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Review

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Immune checkpoint inhibitor-associated myocarditis: a review of current state of knowledge

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Abstract

Background: Immune checkpoint inhibitors (ICIs) have changed the landscape in oncology, providing effective cancer management for a growing population. However, by promoting an immunological attack on cancer cells, healthy cells may be harmed in the process. Increased awareness of ICI-associated myocarditis (ICIMy) as one of the most fatal immune-related adverse events has led to efforts to improve the diagnosis and treatment of this condition. The purpose of this review is to summarize the current state of knowledge regarding ICIMy. Methods: We performed a literature search in Pubmed and Scopus with the relevant keywords, screened the titles and abstracts of the results, and reviewed the selected publications using pre-established criteria. Main findings: Although ICIMy's cumulative incidence is below 0.5% in clinical trials, real-world data reveal a higher incidence of up to 4%. Underlying pathophysiologic mechanisms include T cell clonal expansion, molecular mimicry, and increased inflammatory cytokine signaling pathways leading to ICIMy. The clinical presentation can vary from asymptomatic to fulminant cardiac death and is often accompanied by musculoskeletal adverse events. Emerging diagnostic tools with prognostic value include global longitudinal strain assessment and multiple PET-CT modalities. The mainstay of treatment includes holding the immunotherapy, prompt high-dose methylprednisolone, and close cardiovascular observation. Fulminant and refractory cases benefit from additional immunomodulatory therapies. Principal conclusions: Although ICIMy is a rare adverse event, its non-specific

presentation warrants a high level of suspicion. Once ICIMy is considered a likely diagnosis, immunomodulatory therapies should be initiated promptly.

Keywords: ICI-myocarditis, immune checkpoint inhibitors, immune-related adverse event, cardiotoxicity, autoimmunity

INTRODUCTION

The concept of immune checkpoints emerged in the late 20th century from research identifying molecules involved in the regulation of the immune system[1-4]. Cancer cells take advantage of these immunomodulatory checkpoints to evade immune recognition and response. In 2018, James Allison and Tasuku Honjo shared the Nobel Prize in Physiology or Medicine for the discovery of cancer therapy utilizing inhibition of negative immune regulation. Their work led to the development of immune checkpoint inhibitors (ICI) specifically targeting the checkpoint receptors CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and the PD-1 (programmed cell death protein 1) with its corresponding ligand PD-L1 (programmed cell death ligand 1). Since the Food & Drug Administration (FDA) approval of the first immune checkpoint inhibitor (ICI), ipilimumab, in 2011, several ICIs have been developed and approved for the treatment of a wide array of malignancies [Table 1]. Many checkpoint receptors have been identified, and research continues to identify novel ICIs. The lymphocyte activation gene-3 (LAG-3) inhibitor, relatlimab, was recently approved for the treatment of melanoma [Table 1][5]. The emergence of ICIs has led to a paradigm shift in the treatment of cancer with immunotherapeutic agents with continual expansion of their indications.

However, the growing pool of eligible ICI recipients has been accompanied by an increasing prevalence of ICI toxicity. The toxicities, which are called immune-related adverse events (IRAEs), can occur across all organ sites and manifest as autoimmune inflammation such as colitis, thyroiditis, and myocarditis. A single center's experience described a five-fold increase in yearly ICI recipients and a four-fold increase in annual hospitalizations due to IRAEs from 2014 to 2017[6]. The cumulative incidence of IRAEs of any grade can reach up to 80%, with severe or life-threatening IRAEs occurring in up to 30%[7,8]. Of the potentially fatal IRAEs, ICI-associated myocarditis (ICIMy) is one of the most concerning due to its high mortality, estimated to be 25%-50%. This scoping review will focus on the latest literature regarding the epidemiology, diagnosis, screening, and treatment of ICIMy.

METHODS

On March 19th, 2024, we searched for publications in Scopus with the terms "immune-checkpoint inhibitor" OR "immune-checkpoint inhibitors" OR "immune checkpoint inhibitor" OR "immune-checkpoint inhibitor" OR immunotherapy AND myocarditis in the title, abstract, or keywords with its publication year between 2015 and 2024, yielding a total of 1,065 results. We also searched PubMed and found 1,388 publications (supplementary data). After adjusting for duplicates and corrections, we were left with 1,565 research items. By reviewing the title and abstract of each publication, we excluded 955 publications for multiple reasons: 502 were related to other causes of myocarditis or cardiomyopathy; 149 focused on another IRAE or all IRAEs in general; 105 were either trials or studies assessing ICI efficacy and safety; 59 were editorials, comments, or corrections of already included publications; 20 had a focus on general cardio-oncology or another cardio-oncology topic; 19 were not in English and 101 were unrelated. The remaining 610 studies were reviewed to assess the available evidence on the incidence of ICIMy, clinical symptoms, risk factors, imaging results, laboratory markers, management strategies, and outcomes; 318 were referenced in this review. The remaining 282 studies that were not cited did not offer new or

Table 1. Approved immune checkpoint inhibitors and their indications

ICI	Target	Initial US approval year	Indications
Ipilimumab	CTLA-4	2011	Melanoma, renal cell carcinoma (RCC), microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC), hepatocellular carcinoma (HCC), non-small cell lung cancer (NSCLC), malignant pleural mesothelioma
Nivolumab	PD-1	2014	Melanoma, NSCLC, malignant pleural mesothelioma, RCC, classical Hodgkin lymphoma (cHL), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), CRC, HCC, esophageal cancer, gastric cancer, gastroesophageal junction cancer
Pembrolizumab	PD-1	2014	Melanoma, NSCLC, small cell lung cancer (SCLC), SCCHN, cHL, primary mediastinal large B-cell lymphoma (PMBCL), urothelial carcinoma, MSI-H or dMMR cancer, MSI-H or dMMR CRC, gastric cancer, esophageal cancer, cervical cancer, HCC, Merkel cell carcinoma (MCC), RCC, endometrial cancer, tumor mutational burden-high (TMB-H) cancer, cutaneous squamous cell carcinoma (cSCC), triple-negative breast cancer (TNBC)
Atezolizumab	PD-L1	2016	UC, NSCLC, SCLC, HCC, melanoma.
Avelumab	PD-L1	2017	MCC, UC, RCC
Durvalumab	PD-L1	2017	NSCLC, extensive-stage SCLC, biliary tract cancer, HCC.
Cemiplimab	PD-1	2018	cSCC, basal cell carcinoma, NSCLC
Dostarlimab	PD-1	2021	dMMR endometrial cancer or dMMR solid tumors
Tremelimumab	CTLA-4	2022	HCC.
Relatlimab	LAG-3	2022	Melanoma
Toripalimab	PD-1	2023	Nasopharyngeal carcinoma
Tislelizumab	PD-1	2024	Esophageal squamous cell carcinoma

ICI: Immune checkpoint inhibitor; CTLA-4: cytotoxic T-lymphocyte associated protein 4; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; LAG-3: lymphocyte activation gene 3.

supporting arguments for statements made through the body of our manuscript. These studies included 7 outdated guidelines, 155 case reports or case series, and 130 reviews on the topic. Seventy-eight of our references were obtained through cross-reference or direct search. Figure 1 summarizes the selection process.

Incidence and clinical presentation

Although IRAEs are common, cardiovascular events during ICI therapy are infrequent[7,9-14]. A wide array of cardiovascular events have been reported after ICI therapy, including myocarditis, arrhythmias, heart failure, atherosclerotic events, and pericardial disease[15-20]. A meta-analysis of 51 randomized clinical trials reported a cumulative incidence of cardiovascular events of 3.1% during ICI monotherapy and 5.8% during dual ICI therapy compared to 2.5% in patients receiving non-ICI chemotherapy[21]. Real-world data show that the risk of having a cardiac event may be up to five times higher (reported hazard ratios ranged from 1.6 to 4.93) in patients with cancer treated with ICIs compared to other anti-cancer therapies[22,23]. A retrospective analysis of reported cardiac adverse events occurring in clinical trials with ICIs found that 77.5% of them were grade 3 or higher[24]. Those who experienced a cardiac event while on immunotherapy had a 2.77-fold higher risk of all-cause mortality (95%CI: 1.55-4.95)[25]. Pharmacovigilance studies report a fatal outcome in roughly 30% of cardiac events occurring in ICI recipients[26,27].

ICIMy is the most commonly reported immune-related cardiac adverse event[21,26,28-30]. The reported incidence in clinical trials is very low, ranging from 0.03% to 0.5%[16,31-33]. Underdiagnosis may be a contributor to the apparent low incidence. Over time, however, there have been increased reported cases[15,17,27,34], likely due to increasing awareness as well as ICI-treated patients. Real-world data suggest a potentially higher incidence ranging from 0.07% to 4.59%[22,23,35-42]. The highest cumulative incidence of 4.59% was reported in a single-center, retrospective observational study within a population with baseline

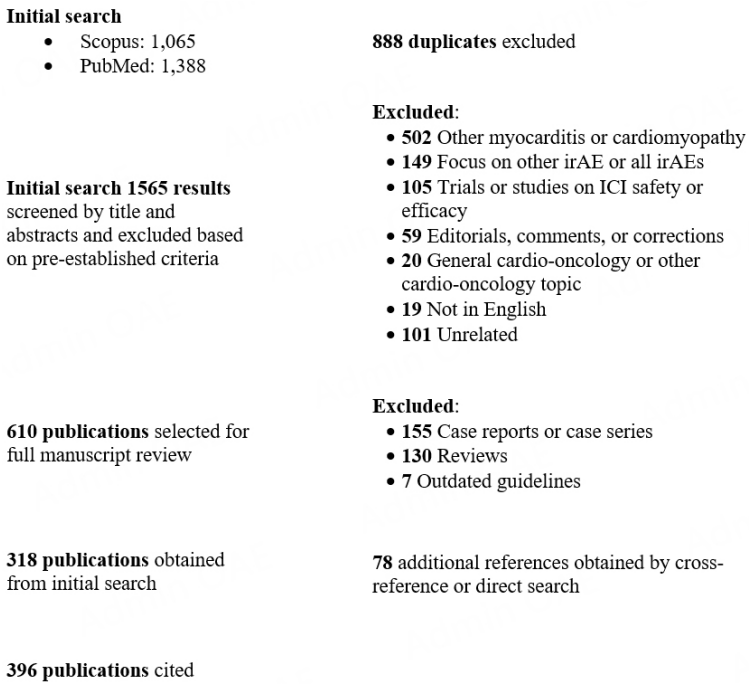

Figure 1. Flowchart of the publication selection process.

cardiovascular disease[40]. All cases met the European Society of Cardiology's (ESC) diagnostic criteria for myocarditis[43], although they were all "possible myocarditis" diagnoses per the categories proposed by Bonaca *et al.*[44] [Table 1]. A prospective study monitoring cardiac biomarkers in a 126-patient cohort starting immunotherapy, reported a cumulative rate of clinically significant ICIMy cases of 3.17%, with asymptomatic or mildly symptomatic ICIMy suspicion occurring in 7.15% of cases[45].

