FACULTADE DE MEDICINA
E ODONTOLOXÍA

Traballo de fin de grao

ABATACEPT FOR THE TREATMENT OF IMMUNE CHECKPOINT INHIBITOR INDUCED MYOCARDITIS: A SYSTEMATIC REVIEW.

ABATACEPT PARA O TRATAMENTO DA MIOCARDITE INDUCIDA POR INHIBIDORES DE PUNTOS DE CONTROL INMUNITARIOS: UNHA REVISIÓN SISTEMÁTICA.

ABATACEPT PARA EL TRATAMIENTO DE MIOCARDITIS INDUCIDA POR INHIBIDORES DE PUNTOS DE CONTROL INMUNITARIOS: UNA REVISIÓN SISTEMÁTICA.

Autor: Iago Lázaro Saiz
Titor: Luis Ángel León Mateos (CHUS)
Cotitora: María José Villanueva Silva (CHUVI)
Departamento: Oncoloxía médica

CONVOCATORIA - XUÑO 2023

Traballo de Fin de Grao presentado na Facultade de Medicina e Odontoloxía da Universidade de Santiago de Compostela para a obtención do Grao en Medicina.

INDEX

ABSTRACT

BACKGROUND: Immune checkpoint inhibitor induced myocarditis is a severe, life-threatening side effect. Abatacept is a fusion protein binding to costimulatory molecules B7 (also known as CD80 and CD86) on antigen presenting cells, blocking interaction with CD-28 on T cells, thereby preventing T cell activation, a mechanism in close relation to immune induced myocarditis.

OBJECTIVE: To perform a systematic review that gathers all scientific evidence on abatacept for the treatment of immune checkpoint inhibitors induced myocarditis.

MATERIAL AND METHODS: An electronic search of published as a research article from 2000 to 2022 was performed, limited to English, Spanish and French language, following a predefined protocol, in accordance with the PRISMA guidelines.

RESULTS: The search identified 607 records. After screening and eligibility process, 7 articles were included with a total of 7 patients.

CONCLUSION: Despite scarcity of conclusive evidence, this systematic review provides proof of concept that abatacept-induced CTLA-4 activation can reverse immunoreactive myocarditis and underscores the need for further research. In the meantime, when faced with a case of this nature, abatacept could be a treatment to consider in cases of corticosteroid-resistant myocarditis.

Key Words: abatacept, immune checkpoint induced, myocarditis, PD-1 checkpoint inhibition, PD-L1 checkpoint inhibition, CTLA-4 checkpoint inhibition.

RESUMO

INTRODUCIÓN: A miocardite inmuno-mediada por tratamentos con inhibidores de puntos de control inmunitarios é un efecto adverso grave e potencialmente letal. O abatacept é unha proteína de fusión que se une ás moléculas coestimuladoras B7 (coñecidas tamén como CD80 e CD86) nas células presentadoras de antíxenos, bloqueando a interacción co CD-28 das células T, e, polo tanto, previndo a súa activación, un mecanismo moi relacionado coa miocardite inmuno-mediada.

OBXECTIVO: Realizar unha revisión sistemática que reúna toda a evidencia científica sobre o abatacept como tratamento da miocardite inmuno-inducida por tratamentos con inhibidores de puntos de control inmunitarios.

MATERIAL E MÉTODOS: Realízase unha busca electrónica da evidencia publicada como artigos de investigación dende o 2000 ata o 2022, limitada a inglés, francés e castelán, e seguindo un protocolo predeterminado dacordo ás guías PRISMA.

RESULTADOS: Coa busca identificáronse 607 resultados. Tra-lo proceso de selección, incluíronse 7 artigos cun total de 7 pacientes.

CONCLUSIÓN: Malia a escaseza de evidencia concluínte, esta revisión sistemática proporciona unha proba de concepto sobre que a activación de CTLA-4 inducida polo abatacept pode revertir a miocardite inmunoreactiva e salienta a necesidade de investigacións adicionais. Entre tanto, ao enfrontar casos desta natureza, o abatacept pode ser un tratamento que considerar en casos de resistencia á terapia corticoidea.

Palabras clave: abatacept, inmuno-mediada, miocardite, inhibición do punto de control PD-1, inhibición do punto de control PD-L1, inhibición do punto de control CTLA-4.

RESUMEN

INTRODUCCIÓN: La miocarditis inmuno-mediada por tratamientos con inhibidores de puntos de control inmunitarios es un efecto adverso grave y potencialmente letal. El abatacept es una proteína de fusión que se une a las moléculas coestimuladoras B7 (conocidas también como CD80 y CD86) en las células presentadoras de antígenos, bloqueando la interacción con CD-28 de las células T, y, por lo tanto, previniendo su activación, un mecanismo muy relacionado con la miocarditis inmuno-mediada.

OBJETIVO: Realizar una revisión sistemática que reúna toda la evidencia científica sobre el abatacept como tratamiento de la miocarditis inmuno-mediada por tratamientos con inhibidores de puntos de control inmunitarios.

MATERIAL Y MÉTODOS: Se realiza una búsqueda electrónica de la evidencia publicada como artículos de investigación desde 2000 hasta el 2022, limitada a inglés, francés y español, y siguiendo un protocolo predeterminado de acuerdo con las guías PRISMA.

RESULTADOS: Con la búsqueda identificaron 607 resultados. Tras el proceso de selección, se incluyeron 7 artículos con un total de 7 pacientes.

CONCLUSIÓN: A pesar de la escasez de evidencia concluyente, esta revisión sistemática proporciona una prueba de concepto sobre que la activación de CTLA-4 inducida por el abatacept puede revertir la miocarditis inmunoreactiva y enfatiza la necesidad de investigaciones adicionales. Mientras tanto, al enfrentar casos de esta naturaleza, el abatacept puede ser un tratamiento que considerar en casos de resistencia a la terapia con corticoides.

Palabras clave: abatacept, inmuno-mediada, miocarditis, inhibición del punto de control PD-1, inhibición del punto de control PD-L1, inhibición del punto de control CTLA-4.

BACKGROUND

Over the last decade, the development of therapies based on immune checkpoint inhibitors (ICIs), either as monotherapy or in combination with other systemic treatments (mainly chemotherapy), has being a turning point in oncology and has transformed the paradigm of cancer treatment as a whole (1). ICIs targeting the Programmed Cell Death Protein-1 (PD-1) receptor, its ligand (PD-L1), or the Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) receptor, have demonstrated unprecedented efficacy in the treatment of several types of tumors, starting with malignant melanoma, and then opening the floor to a wide range of neoplasms, including but not limited to non-small-cell lung cancer, head and neck cancer, urothelial tumors, renal cancers, Hodgkin lymphoma, to name a but a few (2).

