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USE OF INFLIXIMAB IN THE TREATMENT OF IMMUNE CHECKPOINT INHIBITORS-RELATED MYOCARDITIS: A SYSTEMATIC REVIEW OF CASE REPORTS

KHAW CHIA PHING[1], SHUBASHINI GNANASAN[2] AND BALAMURUGAN TANGIISURAN[1]*
[1]School of Pharmaceutical Sciences, Universiti Sains Malaysia, Pulau Pinang, Malaysia
[2]Faculty of Pharmacy, Universiti Teknologi MARA, Puncak Alam Campus, Selangor, Malaysia

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ABSTRACT

Immune-mediated myocarditis is uncommon, progresses rapidly and has high mortality rate. Infliximab has been used in practice, particularly in steroid refractory cases, but evidence supporting the use is still lacking. This review aims to provide an overview of infliximab use in managing immune-related myocarditis. A systematic search was conducted using the PubMed and Cochrane Library databases as well as manual searching of bibliographies, from inception to 1 October 2021. Eligible studies were selected by the inclusion criteria. All the included studies were assessed for methodological quality using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports. There were 13 articles with total 14 reported cases of immune-related myocarditis treated with infliximab. Most patients developed myocarditis with high severity grade, concurrent immune-related adverse events (irAEs), particularly neuromuscular irAEs and multiple potentially fatal complications. Most patients received single dose of infliximab, whereas few received multiple doses. Four patients improved clinically or biochemically, but 10 patients did not improve or deteriorated clinically with the addition of infliximab. Half of the reported cases did not survive due to myocarditis and its complications. Conflicting results were observed when infliximab was used in patients with heart failure and higher dose did not appear to be beneficial in these patients. Concomitant irAEs, high severity grade and occurrence of potentially fatal complications indicate the need to escalate the treatment by using additional immunosuppressive agents such as infliximab. However, there is no standardisation on the infliximab treatment regimen, outcomes have been inconsistent and safety data is limited.

Keywords: Infliximab, Cardiotoxicity, Myocarditis, Immune checkpoint inhibitors, Immunotherapy

*Corresponding author: bala@usm.my

INTRODUCTION

The use of immune checkpoint inhibitors (ICIs) is one of the most significant breakthroughs in cancer treatment over the last decade, and it has dramatically changed the therapeutic landscape for various types of advanced cancers. ICI therapy has been shown to improve cancer patients' clinical outcomes and is generally considered more tolerable than chemotherapy. However, ICIs have been associated with immune-related adverse events (irAEs), which can affect a wide spectrum of organ systems but are most frequently seen in the skin, gastrointestinal tract, lungs and endocrine system (Postow, Sidlow and Hellmann 2018; Raschi *et al*. 2020). Most of these irAEs are generally mild and manageable. However, some are rare but severe, including cardiac, neurological and musculoskeletal adverse effects (Postow, Sidlow and Hellmann 2018).

Myocarditis is one of the rare but potentially fatal irAEs associated with ICI treatment (Wang *et al.* 2018). The incidence rates ranged from < 0.1% in pharmaceutical safety databases (Johnson *et al*. 2016) to 1.14% in a multicentre study (Mahmood *et al.* 2018), but the mortality rate was reported to be as high as 50%. From 2008 to 2018, the World Health Organization (WHO)'s global database of individual case safety reports (VigiBase) revealed an increase in immune-associated myocarditis cases, with 107 reported cases between 2017 and 2018, compared to 15 reported cases between 2013 and 2016 (Salem *et al.* 2018). This was likely related to the increased use of immune checkpoint inhibitors and increased recognition of irAEs.

Due to the high mortality, rapid deterioration and increased reporting of immune-related myocarditis, it is crucial to understand its treatment modalities in order to prevent morbidity and mortality. However, prospective studies specifically investigating the treatment of immune-mediated myocarditis are limited due to the rarity of this adverse effect. Most data are available in the form of case reports or case series, which are devoid of scientific and systematic investigation. Currently, several guidelines (Haanen *et al.* 2017; Brahmer *et al.* 2018; Brahmer *et al.* 2021; Thompson *et al.* 2022) are available for managing this irAE. However, specific and detailed information of the treatment regimen is still lacking, particularly in steroid-refractory cases and the use of second immunosuppressive therapy such as infliximab. Even though infliximab has been used in steroid-refractory patients (Cautela *et al.* 2020; Dearden *et al.* 2021; Lipe *et al.* 2021; Zhang *et al.* 2021), the evidence supporting its use is still limited.

The purpose of this study is to review reported cases in which infliximab was used for the management of immune-related myocarditis, with the aim of providing useful information on the clinical characteristics of patients who require and benefit from the therapy, as well as the treatment regime, clinical outcomes and safety concerns associated with its use.

METHODS

This study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach (Page *et al.* 2021). The study selection process is summarised and illustrated in Figure 1.

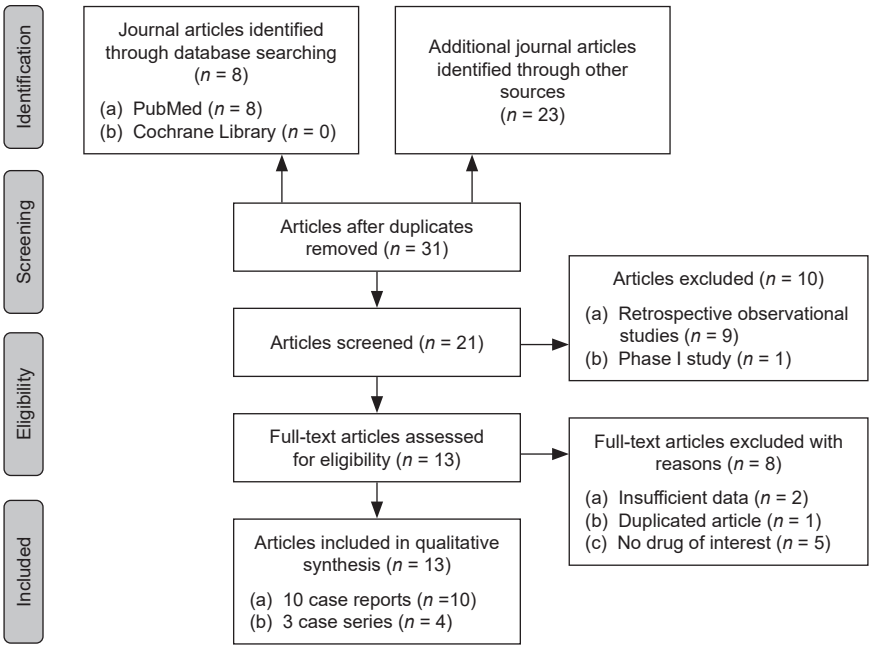

Figure 1: PRISMA flowchart of the study selection process.

Search Strategy

A systematic electronic literature search was conducted using the PubMed and Cochrane Library databases to identify published studies reporting the use of infliximab in the treatment of immune checkpoint inhibitor-related myocarditis from inception to 1 October 2021. Three search concepts were used to identify studies: infliximab, immune-related myocarditis and immune checkpoint inhibitors. The language of published literature was not restricted to English when searching in the electronic databases. The search terms used are listed in Appendix 1. Additional potentially eligible publications were identified by screening the bibliographies of selected articles and relevant reviews. If the full text was unavailable, extra effort was made to contact the authors.