Pathophysiology

The exact pathophysiology of ICIMy has not been fully described, although studies have helped to elucidate some of the potential mechanisms [Figure 2]. It is suspected that ICIs allowing T cells to attack cancer cells can sometimes lead to a break in peripheral tolerance, resulting in autoimmunity against normal organs, including the heart. There has been a variety of cardiac proteins associated with autoimmune myocarditis, including cardiac myosin and β-adrenergic receptors, with autoimmune responses mediated by both antibodies and T cells[46-48]. Notably, the presence of circulating T cells reactive to cardiac antigens, such as cardiac myosin heavy chain α isoform (α-MyHC), indicates a breach of self-tolerance, likely due to inadequate cardiac antigen presentation in thymic epithelial cells[49-53]. Although α-MyHC-specific T cells have been found in human peripheral blood from patients with viral and autoimmune myocarditis[49], the most expanded T cells in ICIMy hearts do not react to α-MyHC[54]. Additionally, the PD-1/PD-L1 axis is crucial for maintaining peripheral tolerance to auto-reactive T cells and its disruption further exacerbates the autoimmune response by enhancing T cell activation and proliferation[55-57]. Further, the overexpression of PD-L1 in myocarditis-affected areas of the myocardium underscores the breakdown of tolerance mechanisms[58]. In addition, it has been demonstrated that ICI administration correlates with an expanded diversity of the T cell receptor repertoire in peripheral blood, potentially prompting autoimmune responses[59]. Given the involvement of autoimmune processes, another potential target for treatment is the immunoproteasome, a specialized form of the proteasome predominantly found in immune cells that perpetuates autoimmune pathology, exacerbating inflammation and fibrosis in ICIMy[60].

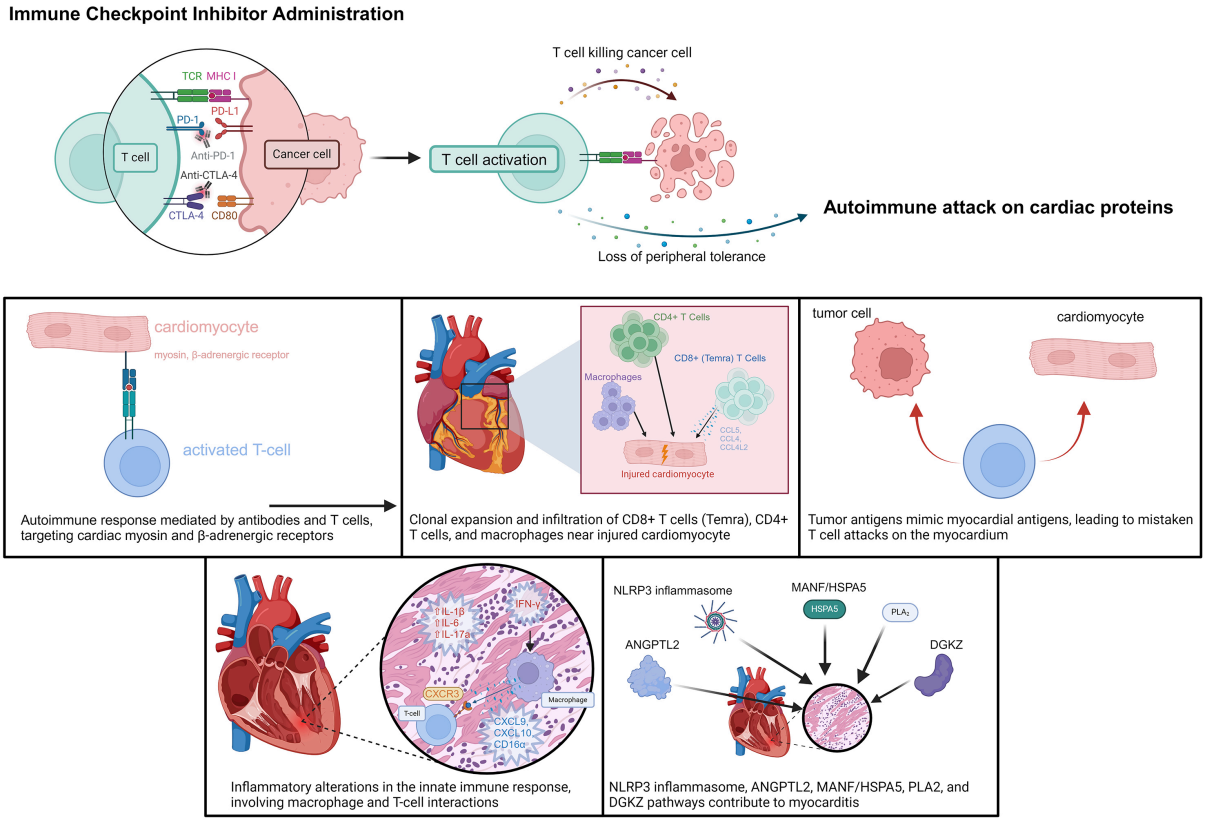

Figure 2. Pathophysiologic mechanisms of ICI myocarditis. Summary of potential mechanisms involved in the pathophysiology of ICI Myocarditis. Further details are provided in the main text. Created with BioRender.com.

Murine models have revealed that single ICI agent administration or knockout of a single immune checkpoint is insufficient to induce myocarditis[61]. While the use of combination ICI agents has been proven sufficient for inducing myocarditis[62-64], alternative interventions, including cardiac antigen immunization[65,66] or sensitization[67], cardiac injury[53,57,68] and tumor inoculation[56,69,70], are required. Molecular mimicry, in which tumor-released antigens resemble those found in the myocardium, is a potential mechanism supporting tumor inoculation. In one ICIMy case, identical T cell clones were detected in the tumor, myocardium, and skeletal muscle[71]. Additionally, a separate ICIMy case reported that histopathologic analysis of a metastatic lesion from a primary neuroendocrine tumor revealed the expression of troponin T and creatine kinase-MB[72]. Lung cancers have also been found to express cardiac biomarkers[73], including troponin T and creatine kinase-MB[74]. Although combination therapy results in macrophage and CD8+ T cell infiltration in the myocardium, as well as focal areas of apoptosis in both tumor-bearing and tumor-free mice[62], cardiotoxicity induced by anti-PD-1 antibodies has been observed only in melanoma-bearing mice[56]. A couple of studies successfully induced ICI-myocarditis in some of their A/J mice simply by administering anti-PD-1, a strain prone to spontaneous tumorigenesis[52,75]. Another study conducted on a C57BL/6J background found that administering anti-PD1 antibody led to decreased left ventricular ejection fraction and global longitudinal strain, as measured by echocardiography, although it did not result in significant mononuclear infiltration of the myocardium[61]. However, the majority of enriched T cell clones in the tumor tissue did not correspond to the enriched T cells in the hearts of ICIMy patients[54]. Other models, however, involve genetic backgrounds predisposed to autoimmunity and employ immune checkpoint blockade to induce myocarditis. For instance, non-obese diabetic mice - a polygenic model of autoimmunity resulting in type 1 diabetes -develop spontaneous but

rarely fatal myocarditis when modified with MHC-I and MCH-II knockout and HLA-DQ8 introduction[76]. However, severe myocarditis accompanied by systolic heart failure and severe myositis occurs after anti-PD1 administration[76]. MRL-Faslpr mice, which have an increased predisposition to autoimmunity, develop fatal myocarditis when Pdcd1 is knocked out[77]. Administering anti-CTLA4 and anti-PD-1 combination therapy in MRL-FAS mice resulted in immune infiltration of the myocardium and sarcomere disarray[78]. Finally, genetic models have also been extensively studied, namely Ctla4 haploinsufficiency in the absence of Pdcd1[50,62,78,79]. A less frequently utilized model involves a loss-of-function mutation in the gene encoding lymphocyte activation gene 3 (LAG-3) with PD-1 knockout in a BALB/c background[80]. The differences in animal models of ICIMy highlight the importance of animal background, tumor inoculation, and genetic and pharmacologic interventions to increase susceptibility to autoimmunity and myocarditis. To account for the complex interactions of the immune system, van der Vegt *et al.* have proposed a mathematical model of ICIMy that takes the dynamics of damaged cardiomyocyte numbers and the number and types of immune cells evolving over time[81,82].

