AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence Status Report: infliximab for the treatment of grade 3–4 steroid-refractory myocarditis induced by immune checkpoint inhibitor (ICI) therapy **(OW31)**

Report prepared by the All Wales Therapeutics and Toxicology Centre
July 2025

Key findings

Licence status
Infliximab is not licensed for treating grade 3–4 steroid-refractory myocarditis induced by immune checkpoint inhibitor (ICI) therapy; its use for this indication is off-label.

Clinical evidence
Evidence comes from systematic reviews, retrospective case series and case reports. No randomised control trials of infliximab in the treatment of ICI-induced myocarditis were identified.

Safety
Infliximab is contra-indicated in patients with moderate or severe heart failure (NYHA class III/IV).

Patient factors
Patients would receive the first dose of infliximab in hospital to enable cardiac monitoring.

Cost effectiveness
No cost-effectiveness evidence was identified for this use of infliximab, and in the absence of any clinical studies of infliximab for this indication, no cost-effectiveness analyses have been undertaken.

Budget impact
The additional use of infliximab is estimated to increase the annual spend associated with this patient group in Wales by between [commercial in confidence figures removed] depending on the degree of displacement of comparator treatments.

Impact on health and social care services
Minimal – due to the severity of the condition, patients with grade 3 and 4 ICI-induced myocarditis are commonly admitted to hospital with extensive monitoring. Adding infliximab to the treatment pathway is likely to have a low additional impact.

Innovation and/or advantages
Infliximab offers an additional treatment option for some patients in this group.

Clinicians in Wales suggest that the specificity of the immunosuppressive activity of infliximab might offer an advantage over other immunosuppressive agents with a broader spectrum of activity which may be detrimental to the ongoing control of the cancer originally targeted by ICI treatment.

Background

Clinicians in Wales consider there is an unmet need for treatment of steroid-refractory myocarditis induced by immune checkpoint inhibitor (ICI) therapy. They have identified a cohort of patients who might benefit from infliximab treatment. Infliximab was considered suitable for assessment though the One Wales medicines process following agreement by the AWMSG Scrutiny Panel.

The All Wales Therapeutics and Toxicology Centre (AWTTC) sought opinions from clinical experts in Wales. Clinical experts expressed a need for a clear treatment strategy or clinical guideline to manage ICI-induced myocarditis in Wales. A small number of patients with steroid-refractory ICI-induced myocarditis in Wales have received infliximab (off-label) through local agreements. A One Wales decision would ensure equity of access to infliximab across the country to treat steroid-refractory ICI-induced myocarditis.

Target group

The indication considered is the treatment of steroid-refractory grade 3–4 myocarditis induced by immune checkpoint inhibitors.

Marketing authorisation date: not applicable, off-label

Infliximab is not licensed for the treatment of steroid-refractory grade 3–4 myocarditis induced by immune checkpoint inhibitors. There are no plans to license infliximab for the indication under consideration.

Dosing information

The proposed dose is 5 mg/kg by intravenous infusion over a 2-hour period at Week 0. This dose is the recommended infliximab dose for the majority of licensed indications[1]. Patients should be observed for at least 1–2 hours post-infusion for acute infusion-related reactions. A second, and third dose may be given, 2 and 6 weeks later. In some cases a shorter interval may be required between doses and specialist advice should be sought from the immunotherapy team.

Clinical background

Immune checkpoint inhibitor (ICI) therapy is a type of immunotherapy for several different types of cancer, including lung cancer and melanoma[2]. Checkpoint proteins stop the immune system from attacking cancer cells; checkpoint inhibitors block these proteins and turn the immune system back on, to find and attack cancer cells[2]. However, ICIs can overstimulate the immune system, leading to various side effects known as immune-related adverse events (irAEs) that can occur in any organ[3].

Myocarditis is a recognised complication of ICI therapy for cancer[4]. Most reported cases of myocarditis have occurred within the first month of therapy. Approximately 1% of patients treated with checkpoint inhibitors develop cardiotoxicity[4].

Symptoms include: fatigue, dyspnoea, chest pain, palpitations, peripheral oedema, pre-syncope, syncope, or evidence of elevated cardiac enzymes/electrocardiogram (ECG) changes even in the absence of symptoms[4]. It is common for patients to be asymptomatic or have minimal symptoms and have significantly abnormal cardiac tests[4].

Grade 3 and 4 myocarditis are severe or life-threatening, and characterised by new onset of severe symptoms at rest or with minimal exertion, and elevated cardiac enzymes:

- troponin T ≥ 100 ng/L
- B-type natriuretic peptide (NT-Pro-BNP) ≥ 3000 ng/L.

Admission to CCU/HDU should be considered, and ICI therapy stopped[4].

Myocarditis is associated with a high mortality rate if not treated[4]. About half of the patients with ICI-myocarditis experience a major adverse cardiac event (cardiovascular death, cardiogenic shock, cardiac arrest or haemodynamically significant complete heart block)[5,6].

Incidence/prevalence

Severe myocarditis develops in <1% of cases, but with increased use of troponin measurement and cardiac imaging, cardiovascular complications can occur in ≤ 5% of patients treated with ICIs[7]. In up to 50% of patients, myocarditis may not respond to high-dose corticosteroids and will require treatment with a second-line immunosuppressant[8].

The Wales National Immunotherapy Toxicity Sub-Group estimates that there are approximately 42 patients across Wales with grade 3-4 ICI-induced myocarditis unresponsive to steroids who would be eligible for treatment each year. Infliximab would not be used for patients with a left ventricular ejection fraction (LVEF) of less than 40%, which accounts for around 20% of cases. Therefore, clinicians estimate that approximately 34 patients per year would be eligible to receive infliximab.

Current treatment options and relevant guidance

All guidelines recommend that ICI treatment should be stopped for patients who develop grade 2 or higher myocarditis, and that high-dose corticosteroid treatment is started[4,7,9-11]. If myocarditis does not respond to high-dose steroids, then additional immunosuppressive agents should be considered[4,9].

The Society for Immunotherapy of Cancer (SITC) consensus definitions for steroid-unresponsive immune-related adverse events state that for life-threatening (grade 3 or 4) adverse events such as myocarditis, steroid-unresponsive immune-related adverse events are those in which there is no clinical improvement after 1–3 days of appropriate steroid therapy[12]. The definition has important implications for informing the time interval to wait before offering additional lines of immunosuppression[12].

Guideline 28 of the UK Acute Oncology Initial Management Guidelines Version 4 (2023) recommends considering mycophenolate mofetil (MMF) or tacrolimus in patients whose condition is not responding optimally to high-dose steroids[4]. If there is a limited response, consider a biologic, such as infliximab, tocilizumab or abatacept.

A further DMARD, such as azathioprine, could also be considered, and local or national subsequent management guidelines should be considered[4].

