term remission in about 25% of patients with an advanced stage of malignant melanoma that was considered terminal disease before immunotherapy (*2*)), the so-called ICI-associated side effect must not be underestimated (*3*). Generally speaking, ~~immune-related adverse events (~~irAEs occur frequently during therapy with ICIs depending on the affected organ. For example, irAEs occur in up to 60% of patients treated with ipilimumab, of which 10-30% are considered serious (grade 3 to 4 according to the National Cancer Institute's Common Terminology Criteria for Adverse Events ~~(CTCAE)~~) (*4*). The most

common irAEs include diarrhea and colitis, and the earliest-occurring adverse events include skin rashes. Less common irAEs include hepatitis and endocrinopathies (such as thyroiditis) (*4*). Cardiovascular irAEs are substantially less common but may be associated with substantially higher fatality rates (*3*,*5*). In one study, an evaluation of VigiBase (the WHO's global database of individual case safety reports from over 130 countries) was conducted and a total of more than 16 million adverse events were identified, of which approximately 31 thousand were cardiovascular in origin (*6*). In this work, it was observed that myocarditis, pericardial disease, and vasculitis increased with immune checkpoint inhibitor therapy and that these cardiovascular irAEs were severe in the majority of cases (>80%) and partly associated with high mortality (50%, 21% and 6% in cases of myocarditis, pericardial disease and vasculitis, respectively). This clearly demonstrates that cardiovascular irAEs under ICI therapy need to be detected early in order to adjust the therapy regimen if necessary and to monitor patients closely. Algorithms for early detection of ICI therapy-induced myocarditis have already been proposed and include recording cardiovascular symptoms, performing an ECG, and determining troponin (*7*,*8*). However, additional procedures such as cardiac MRI may be required to establish the diagnosis of myocarditis. Recently, the potential of nuclear imaging to detect, in particular, the cardiac complications of ICI therapy has been recognized. We have already shown in a previous work that 2-deoxy-2-[18F]fluoro-D-glucose (18F-FDG) PET/MRI is very well suited to detect myocarditis with high sensitivity and to assess the course of disease (*9*). There are preliminary reports demonstrating the utility of 18F-FDG PET in ICI-induced myocarditis. A recent case report demonstrates that 18F-FDG PET/CT can detect ICI-induced myocarditis, which was also manifested by mild troponin elevation, despite unremarkable electrocardiogram, echocardiography, and cardiac magnetic resonance imaging (*10*). Furthermore, the case demonstrated that 18F-FDG PET is also suitable to assess the course of disease in this case. In a recent landmark paper, we demonstrated that ~~programmed death 1 (~~PD1~~)~~ and its ligand ~~(~~PDL1~~)~~, which are the targets of ICI therapy, are strongly expressed on cardiac endothelial cells (*11*). In a melanoma mouse model, we demonstrated that anti-PD1 therapy causes myocardial infiltration of activated CD4- and CD8-positive T-lymphocytes, which led to a significant impairment of left ventricular function under dobutamine stress testing. Furthermore, anti-PD1 ICI therapy significantly affected myocardial metabolism, as evidenced by changes in the proteome and lipidome. Analogous to these findings from the mouse model, patients receiving anti-PD1 therapy with nivolumab for metastatic melanoma showed an ejection fraction reduction on echocardiography both at rest and under dobutamine stress. In some patients recruited for this study, 18F-FDG PET/MRI detected active ICI-induced myocarditis (Fig.), also demonstrating the potential of 18F-FDG PET to detect this irAE. Although this case appears promising, the disadvantage of 18F-FDG PET imaging is that 18F-FDG uptake is relatively nonspecific and successful imaging depends strongly on patient preparation and cooperation to successfully suppress myocardial glucose metabolism. Accordingly, imaging is compromised in certain patient populations with preexisting conditions (e.g. diabetes mellitus) or under certain medications such as glucocorticoids. An alternative, promising target is the fibroblast activation protein (FAP). FAP is strongly overexpressed in the stroma of various tumors (so-called cancer associated fibroblasts, CAFs) and is already used as a target for imaging and radioligand therapy (*12*,*13*). However, FAP is also known to be strongly overexpressed in benign remodeling processes of tissue healing and thus can be detected, e.g., following an acute myocardial infarction, which could reduce the

specificity for imaging inflammation in the setting of irAEs (*14*,*15*). Initial work has ~~now~~ demonstrated the potential of 68Ga-FAPI-PET in a small group of patients with suspected ICI-induced myocarditis (*16*). In this work, patients with elevated troponin, ECG changes, lymphocytic infiltration of the myocardium on biopsy, and wall motion abnormalities on echocardiography showed increased ~~Ga-68-~~68Ga-FAPI uptake compared to ICI-treated patients without evidence of myocarditis. While the results appear promising, studies with larger patient collectives are warranted and these initial results should be viewed with caution. Furthermore, there are other potential radiotracers that show high potential but for which data are lacking to date (e.g., imaging of innervation, somatostatin receptors, mitochondrial damage, or reactive oxygen species (ROS)). In view of the increasing numbers of ICI therapies, the development of new ICIs and also due to the improved monitoring of these patients, the referral to nuclear medicine institutes will increase with the question of irAEs and especially of severe ICI-induced myocarditis.

