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Review

The Self-Amplifying Loop in Immune Checkpoint Inhibitor-Associated Myocarditis: From Immunopathogenesis to Mechanism-Directed Therapy

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Abstract

Immune checkpoint inhibitor-associated myocarditis (ICI-M) is rare (0.3%–1.0%) but carries a mortality rate of 27%–50%, with a clinical course that can progress from initial symptoms to hemodynamic collapse within days. Although T-cell activation, cytokine release, and myocardial injury have each been extensively studied in this context, these processes have largely been examined in isolation. Thus, what remains unclear is how these processes interact to drive fulminant deterioration. In this review, we propose an integrative mechanistic framework centered on a self-amplifying cytokine–injury–damage-associated molecular pattern (DAMP) loop, in which checkpoint blockade triggers T-cell activation and cytokine release, leading to cardiomyocyte injury. The damaged myocardium then releases DAMPs, which activate innate immune pathways (Toll-like receptor (TLR)–nuclear factor kappa B (NF-κB) and cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING)–NLR family pyrin domain containing 3 (NLRP3)), thereby inducing further cytokine production. Once established, this cycle can become self-sustaining even after ICI discontinuation, potentially explaining the acute onset, continued progression, and variable steroid responsiveness characteristic of ICI-M. The diagnosis of ICI-M currently depends on a combination of troponin kinetics, an electrocardiographic (ECG) findings, and cardiac magnetic resonance (CMR) imaging; however, in practice, these tools are more often used to confirm suspected cases than to detect early disease. Therapeutically, high-dose glucocorticoids remain the first-line treatment, while abatacept combined with ruxolitinib has shown promise in steroid-refractory cases. Mechanistically, this combination addresses two critical components of the amplification loop: abatacept interrupts T-cell stimulation at the upstream immunological synapse, whereas ruxolitinib inhibits downstream cytokine signaling. This amplification loop framework provides a rationale for considering early multi-target intervention rather than sequential escalation, since single-agent blockade may be insufficient once the loop is fully operative. While early multi-target therapy is mechanistically appealing, this option is currently supported primarily by observational studies and early-phase evidence rather than definitive prospective trials. This novel self-amplifying loop framework may help guide the design of future trials to evaluate early combination immunosuppression in ICI-M.

Keywords: cardio-oncology; myocardial injury; PD-1/PD-L1 inhibitors; immune checkpoint inhibitors; heart failure

1. Introduction

Immune checkpoint inhibitors (ICIs), including programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, have become a cornerstone of cancer immunotherapy. However, ICI-associated myocarditis (ICI-M) has proven to be among the most lethal immune-related adverse events associated with checkpoint blockade therapy, characterized by an abrupt onset and a clinical course that can progress rapidly from initial symptoms to hemodynamic collapse [1,2,3].

The incidence of ICI-M is estimated at 0.3%–1.0% among patients undergoing ICI treatment, yet mortality rates range from 27% to 50%, with 46% of patients experiencing major adverse cardiovascular events (MACE), including cardiac death, cardiogenic shock, and high-grade atrioventricular block [2,3,4]. This profile of low incidence coupled with high lethality makes ICI-M one of the most concerning immune-related adverse events [4,5,6,7,8,9].

Pathologically, ICI-M is characterized by myocardial $CD4^+$/$CD8^+$ T-cell infiltration and cardiomyocyte damage, with an immunophenotype distinct from that of classical viral myocarditis [4]. We propose that this phenotype is related to checkpoint blockade-mediated disruption of cardiac immune tolerance in affected patients, triggering cytokine-mediated cardiomyocyte injury. Damage-associated molecular patterns (DAMPs) released from the injured myocardium then activate innate immune pathways, creating a self-amplifying loop defined by cyclical cytokine release, myocardial injury, damage-associated molecular pattern (DAMP) release, and innate immune activation. This positive feedback cycle may explain why patients with ICI-M can deteriorate so rapidly once the disease is established.

In this review, we use this amplification loop framework as a tool to re-examine the epidemiology, pathogenesis, diagnosis, and treatment of ICI-M, and to explore whether early, mechanism-directed intervention may im-

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prove outcomes for affected patients. This is a narrative review. We searched PubMed and Embase using terms including "immune checkpoint inhibitor", "myocarditis", "DAMP", "innate immunity", and "cardio-oncology" for articles published through April 2025. Reference lists of key articles were manually reviewed. No formal systematic search protocol or quality appraisal was performed.

2. Incidence

ICI-M exhibits a low incidence (0.3%–1.0%) but has a high mortality (27%–50%). It is currently the most serious immune-related cardiovascular complication associated with checkpoint blockade [2,3,6]. The risk for developing ICI-M is influenced by both the treatment regimen and tumor type: PD-1/PD-L1 monotherapy typically yields an incidence of <0.6%, whereas the combination blockade of PD-1 and CTLA-4 increases the incidence to 1%–2%, a 3–4-fold increase compared to monotherapy [2,3]. Significant variation also exists across tumor types, with thymic epithelial tumors demonstrating the highest incidence (up to 7.1%), significantly higher than the rates reported for melanoma, non-small cell lung cancer, and renal cell carcinoma (generally <1.5%) [6,10]. A nationwide Chinese cohort study (n = 55,219) revealed significantly elevated myocarditis risk in ICI users (HR = 7.41, 95% CI 3.29–16.67), with a cumulative incidence of 4.8 per 1000 person-years [11]. Recent large international real-world cohort analyses have further quantified this risk. For instance, a French national database study including 172,363 ICI-treated patients reported myopathy/myocarditis incidence at approximately 0.7%–0.9%, with isolated ICI-M incidence in 0.3%–0.6% of cases, and simultaneous myocarditis and myositis occurring in approximately 13%–23% of patients [10]. Another global real-world analysis encompassing 88,928 patients showed an ICI-M incidence of 0.48%, with the presence of concurrent pericardial disease (pericarditis, pericardial effusion) significantly reducing overall survival [12]. These findings consistently reinforce the low incidence but high mortality rates that are characteristic of ICI-M.

ICI-M risk differs significantly across checkpoint inhibitor targets. Pembrolizumab, a representative PD-1 inhibitor, currently possesses the most comprehensive clinical dataset. Multiple studies have revealed that, although pembrolizumab monotherapy is associated with a low incidence of myocarditis, cases have nonetheless occurred in both real-world settings and clinical trials. When PD-1 blockade is combined with CTLA-4 inhibitors (e.g., ipilimumab), the risk of myocarditis increases significantly and is predominantly associated with severe clinical presentations [2,13,14]. A Chinese multicenter research study identified camrelizumab, a domestic PD-1 inhibitor, as the most common causative agent in Chinese populations, with an overall mortality of 37.93%, and adverse outcomes being associated with P-wave abnormalities [15]. A considerable proportion of pembrolizumab-associated myocarditis cases present with concurrent myositis or myasthenia gravis, constituting what has been termed myocarditis-myositis-myasthenia gravis (MMM) overlap syndrome, which is linked to a higher risk of mortality [16,17]. In contrast, current real-world data suggest a lower reported incidence of myocarditis with PD-L1 inhibitors compared with PD-1 inhibitors, possibly reflecting partial preservation of the PD-1–PD-L2 pathway following PD-L1 blockade [14,18]. However, these findings are derived from pharmacovigilance databases with inherent confounding, and head-to-head prospective comparisons remain lacking. Whether this differential cardiac risk is offset by comparable antitumor efficacy across indications remains unclear. Prospective studies are warranted to determine whether patients with elevated baseline cardiac risk should preferentially receive PD-L1 inhibitors when oncologically appropriate. Retrospective real-world studies in Chinese populations have identified risk factors and prognostic features of immune-related adverse events (irAEs) [19]. Multimodal biomarker-based risk stratification based on factors including N-terminal pro-B-type natriuretic peptide (NT-proBNP), cardiac troponin T (cTnT), high-sensitivity C-reactive protein (hsCRP), and coronary artery calcium score may facilitate the early identification of high-risk patients [20].

High-risk populations that have demonstrated a higher incidence of irAEs include patients of advanced age, patients with a history of prior cardiovascular disease, patients receiving combination immunotherapy, and patients exhibiting other concurrent irAEs (e.g., myositis, myasthenia gravis) [6,21,22]. Recent evidence has further demonstrated that baseline cardiovascular conditions, including prior heart failure, coronary artery disease, or arrhythmias, multiple concurrent irAEs, use of combined PD-1 and CTLA-4 regimens, and persistently elevated NT-proBNP/high-sensitivity cardiac troponin (hs-cTn) at baseline or early follow-up are all associated with a significantly increased risk of ICI-M and MACE. These patients thus warrant increased clinical consideration and surveillance when selecting and administering immunotherapy agents [6,21,22] (Table 1, Ref. [2,3,6,10,11,14,16,17,18,20,21,22,23,24,25]).

3. Clinical Presentation and Diagnosis of ICI-M

Early recognition and diagnosis of ICI-M are critical for improving the prognosis of affected patients. Due to its nonspecific early symptoms and overlapping clinical features with myocardial ischemia, viral myocarditis, and stress cardiomyopathy, however, early diagnosis of this condition continues to pose considerable challenges [18,26]. This section systematically reviews current understanding of ICI-M diagnostic considerations based on clinical phenotypes, severity stratification, biomarkers, diagnostic investigations, and endomyocardial biopsy.

Table 1. Risk factors for ICI-M.

