Review Article

Therapeutic agents for steroid-refractory immune checkpoint inhibitor-related myocarditis: a narrative review

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Background and Objective: Immune checkpoint inhibitors (ICIs) have become one of the cornerstones of current oncology treatment, and immune checkpoint inhibitor-related myocarditis (IRM) is the most fatal of all immune checkpoint inhibitor-related adverse events (irAEs). Methylprednisolone pulse therapy (500–1,000 mg/day) is the initial treatment for IRM recommended by almost all relevant guidelines. However, subsequent treatment regimens remain unclear for patients who do not respond to methylprednisolone pulse therapy (who are defined as steroid-refractory patients). We propose a potential treatment approach for steroid-refractory IRM.

Methods: The PubMed and the Cochrane Library databases were searched using keywords related to IRM. Relevant English-language articles published from January 2000 to February 2024 were included in this narrative review.

Key Content and Findings: Abatacept is the preferred choice for the treatment of isolated steroid-refractory IRM. For rapidly progressive or interleukin-6 abnormally elevated steroid-refractory IRM, alemtuzumab or tocilizumab/tofacitinib are the preferred therapeutic agents, respectively. For steroid-refractory IRM comorbid with myositis or comorbid with myasthenia gravis, abatacept + ruxolitinib/mycophenolate mofetil (MMF)/intravenous immunoglobulin (IVIG), or MMF + pyridostigmine/IVIG are the preferred therapeutic agents, respectively.

Conclusions: The pathogenesis of steroid-refractory IRM and the treatment regimen remain unclear. A large number of studies need to be conducted to validate or update our proposed treatment approach.

Keywords: Immune checkpoint inhibitors (ICIs); therapeutic agents; steroid-refractory; myocarditis

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Introduction

Background

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of most major tumor types. As of June 30, 2022, nine and 15 ICIs had been approved for 86 and 58 indications in the United States and China, involving 20 and 14 types of tumors, respectively (1). Unlike chemotherapy, targeted therapy, and other immunotherapy agents, the mechanism of action of ICIs is to block the programmed

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death 1/programmed death ligand 1/cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) in T-lymphocytes, thus enhancing anti-tumor effects of T-lymphocytes (2). However, once self-immune tolerance is broken, immune checkpoint inhibitor-related adverse events (irAEs) may occur and affect all organs and systems (3). Among irAEs, immune checkpoint inhibitor-related myocarditis (IRM) is rare but has the highest mortality rate (4). A meta-analysis of 91 clinical trials showed that the incidence of grade 1–5 IRM was 0.35% (43/12,270) (5). A retrospective study of 33 cancer centers across China reported that the mortality rate of IRM was 61.5% (32/52) (6). However, in a prospective clinical trial, the incidence of suspected myocarditis was reported to be 10.3% (13/126) without fatal events (7). These findings indicate that the prevalence of IRM in the real world may be higher than previously estimated. This discrepancy may be attributed, in part, to the fact that the diagnostic criteria for IRM differ from those for traditional myocarditis. In particular, the initial symptoms of IRM may be myositis-related, including myalgia, myasthenia, ptosis, and muscle weakness (8). Early detection and adequate treatment of IRM are critical to improving prognosis (7). To date, no studies have been conducted on the incidence of steroid-refractory IRM (defined as patients who do not respond to methylprednisolone 500–1,000 mg/day pulse therapy). A single-center, case series enrolled 24 patients with confirmed IRM, of whom 67% (16/24) were corticosteroid-resistant, which suggests that the incidence of steroid-refractory IRM in the real world may not be low (9).

Rationale and knowledge gaps

In the last four years, the National Comprehensive Cancer Network (NCCN) (10), the European Society of Cardiology (ESC)/European Hematology Association (EHA)/European Society for Therapeutic Radiology and Oncology (ESTRO)/International Cardio-Oncology Society (IC-OS) (11), the European Society for Medical Oncology (ESMO) (12), The American Society of Clinical Oncology (ASCO) (13), and the Society for Immunotherapy of Cancer (SITC) (14) have published guidelines for the treatment of IRM. Methylprednisolone pulse therapy (500–1,000 mg/day) is the initial treatment for IRM recommended by almost all the guidelines mentioned above. However, for steroid-refractory IRM patients, the subsequent treatment approach remains unclear. Multicenter survey results highlight the current confusion among clinicians on this issue (15). In addition, most oncologists are unfamiliar with the mechanism of action, adverse reactions, and contraindications of the therapeutic agents used to treat steroid-refractory IRM. To the best of our knowledge, there is no published narrative review focusing on steroid-refractory IRM after receiving 500–1,000 mg of methylprednisolone.

Objective

In this study, we sought to propose a potential treatment approach and review the details of current therapeutic agents used to treat steroid-refractory IRM based on the literature published to date. We present this article in accordance with the Narrative Review reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-114/rc).

Methods

To conduct this narrative review, a search was conducted in the PubMed and Cochrane Library databases to retrieve clinical trials, meta-analyses, case reports, and case series published in peer-reviewed journals between January 2000 and February 2024. The search strategy details are provided in *Table 1* and the terms used for the search are listed in Table S1. A total of 582 articles were reviewed by two senior authors based on their abstracts. Ultimately, 45 case reports and case series met the inclusion criteria for this article.

Discussion

Initial treatment of IRM

The most recent IRM guidelines from the ESC/EHA/ESTRO/IC-OS and the ESMO recommend pulse doses of methylprednisolone (500–1,000 mg/day) for the initial treatment of IRM (*Table 2*). Notably, the NCCN and SITC guidelines recommend 1,000 mg/day of methylprednisolone. While the ASCO guidelines recommend 1–2 mg/kg/day of prednisone and increasing the dose to 1,000 mg if the patient does not respond immediately, but this approach may only be appropriate for patients with subclinical IRM (16) or for those who are prescribed glucocorticoid combine with a pacemaker for IRM and who do not have abnormal myocardial contrast echocardiography or transthoracic echocardiography results (17). Given the potential for rapid deterioration of IRM, methylprednisolone pulse therapy should be

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Table 1 The search strategy summary

Items	Specification
Date of search	12/9/2023 to 17/02/2024
Databases and other sources searched	PubMed/Cochrane Library
Search terms used	See Table S1 for details
Timeframe	January 2000 to February 2024
Inclusion and exclusion criteria	Inclusion criteria: (I) the articles are mainly focused on immune checkpoint inhibitor-related myocarditis; (II) the articles are published in full text in peer-reviewed journals; (III) the language of the articles is restricted to English. Exclusion criteria: the dose of glucocorticoids in the case report/case series was unclear or less than 500 mg/day
Selection process	The selection process was conducted by two senior authors (Y.W. and D.C.)

considered for all patients with clinical symptoms, especially those with atrioventricular block, and methylprednisolone pulse therapy may lead to recovery in this group of patients without the implantation of a permanent pacemaker (18-20). Compared with low-dose corticosteroids (<60 mg/day), high dose (501–1,000 mg/day of methylprednisolone or an equivalent) is associated with a 73% lower risk of major adverse cardiac events independent of age, sex, lowest left ventricular ejection fraction, and the time of initiation (hazard ratio: 0.27, 95% confidence interval: 0.09–0.84; P=0.024) (21).

Definition of steroid-resistant IRM

Currently, there are no prospective clinical trials or meta-analyses available to formulate a treatment plan for patients with steroid-refractory IRM. In some cases, the initial steroid therapy dose for IRM may be insufficient, and thus ineffective (22). Thus, we define steroid-refractory IRM as patients who had a poor or worsening response despite the administration of steroid-pulse therapy of 500–1,000 mg/day. *Table 3* lists all patients with steroid-refractory IRM to date. In total, 50 cases were included in the discussion, of which 26 were recovered, 10 patients eventually died, 10 were clinically improved but not recovered, 2 were transferred to hospice care, and 2 did not report outcomes. Seven of the 10 patients who died provided a timeline with a median time from initiation of other immunosuppressive agents to death of 39 days (range, 6–124 days). Abatacept was used in 10 patients, alemtuzumab in 1, anti-thymocyte globulin (ATG) in 5, infliximab in 7, intravenous immunoglobulin (IVIG) in 23, methotrexate in 1, mycophenolate mofetil (MMF) in 23, tocilizumab in 2, and tofacitinib in 6, respectively.