In up to 50% of patients, myocarditis may not respond to high-dose corticosteroids and will require treatment with a second-line immunosuppressant[8]. There is a lack of data to recommend a specific medicine to use, and current guidelines differ slightly in their suggested medicines for use as additional immunosuppressive agents (see Table 1).

Table 1. Guideline recommendations for additional immunosuppression for steroid-refractory ICI-induced myocarditis

Guideline	Additional immunosuppressant treatment
UK Oncology Nursing Society (UKONS) Guideline 28 2023[4]	Consider: • MMF; • tacrolimus. If limited response, consider: • infliximab; • tocilizumab; or • abatacept. A further DMARD e.g. azathioprine, could also be considered.
European Society of Cardiology (ESC) Lyon et al. 2022[13]	MDT discussion recommended due to lack of data to recommend a specific second-line immunosuppression regimen. Agents being investigated include: anti-thymocyte globulin (ATG); MMF; immunoglobulin; plasma exchange; tocilizumab; abatacept; alemtuzumab and tofacitinib. Caution advised against the use of infliximab for steroid-refractory myocarditis and heart failure.
European Society for Medical Oncology (ESMO) Haanen et al. 2022[7]	2nd-line options: • tocilizumab 8 mg/kg; • MMF. 3rd-line options: • ATG; • alemtuzumab; • abatacept.
Society for Immunotherapy of Cancer (SITC) Brahmer et al. 2021[11]	2nd-line options (added if no response within 24 hours): • ATG; • MMF; • abatacept; • alemtuzumab. Caution advised against the use of infliximab for steroid-refractory myocarditis.
American Society of Clinical Oncology (ASCO) Schneider et al. 2021[9]	Consider the addition of either: • MMF; • infliximab; or • ATG. Consider abatacept or alemtuzumab as additional immunosuppression in life-threatening cases.

Guideline	Additional immunosuppressant treatment
	Note that infliximab is contraindicated at high doses (i.e. 5 mg/kg) in patients with moderate-severe heart failure.
National Comprehensive Cancer Network (NCCN) Thompson et al. 2020[10]	If no improvement with high-dose steroids is noted within 24 hours, consider the addition of: • ATG; • infliximab; • intravenous immunoglobulin (IVIG); or • MMF. Note that infliximab is contraindicated for patients who have heart failure.
ATG: anti-thymocyte globulin; DMARD: disease-modifying anti-rheumatic drug; MDT: multi-disciplinary team; MMF: mycophenolate mofetil	

Velindre Cancer Centre's Immunotherapy Toxicity Guideline (v3) states that for myocarditis (grade 3 or 4) that does not respond to steroids, use second-line immunosuppression, such as tacrolimus or MMF or to consider infliximab.

Clinicians in Wales say that when ICI-induced myocarditis does not respond to steroids, they currently use tacrolimus or MMF as second-line immunosuppression. Some patients have received infliximab (see Table 2 for real world data). Clinicians say they would give infliximab to patients who have a preserved LVEF, partly due to their familiarity with using infliximab for treating other immunotherapy toxicities. In addition, clinicians think it appears to be effective without having broad-spectrum effects, unlike abatacept (stated as an option in some clinical guidelines), for example, which has anti cytotoxic T-lymphocyte-associated antigen 4 properties that might affect ongoing cancer control. For patients who have a reduced LVEF (less than 40%) they would prefer to use tocilizumab (requested through an IPFR or non-formulary application).

Clinicians in Wales say that the aim is to give three doses of infliximab (5 mg/kg) – given intravenously at Week 0, then a second dose at Day 15 if symptoms remain. A third dose could be given at Day 43. If the myocarditis did not respond to infliximab, or the patient's condition deteriorated, then there would be an MDT discussion, to agree additional immunosuppression. Clinicians in Wales have already reported their experience in using infliximab for this indication (see Table 2).

Most guidelines recommend that ICI therapy should not be restarted in patients with severe or life-threatening (grade 3 or 4) ICI-induced myocarditis.

Summary of evidence on clinical effectiveness

The All Wales Therapeutics and Toxicology Centre (AWTTC) conducted a literature search during 29–30 May 2025, and 3 June 2025 to look for evidence about the use of infliximab to treat steroid-refractory ICI-induced myocarditis.

Database searches were performed using MEDLINE, EMBASE and the Cochrane Library. Our search terms were: infliximab, renflexis, remicade, zessly, remsima, inflectra, flixabi; myocarditis, carditis, cardiotoxicity, cardiac toxicity (cardiotoxicit* or cardio toxicit* or cardiactoxicit* or cardiac toxici*), (cardi* adj1 toxicit*); immune

checkpoint inhibitor, immune checkpoint inhibit*, (immune adj2 checkpoint adj2 (inhibit* or blockade*)), ((ICI or ICIs) adj2 myocarditis).

The primary outcomes of interest were symptom improvement or resolution in randomised controlled trials (RCT), systematic reviews, network meta-analyses, guidelines, case series, case reports, conference abstracts, retrospective studies, health-related quality of life, economic evaluations, adverse events. No date restrictions were applied; results were restricted to English language. Targeted searches of Google and Google Scholar were also performed. Conference abstracts were included; letters and editorials were excluded. Clinical authors at AWTTC sifted and screened the results of the clinical searches, and health economics authors sifted and screened the results of the searches for economic evaluations and quality of life. See the PRISMA diagram in Appendix 1.

A total of 271 clinical papers were retrieved during the literature search, from which 12 duplicates were removed. 259 clinical papers were screened by inspecting titles and abstracts, and the full texts of 45 papers were reviewed for suitability in this report.

Our literature search identified no clinical trials of infliximab in steroid-refractory ICI-induced myocarditis; only systematic or literature reviews, case reports and case series were identified. Some case reports were published with a systematic review. Other case reports were identified by cross-referencing.

In this evidence summary report we included: 8 guidelines, 6 reviews, 28 case reports of myocarditis (30 patients) and 4 case series (38 patients; outcome data for 15). We excluded reviews in which all of the cases they reported were covered in other reviews. The case reports and cohort studies are listed in Appendix 2. Table 4 also includes case reports and case series mentioned in the systematic reviews covered, some of which were not identified in our literature search, and some were screened out by title and/or abstract. The systematic and narrative reviews are briefly discussed below.

Efficacy

Systematic and narrative reviews

Of the seven systematic literature reviews (CADTH, Daetwyler et al., Phing et al., Wang et al., Tan et al. [all published in 2024], Cozma et al. [2022], Matzen et al. [2021], three searched the PubMed database only, two searched PubMed and Embase, one searched Embase and Cochrane, and one (CADTH) searched Medline, Embase and Cochrane databases[3,5,14-18].

Information provided about the search and methodology varied; some limited their searches or results by date, the search terms used differed slightly. Only two reviews (Tan et al. 2024 and Wang et al. 2024) searched specifically for the treatment of steroid-refractory ICI myocarditis; Phing et al. (2024) searched for infliximab to treat ICI myocarditis, Cozma et al. (2022) searched for treatment of ICI-related cardiotoxicities including myocarditis and Matzen et al. (2021) searched for treatment of ICI-induced myocarditis. Two reviews were broader searches for treatment of all types of immune therapy-related adverse events (Daetwyler et al. 2024), and for

infliximab to treat immune ICI-related toxicities (CADTH 2024)[3,5]. One review, Tan et al., also included two case reports[16].