Category	Risk factor	Evidence/Notes	References
Treatment-related	Combination ICI therapy (PD-1 + CTLA-4)	3–4 fold increased risk vs monotherapy; incidence 1%–2%	[2,3]
	PD-1 inhibitors vs PD-L1 inhibitors	PD-1 inhibitors associated with slightly higher risk	[14,18]
Tumor type	Thymic epithelial tumors	Highest incidence (up to 7.1%)	[6]
	Melanoma	Incidence ~1.1%	[6]
	Non-small cell lung cancer	Incidence ~0.5%	[6]
	Renal cell carcinoma	Incidence ~0.4%	[6]
Baseline cardiovascular conditions	Prior heart failure	Significantly associated with ICI-M risk and MACE	[6,21,22]
	Coronary artery disease		[6,21,22]
	Pre-existing arrhythmias		[6,21,22]
Concurrent irAEs	Myositis	MMM overlap syndrome; associated with higher mortality	[16,17]
	Myasthenia gravis		[16,17]
	Multiple concurrent irAEs		[6,24]
Biomarkers	Elevated baseline NT-proBNP	Predictive of ICI-M risk and adverse outcomes	[20,21]
	Elevated baseline or early hs-cTn		[21,25]
Demographics	Advanced age		[10,11,23]

Abbreviations: ICI-M, immune checkpoint inhibitor-associated myocarditis; MACE, major adverse cardiovascular events; MMM, myocarditis-myositis-myasthenia gravis; irAEs, immune-related adverse events; hs-cTn, high-sensitivity cardiac troponin; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

3.1 Clinical Spectrum

The clinical presentation of ICI-M exhibits marked heterogeneity [2,18,23,24], ranging from asymptomatic troponin elevation to complex phenotypes with multisystem involvement. Common symptoms include chest pain, dyspnea, chest tightness, fatigue, and palpitations, all of which lack specificity [13,18]. Approximately 30%–50% of patients present with concurrent skeletal myositis or myasthenia gravis characteristic of MMM overlap syndrome [16,17]. This is indicative of systemic immune activation and is associated with significantly increased mortality.

3.2 Severity Stratification

The clinical severity of ICI-M demonstrates stratified characteristics, with mild-to-moderate cases typically presenting only with troponin elevation [2,18]. Severe cases, in contrast, frequently manifest with high-grade atrioventricular block, sustained ventricular arrhythmias, cardiogenic shock, or a marked reduction in left ventricular ejection fraction (LVEF) [2,3,26,27]. Importantly, preserved LVEF does not exclude early myocarditis. Real-world data show that 51%–60% of fulminant cases still have a normal LVEF on admission [2,27,28], making ejection fraction alone unreliable for early detection. Global longitudinal strain (GLS) is more sensitive than LVEF as a means of identifying subclinical myocardial involvement [28,29]. Even asymptomatic patients with persistent troponin elevation carry a worse prognosis, emphasizing the potential value of routine biomarker monitoring during early treatment [25,30].

3.3 Biomarkers

Biomarkers play a central role in the early recognition, diagnosis, and risk stratification of ICI-M. Elevated cTn represents the first and most common abnormality observed in affected patients [2,31], making it the most important and sensitive indicator of this condition. The vast majority of ICI-M patients exhibit persistent cTn elevation in the early treatment period, often preceding symptoms, electrocardiographic (ECG) changes, or echocardiographic/cardiac magnetic resonance (CMR) abnormalities. Dynamic analyses of cTn kinetics outperform individual measurements as predictors of patient outcomes, with persistent elevation indicating a higher risk for events [21]. Current clinical practice predominantly employs high-sensitivity cardiac troponin I (hs-cTnI) or high-sensitivity cardiac troponin T (hs-cTnT) for monitoring myocardial injury, and both have demonstrated high sensitivity in ICI-M. Notably, cTnT levels may be elevated in immune-related myositis or myopathy due to skeletal muscle involvement, whereas cardiac

Table 2. Biomarker differentiation between isolated ICI-M and MMM overlap syndrome.

Biomarker/Feature	Isolated ICI-M	MMM overlap syndrome (Myocarditis-Myositis-Myasthenia)	Clinical interpretation
hs-cTnI	Elevated, persistent	Elevated, persistent	Preferred cardiac-specific biomarker
hs-cTnT	Elevated	Disproportionately elevated	May reflect skeletal muscle injury in MMM
CK/CK-MB	Normal or mildly elevated	Markedly elevated	Indicates concomitant myositis
Myoglobin	Usually normal	Elevated	Supports active skeletal muscle injury
NT-proBNP/BNP	Variable elevation	Variable elevation	Reflects myocardial stress, low specificity
CRP/hsCRP	Mild–moderate elevation	Moderate–marked elevation	Reflects systemic inflammation
Inflammatory cytokines (IL-6)	Elevated	Higher and sustained elevation	Suggests cytokine amplification
AChR/MuSK antibodies	Negative	Frequently positive	Supports myasthenia gravis
ECG findings	Arrhythmia, conduction block	Often more severe	ECG is not discriminatory alone
Respiratory muscle function	Preserved	Reduced vital capacity/MIP	Predicts respiratory failure
Troponin response to steroids	Gradual decline	Fluctuating or refractory	Suggests amplification loop persistence

ECG, electrocardiographic; CK, creatine kinase; CK-MB, creatine kinase-MB isoenzyme; MIP, macrophage inflammatory protein; CRP, C-reactive protein; hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; IL-6, interleukin-6.

troponin I (cTnI) exhibits greater cardiac specificity. This distinction is clinically important in patients with suspected MMM overlap. cTnI should be the preferred biomarker for accurate assessment of myocardial injury [32]. BNP/NT-proBNP reflects ventricular load but lacks specificity, and is thus best considered as an adjunctive marker [21,31] (Table 2). Furthermore, a recent multicenter observational study demonstrated that elevated baseline fibrinogen and troponin levels were associated with an increased risk of cardiovascular events in patients receiving anticancer therapy, further supporting the potential value of longitudinal biomarker monitoring in cardio-oncology, although these findings were not specific to ICI-M [33].

3.4 Diagnostic Examinations

ECG abnormalities are common in ICI-M cases [34], including ST-T changes, arrhythmias, and new-onset high-grade conduction block, providing predictive value for severe disease [35]. Echocardiography serves as an initial screening tool but has limited sensitivity [36,37]. GLS is superior to LVEF as a means of identifying early lesions [28,38]. Cardiac magnetic resonance (CMR) provides information on myocardial edema and necrosis, and is the primary imaging modality employed for patient evaluation; however, some early cases may yield false-negative results [18,39]. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) offers complementary value when assessing early inflammation and skeletal muscle involvement [40]. A recent systematic review and meta-analysis further demonstrated that native T1 and T2 values were significantly elevated following ICI treatment, with increased T2 values associated with a higher risk of major adverse cardiovascular events (HR = 1.36, 95% CI: 1.12–1.64). These findings highlight the potential diagnostic and prognostic value of quantitative CMR parameters in ICI-associated cardiotoxicity, although further validation is warranted [41].

3.5 Endomyocardial Biopsy

Endomyocardial biopsy (EMB) remains the gold standard for histological diagnosis of ICI-M, typically showing $CD8^+$ T-cell infiltration and myocardial injury [13,18]. However, its invasive nature and sampling variability limit routine use, and current guidelines reserve EMB for diagnostically uncertain or severe cases [42].

3.6 Diagnostic Summary

Diagnosis of ICI-M relies on multimodal integration, with cTn kinetic monitoring, ECG, GLS, and CMR constituting the primary assessment modalities [21,39]. EMB is reserved for specific circumstances. It is important that clinicians observe the principles of low-threshold

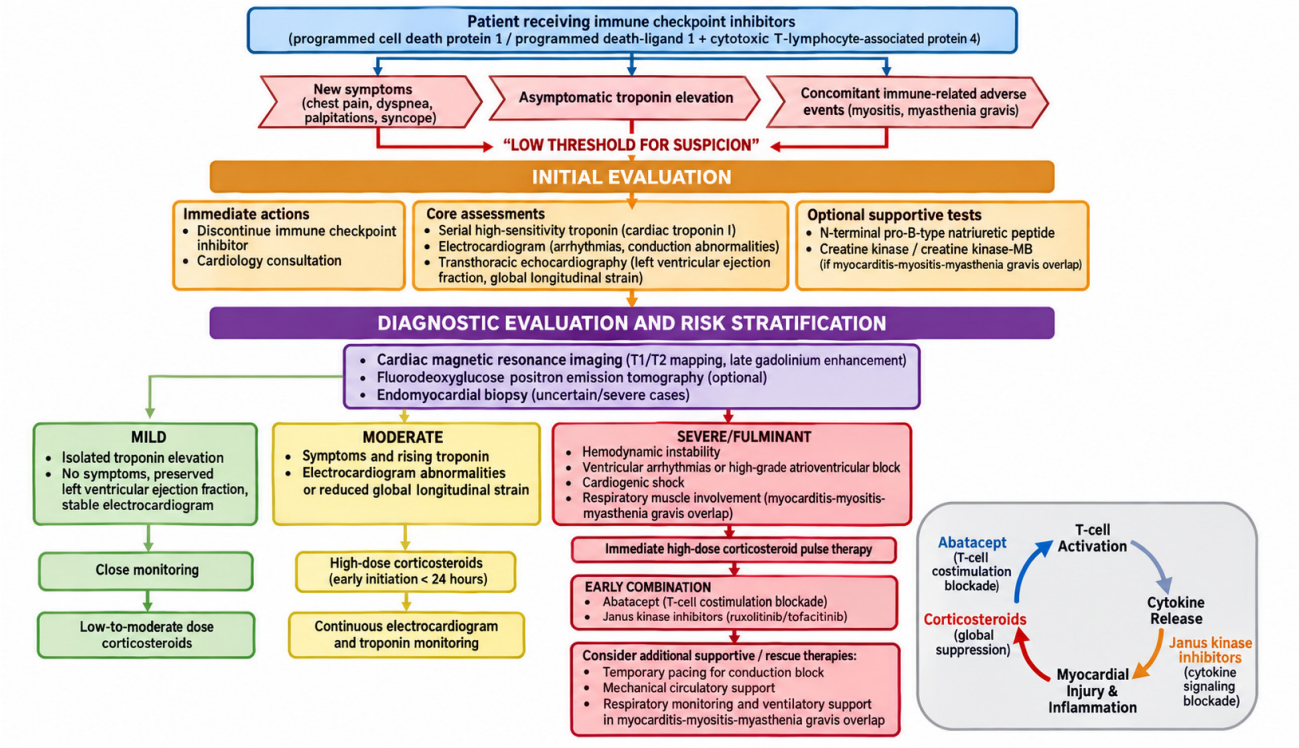


Fig. 1. Diagnostic and therapeutic algorithm for ICI-M.

suspicion, multimodal verification, and serial assessment when evaluating potential ICI-M cases, emphasizing early recognition rather than reliance on typical presentations [18,21,42,43]. Standardized diagnostic criteria and grading systems are lacking, which has limited multicenter research and data comparability [24,42]. The rapid clinical deterioration observed in some patients—potentially reflecting the amplification loop described below—underscores the importance of early detection before fulminant progression develops (Fig. 1).