Study Selection

The titles and abstracts of the retrieved studies were reviewed and examined for initial inclusion by the first reviewer (CP). Further examination of the full texts was conducted to ensure the studies met the inclusion criteria. The second and third reviewer (BT and SG) performed cross-checking. All the relevant case reports and case series were selected.

Studies were required to meet the following inclusion criteria to be considered eligible. First, research with human subjects; second, data of patients' demographic data, clinical characteristics, treatment and outcome were available; third, patients received immune checkpoint inhibitor(s); forth, immune-related myocarditis was reported as an adverse event and fifth, infliximab was used to treat immune-related myocarditis.

Contrarily, studies that fulfilled the specified exclusion criteria, including animal experimental research, cohort studies, case-control studies, cross-sectional studies, randomised controlled trials, post-marketing surveillance studies, republished articles, reviews, editorials, commentaries, presentations of ongoing trials, as well as publications lacking sufficient data of interest, such as demographic characteristics, clinical descriptions, treatment and outcome, were excluded.

In the event of duplication, ambiguity or publications reporting on the same case, the most recent and comprehensive publication was included in the analysis. All disagreements were resolved by discussion and consensus.

Quality Assessment

The methodological quality of publications fulfilling inclusion criteria was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports (Moola *et al.* 2020) (Appendix 2). Ten case reports and four individual cases from three case series were included in the assessment. Each case was evaluated using the eight items in the instrument, with responses of yes, no, unclear or not applicable. The assessment was performed by the first reviewer (CP) and cross-checked by the second and third reviewers (BT and SG). Cases that met most of the criteria in the checklist were included (Appendix 3). All disagreements were resolved through consensus.

Data Extraction

One of the reviewers (CP) extracted data from the study on patient demographics, clinical descriptions of ICI-associated myocarditis, investigative findings, treatment and outcomes. The second and third reviewers (BT and SG) verified the accuracy of the extracted data. All necessary data for the included studies were extracted from the main texts and supplementary documents and tabulated in a predefined data extraction form. All disagreements were resolved through discussion.

RESULTS

Demographic characteristics, clinical descriptions, treatment and clinical outcome of the included case reports (Johnson *et al.* 2016; Tay *et al.* 2017; Frigeri *et al.* 2018; Martinez-Calle *et al.* 2018; Agrawal *et al.* 2019; Gallegos *et al.* 2019; Padegimas *et al.* 2019; Saibil *et al.* 2019; Shah *et al.* 2019; Zlotoff *et al.* 2019; Fuentes-Antrás *et al.* 2020; Giancaterino *et al.* 2020; Portolés Hernández *et al.* 2021) are summarised and tabulated in Tables 1, 2 and 3.

Table 1: Demographic characteristics and clinical descriptions of the 14 reported cases of ICI-related myocarditis treated with infliximab.

Study	Age/ sex	Malignancy	ICI	Onset		Underlying medical conditions
				No. doses	Days (after initiation)	
Agrawal *et al*. (2019) (case 5)	67/M	Melanoma	NIV	3	NR	Hx of CAD with CABG, PAD with stenting in both legs, HTN and DM
Frigeri *et al*. (2018)	76/F	Lung	NIV	7	NR	No hx of CVD
Fuentes-Antrás *et al*. (2020)	75/M	Lung	Pembrolizumab	1	21	No hx of autoimmune disorders
Gallegos *et al*. (2019)	47/F	Melanoma	NIV	NR	120	Hx of carotid artery dissection; 1 cycle of IPI+ NIV 1 year ago; asymptomatic SVT & dyspnoea 1 month ago
Giancaterino *et al*. (2020)	88/M	Melanoma	NIV	1	22	NR
Portolés Hernández *et al*. (2021)	48/F	Thymoma	Pembrolizumab	1	10	No history of previous autoimmune/CV disease
Johnson *et al*. (2016) (case 2)	63/M	Melanoma	IPI + NIV	1	15	HTN (No other cardiac risk factors, no history of statin use, radiation, or cardiac metastases)
Martinez-Calle *et al*. (2018)	67/F	Multiple myeloma	Pembrolizumab	1	14	Hx of localised bilateral breast carcinoma; no prior CV history; presence of baseline anti-Tn and -T antibodies
Padegimas *et al*. (2019) (case 1)	53/F	Ovarian	Pembrolizumab.	1	4	NR
Padegimas *et al*. (2019) (case 2)	62/F	Renal	NIV	NR	35	NR
Saibil *et al*. (2019)	67/M	Melanoma	IPI + NIV	1	13	Dyslipidemia; HTN
Shah *et al*. (2019) (case1)	73/M	Urothelial Carcinoma	IPI + NIV	2	NR	NR
Tay et al. (*2017)*	64/F	Glioblastoma	NIV	2	36	No history of autoimmune or cardiac disease
Zlotoff *et al*. (2019)	88/M	Melanoma	Pembrolizumab	NR	NR	NR

Notes: CABG = Coronary artery bypass graft; CAD = Coronary artery disease; CV = Cardiovascular; CVD = Cardiovascular disease; DM = Diabetes Mellitus; F = Female; HTN = Hypertension; Hx = History; ICI = Immune checkpoint inhibitor; IPI = Ipilimumab; M = Male; NIV = Nivolumab; NR = Not reported; PAD = Peripheral arterial disease; SVT = Supraventricular tachycardia; Tn = Troponin

Table 2: Clinical descriptions of the 14 reported cases of ICI-related myocarditis treated with infliximab.

Study	Clinical presentation	Other IrAEs	Findings	Grade of myocarditis	Complication
Agrawal *et al.* (2019) (case 5)	Visit 1: Left-sided chest pain, Palpitations	Neuritis (after 4 months)	Elevated Tn CK-MB and myoglobin: (-) ECG: new lateral ST segment depressions. Later developed new onset atrial fibrillation/atypical flutter with a rapid ventricular response Echocardiogram: mild bi-ventricular dilatation with reduced right ventricular systolic function, bi-atrial dilatation, EF 55% Coronary angiogram (-) Cardiac MRI: elevated regional T2 ratio and early gadolinium enhancement ratio suggestive of myocardial oedema confirmed myocarditis	G3	Arrhythmia Heart failure/ reduced EF
	Visit 2 (follow-up): Recurrent chest pain		Tn: Elevated Echocardiogram: EF 55%–60% Cardiac MRI: lack of myocardial oedema, EF reduced from 55% to 31%	G3	Arrhythmia Heart failure/ reduced EF
Frigeri *et al.* (2018)	Signs of heart failure, including bibasilar pulmonary rales and lower limb oedema	Nil	Elevated NT-proBNP and Tn Echocardiogram: severely reduced EF 15% and multiple apical thrombi Coronary angiograpm (-) Viral antibody titers (-) Cardiac MRI: compatible with myocarditis	G4	Heart failure/ reduced EF Cardiogenic shock

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Table 2: (*continued*)