Immune checkpoints are proteins that enable the immune system to maintain self-tolerance, thus preventing autoimmunity (3). Both CTLA-4 and PD-1 are believed to modulate T-cell response, upon reaching the threshold for the purpose for which they were initiated. As such, CTLA-4 inhibits the immune response by ceasing T-cell activation once a sufficient amount of T cell lymphocyte has been activated by antigen-presenting cells (mainly dendritic cells, macrophages or B cell) at early stages (lymph node level). Subsequently, PD-1 activation induces apoptosis of activated T lymphocytes (at the peripheral tissue level) (4). It is precisely this down-regulation of T-cell activity that is one of the major pathways utilized by tumors to modulate immunogenicity and escape the immune system response (5). Therefore, inhibition of these proteins can be expected to induce immune system activation (6) and, consequently, a proinflammatory tumor microenvironment, which would improve tumor control.

Nevertheless, in spite of the efficacy and success of ICIs-based cancer therapies, one of the major drawbacks of these treatments is the development of significant immune-related adverse events (irAEs) due to excessive immune activation. Many of these irAEs are life-threatening, often involving multiple organs and systems (1,7), leading to treatment discontinuation as well as the prescription of long-term immunosuppressive therapies, with potential diminished tumor efficacy (7,8). Although many irAEs can be successfully managed with corticosteroid therapy or other immunomodulators (8), fatal toxic events do occur with an estimated incidence, according to recent studies, of 0.3% to 1.3% (9,10).

Regarding the incidence of irAEs in relation to ICIs types, it should be noted that the incidence of irAEs is lower with PD-1/PD-L1inhibitors compared to anti-CTLA-4 therapies (10). In addition, several studies have shown that incidence of irAEs is significantly higher with combinations of anti-CTLA-4 and anti-PD-1 as compared with ICI monotherapy (8,10,11), Notably, the severity and fatality rates associated with these irAEs also seem to follow the same trend (12,13). Similarly, with respect to anti-CTLA-4 monotherapy, the incidence of irAEs – including global and organ-specific adverse events– varies as a function of drug dosage, with a higher incidence with increased doses (9,10).

With respect to timing, there is no established timing of irAEs, they can appear at any time, with a wide range, including several days after treatment initiation to several months up to one year after cessation of ICIs therapy (4,10). Nonetheless, the most frequent ones tend to appear during the first 10-12 weeks after treatment initiation (9). An earlier onset of adverse events have been observed in combination therapies in comparison with ICI monotherapy (10,14), being the median time of onset 14,5 days for combined therapy and 40 for monotherapy (10).

As far as cardiac toxicity is concerned, heart immune-related toxicity is a rare complication, with a reported incidence up to 1% (8), although this percentage remains uncertain. Cardiotoxicity may present with different clinical pictures, including pericarditis, arrhythmias, ischemic cardiopathy or tako-tsubo syndrome, to name a few, being myocarditis the most common presentation in the reported series (15). These irAEs, although uncommon, hold the highest lethality rates (14), being fatal in between 27% to 46% of myocarditis reported cases (12).

The mechanism underlying immune-related cardiotoxicity is still not clearly understood. Nonetheless, infiltration of CD4+/CD8+ T-cells and macrophages has been reported on histological biopsies of patients with ICI-induced myocarditis (16), therefore cellular immunity might be considered as the main cause cardiotoxicity (15,16) with no humoral immunity implication proved so far, as no specific autoantibodies had been reported to be present in the analyzed specimens (12,17).

As mentioned beforehand, both CTLA-4 and PD-1 mediated immune down-regulation are pathways used by tumors to avoid immune response (5). Cardiac myocytes are believed to utilize these same pathways to induce immune tolerance and prevent T-cell hyperactivation, just like tumor cells (16,17), as shown in animal models genetically predisposed due to immune checkpoint deficiency (15,16). Therefore, following the same route as antitumoral response, the inhibition of CTLA-4 or PD-1/PD-L1 can lead to autoimmunity and appearance of cardiotoxicity.

Alternatively, another hypothesis under study is based on the shared antigen theory (18), according to which, both myocardium muscle and tumor share a common antigen, which is targeted by T cells overactivated by ICIs (8,18). Furthermore, a frequent association between myocarditis –cardiac muscle– and myositis –skeletal muscle– has been reported, both immune-related, whose appearance can occur concomitantly or sequentially. (19)

As aforementioned, despite the fact that myocarditis is a rare complication, it is indeed the irAE with highest mortality rates (8,12,14) and, paralleling other immune-related toxicities, it appears to be more frequent and lethal in patients receiving combination ICI therapy compared with monotherapy (8,12–14,18). The reported overall prevalence of immune-related

myocarditis was 1.14% for monotherapy and up to 2.5% for ICIs in combination (two or more). (20). Almost one-half of the patients with immune-myocarditis end up developing a major adverse cardiac event (MACE), defined as the composite of any of the following: cardiovascular death, cardiogenic shock, cardiac arrest, ventricular and atrial arrythmia, and hemodynamically significant heart block (20).

Time of onset of myocarditis varies significantly among studies, with a median time ranging from 34 to 65 days after ICI initial administration (16,20). However, it can appear as early as the first or second day of the first cycle up to one year after initiation of ICI treatment (21). Interestingly enough, some studies agree on an earlier onset in patients treated with ICI combination compared to monotherapy (8,16).

ICI induced myocarditis may occur in two forms, a high-grade form with a more fulminant course and increased inflammatory cell infiltration, and a low-grade, more indolent form, with less degree of inflammatory cell infiltration (22). More severe cases, i.e. fulminant myocarditis tend to occur earlier.

As for clinical presentation, non-specific signs and symptoms, including dyspnea, chest pain, palpitation and signs of congestive heart failure seem to be the most common clinical manifestations (21). Clinical presentation might come from cardiovascular complications as arrhythmias, atrioventricular block, myocardial infarction or cardiogenic shock (16,23). Regarding diagnosis, the vast majority of patients present troponin elevation (94%) and abnormal EKG (89%) (20,21), hence being sensitive but unspecific markers. Curiously enough, left-ventricle function was normal in 51% of patients (20), meaning LVFE-measure might not be a good diagnostic tool nor a good follow-up strategy.

Diagnosis requires high index of suspicion and should made on the basis of clinical manifestations and the performance of additional tests including cardiac biomarkers (troponins, CPK, CK, BNP, etc.), ECG, echocardiography, cardiac magnetic resonance (CMR) and/or endomyocardial biopsy. CMR is an accurate way for detecting fibrosis, inflammation, edema or necrosis (16). The diagnoses should be established applying the new Lake Louise criteria of myocarditis (24).

Endomyocardial biopsy (EMB) is considered the gold-standard test (25), showing histopathological findings of inflammation and lymphocyte infiltration within the myocardium – CD4 and CD8 T-cells mainly (16,20,23). However, due to the invasive nature of this test, it is rarely performed.