4. Pathogenesis

The pathogenesis of ICI-M involves multiple interconnected processes. Integrating current evidence, we suggest that these mechanisms form a self-amplifying loop in which checkpoint blockade triggers T-cell activation and cytokine release. Cytokines cause cardiomyocyte injury, and the injured myocardium then releases DAMPs that activate innate immune pathways through TLR and NLR family pyrin domain containing 3 (NLRP3) signaling [44]. This process is defined by positive feedback, as DAMPs activate innate immunity, producing cytokines that cause further injury. Once established, this cycle can self-perpetuate even after ICIs have been discontinued. This explains why ICI withdrawal alone is typically insufficient and why early high-dose corticosteroid pulse therapy is required to suppress the ongoing inflammatory cascade [45] (Fig. 2).

4.1 Immune Checkpoint Blockade and Loss of Cardiac Immune Tolerance

The PD-1/PD-L1 pathway plays an inhibitory role in maintaining peripheral immune tolerance and limiting myocardial involvement [46,47]. PD-L1 expression on cardiomyocyte surfaces suppresses cytotoxic T-cell activity; upon pathway blockade, ZAP-70 phosphorylation intensifies and upregulates effector pathways, including nuclear factor of activated T cells (NFAT), nuclear factor kappa B (NF-κB), and phosphoinositide 3-kinase–protein kinase B–mechanistic target of rapamycin (PI3K-Akt-mTOR) signaling, maintaining $CD8^+$ T-cells in a persistently hyperactivated state within the myocardium [1]. ICI-M patient EMB samples and autopsies reveal dense myocardial immune infiltration predominantly comprising $CD8^+$ T-cells, accompanied by granzyme and perforin release [48]. Single-cell sequencing and TCR clonality analyses have revealed clonal overlap between myocardial and tumor-infiltrating lymphocytes, providing an antigenic basis for the autoimmune myocardial attack [13,48].

Axelrod et al. [49] identified α-myosin heavy chain as a key autoantigen associated with ICI-M, demonstrating that α-myosin-specific $CD8^+$ T-cells constitute the principal effectors mediating myocardial injury. Won et al. [50] confirmed in A/J model mice that myosin-specific T-cells can mediate ICI-M development and progression. PD-1-deficient mice spontaneously develop autoimmune dilated cardiomyopathy, genetically validating the central role of PD-1 signaling in cardiac immune tolerance [46].

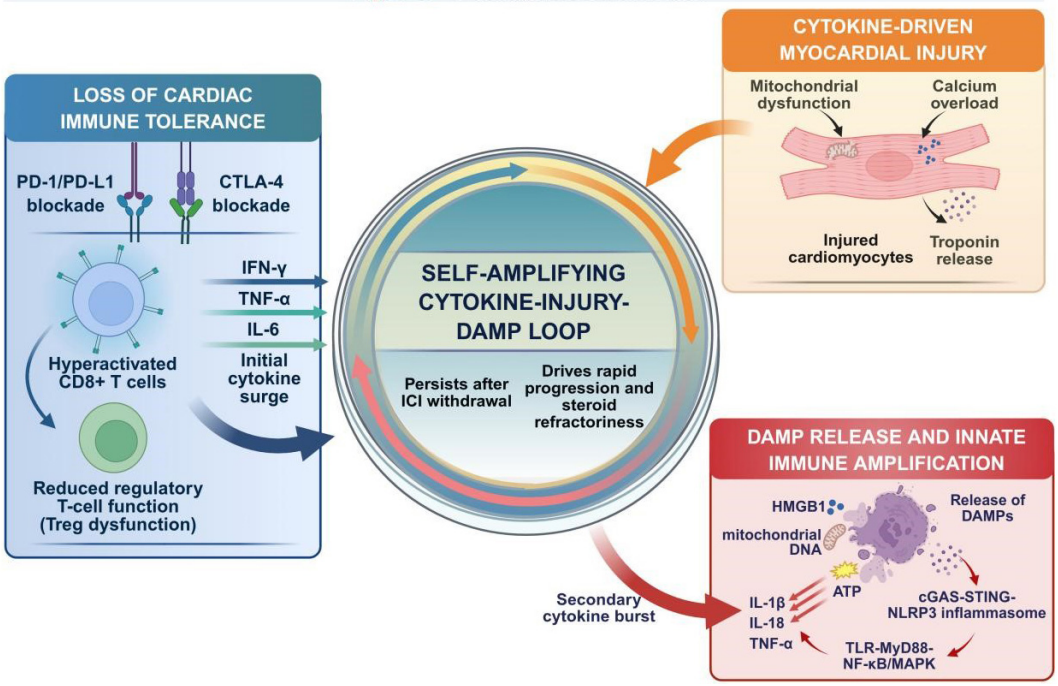


Fig. 2. Schematic overview of the pathogenesis of ICI-M. IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α; DAMPs, damage-associated molecular patterns; HMGB1, high mobility group box 1; TLR-MyD88-NF-κB/MAPK, Toll-like receptor–myeloid differentiation primary response 88–nuclear factor kappa B/mitogen-activated protein kinase; cGAS-STING-NLRP3, cyclic GMP-AMP synthase–stimulator of interferon genes–NLR family pyrin domain-containing 3.

PD-1/PD-L1 signaling also maintains regulatory T-cell (Treg) differentiation and functional stability. Following blockade, $FOXP3^+$ Treg cell numbers decrease, while interleukin (IL)-10 and transforming growth factor-beta (TGF-β) production is reduced, resulting in an elevated $CD8^+$/Treg ratio and weakened immunosuppression [51]. Clinical and experimental studies have established that $CD8^+$/Treg imbalance is correlated with disease severity and prognosis [48].

In combination therapy, CTLA-4 blockade enhances costimulatory signals during initial activation and reduces peripheral Treg maintenance, while PD-1 blockade relieves terminal inhibition during the effector phase. This dual blockade renders T-cells uninhibited at both the activation and effector stages, establishing an immunological foundation for the subsequent initiation of an inflammatory feedback loop [1,49,52]. Notably, $CD69^+PD\text{-}1^+$ tissue-resident memory T-cells (TRMs) accumulate in pericardial adipose tissue following myocardial injury, when ICIs block PD-1 signaling. These pre-existing TRMs can be rapidly activated—potentially explaining the occurrence of myocarditis after the first ICI administration [53].

While α-Myosin has been identified as a key autoantigen in ICI-M, it remains uncertain as to why only a small fraction of ICI-treated patients develop myocarditis. One plausible explanation is a 'second-hit' model. In these patients, the myocardium may have already sustained a subclinical injury from prior viral myocarditis, anthracycline chemotherapy, or an inherited susceptibility, leading to the subclinical accumulation of autoreactive T-cells or low-grade inflammation. Under normal conditions, the PD-1 pathway maintains immune homeostasis. Once ICIs release that brake, however, the latent immune response flares into overt disease. While clinically intriguing, no biomarkers currently exist to identify these high-risk patients before the start of ICI treatment [49,50]. Anthracycline exposure, subclinical viral myocarditis, and pre-existing autoimmune conditions are the most likely underlying etiologies for ICI-M in these patients. At the genetic level, in addition to human leukocyte antigen (HLA) alleles, polymorphisms in cardiac autoantigen genes (e.g., *MYH6*), cytokine signaling components, and innate immune regulators are all plausible risk factors, but none have been validated in ICI-M cohorts to date.

4.2 Cytokine-Mediated Myocardial Injury

Following the disruption of immune tolerance and excessive $CD8^+$ T-cell activation, pro-inflammatory cytokines function as key mediators of myocardial injury [54]. Interferon-γ (IFN-γ) upregulates myosin heavy chain (MHC) and adhesion molecule expression via the JAK-STAT1 pathway, thereby increasing cardiomyocyte susceptibility to T-cell-mediated cytotoxicity and promoting the expression of pro-apoptotic genes [55,56,57]. Tumor necrosis factor-α (TNF-α) activates the NF-κB and p38 MAPK signaling pathways, leading to death receptor acti-

vation, mitochondrial dysfunction, and amplification of inflammatory cascades. IL-1β promotes inflammatory cell infiltration and matrix degradation, while IL-6 enhances metabolic stress and myocardial remodeling through JAK-STAT3 [55,56]. Transcriptomic studies reveal that IFN-γ-driven pathways constitute a core immune phenotype of ICI-M [57]. IL-17A has also been implicated in cardiac dysfunction following anti-PD-1 therapy, suggesting Th17-related pathways as potential therapeutic targets [58].

These cytokines collectively target mitochondria, sarcoplasmic reticulum, and redox systems. In this inflammatory context, mitochondrial membrane potential declines, ATP generation decreases, and oxidative phosphorylation becomes impaired, while sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) and calcium channel dysregulation lead to calcium overload, and the dysregulation of the caspase cascade and Bcl-2 family proteins induces programmed cell death [55,56,57]. Clinically, this manifests as a precipitous rise in troponin levels, left ventricular dysfunction, and early conduction abnormalities [18].