All the systematic literature reviews identified only case reports and case series. The conclusions of each review were broadly similar; the evidence identified is very low quality (case reports and case series), and there is not enough published evidence to recommend the use of infliximab to treat ICI-induced steroid-refractory myocarditis.

The authors of one review stated that for steroid-refractory immune-related myocarditis, infliximab has been reported to be completely effective in a limited number of cases. They propose a potential algorithm for treatment of steroid-refractory ICI-related myocarditis[15] and indicate the use of infliximab only when TNF-alfa is elevated and there are no other therapeutic options[15].
Clear evidence with regard to treatment cannot be provided as all available publications are case reports of one patient or only small case series. Details of the cases included in each review, including dosing (where available) and outcomes are given in Appendix 2 and summarised in the section below.

Case reports and case series

Thirty case reports are listed in Table 4 in Appendix 2. Four of these case reports were not covered in any of the reviews: Vu et al. 2025, Gomez et al. 2025, Qin et al. 2024 and Dearden et al. 2021[19-22].

Of the 30 cases, nine had other ICI-induced toxicities in addition to myocarditis including myositis (2 cases)[23,24], myasthenia gravis (2)[25,26], myasthenia gravis and myositis (3)[16,20,27], hepatitis, nephritis, pancreatitis and peripheral nervous system toxicity (1)[21] and, myasthenia gravis, myositis, pneumonitis, thyroiditis and hepatitis (1)[28].

In 23 cases the dose of infliximab given was specified. The most common dose was 5 mg/kg, given to 15 patients[19,24,26,28-38]. Three patients had 500 mg[20,27,39], one had 350 mg[40] and two had 200 mg[16] (patient weights not given), and one patient had 10 mg/kg[41]. The number of doses of infliximab given was reported in 29 cases. Of these, 20 patients received one dose[19-21,23,24,26-29,31-33,37-40,42-45], six patients had two doses[22,25,30,34,35,41] and three patients had three doses[16,36].

Myocarditis symptoms improved in all three patients who had three doses of infliximab[16,36]. Of those patients who had two doses, myocarditis improved in three cases[25,30,34], did not improve in two cases[22,41] and further immunosuppressive treatment was required in the other case[35]. Of the 20 patients who had one dose, myocarditis resolved in eight cases[19-21,29,32,40,43], in eight cases patients went on to other treatments[23,27,28,33,38,42,44,45] and in four patients one dose of infliximab did not improve symptoms[26,31,37,39].

For the 21 cases where only myocarditis was present, infliximab treatment led to improvement of myocarditis symptoms in 10 cases[16,19,29,30,32,34,36,40,43]. In five cases infliximab treatment failed to improve myocarditis[22,31,37,39,41], and in six cases patients were given additional immunosuppressants after infliximab[33,35,38,42,44,45]. For the cases with multiple toxicities, infliximab treatment led to improvement in four of the nine cases reported[16,20,21,25].

Case series

Zhang et al. (2021) noted myocarditis improved in all four patients given one dose of 5 mg/kg infliximab; however, two later died from septic shock, both were receiving steroids[46]. Lipe et al. (2021) of three patients with confirmed ICI-induced myocarditis given infliximab, all required further immunosuppressive treatments[47]. In a case series of eight patients given infliximab (Cautela et al. 2020), myocarditis symptoms improved in four[48]. The authors noted that patients who received infliximab were more likely to die from cardiovascular causes (OR, 12.0; 95% CI 2.1 to 67.1; p=0.005)[48] .

Ali et al. (2024) investigated outcomes on ICI-induced myocarditis in relation to TNF-alpha levels, and included 23 patients with grade 3 or 4 myocarditis who were given infliximab (5 mg/kg)[49]. None of the patients who received infliximab developed worsening heart failure after infliximab administration, and MACE-free and overall survival were similar between all patients and those with elevated TNF-alpha levels. The number of patients with grade 3 or 4 cardiotoxicity was too small for a comparison of outcomes for those receiving infliximab versus those who did not receive it. They concluded that the role of TNF-alpha levels in the prognosis and guidance of immunomodulatory treatment is limited[49] .

Overall, the evidence for the use of infliximab from the case reports and case series is mixed, and of very low quality. It is not clear how many patients had grade 3 or 4 myocarditis.

Safety

The SmPC lists common cardiac disorders as tachycardia and palpitation. Uncommon cardiac disorders listed are cardiac failure (new onset or worsening), arrhythmia, syncope and bradycardia[1]. The most serious adverse drug reactions associated with the use of TNF blockers that have been reported for infliximab include hepatitis B virus reactivation, congestive heart failure, and serious infections (including sepsis, opportunistic infections and tuberculosis)[1].

Infliximab is contra-indicated in patients with moderate or severe heart failure (NYHA class III/IV)[1]. Patients should be closely monitored and infliximab must not be continued in patients who develop new or worsening symptoms of heart failure. Patients taking TNF-blockers may be more susceptible to infections. Co-administration with abatacept is not recommended, due to increased risk of infections[1].

The case reports and case series of ICI-induced myocarditis do not specifically describe adverse effects resulting from treatment with infliximab; they focus on the outcome of treatment – whether myocarditis improved after treatment.

Cautela et al. 2020 reported that patients who received infliximab were more likely to die from cardiovascular causes than other causes (OR, 12.0; 95% CI 2.1 to 67.1; p=0.005)[48], patient numbers were small and no details of the dose and number of doses received were given. Ali et al. (2024) reported that none of the 23 patients who received infliximab developed worsening heart failure after infliximab administration[49]. Zhang et al (2021) reported two patients treated with infliximab died from septic shock 2 and 3 months, respectively, after initial myocarditis treatment whilst on

prolonged steroid taper[46]. Clinicians in Wales also reported [confidential information removed]. In all cases, patients were receiving immunosuppressive agents additional to infliximab including steroids.

Experience of using infliximab in NHS Wales

Since January 2024, clinicians in NHS Wales have used infliximab at a dose of 5 mg/kg to treat steroid-refractory ICI-induced myocarditis in [confidential information removed] patients (see Table 2). [Confidential information removed]. Clinicians also reported delays in reporting cases to the IO Toxicity Team, which might have delayed the start of additional immunosuppressant treatment such as infliximab in some cases.