Mechanisms of steroid-refractory IRM

The precise mechanism of IRM remains elusive, and potential mechanisms may include patients' primary resistance to glucocorticoids and immunosuppressive agents, which may not fully account for the full range of IRM mechanisms. The main cause of glucocorticoid resistance is the perturbation of the glucocorticoid receptor alpha functional pool (68). Glucocorticoid receptor beta isoform overexpression may be used as a biomarker for steroid-refractory IRM (69). The cause of glucocorticoid refractory IRM may be related to the inability of glucocorticoids to cover all potential mediators of the IRM (*Table 4*). The mechanisms of IRM have not yet been well characterized, but the current potential etiologies include the cellular mediators, the participating molecular signals and soluble factors (such as cytokines and chemokines), and T cell receptor clonality and specificity (70). Glucocorticoid can act directly on cluster of differentiation (CD)8^+ T cells, $CD4^+$ T cells, and macrophages, but its direct effect on B-lymphocytes and dendritic cells is weak (71). In addition, glucocorticoid does not directly inhibit cytokines, such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ) (71). The adverse effects of pulse glucocorticoid therapy include cardiac arrhythmias, circulatory collapse, and cardiac arrest, which may lead to the misdiagnosis of steroid-refractory IRM (72).

Therapeutic agents for steroid-refractory IRM

Abatacept

Abatacept is a fully human, recombinant, soluble fusion protein, comprising the extracellular domain of human

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Table 2 Clinical guidelines for immune checkpoint inhibitor-related myocarditis

Guidelines	NCCN	ESC/EHA/ESTRO/IC-OS	ESMO	ASCO	SITC
Online	2024	2022	2022	2021	2021
ICIs	Discontinue	Interruption in suspected cases and cessation in confirmed cases	In most cases, if IRM is confirmed, permanent discontinuation of ICIs	Hold ICIs for grade 1 (abnormal cardiac biomarker testing without symptoms and with no ECG abnormalities) and discontinue for ≥ grade 2	Permanent discontinuation of ICIs therapy should be seriously considered
Corticosteroids	IV methylprednisolone 1 g/day for 3–5 days	Methylprednisolone 500–1,000 mg intravenous bolus once daily for the first 3–5 days	intravenous methylprednisone 500–1,000 mg should be initiated daily for 3 days	1–2 mg/kg/d of prednisone, oral or intravenous depending on symptoms. In patients without an immediate response to initial high-dose corticosteroids, consider methylprednisolone 1 g every day	1,000 mg methylprednisolone intravenous or equivalent daily for 3–5 days, until troponin normalizes
Response to corticosteroids	Switch to oral prednisolone (1 mg/kg)	Switch to oral prednisolone (start at 1 mg/kg up to 80 mg/day)	Switch to oral prednisolone (start at 1 mg/kg up to 80 mg/day)	Not mentioned	1–2 mg/kg prednisone
Taper of corticosteroids	Taper slowly over 6–12 weeks based on clinical response and improvement of biomarkers	Reduction 10 mg per week until the prednisolone dose is reduced to 20 mg/day and then continue weaning the prednisolone by 5 mg per week to 5 mg/day, and a final reduction from 5 mg/day in 1-mg per week steps	Reducing by 10 mg/week with troponin monitoring providing cardiovascular stability continues	Not mentioned	4–6 weeks
Steroid-refractory	Abatacept, alemtuzumab, ATG, IVIG, MTX, MMF, and PE	MMF, ATG. IVIG, PE, tocilizumab, abatacept, alemtuzumab, and tofacitinib	Continue intravenous methylprednisone 1,000 mg/day. Add second-line immunosuppressive (e.g., tocilizumab 8 mg/kg or MMF); third-line options: ATG, alemtuzumab, abatacept	Addition of either MMF, infliximab, or ATG. Consider abatacept or alemtuzumab as additional immunosuppression in life-threatening cases	ATG, MMF, abatacept, or alemtuzumab
Infliximab	Use with extreme caution in patients with reduced LVEF	Caution is advised against the use of infliximab for steroid-refractory IRM and HF	Not mentioned	No special tips	Caution
Rechallenge of ICIs	Grade 1 IRM: consider resuming on resolution of symptoms. Permanent discontinuation is warranted in the setting of grade 2–4 IRM	MDT	MDT discussion is recommended before restarting ICIs treatment in patients with mild, clinically uncomplicated IRM. In all steroid-refractory cases，permanently stop ICIs therapy	May consider resuming once normalized for grade 1 IRM or if IRM is believed not to be related to ICIs	Not mentioned

ICIs, immune checkpoint inhibitors; NCCN, National Comprehensive Cancer Network; IV, intravenous; ATG, anti-thymocyte globulin; IVIG, intravenous immunoglobulin; MTX, methotrexate; MMF, mycophenolate mofetil; PE, plasma exchange; LVEF, left ventricular ejection fraction; IRM, immune checkpoint inhibitor-related myocarditis; ESC, European Society of Cardiology; EHA, European Hematology Association; ESTRO, European Society for Therapeutic Radiology and Oncology; IC-OS, International Cardio-Oncology Society; HF, heart failure; MDT, multidisciplinary team; ESMO, European Society for Medical Oncology; ASCO, American Society of Clinical Oncology; ECG, electrocardiogram; SITC, Society for Immunotherapy of Cancer.

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Table 3 Case report of immune checkpoint inhibitor-related myocarditis refractory to methylprednisolone (500–1,000 mg/day)

Malignancy	ICIs	EMB	Immunocyte	Cytokine	Initial treatment	Second-line	Third-line	Subsequent	Result	Reference
Thymoma	Tislelizumab	No	–	–	mPSL 1,000 mg; IVIG 10 g/day	mPSL 250 mg; PE; MMF 0.75g bid; pyridostigmine 90 mg tid			Unknown	(23)
GC	Pembrolizumab	No	–	–	mPSL 1,000 mg	Infliximab 5 mg/kg; mPSL 1,000 mg			Recovery	(24)
BC	Pembrolizumab	No	–	–	mPSL 500 mg	Abatacept 15 mg/kg; steroid			Recovery	(25)
Thymoma	Toripalimab	No	–	–	mPSL 1,000 mg; IVIG 20 g/day	Pyridostigmine; MMF; steroid			Recovery	(26)
GEJA	Pembrolizumab	No	–	–	mPSL 1 mg/kg/day; mPSL 1,000 mg/day	ATG 500 mg; MMF 1 g bid			Death due to diastolic heart failure	(27)
LC	Ipilimumab and nivolumab	No	–	–	mPSL 1,000 mg/day	MMF 1 g/day; mPSL 2 mg/kg	IVIG 25 g/day; MMF 2 g/day; mPSL 2 mg/kg		Clinical improvement	(28)
Cer-C	Atezolizumab	Yes	T-lymphocytes and macrophages	–	mPSL 1,000 mg/day	Abatacept 11.4 mg/kg; prednisone 50 mg	IVIG 400 mg/kg; abatacept 11.4 mg/kg; prednisone 50 mg		Recovery	(29)
Thymoma	Tislelizumab				mPSL 1,000 mg; IVIG 20 g/day	mPSL 1,000 mg/day; IVIG 10 g/day; MMF 1,000 mg bid			Partial recovery	(30)
Cholangiocarcinoma	Sintilimab	No			mPSL 500 mg; IVIG 400 mg/kg/day	Tacrolimus 3 mg/day; mPSL; IVIG			Recovery	(31)
GC	Nivolumab	Yes	EMB: $CD8^+$T-lymphocytes. Autopsy:$CD8^+$T-lymphocytes and $CD68^+$ histiocytes		Prednisone 1 mg/kg; mPSL 1,000 mg/day	mPSL 1,000 mg/day; IVIG 1 g/kg	Prednisone 1 mg/kg; PE		Death due to septic	(32)
Endo-cancer	Pembrolizumab	Yes	$CD8^+$T-lymphocytes		mPSL 1,000 mg/day	Abatacept 500 mg ×2; abatacept 1,000 mg ×1; MMF 750 mg bid; methotrexate 15 mg weekly			Recovery	(33)

