Toxicities

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Combination immunomodulation for immune-checkpoint-inhibitor-associated myocarditis

Douglas B. Johnson & Alexander M. Menzies

Immune-checkpoint-inhibitor-associated myocarditis has a high fatality rate, warranting the development of more-effective treatment strategies. Herein, we discuss a recent report of a series of patients who were managed using a novel approach that involved personalized abatacept dosing, ruxolitinib and close respiratory monitoring, which was associated with low mortality.

Refers to Salem, J. E. et al. Abatacept/ruxolitinib and screening for concomitant respiratory muscle failure to mitigate fatality of immune-checkpoint inhibitor myocarditis. *Cancer Discov*. https://doi.org/10.1158/2159-8290.CD-22-1180 (2023).

Immune-checkpoint-inhibitor (ICI)-associated myocarditis is one of the most feared and deadly toxicities to arise from these transformative anticancer therapies. Although rare (occurring in, at most, 1% of patients treated with ICIs), clinically overt myocarditis has been associated with fatality rates that range from 20% up to 50% in retrospective series[1,2]. Often diagnosed in a delayed fashion owing to nonspecific symptoms and inconsistent screening, the lethality of this immune-related toxicity has at least three different causes. First, refractory arrhythmias or heart failure can occur as a result of myocardial necrosis. Second, dysfunction and necrosis of the diaphragm owing to concurrent skeletal muscle involvement (that is, myositis and rhabdomyolysis) can lead to respiratory failure, even when myocardial inflammation and function seem to have stabilized[3]. Finally, the patients are often critically ill, and complications arising in the intensive care unit (for example, secondary infections) can lead to death.

Management guidelines for ICI-associated myocarditis follow the traditional pathway that is used for other immune-related adverse events (irAEs), with corticosteroids as the initial therapy[4,5]. Evidence from retrospective studies indicates that pulse doses of intravenous steroids (such as methylprednisolone at 1 g daily for several days) are associated with superior outcomes (specifically lower rates of major adverse cardiac events) compared with oral prednisone at 1–2 mg/kg daily or equivalent[2]. Despite this approach and consistent with other severe irAEs, patients often do not have improvement or resolution of myocarditis and require additional treatment with other agents. Supporting case reports and anecdotal data are available for a variety of additional agents, including mycophenolate, anti-thymocyte globulin, tacrolimus, intravenous immunoglobulin, alemtuzumab and abatacept, but the optimal treatment regimen has remained elusive[4].

Within this context, Salem et al.[6] recently published their experience in treating 40 consecutive patients who were admitted to a single cardio-oncology unit (at Hôpital Pitié-Salpétrière, Paris, France) for ICI-associated myocarditis using various therapeutic strategies. The initial 10 patients received guideline-based care between mid-2018 and early 2020, with high-dose steroids and – in most patients – additional second-line therapies, including fixed-dose abatacept (10 mg/kg every 2 weeks; $n = 7$), plasmapheresis ($n = 8$) and/or mycophenolate mofetil ($n = 4$). The fatality rate in this first group was 60%. Among the next 30 patients (treated March 2020–August 2021), 22 patients with grade ≥ 3 myocarditis received corticosteroids in combination with the selective costimulation modulator abatacept and, in 17 patients, the JAK1 and JAK2 inhibitor ruxolitinib. Lower doses of steroids were also used in the second group (>500 mg per day in 9/10 patients versus in 13/30 patients). Abatacept was initiated at a higher dosage (20 mg/kg on days 0, 5 and 14) and then titrated on the basis of CD86 receptor occupancy, which was serially monitored at regular intervals during therapy. Furthermore, intensive monitoring of respiratory status was initiated for these 30 patients, with prompt elective ventilatory support provided for those with early signs of respiratory failure ($n = 8$). Impressively, only 1 patient in this second group died as a result of ICI-associated myotoxicity (3.4%)[6].

Following the experience of Salem and co-workers, the question arises of whether the combination of abatacept and ruxolitinib is a reasonable treatment strategy for ICI-associated myocarditis. To address this question, several important aspects should be considered – first, whether a mechanistic rationale exists. Abatacept is a CTLA4–Fc fusion protein that binds to CD80 and CD86 on antigen-presenting cells and prevents these ligands from interacting with the T cell co-stimulatory receptor CD28, thereby suppressing T cell activation. Simplistically, this agent could be considered as having opposite activity to ipilimumab or other antagonistic anti-CTLA4 antibodies (which, by blocking CTLA4, indirectly promote the interaction of CD80 and CD86 with CD28 and, thus, T cell co-stimulation), and is approved in the USA for the treatment of graft-versus-host disease, rheumatoid arthritis and psoriatic arthritis. As an inhibitor of JAK1 and JAK2, ruxolitinib has diverse anti-inflammatory and immunosuppressive properties, including the suppression of cytokine sensing and production, chemotaxis, and T cell priming and expansion[7]; this agent is approved for the treatment of both acute and chronic steroid-refractory graft-versus-host disease. Abatacept has successfully been used for the treatment of ICI-associated myocarditis in individual case reports[8], whereas ruxolitinib has less supporting evidence for this indication. The combination has