Study	Clinical presentation	Other IrAEs	Findings	Grade of myocarditis	Complication
Fuentes-Antrás *et al.* (2020)	Visit 1: Severe asthenia, myalgia, profuse sweating & palpitations.	Myositis, MG, thyroiditis, hepatitis, pneumonitis	Blood tests: hyperthyroidism thyroid scintigraphy: compatible with thyroiditis	–	–
	Visit 2 (1 week later): Symptoms were aggravated with ocular symptoms, bulbar symptoms and proximal muscular weakness		Elevated CK, CK-MB, Tn-I ECG: complete AV block AChR-Ab (+), Anti-striated muscle Ab (+), anti-SRP, Ro52, PM/Scl100 Ab: (+) Elevated AST & ALT (grade 4 hepatotoxicity) Elevated free T4 Postmortem: multiorgan damage (necrotising myocarditis, lymphocytic thyroiditis with follicular destruction and thyroid atrophy, necrotising myopathy and bilateral focal pneumonitis)	G4	Conduction abnormalities Respiratory failure Multiorgan failure
Gallegos *et al.* (2019)	Dyspnoea, tachypnoeic, hypotensive, tachycardic, pulmonary oedema, jugular venous distension and lower extremity oedema	–	Elevated NT-proBNP Tn and CK (-) ECG: regular, narrow-complex rhythm, concerning for atrial tachycardia and without ischaemic changes Echocardiogram: global biventricular failure, EF 26%. severely dilated left ventricle, and a trivial pericardial effusion CMR: suggestive of myocarditis Autopsy: evidence of moderate lymphocytic myocarditis. No significant coronary artery disease	G4	Arrhythmia Heart failure/ reduced EF Cardiogenic shock

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Table 2: (*continued*)

Study	Clinical presentation	Other IrAEs	Findings	Grade of myocarditis	Complication
Giancate-rino *et al.* (2019)	Generalised weakness	Myositis (suspected)	Elevated Tn-T, CK-MB and CK ECG: initially normal, later progressed to complete heart block Echocardiogram (-) Telemetry: intermittent complete heart block	G4	Arrhythmia Conduction abnormalities Cardiac arrest
Portolés Hernández *et al.* (2021)	Visit 1: Progressive shortness of breath	MG	Mildly increased Tn ECG and echocardiogram: (-) Chest radiography: severe right pleural effusion	G2	
	Visit 2 (3 days later): Recurrent dyspnea, progressive bilateral ptosis, blurred vision, dysphagia		Elevated NT-proBNP, Tn, CRP, CK ECG: complete AV block Chest radiography: reappearance of pleural effusion Echocardiogram: new-onset mildly depressed LVEF 45% to 50%. Later developed biventricular dysfunction and LVEF progressively reduce to 10% Coronary angiogram (-) Endomyocardial biopsy: acute lymphocytic myocarditis AChR-Ab (+); Mildly elevated transaminase	G4	Conduction abnormalities Heart failure/ reduced EF Cardiogenic shock Respiratory failure
Johnson *et al.* (2016) (case 2)	Fatigue and myalgia	Myositis (with rhabdomyolysis)	Elevated Tn- I, CK-MB and CK ECG: ST-segment depression, conduction delay Serial Echocardiogram: low-normal left ventricular systolic function, EF 50% Pathology: lymphocytic myocarditis and myositis	G4	Conduction abnormalities Cardiac arrest

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Table 2: (*continued*)

Study	Clinical presentation	Other IrAEs	Findings	Grade of myocarditis	Complication
Martinez-Calle *et al.* 2018	Malaise, dyspnoea on minimal exertion	Myositis	Elevated Tn, CK & CK-MB	G4	Arrhythmia
			ECG: newly appearing anterolateral ST-segment elevation, and RBBB. Later showed flares of VT and complete AV-block		Conduction abnormalities
			Echocardiogram: depressed ventricular contractility without focal hypokinesis		Heart failure/ reduced EF
			Coronariography: rule out ischemic cardiomyopathy		Multiorgan failure
			Elevated liver enzymes (AST, ALT, ALP and GGT)		
			Autopsy: necrotising immune myositis and myocarditis		
Padegimas *et al.* (2019) (case 1)	Visit 1: Neurological symptoms	–	Elevated Tn-T ECG: (-) Echocardiogram: EF 50%	G2	–
	Visit 2 (1 month later, during steroid taper): Exertional chest pressure		Elevated Tn-T, Nt-BNP and transaminase (mild)	G3	Arrhythmia
			ECG: accelerated idioventricular rhythm (AIVR) alternating with NSR		Heart failure/ reduced EF
			Later showed irregular ventricular tachycardia with occasional fusion and capture beats		
			Echocardiogram: EF 35% and right ventricular dysfunction		
			Coronary angiogram (-)		
			CMR: patchy delayed gadolinium enhancement		

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Table 2: (*continued*)

Study	Clinical presentation	Other IrAEs	Findings	Grade of myocarditis	Complication
Padegimas *et al.* (2019) (case 2)	Sudden dyspnoea on exertion and chest tightness	–	Elevated Tn-T, AST, ALT and lactate ECG: diffuse ST elevations Echocardiogram: severe right ventricular dysfunction, EF 25% and a small pericardial effusion Coronary angiogram: (-) Right heart catheterisation haemodynamics: cardiogenic shock EMB: nondiagnostic and showed fibrosis and absent myocardium CMR: patchy delayed gadolinium enhancement	G4	Arrhythmia Conduction abnormalities Heart failure/ reduced EF Cardiogenic shock
Saibil *et al.* (2019)	Fatigue, weakness, dyspnoea, feeling pre-syncopal, bradycardia	Myositis (rhabdo-myositis)	Elevated Tn-I and CK Elevated interleukin 6; other inflammatory cytokines (-) ECG: third-degree block Echocardiogram: (-); coronary angiogram: (-) Histological examination of myocardium and skeletal muscle: cardiomyolysis and rhabdomyolysis	G4	Conduction abnormalities Heart failure/ reduced EF Respiratory failure Multiorgan failure
Shah *et al.* (2019) (case 1)	Initially mild jaw and throat discomfort when swallowing, followed by significant generalised weakness and myalgia, with bilateral ptosis and extraocular muscle weakness	Myositis (with rhabdo-myolysis)	Elevated CK, CK-MB and Tn-I myoglobinuria ECG: first degree AV block and an abnormal ST–T wave Echocardiogram: (-) AChR-Ab (-), anti-striated muscle-Ab (+) EMG: moderate-to-severe muscle injury, with no features compatible with myasthenia gravis or peripheral neuropathy Elevated AST and ALT	G4	Conduction abnormalities Respiratory failure

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Table 2: (*continued*)

Study	Clinical presentation	Other IrAEs	Findings	Grade of myocarditis	Complication
Tay *et al.* *(2017)*	Diplopia, diffuse myalgia and proximal weakness	Myositis	Elevated CK and Tn-I ECG: Ventricular bigeminy and frequent ectopy Echocardiogram: moderate systolic dysfunction; EF 37% Cardiac biopsy: multifocal lymphocytic and histiocytic infiltrates associated with focal areas of myocyte necrosis Coronary angiogram (-) EMG: excluded neuromuscular junction pathology	G4	Arrhythmia Conduction abnormalities Heart failure/ reduced EF
Zlotoff *et al.* (2019)	Fatigue	Myositis (suspected)	Elevated Tn-T, CK and CK-MB ECG (-) Echocardiogram (-) CMR: no evidence of myocarditis CMB: consistent with ICI myocarditis	G2	–

Notes: (-) = Normal; (+) = Positive; Ab = Antibody; AChR-Ab = Acetylcholine receptor antibody; AIVR = Accelerated idioventricular rhythm; ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; AV = Atrioventricular; BNP = brain natriuretic peptide; CK = Creatine kinase; CK-MB = Creatine kinase-MB; CMR = Cardiovascular magnetic resonance imaging; CRP = C-reactive protein; ECG = Electrocardiogram; EF = Ejection fraction; EMB = Endomyocardial biopsy; GGT = Gamma-glutamyl transferase; irAEs = Immune-related adverse events; LVEF = Left ventricular ejection fraction; MG = Myasthenia gravis; MRI = Magnetic resonance imaging; NT-proBNP = N-terminal pro-brain natriuretic peptide; PM/Scl = Polymyositis and scleroderma; RBBB = Right bundle branch **block;** RVEF = Right ventricular ejection fraction; SRP = signal recognition particle; Tn = Troponin; VT = Ventricular tachycardia

Table 3: Treatment and outcome of the 14 reported cases of ICI-related myocarditis treated with infliximab.