Table 3 *(continued)*

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Table 3 *(continued)*

Malignancy	ICIs	EMB	Immunocyte	Cytokine	Initial treatment	Second-line	Third-line	Subsequent	Result	Reference
Melanoma	Nivolumab and relatlimab	No			Corticosteroid 3 mg/kg/day; mPSL 1,000 mg/day	PE; abatacept 500 mg; corticosteroid 2 mg/kg			Recovery	(34)
Melanoma	Nivolumab, ipilimumab and relatlimab	Yes	Mononuclear lymphocytes and macrophages		Corticosteroid 1 mg/kg/day; mPSL 1,000 mg/day; Corticosteroid 2 mg/kg/day	Infliximab 500 mg; mPSL 2 mg/kg/day	IVIG 0.4 g/kg/day; prostigmine; corticosteroid?	Corticosteroid 1,000 mg/day; abatacept 500 mg PE	Death	
NC	Toripalimab	No		IL-6	mPSL 4 mg/kg/day; mPSL 500 mg/day; IVIG 0.4 g/kg/day	Tofacitinib 5 mg bid; mPSL			Recovery	(35)
RCC	Nivolumab and ipilimumab	No			mPSL 1,000 mg/day	mPSL 1 mg/kg/day; IVIG			Recovery	(36)
RCC	Nivolumab and ipilimumab				mPSL 2 mg/kg/day; mPSL 500 mg/day	mPSL 1,000 mg/day; MMF 1,000 mg bid			Death due to tumor progression, pneumonia, or abdominal sepsis	(37)
RCC	Nivolumab and ipilimumab				mPSL 500 mg/day	MMF 1,000 mg bid; mPSL 500 mg/day			Unknown	
Cholangiocarcinoma	Camrelizumab				mPSL 1,000 mg/day	IVIG 10g/day; MMF 500 mg/day then 1,000 mg/day; mPSL			Recovery	(38)
LC	Pembrolizumab				mPSL 1,000 mg/day; IVIG	MMF 500 mg tid; IVIG?; corticosteroid?			Death	(39)
RCC	Pembrolizumab	Yes	Rare scattered CD3 and CD8 T cells and CD4 did not stain myocytes		mPSL 1,000 mg/day	MMF 1,000 mg bid; mPSL; pyridostigmine 60 mg tid			Recovery	(40)
BC	Nivolumab and ipilimumab	Yes	$CD3^+CD8^+$ lymphocytes and lesser numbers of $CD68^+$ macrophages		mPSL 1,000 mg/day; pyridostigmine 90 mg tid	MMF 750 mg bid; mPSL?; pyridostigmine?			Recovery	
Melanoma	Nivolumab	No			mPSL 1,000 mg/day	IVIG 2 g/kg; prednisone 60 mg/day; pyridostigmine 30 mg tid			Recovery	

Table 3 *(continued)*

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Table 3 *(continued)*

Malignancy	ICIs	EMB	Immunocyte	Cytokine	Initial treatment	Second-line	Third-line	Subsequent	Result	Reference
Thymoma	Pembrolizumab	Yes	$CD3^+$ T-cells and $CD68^+$ macrophages		mPSL 1,000 mg/day; MMF	Abatacept 20 mg/kg; ruxolitinib 15 mg bid; mPSL 2 mg/kg			Recovery	(41)
GC	Nivolumab	Yes	$CD8^+$ T cells and macrophage		mPSL 1,000 mg/day	mPSL 1,000 mg/day; IVIG 22.5 g/kg; PE			Death due to myasthenia gravis	(42)
RCC	Nivolumab and ipilimumab	No			mPSL 2 mg/kg/day; mPSL 1,000 mg/day	Abatacept 500 mg; MMF 1,000 mg bid; mPSL 2 mg/kg/day			Partial recovery	(43)
Melanoma	Nivolumab and ipilimumab	No			mPSL 1,000 mg/day; MMF 1,000 mg bid	Abatacept 200 mg; MMF?; mPSL?			Recovery	(44)
UC	Atezolizumab	No			mPSL 1,000 mg/day; IVIG; infliximab	ATG; prednisone 1.5 mg/kg			Partial recovery	(45)
Liposarcoma	Pembrolizumab	No			mPSL 1,000 mg/day	IVIG 2 g/kg; mPSL 2 mg/kg/day	MMF 500 mg bid; mPSL 2 mg/kg/day; IVIG?		Recovery	(46)
BC + HL	Sintilimab	No		TNF; IL-2 receptor; IL-6	mPSL 500 mg/day	PE; mPSL 2 mg/kg	Tofacitinib 5 mg bid; mPSL 2 mg/kg		Recovery	(47)
PC	Pembrolizumab	No			MMF 1,000 mg bid; mPSL 125 mg/day then 1,000 mg/day	PE			Partial recovery	(48)
KC	Nivolumab and ipilimumab	No			Prednisolone 80 mg; mPSL 1,000 mg/day	Infliximab 5 mg/kg; prednisolone 80 mg			Improved	(49)
RCC	Nivolumab and ipilimumab	No			mPSL 1,000 mg/day	PE; mPSL 200 mg			Recovery	(50)
Melanoma	Pembrolizumab	No			mPSL 1,000 mg bid; mPSL 1,000 mg qd	MMF 750 mg bid; mPSL	Abatacept 10 mg/kg; PE; prednisone		Partial recovery	(51)
Melanoma	Nivolumab	No			Prednisone 40 mg/day; mPSL 124 mg/day; mPSL 1,000 mg/day	Infliximab 5 mg/kg; corticosteroid?			Death due to ventricular fibrillation	(52)
LSNC	Nivolumab and ipilimumab	No			mPSL 1,000 mg/day; mPSL 200 mg/day	Tocilizumab 8 mg/kg; corticosteroid?			Recovery	(53)

Table 3 *(continued)*

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Table 3 *(continued)*

Malignancy	ICIs	EMB	Immunocyte	Cytokine	Initial treatment	Second-line	Third-line	Subsequent	Result	Reference
CSCC	Cemiplimab	Yes	Inflammatory cellular		mPSL 1,000 mg/day	PE; IVIG; corticosteroid?			Death due to pulseless electrical activity arrest	(54)
TC	Pembrolizumab	Yes	Predominantly lymphocytes and macrophages with a minor component of neutrophils and eosinophils		mPSL 1,000 mg/day	PE; pyridostigmine 60 mg, every 6 h; mPSL 1,000 mg/day; prednisone 1 mg//kg/day			Partial recovery	(55)
RCC	Nivolumab and ipilimumab	Autopsy	Predominance of CD3-positive T cells with occasional CD20-positive B and numerous CD68-positive macrophages. More CD4-positive cells than CD8-positive cells		mPSL 1 mg/kg/day; mPSL 500 mg/day	PE; corticosteroid?			Death	(56)
LC	Sintilimab	No			mPSL 2 mg/kg/day then 500 mg/day; IVIG 400 mg/kg/day; pyridostigmine bromide 120 mg bid	PE; pyridostigmine bromide?; prednisone?			Partial recovery	(57)
Melanoma	Pembrolizumab	No			mPSL 1,000 mg/day; mPSL 2 mg/kg/day; MMF 1,000 mg bid; PE ×5; rituximab 375 mg weekly	Alemtuzumab 30 mg; mPSL; MMF; rituximab			Recovery	(58)
LC	Pembrolizumab	No		IL-6, IL-8	mPSL 1,000 mg/day; IVIG 20 g/day	Tocilizumab 8 mg/kg; mPSL			Recovery	(59)
Melanoma	Pembrolizumab	No			mPSL 1,000 mg/day	MMF 1,500 mg bid; prednisolone?			Recovery	(60)
Melanoma	Pembrolizumab	No			mPSL 2 mg/kg/day; mPSL 1,000 mg/day	MMF 1,000 mg bid; mPSL?	mPSL 2 mg/kg/day; IVIG 2 g/day; MMF 1,000 mg bid		Partial recovery	
RCC	Nivolumab and ipilimumab	Yes	Lymphocytes, eosinophils, and histiocytes		mPSL 1,000 mg/day; ATG 66 mg/day	MMF; prednisone 1 mg/kg/day			Recovery	(61)