Immunohistochemical and transcriptomic studies have helped to elucidate the interaction between the immune system and ICIMy. In the pathophysiology of ICIMy, T cell subsets especially emerge as central players[55,83]. Specifically, CD4+ T cells are implicated in driving heart-specific autoimmunity, with a notable accumulation of T cells and macrophages near injured cardiomyocytes[69,84]. Additionally, the expansion of cytotoxic CD8+ effector T cells, termed Temra CD8+ cells, is observed in ICIMy patients and mice models compared to controls[50,69,83,85,86]. These cells, as their name suggests, demonstrate a highly activated and cytotoxic phenotype. Transcriptomic analysis further reveals elevated expression levels of proinflammatory chemokines (CCL5/CCL4/CCL4L2) in Temra CD8+ cells, suggesting active involvement in myocarditis pathogenesis. Moreover, ligand-receptor analysis highlights interactions between Temra CD8+ cells and innate immune cells, underscoring their role in the inflammatory response within the myocardium[87]. Overall, the orchestrated activation and interaction of T cell subsets, particularly cytotoxic CD8+ T cells and CD4+ T cells, play pivotal roles in the development and progression of ICIMy[50,87-89].

Transcriptomic analyses have revealed differential gene expression patterns in ICIMy that are associated with inflammatory pathways, particularly interferon responses, highlighting dysregulation of innate immunity[85-87,90-93]. There is generally upregulation of inflammatory cytokines such as IL-1β and IL-6[51,93]. Similarly, TNF-α has been shown to be elevated in the peripheral blood and serum of ICIMy patients and could contribute to their reduced cardiac function[94,95]. Thymic inflammatory gene expression analysis also demonstrates upregulated levels of proinflammatory cytokines, especially IL-17a, suggesting that remote cytokine production may also be implicated in cardiac dysfunction induced by ICIs[61]. Overall, the dysregulation of innate immunity specifically involves innate immune cell populations such as monocytes, NK cells, and B cells, which demonstrate changes in both intercellular communication and composition during ICIMy activity and remission[96]. Additionally, inflammatory macrophages expressing CXCL9, CXCL10, and CD16α are increased in ICIMy, with interactions identified between T cells and these macrophages via IFN-γ and CXCR3 signaling pathways[67,86,97,98]. In the context of PD-1 inhibitors specifically, macrophage-derived exosomes appear to upregulate miR-34a-5p in cardiomyocytes, inducing cardiac senescence and injury. Therefore, the miR-34a-5p/PNUTS signaling pathway could supply new targets for lessening cardiac injury in patients receiving PD-1 inhibitors[99,100]. Further, depleting CD8+ T cells or macrophages and blocking IFN-γ signaling through antibody neutralization studies have been shown to reduce myocarditis severity, highlighting the intricate interplay between adaptive and innate immune responses in the pathogenesis of ICI-induced myocarditis[97].

There are some other inflammatory mechanisms that may be implicated as part of ICIMy. Studies of PD-1 blockage of CD8+ T cells in tumor cells and primary cardiomyocytes have demonstrated that the pyrin domain-containing protein 3 (NLRP3) inflammasome is upregulated[62,101]. Another inflammatory mediator that has been studied for ICI-related myocarditis is ANGPTL2, which is expressed abundantly by cardiac fibroblasts and promotes chemokine expression, enhancing T cell recruitment[67]. On the other hand, MANF and HSPA5 are proteins with estradiol-dependent expression that are believed to be important in attenuating myocardial inflammation in ICIMy[62]. Therefore, NLPR3, ANGPTL2, and MANF/HSPA5 could all be suitable targets related to autoimmune inflammation.

Furthermore, immunohistochemical studies of endomyocardial biopsy specimens have provided further insights into the pathological mechanisms underlying ICIMy[102,103]. Necrotic cardiomyocytes often stain positive for complement activation product C4d[104]. This observation suggests a possible role for antigen-antibody interactions and immune complex formation, followed by complement fixation, in the development of myocardial injury within the context of ICI therapy[105].

In addition to the immunological mechanisms driving ICIMy, emerging research highlights the significant involvement of metabolic pathways, especially glycerolipid metabolism, in the progression of ICIMy. Metabolic dysregulation, mediated by enzymes such as phospholipase A2 (PLA2), appears to promote inflammatory cardiac injury and oxidative stress, exacerbating myocardial damage. Diacylglycerol kinase zeta (DGKZ) is a significant glycerolipid metabolism regulator, with DGKZ-mediated signaling pathways contributing to aberrant metabolism and promoting myocardial inflammation[84]. Finally, a proteomic analysis comparing ICIMy and viral myocarditis biopsies suggested differences in mitochondrial metabolism[106].

Risk factors

The two established risk factors for developing ICIMy are the use of dual ICI therapy and the presence of thymic cancer being treated with ICIs. Data from pharmacovigilance studies and real-world data have demonstrated the increased risk of ICIMy with dual ICI therapy compared with monotherapy, with a reporting odds ratio of 1.93-4.31[15,17,37,71,78,107,108]. Additionally, myocarditis stemming from dual ICI therapy tends to be more severe and fatal compared to monotherapy[17,71,109]. Studies have reported that patients with thymic epithelial tumors (TET) undergoing ICI treatment face an increased risk of developing myocarditis and myositis, compared to other cancer types[89,110-115]. Additionally, ICIMy in these patients is associated with higher mortality compared to ICIMy in other cancers[89,116].

Other factors have been suggested but have not definitively been associated with an increased risk of ICIMy. When comparing immunotherapies by their targeted molecules, anti-PD-1 or anti-PD-L1 monotherapies showed a higher risk of ICIMy compared to anti-CTLA-4 monotherapy[15,17], although findings have been inconsistent[117]. Specific ICIs could also have different risk profiles. Nivolumab may be associated with a higher risk of developing ICIMy[37,118] or arrhythmias[119] compared to pembrolizumab, with cemiplimab showing a higher risk of heart failure and myocarditis than nivolumab or pembrolizumab[119]. Pre-existing cardiac comorbidities may pose an increased risk[120-124]. One study reported a cumulative incidence of 4.5% of ICIMy in a population with pre-existing cardiovascular disease undergoing treatment with ICI[121]. A history of hypertension may be associated with developing left ventricular dysfunction during ICI treatment, including left ventricular diastolic dysfunction and cancer therapy-related cardiac dysfunction[122]. Importantly, patients with ICIMy are more likely to have a history of coronary artery disease or heart failure compared to patients undergoing immunotherapy without ICIMy[123]. A study contrasting ICIMy and ICI-associated non-inflammatory left ventricular dysfunction (NILVD) found that

hypertension may be a risk factor for the former while cardiac disease may be a risk factor for the latter[28]; further studies comparing these entities are warranted. A pharmacovigilance study found that the use of loop or thiazide diuretics is correlated with ICIMy reports[125]. Patients with diabetes mellitus[37,126] or autoimmune diseases[127,128] may also be at increased risk. There are very limited data on whether prior solid-organ transplant recipients have a different risk profile, considering they are on chronic immunosuppression[129]. Regarding demographic characteristics, females may be at an increased risk of ICIMy[62,107], although there are conflicting findings[15,123,130,131]. African Americans may have a higher risk of ICI cardiotoxicity in general, but findings are conflicting as well[25,132].

Hematologic markers have also been identified as potential risk factors. Patients who developed an ICI cardiotoxicity were more likely to have a higher neutrophil-to-lymphocyte ratio (NLR)[121] or a lower lymphocyte-to-monocyte ratio (LMR)[126] at baseline compared to patients undergoing immunotherapy without cardiotoxicities. Additionally, an elevated NLR at baseline is a risk factor for overall severe IRAEs (grades 4-5)[133]. One study using the American Society of Clinical Oncology's CancerLinQ database, which aggregates data from oncological practices across the United States, identified risk factors for developing cardiotoxicity identified through machine learning[130]. They included increased age, lower absolute lymphocyte count (ALC), higher absolute neutrophil count, anti-PD-L1 treatment (*vs.* anti-PD-1), a trend of increased weight over time, not receiving an angiotensin-converting enzyme inhibitor, and not receiving a loop diuretic, among others[130]. After applying a prediction model based on these, there was a significant difference between the cumulative incidence of cardiac events in the low-risk group compared to the high-risk group (3.3% *vs.* 6.1%, respectively, $P < 0.001$)[130].

Diagnosis

The diagnosis of ICIMy relies on clinical criteria, laboratory biomarkers, imaging studies, and at times, histopathologic analysis. Several societies have proposed diagnostic criteria for ICIMy with slight differences in definitions. Given the severity of ICIMy, Bonaca *et al.* proposed diagnostic criteria for ICIMy with the intended purpose of aiding in identifying and adjudicating cases of myocarditis in a clinical trial setting[44]. Utilizing a uniform definition of myocarditis during reporting events establishes a foundation for better analysis and understanding of the true rates and spectrum of the disease. The criteria are organized hierarchically based on the strength of diagnostic evidence [Table 2]. Since then, the International Cardio-Oncology Society (IC-OS)[134] proposed another set of diagnostic criteria, and these have been incorporated in the latest 2022 ESC Guidelines on cardio-oncology[135]. This new set of diagnostic criteria aims to aid clinicians in real-life settings in establishing a diagnosis of ICIMy [Table 2]. Using Bonaca's criteria, a clinical diagnosis of "definitive myocarditis" requires an imaging abnormality independent of troponin, whereas a clinical diagnosis using the IC-OS/ ESC cardio-oncology guidelines criteria requires a troponin elevation independent of imaging abnormalities. For instance, only 18 out of 33 cases from a single-center cohort of ICIMy initially diagnosed per the clinical trial setting criteria met the IC-OS/ESC definition[28].