Table 2. Real world outcomes of infliximab to treat steroid-refractory ICI myocarditis in patients in Wales [table of confidential information removed]

Discussion

In this evidence summary, we identified 68 patients from the published literature and [confidential information removed] from NHS Wales who have received infliximab to treat ICI-induced myocarditis. Of these, outcomes are available for [confidential information removed] patients, of which [confidential information removed] reported a response to treatment with infliximab, [confidential information removed] reported no improvement and [confidential information removed] were given additional immunosuppressants after infliximab. [Confidential information removed]

There are no clinical studies that evaluated the efficacy of infliximab to treat ICI-induced myocarditis. Evidence is only available from case reports and case series, and systematic narrative reviews of case reports and case series; overall patient numbers remain low. Case reports are generally the lowest grade of evidence. It is difficult to compare cases; cases may not be generalisable. The amount of information given about each case varies; dose and outcome data vary. In some cases, it is not clear when infliximab was given (if the case was steroid-refractory). Patients often had complex diagnoses with multiple immune-related toxicities and treatment rarely followed clinical guidelines in terms of escalation of additional immunosuppression treatments after inadequate response to first-line steroids.

Although the grade of myocarditis was not stated in many studies, nearly all case reports are for patients where myocarditis symptoms were severe. Nearly one-third of the case reports were for patients with multiple ICI-induced toxicities, which may have affected clinical outcomes. Many patients were treated with a number of immunosuppressive agents in addition to steroids and so the relative benefit of infliximab is difficult to ascertain. The concomitant use of immunosuppressive agents may be expected to have a compounding effect on suppressing the immune system; a number of patients developed infections, some proving fatal, which may have been attributable to this effect. Some cases reported LVEFs of below 40% and a dose of 10 mg/kg was given in one case; this would not normally be recommended in this patient group due to the risk of the known cardiovascular side effects associated with infliximab.

The systematic reviews identified have included different case reports. The search terms used by each review team varied widely and the number of databases searched also varied. Some of the reviews limited their searches by date. Evidence was difficult to identify; some case reports were initially excluded by screening, as the report focused on a different aspect or did not mention infliximab in the abstract.

The systematic reviews conclude that the evidence for the use of infliximab to treat steroid-refractory ICI-induced myocarditis is mixed and inconclusive.

Guidelines differ in their suggestions of additional immunosuppressive medicines to treat steroid-refractory ICI-induced myocarditis; some guidelines state that use of infliximab should be considered; others do not include infliximab as a medicine to consider using. There is a paucity of data to inform comparisons between different second line immunosuppressive therapies for this indication. All guidelines indicate that recommendations on treatment options are based on a low-quality evidence base, mainly derived from clinical expert opinion and that clinical opinion can also be informed by preference and experience of using specific treatments.

All guidelines recommend stopping or discontinuing (rather than pausing) ICI therapy in cases of ICI-induced myocarditis. One states that the appropriateness of rechallenge is unknown.

Infliximab is contra-indicated in heart failure. Two guidelines caution against its use and the European guideline (ESMO) does not suggest it as an additional immunosuppressant. However, patients in Wales with an LVEF of 40% or below (indicative of heart failure) would be given tocilizumab in preference to infliximab for the treatment of ICI-induced myocarditis unresponsive to steroids.

Patient submission

We received a submission from the patient organisation Melanoma Focus, commenting on our assessment of infliximab to treat steroid-resistant ICI myocarditis. The main points of the submission are listed below.

- There is a growing population of melanoma patients who are younger in age; in the 15–44 years age group, melanoma is the second most common form of cancer in males and the third most common cancer in females.
- Checkpoint inhibitors, alone or in combination, are standard of care for all patients with metastatic melanoma.
- Patients will generally accept significant toxicities in order to live longer. For metastatic melanoma, the longer-term survival rate is better for those treated with combination treatment. Therefore, patients, if fit enough, will likely be treated with combination therapy at the expense of approximately 60% of patients reporting grade 3–4 toxicities.
- Immune checkpoint inhibitors (ICIs) have revolutionised melanoma care; 50% of patients treated with metastatic disease are now alive at 10 years. However, life-threatening (grade 3–4) toxicities are reported in 50–60% of patients on combination ICI therapy, and in about 20% of patients on single agent ICI therapy.
- Cardiac toxicity is an increasingly recognised complication of ICI therapy, occurring in around 10% of treated patients. Myocarditis can occur in 4% of patients and its incidence is rising every year.

- Myocarditis is potentially fatal and early assessment and intervention are key. Standard guidelines for grade 3–4 toxicity recommend initial, high-dose corticosteroid treatment. Patients with myocarditis often need additional immunosuppression with additional medicines, some of which target different chemicals released as part of the inflammatory process associated with checkpoint inhibitors and include infliximab, tocilizumab and abatacept.
- Melanoma Focus supports the co-creation of guidelines for worsening or refractory myocarditis with the cardiologist or medical oncologist. As patients with this condition can deteriorate rapidly, patients and emergency departments need to be aware to swiftly report symptoms which may suggest possible myocarditis, and that it should be treated appropriately to avoid unnecessary long-term complications or worse, death.

Ongoing clinical studies
Two clinical studies are under way of abatacept in the treatment of ICI-induced myocarditis[50,51]. No studies are under way for infliximab in this indication.

Cost-effectiveness evidence

No cost-effectiveness evidence was identified for this use of infliximab, and in the absence of any clinical studies of infliximab for this indication, no cost-effectiveness analyses have been undertaken.

Budget impact

Infliximab procurement costs are informed by a confidential NHS Wales contract price with a unit cost of a 100 mg vial ranging between [commercial in confidence figures removed] for the various biosimilars on all-Wales contract. NHS Wales prescribing figures from 2024 for infliximab 100 mg are used to calculate a weighted average procurement cost. The weighted average cost per 100 mg vial is [commercial in confidence figure removed] excluding VAT.

The average patient weight is calculated using population averages with an equal percentage of male and females. The recommended dose of 5 mg/kg for an average patient weight of 79 kg results in 4 vials per dose[52]. There is an assumption of no vial sharing; wastage is applied. The total infliximab procurement cost for a single dose is [commercial in confidence figure removed] excluding VAT.

The administration cost for the delivery of infliximab is sourced from the NHS reference costs 2023/24 with cost code SB12Z used for the first administration and SB15Z for additional delivery[53]. The first administration cost is £418. Delivery of subsequent dose is costed at £426. Based on clinical expert opinion, it is assumed patients receive three doses of infliximab at 5 mg/kg, the cost of which is [commercial in confidence figure removed] per patient excluding VAT.

Clinicians in Wales indicate that currently patients with steroid-refractory ICI-induced myocarditis are predominantly treated with mycophenolate mofetil (MMF) and/or tacrolimus. A typical regimen for MMF is 500 mg twice daily for 3 days increasing to between 1 – 1.5 g twice daily depending on response. Tacrolimus is usually initiated at a dose of 3 mg twice daily and adjusted according to trough levels. Treatment with

MMF or tacrolimus is continued until the patient has been weaned off steroids and is stable; this is usually between 8-12 weeks after initiation of treatment.