Importantly, cytokine-mediated injury is not the endpoint but the trigger for the next phase of ICI-M pathogenesis, as DAMPs released from damaged cardiomyocytes activate innate immune pathways, perpetuating inflammation [18,55,56,57].

The prognostic value of specific cytokine profiles in ICI-M remains to be prospectively validated. Whether early cytokine-directed therapy (e.g., IL-6, IL-1β, or IL-17A blockade) can prevent progression to fulminant disease warrants further investigation [58].

4.3 DAMP Release and Innate Immune Amplification

Myocardial injury represents both an inflammatory endpoint and a novel inflammatory driver in ICI-M. The DAMP-mediated innate immune amplification pathways described below have been extensively characterized in ischemic, microembolic, and other forms of cardiac injury. Their role in ICI-M is supported by emerging preclinical evidence but remains to be directly validated in patient cohorts. Specifically, T-cell clonal sharing (Section 4.1), α-myosin autoantigen identification (Section 4.1), macrophage expansion (Section 4.4), and cytokine profiles (Section 4.2) are supported by direct human ICI-M data, whereas the DAMP–TLR–NLRP3 amplification pathways (Sections 4.3.1–4.3.2) are primarily inferred from preclinical models and related cardiac inflammatory conditions. Necrotic and severely stressed cardiomyocytes release DAMPs, including high mobility group box 1 (HMGB1), ATP, and heat shock proteins, which activate innate immunity through TLR4, RAGE, and the NLRP3 inflammasome, thereby inducing repeated IL-1β, IL-18, and TNF-α release [55,59,60]. This process marks the transition from "passive injury" to "active inflammatory amplification" as inflammatory activity shifts from exogenous drive to endogenous self-amplification. Quagliariello et al. [61] demonstrated significant systemic upregulation of DAMPs (fibronectin-end-diastolic area (EDA), S100/calgranulin) and NLRP3-myeloid differentiation primary response 88 (MyD88)-chemokine pathways following ICI treatment in preclinical models, providing foundational evidence that DAMP-mediated innate immune activation operates in the context of checkpoint blockade.

4.3.1 The TLR–MyD88–NF-κB/MAPK Axis

Upon binding to TLR4 and TLR9, DAMPs trigger MyD88-dependent IRAK-TRAF6 signaling, sustaining NF-κB and MAPK (extracellular signal-regulated kinase (ERK)/p38/c-Jun N-terminal kinase (JNK)) activation and inducing substantial production of IL-1β, IL-6, TNF-α, and chemokines [61,62]. NF-κB-upregulated cytokines enhance JAK-STAT responsiveness, forming a bidirectional amplification loop [56]. The inflammatory burst driven by this axis correlates with the rapid concurrent elevation of inflammatory and myocardial injury markers observed clinically [2]. Persistent activation represents a critical molecular basis for early cardiomyocyte necrosis and precipitous troponin elevations [62,63].

4.3.2 The cyclic GMP-AMP synthase (cGAS)–STING–NLRP3 Axis

Mitochondrial injury leads to mitochondrial DNA (mtDNA) leakage, triggering cGAS-STING activation and inducing type I interferon and pro-inflammatory cytokine expression [64,65]. cGAS-STING activation additionally promotes NLRP3 inflammasome assembly, pro-IL-1β/pro-IL-18 maturation, and the initiation of pyroptosis [66]. Transcriptomic studies have revealed significant *NLRP3* upregulation in ICI-M patients, while NLRP3 inhibitors have been found to improve cardiac function and reduce inflammatory infiltration in animal models [61]. Reciprocal reinforcement exists between NLRP3 and NF-κB signaling such that NF-κB promotes NLRP3 expression, while NLRP3-mediated IL-1β production further activates T-cells and NF-κB signaling, forming a positive feedback loop between innate and adaptive immunity [67].

Oxidative stress and pyroptosis enhance mtDNA leakage and NLRP3 inflammasome activation [44]. Together, the TLR and cGAS–STING–NLRP3 pathways constitute dual amplification loops comprised of myocardial injury that triggers PRR sensing, leading to signal amplification and re-injury, closing the loop and enabling inflammation to escalate independently of the original trigger [55,59,63].

Direct measurement of cardiac DAMP levels in clinical ICI-M cohorts remains limited, although preclinical data have demonstrated systemic DAMP elevation following ICI treatment. The relative contribution of each innate immune pathway (TLR vs. cGAS-STING vs. NLRP3) to disease progression, and whether pathway-specific inhibitors offer therapeutic benefit, requires further investigation [61].

4.4 Microenvironment Remodeling and Electrophysiological Instability

In addition to sustaining inflammatory activity, this deleterious amplification loop also reshapes the local immune landscape in ways that directly disrupt cardiac conduction. Under homeostatic conditions, resident macrophages help maintain Connexin-43 expression and support electrical coupling between cardiomyocytes [68,69]. As the loop progresses, IFN-γ, TNF-α, and chemokines recruit large numbers of $CCR2^+$ monocyte-macrophages into the myocardium, which displace the resident population and shift the microenvironment toward an M1-predominant, pro-inflammatory state [68,70].

Through single-cell transcriptomic analysis, Ma et al. [71] identified a marked expansion of $Cxcl9^+$, $Cxcl10^+$, and $CCR2^+$ macrophages in ICI-M, which was driven by IFN-γ signaling. Importantly, they found that IFN-γ-neutralizing antibodies effectively attenuated myocardial inflammation in mouse models, suggesting the IFN-γ–macrophage axis as a potential therapeutic target [71].

Pro-inflammatory macrophages secrete TNF-α, IL-1β, nitric oxide, reactive oxygen species, and matrix metalloproteinases, causing extracellular matrix degradation and interstitial structural disruption. This contributes to the formation of heterogeneous fibrotic substrates that increase reentry propensity [68,69]. Sustained inflammation and structural remodeling reduce conduction velocity and disrupt electrical coupling, resulting in conduction abnormalities and ventricular arrhythmias [34].

Clinically, conduction disturbances are a hallmark of ICI-M: 68.7% of patients develop conduction abnormalities during hospitalization, with complete atrioventricular block occurring in 17% of cases and being closely associated with adverse outcomes [34]. This amplification loop thus transforms the initial state of inflammatory injury into one of structural–electrophysiological vulnerability [68,70].

How specific inflammatory mediators actually damage the conduction system is still poorly understood. Whether early anti-inflammatory treatment can prevent irreversible conduction injury is still an open question that will require prospective investigation.

4.5 Limitations and Future Directions

The amplification loop framework we propose offers a plausible explanation for several puzzling clinical features of ICI-M, including why patients deteriorate so rapidly, why the disease can progress even after ICI discontinuation, and why steroid responsiveness varies widely. However, several limitations to this model should be noted.

First, while each component of the loop has supporting evidence, direct confirmation that the complete cycle operates in ICI-M patients is lacking. Specifically, the serial measurement of circulating HMGB1, cell-free mtDNA, and NLRP3 inflammasome products (such as IL-18 or apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) specks) to examine their correlations with troponin kinetics and clinical trajectory would provide direct evidence for this feedback loop *in vivo*. Prospective cohort studies incorporating such biomarker panels at baseline, during acute disease, and following immunosuppression are needed to establish whether loop activity predicts disease severity and treatment response. Most evidence for the DAMP-innate immunity axis stems from preclinical models or related cardiac inflammatory conditions rather than specific ICI-M cohorts [61]. Second, the threshold and kinetics of loop initiation remain unknown, and why some patients develop fulminant disease while others remain subclinical is unclear [49,50]. Third, biomarkers reflecting loop activation (e.g., circulating DAMPs, inflammasome products) have not been validated for clinical risk stratification or treatment monitoring.

Future studies should address: (1) prospective measurement of DAMP and innate immune markers in ICI-M cohorts and their correlation with clinical severity and treatment response; (2) identification of predictive biomarkers for loop initiation in at-risk patients before ICI treatment—preliminary evidence suggests that specific HLA alleles (e.g., HLA-DQB1*03:03, HLA-B*52:01) may be associated with ICI-M susceptibility, though these findings require validation in larger, multi-ethnic cohorts [72]; (3) evaluation of NLRP3 or STING inhibitors as adjunctive therapies in steroid-refractory cases [44,61]; and (4) determination of optimal timing for multi-target intervention—whether early combination therapy can prevent loop establishment warrants investigation through randomized controlled trials.

5. Treatment

The amplification loop framework described above has direct therapeutic implications. If inflammation is driven by a self-reinforcing cycle of cytokine release, myocardial injury, and DAMP-mediated innate immune activation, then treatment strategies should aim to interrupt this cycle at multiple levels. Early intervention before the loop has been fully established may be more effective than delayed escalation after steroid failure. For patients with established or severe disease, multi-target combination therapy addressing both adaptive immunity (T-cell activation) and innate immunity (cytokine signaling, inflammasome activation) may be required [73,74,75].

5.1 General Principles

Once ICI-M is confirmed or highly suspected, ICIs should be immediately discontinued, and the patient should be admitted to an intensive care unit equipped with the equipment needed for continuous cardiac monitoring and hemodynamic support. For hemodynamically unstable patients, cardiogenic shock protocols should be implemented, with mechanical circulatory support initiated when necessary. Conduction system involvement represents a promi-

nent feature of ICI-M. An international multicenter study of 147 ICI-M cases reported that 68.7% of patients developed conduction abnormalities during hospitalization, with complete atrioventricular block occurring in 17% of cases and being closely associated with adverse outcomes [34]. Therefore, routine monitoring of ECG and troponin kinetics is essential, with early assessment for the need for temporary pacing. Management of ICI-M requires close collaboration among cardiology, oncology, and critical care medicine [76].