The criteria proposed by Bonaca *et al.* should be interpreted as an indicator of the degree of evidence in favor of myocarditis[44]. Some patients may be unstable and unable to undergo the full workup, and the most specific tests, such as cardiac MRI and endomyocardial biopsy (EMB), may not be performed at all. A multicenter retrospective cohort consisting of 34 patients who met the Bonaca criteria reported that possible cases of myocarditis had higher mortality than definite cases (HR: 10.68, $P = 0.03$)[136]. Potentially, these patients were too unstable to undergo sufficient testing, or they had accompanying non-myocarditis diagnoses contributing to their deaths. Taking this into consideration, one could diagnose ICIMy per the IC-OS/ESC definition, and then attempt to classify it as possible, probable, or definite per Bonaca to denote the degree of evidence to support the diagnosis[127]. Figure 3 illustrates the pillars involved in the diagnosis of ICIMy.

Table 2. Current diagnostic criteria for ICI-associated myocarditis

Bonaca *et al.* (2019)[44]

- **Definite myocarditis**: any of the following
  - Pathology
  - Diagnostic CMR + syndrome + biomarker or ECG
  - Echo WMA + syndrome + biomarker + ECG + negative angiography
- **Probable myocarditis**: any of the following
  - Diagnostic CMR (no syndrome, ECG, biomarker)
  - Suggestive CMR with either syndrome, ECG or biomarker
  - Echo WMA and syndrome (with either biomarker or ECG)
  - Syndrome with PET scan evidence and no alternative diagnosis
- **Possible myocarditis**: any of the following
  - Suggestive CMR with no syndrome, ECG or biomarker
  - Echo WMA with syndrome or ECG only
  - Elevated biomarker with syndrome or ECG and no alternative diagnosis

IC-OS consensus (2021) /ESC guideline (2023)

- **Either pathohistological diagnosis**: Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy of cardiac tissue samples
- **Or clinical diagnosis**: A troponin elevation (new, or significant change from baseline) with 1 major criterion or a troponin elevation (new, or significant change from baseline) with 2 minor criteria after exclusion of acute coronary syndrome or acute infectious myocarditis based on clinical suspicion
  - Major criterion
    - CMR diagnostic for acute myocarditis (modified Lake Louise criteria)
  - Minor criteria
    - Clinical syndrome (including any one of the following: fatigue, muscle weakness, myalgias, chest pain, diplopia, ptosis, shortness of breath, orthopnea, lower extremity edema, palpitations, lightheadedness/dizziness, syncope, cardiogenic shock)
    - Ventricular arrhythmia and/or new conduction system disease
    - Decline in cardiac (systolic) function, with or without regional WMA in a non-Takotsubo pattern
    - Other immune-related adverse events, particularly myositis, myopathy, myasthenia gravis
    - Suggestive CMR (meeting some but not all the modified Lake Louise criteria)

CMR: Cardiac magnetic resonance; ECG: electrocardiogram; WMA: wall motion abnormality.

Clinical syndrome

Diagnosing ICIMy poses a significant challenge due to the highly variable and non-specific clinical presentation. Myocarditis may manifest with non-specific symptoms such as fatigue, weakness, dyspnea, and cough, or cardiac-specific symptoms like palpitations, chest pain, syncope, and orthopnea, among others[137]. However, many of these may even be part of the oncologic patient's baseline repertoire of symptomatology. Adding to the complexity, there has been an increase in reporting of subclinical/asymptomatic cases[137-146]. The clinical importance and management of such cases are yet to be established.

Most of the literature available reports that the median time to onset is within 12 weeks after ICI treatment initiation[37,109,115,137,147-151]. Severe cases usually occur earlier than non-severe cases[29,133]. Nevertheless, multiple cases with a presentation occurring after a prolonged ICI therapy period (months to years) have been reported[152-155]. Even though these cases are referred to as delayed or late-onset, the Society for Immunotherapy for Cancer's (SITC) consensus for definitions established that delayed or late-onset IRAEs are those that appear three months after the discontinuation of immunotherapy [Table 3][156]. Even though they did acknowledge that most IRAEs occur within 12 weeks of ICI initiation, they did not propose a term to describe the cases that occur later in the treatment period[156]. Limiting the timeframe of occurrence of ICIMy to 12 weeks from the treatment start date might increase specificity in the diagnosis[157]. However, as of the current state of knowledge, there is no maximum timeframe within which ICIMy can occur.

Considering the broad clinical presentation and associated high mortality, it is of critical importance to maintain a low threshold of suspicion of myocarditis in a patient undergoing ICI treatment. If suspected, a comprehensive evaluation is needed, including laboratory tests, imaging modalities, and consideration of invasive procedures like heart catheterization with EMB.

Table 3. Definitions of ICIMy according to the timeline based on SITC consensus for definitions for IRAEs

Re-emergent ICIMy: - Occurs in the heart at least twice - Occurs after a patient has temporarily or permanently discontinued immune checkpoint inhibition - Must completely resolve while a patient is not actively receiving immunotherapy (i.e., absence of all clinical signs and symptoms as opposed to resolving to grade 1), with re-emergence of symptoms (i.e., deterioration in labs or imaging alone do not qualify as re-emergence)) with or without re-starting the immune checkpoint inhibitor - Must have a well-established association with the prior immunotherapy treatment if it occurs after discontinuation of immune checkpoint inhibition. However, it is not temporally related to the steroid taper - May occur at any time after discontinuation of immunotherapy; however, other potential causes should be investigated for events occurring more than 1 year after the last dose of the immune check-point inhibitor
Chronic ICIMy: ICIMy that persists beyond 3 months of immune checkpoint inhibitor discontinuation - ICIMy is defined as chronic and active if it persists in the setting of ongoing inflammation of an organ and requires ongoing immunosuppression - ICIMy is defined as chronic and inactive if it persists in the absence of ongoing inflammation in the heart and does not require ongoing immunosuppression
Delayed/late-onset ICIMy: Manifests more than 3 months after discontinuation of immunotherapy
Adapted from the SITC consensus definitions for immune checkpoint inhibitor-associated immune-related adverse events terminology

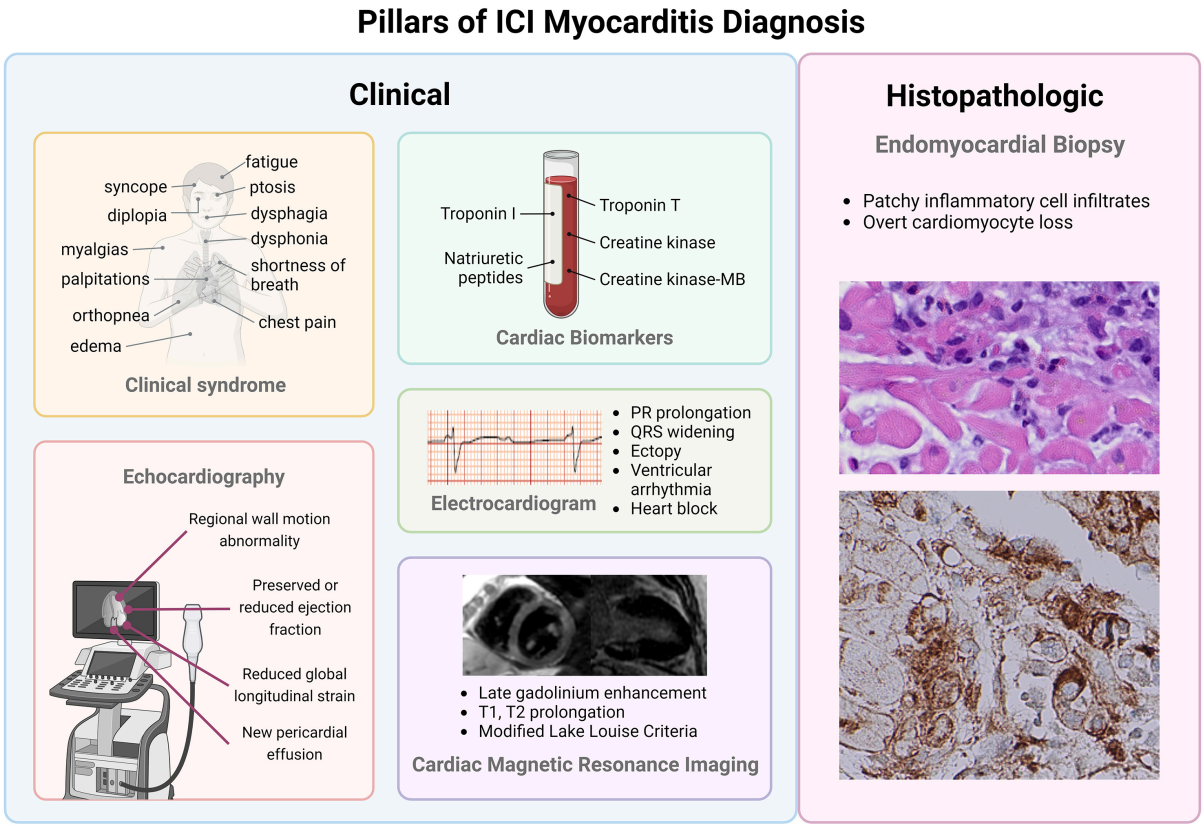

Figure 3. Pillars of ICI myocarditis diagnosis. The diagnosis of ICIMY can be clinical or histopathologic. A clinical diagnosis is more likely to be true with increasing pathologic findings. The clinical syndrome may include non-specific symptoms, cardiac symptoms, or comorbid IRAE symptoms. Typically, cases will have elevation in cardiac-specific troponins. Although alterations in ECG or imaging studies are not necessarily specific, the typically encountered alterations are denoted in the figure. Created with BioRender.com.