Study	Steroid		Infliximab				Other IST	Outcome
	Regimen	Response	Indication	Dose	Response	Timing after steroid		
Agrawal *et al.* (2019) (case 5)	Visit 1: IV MP 1 g × 3 days, then PO prednisone 80 mg bd for 5 days then tapering	Clinical improvement	--	--	–	–	–	Resolved and discharged
	Visit 2 (follow-up): –	–	Recurrent myocarditis	2 doses	significant clinical and biochemical improvement Tn returned to baseline clinical symptoms improved significantly	NR (follow-up visit)	–	Survived
Frigeri *et al.* (2018)	IV MP 5 mg/kg/d	Worsening HF with increased NT-proBNP and reduced EF	Steroid refractory	3 doses (5 mg/kg)	clinical and biological improvement (reduction in NT-proBNP level & improvemnt of EF) (ECMO, IABP, and inotropic support were weaned on days 12, 12, and 14)	2 days	PLEX IVIG (1g/kg)	Survived

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Table 3: (*continued*)

Study	Steroid		Infliximab				Other IST	Outcome
	Regimen	Response	Indication	Dose	Response	Timing after steroid		
Fuentes-Antra´s *et al.* (2020)	Visit 1: – Visit 2 (1 week later): a) High-dose IV dexamethasone 4 mg 6 h (suspected autoimmune thyrotoxicosis and hepatitis) b) escalated to IV MP 1 g daily for 5 days (suspected MG and myositis)	– a) Rapid decline of respiratory function and psychomotor agitation Improved cardiac biomarkers and transaminases b) Progressive impairment of ventilatory mechanics led to global respiratory insufficiency Improved cardiac biomarkers and transaminases	– Steroid refractory	– 1 dose (5 mg/kg)	– NR	– 5 days	– IVIG	Death (mutiorgan failure; 7 days after admission)
Gallegos *et al.* (2019)	IV MP 500 mg bd for 5 days	Developed cardiogenic shock refractory to inotropic support	Concurrent with steroid	2 doses (10 mg/kg/day for 2 days)	Developed cardiogenic shock refractory to inotropic support (declined advanced haemodynamic support) Progressed to severe biventricular dysfunction (LVEF 16%; and RVEF 12%)	Concurrent	–	Death (due to cardiogenic shock; 1 week after admission)

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Table 3: (*continued*)

Study	Steroid		Infliximab				Other IST	Outcome
	Regimen	Response	Indication	Dose	Response	Timing after steroid		
Giancaterino *et al.* (2019)	PO prednisone 40 mg daily Escalated to IV MP 125 mg/day for 2 days then increased to IV MP 1 g/day	Progressed to complete heart block CK and CK-MB reduced but Tn increased	Steroid refractory	1 dose (5 mg/kg)	Lack of improvement	9 days	–	Death (due to VF followed by asystole; 15 days after admission)
Portolés Hernández *et al.* (2021)	Visit 1: – Visit 2 (3 days later): IV MP 2 mg/kg, escalated to 1 g daily for 5 days, and subsequently continued with previous dose (2mg/kg)	AV block persisted and both cardiac biomarkers (Tn) and CRP increased	Steroid refracttory	1 dose (5 mg/kg)	Conduction disturbances and clinical status worsened (NT-proBNP increased) Developed biventricular failure along with signs and symptoms of congestive heart failure, LVEF decreased to 25%–30%	– NR	– ATG × 2 doses	Death (cardiogenic shock, respiratory failure; 10 days after admission)
Johnson *et al.* (2016) (case 2)	High dose IV MP 1 g/kg daily for 4 days	NR	NR	1 dose (5 mg/kg)	Complete heart block and cardiac arrest developed	NR	–	Death (due to cardiac arrest)
Martinez-Calle *et al.* (2018)	MP 1.5 mg/kg	Cardiac function progressively deteriorated (developed ventricular tachycardia and complete AV-block; LVEF dropped < 30%, leading to renal failure)	Steroid refractory	1 dose (5 mg/kg)	No immediate response was observed Progressed to multiorgan failure	2 days	–	Death (multiorgan failure; 10 days after admission)

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Table 3: (*continued*)

Study	Steroid		Infliximab				Other IST	Outcome
	Regimen	Response	Indication	Dose	Response	Timing after steroid		
Padegimas *et al.* (2019) (case 1)	Visit 1: PO Prednisone 50 mg then tapering down (for neurological symptoms) Visit 2 (1 month later, during steroid taper): a) Prednisone 1 mg/kg b) Later escalate to MP 1 g for 3 days then taper down	Developed chest discomfort during steroid taper AIVR and VT continued b) Arrhythmia improved but recurred upon steroid taper. EF normalised but Tn still elevated	– Steroid refractory	– 1 dose (5 mg/kg)	– Arrhythmias terminated ECG normalised 2 weeks after IFX Tn normalised after 9 months	– NR	– –	Survived
Padegimas *et al.* (2019) (case 2)	IV MP 1mg/kg Then escalate to IV MP 2g od for 3 days	Developed episodic VT and CHB	Steroid refractory	1 dose (5 mg/kg)	Conduction block resolved (ECG normalised 8 days post-IFX) Improved EF 55% 17 days post-IFX Recovered from cardiogenic shock	–	–	Death (due to fatal bacteremia and PE; 2 months later)
Saibil *et al.* (2019)	MP 200 mg on day 1, then 1 g daily for 3 days	Initially stabilised but developed increased respiratory distress and hypotension progressing to hypercapnic respiratory failure	Steroid refractory	1 dose (5 mg/kg)	Condition worsened, requiring dialysis for acute kidney injury and progressed to multi-organ failure	3 days	IVIG × 2 doses	Death (due to multi-organ failure in the context of rhabdomyositis and myocarditis; 18 days after admission)

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Table 3: (*continued*)

Study	Steroid		Infliximab				Other IST	Outcome
	Regimen	Response	Indication	Dose	Response	Timing after steroid		
Shah *et al.* (2019) (case1)	IV MP 1 mg/kg bd	Mild response and deteriotared (developed respiratory failure)	Steroid refractory	1 dose	Lack of improvement (Muscle strength improved but underwent tracheostomy)	NR	PLEX × 12 rounds IVIG	Death (due to cancer progression)
Tay *et al.* (2017)	IV MP 500 mg daily for 3 days then tapering to oral prednisolone 100 mg daily *During tx with MMF, Prednisolone 100 mg was weaned by 5 mg every week	Developed malignant arrhythmias refractory to high-dose corticosteroids	Steroid refractory	1 dose (5 mg/kg)	Clinical condition acutely deteriorated (Episodes of ventricular tachycardia and haemo-dynamic compromise) Diplopia and proximal muscle weakness markedly improved	1 day	ATG (500 mg on day 1, titrating by 250 mg increment to daily CD2/3 levels for total 5 days) MMF (1 g bd for 4 weeks then slowly weaned over a 12 week)	Survived
Zlotoff *et al.* (2019)	IV MP 1g daily × 5 days then PO prednisone 60 mg od IV MP 250 mg after 2nd dose of IFX, then PO prednisone 60 mg od	Tn increased after pulse steroid	Steroid refractory	2 doses (5 mg/kg)	Lack of improvement (Tn continued to rise after 2 doses)	5 days	MMF (750 mg bd, later escalate to 1g bd) IVIG (0.4 g/kg × 2 doses)	Survived

Notes: ATG = anti-thymocyte globulin; AV = atrioventricular; ECG = electrocardiogram; EF = ejection fraction; IFX = infliximab; IST = immunesuppresive therapy; IV = intravenous; IVIG = intravenous immune globulin; LVEF = left ventricular ejection fraction; MG = myasthenia gravis; MMF = mycophenolate mofetil; MP = methylprednisolone; NR = not reported; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAD = peripheral arterial disease; PE = pulmonary embolism; PLEX = plasma exchange; PO = oral; RVEF = right ventricular ejection fraction; Tn = troponin.