Table 3 *(continued)*

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Table 3 *(continued)*

Malignancy	ICIs	EMB	Immunocyte	Cytokine	Initial treatment	Second-line	Third-line	Subsequent	Result	Reference
LC	Nivolumab	No			mPSL 500 mg/day; PE	Abatacept 500 mg/day; corticosteroid?			Recovery	(62)
Melanoma	Nivolumab and ipilimumab	Autopsy	$CD68^+$ myeloid cells and $CD4^+$ and $CD8^+$ T lymphocytes		mPSL 200 mg/day; mPSL 1,000 mg/day	Infliximab 5 mg/kg; IVIG			Death due to multiple organ failure in the context of rhabdomyositis and myocarditis	(63)
Melanoma	Nivolumab and ipilimumab	No			mPSL 125 mg/day; mPSL 1,000 mg/day	mPSL 1,000 mg/day; IVIG 2 g/kg	PE; mPSL 150 mg/day		Inpatient hospice care	(64)
Melanoma	Nivolumab and ipilimumab	Yes	$CD3^+$ and $CD20^-$ T cell		mPSL 500 mg bid	ATG 1.5 mg/kg; corticosteroid?			Palliative care and inpatient hospice	(65)
Melanoma	Nivolumab and ipilimumab	No			mPSL 1,000 mg/day IVIG	PE; mPSL 2 mg/kg/day	Tacrolimus; mPSL 2 mg/kg/day		Recovery	(66)
Glioblastoma	Nivolumab	Yes	Lymphocytic ($CD3^+$, $CD8^+$ predominant with mixed $CD3^+$ $CD4^+$ subtypes) and histiocytic		mPSL 500 mg/day; infliximab 5 mg/kg	ATG 500 mg with titration; MMF 1,000 mg bid; prednisolone 100 mg/day			Recovery	(67)

?, it is unclear whether it was still employed in subsequent treatments. GC, gastric adenocarcinoma; BC, breast cancer; GEJA, gastroesophageal junction adenocarcinoma; LC, lung cancer; Cer-C, cervical cancer; Endo-cancer, endometrial cancer; NC, nasopharyngeal carcinoma; RCC, renal cell carcinoma; UC, urothelial cancer; HL, Hodgkin's lymphoma; PC, prostate cancer; KC, kidney cancer; LSNC, lung small-cell neuroendocrine carcinoma; CSCC, cutaneous squamous cell carcinoma; TC, thymic carcinoma; ICIs, immune checkpoint inhibitors; EMB, endomyocardial biopsy; IL, interleukin; TNF, tumor necrosis factor; mPSL, methylprednisolone; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; PE, plasma exchange; ATG, anti-thymocyte globulin.

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Table 4 Mediators of immune checkpoint inhibitor-related myocarditis and the spectrum of immunosuppressive effects of therapeutic agents

Mediators	Glucocorticoids	Abatacept	Alemtuzumab	Anti-thymocyte globulin	Infliximab	Intravenous immunoglobulin	Methotrexate	Mycophenolate mofetil	Tocilizumab	Tofacitinib
Cell										
$CD8^+$ T-lymphocytes	↓	↓	↓	↓	–	–	↓	↓	–	–
$CD4^+$ T-lymphocytes	↓	↓	↓	↓	↓	–	↓	↓	–	–
B-lymphocytes	–	↓	↓	↓	–	↓	↓	↓	–	↑
Macrophage	↓	–	↓	↓	–	↓	–	–	–	–
Dendritic cell	–	–	↓	↓	–	↓	–	–	–	–
Cytokine										
Interferon γ	↓	–	–	–	–	–	↓	↓	–	↓
TNF-α	↓	–	–	–	↓	–	↓	↓	–	–
Interleukin-1β	↓	–	–	–	–	–	↓	–	–	–
Interleukin-6	↓	–	–	–	–	–	↓	↓	↓	↓
Interleukin-8	–	–	–	–	–	–	–	–	–	↓
Interleukin-10	↑↓	–	–	–	–	–	↑↓	–	–	–
CCL5	–	–	–	–	–	–	–	–	–	–
CXCL9[§]	–	–	–	–	–	–	–	–	–	–
CXCL10	–	–	–	–	–	–	–	–	–	↓
CXCL11	–	–	–	–	–	–	–	–	–	–
CXCL12	–	–	–	–	–	–	–	–	–	–
CXCL13	–	–	–	–	–	–	–	–	–	↓
VEGF-A	–	–	–	–	–	–	–	–	–	–
Autoantigen										
α-myosin	–	–	–	–	–	–	–	–	–	–

↑, up-regulate; ↓, down-regulate. TNF, tumor necrosis factor; CCL, CC motif chemokine ligand; CXCL, (C-X-C motif) ligand; VEGF, vascular endothelial growth factor.

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CTLA-4, and a fragment of the Fc portion of human immunoglobulin G (IgG) 1. The mechanism of action of abatacept is to block the interaction between CD80/CD86 on antigen-presenting cells CD28 on T cells (73). For steroid-refractory IRM, the dose of abatacept is usually 500 mg/day (adjusted according to body weight). In current cases of steroid-refractory IRM, the addition of abatacept to second or third-line treatment regimens has resulted in good or acceptable outcomes (25,33,34,41,43,44,51,62). However, there was one case of a fourth-line patient who died after using an abatacept containing an immunosuppressive regimen, which suggests that the etiology of steroid-refractory IRM may change over time, such that activated T cells may predominate in the early stages, while other factors, such as cytokines, may predominate in the later stages (34). Abatacept, in combination with ruxolitinib [a Janus kinase (JAK) inhibitor], may be more suitable for patients with concomitant steroid-refractory IRM and myositis (74); however, the efficacy of this treatment may be limited in patients with concomitant steroid-refractory IRM comorbid with myasthenia gravis (75). *Table 5* lists the contraindications and common adverse effects of abatacept and the other immunosuppressants reviewed in this study. The ATRIUM study (NCT05335928) is a phase 3, investigator-initiated, randomized, double-blind, placebo-controlled trial that is evaluating the use of abatacept in treating IRM (86).

Alemtuzumab

Alemtuzumab is a monoclonal antibody that binds to CD52, a cell surface antigen present on T and B lymphocytes, natural killer cells, monocytes, and macrophages. After binding to the peripheral immune cells, alemtuzumab causes antibody-dependent cellular cytolysis and complement-mediated lysis (87). For steroid-refractory IRM, alemtuzumab is recommended at a single dose of 30 mg in cases in which multiple immunosuppressive agents are ineffective (58). As alemtuzumab rapidly clears a wide range of immune cells, it may also be considered the drug of choice for fulminant steroid-refractory IRM.

ATG

ATG is a polyclonal antibody that depletes T cells, B cells, macrophages, and dendritic cells by inducing apoptosis, complement-mediated or natural killer cell-mediated lysis (88). For steroid-refractory IRM, ATG has been reported to be not enough effective in a few cases, this may be due to the patients receiving a dose of less than 500 mg/day (45,61,65,89). However, even ATG doses of up to 500 mg/day may be ineffective (27), which indicates that ATG may be suitable for cases in which the biopsy tissue only contains T-lymphocytes (67).

Infliximab

Infliximab acts by binding to TNF-α and blocking its binding to the receptor (90). Infliximab is commonly used in ICIs-related colitis (91). For steroid-refractory IRM, infliximab has been reported to be completely effective in a limited number of cases (34,45,49,52,63,67,92). Thus, infliximab is indicated only when TNF-α is elevated and there are no other therapeutic options (93).

IVIG

IVIG is a mixture of immunoglobulins, such as IgM, IgG, IgD, IgA, and IgE, isolated from the blood of healthy donors. IVIG is dose-dependent, such that low doses exert passive immunity, while high doses (e.g., 2 g/kg/day) exert anti-inflammatory effects (94). IVIG, in combination with other immunosuppressive agents, is not completely effective in the treatment of simple steroid-refractory IRM (30,32) and may be more appropriate for patients with combined myositis and myasthenia gravis (31,36,38,39,46). For patients who develop steroid-refractory IRM with concomitant myositis and myasthenia gravis, the use of a combination of immunosuppressive agents and pyridostigmine may be critical for complete recovery (39,42,54,63,64).