Electrocardiographic changes

An ECG should be performed in patients receiving immunotherapy who present with symptoms consistent with the myocarditis clinical syndrome. Preferably, a baseline ECG should be obtained prior to initiating ICI therapy to assess if there have been changes during therapy and thereafter[135,158]. Any change in ECG

from baseline could be indicative of myocarditis[137,159-163]. However, in isolation, a new ECG change is not diagnostic of ICIMy[122]. A study comparing baseline and presenting ECGs in 52 cases obtained from an international multicenter registry revealed that conduction disorders and repolarization abnormalities were frequently observed compared to baseline[164]. Further, new onset conduction abnormalities in ICI-treated patients are associated with a higher risk of cardiovascular death[147,165]. All-cause mortality correlated with the presence of pathological Q waves and inversely correlated with the Sokolow-Lyon Index[164]. An international registry of 140 ICIMy cases compared their baseline and presentation ECGs to those from patients receiving ICI treatment without myocarditis and found a prolonged QRS duration (> 110 ms) was associated with an increased risk of MACE. For every 10 ms increase in QRS duration, there was a 1.3-fold increase in the odds of MACE[166].

Numerous cases of complete heart block (CHB) have been reported and it is one of the most feared conduction abnormalities[162,167-174]. Its presence categorizes any case as severe and fulminant and has been associated with increased all-cause mortality[136,164,165]. Remarkably, temporary or permanent pacemaker placement may not increase survival[136]. Fortunately, CHB associated with ICIMy has been reported to be reversible after immunosuppressive therapies[175-178]. Fulminant cases of ICIMy may present with other life-threatening dysrhythmias, including ventricular tachycardia and ventricular fibrillation, which may occur abruptly or be preceded by other changes on the ECG[111,162,179,180].

Although the Bonaca diagnostic criteria do not include specific ECG changes[44], ventricular arrhythmias and conduction system abnormalities are specifically mentioned in the IC-OS/ESC criteria[134]. The ECG plays a crucial role in the assessment of suspected ICIMy patients due to its wide availability and relatively low cost. While ECG alone should not serve as the primary diagnostic tool, performing serial ECGs can help monitor disease progression or reversibility. When combined with troponin measurements, these tests provide a straightforward and accessible approach to identifying ICIMy. Given their accessibility, close surveillance using ECG and troponin should be used, aligning with the ESC guidelines, which prioritize these practical tools over more complex imaging techniques for routine assessment and monitoring of ICIMy[135,181].

Laboratory findings

Baseline cardiac biomarkers, especially troponin, are suggested for patients prior to initiation of immunotherapy[135,158,182]. An elevated troponin at baseline before starting ICIs is associated with an increased risk of MACE[183,184]. Several retrospective studies have shown that at the time of ICIMy diagnosis, high-sensitivity troponin T (TnT) is elevated in 94%-100% of patients[37,123,185]. Higher troponin values correlated with severity[37,185-187]. A two-center prospective study following 60 patients with ICIMy found that a TnT that is 32-fold higher than the upper limit of normal (ULN) within the first 72 h of admission was associated with a higher risk for developing MACE (composite of heart failure, ventricular arrhythmia, atrioventricular or sinus block requiring pacemaker, respiratory muscle failure requiring mechanical ventilation, and sudden cardiac death) within 90 days[185]. An ICIMy cohort from a multicenter registry had a fourfold increase in the risk of developing MACE when TnT levels ≥ 1.5 ng/dL at the time of discharge[37]. However, elevated TnT levels in patients with concurrent myositis can complicate the diagnosis of myocardial injury[44,134,188]. While an initial expert consensus report suggested troponin I (TnI) to be more specific in these scenarios, relying solely on TnI could result in missed cases of ICIMy[185,188]. A retrospective study looking at 825 patients receiving ICI therapy found that any TnI elevation was associated with increased cardiovascular events and all-cause mortality[187]. Ultimately, when serum troponin is elevated, other causes of myocardial injury should be ruled out[44,134]. There is not an established cut-off value for troponin elevation to make a diagnosis of ICIMy, and one prospective clinical trial (NCT05335928) for the treatment of ICIMy is using a cut-off of 5 times the upper limit of normal. After treatment of ICIMy, troponin elevation may persist and

may remain elevated for months after treatment and case resolution, but this is more commonly observed with TnT than TnI[185,189,190]. Troponin surveillance during ICI treatment may result in delays in treatment and increased visits to the emergency room[191-195]. However, prospective observational studies monitoring TnT in patients undergoing immunotherapy also showed that ICIs may be safely continued in smoldering and mild cases[45,146].

Higher BNP and NT-proBNP levels may correlate with the degree of severity of ICIMy, consistent with more severe cases having left ventricular dysfunction[37,148,196]. Since they are not specific to myocarditis, these cardiac biomarkers are useful for assessing NILVD and not as part of the diagnostic criteria for ICIMy[37,122,197]. Creatinine phosphokinase (CK)[123], its myocardial isoenzyme (CK-MB)[198], transaminases, and lactate dehydrogenase (LDH)[115,148] are sensitive markers commonly elevated in ICIMy, but again lack specificity. They may aid in monitoring treatment response or comorbid muscle IRAEs. Higher CK, transaminases, and LDH correlate with greater severity of ICIMy and with MACE[123,186,196,199]. Hepatic immunotoxicity should be considered with elevations in liver enzymes[199].

In recent years, hematologic markers have been found to be associated with IRAEs[200,201]. When compared to baseline, a significant increase in NLR[40,115,202] and neutrophil to eosinophil ratio (NER)[203], as well as a decrease in ALC[115,202], have been noted at ICIMy presentation, with larger changes in patients who experienced MACE or in those with greater disease severity[202,203]. Within a single-center ICIMy cohort of 81 patients, a lower platelet, lymphocyte, or monocyte count was found in those who experienced MACE compared to those who did not[196].

Lastly, serum cytokines and chemokines have been found to be elevated with ICIMy, although their usefulness is yet to be estimated. Significant elevations of IL-6, IL-10, IL-8, GM-CSF, and interferon-g have been reported[94,115,204]. The diagnostic performance of different serum cytokines was measured in a small cohort of cases and revealed that IL-6 and CXCL13 were sensible markers while CXCL9 and CXCL10 were more specific[205]. Further studies are required to understand their diagnostic utility and whether targeted therapies against these cytokines are of therapeutic value.

IMAGING

Echocardiography

In accordance with the ESC guidelines[135], baseline transthoracic echocardiography (TTE) is recommended for cancer patients at high or very high risk of cardiovascular toxicity before beginning cancer therapy. Surveillance with TTE for patients undergoing immunotherapy has not proven to be valuable[183]. Given that TTE is a readily available test, it serves as the initial imaging modality when acute myocarditis is suspected[206,207]. In ICIMy, echocardiographic findings can range from a normal examination to changes in left ventricular ejection fraction (LVEF), new wall motion abnormalities, diastolic dysfunction, and pericardial effusion[206,208]. A retrospective study showed that a preserved LVEF was present in more than half of the 75 patient-cohort diagnosed with ICIMy[209]. It is essential to emphasize that a normal LVEF does not portend a better prognosis[37,206,209], and can remain within normal ranges even in cases of fulminant myocarditis[37,210].

Global longitudinal strain (GLS) is an independent predictor of MACE in patients with ICIMy, potentially providing utility as a tool for risk stratification[211-213]. A study by Awadalla *et al.* involving 101 patients diagnosed with ICIMy showed that each percent reduction in GLS was linked to a 1.5-fold increase in MACE risk in patients with reduced left ventricular ejection fraction, and a 4.4-fold increase in MACE in those with preserved ejection fraction[213]. Echocardiography with GLS measurement may serve as a tool for

the detection of ICIMy and risk stratification for timely treatment[214,215].

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (CMR) plays a pivotal role in the diagnosis of ICIMy[216-218]. Consensus criteria for the diagnosis of myocarditis using CMR were delineated by the Lake Louise Criteria in 2009 and updated in 2018[219]. These have been integrated into various documents such as the ESC Cardio-Oncology guidelines[135] and the International Cardio-Oncology Society consensus statement[134]. The diagnosis requires the presence of two major criteria:

(I) Non-ischemic myocyte injury, assessed through T1 mapping, extracellular volume fraction (ECV), or late gadolinium enhancement (LGE)

(II) Myocardial edema, assessed through T2-weighted imaging or T2 parametric maps

Additionally, supportive criteria include: (i) Pericardial effusion, assessed through CMR images or high signal intensity (SI) of the pericardium in LGE images, T1-mapping, or T2-mapping; (ii) Abnormal systolic LV wall motion in cine CMR images[219,220]. These may help support the clinical suspicion in conjunction with other clinical findings but are not diagnostic. In contrast to non-ICIMy, myocardial edema in ICIMy is often subtle or absent, particularly when steroid therapy has already been initiated. Therefore, elevated T2 signals appear to be more common in other forms of myocarditis, such as viral infections[221,222]. Conversely, T1 mapping has emerged as a robust diagnostic tool, offering a higher diagnostic yield[220,223-227]. A meta-analysis by Pan *et al.* revealed that native T1 mapping showed a sensitivity of 85% and specificity of 74% for acute myocarditis diagnosis[224]. Similarly, in a retrospective study from a national registry, 78% of patients with biopsy-proven ICIMy exhibited abnormal native T1 values, and this was independently associated with subsequent MACE, suggesting its potential prognostic value[225,226,228]. LGE in ICIMy predominantly presents in mid-myocardial and subepicardial patterns, with the most commonly affected segments being the anteroseptum, inferoseptum, inferior, and inferolateral walls[223,229-232]. On the other hand, studies examining the diagnostic value of LGE in ICIMy have yielded contradictory results[223,226,228,233-235]. A potential explanation for these inconsistencies may lie in the time interval between symptom onset and the timing of CMR, as suggested by a study conducted by Zhang *et al.* involving 106 patients with ICIMy. The study demonstrated that the prevalence of LGE increased substantially from 21.6% when CMR was performed within 4 days of admission to 72.0% when CMR was conducted on day 4 or later[223]. Given that LGE serves as a marker of myocardial fibrosis, it may take some time for changes to become fully apparent on CMR, potentially serving more as a prognostic marker rather than a diagnostic tool[233,235,236]. Notably, the left ventricular sub-endocardial global longitudinal strain measured by cardiac MRI was associated with corticoid-resistant ICIMy[237]. Further research is warranted to better identify the specific CMR findings associated with ICIMy.