Demographic and Clinical Characteristics

Males and females were equally represented in the 14 studied cases. The mean age of the patients was 67 years old, ranging from 47 years old to 88 years old. Nearly half of them (six patients, 42.9%) had melanoma, two had lung cancer and others had ovarian cancer, renal cancer, urothelial cancer, multiple myeloma, glioblastoma and thymoma, with one respectively. Of these 14 patients, 9 patients had underlying medical conditions. Four patients were reported to have a history of cardiovascular diseases, two denied any history of cardiovascular diseases, one without prior autoimmune disorders, and the remaining two patients denied both histories of cardiovascular diseases and autoimmune disorders.

Most of the patients (11 out of 14) were treated with single immune checkpoint inhibitor, whereas three patients received a combination of nivolumab and ipilimumab. Of these 11 patients, 6 patients (54.5%) received single-agent of nivolumab and 5 patients (45.5%) received pembrolizumab. In most of the patients, the onset of the symptoms occurred early, namely after 1–3 cycles following initiation of ICI therapy. Only two patients reported by Gallegos *et al.* (2019) and Frigeri *et al.* (2018) presented the symptoms after 120 days and seven cycles of therapy, respectively.

As shown in Table 2, clinical presentations of the patients were heterogeneous, and the severity ranged from mild such as fatigue, to severe or life-threatening signs and symptoms. Most of the patients showed symptoms consistent with myocarditis, such as dyspnoea, chest pain and palpitation, whereas some patients presented with neuromuscular symptoms predominantly, for instances, myalgia, ptosis and diplopia. Two patients reported non-specific symptoms such as fatigue and generalised weakness. All patients had troponin elevation upon presentation except for the patient reported by Gallegos *et al.* (2019). Nine of fourteen case reports described the occurrence of the concomitant neuromuscular irAEs, i.e. myositis and/or myasthenia gravis. One patient was reported to develop neuritis four months after recovery from myocarditis (Agrawal *et al*. 2019).

Of 14 patients, 11 patients were categorised as grade 4 myocarditis according to the grading of the American Society of Clinical Oncology (ASCO) practice guidelines (Brahmer *et al.* 2018). Only three patients were considered as mild to moderate in severity, with two patients had grade 3 myocarditis and one patient exhibited grade 2 clinical features. Several potentially fatal complications such as arrhythmia, conduction abnormalities, heart failure, respiratory failure and multiple organ failure were reported. Most of the patients developed at least two of these complications, seven of them developed arrhythmia, nine had conduction disorders, nine showed symptoms of heart failure or reduced ejection fraction, four had cardiogenic shock, four developed respiratory failure and three succumbed to multiorgan failure. The complication of respiratory failure observed in the patients was associated with the concomitant immune-related myositis and myasthenia gravis.

Treatment

Steroid was used as first-line therapy in all 14 patients, with variable initial dosing, and the dose was tapered according to clinical response. In most of the patients (11 out of 14), infliximab was given as add-on therapy due to steroid refractory myocarditis and other concomitant non-cardiac immune-related adverse events. One patient was given infliximab for the indication of recurrent myocarditis, whereas another patient received infliximab with concomitant initiation of steroid. No clear indication of infliximab was documented in one reported case following steroid administration.

Timing of starting infliximab ranged from 0 day (concurrently with steroid) to 9 days after steroid initiation, with no specific interval documented in five patients. Most of the patients received a dose of 5mg/kg, one patient was prescribed with 10mg/kg for 2 days and the dosage received by two patients was not documented. Most of the patients (10 out of 14) were given a single dose of infliximab, three patients were reported to receive 2 doses and one patient was prescribed with 3 doses. In those patients with multiple doses of infliximab, the second dose was given as early as the next consecutive day, 5 days and 11 days following the first dose, respectively. No specific interval was indicated in one reported case.

In addition to infliximab, the use of at least one of the other immunosuppressive agents was reported in seven patients. These included anti-thymocyte globulin (ATG), mycophenolate mofetil, intravenous immunoglobulin (IVIG) and plasma exchange. The use of anti-thymocyte globulin was reported in two patients following failure of infliximab to improve the clinical condition. Tay *et al.* (2017) described the successful use of anti-thymocyte globulin, in contrast, Portolés Hernández *et al.* (2021) reported a patient who failed to respond after 2 doses of anti-thymocyte globulin. Use of mycophenolate mofetil was documented in two patients. First, in the case reported by Zlotoff *et al.* (2019), failure of the first dose of infliximab prompted the use of a second dose of infliximab and add-on of mycophenolate mofetil and IVIG. Second, Tay *et al.* (2017) reported the initiation of mycophenolate mofetil after the patient showed significant improvement with anti-thymocyte globulin, and it was continued for 4 weeks and weaned over 12 weeks. Five authors reported the use of immunoglobulin as an add-on therapy. Plasma exchange was performed in two out of five patients. Shah *et al.* (2019) reported that plasma exchange and immunoglobulin were added on infliximab therapy following the mild steroid response. In the case presented by Frigeri *et al.* (2018), plasma exchange and immunoglobulin were initiated before the administration of infliximab. In two cases reported by Saibil *et al.* (2019) and Fuentes-Antrás *et al.* (2020), immunoglobulins were given with infliximab when the patients did not respond to steroid therapy. In the case described by Zlotoff *et al.* (2019), immunoglobulin was administered after initiation of infliximab and mycophenolate mofetil.

Clinical Outcome

Four patients were reported to have improvement clinically or biochemically following infliximab therapy, with reduction or normalisation of troponin, improvement of ECG and resolution of arrhythmia or conduction disorders. All four patients recovered from myocarditis. In contrast, 10 patients showed a lack of improvement or deterioration of clinical condition with the addition of infliximab.

Out of the 14 patients, seven (50%) died from immune-mediated myocarditis and related complications. These patients showed rapid deterioration, developed grade 4 myocarditis and died as early as 7 days and up to 18 days after admission. Complications that contribute to mortality include multiorgan failure, cardiogenic shock, cardiac arrest and respiratory failure. Of note, all these patients did not show significant improvement after receiving infliximab. Interestingly, nearly all of these patients had at least one neuromuscular irAEs concurrently, four developed myositis, one had myasthenia gravis, and one had multiple irAEs consisting of myositis, myasthenia gravis, pneumonitis, hepatitis and thyroiditis.

On the other hand, seven patients survived myocarditis and its complications. Four patients were reported to show clinical and biochemical improvement following treatment of infliximab but three patients did not. However, of the seven survived patients, two patients died later due to cancer progression and development of bacteremia and pulmonary embolism, respectively.