MMF and tacrolimus procurement costs are informed by confidential NHS Wales contract prices for each. The unit cost of MMF for 50 x 500 mg tablets ranges from [commercial in confidence figures removed] excluding VAT. Using the second lowest price of [commercial in confidence figure removed], the maximum acquisition cost of 1.5 mg MMF twice daily for 12 weeks is calculated as [commercial in confidence figure removed]. The unit cost of tacrolimus (100 x 1 mg tablets) is [commercial in confidence figure removed] excluding VAT. The maximum acquisition cost of 3 mg tacrolimus twice daily for 12 weeks is [commercial in confidence figure removed].

The NHS Wales National Immunotherapy Toxicity Sub-Group estimates that approximately 42 patients with steroid-resistant grade 3-4 ICI-induced myocarditis across Wales would be eligible for treatment each year. However, tocilizumab would be used in preference to infliximab for patients with a LVEF of less than 40%. Clinicians estimate that 1 in 5 patients would be treated with tocilizumab meaning that approximately 34 patients per year would receive infliximab. The estimated range of total annual costs for 3 doses of infliximab, assuming both full and no displacement of comparator treatments is given in Table 3.

Table 3. Estimated annual net cost for infliximab in comparison to MMF and tacrolimus in Wales

	Per patient	For 34 patients
Medicine acquisition and administration costs		
Infliximab (3 doses)	¶¶	¶¶
MMF (1.5 mg twice daily for 12 weeks)	¶¶	¶¶
Tacrolimus (3 mg twice daily for 12 weeks)	¶¶	¶¶
Annual net cost of infliximab		
Assuming no displacement of comparators	¶¶	¶¶
Assuming full displacement of MMF only	¶¶	¶¶
Assuming full displacement of tacrolimus only	¶¶	¶¶
Assuming full displacement of MMF and tacrolimus	¶¶	¶¶
MMF: mycophenolate mofetil ¶¶ commercial in confidence figure removed		

The introduction of infliximab for the treatment of grade 3–4 steroid refractory myocarditis induced by immune checkpoint inhibitor (ICI) therapy will increase the spend for this patient group. Based on an estimated uptake of 34 patients receiving three doses of 5 mg/kg infliximab, the annual net budget impact is expected to range between [commercial in confidence figures removed] depending on the degree of displacement of comparator treatments.

Budget impact issues

- Infliximab biosimilar NHS Wales contract costs have been used in the calculations; costs may be higher for other products.
- Costs of additional screening and monitoring for bacterial, viral and fungal infections and adverse event costs are excluded from the budget impact both

for infliximab and for comparator treatments. Tacrolimus also requires therapeutic drug monitoring; this cost has been excluded from the budget impact.

- The degree of displacement of the comparator treatments MMF and tacrolimus is difficult to estimate at present. Outcome data for [confidential information removed] patients treated with infliximab in Wales shows that all had also received MMF with [confidential information removed] also receiving tacrolimus. Clinicians in Wales indicate that infliximab would be the preferred treatment option for this patient cohort and so it could be expected that these comparator treatments may be displaced if routine access to infliximab is enabled. However, acquisition costs of both MMF and tacrolimus are low and so the impact of their displacement on the overall budget impact would be expected to be modest.
- Clinical experts suggest that infliximab may result in better clinical outcomes for some patients and avoid the need for additional further treatments and shorten hospital stay. The lack of comparative data between treatments means that any additional benefit from infliximab cannot be quantified and taken into account in budget impact calculations.
- The budget impact calculations assume that all patients will receive the maximum 3 doses of infliximab; clinicians in Wales state that this is the usual intention although data for [confidential information removed] patients already treated in Wales indicates that this is not achieved or required in all cases. Therefore, the budget impact may be overestimated.
- Administration costs for oral treatments (i.e. MMF and tacrolimus) are assumed to be zero but may be associated with administration costs. However, these are expected to be minimal in comparison to administration costs associated with infliximab which is delivered by intravenous infusion.
- Medicine acquisition costs may be liable to VAT which has not been included in budget impact calculations.
- The use of ICIs is continually growing and it is anticipated that patient numbers will increase over the next few years, which will have an additional budgetary impact in Wales.

Equality and health impact assessment

AWTTC have completed an Equality and Health Impact Assessment in parallel with each development stage of the project. This follows the five ways of working for public bodies, and work to achieving the wellbeing goals, outlined in the Well-Being of Future Generations (Wales) Act 2015.

It is not expected that infliximab will have significant potential negative impact on people based on the protected characteristics of the Equality Act 2010.

Additional factors

Infliximab is not licensed to treat this indication and is therefore ‘off label’. Providers should consult the relevant guidance on prescribing unlicensed medicines before any off-label medicines are prescribed.

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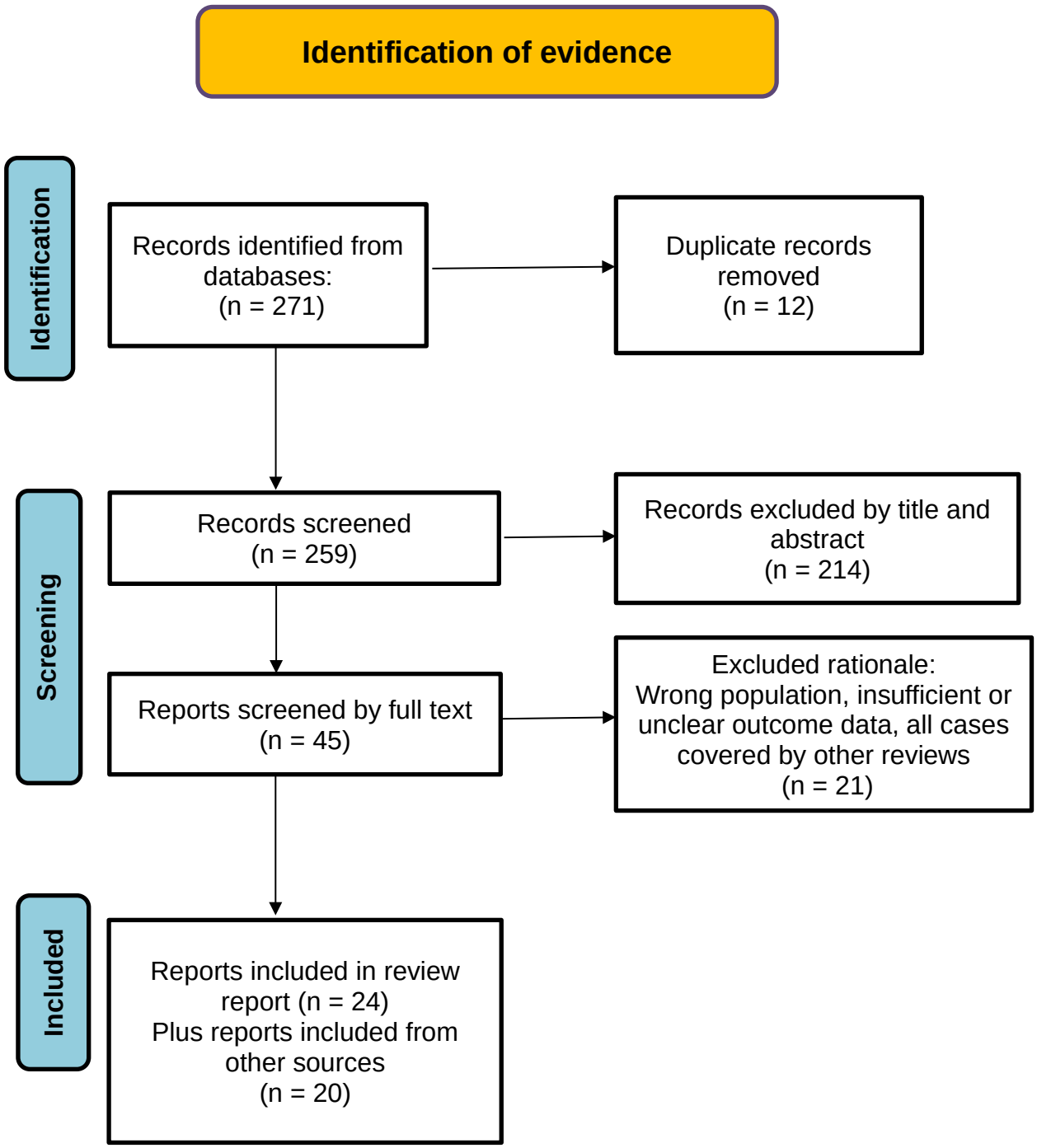
Appendix 1. PRISMA flow diagram – clinical evidence