Methotrexate

Methotrexate is a folate antagonist that interferes with the synthesis of deoxyribonucleic acid, ribonucleic acid, and protein by inhibiting dihydrofolate reductase and thymidylate synthase (95). There is only one case report of steroid-refractory IRM; however, since methotrexate is used in combination with abatacept and MMF, it is not clear whether methotrexate alone is effective (33). In addition, methotrexate has been reported to cause several types of adverse reactions (*Table 5*) and should only be considered for subsequent lines of therapy in steroid-refractory IRM.

MMF

MMF is the prodrug of mycophenolic acid, which reversibly inhibits inosine monophosphate dehydrogenase, a rate-limiting enzyme of *de novo* purine synthesis that ultimately exerts immunosuppressive effects (96). MMF has been shown to impair T- and B-lymphocyte proliferation, attenuate

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Table 5 Commonly used immunosuppressants: indications, contraindications, and adverse reactions

Drug name	Active ingredients	Indications (FDA)	Contraindications	AE and AESI	Reference
ORENCIA	Abatacept	RA, pJIA, PsA, aGVHD	None	Serious infections, hypersensitivity reactions	(76)
LEMTRADA®	Alemtuzumab	MS	Hypersensitivity; HIV; active infection	Serious infections, infusion reactions, thyroid disorders, immune thrombocytopenia	(77)
ATGAM®	Anti-thymocyte globulin (equine)	RAR, AA	Hypersensitivity	Anaphylaxis, infection, thrombocytopenia, leukopenia, arthralgia, edema, bradycardia, and abnormal renal and liver function tests	(78)
THYMOGLOBULIN®	Anti-thymocyte globulin (rabbit)	RAR	Hypersensitivity; active infection	Urinary tract infection, abdominal pain, hypertension, nausea, shortness of breath, fever, headache, anxiety, chills, increased potassium levels in the blood, and low counts of platelets and white blood cells	(79)
INFLIXIMAB	Infliximab	CD, UC, RA, AS, PsA, PP	Moderate or severe heart failure, hypersensitivity	Serious infections, hypersensitivity, heart failure, hepatotoxicity, cardiovascular and cerebrovascular reactions during and after infusion	(80)
GAMMAGARD LIQUID	Intravenous immunoglobulin	PI, MMN, CIDP	Hypersensitivity, autoantibodies against IgA	Hypersensitivity, renal dysfunction/ failure, thrombosis, transmissible infectious agents	(81)
METHOTREXATE	Methotrexate	ALL, ML, NHL, osteosarcoma, BC, HNSCC, GTN, RA, pJIA, psoriasis	Hypersensitivity, pregnancy	Serious infections, myelosuppression, renal toxicity, hepatotoxicity, neurotoxicity, gastrointestinal toxicity, pulmonary toxicity, dermatologic reactions	(82)
CELLCEPT®	Mycophenolate mofetil	Allogeneic kidney, heart, or liver transplants	Hypersensitivity	Serious infections, blood dyscrasias, gastrointestinal complications	(83)
ACTEMRA®	Tocilizumab	RA, GCA, SSc-ILD, pJIA, SJIA, CRS, COVID-19	Hypersensitivity	Serious infections, hepatotoxicity, gastrointestinal perforations, hypersensitivity	(84)
XELJANZ®	Tofacitinib	RA, PsA, AS, UC, pJIA	None	Serious infections, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, thrombosis, gastrointestinal perforations, hypersensitivity	(85)

FDA, Food and Drug Administration; RA, rheumatoid arthritis; pJIA, polyarticular juvenile idiopathic arthritis; PsA, psoriatic arthritis; aGVHD, acute graft versus host disease; MS, multiple sclerosis; RAR, renal allograft rejection; AA, aplastic anemia; CD, Crohn's disease; UC, ulcerative colitis; AS, ankylosing spondylitis; PP, plaque psoriasis; PI, primary humoral immunodeficiency; MMN, multifocal motor neuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; ALL, acute lymphoblastic leukemia; ML, meningeal leukemia; NHL, non-Hodgkin's lymphoma; BC, breast cancer; HNSCC, head and neck squamous cell carcinoma; GTN, gestational trophoblastic neoplasia; GCA, giant cell arteritis; SSc-ILD, systemic sclerosis-associated interstitial lung disease; SJIA, systemic juvenile idiopathic arthritis; CRS, cytokine release syndrome; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; IgA, immunoglobulin A; AE, adverse event; AESI, adverse event of special interest.

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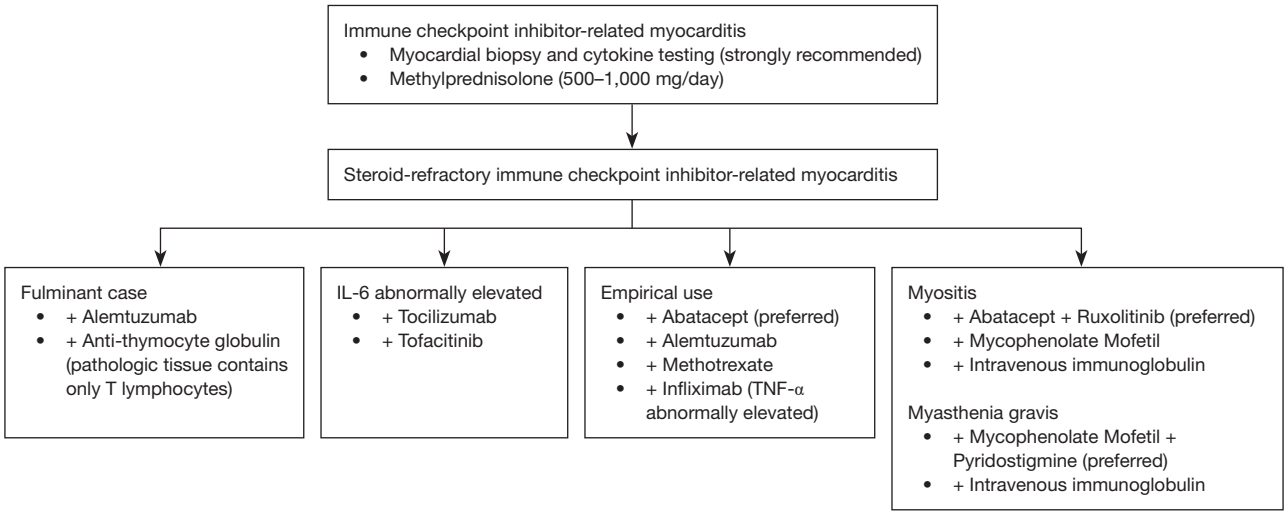

Figure 1 Potential treatment algorithm for steroid-refractory immune checkpoint inhibitor-related myocarditis. IL, interleukin; TNF, tumor necrosis factor.

T-lymphocyte activation, and decrease the production of cytokines, such as IFN-γ, IL-6, and TNF-α (83). For steroid-refractory IRM, the dose of MMF is usually 0.5–1 g every 12 hours (10). Anti-acids, such as proton pump inhibitors (PPIs) or H2 receptor blockers (HRBs), which may be co-administered, are commonly used during glucocorticoid-shock therapy and maintenance therapy; however, the co-administration of PPIs or HRBs may reduce the bioavailability of MMF in the treatment of steroid-refractory IRM. In addition, MMFs may have adverse effects, such as gastrointestinal bleeding requiring hospitalization, ulceration, and perforations, which may limit their use, especially in patients with comorbid gastrointestinal disorders (97). Coupled with the fact that the type of immune cells and cytokines suppressed by MMF is similar to that of glucocorticoids (*Table 2*), MMF may not be suitable as a preferred therapeutic regimen for steroid-refractory IRM for these reasons. MMF is not completely effective in the treatment of isolated steroid-refractory IRM (27,28,30,37,92) and may be more appropriate for patients with myositis, or when used in combination with pyridostigmine in the treatment of patients with myasthenia gravis (26,38,40,60).

Tocilizumab

Tocilizumab is a monoclonal antibody against the IL-6 receptor (98). There have been two case reports of complete recovery from concomitant steroid-refractory IRM and myositis in patients treated with tocilizumab (53,59). Conversely, a recent retrospective study showed that tocilizumab treatment was ineffective in three patients with steroid-refractory IRM who had myositis and/or myasthenia gravis (99). Therefore, tocilizumab may only be appropriate when IL-6 is elevated.