Positron emission tomography

Cardiac fluorodeoxyglucose positron emission tomography (FDG-PET) is a potential tool for assessing ICIMy, particularly in scenarios where CMR is unavailable, contraindicated, or yields equivocal results[206,238-243]. In a prospective pilot study of 10 patients, this imaging modality demonstrated a sensitivity of 75% and a specificity of 67% in diagnosing ICIMy[241]. However, a larger retrospective cohort showed a sensitivity of 9.5% and a specificity of 85.7%, albeit with an important methodologic difference whereby it used a modified version of the Bonaca criteria for diagnosis[244].

On the other hand, 68Ga-DOTATOC PET has shown significant promise in detecting ICIMy, particularly during the early stages of myocardial inflammation, where cardiac MRI may fail to detect changes[205,245]. In the same manner, Ga-FAPI PET-CT has demonstrated positive results in diagnosing ICIMy and its associated complications[246-248]. However, additional research is required to determine the diagnostic yield of other PET tracers for the diagnosis of ICIMy.

Endomyocardial biopsy

Despite advances in non-invasive imaging techniques, EMB remains the gold standard for diagnosing myocarditis, particularly in cases where imaging findings yield uncertain results[249,250]. Traditionally, the histopathologic diagnosis of myocarditis has relied on the Dallas criteria, which require both an inflammatory infiltrate and myocardial necrosis[251]. Common findings include CD4+ T cells, CD8+ T cells, and CD68+ macrophages, alongside PD-L1 expression on cardiomyocytes[102,104,142,249,252-255]. However, the histological presentation in ICIMy is heterogeneous, showing a spectrum in the severity of the inflammatory burden based on the density of inflammatory infiltrate and the presence or absence of myocyte loss[142,253]. The need for standardized histopathologic reporting in ICIMy has prompted the development of grading systems, which could potentially aid in risk stratification. Champion *et al.* classified ICIMy into low-grade (≤ 50 CD3+ cells/hpf) and high-grade (> 50 CD3+ cells/hpf), with low-grade patients showing a milder clinical course and a more favorable prognosis[104]. Another proposed grading system [Table 4] was developed after finding that ICIMy can present with different grades of inflammation, with the highest grade being associated with a significantly higher TnT than the lower grades of inflammation[142]. A subset of patients with low-grade (Grades 1A and 1B) ICIMy received no treatment and even continued ICI therapy without cardiovascular complications[142]. Further studies are needed to establish the prognostic and therapeutic value of these grading systems.

EMB is limited by its relatively low sensitivity[256], potential sampling error, high interobserver variability, and the complexities associated with biopsy interpretation[102]. At least five specimens are recommended to enhance diagnostic accuracy when acute myocarditis is suspected[257]. Other important limitations include the risks related to the invasive procedure[253]. Although at experienced centers, EMB is associated with a low complication rate, with periprocedural mortality rates ranging from 0% to 0.07%, primarily attributed to malignant arrhythmias, high-degree atrioventricular block, and cardiac tamponade[250]. Of note, caution is needed in hemodynamically unstable patients with severe heart failure and those with dilated cardiomyopathy, who may face an increased risk of complications[250].

Differential diagnosis

Although myocarditis is the most recognized cardiovascular IRAE, it is important to consider other conditions when a patient presents with non-specific cardiac symptoms[25,33,258]. The most frequently reported cardiovascular events associated with ICIs are arrhythmias, heart failure, vasculitis, and pericarditis[25,28,33,38,258-260]. Particularly, acute myocarditis and acute coronary syndromes (ACS) share similar clinical and diagnostic features[261,262]. Previous studies have suggested a correlation between ICI therapy and accelerated atherosclerosis[25,263], potentially contributing to the increased risk of myocardial infarction seen in ICI-treated patients[23,259,264,265]. Therefore, coronary angiography and/or functional stress testing should be considered for all individuals with suspected myocarditis to rule out ACS[43,231,261,262,266,267]. Furthermore, it is important to consider the potential coexistence of these two entities, as upregulation of PD-L1 has been observed in the ischemic myocardium, likely serving as a protective mechanism to attenuate T cell-mediated immune responses to the damaged tissue. Since symptoms and diagnostic workup findings may overlap with ischemic findings, it is common to perform an ischemic evaluation with either coronary angiography and/or functional stress testing in patients presenting with suspected ICIMy. Consequently, patients receiving anti-PD-1 therapy may be at an increased risk for developing ICIMy[231,268,269]. New-onset

Table 4. Pathology grading system of myocardial inflammation during ICI therapy

Diagnosis per EMB	Grade	EMB findings
Negative	0	Negative
Myocardial inflammation	1A	Mild inflammatory cell score by immunohistochemistry (10-20 inflammatory cells/high power field)
	1B	At least moderate inflammatory cell score by immunohistochemistry (> 20 inflammatory cells/high power field)
Definite myocarditis	2	Multifocal inflammatory cell infiltrates (> 40 inflammatory cells/high power field) with overt cardiomyocyte loss by light microscopy

myocardial dysfunction without signs of active inflammation, such as elevated troponin or a negative CMR, should prompt suspicion of NILVD, and an EMB can be considered to further aid in establishing the diagnosis[28]. Other potentially life-threatening conditions that warrant consideration include pericardial disease, especially in severe cases requiring pericardiocentesis[270-272], and Takotsubo cardiomyopathy[28,273-275], for which EMB may facilitate differentiation from ICIMy[274,276]. Less commonly encountered diagnoses, but still important in the differential, include viral myocarditis[222,277-280], late cardiovascular effects of previous antineoplastic agents, pericardiac metastatic disease[281], and other immune-related cardiotoxicities or IRAEs[242,282], including cytokine release syndrome[28,283] and pneumonitis.

In patients diagnosed with ICIMy, encountering additional immune-related adverse events (IRAEs) is not uncommon. Around 50%-80% of ICIMy patients present with another IRAE[24,137,186,284,285]. A comorbid IRAE, as one of the minor IC-OS/ESC criteria, reflects their frequent association with ICIMy[134]. When ICIMy occurs along with ICI-related myositis, it is associated with increased mortality[24,149,286,287]. Symptoms of myositis can manifest as restricted neck extension, myalgias, limb-girdle and/or axial weakness, and fatigue[158,288]. Retrospectively, myositis was identified in 53% of ICIMy patients who experienced MACE[24]. The significant association between these myotoxicities reflects how ICIMy should be ruled out in a patient presenting with isolated musculoskeletal symptoms[134,289-291].

ICI-associated myasthenia gravis (MG) can concomitantly occur with myocarditis and myositis, and the simultaneous occurrence of these is known as overlap syndrome (IM3OS)[180,292-300]. Oculomotor disturbances, dysphagia, dyspnea, myalgias, and muscle weakness are commonly reported symptoms in patients with IM3OS[245,292,301]. Those with bulbar and diaphragmatic weakness have a higher mortality[302]. The ICI-MG-related mortality is reported to be around 23%-29.8%[302,303]. Up to 46% of ICI-MG cases are part of an IM3OS picture[303]. A pharmacovigilance study found that 25% of severe ICIMy cases had concurrent myositis and 11% had MG[109]. This is a life-threatening syndrome and should be addressed attentively, with some authors suggesting routine diaphragmatic evaluation to detect impending respiratory failure[110,178,298]. An institutional case series of 10 patients with IM3OS revealed that a higher TnT on admission correlated with mortality[304]. Given the high frequency of concurrent myositis and MG with ICIMy, it is appropriate to consider testing for autoantibodies[112,127,295,305-307] and electrophysiological studies[44,181,308,309] for these neuromuscular IRAEs. However, IM3OS can be diagnosed clinically, irrespective of serologies and/or electrophysiological studies[306,310].

Management strategies

When suspecting ICIMy, the first step is to hold the next dose of immunotherapy while performing a rapid evaluation. Given the high mortality associated with ICIMy, patients are often admitted for joint management involving oncology and cardiology services, along with neurology and rheumatology, considering the overlap with neuromuscular IRAEs[135,158,181]. Steroids are the mainstay of treatment, with the intent of reducing inflammation and stopping further immune-mediated toxicity [Figure 4]. If a patient presents with a severe or fulminant form ICIMy, often with high-grade atrioventricular block, ventricular