5.2 Glucocorticoids

Glucocorticoids constitute the cornerstone of first-line therapy for ICI-M. Zhang et al. [77], in a study based on international multicenter registry data, demonstrated that both timing and dosages of corticosteroids significantly correlate with the incidence of MACE. Patients receiving corticosteroids within 24 hours exhibited a MACE incidence of only 7.0%, compared to 34.3% and 85.1% for those initiated at 24–72 hours and beyond 72 hours, respectively ($p < 0.001$). The high-dose group (methylprednisolone 501–1000 mg/d) showed a MACE incidence of 22.0%, which was significantly lower than that for the intermediate-dose (54.6%) and low-dose groups (61.9%) ($p < 0.001$) [77]. Based on this evidence, for moderate-to-severe cases, intravenous methylprednisolone pulse therapy at 500–1000 mg/d for 3 days is recommended, followed by transition to oral administration at 1 mg/kg·d with gradual tapering. In mild cases, initiation at 1–2 mg/kg·d can be considered [78,79]. However, despite early aggressive corticosteroid use, approximately 30%–50% of patients develop steroid-refractory disease or relapse, underscoring the need for more targeted therapeutic strategies.

Corticosteroid tapering presents a clinical challenge, as premature reduction risks disease flare-up, while prolonged exposure increases the risk of infection and metabolic complications. Current practice guidelines recommend initiating the tapering process only after troponin normalization and clinical stabilization, typically over 4–6 weeks [79,80]. Serial troponin monitoring during tapering can identify early relapse; any troponin re-elevation should prompt an increased dose or escalation to targeted therapy [80]. Optimal tapering protocols, including the potential role of steroid-sparing agents, remain to be defined through prospective studies.

5.3 Conventional Second-Line Immunosuppressive Therapy

When troponin levels continue to rise or hemodynamic deterioration occurs within 24–48 hours, escalation to second-line therapy should be considered. Conventional regimens include mycophenolate mofetil (MMF), anti-thymocyte globulin (ATG), intravenous immunoglobulin (IVIG), and plasma exchange. A systematic review encompassing 244 clinical cases reported utilization rates of 22.6% for IVIG, 11.5% for MMF, 6.8% for infliximab, 3.4% for ATG, and 9% for plasma exchange [31]. However, these therapies lack prospective clinical trial data, with efficacy evidence derived solely from small case series or individual case reports [80,81]. This evidence gap underscores the urgent need to explore mechanism-directed therapeutic strategies.

5.4 Targeted Combination Therapy

A 2023 study published in *Cancer Discovery* represents a significant advance in the treatment of ICI-M. Salem et al. [73] reported outcomes from a single-center study of 40 confirmed ICI-M patients, where the initial 10 cases received guideline-recommended standard therapy (high-dose corticosteroids with sequential second-line immunosuppression in patients refractory to steroids), while the subsequent 30 cases received a modified regimen (high-dose abatacept combined with ruxolitinib, coupled with respiratory muscle function monitoring and proactive ventilatory support). The results demonstrated a myocarditis-related mortality of 60% (6/10) in the standard therapy group versus only 3.3% (1/30) in the modified regimen group. In the ≥grade 3 cardiotoxicity subgroup, mortality was 75.0% (6/8) with standard therapy compared to 5% (1/22) with the modified regimen [73]. Abatacept, a CTLA-4–Ig fusion protein [82], binds CD80/CD86 on antigen-presenting cells with high affinity, blocking co-stimulatory signal transmission to CD28 on T-cells, thereby restoring immune checkpoint regulatory function at the upstream immunological synapse. Ruxolitinib, a JAK1/2 inhibitor, blocks signal transduction induced by pro-inflammatory cytokines, including IFN-γ and IL-6, while reducing macrophage CD86 expression, thereby synergizing with abatacept. This study further introduced real-time monitoring technology for CD86 receptor occupancy (CD86RO) [73,83], titrating abatacept dosage to achieve ≥80% occupancy for individualized precision therapy. This flow cytometry-based assay remains investigational and is not yet widely available in clinical practice, which may limit the immediate generalizability of this dose-titration approach. It should be noted that this study employed a non-randomized design with several important limitations. The standard therapy group comprised only 10 patients, limiting statistical power. The use of historical controls introduces potential selection bias, as patients treated later may have benefited from increased clinical experience, improved supportive care, and heightened awareness of respiratory muscle monitoring rather than the specific drug regimen alone. While these results are encouraging, the abatacept/ruxolitinib combination cannot be considered standard of care until confirmed by prospective randomized trials. Currently, two pivotal clinical trials are underway. The ATRIUM trial, a phase III multicenter, randomized, double-blind, placebo-controlled study [84], plans to enroll 390 hospitalized ICI-M patients to evaluate

whether abatacept combined with standard corticosteroid therapy reduces the incidence of MACE. Additionally, the ACHLYS trial, a phase II dose-exploration study, aims to determine the optimal starting dosage for abatacept [85]. Results from these trials will provide higher-level evidence-based medicine support for targeted ICI-M therapy [86]. Notably, mouse model studies have confirmed that abatacept effectively reverses ICI-induced myocardial inflammation, providing an experimental basis for clinical translation of mechanism-directed therapy [87].

5.5 Exploration of Other Targeted Agents

Tocilizumab: Doms et al. [74] reported a case of steroid-refractory ICI-M with concurrent myositis in which troponin levels continued to rise from 1291 to 18,522 µg/L despite methylprednisolone administration at 200 mg/day. Following tocilizumab administration at 8 mg/kg (days 7 and 14), troponin, creatine kinase, and ferritin levels rapidly declined, achieving the resolution of both myocarditis and myositis [74]. Mechanistically, IL-6 occupies an upstream hub position in the inflammatory cascade such that IL-6 blockade can effectively interrupt the cytokine storm. However, current experience with tocilizumab in ICI-M remains extremely limited (only 0.4% utilization in a systematic review of 244 cases), with efficacy and safety requiring validation through larger-scale studies.

Tofacitinib: A single-center retrospective study from China enrolled 24 ICI-M patients, of whom 16 (67%) were steroid-refractory. Among 11 steroid-refractory patients receiving tofacitinib 5 mg bid, 7 (64%) achieved remission of myocarditis [80]. As an oral JAK inhibitor, tofacitinib offers practical advantages over intravenous ruxolitinib in clinical practice and is particularly suited for patients in relatively stable condition encountering difficulty tapering corticosteroids.

Alemtuzumab: As an anti-CD52 monoclonal antibody, alemtuzumab induces profound lymphocyte depletion and should be considered only as a last resort when all other therapies have failed, with careful weighing of risks, including severe infection [88].

5.6 Management of Conduction Disturbances

Conduction abnormalities are common in ICI-M and associated with adverse outcomes. An international multicenter study demonstrated that 68.7% of patients developed conduction disturbances during hospitalization, with complete atrioventricular block occurring in 17% [34]. P-wave abnormalities have also been identified as independent predictors of adverse outcomes in Chinese cohorts [15].

Management requires continuous ECG monitoring from the time of admission. Temporary pacing should be considered early in patients with high-grade atrioventricular block or symptomatic bradycardia, as progression can be rapid and unpredictable. The decision for permanent pacemaker implantation should be deferred until the acute inflammatory phase resolves, since conduction abnormalities may be reversible with effective immunosuppression [34,35].

Whether early aggressive immunosuppression can prevent progression to irreversible conduction system damage remains unclear. Given the mechanistic link between inflammatory amplification and electrophysiological instability described above, prompt initiation of immunotherapy may offer conduction-protective benefits, though prospective data are lacking.

5.7 Management of Overlap Syndromes

Approximately 30%–50% of ICI-M patients present with concurrent skeletal myositis or myasthenia gravis in the form of MMM overlap syndrome [16,17]. This triad indicates systemic immune activation and is associated with significantly elevated mortality. Respiratory muscle involvement is of particular concern. Salem et al. [73] emphasized proactive monitoring of respiratory muscle function, including serial measurement of vital capacity and maximal inspiratory pressure. Early ventilatory support should be initiated when respiratory decline is detected, as respiratory failure is a major cause of death in MMM overlap [73].

Therapeutically, the overlap syndrome may require more aggressive immunosuppression. Abatacept combined with ruxolitinib has shown benefit in this patient population [73,82]. Tocilizumab has also been reported to be effective in cases with concurrent myositis [74]. Plasma exchange or IVIG may be considered for the myasthenia gravis components, though evidence specific to ICI-related MMM is limited [31]. Multidisciplinary collaboration among cardiology, neurology, rheumatology, and critical care remains essential for managing these complex cases.

5.8 Integration and Future Perspectives on Therapeutic Strategies

Based on current evidence, treatment strategies for ICI-M should be stratified according to clinical severity. For mild cases presenting solely with slight troponin elevation, absence of symptoms, and no significant ECG/imaging abnormalities, cautious observation under close monitoring or low-dose corticosteroids may be considered. Moderate cases should receive adequate corticosteroid therapy (methylprednisolone 1–2 mg/kg·d) within 24 hours. For severe or fulminant cases, particularly those with hemodynamic instability, arrhythmias, or respiratory muscle involvement, early combination with targeted therapies such as abatacept/ruxolitinib may be considered rather than waiting for steroid therapy failure before sequential escalation. Additionally, regarding ICI rechallenge after myocarditis resolution, standardized criteria remain lacking, requiring individualized decision-making following thorough assessment of tumor benefit versus cardiac risk [89,90,91]. It should be emphasized that the mechanism-directed thera-

peutic strategies discussed above remain largely based on pathophysiological reasoning and early-phase clinical observations; they represent a theoretical framework for future investigation rather than established alternatives to current guideline-recommended approaches.

6. Conclusion

ICI-M remains a rare but potentially fatal complication characterized by rapid deterioration and unpredictable disease progression. In this review, we propose that the aggressive clinical course of ICI-M can be understood through a self-amplifying loop comprising checkpoint blockade–induced T-cell activation, cytokine-mediated cardiomyocyte injury, and DAMP-triggered innate immune amplification. Once established, this cycle can self-perpetuate even after ICI discontinuation, providing a unifying explanation for the acute onset, rapid progression, and variable steroid responsiveness that are clinically observed.