Appendix 2

Table 4. Case reports and case series of steroid-refractory ICI myocarditis treated with infliximab

Author and date	Patient details	1st-line treatment	Additional immunosuppressant treatment	Outcomes	Cited in reviews
Case reports					
Vu et al. 2025[19] (conference abstract)	A 74-year-old man with right renal clear cell carcinoma who presented for shortness of breath and bradycardia, four weeks after completing one cycle of neoadjuvant pembrolizumab and lenvatinib.	methylprednisone 1000 mg for 3 days then 1 mg/kg	One dose of iv infliximab, 5 mg/kg was given.	Heart rhythm recovered to atrial fibrillation; ejection improved to 55%; patient extubated.	-
Gomez et al. 2025[20]	An 80-year-old man receiving pembrolizumab as first-line treatment for MSI locally advanced gastric adenocarcinoma, presented 3 weeks after the second dose of ICI with progressive fatigue, muscle weakness, blurred vision, binocular diplopia and left ptosis. ICI-induced myocarditis, myositis and myasthenia gravis overlap (triple M) syndrome was established	intravenous methylprednisolone 1.5 mg/m^2 – no clinical improvements after 3 days	iv methylprednisolone (1 g/day), iv immunoglobulin (IVIG) 2 mg/kg over 5 days and iv infliximab 500 mg	Gradual improvement of CV symptoms	
Tan et al. 2024[16]	A 62-year-old man presented with dizziness, bilateral ptosis	Methylprednisolone 80 mg/day then	IVIG (20 g/ day) and MMF (1,000 mg/day) for	Symptoms resolved gradually	Tan 2024[16]

Author and date	Patient details	1st-line treatment	Additional immunosuppressant treatment	Outcomes	Cited in reviews
	and eye movement disorders 2 weeks after 2 cycles of ICI combination treatment. The diagnosis of ICI-induced myocarditis (grade 3), and myositis-myasthenia gravis overlap syndrome was diagnosed.	pulse dose methylprednisolone 500 mg/day for 7 days.	6 days. Symptoms persisted; elevated TNF-alpha detected. Infliximab (200 mg/day) was given on Days 23, 37 and 64.		
	A 57-year-old woman with lung cancer diagnosed with grade 3 ICI-induced myocarditis after 3 cycles of ICI treatment. Symptoms initially improved with steroid treatment by on day 16 and steroid-refractory ICI-induced myocarditis was diagnosed.	Methylprednisolone (80 mg/day for 9 days, with gradually decreasing doses)	Pulse-dose methylprednisolone (500 mg/day) for 3 days, MMF (1,000 mg/day) for 11 days and IVIG (20 g/day) for 3 days. Elevated TNF-alpha detected. Infliximab (200 mg) was administered on Days 31, 45 and 73. Oral prednisone (50 mg/day, tapering dose.	Symptoms resolved	
Feng et al. 2024[25]	A 58-year-old man with thymoma was diagnosed with myocarditis after treatment with toripalimab. Also diagnosed with myasthenia with positive anti-acetylcholine receptor antibodies.	Corticosteroids (250 mg/q12h) and immunoglobulin (400 mg/kg for 5 days) administered, with little improvement.	Two weekly infusions of infliximab	Myocarditis improved	Tan 2024[16]

Author and date	Patient details	1st-line treatment	Additional immunosuppressant treatment	Outcomes	Cited in reviews
Koelmeyer et al. 2024[42]	A 68-year-old woman with urothelial cancer who developed shortness of breath and chest pain one week after receiving combination ICI therapy. Her condition deteriorated, with reduced ejection fraction.	Pulse-dose methylprednisolone	Additional anti-inflammatory agents administered, including mycophenolate, infliximab, and anti-thymocyte globulin.	Little improvement in clinical status; the patient died.	
Qin et al 2024[21]	A retrospective review of 31 patents with ICI-induced myocarditis; 21 had grade 3-4 myocarditis. One 36-year-old man developed grade 4 myocarditis after 1 treatment cycle.	Methylprednisolone 500 mg	The patient was given IVIG, infliximab (300 mg) and plasmapheresis	Symptoms improved; no myocarditis relapse. Patient died of cancer progression	
Eslinger et al. 2023[29]	An 85-year-old man presented with significant chest pain and progressive shortness of breath after a second infusion of pembrolizumab. A diagnosis of grade 4 myocarditis was made and the ICI treatment was stopped. He was discharged after initial treatment, but presented with symptoms on myocarditis on 3 separate occasions; refractory myocarditis was considered.	Methylprednisolone at 1,000 mg for 3 days followed by 60 mg of oral prednisone daily, tapered by 10 mg every 7 days.	One dose of 5 mg/kg infliximab with pulsed methylprednisolone at 1,000 mg for 3 days and transitioned to a slow prednisone taper.	Symptoms resolved; no recurrence of myocarditis.	Wang 2024[15]
Deharo et al. 2022[27]	A 70-year-old man was admitted to intensive care after 2 cycles of ICI therapy; diagnosed as grade 3/severe	Methylprednisolone 1000 mg/day	Infliximab 500 mg Patient then developed atrio-ventricular block treated with a	Patient died.	Wang 2024[15]