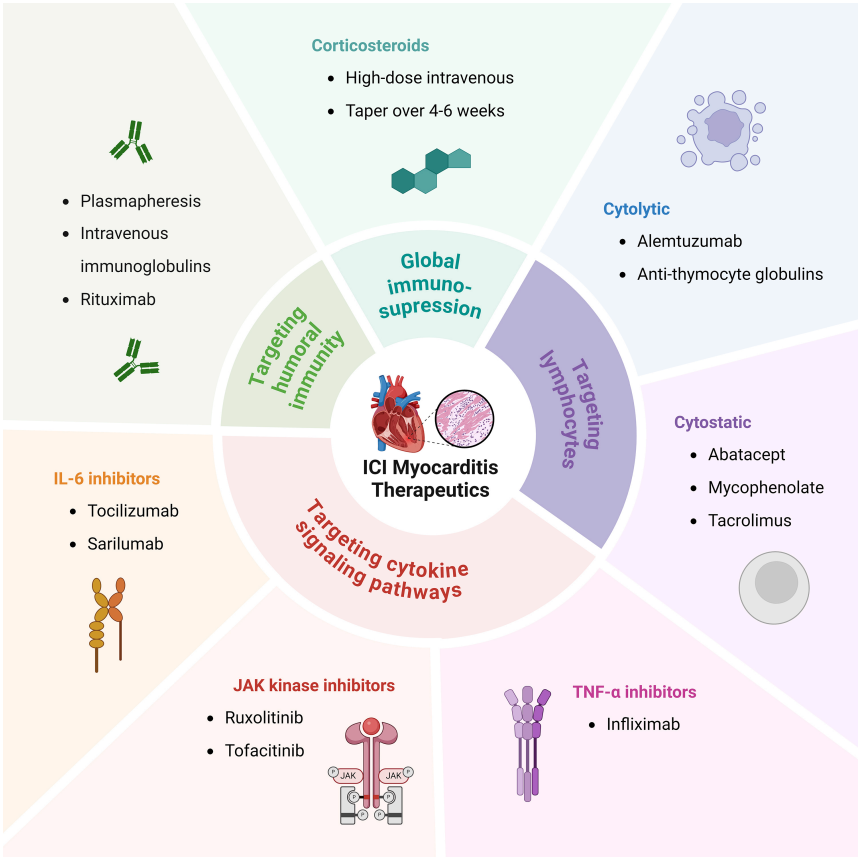

Figure 4. Treatment Options for ICI Myocarditis. High-dose corticosteroids are the mainstay of ICIMy treatment, given their broad immunosuppressive action. However, other medications that target more specific aspects of the immunologic response should be considered and administered in severe or steroid-unresponsive cases. Created with BioRender.com.

tachyarrhythmias, or cardiogenic shock, then empiric treatment with at least one high dose of methylprednisolone should begin as soon as possible before awaiting any confirmatory testing[135]. One retrospective study showed early initiation of high-dose steroids was associated with reduced MACE[311-313]. The American Society of Clinical Oncology (ASCO) clinical practice guidelines recommend initiating high-dose oral prednisone or IV methylprednisolone 1-2 mg/kg/day within 24 h for cardiotoxicities grade 2 or higher, depending on symptoms, with the addition of abatacept or alemtuzumab for life-threatening cases[181]. Most other guidelines recommend the use of pulse dose steroids (500-1,000 mg IV methylprednisolone daily) for 3 to 5 days, followed by a 4-6-week tapering[135,158,181,314]. Severe cases with hemodynamic or electrical instability should be managed according to guidelines specific to these scenarios, including, but not limited to, the use of temporary pacemakers[175] or mechanical-circulatory support[312,315].

ICIMy can be classified regarding its responsiveness to steroids [Table 5]. The ESC guidelines on cardio-oncology define clinical improvement and response to steroids as a reduction in cardiac-specific troponin by greater than 50% from peak level within 3 days of high-dose IV methylprednisolone and resolution of left ventricle dysfunction and atrioventricular block or other arrhythmias[135]. With clinical improvement and adequate response, a steroid taper should follow. There are insufficient data on treating ICIMy based on the grade of severity on presentation, and research is ongoing to identify those who might benefit from a less intensive immunosuppressive regimen.

Table 5. Definitions of steroid responsiveness in ICI myocarditis

- **Steroid-unresponsive myocarditis**: Myocarditis in which there is no clinical improvement after 1-3 days of appropriate directed steroid therapy. Can be further classified as:
  - **Steroidrefractory myocarditis**: Cases in which there is no clinical benefit from steroids
  - **Steroid-resistant myocarditis**: Cases that show some clinical benefits without resolution of the event
- **Steroiddependent myocarditis**: Cases that respond to guideline-based directed steroid therapy but show *symptomatic* deterioration or lack of response on tapering, and tapering is not possible. If ongoing steroids are required for ≥ 12 weeks, the condition is classified as "**chronically steroid-dependent**"
  - In contrast, re-emergent myocarditis occurs temporally unrelated to the steroid tapering

Adapted from the SITC consensus definitions for immune checkpoint inhibitor-associated immune-related adverse events terminology

The ESC guidelines were the first to recommend upfront use of additional immunosuppressive agents, alongside steroids, for patients presenting with fulminant ICIMy[135,181]. Prompt identification of patients with high-risk features, including life-threatening arrhythmias and high-grade atrioventricular block[111,136,162,164-166,179,180], notoriously elevated biomarkers[37,185-187], and features of IM3OS[24,110,149,178,286,287,292,293,298,302], should prompt clinicians to consider early initiation of other forms of immunosuppression. High-quality, evidence-based recommendations for specific second-line immunomodulators are lacking. A study conducted by Cautela *et al.* examined a pooled set of ICIMy cases that met Bonaca's criteria, including cases from their institution and those reported in the literature. The study compared patients treated with steroids alone *vs.* those treated with steroids and second-line immunomodulatory therapies[316]. The analysis revealed insufficient data to recommend a particular second-line immunomodulator or combination of immunomodulators over another[316]. Case series and reports sharing their experience have elucidated potential useful treatments, such as anti-thymocyte globulins (ATG), mycophenolate mofetil (MMF), abatacept, alemtuzumab, infliximab, plasma exchange (PLEX), intravenous immunoglobulins (IVIG), rituximab, ruxolitinib, tofacitinib, tocilizumab, and tacrolimus.

ATG or thymoglobulin are polyclonal IgG antibodies directed toward various components of T cells, ultimately depleting them in circulation[317]. It is employed as an immunosuppressive agent for prophylaxis and treatment of transplant rejections[317]. It has been employed in treatment-unresponsive cases[307,318-321], a steroid-dependent case[322], and upfront along with steroids in a severe case[280], most without a clear benefit. A single-center experience of ICIMy cases revealed that nine out of eleven patients who were initially treated with steroids plus upfront ATG still required further immunosuppression due to increasing troponin upon steroid tapering[323]. Lastly, infectious consequences leading to death after immunosuppression with ATG have been reported[307,319].

Mycophenolate mofetil (MMF) preferentially inhibits the rate-limiting enzyme in de novo synthesis of guanosine nucleotide on active lymphocytes, leading to their apoptosis and, within a couple of days, a significant reduction in systemic cytokines[324]. It has been shown to improve significant conduction abnormalities in steroid-refractory cases[177,325]. Half of the IM3OS patients at a single center who were unresponsive to initial therapy did not require further immunosuppression after the addition of MMF[326]. One case of ICI-myotoxicity resistant to steroids and IVIG was managed successfully with MMF[327]. A moderate response has been reported when employed after ATG[318,322]. Yet, there have been various severe ICIMy cases that are resistant or refractory to steroid and MMF-based therapy, often requiring further immunosuppression[155,189,320,326,328-332].

Abatacept is a recombinant CTLA-4 immunoglobulin that blocks its ligands' (CD80/86) ability to interact with the stimulatory B7-CD28 on T cells, preventing their activation[78]. There are various reports of therapeutic benefits of treating refractory cases with abatacept[178,189,295,297,326,329,333,334]. Only a few cases showed

minimal to no response after treatment with abatacept[295,326,330]. The standard administration scheme consists of about 10 mg/kg/dose every two weeks. Notably, Nguyen *et al.* administered abatacept treatment with higher and more frequent doses to patients with steroid-refractory ICI-myotoxicity, giving up to three 20 mg/kg doses within 10 days[329]. In one of their studies, using a higher mean total administered dose of 60 mg/kg within 15 days, adding ruxolitinib for synergy, and implementing screening and management for respiratory muscle involvement, mortality was reduced to only 3%. Importantly, dosing was guided by real-time monitoring of CD86 receptor occupancy, a pharmacodynamic biomarker of clinical activity[178,329]. Currently, there are two clinical trials evaluating abatacept for the treatment of ICIMy (NCT05335928, NCT05195645).

Alemtuzumab, a CD52-directed cytolytic monoclonal antibody, has only been described in one case report of fulminant IM3OS, where the patient was refractory to initial treatment consisting of high-dose methylprednisolone and MMF for the myocarditis component and rituximab and IVIG for myositis and MG[331]. Consequently, the patient received a single dose of 30 mg of alemtuzumab with rapid T cell depletion and resolution of life-threatening arrhythmias[331].

Infliximab and etanercept are monoclonal antibodies against tumor necrosis factor-α (TNF-α). Infliximab is one of the recommended second-line immunosuppressants for ICIMy in the ASCO guidelines[181]. However, caution is advised against it in the ESC[135] and SITC guidelines[158], with a study by Cautela *et al.* revealing that ICIMy patients treated with infliximab seem to have higher mortality compared to those that received other immunomodulatory therapies[316]. Data from case reports suggest that treating with infliximab does not result in better outcomes[71,190,318,320,335-338] and may even be associated with life-threatening infections[339,340]. However, some steroid-dependent[307,340] and severe[340] cases have responded to infliximab.

Plasmapheresis or plasma exchange (PLEX) may have a dual-therapeutic effect in ICIMy. It is a frequent treatment modality in various autoimmune disorders, working to remove circulating autoantibodies, immune complexes, complement proteins, and cytokines[341]. In the context of ICI-mediated toxicity, it aids by lowering the plasma concentration of the ICI[178,328,342] and removing systemic cytokines and anti-cardiac antibodies that are potentially contributing to the inflammatory picture[328,343]. However, it cannot completely remove the ICI antibody and may remain detectable in plasma months later[178]. Case series report its utility in ICIMy cases that were refractory to initial treatment, being employed in combination with other immunomodulators[189,280,328,344-346] or alone[113,347,348]. Additionally, some have reported success in patients with IM3OS managed with high-dose steroids and upfront PLEX[298,342]. However, some are still refractory after employing PLEX and require further immunosuppression[294,298,334,349].