Tofacitinib

Tofacitinib exerts anti-inflammatory effects by inhibiting JAK (100). In a retrospective study, seven patients were treated with initial doses of 500 mg of methylprednisolone pulse therapy and then subsequently treated with tofacitinib + immunoglobulin. Of these seven patients, three improved and four patients died (two died from the progression of myositis, and two died from infection) (9). Thus, tofacitinib may only be indicated in patients with simple steroid-refractory IRM with elevated IL-6 (35,47).

Potential treatment algorithm for steroid-refractory IRM

Based on the results of the relevant literature and the characteristics of the therapeutic agents, we propose a potential treatment approach for steroid-refractory IRM (*Figure 1*).

Strengths and limitations

Strengths

To the best of our knowledge, this is the first narrative review focusing on steroid-refractory IRM after receiving

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500–1,000 mg of methylprednisolone. In this review, based on the current research on the etiology of IRM, we proposed a potential cause of steroid-refractory IRM by combining the mechanism of action of glucocorticoids with the mechanism of glucocorticoid resistance to provide a reference for future research. In addition, based on our new definition of steroid-refractory IRM, we searched for and retrieved all the relevant literature and proposed a potential treatment approach in combination with the mechanism of action of therapeutic agents recommended by the guidelines.

Limitations

First, according to our definition of steroid-refractory IRM, only case reports and case series were available; however, we proposed a therapeutic process based on these case reports and case series rather than on clinical trials and meta-analyses. Second, most of the patients in the current case reports and case series did not undergo endomyocardial biopsy (EMB) or cytokine testing at the time of diagnosis of steroid-refractory IRM. Therefore, we were unable to speculate on the mechanism of steroid-refractory IRM. Moreover, Given that the majority of currently available immune checkpoint inhibitors (ICIs) are used in combination with chemotherapy, tyrosine kinase inhibitors, or other ICIs, there is a risk of misdiagnosis for cases of IRM included in this article that were not subsequently confirmed via an EMB (101). However, we attempted to collect all the information available on steroid-refractory IRM and undertook this narrative review. We hope that it will be helpful for future research on steroid-refractory IRM.

Conclusions

IRM is the irAE with the highest mortality rate, and methylprednisolone pulse therapy is the preferred initial treatment regimen, but the optimal treatment strategy for steroid-refractory IRM remains unclear. Hence, we proposed a potential treatment approach for steroid-refractory IRM. However, more basic studies need to be conducted to reveal the exact mechanism of IRM. Further, more clinical trials are needed to validate the optimal drug selection, dosage selection, chronology of administration, and combination regimen.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Jin Y, Li H, Zhang P, et al. The regulatory approvals of immune checkpoint inhibitors in China and the United States: A cross-national comparison study. Int J Cancer 2023;152:2351-61.
2. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.
3. Dougan M, Luoma AM, Dougan SK, et al. Understanding and treating the inflammatory adverse events of cancer immunotherapy. Cell 2021;184:1575-88.
4. Wang DY, Salem JE, Cohen JV, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. JAMA Oncol 2018;4:1721-8.

© Cardiovascular Diagnosis and Therapy. All rights reserved.

5. Liu M, Cheng X, Ni R, et al. Cardiotoxicity of immune checkpoint inhibitors: A frequency network meta-analysis. Front Immunol 2022;13:1006860.
6. Xu Y, Song Y, Liu X, et al. Prediction of major adverse cardiac events is the first critical task in the management of immune checkpoint inhibitor-associated myocarditis. Cancer Commun (Lond) 2022;42:902-5.
7. Furukawa A, Tamura Y, Taniguchi H, et al. Prospective screening for myocarditis in cancer patients treated with immune checkpoint inhibitors. J Cardiol 2023;81:63-7.
8. Frascaro F, Bianchi N, Sanguettoli F, et al. Immune Checkpoint Inhibitors-Associated Myocarditis: Diagnosis, Treatment and Current Status on Rechallenge. J Clin Med 2023;12:7737.
9. Wang C, Lin J, Wang Y, et al. Case Series of Steroid-Resistant Immune Checkpoint Inhibitor Associated Myocarditis: A Comparative Analysis of Corticosteroid and Tofacitinib Treatment. Front Pharmacol 2021;12:770631.
10. National Comprehensive Cancer Network®. NCCN-guidelines-Management of Immunotherapy-related Toxicities 2024 version1. Available online: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed Feb 28, 2024.
11. Lyon AR, López-Fernández T, Couch LS, 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). Eur Heart J 2022;43:4229-361.
12. Haanen J, Obeid M, Spain L, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2022;33:1217-38.
13. Schneider BJ, Naidoo J, Santomasso BD, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update. J Clin Oncol 2021;39:4073-126.
14. Brahmer JR, Abu-Sbeih H, Ascierto PA, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 2021;9:e002435.
15. Riveiro-Barciela M, Soler MJ, Barreira-Diaz A, et al. Expert Clinical Management of Severe Immune-Related Adverse Events: Results from a Multicenter Survey on Hot Topics for Management. J Clin Med 2022;11:5977.
16. Hu Y, Liu C, Jin S, et al. A case of subclinical immune checkpoint inhibitor-associated myocarditis in non-small cell lung cancer. BMC Pulm Med 2023;23:119.
17. Su L, Liu C, Wu W, et al. Successful Therapy for Myocarditis Concomitant With Complete Heart Block After Pembrolizumab Treatment for Head and Neck Squamous Cell Carcinoma: A Case Report With Literature Review. Front Cardiovasc Med 2022;9:898756.
18. Maetani T, Hamaguchi T, Nishimura T, et al. Durvalumab-associated Late-onset Myocarditis Successfully Treated with Corticosteroid Therapy. Intern Med 2022;61:527-31.
19. Fukasawa Y, Sasaki K, Natsume M, et al. Nivolumab-Induced Myocarditis Concomitant with Myasthenia Gravis. Case Rep Oncol 2017;10:809-12.
20. Luo YB, Tang W, Zeng Q, et al. Case Report: The Neuromusclar Triad of Immune Checkpoint Inhibitors: A Case Report of Myositis, Myocarditis, and Myasthenia Gravis Overlap Following Toripalimab Treatment. Front Cardiovasc Med 2021;8:714460.
21. Zhang L, Zlotoff DA, Awadalla M, et al. Major Adverse Cardiovascular Events and the Timing and Dose of Corticosteroids in Immune Checkpoint Inhibitor-Associated Myocarditis. Circulation 2020;141:2031-4.
22. Hu C, Zhao L, Zhou C, et al. Pacemakers and methylprednisolone pulse therapy in immune-related myocarditis concomitant with complete heart block. Open Med (Wars) 2022;17:2109-16.
23. Ke G, Chen P, Luo J, et al. Plasma exchange plus glucocorticoids in the treatment of immune checkpoint inhibitor-induced myocarditis: A case series and review. Clin Cardiol 2023;46:1481-7.
24. Eslinger C, Walden D, Barry T, et al. Rechallenge With Switching Immune Checkpoint Inhibitors Following Autoimmune Myocarditis in a Patient With Lynch Syndrome. J Natl Compr Canc Netw 2023;21:894-9.
25. Mohammad KO, Fanous H, Vakamudi S, et al. Refractory right ventricular myocarditis induced by immune checkpoint inhibitor despite therapy cessation and immune suppression. Cardiooncology 2023;9:15.
26. Zhong P, Zhang C, Guan H, et al. Myocarditis and myasthenia gravis induced by immune checkpoint inhibitor in a patient with relapsed thymoma: A case report. Clin Case Rep 2023;11:e7039.
27. Baclig NV, Ngo C, Yeh AC, et al. Steroid-Refractory Autoimmune Myocarditis after Pembrolizumab Therapy: Failure of Equine Anti-Thymocyte Globulin to Prevent Heart Failure. J Clin Case Rep 2019;2:1-4.
28. Fukumitsu M, Ariyasu R, Ishiyama M, et al. Myocarditis associated with immune-checkpoint inhibitors diagnosed by cardiac magnetic resonance imaging. Int Cancer Conf J