Author and date	Patient details	1st-line treatment	Additional immunosuppressant treatment	Outcomes	Cited in reviews
	ICI-induced myocarditis, myositis and myasthenia gravis syndrome.		pacemaker; Abatacept (500 mg) and five sessions of plasmapheresis.		
Kadokawa et al. 2021[30]	A 66-year-old man developed disseminated intravascular coagulation (DIC) and myocarditis after ICI therapy.	Prednisolone 80 mg iv days 34–36; methyl prednisolone sodium succinate 1000 mg iv days 37–39; prednisolone 80mg iv days 40-44	Day 40: infliximab (5 mg/kg); prednisolone dose tapered; Day 54 second dose of infliximab (5 mg/kg)	Day 49 – DIC improved; Day 69 – myocarditis improved	Tan 2024[16] CADTH 2024[3] Wang 2024[15]
Barry et al. 2021[23]	An 82-year-old man with urothelial cancer developed ICI myocarditis	Methylprednisone 1g daily for 5 days	IVIG then single dose of infliximab (due to concomitant myositis)	No improvement; ATG started and symptoms improved.	Wang 2024[15]
Portoles-Hernandez et al. 2021[26]	A 48-year-old woman with thymoma who developed complete atrioventricular block associated with fulminant myocarditis and myasthenia gravis 2 weeks after starting pembrolizumab.	Methylprednisolone dose (2 mg/kg)	Infliximab (5 mg/kg) was administered, a temporary pacemaker implanted and methylprednisolone dosage escalated (1 g per day, intravenously, for 5 days), and subsequently continued with previous dose (2 mg/kg)	Developed cardiogenic shock and respiratory failure; died 10 days after admission.	Phing 2024[14] Cozma 2022[17]
Puzanov et al. 2021[43]	A retrospective study of 15 patients who had ICI-associated myocarditis; 11 of whom had severe (grade 3–4) myocarditis. One patient had	Patient given infliximab started on oral prednisone 160 mg twice daily, and had two doses of iv	Patient given infliximab on Day 86, then oral prednisone.	Myocarditis resolved.	Tan 2024[16]

Author and date	Patient details	1st-line treatment	Additional immunosuppressant treatment	Outcomes	Cited in reviews
	additional treatment with infliximab.	methylprednisolone 1 g at Day 29 and Day 81.			
Wang et al. 2021[39]	Case series of 24 patients with ICI-induced myocarditis. One patient with corticosteroid-resistant myocarditis given infliximab.	Corticosteroids Methylprednisolone iv 500 mg	Single dose of infliximab (500 mg iv)	No improvement – death from myocarditis progression	Daetwyler 2024[5]
Wintersperger et al. 2021[40]	A series of 4 patients with ICI-induced myocarditis. One patient's myocarditis improved after high-dose steroids but he was readmitted 79 days after initial presentation and given infliximab and mycophenolate.	Methylprednisolone 1 g for 5 days then oral prednisone 2 mg/kg	Infliximab 350 mg and mycophenolate mofetil iv (1000 mg twice daily)	Symptoms improved.	Cozma 2022[17]
Dearden et al. 2021[22]	Of 82 patients who developed hyperacute toxicity after treatment with ipilimumab and nivolumab, two developed myocarditis (grade 5, with death 16 days and 24 days after treatment).	Not specified	One patient received 2 days of infliximab.	Patients died from myocarditis.	
Giancaterino et al. 2020[31]	An 88-year-old man who developed generalised weakness 22 days after a first dose of nivolumab for melanoma. Steroids were started for suspected myocarditis, but he developed heart block.	Methylprednisolone 125 mg daily iv on Days 5–6; then increased to 1 g iv methylprednisolone daily	One dose of infliximab 5 mg/kg given on Day 9.	Symptoms did not improve; pacemaker fitted; patient died on Day 15.	Tan 2024[16] Phing 2024[14] Cozma 2022[17] Wang 2024[15]

Author and date	Patient details	1st-line treatment	Additional immunosuppressant treatment	Outcomes	Cited in reviews
Fuentes-Antras et al. 2020[28]	A 75-year-old man with lung adenocarcinoma who presented with hyperthyroidism and mild hepatotoxicity after a single cycle of ICI therapy that led to thyrotoxicosis and hepatitis.	High-dose dexamethasone (4 mg every 6 h) 1 g iv methylprednisolone bolus daily for 5 days	Infliximab 5 mg/kg then iv immunoglobulins	Infliximab and IVIG started due to rapid progression to myocarditis, pneumonitis and MG. Death on Day 7.	Phing 2024[14] Cozma 2022[17]
Norwood et al. 2020[44]	A 57-year-old woman developed ICI-induced myocarditis treated with steroids. After 15 months another dose of ICI therapy was given and myocarditis recurred.	Methylprednisolone 125 mg/day for 12 days, followed by prednisone 1 mg/kg/day	A single dose of infliximab	No improvement after infliximab – treated with ATG, tacrolimus, mycophenolate and prednisone and symptoms improved,	Cozma 2022[17]
Padegimas et al. 2019[32]	53-year-old woman with metastatic ovarian adenocarcinoma who had increased troponin 4 days after starting pembrolizumab treatment. She was discharged on 50 mg of prednisone but presented one month later with exertional chest pressure and myocarditis was diagnosed.	Prednisone 1 mg/kg was started, then 1 g methylprednisolone for 3 days.	Symptoms recurred after steroid taper and infliximab (5 mg/kg) was given.	Arrhythmias terminated and she was discharged on steroid taper. Troponin normalised in 9 months.	Tan 2024[16] Phing 2024[14] CADTH 2024[3]
	A 62-year-old woman with metastatic renal cell carcinoma who developed sudden dyspnoea 5 weeks after starting nivolumab	Methylprednisolone iv 1 mg/kg; then 2 g methylprednisolone for 3 days.	One dose of infliximab (5 mg/kg) given after 3 days.	Conduction block resolved; she had a single-chamber cardioverter-defibrillator placement and	

Author and date	Patient details	1st-line treatment	Additional immunosuppressant treatment	Outcomes	Cited in reviews
	treatment. She developed cardiogenic shock and finding were consistent with perimyocarditis.			recovered from cardiogenic shock. She died 2 months later of bacteraemia and pulmonary embolism.	
Saibil et al. 2019[33]	A 67-year-old man with metastatic melanoma treated with ipilimumab and nivolumab developed increasing fatigue, weakness and dyspnoea 16 days later. Myocarditis was diagnosed.	High-dose methylprednisone (200 mg on Day 1, then 1000 mg daily for 3 days)	Symptoms worsened – given one dose of infliximab (5 mg/kg) and 2 doses of intravenous immunoglobulin.	Condition worsened and he died on Day 18 of multiple organ failure including myocarditis and rhabdomyositis.	Tan 2024[16] Daetwyler 2024[5] CADTH 2024[3] Phing 2024[14] Cozma 2022[17] Wang 2024[15]
Gallegos et al. 2019[41]	A 47-year-old woman with a history of carotid artery dissection and metastatic melanoma presented with acute heart failure, 4 months after restarting nivolumab. LVEF = 26%	Methylprednisolone 500 mg intravenous BID for 5 days	Infliximab (10 mg/kg/day for 2 days)	Symptoms worsened and patient died	Tan 2024[16] Phing 2024[14]
Shah et al. 2019[45]	A 73-year-old man with urothelial carcinoma who developed ICI-induced myocarditis.	Methylprednisolone iv (1 mg/kg twice daily), with mild response	A single infliximab infusion followed by 12 rounds of plasmapheresis, and subsequent IVIG infusions.	Underwent a tracheostomy; death primarily due to cancer progression.	Phing 2024[14]
Agrawal et al. 2019[34]	A case series of 5 patients with ICI-related cardiotoxicity, including one patient, a 67-year-old man with melanoma treated with nivolumab, who received infliximab for recurrent myocarditis.	Pulse dose steroid (1,000 mg/day) given for 3 days then prednisolone (80 mg BID)	Infliximab 5 mg/kg for two doses.	Myocarditis improved after second infusion; no cardiovascular mortality in 120 days of follow-up	Tan 2024[16] Phing 2024[14]