DISCUSSION

The review of 14 cases revealed that most patients developed immune-related myocarditis with a high grade of severity, concomitant irAEs, particularly neuromuscular irAEs and multiple potentially fatal complications. Most of them were treated with a single dose of infliximab, whereas a few only received multiple doses. Only about a quarter of individuals showed clinical or biochemical improvement. Half of the patients did not survive due to myocarditis and its complications.

Steroid Refractory Myocarditis

High-dose corticosteroid is the standard initial treatment once ICI-associated myocarditis is suspected or confirmed (Haanen *et al.* 2017; Brahmer *et al.* 2018; Brahmer *et al.* 2021; Thompson *et al.* 2022). Several studies (Wang *et al.* 2017; Mahmood *et al.* 2018; Zhang *et al.* 2020) showed that patients who received earlier and higher initial doses of corticosteroid had more favourable outcomes such as less occurrence of major adverse cardiovascular events (MACE) and lower troponin levels. When clinical deterioration occurs despite high dose corticosteroid therapy, treatment should be escalated by adding other immunosuppressants such as infliximab, mycophenolate mofetil, IVIG, and tacrolimus, ATG or plasmapheresis, which may help in the functional improvement and increased survival (Haanen *et al.* 2017; Brahmer *et al.* 2018; Brahmer *et al.* 2021; Thompson *et al.* 2022). However, there is no clear definition for steroid failure. In general, response to steroids is monitored based on the clinical symptoms and biomarkers such as the resolution of symptoms, normalisation of troponin levels, resolution of ECG abnormality and improvement of ejection fraction. Several studies have shown that corticosteroids alone might not be sufficient to resolve immune-mediated myocarditis, as many patients still developed complications such as malignant arrhythmias and heart failure (Heinzerling *et al.* 2016; Mahmood *et al.* 2018). Only about 50% of patients with fulminant myocarditis responded to corticosteroid monotherapy (Agrawal *et al*. 2019) and up to two-thirds of patients showed reversal of cardiotoxicity due to systolic dysfunction with corticosteroid therapy (Escudier *et al.* 2017)**.** Literature on the timing of initiation and selection of second-line immunosuppressive therapies is still lacking. In general, most guidelines recommended additional therapies should be considered if patients did not respond to corticosteroid therapy within 24 h (Brahmer *et al.* 2021; Thompson *et al.* 2022). Some suggested adding second-line immunosuppressive agents such as mycophenolate mofetil, infliximab or ATG with higher doses of corticosteroid for those with more severe disease (grade 3 to 4) and failed to respond to initial corticosteroid dosing within 3 days to 5 days (Brahmer *et al.* 2018).

Clinical Characteristics Associated with the Use of Additional Immunosuppressive Therapy

In this review, we found that most of the patients (9 out of 14) treated with infliximab had concomitant neuromuscular irAEs. Approximately 90% of these nine patients had grade 4 myocarditis. Two-thirds of them required at least two additional immunosuppressive treatments following initiation of corticosteroid. This highlighted the severity of the overlap syndrome and it caused the treatment to be more complicated. This finding was consistent with the results from several studies. Power *et al.* (2020) reported that having one or more concomitant non-cardiac irAE(s) was one of the predictors of steroid-refractory myocarditis, particularly concomitant myasthenia gravis-like syndrome and myositis. In another study, Cautela *et al.* (2020) reported similar findings, patients requiring intensified immunosuppressive therapy (IIST) were more likely to have other irAEs simultaneously, particularly myositis and myasthenia gravis. Arora *et al.* (2020) also reported a case series of ICI-associated myocarditis overlapping with neuromuscular toxicities, which presented in severe form and required treatment of multiple immunosuppressant and/or antibody depleting therapies, including infliximab. Other studies also showed that treating patients with multiple irAEs was challenging as these patients tended to have a more severe clinical presentation and are frequently related to poorer outcomes (Safa *et al.* 2019; Suzuki *et al.* 2017; Aldrich *et al.* 2021).

Apart from having concurrent irAEs, we found that most patients who developed complications such as heart failure, conduction abnormalities, arrhythmia, cardiogenic shock and cardiac arrest progressed very rapidly. This was consistent with the findings from a study conducted by Zhang *et al.* (2021), whereby patients in the infliximab group had more severe myocarditis by ASCO classification and a higher rate of complications such as MACE, ventricular tachycardia and cardiogenic shock compared to those who received corticosteroid alone.

Another potential predictor that is associated with escalation of treatment is troponin level. Power *et al.* (2020) reported higher initial troponin level was significantly related to steroid failure. Cautela *et al.* (2020) also revealed that persistently elevated troponin was an indication of intensive immunosuppressive therapy beyond corticosteroid. Similarly, Zhang *et al.* (2021) found patients in the infliximab group were more likely to have higher troponin levels, which was associated with an increased risk of MACE, compared to those who received corticosteroid alone. Other predictors of using additional immunosuppressive agents include female (Power *et al.* 2020), higher body mass index (Power *et al.* 2020), higher initial creatine kinase (Power *et al.* 2020), prior treatment of combined ICIs (Zhang *et al.* 2021) and earlier occurrence of myocarditis after ICI administration (Zhang *et al.* 2021). Due to insufficient data retrieved from the case reports, we cannot conclude whether these factors are associated with the use of add-on immunosuppressants.

Treatment Regime of Infliximab

In most guidelines or consensus, infliximab has been recommended as one of the immunosuppressive agents to be considered if corticosteroid fails to resolve myocarditis (Haanen *et al.* 2017; Brahmer *et al.* 2018; Thompson *et al.* 2022). However, no specific dose, indication of re-dosing and dosing intervals have been recommended. The use of infliximab has been mostly extrapolated from the management of other immune-related adverse events, particularly colitis (Pages *et al*. 2013; Merrill *et al.* 2014; Hillock *et al.* 2017; Nassri *et al.* 2019). In this review, most patients received a single dose of 5 mg/kg, whereas few were treated with multiple doses with varying dosing intervals. Limited

data showed that a single dose of infliximab 5 mg/kg had been effective and safe in the treatment of ICI-associated myocarditis (Zhang *et al.* 2021). Timing of starting infliximab following initiation of steroid varied widely, and it was inconclusive whether earlier use of infliximab was associated with better clinical outcomes, particularly in patients showing rapid deterioration of the clinical condition. Similarly, it was also unclear whether multiple doses of infliximab or add-on of other immunosuppressive agents had beneficial effects, especially when initial use of infliximab failed to show improvement.

Clinical Outcome

Consistent with the clinical outcomes from several studies (Cautela *et al.* 2020; Zhang *et al.* 2021), our review of 14 reported cases also showed mixed results on using infliximab in treating immune-related myocarditis. Nearly one-third of the patients showed improvement, whereas about two-thirds of them did not improve or deteriorate with addition of infliximab. Half of the patients did not survive from myocarditis and its complications.

The lack of standardised guide to monitor the response of infliximab treatment is another concern. Similar to steroids, monitoring of the response to treatment is generally based on the resolution of clinical symptoms and improvement of biomarkers such as troponin levels. Troponin is deemed as a reliable and early predictor of progression to severe myocarditis and mortality (Sarocchi *et al.* 2018). In this review, nearly all patients had troponin elevation upon presentation to hospitals; however, the progress of troponin levels following infliximab was not clearly documented.