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2022;12:109-14.
29. Ramayya T, Mitchell JD, Hartupee JC, et al. Delayed Diagnosis and Recovery of Fulminant Immune Checkpoint Inhibitor-Associated Myocarditis on VA-ECMO Support. JACC CardioOncol 2022;4:722-6.
30. Liu S, Ma G, Wang H, et al. Severe cardiotoxicity in 2 patients with thymoma receiving immune checkpoint inhibitor therapy: A case report. Medicine (Baltimore) 2022;101:e31873.
31. Yin B, Xiao J, Wang X, et al. Myocarditis and myositis/myasthenia gravis overlap syndrome induced by immune checkpoint inhibitor followed by esophageal hiatal hernia: A case report and review of the literature. Front Med (Lausanne) 2022;9:950801.
32. Naganuma K, Horita Y, Matsuo K, et al. An Autopsy Case of Late-onset Fulminant Myocarditis Induced by Nivolumab in Gastric Cancer. Intern Med 2022;61:2867-71.
33. Onderko LL, Heinrich R, Gosling K, et al. Myocarditis Following Immune Checkpoint Inhibition With Pembrolizumab: Management in a Context of Steroid Intolerance. CJC Open 2022;4:854-7.
34. Deharo F, Carvelli J, Cautela J, et al. Immune Checkpoint Inhibitor-Induced Myositis/Myocarditis with Myasthenia Gravis-like Misleading Presentation: A Case Series in Intensive Care Unit. J Clin Med 2022;11:5611.
35. Xing Q, Zhang Z, Zhu B, et al. Case Report: Treatment for steroid-refractory immune-related myocarditis with tofacitinib. Front Immunol 2022;13:944013.
36. Lorente-Ros Á, Rajjoub-Al-Mahdi EA, Monteagudo Ruiz JM, et al. Checkpoint Immunotherapy-Induced Myocarditis and Encephalitis Complicated With Complete AV Block: Not All Hope Is Lost. JACC Case Rep 2022;4:1032-6.
37. Osinga TE, Oosting SF, van der Meer P, et al. Immune checkpoint inhibitor-associated myocarditis : Case reports and a review of the literature. Neth Heart J 2022;30:295-301.
38. Liu Z, Fan Y, Guo J, et al. Fulminant myocarditis caused by immune checkpoint inhibitor: a case report and possible treatment inspiration. ESC Heart Fail 2022;9:2020-6.
39. Kee W, Ng KYY, Lee JJX, et al. Myasthenia Gravis and Myocarditis After Administration of Pembrolizumab in a Patient With Metastatic Non-small Cell Lung Cancer and Resected Thymoma. Clin Lung Cancer 2022;23:e293-5.
40. Rhee JY, Torun N, Neilan TG, et al. Consider Myocarditis When Patients Treated with Immune Checkpoint Inhibitors Present with Ocular Symptoms. Oncologist 2022;27:e402-5.
41. Nguyen LS, Bretagne M, Arrondeau J, et al. Reversal of immune-checkpoint inhibitor fulminant myocarditis using personalized-dose-adjusted abatacept and ruxolitinib: proof of concept. J Immunother Cancer 2022;10:e004699.
42. Komatsu M, Hirai M, Kobayashi K, et al. A rare case of nivolumab-related myasthenia gravis and myocarditis in a patient with metastatic gastric cancer. BMC Gastroenterol 2021;21:333.
43. Jespersen MS, Fanø S, Stenør C, et al. A case report of immune checkpoint inhibitor-related steroid-refractory myocarditis and myasthenia gravis-like myositis treated with abatacept and mycophenolate mofetil. Eur Heart J Case Rep 2021;5:ytab342.
44. Kalapurackal Mathai V, Black A, Lovibond S, et al. Use of abatacept in steroid refractory, immune checkpoint-induced myocarditis. Intern Med J 2021;51:1971-2.
45. Barry T, Gallen R, Freeman C, et al. Successful Treatment of Steroid-Refractory Checkpoint Inhibitor Myocarditis with Globulin Derived-Therapy: A Case Report and Literature Review. Am J Med Sci 2021;362:424-32.
46. Sanchez-Sancho P, Selva-O'Callaghan A, Trallero-Araguás E, et al. Myositis and myasteniform syndrome related to pembrolizumab. BMJ Case Rep 2021;14:e241766.
47. Liu Y, Jiang L. Tofacitinib for treatment in immune-mediated myocarditis: The first reported cases. J Oncol Pharm Pract 2020. [Epub ahead of print]. doi: 10.1177/1078155220947141.
48. Yogasundaram H, Alhumaid W, Chen JW, et al. Plasma Exchange for Immune Checkpoint Inhibitor-Induced Myocarditis. CJC Open 2020;3:379-82.
49. Kadokawa Y, Takagi M, Yoshida T, et al. Efficacy and safety of Infliximab for steroid-resistant immune-related adverse events: A retrospective study. Mol Clin Oncol 2021;14:65.
50. Yanase T, Moritoki Y, Kondo H, et al. Myocarditis and myasthenia gravis by combined nivolumab and ipilimumab immunotherapy for renal cell carcinoma: A case report of successful management. Urol Case Rep 2020;34:101508.
51. Liu S, Chan J, Brinc D, et al. Immune Checkpoint Inhibitor-Associated Myocarditis With Persistent Troponin Elevation Despite Abatacept and Prolonged Immunosuppression. JACC CardioOncol 2020;2:800-4.
52. Giancaterino S, Abushamat F, Duran J, et al. Complete heart block and subsequent sudden cardiac death from immune checkpoint inhibitor-associated myocarditis. HeartRhythm Case Rep 2020;6:761-4.
53. Doms J, Prior JO, Peters S, et al. Tocilizumab for

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refractory severe immune checkpoint inhibitor-associated myocarditis. Ann Oncol 2020;31:1273-5.
54. Jeyakumar N, Etchegaray M, Henry J, et al. The Terrible Triad of Checkpoint Inhibition: A Case Report of Myasthenia Gravis, Myocarditis, and Myositis Induced by Cemiplimab in a Patient with Metastatic Cutaneous Squamous Cell Carcinoma. Case Reports Immunol 2020;2020:5126717.
55. Szuchan C, Elson L, Alley E, et al. Checkpoint inhibitor-induced myocarditis and myasthenia gravis in a recurrent/metastatic thymic carcinoma patient: a case report. Eur Heart J Case Rep 2020;4:1-8.
56. Hardy T, Yin M, Chavez JA, et al. Acute fatal myocarditis after a single dose of anti-PD-1 immunotherapy, autopsy findings: a case report. Cardiovasc Pathol 2020;46:107202.
57. Xing Q, Zhang ZW, Lin QH, et al. Myositis-myasthenia gravis overlap syndrome complicated with myasthenia crisis and myocarditis associated with anti-programmed cell death-1 (sintilimab) therapy for lung adenocarcinoma. Ann Transl Med 2020;8:250.
58. Esfahani K, Buhlaiga N, Thébault P, et al. Alemtuzumab for Immune-Related Myocarditis Due to PD-1 Therapy. N Engl J Med 2019;380:2375-6.
59. Wang H, Tian R, Gao P, et al. Tocilizumab for Fulminant Programmed Death 1 Inhibitor-Associated Myocarditis. J Thorac Oncol 2020;15:e31-2.
60. Guo CW, Alexander M, Dib Y, et al. A closer look at immune-mediated myocarditis in the era of combined checkpoint blockade and targeted therapies. Eur J Cancer 2020;124:15-24.
61. Itzhaki Ben Zadok O, Ben-Avraham B, Nohria A, et al. Immune-Checkpoint Inhibitor-Induced Fulminant Myocarditis and Cardiogenic Shock. JACC CardioOncol 2019;1:141-4.
62. Salem JE, Allenbach Y, Vozy A, et al. Abatacept for Severe Immune Checkpoint Inhibitor-Associated Myocarditis. N Engl J Med 2019;380:2377-9.
63. Saibil SD, Bonilla L, Majeed H, et al. Fatal myocarditis and rhabdomyositis in a patient with stage IV melanoma treated with combined ipilimumab and nivolumab. Curr Oncol 2019;26:e418-21.
64. Fazel M, Jedlowski PM. Severe Myositis, Myocarditis, and Myasthenia Gravis with Elevated Anti-Striated Muscle Antibody following Single Dose of Ipilimumab-Nivolumab Therapy in a Patient with Metastatic Melanoma. Case Reports Immunol 2019;2019:2539493.
65. Jain V, Mohebtash M, Rodrigo ME, et al. Autoimmune Myocarditis Caused by Immune Checkpoint Inhibitors Treated With Antithymocyte Globulin. J Immunother 2018;41:332-5.
66. Arangalage D, Delyon J, Lermuzeaux M, et al. Survival After Fulminant Myocarditis Induced by Immune-Checkpoint Inhibitors. Ann Intern Med 2017;167:683-4.
67. Tay RY, Blackley E, McLean C, et al. Successful use of equine anti-thymocyte globulin (ATGAM) for fulminant myocarditis secondary to nivolumab therapy. Br J Cancer 2017;117:921-4.
68. Wilkinson L, Verhoog NJD, Louw A. Disease- and treatment-associated acquired glucocorticoid resistance. Endocr Connect 2018;7:R328-49.
69. Hasan MM, Tory S. Association between glucocorticoid receptor beta and steroid resistance: A systematic review. Immun Inflamm Dis 2024;12:e1137.
70. Gong J, Neilan TG, Zlotoff DA. Mediators and mechanisms of immune checkpoint inhibitor-associated myocarditis: Insights from mouse and human. Immunol Rev 2023;318:70-80.
71. Kalfeist L, Galland L, Ledys F, et al. Impact of Glucocorticoid Use in Oncology in the Immunotherapy Era. Cells 2022;11:770.
72. Sinha A, Bagga A. Pulse steroid therapy. Indian J Pediatr 2008;75:1057-66.
73. Conigliaro P, Triggianese P, Giampà E, et al. Effects of Abatacept on T-Lymphocyte Sub-populations and Immunoglobulins in Patients Affected by Rheumatoid Arthritis. Isr Med Assoc J 2017;19:406-10.
74. Salem JE, Bretagne M, Abbar B, et al. Abatacept/Ruxolitinib and Screening for Concomitant Respiratory Muscle Failure to Mitigate Fatality of Immune-Checkpoint Inhibitor Myocarditis. Cancer Discov 2023;13:1100-15.
75. Menachery SM, Hang Y, Pritchard L, et al. Immune Checkpoint Inhibitor Rechallenge in a Patient With Previous Fulminant Myocarditis. Am J Cardiol 2023;199:33-6.
76. ORENCIA (abatacept) for injection, for intravenous use [Prescribing Information], Bristol-Myers Squibb Company Princeton, New Jersey 08543 USA. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125118s249lbl.pdf. Accessed Feb 26, 2024.
77. LEMTRADA ® (alemtuzumab) injection, for intravenous use [Prescribing Information], Genzyme Corporation Cambridge, MA 02141. A SANOFI COMPANY. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/103948s5192lbl.pdf. Accessed Feb 26, 2024.
78. ATGAM ® (lymphocyte immune globulin, anti-thymocyte globulin [equine]), sterile solution, for intravenous use only