IVIG are non-specific antibodies that are extracted from the plasma of healthy subjects[350,351]. Although they were originally intended to provide passive immunity for individuals with immunodeficiencies, they have also been observed to provide anti-inflammatory properties to treat autoimmune conditions[350,351]. Many reports show a therapeutic response after treating ICIMy with IVIG[102,110,143,299,300,352,353], albeit the majority receive more than one second-line immunosuppressive agent[326,346,348,354,355] or are supported by extracorporeal membrane oxygenation (ECMO)[356,357]. Some case reports did not show a therapeutic response when ICIMy was severe, even when administered with other immunomodulators[335,358]. When administered upfront, many were still refractory, requiring further immunosuppressive interventions[114,326,327,331,344,348,359-362].

Rituximab is a monoclonal antibody directed against CD20, a B-cell specific marker, depleting these cells in circulation[363], thereby reducing available plasma cell precursors and antibody production[364]. IM3OS cases

have shown appropriate responses after its administration upfront[298] and in some refractory cases[114,298,326]. Others, however, did not respond to rituximab[298,326,331]. Additionally, profound immunosuppression and sepsis led to a fatal outcome[114]. To our knowledge, there are no cases of isolated ICIMy reporting the use of rituximab.

Janus Kinase (JAK) inhibitors, such as ruxolotinib and tofacitinib, are theorized to be beneficial for ICIMy due to their anti-inflammatory and immunosuppressive effects[365,366]. Some reported cases suggest successful management of steroid-dependent cases with tofacitinib[323,359,367]. The available research on ruxolitinib for ICIMy comes from Salem *et al.*, rationalizing its benefit due to its synergistic effect with abatacept as well as an immunomodulatory bridge while awaiting abatacept's slow onset of action[178,329].

Interleukin-6 (IL-6) is essential for the differentiation of helper CD4+ T cells to T helper 17 cells (Th17), which have been directly implicated in autoimmune inflammation that is unresponsive to steroids[368]. Currently available IL-6 inhibitors are tocilizumab and sarilumab. A severe steroid-refractory case was successfully managed with tocilizumab[369]. Additional reports of cases unresponsive to initial treatment do not reveal a significant benefit after adding tocilizumab[176,362,370]. Moreover, a multicenter retrospective study did not find IL-6 inhibitors to be beneficial for patients with ICI-related myositis with MG and/or myocarditis[371].

Tacrolimus is a calcineurin inhibitor known to significantly reduce IL-2 expression, directly affecting T cell proliferation and indirectly affecting B cells[372]. Most reported ICIMy cases treated with tacrolimus do not show overt benefit[155,320,344,353,360]. Two very similar cases managed with high-dose methylprednisolone and upfront IVIG that progressed to require ECMO were able to recover with continued steroids and adding tacrolimus[344,360]. Whether these patients truly benefited directly from the tacrolimus or merely required circulatory support before showing response to the steroids is uncertain. Unsuccessful management with basiliximab, an IL-2 receptor antagonist, was reported in a refractory case[155].

Eculizumab and ravulizumab are monoclonal antibodies that inhibit the formation of the complement membrane attack complex (MAC) currently approved for the treatment of paroxysmal nocturnal hemoglobinuria[373]. However, they have been used off-label for MG treatment[374]. Two severe IM3OS cases refractory to high-dose steroids and PLEX reported recovery of functional status after treating with eculizumab alone or with ravulizumab[374,375]. Further investigations are required to determine if these prove to be beneficial in isolated myocarditis cases.

Resumption (rechallenge) and discontinuation of immunotherapy

Discontinuation of immunotherapy is recommended if the patient presents with clinically significant disease[135,158,181]. However, the decision to resume ICI therapy is complex and should be made on a case-by-case basis through multidisciplinary discussions. The patient's comorbidities, cancer status, prior response to and toxicity from ICIs, and the availability of alternative therapies must be considered[181,376-378]. Several reported cases have shown that patients with ICIMy who were rechallenged with immunotherapy did not experience re-emergence of myocarditis[102,127,142,147,377,379-382] and, in some instances, even demonstrated improved outcomes[378]. Nevertheless, ICI rechallenge should be avoided in patients with severe left ventricular dysfunction, advanced conduction abnormalities, or critical arrhythmias[383]. The use of troponin levels to determine the response or safety of rechallenge is an area of active research. Currently, no specific threshold values exist. Further research is needed to better identify patients at low risk for myocarditis recurrence, enabling the continuation of potentially life-prolonging immunotherapy in these individuals[376,384].

Prognosis and outcomes

ICIMy is a life-threatening, but treatable condition. The mortality associated with ICIMy is high and can occur in up to half of patients, with pharmacovigilance studies reporting mortality from 33% to 50%[17,34,71,385,386]. A systematic review of case reports and case series found a fatality rate of 42%[387]. Combination ICI therapy may have a higher associated mortality compared to monotherapy[71,109]. Data from an international multicenter registry found an incidence of major adverse cardiac events (MACE), including cardiovascular death, cardiogenic shock, cardiac arrest, or CHB, in 46% of ICIMy, with cardiovascular death occurring in 38%[37]. However, both pharmacovigilance and published reports are subject to reporting bias, often focusing on more severe or unusual cases, which can lead to an overestimation of the true fatality rate. Although a single-center, retrospective study with 12 cases of ICIMy reported 5 deaths (42%)[120], multiple single and multicenter studies reveal lower cardiovascular mortality, ranging from no deaths in a 33-patient cohort up to 26.9% in a 52-patient cohort[28,127,137,164,165,186]. Because large-scale prospective studies are lacking and the definition of ICIMy-related death may differ between centers, the true incidence and outcomes of ICI-induced myocarditis are unclear. Earlier identification and treatment, increasing detection of mild and subclinical cases[145,146,187,193,282,388], or improved management of ICIMy might lead to a decreasing trend of fatality rates. Cardiovascular and all-cause mortality rates may not differ between severe, non-severe and negative cases[148,381], although other authors report a significant association between severe cases and decreased overall survival (OS)[196]. As the identification of lower-grade ICIMy cases increases, the attributable mortality of this adverse event might decrease.

Very few studies have reported cancer outcomes after ICIMy. One study reported that the onset of myocarditis within two months of immunotherapy initiation is associated with progression and shorter progression-free survival (PFS) in a cohort of fourteen patients with NSCLC[148]. On the other hand, studies have shown that those who experience any IRAE have a better PFS and OS[389-395]. Surprisingly, an ICIMy case with multi-organ system immunotoxicity did not have residual primary tumor or metastatic lesions on autopsy[168]. Consistent with this, interruption of ICI or glucocorticoid for an IRAE correlates with a worse PFS and trends toward a shorter OS[396]. However, whether myocarditis-specific intensive immunosuppressive therapy interferes with or reverses the immunotherapy's cancer-fighting properties is yet to be determined. Lastly, there is a high economic burden of ICIMy, being the IRAE with the longest length of stay, with a median of 11 days (IQR, 7-18)[6] and the third-most expensive IRAE, with an estimated mean cost of $45,341 USD per event[8].

Future directions

The understanding of the pathophysiology, diagnosis, and management of ICIMy has evolved over the short time period of its first recognition as a complication of ICI therapy. One of the critical gaps in understanding pathophysiology is the development of an adequate animal model that includes both tumor and cardiac responses to immune checkpoint therapy. The current models focus on either the cardiac or tumor level, which limits the ability to test the hypothesis related to diagnosis, treatment, and response to therapies at both levels. Another unmet need is to identify a non-invasive diagnostic test to diagnose ICIMy. Currently, endomyocardial biopsy is the gold standard, and CMR and nuclear have limitations in feasibility and diagnostic accuracy. However, most centers are not equipped to perform endomyocardial biopsies and lack the pathology expertise to make an accurate diagnosis. Future directions for diagnosis may exist in novel nuclear tracers tied to the immune infiltrate observed in ICIMy. Lastly, our understanding of the treatment of ICIMy continues to change. As the disease is better recognized, so is the spectrum from mild to severe cases. A one-size-fits-all approach may not be appropriate and further research is needed to risk stratify or tailor specific immunomodulatory treatment based on the severity or exact inflammatory infiltrate observed in individual cases. There is ongoing research to address all of these unmet needs with the hope that ICIMy will become a treatable condition.

CONCLUSION

ICIMy is a significant and potentially life-threatening adverse event in patients treated with immune checkpoint inhibitors. Patients at an increased risk of developing ICIMy include those undergoing dual-ICI therapy and those with underlying TETs. Additionally, these patients have a worse prognosis if they develop ICIMy. The clinical presentation can range from mild to severe and may or may not be accompanied by symptoms, including chest pain, shortness of breath, and myalgias. The diagnosis of ICIMy is often challenging and requires a combination of laboratory tests and imaging studies.

Despite the high mortality rate associated with ICIMy, early initiation of high-dose steroids helps mitigate its severity. Several potential therapeutic targets are available for steroid-unresponsive cases. These include immunomodulatory therapies that target cellular or humoral immunologic responses or interfere with cytokine signaling pathways. With an increased understanding of the pathophysiology of ICIMy, the best therapies aimed at its underlying mechanisms will be refined.

Fundamentally, clinicians should maintain a high level of suspicion for ICIMy when a patient presents with cardiac or neuromuscular symptoms. Suspected cases should be managed at specialized centers with expertise in this condition, where a collaborative approach involving oncologists, cardiologists, and neurologists - such as through multidisciplinary clinical boards - can ensure that patients receive comprehensive, tailored care for the complexity of ICIMy[135]. Early detection, holding immunotherapy, and treatment of ICIMy may result in improved outcomes for patients.

DECLARATIONS

Authors' contributions

Prepared figures using BioRender.com: Palaskas NL, Ostos-Mendoza KC, Wang E.
Drafted the manuscript: Ostos-Mendoza KC, Saraiba-Rabanales V, Gutierrez-Gallegos P, Wang E
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Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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