As far as treatment is concerned, according to SITC and ASCO clinical practice guidelines for treatment of irAEs (25,26), first-line treatment for all irAEs include systemic corticosteroid administration. In those patients who do not respond to initial treatment, second-line immunosuppressive agents might be administered. When any irAE is suspected or

diagnosed, ICI discontinuation should be considered, and re-challenging could be an option provided that toxicity has resolved and always based on a risk-benefit decision (Figure 1).

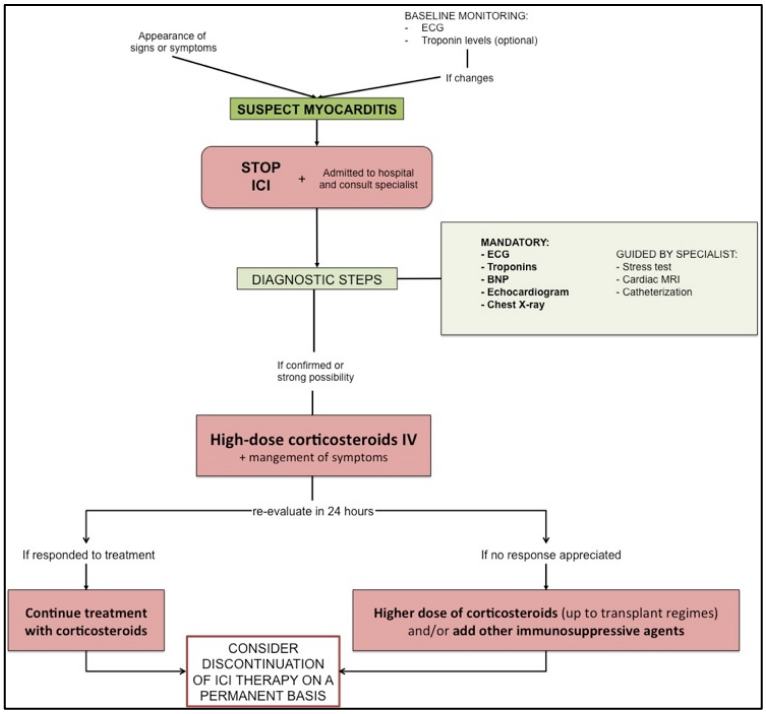

Figure 1. Flow diagram of ICI-related myocarditis diagnosis and treatment. BNP: brain natriuretic peptide; ECG: electrocardiogram; ICI: immune checkpoint inhibitor; IV: intravenous; MRI: magnetic resonance imaging.

Immune myocarditis follows the same general recommendations as any other irAE, nonetheless, upon diagnostic suspicion of myocarditis, and regardless of the degree of toxicity, patients should be admitted to hospital, referred to a cardiology specialist and undergo full diagnostic testing. As for the treatment itself, early high-dose corticosteroids should be administered as soon as diagnosis is likely, as it leads to a lower rate of major adverse cardiac events and fatality (16). If signs or symptoms do not respond during the first 24 hours, other immunosuppressive therapies, such as ATG (antithymocyte globulin), abatacept, mycophenolate mofetil or alemtuzumab, should be considered empirically, owing T-cell overactivation as the potential underlying mechanism. Indeed, in cases of myocarditis, permanent discontinuation of ICIs should be considered (25,26).

Abatacept is a fusion protein comprised of the extracellular domain of CTLA4 and the Fc portion of Immunoglobulin-G (CTLA4-Ig) (27). It binds to costimulatory molecules B7 (also known as CD80 and CD86) on antigen presenting cells, thus preventing their interaction with CD28, and, consequently, T-cell activation. Therefore, abatacept down-regulates the immune response by preventing T cell activation (27,28). Abatacept mechanism of action is represented in Figure 2.

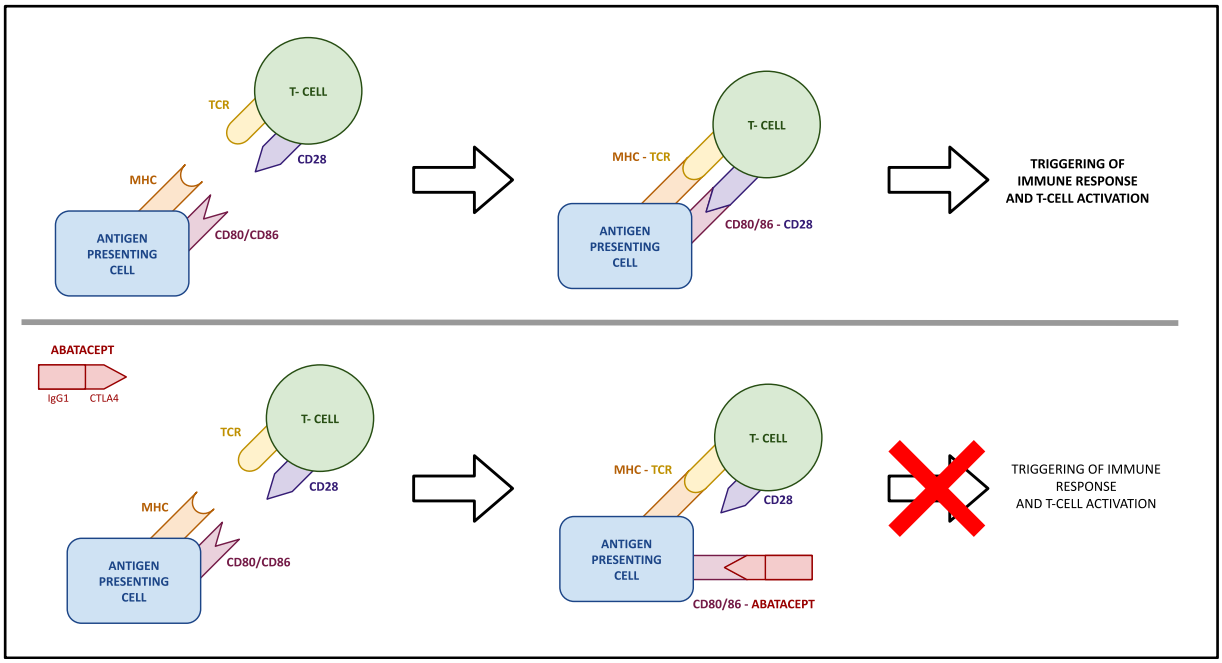

Figure 2. Abatacept mechanism of action. MHC: Major histocompatibility complex; TCR: T-cell receptor.

Treatment with abatacept has been shown to be effective in patients with various autoinflammatory diseases, including rheumatoid arthritis, and could potentially reverse immune checkpoint inhibitors-derived T cell activation.

On account of the similarities between the pathophysiological pathways of ICI-related cardiotoxicity and the mechanism of action of abatacept, a potential benefit in the use of this drug in immune myocarditis can be hypothesized. Thereby, the main objective of the present final degree thesis is to conduct a systematic review in search of published data, to provide insight and perspective on the subject.