Compared to the use of infliximab in the treatment of ICI-related myocarditis, research on its use in managing ICI-related colitis is more extensive. However, efficacy data reported in these studies may not be applicable in managing myocarditis. In a study conducted on patients with immune-mediated colitis, the median time to symptoms resolution and total steroid duration were shorter in the infliximab group compared to the corticosteroid monotherapy group (Johnson *et al.* 2018). In contrary to this, in a study of patients with ICI-myocarditis, Zhang *et al.* (2021) found that both duration of troponin normalisation and steroid taper were longer in the patients treated with infliximab compared to those treated solely with corticosteroid. This could be explained by higher grade of severity, higher cardiac complication rates and higher troponin levels at admission in the infliximab group.

In a retrospective study conducted by Kadokawa *et al.* (2021), patients with steroid-refractory immune related colitis responded to infliximab at a median of 18 (range 9–32) days after administration. Even though this finding was derived from patients with immune-mediated colitis, few case reports in our review also showed a similar outcome. In a case reported by Padegimas *et al.* (2019), it took 2 weeks to resolve the ECG abnormalities and 9 months to normalise the troponin levels. In addition to this, several case reports (Haanen *et al.* 2017; Martinez-Calle *et al.* 2018; Giancaterino *et al*. 2020; Portolés Hernández *et al.* 2021) in this review showed the patients did not survive after receiving infliximab; this could be attributed to rapid deterioration before infliximab showing any positive effects.

Safety of Infliximab

In this review, despite adverse effects were not identified in most of the case reports, there were some safety concerns associated with the use of infliximab. These included the use of infliximab in patients with heart failure as well as increased risk of cardiovascular death, opportunistic infection, pulmonary embolism and hepatoxicity.

Few unfavourable reports showed that use of infliximab was associated with heart failure. According to Kwon *et al.* (2003), infliximab might induce new-onset heart failure or exacerbate existing disease based on the FDA's MedWatch programme adverse events reports of using TNF-alpha antagonists in the treatment of various diseases such as rheumatoid arthritis and Crohn's diseases. Curtis *et al.* (2007) observed similar findings in their study, which showed an increased relative risk of heart failure among the patients receiving TNF-alpha antagonists for treatment of rheumatoid arthritis and Crohn's diseases, but the results were not statistically significant. On the other hand, Zhang *et al.* (2021) reported that infliximab improved decompensated heart failure and cardiogenic shock due to ICI-related myocarditis. Similarly, our review also showed the mixed outcome in nine patients who showed signs and symptoms of heart failure upon presentation to the hospital or throughout the clinical course of myocarditis. Of these nine patients, four patients died, whereas five patients survived from myocarditis. Patients showed improvement in ejection fraction after administration of infliximab in the cases reported by Padegimas *et al.* (2019) (case 2) and Frigeri *et al.* (2018). On the other hand, Tay *et al.* (2017), Martinez-Calle *et al.* (2018), Gallegos *et al.* (2019) and Portolés Hernández *et al.* (2021) observed that infliximab treatment resulted in a worsening of heart failure. Gallegos *et al.* (2019) also reported that a patient who was treated with a higher dose (10 mg/kg) of infliximab for 2 consecutive days concurrently with the initiation of corticosteroid did not show improvement but developed cardiogenic shock and died. According to Chung *et al*. (2003), high doses (10 mg/kg) of infliximab adversely affected the clinical condition of patients with moderate-to-severe chronic heart failure, increasing the combined risk of death from any cause or hospitalisation for heart failure. It is worth noting that early initiation of infliximab with 5 mg/kg–10 mg/kg dosing may be offered in other grade 4 immune-related adverse events such as colitis, it is however contraindicated in myocarditis patients with moderate-severe heart failure according to ASCO guidelines (Brahmer *et al.* 2018).

Given the increased risk of heart failure, numerous guidelines and consensus (Brahmer *et al.* 2018; Palaskas *et al.* 2020; Brahmer *et al.* 2021; Thompson *et al.* 2022) suggested using infliximab with extreme caution in patients with heart failure or reduced ejection fraction and highlighted high doses should be avoided in patients with moderate-severe heart failure. Additionally, it is also crucial for clinicians to be aware of the treatment modalities and their safety considerations in managing this group of patients (Atallah-Yunes *et al.* 2019). Evidence on the use of other immunosuppressive agents in the treatment of ICI-related myocarditis with the presence of heart failure is also limited. In the unstable patients who do not respond to corticosteroids, ATG, IVIG or plasma exchange can be considered (Wang *et al.* 2017; Ganatra and Neilan 2018; Kociol *et al.* 2020). In stable patients who failed to respond to corticosteroids, tacrolimus or mycophenolate mofetil can be considered based on their efficacy in treating cardiac allograft rejection (Kobashigawa *et al*. 2006; Ganatra and Neilan 2018; Hu *et al*. 2019).

In a retrospective study conducted by Cautela *et al.* (2020), the use of infliximab for the treatment of ICI-induced myocarditis was associated with a significantly increased risk of cardiovascular death (OR = 12.0, p = 0.005). Additionally, the authors revealed that patients who received second-line immunosuppressive agents had a greater all-cause mortality rate than those treated with steroids alone (50% versus 21%, p = 0.02). This has raised the safety concern of infliximab use as second-line therapy in steroid-refractory myocarditis. However, the result should be interpreted with caution due to the small sample size and absence of a control group in the study design.

Infliximab carries a black box warning of increased risk of opportunistic infection (Janssen Biotech, Inc. 2021) as it has been associated with reports of mycobacterial infections, invasive fungal infections, viral infections as well as bacteraemia (Wolfe *et al.*

2004; Koo, Marty and Baden 2010; Ali *et al.* 2013; Andersen and Jess 2014). Several cases of pulmonary embolism associated with infliximab use were documented (Eklund, Peltomaa and Leirisalo-Repo 2003; Lee and Moosavy 2014; Bala *et al.* 2020). In this review, Padegimas *et al.* (2019) reported that a patient died due to bacteraemia and pulmonary embolism. However, there was no clear or direct causal relationship between the incident and the use of infliximab in this patient. Concomitant corticosteroid treatment in this patient also increased the risk of infection and the underlying malignancy was considered a risk factor for developing venous thromboembolism (Biedka, Ziółkowska and Windorbska 2012; Qdaisat *et al.* 2020).

A rare but significant side effect of infliximab treatment is hepatoxicity (Mancini *et al.* 2010; Sokolove *et al.* 2010; Ghabril *et al.* 2013). The FDA issued a drug warning on the risk of hepatotoxicity in course of infliximab therapy (Janssen Biotech, Inc. 2021). In this review, Fuentes-Antrás *et al.* (2020) reported a patient who developed grade 4 hepatitis concomitantly with myocarditis. Given the risk of liver injury, infliximab should be best avoided and other immunosuppressants such as mycophenolate mofetil may serve as a better alternative (Thompson *et al.* 2022; Brahmer *et al*. 2018; Haanen *et al.* 2017).

Limitation

Literature on infliximab use in the management of immune-related myocarditis is not extensive and the available studies vary significantly in quality. This review is based on the small number of reported cases. Hence, its generalisability is limited. Due to the retrospective design of case reports, we could not retrieve the missing data to determine the efficacy and safety of infliximab in treating steroid-refractory myocarditis. However, it provides exploratory data and raises some safety concerns on the use of infliximab. In addition, few cases were reported using multiple immunosuppressive agents, which could add to the difficulties in interpreting the response to infliximab. Adverse effects associated with infliximab use were not reported in most of the case reports. Thus, we do not have sufficient data to discuss drug safety issues.