This mechanistic framework has direct therapeutic implications. Early high-dose glucocorticoids remain the cornerstone of treatment, but the amplification loop model suggests that the conventional strategy of escalation after steroid failure may be suboptimal—once the loop is fully operative, single-target blockade may be insufficient. For high-risk or rapidly progressing patients, early multi-target combination therapy (e.g., corticosteroids combined with abatacept and JAK inhibitors) may offer advantages over sequential escalation, though prospective validation is needed.

Several knowledge gaps remain. Direct demonstration of the complete amplification cycle in ICI-M patients is lacking, and biomarkers reflecting loop activation have not been validated for clinical use. Future studies should focus on prospective measurement of DAMP and innate immune markers, evaluation of pathway-specific inhibitors (NLRP3, STING) in steroid-refractory cases, and determination of optimal timing for multi-target intervention through randomized trials.

Management of ICI-M requires close multidisciplinary collaboration among cardiology, oncology, and critical care. With continued mechanistic investigation and clinical validation, mechanism-directed therapeutic strategies may ultimately improve outcomes while preserving the antitumor benefits of immunotherapy.

Author Contributions

JFY and WJW conceived and designed the review. JFY and JLL conducted the comprehensive literature search and screening. JFY performed the primary literature analysis, synthesized the mechanistic framework, and wrote the initial draft of the manuscript. QYS assisted with literature organization and data synthesis. JLL and GDL contributed to literature analysis and manuscript review. WJW provided supervision and approved the final manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Wei SC, Duffy CR, Allison JP. Fundamental Mechanisms of Immune Checkpoint Blockade Therapy. Cancer Discovery. 2018; 8: 1069–1086. https://doi.org/10.1158/2159-8290.CD-18-0367

[2] Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. Journal of the American College of Cardiology. 2018; 71: 1755–1764. https://doi.org/10.1016/j.jacc.2018.02.037

[3] Salem JE, Manouchehri A, Moey M, Lebrun-Vignes B, Bastarache L, Pariente A, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. The Lancet. Oncology. 2018; 19: 1579–1589. https://doi.org/10.1016/S1470-2045(18)30608-9

[4] Escudier M, Cautela J, Malissen N, Ancedy Y, Orabona M, Pinto J, et al. Clinical Features, Management, and Outcomes of Immune Checkpoint Inhibitor-Related Cardiotoxicity. Circulation. 2017; 136: 2085–2087. https://doi.org/10.1161/CIRCULATIONAHA.117.030571

[5] Song W, Zheng Y, Dong M, Zhong L, Bazoukis G, Perone F, et al. Electrocardiographic Features of Immune Checkpoint Inhibitor-Associated Myocarditis. Current Problems in Cardiology. 2023; 48: 101478. https://doi.org/10.1016/j.cpcardiol.2022.101478

[6] Hu JR, Florido R, Lipson EJ, Naidoo J, Ardehali R, Tocchetti CG, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors. Cardiovascular Research. 2019; 115: 854–868. https://doi.org/10.1093/cvr/cvz026

[7] Liu M, Cheng X, Ni R, Zheng B, Huang S, Yang J. Cardiotoxicity of immune checkpoint inhibitors: A frequency network meta-analysis. Frontiers in Immunology. 2022; 13: 1006860. https://doi.org/10.3389/fimmu.2022.1006860

[8] Raschi E, Rossi S, De Giglio A, Fusaroli M, Burgazzi F, Rinaldi R, et al. Cardiovascular Toxicity of Immune Checkpoint Inhibitors: A Guide for Clinicians. Drug Safety. 2023; 46: 819–833. https://doi.org/10.1007/s40264-023-01320-5

[9] Chen X, Jiang A, Zhang R, Fu X, Liu N, Shi C, et al. Immune Checkpoint Inhibitor-Associated Cardiotoxicity in Solid Tumors: Real-World Incidence, Risk Factors, and Prognos-

tic Analysis. Frontiers in Cardiovascular Medicine. 2022; 9: 882167. https://doi.org/10.3389/fcvm.2022.882167

[10] Salem JE, Ajrouche A, Rozes A, Pinto S, De Rycke Y, Tubach F. Incidence and risk factors of immune checkpoint inhibitor myocardial and muscle toxicity: a French nationwide study. European Heart Journal. 2026; 47: 1014–1030. https://doi.org/10.1093/eurheartj/ehaf682

[11] Li FX, Cai JX, Li JB, Luo KJ, Wang SY, Meng WH, et al. Immune checkpoint inhibitors and myocarditis in advanced non-small cell lung cancer: a nationwide cohort study. Cardio-oncology (London, England). 2025; 11: 33. https://doi.org/10.1186/s40959-025-00325-6

[12] Ozaki AF, Sayer M, Hamano H, Nagasaka M, Lee BJ, Doh J, et al. Incidence and survival outcomes of myocarditis and pericardial diseases associated with immune checkpoint inhibitor therapy. Cardio-oncology (London, England). 2025; 11: 26. https://doi.org/10.1186/s40959-025-00300-1

[13] Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. The New England Journal of Medicine. 2016; 375: 1749–1755. https://doi.org/10.1056/NEJMoa1609214

[14] Makunts T, Saunders IM, Cohen IV, Li M, Moumedjian T, Issa MA, et al. Myocarditis occurrence with cancer immunotherapy across indications in clinical trial and post-marketing data. Scientific Reports. 2021; 11: 17324. https://doi.org/10.1038/s41598-021-96467-5

[15] Song W, Chen Z, Zheng Y, Xu Y, Sun Y, Zhao Z, et al. Clinical and electrocardiographic characteristics of immune checkpoint inhibitor-related myocarditis. Journal of Electrocardiology. 2024; 86: 153779. https://doi.org/10.1016/j.jelectrocard.2024.153779

[16] Touat M, Maisonobe T, Knauss S, Ben Hadj Salem O, Hervier B, Auré K, et al. Immune checkpoint inhibitor-related myositis and myocarditis in patients with cancer. Neurology. 2018; 91: e985–e994. https://doi.org/10.1212/WNL.0000000000006124

[17] Suzuki S, Ishikawa N, Konoeda F, Seki N, Fukushima S, Takahashi K, et al. Nivolumab-related myasthenia gravis with myositis and myocarditis in Japan. Neurology. 2017; 89: 1127–1134. https://doi.org/10.1212/WNL.0000000000004359

[18] Palaskas N, Lopez-Mattei J, Durand JB, Iliescu C, Deswal A. Immune Checkpoint Inhibitor Myocarditis: Pathophysiological Characteristics, Diagnosis, and Treatment. Journal of the American Heart Association. 2020; 9: e013757. https://doi.org/10.1161/JAHA.119.013757

[19] Kong H, Xie R, Liu Z. Predictive factors and outcomes of immune-related adverse events in Chinese patients treated with immune checkpoint inhibitors: a real-world retrospective study. Frontiers in Immunology. 2025; 16: 1655724. https://doi.org/10.3389/fimmu.2025.1655724

[20] Chen Z, Lan R, Ran T, Tao L, Zhu Y, Li Y, et al. A multimodality score strategy for assessing the risk of immune checkpoint inhibitors related cardiotoxicity. Scientific Reports. 2024; 14: 24821. https://doi.org/10.1038/s41598-024-76829-5

[21] Murtagh G, deFilippi C, Zhao Q, Barac A. Circulating biomarkers in the diagnosis and prognosis of immune checkpoint inhibitor-related myocarditis: time for a risk-based approach. Frontiers in Cardiovascular Medicine. 2024; 11: 1350585. https://doi.org/10.3389/fcvm.2024.1350585

[22] Sharma A, Alexander G, Chu JH, Markopoulos A, Maloul G, Ayub MT, et al. Immune Checkpoint Inhibitors and Cardiotoxicity: A Comparative Meta-Analysis of Observational Studies and Randomized Controlled Trials. Journal of the American Heart Association. 2024; 13: e032620. https://doi.org/10.1161/JAHA.123.032620

[23] Moslehi JJ, Salem JE, Sosman JA, Lebrun-Vignes B, Johnson DB. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. Lancet (London, England). 2018; 391: 933. https://doi.org/10.1016/S0140-6736(18)30533-6

[24] Bonaca MP, Olenchock BA, Salem JE, Wiviott SD, Ederhy S, Cohen A, et al. Myocarditis in the Setting of Cancer Therapeutics: Proposed Case Definitions for Emerging Clinical Syndromes in Cardio-Oncology. Circulation. 2019; 140: 80–91. https://doi.org/10.1161/CIRCULATIONAHA.118.034497

[25] Gvili Perelman M, Brzezinski RY, Waissengrin B, Leshem Y, Raphael A, Perelman M, et al. The predictive value of serial troponin measurements in patients treated with immune checkpoint inhibitors. The Oncologist. 2025; 30: oyaf147. https://doi.org/10.1093/oncolo/oyaf147

[26] Lehmann LH, Cautela J, Palaskas N, Baik AH, Meijers WC, Allenbach Y, et al. Clinical Strategy for the Diagnosis and Treatment of Immune Checkpoint Inhibitor-Associated Myocarditis: A Narrative Review. JAMA Cardiology. 2021; 6: 1329–1337. https://doi.org/10.1001/jamacardio.2021.2241

[27] Zhang L, Awadalla M, Mahmood SS, Nohria A, Hassan MZO, Thuny F, et al. Cardiovascular magnetic resonance in immune checkpoint inhibitor-associated myocarditis. European Heart Journal. 2020; 41: 1733–1743. https://doi.org/10.1093/eurheartj/ehaa051