OBJECTIVE

To perform a systematic review with the purpose of identifying and summarizing all the available evidence on abatacept for the treatment of immune-related myocarditis.

MATERIAL AND METHODS

Articles including immune-related myocarditis treatment with abatacept, either in monotherapy or in combination, published as a research article from January 2000 to December 2022 were scoured. A PROSPERO-LIKE protocol was predesigned and followed during the search, in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guideline for systematic review. Population was defined as immune-related myocarditis induced by checkpoint inhibitors. Intervention was defined as treatment with abatacept, as described in the search and strategy below.

Immune myocarditis not related to immune checkpoint inhibition was excluded.

Article selection was accomplished by author of the present graduation work with double check with the librarian, supervised by the cotutor. Article selection was restricted to English, Spanish and French language.

SEARCH STRATEGY

An electronically search was conducted in PubMed, Embase, Web of Science for articles reporting abatacept AND immune myocarditis AND a combination of broad terms related to immune checkpoint inhibition ("anti-PD1" OR "anti-PDL1" OR "anti-CTLA4" OR "pembrolizumab" OR "nivolumab" OR "avelumab" OR "atezolizumab" OR "ipilimumab" OR "tremelimumab"). Other possible combination of these terms where used. In addition, a comprehensive manual search of the Reference section as well as the Appendix section, when available, was undertaken.

ARTICLE SELECTION

Inclusion criteria were articles involving abatacept for the treatment of immune checkpoint inhibitor induced myocarditis published as research articles between January 2000 and December 2022 (search criteria are displayed on Table 1). Abstract language selection was restricted to English, Spanish and French.

Table 1. Search criteria for the selection process

ARTICLE TYPE	RESEARCH ARTICLE, CASE REPORT, RETROSPECTIVE O PROSPECTIVE COHORTS, LETTERS.
Condition or domain being studied	ABATACEPT FOR THE TREATMENT OF CHECKPOINT INHIBITOR INDUCED-MYOCARDITIS
Participants/Population	Adult and pediatric population.
Timeline criteria	From January 2000 to December 2021
Linguistic criteria	English, Spanish, French

Exclusion criteria were: (i) immune myocarditis not related to checkpoint inhibition, (ii) non-myocarditis immune checkpoint toxicity, (iii) immunosuppressant agent other than abatacept, (iv) editorials, news articles or commentaries. (v) In the event of multiple publications reporting the study or trial, only the most recent data were considered. (vi) Preference prospective articles over retrospective review was applied.

DATA EXTRACTION

After the identification process, the retrieved articles were screened for relevance. Those deemed to be potentially eligible were fully evaluated in order to assess the requirements of the inclusion criteria. The articles were accepted or rejected based on predefined inclusion and exclusion criteria, mentioned above.

From each included article the following information was extracted, with close attention to AMSTAR checklist for systematic review evaluation, including: age, gender, underlying autoimmune disease (yes/no; type; severity), cardiac comorbidity (yes/no; type; severity), cardiovascular risk factors (smoking habit, hypertension, diabetes, dyslipidemia), lung comorbidity (yes/no; type; severity), renal comorbidity (yes/no; type; severity), other comorbidities (yes/no; type; severity), tumor type, tumor stage, tumor burden (1 or 2 metastatic sites versus > 2 metastatic sites), performance status, prior chemotherapy (yes/no; number of lines); prior radiotherapy (yes/no; field location), immune checkpoint employed (drug, monotherapy or combination), number of courses delivered, myocarditis associated signs and symptoms, myocarditis diagnostic criteria fulfilled, myocarditis diagnostic test performed, timing of myocarditis, circulating blood counts, troponin I, NT-proBNP, other serum biomarkers performed (autoantibodies, cytokines, HLA genotypes, microRNA, gene expression profiling, and serum proteins), myocarditis treatment (corticoid, other immunosuppressive treatments, timing), abatacept treatment (dose, schedule, timing), outcome.

RESULTS

A search on three major medical and scientific databases articles yielded 607 records, through database searching. After identification, 544 were rejected, 424 based on title and 120 based on publication date. Of the 63 remaining for screening, 53 were excluded either based on abstract (21), or for duplication (32). 10 articles were assessed for eligibility, of which 3 were rejected after reviewing the article and appendix because of treatment other than the object of study (1) or no cases reported (2). Finally, 7 was the total number of articles included after the research, whose results are described in the following paragraphs.

Figure 3 represents a diagram of this systematic review, starting with the identification of articles, subsequent screening, and assessment for eligibility, with the abstract and research articles definitively included meeting all inclusion criteria and none of the exclusion criteria.