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[Prescribing Information], Pharmacia&Upjohn Company LLC, A subsidiary of Pfizer Inc. New York, NY 10001. Available online: https://www.fda.gov/media/78206/download?attachment. Accessed Feb 26, 2024.
79. THYMOGLOBULIN (Anti-Thymocyte Globulin [Rabbit]) for Intravenous Use [Prescribing Information], Genzyme Corporation, 500 Kendall Street, Cambridge, MA 02142 USA. Available online: https://www.fda.gov/media/74641/download?attachment. Accessed Feb 26, 2024.
80. INFLIXIMAB for injection, for intravenous use [Prescribing Information], Janssen Biotech, Inc. Horsham, PA 19044. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103772s5401lbl.pdf. Accessed Feb 26, 2024.
81. GAMMAGARD LIQUID, Immune Globulin Infusion (Human), 10% Solution, for intravenous and subcutaneous administration [Prescribing Information], Takeda Pharmaceuticals U.S.A., Inc. Lexington, MA 02421. Available online: https://www.fda.gov/media/70812/download?attachment. Accessed Feb 26, 2024.
82. METHOTREXATE injection, for intravenous, intramuscular, subcutaneous, or intrathecal use [Prescribing Information], Hospira, Inc. Lake Forest, IL 60045. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/011719s138lbl.pdf. Accessed Feb 26, 2024.
83. CELLCEPT (mycophenolate mofetil) Capsules, for Oral Use [Prescribing Information], Genentech USA, Inc. A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/050722s050,050723s050,050758s048,050759s055lbl.pdf. Accessed Feb 26, 2024.
84. ACTEMRA ® (tocilizumab) injection, for intravenous or subcutaneous use [Prescribing Information], Genentech USA, Inc. A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125472s049lbl.pdf. Accessed Feb 26, 2024.
85. Xr X. XELJANZ ® (tofacitinib) tablets, for oral use [Prescribing Information], Pfizer Labs, Division of Pfizer Inc, NY, NY 10017. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/203214s028,208246s013,213082s003lbl.pdf. Accessed Feb 26, 2024.
86. Reynolds K, Mooradian M, Zlotoff D, et al. 696 Abatacept for immune checkpoint inhibitor associated myocarditis (ATRIUM): a phase 3, investigator-initiated, randomized, double blind, placebo-controlled trial. In: Regular and Young Investigator Award Abstracts [Internet]. BMJ Publishing Group Ltd.; 2022:A726. Available online: https://jitc.bmj.com/lookup/doi/10.1136/jitc-2022-SITC2022.0696
87. Babij R, Perumal JS. Comparative efficacy of alemtuzumab and established treatment in the management of multiple sclerosis. Neuropsychiatr Dis Treat 2015;11:1221-9.
88. Bosch M, Dhadda M, Hoegh-Petersen M, et al. Immune reconstitution after anti-thymocyte globulin-conditioned hematopoietic cell transplantation. Cytotherapy 2012;14:1258-75.
89. Stein-Merlob AF, Hsu JJ, Colton B, et al. Keeping immune checkpoint inhibitor myocarditis in check: advanced circulatory mechanical support as a bridge to recovery. ESC Heart Fail 2021;8:4301-6.
90. Levin AD, Wildenberg ME, van den Brink GR. Mechanism of Action of Anti-TNF Therapy in Inflammatory Bowel Disease. J Crohns Colitis 2016;10:989-97.
91. Daetwyler E, Wallrabenstein T, König D, et al. Corticosteroid-resistant immune-related adverse events: a systematic review. J Immunother Cancer 2024;12:e007409.
92. Norwood TG, Lenneman CA, Westbrook BC, et al. Evolution of Immune Checkpoint Blockade-Induced Myocarditis Over 2 Years. JACC Case Rep 2020;2:203-9.
93. Rossi VA, Gawinecka J, Dimitriou F, et al. Value of troponin T versus I in the diagnosis of immune checkpoint inhibitor-related myocarditis and myositis: rechallenge?. ESC Heart Fail 2023;10:2680-5.
94. Arumugham VB, Rayi A. Intravenous Immunoglobulin (IVIG). In: StatPearls. Treasure Island (FL): StatPearls Publishing; July 3, 2023.
95. Zhao Z, Hua Z, Luo X, et al. Application and pharmacological mechanism of methotrexate in rheumatoid arthritis. Biomed Pharmacother 2022;150:113074.
96. Bhat R, Tonutti A, Timilsina S, et al. Perspectives on Mycophenolate Mofetil in the Management of Autoimmunity. Clin Rev Allergy Immunol 2023;65:86-100.
97. Alex G, Shanoj KC, Varghese DR, et al. Co prescription of anti-acid therapy reduces the bioavailability of mycophenolate mofetil in systemic sclerosis patients: A crossover trial. Semin Arthritis Rheum 2023;63:152270.
98. Scott LJ. Tocilizumab: A Review in Rheumatoid Arthritis. Drugs 2017;77:1865-79.
99. Fa'ak F, Buni M, Falohun A, et al. Selective immune suppression using interleukin-6 receptor inhibitors for management of immune-related adverse events. J

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Immunother Cancer 2023;11:e006814.
100. Dhillon S. Tofacitinib: A Review in Rheumatoid Arthritis. Drugs 2017;77:1987-2001.
101. Mohamed A, Salman B, Shaikh AJ. Evaluating the clinical benefit of pembrolizumab as a first-line agent in advanced solid tumors: A comprehensive review. J Oncol Pharm Pract 2024. [Epub ahead of print]. doi: 10.1177/10781552241252100.

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