[28] Awadalla M, Mahmood SS, Groarke JD, Hassan MZO, Nohria A, Rokicki A, et al. Global Longitudinal Strain and Cardiac Events in Patients With Immune Checkpoint Inhibitor-Related Myocarditis. Journal of the American College of Cardiology. 2020; 75: 467–478. https://doi.org/10.1016/j.jacc.2019.11.049

[29] Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography: Official Publication of the American Society of Echocardiography. 2014; 27: 911–939. https://doi.org/10.1016/j.echo.2014.07.012

[30] Shibutani Y, Imaoka T, Suzuki A, Tajiri K. Asymptomatic Troponin Elevation and Early Mortality Following Immune Checkpoint Inhibitor Therapy in Patients Without Cardiac Adverse Events. Cancer Diagnosis & Prognosis. 2025; 5: 634–641. https://doi.org/10.21873/cdp.10479

[31] Zotova L. Immune Checkpoint Inhibitors-Related Myocarditis: A Review of Reported Clinical Cases. Diagnostics (Basel, Switzerland). 2023; 13: 1243. https://doi.org/10.3390/diagnostics13071243

[32] Lehmann LH, Heckmann MB, Bailly G, Finke D, Procureur A, Power JR, et al. Cardiomuscular Biomarkers in the Diagnosis and Prognostication of Immune Checkpoint Inhibitor Myocarditis. Circulation. 2023; 148: 473–486. https://doi.org/10.1161/CIRCULATIONAHA.123.062405

[33] Provinciali N, Piccininno M, Siri G, Gennari A, Antonucci G, Ricci D, et al. Serum Biomarkers to Dynamically Predict the Risk of Cardiovascular Events in Patients under Oncologic Therapy. A Multicenter Observational Study. Reviews in Cardiovascular Medicine. 2024; 25: 256. https://doi.org/10.31083/j.rcm2507256

[34] Power JR, Alexandre J, Choudhary A, Ozbay B, Hayek S, Asnani A, et al. Electrocardiographic Manifestations of Immune Checkpoint Inhibitor Myocarditis. Circulation. 2021; 144: 1521–1523. https://doi.org/10.1161/CIRCULATIONAHA.121.055816

[35] O'Shea MP, Karikalan SA, Yusuf A, Barry T, Habib E, O'Shea J, et al. Complete heart block is a significant predictor of mortality in immune checkpoint inhibitor myocarditis. Cardio-oncology (London, England). 2023; 9: 34. https://doi.org/10.1186/s40959-023-00185-y

[36] Ederhy S, Salem JE, Dercle L, Hasan AS, Chauvet-Droit M,

Nhan P, et al. Role of Cardiac Imaging in the Diagnosis of Immune Checkpoints Inhibitors Related Myocarditis. Frontiers in Oncology. 2021; 11: 640985. https://doi.org/10.3389/fonc.2021.640985

[37] Ostos-Mendoza KC, Saraiba-Rabanales V, Gutierrez-Gallegos P, Wang E, Koutroumpakis E, Kumar S, et al. Immune checkpoint inhibitor-associated myocarditis: a review of current state of knowledge. The Journal of Cardiovascular Aging. 2025; 5: 5. http://dx.doi.org/10.20517/jca.2024.13

[38] Sławiński G, Hawryszko M, Liżewska-Springer A, Nabiałek-Trojanowska I, Lewicka E. Global Longitudinal Strain in Cardio-Oncology: A Review. Cancers. 2023; 15: 986. https://doi.org/10.3390/cancers15030986

[39] Thavendiranathan P, Zhang L, Zafar A, Drobni ZD, Mahmood SS, Cabral M, et al. Myocardial T1 and T2 Mapping by Magnetic Resonance in Patients With Immune Checkpoint Inhibitor-Associated Myocarditis. Journal of the American College of Cardiology. 2021; 77: 1503–1516. https://doi.org/10.1016/j.jacc.2021.01.050

[40] Tong J, Vogiatzakis N, Andres MS, Senechal I, Badr A, Ramalingam S, et al. Complementary use of cardiac magnetic resonance and 18 F-FDG positron emission tomography imaging in suspected immune checkpoint inhibitor myocarditis. Cardio-oncology (London, England). 2024; 10: 53. https://doi.org/10.1186/s40959-024-00250-0

[41] Li J, Li Y, Tao L, Zhang C, Zuo Z. Diagnostic and Prognostic Value of Cardiac Magnetic Resonance for Cardiotoxicity Caused by Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. Reviews in Cardiovascular Medicine. 2025; 26: 25508. https://doi.org/10.31083/RCM25508

[42] Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). European Heart Journal. 2022; 43: 4229–4361. https://doi.org/10.1093/eurheartj/ehac244

[43] Patel S, Dave K, Garcia MJ, Gongora CA, Travin MI, Zhang L. Multimodal Imaging of Immune Checkpoint Inhibitor Myocarditis. Journal of Clinical Medicine. 2025; 14: 2850. https://doi.org/10.3390/jcm14082850

[44] Sun SJ, Jiao XD, Chen ZG, Cao Q, Zhu JH, Shen QR, et al. Gasdermin-E-mediated pyroptosis drives immune checkpoint inhibitor-associated myocarditis via cGAS-STING activation. Nature Communications. 2024; 15: 6640. https://doi.org/10.1038/s41467-024-50996-5

[45] Mir H, Alhussein M, Alrashidi S, Alzayer H, Alshatti A, Valettas N, et al. Cardiac Complications Associated With Checkpoint Inhibition: A Systematic Review of the Literature in an Important Emerging Area. The Canadian Journal of Cardiology. 2018; 34: 1059–1068. https://doi.org/10.1016/j.cjca.2018.03.012

[46] Nishimura H, Okazaki T, Tanaka Y, Nakatani K, Hara M, Matsumori A, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. Science (New York, N.Y.). 2001; 291: 319–322. https://doi.org/10.1126/science.291.5502.319

[47] Nishimura H, Honjo T. PD-1: an inhibitory immunoreceptor involved in peripheral tolerance. Trends in Immunology. 2001; 22: 265–268. https://doi.org/10.1016/s1471-4906(01)01888-9

[48] Zhu H, Galdos FX, Lee D, Waliany S, Huang YV, Ryan J, et al. Identification of Pathogenic Immune Cell Subsets Associated With Checkpoint Inhibitor-Induced Myocarditis. Circulation. 2022; 146: 316–335. https://doi.org/10.1161/CIRCULATIONAHA.121.056730

[49] Axelrod ML, Meijers WC, Screever EM, Qin J, Carroll MG, Sun X, et al. T cells specific for α-myosin drive immunotherapy-related myocarditis. Nature. 2022; 611: 818–826. https://doi.org/10.1038/s41586-022-05432-3

[50] Won T, Kalinoski HM, Wood MK, Hughes DM, Jaime CM, Delgado P, et al. Cardiac myosin-specific autoimmune T cells contribute to immune-checkpoint-inhibitor-associated myocarditis. Cell Reports. 2022; 41: 111611. https://doi.org/10.1016/j.celrep.2022.111611

[51] Francisco LM, Salinas VH, Brown KE, Vanguri VK, Freeman GJ, Kuchroo VK, et al. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. The Journal of Experimental Medicine. 2009; 206: 3015–3029. https://doi.org/10.1084/jem.20090847

[52] Buchbinder EI, Desai A. CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. American Journal of Clinical Oncology. 2016; 39: 98–106. https://doi.org/10.1097/COC.0000000000000239

[53] Kalinoski H, Daoud A, Rusinkevich V, Jurčová I, Talor MV, Welsh RA, et al. Injury-induced myosin-specific tissue-resident memory T cells drive immune checkpoint inhibitor myocarditis. Proceedings of the National Academy of Sciences of the United States of America. 2024; 121: e2323052121. https://doi.org/10.1073/pnas.2323052121

[54] Lim SY, Lee JH, Gide TN, Menzies AM, Guminski A, Carlino MS, et al. Circulating Cytokines Predict Immune-Related Toxicity in Melanoma Patients Receiving Anti-PD-1-Based Immunotherapy. Clinical Cancer Research: an Official Journal of the American Association for Cancer Research. 2019; 25: 1557–1563. https://doi.org/10.1158/1078-0432.CCR-18-2795

[55] Frangogiannis NG. The inflammatory response in myocardial injury, repair, and remodelling. Nature Reviews. Cardiology. 2014; 11: 255–265. https://doi.org/10.1038/nrcardio.2014.28

[56] Gordon JW, Shaw JA, Kirshenbaum LA. Multiple facets of NF-κB in the heart: to be or not to NF-κB. Circulation Research. 2011; 108: 1122–1132. https://doi.org/10.1161/CIRCRESAHA.110.226928

[57] Finke D, Heckmann MB, Salatzki J, Riffel J, Herpel E, Heinzerling LM, et al. Comparative Transcriptomics of Immune Checkpoint Inhibitor Myocarditis Identifies Guanylate Binding Protein 5 and 6 Dysregulation. Cancers. 2021; 13: 2498. https://doi.org/10.3390/cancers13102498

[58] Gergely TG, Kucsera D, Tóth VE, Kovács T, Sayour NV, Drobni ZD, et al. Characterization of immune checkpoint inhibitor-induced cardiotoxicity reveals interleukin-17A as a driver of cardiac dysfunction after anti-PD-1 treatment. British Journal of Pharmacology. 2023; 180: 740–761. https://doi.org/10.1111/bph.15984

[59] Toldo S, Abbate A. The role of the NLRP3 inflammasome and pyroptosis in cardiovascular diseases. Nature Reviews. Cardiology. 2024; 21: 219–237. https://doi.org/10.1038/s41569-023-00946-3

[60] Raucci A, Di Maggio S, Scavello F, D'Ambrosio A, Bianchi ME, Capogrossi MC. The Janus face of HMGB1 in heart disease: a necessary update. Cellular and Molecular Life Sciences: CMLS. 2019; 76: 211–229. https://doi.org/10.1007/s00018-018-2930-9