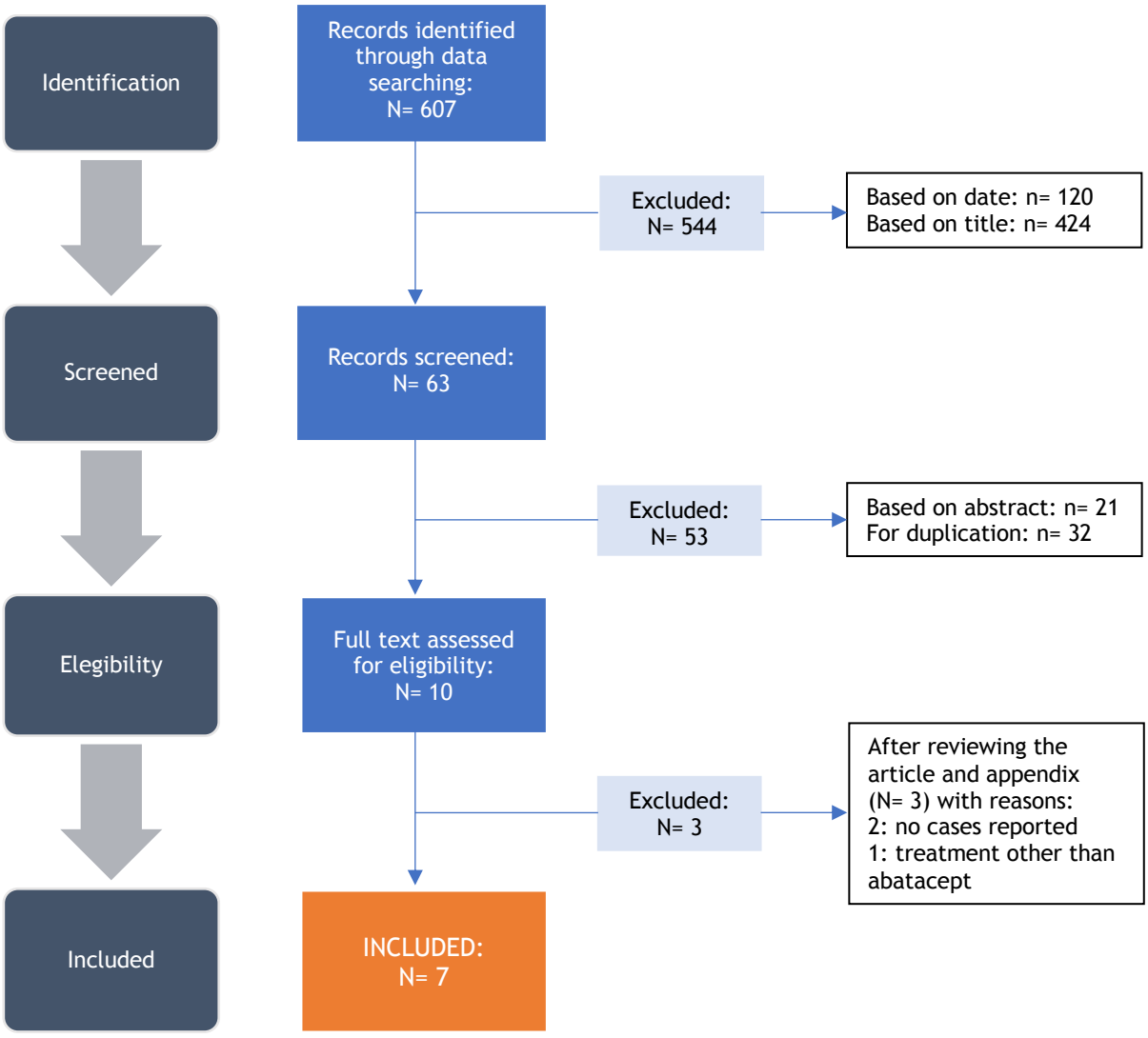

Figure 3. FLOWCHART ACCORDING TO PROSPERO-LIKE PROTOCOL (PRISMA GUIDELINES).

Jespersen *et al*. (29) reported a case of steroid-refractory ICI-related myocarditis and myositis in a metastatic **renal** cell carcinoma patient (57 years old male), appearing twelve days after the first dose combination immunotherapy comprising **nivolumab** (anti-programmed cell death-1) and **ipilimumab** (anti-cytotoxic T-lymphocyte-associated antigen-4). The patient was admitted to the hospital due to pain in the extremities, palpitations, and headache. Laboratory findings showed elevated inflammatory markers and cardiac enzymes. Electrocardiogram revealed right bundle branch block and first-degree atrioventricular (AV) block which developed into complete heart block within 48 h. Despite immediate initiation of **methylprednisolone**, clinical deterioration occurred and **abatacept** and **MMF** was added to the treatment with progressive improvement and eventual recovery.

Kalapurackal *et al*. (30) shared a case of ICI-related myocarditis associated to other adverse events (pneumonitis and hepatitis) in a 65-years-old male with **metastatic melanoma** who received combination therapy with **ipilimumab** and **nivolumab**. Although other adverse events occurred 48 hours after the first dose of immunotherapy was administered and in spite of being under weaning steroid treatment for previous irAEs, ICI-related myocarditis appeared one week later showing chest pain and palpitations. Initial diagnostic steps only revealed elevated high-sensitivity troponin-1 and creatine kinase, with normal electrocardiogram and left ventricle ejection fraction. A cardiac magnetic resonance performed 24 hours later showed late-gadolinium enhancement consistent with ICI-myocarditis. Although high-dose **steroid** and **mycophenolate** were reintroduced, symptoms persisted, cardiac enzymes continued to rise, and alterations appeared on both electrocardiogram and echocardiography. Therefore, **abatacept** was added to treatment leading to progressive resolution and patient full recovery.

Nguyen and colleagues (31) described a case of **pembrolizumab** (anti-PD1)-induced myocarditis and concurrent myositis two weeks after first injection for stage IIIA **thymoma** treatment, which had previously been treated with first-line chemotherapy. The 25-year-old male patient developed sustained ventricular arrhythmia, and cardiogenic shock requiring urgent extracorporeal life support, despite prompt initiation of corticosteroids and mycophenolate-mofetil. **Abatacept** was initiated combined with **ruxolitinib** and **methylprednisolone**. High doses of abatacept were delivered within the first 10 days 60 mg/kg distributed in three doses (20 mg/kg each), followed by two additional doses. Resolution of systolic cardiac dysfunction, and ventricular arrhythmias occurred within 7 days, enabling discontinuation of immunosuppressive therapies and full recovery after 40 days. Despite further tests demonstrated possibility of surgical procedure, the patient refused surgery and was treated consequently with chemotherapy.

Ramayya *et al*. (32) reported a case of a 50-year-old woman with a **metastatic cervical cancer** treated with an ICI plus chemotherapy combination (consisting of **etoposide, carboplatin, and atezolizumab**). The patient developed symptoms 21 days after the start of the combination, 42 days after the first dose of atezolizumab, which worsened progressively over a month until diagnosis of ICI-myocarditis was stablished based on cardiac magnetic

resonance, echocardiography and endomyocardial biopsy. After initiation of high-dose **methylprednisolone** therapy, the patient suffered further hemodynamic deterioration leading to a cardiac arrest and needing venoarterial extracorporeal membrane oxygenation. In addition to methylprednisolone therapy, **abatacept and intravenous immunoglobulin** were added to treatment leading to progressive improvement and, eventually, recovery.

Salem *et al*. (33) communicated a nivolumab-related case in a 66-year-old female patient diagnosed with **metastatic lung cancer**. After receiving three doses of **nivolumab** initiated 1 month earlier, the patient developed diplopia, ptosis, and painful paresis affecting the proximal muscles. Subsequently, she developed chest pain and electrocardiographic repolarization abnormalities, leading to diagnose of myocarditis and concurrent myositis based on laboratory findings, cardiac magnetic resonance and muscle biopsy. No recovery was observed in spite of **methylprednisolone** and **plasmapheresis**, hence **abatacept** was administered. Laboratory abnormalities rapidly resolved, and signs and symptoms of both myocarditis and myositis decreased.

Wakefield and colleagues (34) reported a fulminant myocarditis after the first dose of adjuvant **pembrolizumab** for a stage IIIA **malignant melanoma** in a 55-years-old woman. She presented shortness of breath and weakness and laboratory findings showed elevated troponins. Symptoms were refractory to high-dose steroids, leading to third-degree heart block and ventricular tachycardia which required cardiopulmonary resuscitation and subsequent mechanical ventilation. After lack of improvement with intravenous **methylprednisolone** and **plasmapheresis**, **abatacept** was initiated for a total of five doses in addition to **intravenous immunoglobulin**. Subsequently, the patient showed symptomatic improvement and recovery of cardiac disfunction.