at least a plausible complementary mechanistic rationale, as noted by Salem et al.[6], given that abatacept might have slower-onset and more T-cell-specific effects, whereas ruxolitinib has more rapid activity and also modulates innate immune function. The authors further provided preclinical support using a well-described *Ctla4*$^{+/-}$*Pdcd1*$^{-/-}$ mouse model of ICI-associated myocarditis[9]; RNA-sequencing data demonstrated that JAK2 and the JAK–STAT signalling pathway more broadly are substantially upregulated in cardiac tissue from these mice relative to unaffected *Ctla4*$^{+/+}$*Pdcd1*$^{-/-}$ control mice[6]. *JAK2* was also found to be overexpressed in endomyocardial biopsies samples from an independent group of patients with ICI-associated myocarditis ($n = 9$), compared with ICI-treated patients without myocarditis ($n = 4$)[6].

Second, and potentially more importantly, whether the study by Salem et al. provides actionable clinical data that support routine application for patients with severe ICI-associated myocarditis should be considered. Although systematic and comprehensively documented, this study still raises the question of whether any observational, non-randomized, semi-retrospective study has sufficient rigour to inform the standard of care. Some would argue that — given the rarity of the condition and the fairly dramatic nature of the results — this study might meet that threshold. However, others will argue that data from randomized trials are needed to truly validate such a regimen, particularly one with potentially detrimental effects on the antitumour immune response and with substantial financial costs. Even in this well-performed observational study, it is notable that two patients remained ventilator-dependent 6 months after therapy and eight additional patients died of other causes (including COVID-19 and sepsis)[6], thus providing potential confounders. Although clinicopathological characteristics were relatively well-balanced between the first and second groups, it is possible that earlier diagnostic assessment for myocarditis (owing to better awareness) or other factors contributed to the improved outcomes in the latter group. It is also possible that the slight differences in the frequency of concurrent CTLA4 inhibition with ipilimumab during anti-PD-(L)1 antibody therapy (10% in group 1 versus 30% in group 2)[6] could have affected the efficacy of abatacept, although whether this approach is likely to confer sensitivity or resistance to abatacept remains unclear. Finally, disentangling the relative contributions of higher and personalized abatacept dosing, ruxolitinib and close monitoring of respiratory function is impossible.

The study by Salem and colleagues raises broader questions surrounding the investigation and management of rare (and perhaps even common) ICI-associated toxicities[10]. The diversity and generally low incidence of these irAEs, together with the necessary urgency surrounding starting treatment and a reluctance to interfere with the antitumour immune response, has limited trials in this area, although several are in process (such as NCT05335928, NCT04438382, NCT04305145 and NCT05660421). One comparative study (NCT05335928) is in fact randomly assigning patients with ICI-associated myocarditis to receive abatacept (10 mg/kg on days 0, 1, 14 and 28) or placebo, concurrently with corticosteroids. This study might provide key insights and validation; however, if negative, it will be unclear whether the therapy is ineffective, whether a higher dose of abatacept or concurrent ruxolitinib would have altered the results, or whether the optimal management regimen is dependent on the underlying ICI regimen (anti-PD-(L)1 antibody monotherapy versus concurrent CTLA4 or LAG3 inhibition).

Ultimately, the results of the study by Salem et al. are compelling, with impressive survival rates in patients with this often-fatal toxicity. Whether the management approach used is superior to other mitigation strategies remains to be determined; randomized studies are required to determine the best management of myocarditis and other severe irAEs, which will only increase in prevalence as immunotherapies are prescribed more widely in the future.

Douglas B. Johnson [1] ✉ **& Alexander M. Menzies**[2]

[1]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA. [2]Melanoma Institute of Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, New South Wales, Australia.

✉e-mail: douglas.b.johnson@vumc.org

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Competing interests

D.B.J. has served on advisory boards or as a consultant for Bristol Myers Squibb, Catalyst Biopharma, Iovance, Jansen, Mallinckrodt, Merck, Mosaic ImmunoEngineering, Novartis, Oncosec, Pfizer, Targovax and Teiko; has received research funding from Bristol Myers Squibb and Incyte; and has patents pending for use of MHC class II as a biomarker for immune-checkpoint-inhibitor response, and abatacept as treatment for immune-related adverse events. A.M.M. has served on advisory boards for Bristol Myers Squibb, MSD, Novartis, Pierre-Fabre, QBiotics and Roche.