Author and date	Patient details	1st-line treatment	Additional immunosuppressant treatment	Outcomes	Cited in reviews
Zlotoff et al. 2019[35] Conference abstract	An 88-year-old man developed fatigue after starting pembrolizumab for metastatic melanoma. He was diagnosed with ICI myocarditis after endomyocardial biopsy and increased troponin levels.	Methylprednisolone 1 g iv daily	After 5 days, troponin increased to 719 ng/L and 5 mg/kg infliximab was given. Troponin continued to rise and a second dose of infliximab was given and mycophenolate mofetil started: 750 mg twice daily. Troponin increased further.	Discharged after 3 weeks; continued oral prednisone 60 mg daily and mycophenolate mofetil 1000 mg twice daily and had two infusions of intravenous immunoglobulin. His troponin values gradually fell to 578 ng/L at one month after discharge.	Phing 2024[14]
Frigeri et al. 2018[36]	A 76-year-old woman with lung adenocarcinoma in remission after 7 bi-weekly treatments with nivolumab, who developed signs of heart failure and developed cardiogenic shock. LVEF <10%	Methylprednisolone (5 mg/kg/day) then plasmapheresis and IVIG (1000 mg/kg/day)	Infliximab 5 mg/kg on Day 6, Day 27 and Day 39 (3 doses)	Myocarditis improved; no cardiovascular mortality in 180 days of follow-up	Tan 2024[16] Phing 2024[14] Cozma 2022[17]
Martinez-Calle et al. 2018[37]	A 67-year-old woman with multiple myeloma who developed myocarditis after starting pembrolizumab treatment.	Methylprednisolone 1.5 mg/kg/day	Infliximab 5 mg/kg – one dose	No improvement; patient died of multi-organ failure	Tan 2024[16] Phing 2024[14] Cozma 2022[17]
Tay et al. 2017[38]	A 64-year-old woman with glioblastoma developed arrhythmias secondary to histologically confirmed severe immune-mediated myocarditis. LVEF = 37%	Methylprednisolone 500 mg daily for 3 days before tapering to oral prednisolone 100 mg daily.	A single dose of iv infliximab 5 mg/kg administered on Day 2	Myocarditis did not improve after infliximab; symptoms improved after ATG then mycophenolate	Tan 2024[16] Daetwyler 2024[5] Phing 2024[14] Cozma 2022[17] Wang 2024[15]

Author and date	Patient details	1st-line treatment	Additional immunosuppressant treatment	Outcomes	Cited in reviews
Johnson et al. 2016[24]	A 63-year-old man with metastatic melanoma developed fatigue and myalgias 15 days after a first dose of ICI therapy. Myocarditis and myositis were diagnosed. LVEF = 50%	Methylprednisolone iv administered at 1 g/kg daily for 4 days	Infliximab 5 mg/kg – one dose	Complete heart block developed followed by cardiac arrest and death.	Tan 2024[16] Phing 2024[14]
Retrospective cohort studies, case series					
Ali et al. 2024[49]	A single-centre, retrospective cohort study of 99 patients with ICI-induced myocarditis. 44 of 65 (68%) of patients with cytokine data available had peak TN-alpha above normal limits (>22 pg/mL). 50 patients had grade 3 or 4 myocarditis.	81 patients given steroids and 61 given immunomodulators	23 patients given infliximab (5 mg/kg): included 6 with TNFalpha ≥22 pg/ml and 16 with TNF-alpha >22 pg/ml. Administration of infliximab showed similar MACE-free and overall survival between all patients and those with elevated TNF-alpha levels.	None of the patients who received infliximab developed worsening heart failure after infliximab administration. Conclusion: the use of infliximab did not lead to different survival outcomes.	
Zhang et al. 2021[46]	A retrospective case series of 11 patients who developed ICI-induced myocarditis; 4 patients (mean age 61.8 years) had grade 4 myocarditis treated with infliximab due to worsening clinical status despite high-dose steroids (refractory myocarditis).	High-dose steroids - iv methylprednisolone 1 g x 3 days	All 4 patients received a single dose of infliximab (5 mg/kg).	All 4 patients survived initial hospitalisation but needed prolonged steroid tapers. Two patients died from septic shock 2 and 3 months after initial myocarditis treatment. The other 2 patients completed steroid tapers with no evidence of myocarditis.	Tan 2024[16] Daetwyler 2024[5] CADTH 2024[3]

Author and date	Patient details	1st-line treatment	Additional immunosuppressant treatment	Outcomes	Cited in reviews
Lipe et al. 2021[47]	Retrospective chart review of 7 patients with ICI-associated myasthenia gravis, myositis and myocarditis overlap syndrome. 4 patients had confirmed myocarditis by an endomyocardial biopsy.	High-dose glucocorticoids (1–2 mg/kg of prednisone or equivalent)	Three patients with confirmed myocarditis given infliximab.	All three patients needed further treatments after infliximab; these were rituximab and plasma exchange in 2 patients who survived; the 3rd patient had plasma exchange and IVIG but died.	Tan 2024[16]
Cautela et al. 2020[48]	A case-control study of 60 patients (aged 69 ± 12 years) who developed ICI-induced myocarditis. 36 patients had grade 4 myocarditis and required IIST; 20 patients had grade 3–4 myocarditis and did not require IIST.	High-dose corticosteroids	36 patients required IIST: 8 were treated with infliximab. Patients who received infliximab were more likely to die from cardiovascular causes (OR, 12.0; 95% CI 2.1 to 67.1; p=0.005).	5 patients died, 4 of cardiovascular causes. In patients receiving IIST, infliximab treatment was associated with a significantly increased risk of cardiovascular death.	

ATG: anti-thymocyte globulin; CI: confidence interval; ICI: immune checkpoint inhibitor; IIST: intensified immunosuppressive therapy; IVIG: intravenous immunogloblin; IV: intravenous; MACE: major adverse cardiovascular events; MG: myasthenia gravis; MMF: mycophenolate mofetil; OR: Odds ratio