Liu and colleagues (35) shared a case of ICI-induced myocarditis in a 78-year-old female patient, treated with **pembrolizumab** for stage IIIC malignant **melanoma**. Symptoms including dyspnea, dysphagia and muscle weakness started thirty days after the second pembrolizumab dose, being diagnosed as myocarditis and neuromuscular complications using a combination of clinical, biomarkers and imaging features. Although intravenous high-dose **methylprednisolone** was started, ventricular tachycardia and high-grade heart block developed, requiring resuscitation and a temporary pacemaker. Due to lack of symptomatic resolution and persistent troponin elevation after corticosteroid weaning regime and addition of **mycophenolate**, **abatacept** was started, showing improvement of symptoms and slow decrease on biomarkers after the second dose. Eventually, corticosteroids and mycophenolate were successfully discontinued, although troponins remained persistently elevated.

A comparison of patient characteristics, tumor type and oncological treatment of all patients included in this systematic review is collected in Table 2.

	Age	Cancer type	Tumor burden	Previous treatment	ICI	Timing after 1st dose
Jespersen *et al*	57	Renal cell carcinoma	≥2 metastatic sites	None	Nivolumab + ipilimumab	12 days
Kalapurackal *et al*	65	Melanoma	Not reported	None	Nivolumab + ipilimumab	9 days
Liu *et al*	78	Melanoma	Not reported	None	Pembrolizumab	30 days
Nguyen *et al*	25	Thymoma	≥2 metastatic sites	Cyclophosphamide + doxorubicin + cisplatin	Pembrolizumab	14 days
Ramayya *et al*	50	Cervical cancer	Not reported	Etoposide + carboplatin	Atezolizumab	42 days
Salem *et al*	66	Lung cancer	Not reported	Carboplatin + pemetrexed	Nivolumab	30 days
Wakefield *et al*	55	Melanoma	<2 metastatic sites	None	Pembrolizumab	26 days

Table 2: comparison of main characteristics of patients, tumor type and treatment of the cases included in this review. ICI: immune checkpoint inhibitor.

A comparison of treatment administered for immune-related myocarditis, including abatacept dosage and schedule, combination therapy and outcome is represented in Table 3.

	Abatacept start (after myocarditis onset)	Dose	Schedule	Combination with immunosuppressive therapies (other than corticosteroids)	Outcome
Jespersen *et al*	6 days	500 mg IV	Every 2 weeks (total of 5 doses)	MMF 1g - 2x/day for 3 months	Progressive resolution
Kalapurackal *et al*	7 days	200 mg IV	One dose	MMF 1g (*schedule not reported*)	Complete resolution
Liu *et al*	12 days	10 mg/kg IV	Every 2 weeks (total of 5 doses)	MMF 750mg - 2x/day for 5 months Plasmapheresis	Resolution with persistent troponin elevation
Nguyen *et al*	8 days	20 mg/kg IV	First two doses with a 3-day difference, followed by 3 additional doses every 7 days. (total of 5 doses)	MMF 1g - 2x/day Ruxolitinib 15 mg - 2x/day for 21 days	Resolution
Ramayya *et al*	46 days	1000 mg IV	Every 3 days (total of 3 doses)	IVIG 400mg/kg over 2 days	Subtotal resolution
Salem *et al*	17 days	500 mg IV	Every 2 weeks (total of 5 doses)	Plasmapheresis	Resolution
Wakefield *et al*	10 days	500 mg IV	Every 2 weeks (total of 5 doses)	IVIG (*schedule not reported*) Plasmapheresis	Subtotal resolution

Table 3: comparison of treatment administered for immune-related myocarditis of the cases included in this review. MMF: mycophenolate mofetil; IVIG: intravenous immunoglobulin.

Table 4 collects data of myocarditis presentation and characteristics, including time of onset, symptoms, and other findings, clustered according to whether they received ICI monotherapy or a dual ICI agent treatment.

	Monotherapy (n=5)	Dual therapy (n=2)
Cancer type, % (n)		
Melanoma	40 (2)	50 (1)
Lung	20 (1)	-
Renal cell	-	50 (1)
Cervix	20 (1)	-
Thymoma	20 (1)	-
Time of onset, days		
Mean	28	11
Range	[14-42]	[9-12]
Symptoms, % (n)		
Chest pain	60 (3)	50 (1)
Palpitations	0	100 (2)
Dyspnea	60 (3)	0
Muscle weakness/pain	100 (5)	50 (1)
Findings on admission, % (n)		
Abnormal ECG	40 (2)	50 (1)
Biomarkers	100 (5)	100 (2)
Altered CMR/Echocardiography	80 (4)	100 (2)
Histology	40 (2) * Only 2 performed	Not performed
Associated myositis, % (n)		
Present	100 (5)	50 (1)
Absent	0 (0)	50 (1)

Table 4: myocarditis presentation characteristics comparison grouped according to ICI regime received (monotherapy vs. dual agent therapy). ECG: electrocardiogram; CMR: cardiac magnetic resonance.

DISCUSSION

Firstly, scarcity of evidence regarding abatacept as therapy for ICI-associated myocarditis should be emphasized and noted deeply, together with the absence of collected prospective data and randomized clinical trials. This lack of data hinders the collection of conclusive evidence and proved results for future management of myocarditis as an adverse event of these increasingly administered oncological therapies.

The current review showed an early timing of fulminant myocarditis, with a mean time of onset of twenty-three days [9-42 days]. Immune-related myocarditis appeared sooner on those patients receiving combined immunotherapy (n=2), with a mean time of onset of 11 days, compared to cases of myocarditis receiving monotherapy (n=5) whose mean time of onset was 28 days. On those patients receiving monotherapy, all of them were treated with a PD-1/PD-L1 inhibitor, including pembrolizumab, atezolizumab or nivolumab, whereas the two cases treated with a dual immunotherapy targeted both CTLA-4 (ipilimumab) and PD-1 (nivolumab).

These results differ from the ones obtained in a previous study by Ruste *et al* (36), which reported that severe immune-related adverse events tend to appear within a median of forty-one days after ICI initiation, being significantly later for non-severe irAEs.

This difference shows a particularly earlier time of presentation of severe myocarditis when compared to irAEs affecting other organs or systems, although other studies reported wide variations on this behalf. (16,20)

Interestingly, Kalinich *et al* (37) reported an increased risk of severe irAEs in younger patients, suggesting that older age might be a protective factor of severity of irAEs, probably due to immune senescence in older patients, use of more cautious and less aggressive treatments, lower proportion of combination therapy in elderly… This hypothesis agrees with the results obtained in this review, as only two of the patients included (29%) were older than 65 years old –being the mean age of 57 years old–.

Sex differences have been found in previous studies (38) regarding nature of irAEs, reporting that male individuals are more likely to suffer cardiovascular events, whereas women seem more prone to have endocrinopathies (39). Our systematic review showed no differences between male and female patients.

Previous studies (40) have found a significant association between the use of dual-agent immunotherapy and risk of developing a high-grade irAE. The same study showed no significant differences regarding other baseline characteristics (including demography, previous treatments...), although a strong correlation –yet not statistically significant– was reported when analyzing tumor stage, type of cancer (lung cancer) and burden of disease.