In conclusion, nuclear imaging may be helpful with regard to the detection of cardiotoxicity from ICI therapies. Cardio-oncologic monitoring during therapy for early detection of irAEs includes physical examination, ECG/Holter-ECG, cardiac biomarkers, and echocardiography. In patients with suspected ICI-induced myocarditis, further workup may include MRI, nuclear medicine imaging, or cardiac catheterization. Nuclear medicine imaging is characterized by a high sensitivity and could help in case of unclear findings on MRI or echo or be used for follow-up. However, a broader data base is still needed for a final recommendation. In addition, given the complexity of cardiovascular irAEs, interdisciplinary teams should determine treatment and interdisciplinary guidelines need to be elaborated. ~~However, with regard to the capabilities in nuclear medicine, we are well equipped for this new demand.~~

DISCLOSURE:

Dr. Rischpler reports a research grant from Pfizer, consultancy for Adacap and Pfizer, speaker honoraria from Adacap, Alnylam, BTG, Curium, GE Healthcare, Pfizer and Siemens Healthineers.
Dr. Totzeck and Dr. Rassaf report personal fees and other from Edwards, Novartis, personal fees and other from Bristol Myers Squibb, personal fees and other from Bayer, personal fees and other from Daiichi Sankyo, personal fees and other from AstraZeneca, outside the submitted work.
Dr. Umutlu reports speaker honoraria from Bayer, speaker honoraria/research grants from Siemens Healthcare and a research grant from the German Research Foundation (DFG).
Dr. Herrmann reports personal fees from Bayer, personal fees and other from Sofie Biosciences, personal fees from SIRTEX, non-financial support from ABX, personal fees from Adacap, personal fees from Curium, personal fees from Endocyte, grants and personal fees from BTG, personal fees from IPSEN, personal fees from Siemens Healthineers, personal fees from GE Healthcare, personal fees from Amgen, personal fees from Novartis, personal fees from ymabs, personal fees from Aktis Oncology, personal fees from Theragnostics, personal fees from Pharma15, outside the submitted work.
No other potential conflicts of interest relevant to this article exist.

References

1. Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. *Nat Commun*. 2020;11:3801.

2. Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. *J Clin Oncol*. 2015;33:1889-1894.

3. Totzeck M, Lutgens E, Neilan TG. Are we underestimating the potential for cardiotoxicity related to immune checkpoint inhibitors? *European Heart Journal*. 2021;42:1632-1635.

4. Martins F, Sofiya L, Sykiotis GP, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol*. 2019;16:563-580.

5. D'Souza M, Nielsen D, Svane IM, et al. The risk of cardiac events in patients receiving immune checkpoint inhibitors: a nationwide Danish study. *Eur Heart J*. 2021;42:1621-1631.

6. Salem J-E, Manouchehri A, Moey M, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *The Lancet Oncol*. 2018;19:1579-1589.

7. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol* 2018;71:1755-1764.

8. Rassaf T, Totzeck M, Backs J, et al. Onco-Cardiology: Consensus paper of the German Cardiac Society, the German Society for Pediatric Cardiology and Congenital Heart Defects and the German Society for Hematology and Medical Oncology. *Clin Res Cardiol*. 2020;109:1197-1222.

9. Nensa F, Kloth J, Tezgah E, et al. Feasibility of FDG-PET in myocarditis: Comparison to CMR using integrated PET/MRI. *J Nucl Cardiol*. 2018;25:785-794.

10. Arponen O, Skyttä T. Immune checkpoint inhibitor-induced myocarditis not visible with cardiac magnetic resonance imaging but detected with PET-CT: a case report. *Acta Oncol*. 2020;59:490-492.

11. Michel L, Helfrich I, Hendgen-Cotta UB, et al. Targeting early stages of cardiotoxicity from anti-PD1 immune checkpoint inhibitor therapy. *Eur Heart J.* August 2021:ehab430.

12. Kratochwil C, Flechsig P, Lindner T, et al. 68Ga-FAPI PET/CT: Tracer uptake in 28 different kinds of cancer. *J Nucl Med*. 2019;60:801-805.