CONCLUSION

Concomitant irAEs, high grade of severity and presence of potentially fatal complications are the indicators of escalating the immunosuppressive therapy. Infliximab may be considered an option, however, there is no standardisation on the treatment regime, and the outcome was inconsistent. Safety data on infliximab use is scarce and should be avoided in patients with heart failure. Due to the rarity of this irAE, our knowledge of the use of infliximab in managing immune-related myocarditis is still restricted to the data from case reports, case series and retrospective studies. From this review, we learned that the rates of mortality and complications remain high despite the use of multiple immunosuppressive drugs. Hence, it is crucial to identify the patients with more severe myocarditis as corticosteroid therapy alone may not be sufficient and these patients may require more intensive immunosuppressive therapy. This can be achieved by standardising therapeutic strategies and adopting a multidisciplinary approach in managing immune-related myocarditis. We hope this review provides the groundwork for further studies to further explore the use of immunosuppressive agents in the treatment of ICI-associated myocarditis.

Data Availability

All data presented in this review are included in this published article and its supplementary information files.

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APPENDIX 1: SEARCH TERMS USED IN LITERATURE SEARCHING

First concept

"infliximab"[Mesh] OR infliximab[tw] OR "infliximab-dyyb"[tw] OR "infliximab-abda"[tw] OR "infliximab-qbtx"[tw] OR "infliximab-axxq"[tw] OR Remicade[tw] OR Inflectra[tw] OR Renflexis[tw] OR Remsima[tw] OR "Monoclonal Antibody cA2" [tw] OR "MAb cA2"[tw]

Second concept

"myocarditis" [Mesh] OR myocarditis [tw] OR carditis [tw] OR myocarditides [tw]

Third concept

"immune checkpoint inhibitors"[Mesh] OR "immune checkpoint inhibitor*"[tw] OR "immune checkpoint blocker*"[tw] OR "checkpoint inhibitor*"[tw] OR "check-point inhibitor*"[tw] OR "check point inhibitor*"[tw] OR "Programmed death-1 inhibitor*"[tw] OR "Programmed death 1 inhibitor*"[tw] OR "Programmed cell death-1 inhibitor*"[tw] OR "Programmed cell death 1 inhibitor*"[tw] OR "Anti-programmed death-1"[tw] OR "PD 1 inhibitor*"[tw] OR "PD-1 inhibitor*"[tw] OR "Anti-PD-1"[tw] OR "Anti-PD 1"[tw] OR "Programmed death-ligand 1 inhibitor*"[tw] OR "Programmed death ligand 1 inhibitor*"[tw] OR "Programmed cell death-ligand 1 inhibitor*"[tw] OR "Programmed cell death ligand 1 inhibitor*"[tw] OR "Programmed cell death protein 1 inhibitor*"[tw] OR "Anti-programmed death protein-1"[tw] OR "Anti-programmed death ligand-1"[tw] OR "Anti-programmed death receptor-1"[tw] OR "PDL 1 inhibitor*"[tw] OR "PD-L 1 inhibitor*"[tw] OR "PD-L1 inhibitor*"[tw] OR "PD L1 inhibitor*"[tw] OR "anti-PDL 1"[tw] OR "anti-PD L 1"[tw] OR "anti-PD-L 1"[tw] OR "cytotoxic T-lymphocyte-associated antigen 4 inhibitor*"[tw] OR "anti-cytotoxic T-lymphocyte associated antigen 4"[tw] OR "cytotoxic T-lymphocyte-associated protein 4 inhibitor*"[tw] OR "cytotoxic T lymphocyte associated protein 4 inhibitor*"[tw] OR "anti-cytotoxic T lymphocyte associated protein 4"[tw] OR "CTLA-4 inhibitor*"[tw] OR "CTLA 4 inhibitor*"[tw] OR "anti-CTLA-4"[tw] OR "PD-1-PD-L1 inhibitor*"[tw] OR "PD-1-PD-L1 blocker*"[tw] OR "PD 1 PD L1 inhibitor*"[tw] OR "PD 1 PD L1 blocker*"[tw] OR "PD-1/PD-L1 inhibitor*"[tw] OR "PD-1/PD-L1 blocker*"[tw] OR Nivolumab [tw] OR Opdivo [tw] OR Pembrolizumab [tw] OR Keytruda [tw] OR Lambrolizumab [tw] OR Cemiplimab [tw] OR Libtayo [tw] OR Atezolizumab [tw] OR Tecentriq [tw] OR Durvalumab [tw] OR Imfinzi [tw] OR Avelumab [tw] OR Bavencio [tw] OR Ipilimumab [tw] OR Yervoy [tw] OR Tremelimumab [tw] OR Ticilimumab [tw] OR Dostarlimab [tw]

APPENDIX 2: THE JOANNA BRIGGS INSTITUTE (JBI) CRITICAL APPRAISAL CHECKLIST FOR CASE REPORTS

JBI Critical Appraisal Checklist for Case Reports

Reviewer_____Date_____

Author _____Year_____Record Number_____.

	Yes	No	Unclear	Not applicable
1. Were patient's demographic characteristics clearly described?	☐	☐	☐	☐
2. Was the patient's history clearly described and presented as a timeline?	☐	☐	☐	☐
3. Was the current clinical condition of the patient on presentation clearly described?	☐	☐	☐	☐
4. Were diagnostic tests or assessment methods and the results clearly described?	☐	☐	☐	☐
5. Was the intervention(s) or treatment procedure(s) clearly described?	☐	☐	☐	☐
6. Was the post-intervention clinical condition clearly described?	☐	☐	☐	☐
7. Were adverse events (harms) or unanticipated events identified and described?	☐	☐	☐	☐
8. Does the case report provide takeaway lessons?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

_____

_____

_____

APPENDIX 3: METHODOLOGICAL QUALITY ASSESSMENT OF THE RETRIEVED STUDIES BASED ON JBI CRITICAL APPRAISAL CHECKLIST FOR CASE REPORTS

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Overall Appraisal
Agrawal *et al*. 2019 (case 5)	Y	Y	Y	Y	UC	Y	N	Y	Include
Frigeri *et al*. 2018	Y	UC	Y	Y	Y	Y	N	Y	Include
Fuentes-Antrás *et al*. 2020	Y	Y	Y	Y	Y	N	N	Y	Include
Gallegos *et al*. 2019	Y	Y	Y	Y	Y	Y	N	Y	Include
Giancaterino *et al*. 2020	Y	UC	Y	Y	Y	Y	N	Y	Include
Portolés Hernández *et al*. 2021	Y	Y	Y	Y	Y	Y	N	Y	Include
Johnson *et al*. 2016 (case 2)	Y	Y	Y	Y	UC	Y	N	Y	Include
Martinez-Calle *et al*. 2018	Y	Y	Y	Y	Y	UC	N	Y	Include
Padegimas *et al*. 2019 (case 1)	Y	UC	Y	Y	Y	Y	N	Y	Include
Padegimas *et al*. 2019 (case 2)	Y	UC	Y	Y	Y	Y	N	Y	Include
Saibil *et al*. 2019	Y	Y	Y	Y	Y	Y	N	Y	Include
Shah *et al*. 2019 (case1)	Y	UC	Y	Y	UC	UC	N	Y	Include
Tay et al. 2017	Y	Y	Y	Y	Y	Y	N	Y	Include
Zlotoff *et al*. 2019	Y	N	Y	Y	Y	Y	N	UC	Include

Abbreviations: Y = Yes, N = No, UC = Unclear