Further reviews (37,41) show the same directions regarding combination therapy, while additional reports (41,42) add more information describing that anti-CTLA4 therapies have a higher risk of developing severe irAEs than anti-PD1 or PD-L1. Another study (43) adds evidence on this behalf, describing an increased risk on patients who received concomitant or previous chemotherapy in addition to ICI therapy.

Contrary to what was mentioned above, all cases included in this review received an ICI targeting the PD-1/PD-L1 pathway, either in monotherapy (71%, n=5) or as dual ICI therapy (29%, n=2). Nevertheless, neoadjuvant or concomitant chemotherapy had been administered to three out of the five patients who received ICI in a monotherapy regime. This means that a total of 5 cases (71%) might have had a possible risk factor related to medication history or current treatment.

Current evidence (44–46) suggests that irAEs are more frequent on patients with a history –either personal or family history– of preexisting autoimmune diseases than in those without a previous diagnosis of autoimmunity. Also, ICI therapy has been often reported to exacerbate previous autoimmune disorders –mainly rheumatological–, particularly if they were active or poorly controlled at treatment start (45,46).

Chennamadhavuni *et al* (39) observed an increased risk of developing irAEs on patients with organ-specific comorbidities –especially cardiac or pulmonary comorbidities–. Pre-existing lung diseases (COPD, asthma, fibrosis, interstitial lung diseases…) and even smoking, were found to predispose to suffer irAE-pneumonitis, whereas cardiovascular risk factors and established heart damage (heart failure, myocardial infarction) seem to increase risk for cardiac-irAEs. On the other hand, underlying kidney disfunction and a sustained eGFR loss was associated not only with renal-irAEs, but also any kind of organ-nonspecific irAE. In addition to what was already mentioned, other risk factors found on this study were high-BMI –even if low metabolic risk– and a poor performance status on the beginning of ICI therapy.

In our review, we could not analyze this data, as previous comorbidities and individual risk factors were not universally reported among all cases included.

The same study by Chennamadhavuni *et al* (39) revealed differences on severity and profiles of irAEs depending on histology and tumor burden. Melanoma patients were reported to present more gastrointestinal, endocrinological and dermatological adverse events, whereas lung cancer and renal cell carcinoma tend to have more lung-related adverse events. Interestingly, irAEs in melanoma patients were found to have a later presentation than other tumor types. Regarding tumor burden, a higher incidence of irAEs has been observed in patients with ≥2 metastatic sites than in those patients with low tumor burden.

Our systematic review included three patients with melanoma (43%) and one with each of lung cancer, cervical cancer, renal cell carcinoma and thymoma (Figure 4), showing a possible increased risk for myocarditis in melanoma patients. It should be noted the thymoma case included in this review, since despite of low incidence and rareness of this malignancy, it has been found that it might be related with a higher incidence of irAEs –especially myasthenia gravis and myocarditis–, probably due to the role that thymus have on modulating immune response and preserving immune tolerance (47–49).

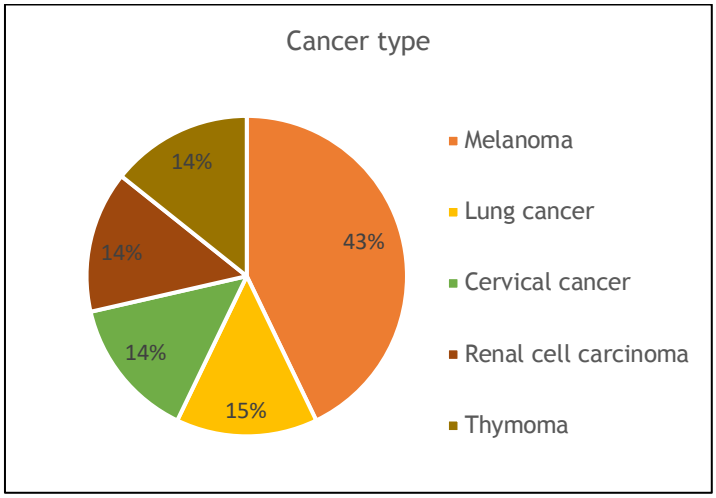

Figure 4. Cancer type of patients included in this systematic review.

It should be taken into account that certain types of cancer such as lung or breast cancer are significantly more likely to have received other oncological treatments than other patients like melanoma, including chemotherapy or radiation, which, according to evidence mentioned beforehand, might increase risk of overall irAEs.

As a consequence of all emerging evidence mentioned beforehand, an increased level of awareness for irAEs might be needed, especially myocarditis and other potentially lethal adverse reactions. Patients' characteristics, along with tumor and treatment related features should be noted for identifying patients with a higher risk of developing any kind of irAE, in order to predict, monitor, prevent and institute an early treatment for irAEs in case of appearance.

In this review, a strong association between myocarditis and concurrent skeletal muscle myositis has been found, as six out of the seven included patients (86%) showed symptoms of concurrence, such as muscle pain and weakness or diplopia. In some cases, a skeletal muscle biopsy was performed and confirmed diagnosis of myositis.

This finding has been previously reported on other studies (50,51), who outline that the presence of concomitant skeletal myositis should raise suspicion of immune related myocarditis (52), due to high prevalence of concurrence between these two irAEs. Gürdoğan *et al* (51)

suggested that myositis might precede the evolution of myocarditis and, therefore, might be useful as a predictor of this potentially fatal irAEs.

Emerging evidence suggest that irAEs occurrence is predictive of a greater tumor response to ICI therapy (45,53,54). Hsiehchen *et al* (54) demonstrated that patients who develop irAEs have more favorable outcomes in terms of tumor objective response, progression free survival and overall survival, especially in patients with late onset irAEs (>3 months).

Regarding outcome and efficacy of abatacept as treatment for immune related myocarditis in this systematic review, results have shown that it might be an effective alternative, since all cases reported a successful (complete or subtotal) resolution in their patients. It should be considered that all cases reported in the current study were events of corticoid-resistant myocarditis, therefore abatacept might be considered as a worthwhile and helpful recourse for this type of patients.

This review showed no uniformity in dosage and schedule of abatacept among the studies included. All cases but one required the administration of more than one abatacept dose, and 71% (five out of seven case reports) administered up to five intravenous doses. Three of the cases used the same posology of abatacept 500mg administered every 2 weeks for a total of five doses, whereas another case reported the administration of three doses of abatacept 1000mg every three days. The two remaining cases expressed abatacept dosage in mg/kg, and although weight of the patient was not reported, total dose would presumably be higher of 500mg. Schedule of administration and dosage of abatacept is represented on Figure 5.