13. Ferdinandus J, Fragoso Costa P, Kessler L, et al. Initial clinical experience with 90Y-FAPI-46 radioligand therapy for advanced stage solid tumors: a case series of nine patients. *J Nucl Med*. August 2021:jnumed.121.262468.

14. Siebermair J, Köhler MI, Kupusovic J, et al. Cardiac fibroblast activation detected by Ga-68 FAPI PET imaging as a potential novel biomarker of cardiac injury/remodeling. *J Nucl Cardiol*. 2021;28:812-821.

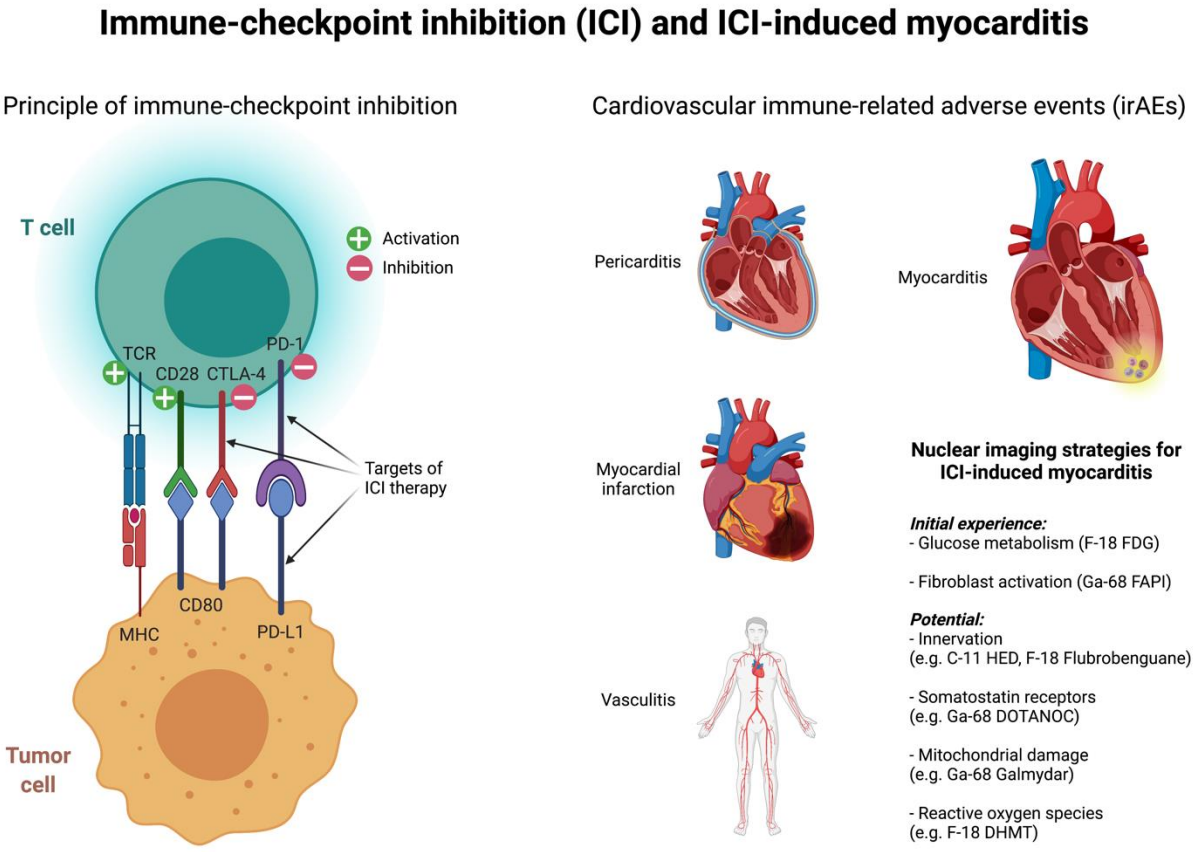
15. Totzeck M, Siebermair J, Rassaf T, Rischpler C. Cardiac fibroblast activation detected by positron emission tomography/computed tomography as a possible sign of cardiotoxicity. *Eur Heart J*. 2020;41:1060.

16. Finke D, Heckmann MB, Herpel E, et al. Early detection of checkpoint inhibitor-associated myocarditis using 68Ga-FAPI PET/CT. *Front Cardiovasc Med*. 2021;8:614997.

Graphical Abstract

To illustrate the mechanism of action of immune checkpoint inhibitor therapy and potential cardiovascular immune-realted adverse events (irAEs) triggered by it.

Graphical abstract was created with BioRender.com.



Figure

In the present patient, clinical suspicion of ICI-induced myocarditis was raised due to an elevated troponin. MRI reveals a faint late gadolinium enhancement in the basal lateral wall (red arrows). 18F-FDG-PET shows a clear tracer accumulation in this area (light blue arrows), which is indicative of active myocarditis.