[61] Quagliariello V, Passariello M, Di Mauro A, Cipullo C, Paccone A, Barbieri A, et al. Immune checkpoint inhibitor therapy increases systemic SDF-1, cardiac DAMPs Fibronectin-EDA, S100/Calgranulin, galectine-3, and NLRP3-MyD88-chemokine pathways. Frontiers in Cardiovascular Medicine. 2022; 9: 930797. https://doi.org/10.3389/fcvm.2022.930797

[62] Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nature Immunology. 2010; 11: 373–384. https://doi.org/10.1038/ni.1863

[63] Su Q, Li L, Sun Y, Yang H, Ye Z, Zhao J. Effects of the TLR4/Myd88/NF-κB Signaling Pathway on NLRP3 Inflammasome in Coronary Microembolization-Induced Myocardial In-

jury. Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology. 2018; 47: 1497–1508. https://doi.org/10.1159/000490866

[64] West AP, Khoury-Hanold W, Staron M, Tal MC, Pineda CM, Lang SM, et al. Mitochondrial DNA stress primes the antiviral innate immune response. Nature. 2015; 520: 553–557. https://doi.org/10.1038/nature14156

[65] Kim J, Kim HS, Chung JH. Molecular mechanisms of mitochondrial DNA release and activation of the cGAS-STING pathway. Experimental & Molecular Medicine. 2023; 55: 510–519. https://doi.org/10.1038/s12276-023-00965-7

[66] Swanson KV, Deng M, Ting JPY. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. Nature Reviews. Immunology. 2019; 19: 477–489. https://doi.org/10.1038/s41577-019-0165-0

[67] Bauernfeind FG, Horvath G, Stutz A, Alnemri ES, MacDonald K, Speert D, et al. Cutting edge: NF-kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. Journal of Immunology (Baltimore, Md.: 1950). 2009; 183: 787–791. https://doi.org/10.4049/jimmunol.0901363

[68] Xia R, Tomsits P, Loy S, Zhang Z, Pauly V, Schüttler D, et al. Cardiac Macrophages and Their Effects on Arrhythmogenesis. Frontiers in Physiology. 2022; 13: 900094. https://doi.org/10.3389/fphys.2022.900094

[69] Hulsmans M, Clauss S, Xiao L, Aguirre AD, King KR, Hanley A, et al. Macrophages Facilitate Electrical Conduction in the Heart. Cell. 2017; 169: 510–522.e20. https://doi.org/10.1016/j.cell.2017.03.050

[70] Bajpai G, Bredemeyer A, Li W, Zaitsev K, Koenig AL, Lokshina I, et al. Tissue Resident CCR2- and CCR2+ Cardiac Macrophages Differentially Orchestrate Monocyte Recruitment and Fate Specification Following Myocardial Injury. Circulation Research. 2019; 124: 263–278. https://doi.org/10.1161/CIRCRESAHA.118.314028

[71] Ma P, Liu J, Qin J, Lai L, Heo GS, Luehmann H, et al. Expansion of Pathogenic Cardiac Macrophages in Immune Checkpoint Inhibitor Myocarditis. Circulation. 2024; 149: 48–66. https://doi.org/10.1161/CIRCULATIONAHA.122.062551

[72] Lin X, Liu P, Jin M, Qi G. Clinical features and HLA typing of immune checkpoint inhibitor-associated myasthenia gravis, myocarditis and myositis. Frontiers in Oncology. 2025; 15: 1646231. https://doi.org/10.3389/fonc.2025.1646231

[73] Salem JE, Bretagne M, Abbar B, Leonard-Louis S, Ederhy S, Redheuil A, et al. Abatacept/Ruxolitinib and Screening for Concomitant Respiratory Muscle Failure to Mitigate Fatality of Immune-Checkpoint Inhibitor Myocarditis. Cancer Discovery. 2023; 13: 1100–1115. https://doi.org/10.1158/2159-8290.CD-22-1180

[74] Doms J, Prior JO, Peters S, Obeid M. Tocilizumab for refractory severe immune checkpoint inhibitor-associated myocarditis. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2020; 31: 1273–1275. https://doi.org/10.1016/j.annonc.2020.05.005

[75] Liu Y, Jiang L. Tofacitinib for treatment in immune-mediated myocarditis: The first reported cases. Journal of Oncology Pharmacy Practice: Official Publication of the International Society of Oncology Pharmacy Practitioners. 2020; 1078155220947141. https://doi.org/10.1177/1078155220947141

[76] Brahmer JR, Abu-Sbeih H, Ascierto PA, Brufsky J, Cappelli LC, Cortazar FB, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. Journal for Immunotherapy of Cancer. 2021; 9: e002435. https://doi.org/10.1136/jitc-2021-002435

[77] Zhang L, Zlotoff DA, Awadalla M, Mahmood SS, Nohria A, Hassan MZO, et al. Major Adverse Cardiovascular Events and the Timing and Dose of Corticosteroids in Immune Checkpoint Inhibitor-Associated Myocarditis. Circulation. 2020; 141: 2031–2034. https://doi.org/10.1161/CIRCULATIONAHA.119.044703

[78] Man X, Wang H, Chen C, Cong X, Sun L, Sun X, et al. Efficacy of high-dose steroids versus low-dose steroids in the treatment of immune checkpoint inhibitor-associated myocarditis: a case series and systematic review. Frontiers in Immunology. 2025; 16: 1455347. https://doi.org/10.3389/fimmu.2025.1455347

[79] Puzanov I, Diab A, Abdallah K, Bingham CO, 3rd, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. Journal for Immunotherapy of Cancer. 2017; 5: 95. https://doi.org/10.1186/s40425-017-0300-z

[80] Wang C, Lin J, Wang Y, Hsi DH, Chen J, Liu T, et al. Case Series of Steroid-Resistant Immune Checkpoint Inhibitor Associated Myocarditis: A Comparative Analysis of Corticosteroid and Tofacitinib Treatment. Frontiers in Pharmacology. 2021; 12: 770631. https://doi.org/10.3389/fphar.2021.770631

[81] Zhang RS, Padegimas A, Murphy KM, Evans PT, Peters CJ, Domenico CM, et al. Treatment of corticosteroid refractory immune checkpoint inhibitor myocarditis with Infliximab: a case series. Cardio-oncology (London, England). 2021; 7: 13. https://doi.org/10.1186/s40959-021-00095-x

[82] Salem JE, Allenbach Y, Vozy A, Brechot N, Johnson DB, Moslehi JJ, et al. Abatacept for Severe Immune Checkpoint Inhibitor-Associated Myocarditis. The New England Journal of Medicine. 2019; 380: 2377–2379. https://doi.org/10.1056/NEJMc1901677

[83] Nguyen LS, Bretagne M, Arrondeau J, Zahr N, Ederhy S, Abbar B, et al. Reversal of immune-checkpoint inhibitor fulminant myocarditis using personalized-dose-adjusted abatacept and ruxolitinib: proof of concept. Journal for Immunotherapy of Cancer. 2022; 10: e004699. https://doi.org/10.1136/jitc-2022-004699

[84] Reynolds KL, Zlotoff DA, Mooradian M, Zubiri L, Ridker P, Neilan TG. Abatacept for immune checkpoint inhibitor associated myocarditis (ATRIUM): Phase 3, investigator-initiated, randomized, placebo-controlled study to evaluate the efficacy and safety of abatacept compared to placebo in hospitalized patients with immune checkpoint inhibitor associated myocarditis. Journal of Clinical Oncology. 2023; 41: TPS2680. https://doi.org/10.1200/JCO.2023.41.16_suppl.TPS2680

[85] Salem JE, Ederhy S, Belin L, Zahr N, Tubach F, Procureur A, et al. Abatacept dose-finding phase II triaL for immune checkpoint inhibitors myocarditis (ACHLYS) trial design. Archives of Cardiovascular Diseases. 2025; 118: 106–115. https://doi.org/10.1016/j.acvd.2024.12.005

[86] Johnson DB, Menzies AM. Combination immunomodulation for immune-checkpoint-inhibitor-associated myocarditis. Nature Reviews. Clinical Oncology. 2023; 20: 427–428. https://doi.org/10.1038/s41571-023-00762-1

[87] Wei SC, Meijers WC, Axelrod ML, Anang NAAS, Screever EM, Wescott EC, et al. A Genetic Mouse Model Recapitulates Immune Checkpoint Inhibitor-Associated Myocarditis and Supports a Mechanism-Based Therapeutic Intervention. Cancer Discovery. 2021; 11: 614–625. https://doi.org/10.1158/2159-8290.CD-20-0856

[88] Esfahani K, Buhlaiga N, Thébault P, Lapointe R, Johnson NA, Miller WH, Jr. Alemtuzumab for Immune-Related Myocarditis Due to PD-1 Therapy. The New England Journal of Medicine. 2019; 380: 2375–2376. https://doi.org/10.1056/NEJMc1903064

[89] Dolladille C, Ederhy S, Sassier M, Cautela J, Thuny F, Cohen AA, et al. Immune Checkpoint Inhibitor Rechallenge Af-

ter Immune-Related Adverse Events in Patients With Cancer. JAMA Oncology. 2020; 6: 865–871. https://doi.org/10.1001/jamaoncol.2020.0726

[90] Ganatra S, Neilan TG. Immune Checkpoint Inhibitor-Associated Myocarditis. The Oncologist. 2018; 23: 879–886. https://doi.org/10.1634/theoncologist.2018-0130

[91] Frascaro F, Bianchi N, Sanguettoli F, Marchini F, Meossi S, Zanarelli L, et al. Immune Checkpoint Inhibitors-Associated Myocarditis: Diagnosis, Treatment and Current Status on Rechallenge. Journal of Clinical Medicine. 2023; 12: 7737. https://doi.org/10.3390/jcm12247737