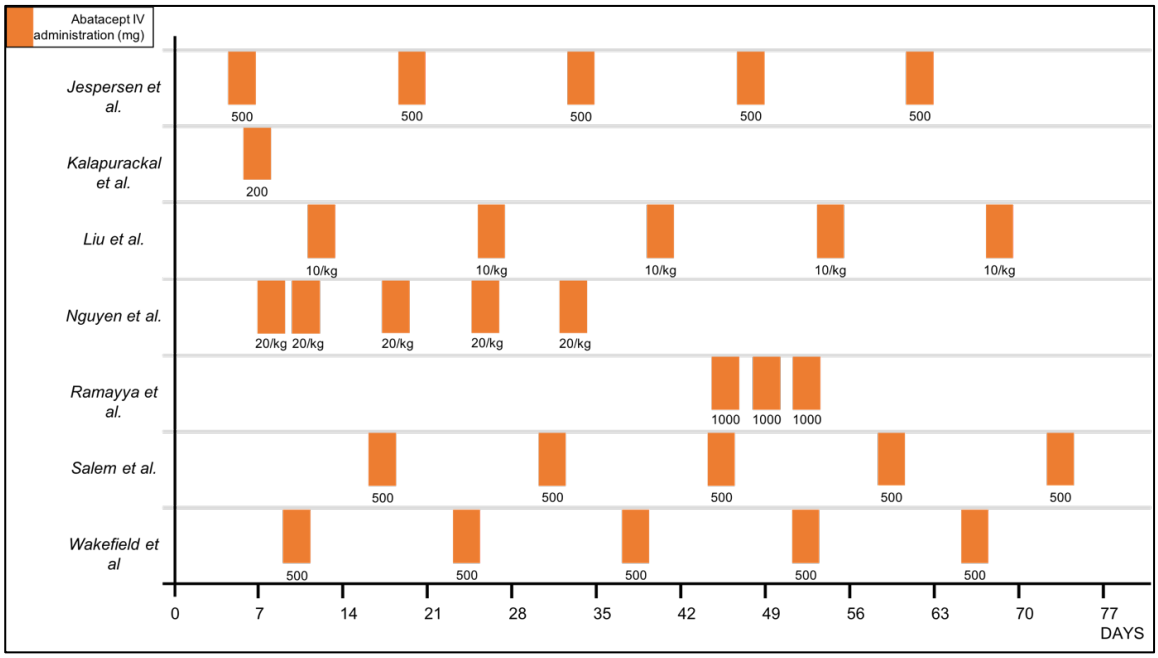

Figure 5. Dosage and schedule of abatacept administration of the cases included in this review.

The use of other immunosuppressive agents –other than corticosteroid–, also showed no concordance between case reports (Figure 6). Only one of them used abatacept as monotherapy for immunosuppression, while the rest administered a combined treatment. In four cases, mycophenolate was administered, and one of which received also ruxolitinib, conforming a triple therapy. The two remaining cases combined abatacept and IVIG.

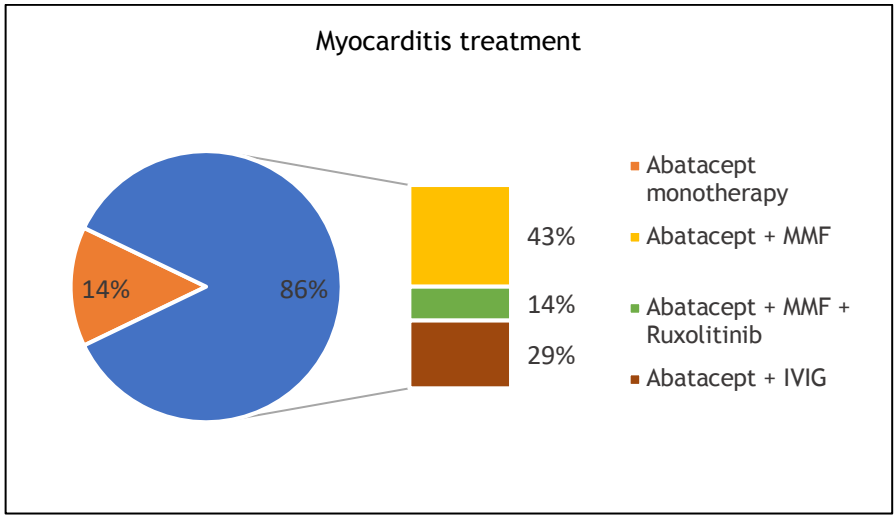

Figure 6. Immunosuppressive agents other than corticosteroid administered on patients included in this review. MMF: mycophenolate mofetil; IVIG: intravenous immunoglobulins.

Several investigations have studied the possibility of an increased risk of malignancies or malignancy progression associated with the use of biological immunosuppressive agents, including abatacept, reaching no consensus among them. Some studies reported that these biological therapies –used mainly in rheumatological diseases– do not seem to increase overall risk of developing cancer in patients receiving these treatments (55,56) and suggested that association may be casual.

Nevertheless, more recent studies by Montastruc *et al* (57) and Simon *et al* (58) reported a small but statistically significant increased risk of developing malignancies on patients initiating abatacept –for rheumatoid arthritis– compared to those patients initiating other biological therapies. These results might occur due to abatacept mechanism of action –CTLA-4 analogue– modulating immune system activity, leading to weakened antitumor response and probable tumor progression.

However, it should be strongly considered that these studies focus on long-term therapies with immunosuppressive agents for treatment of rheumatologic diseases and might not be accurately applicable and valid when these therapies are used promptly as treatment of an acute event. There is no evidence regarding abatacept used in a shorter schedule in patients with stablished cancer under oncological treatment.

In the current systematic review, three cases reported no recurrence of disease after abatacept administration and ICI permanent discontinuation, while two cases reported disease progression (Figure 7). This data is not consistent enough to reach any conclusion about abatacept safety. Nevertheless, and due to lack of evidence so far, it seems reasonable to suggest that abatacept might be only considered an option in cases of very severe, corticoid-resistant or refractory myocarditis, whereas lower grade events might be managed –if possible– with corticosteroid therapy.

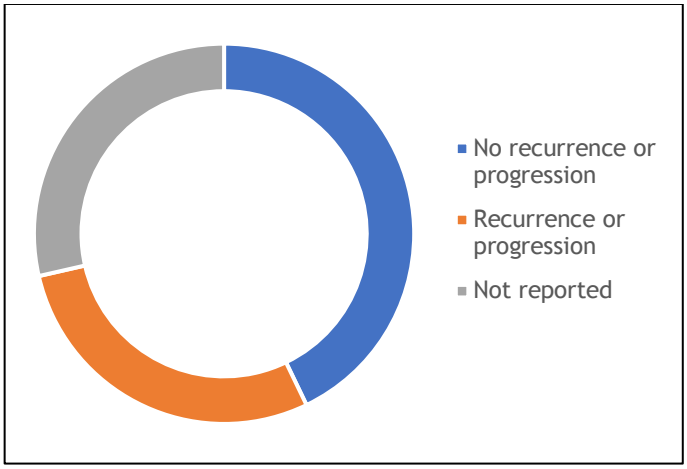

Figure 7. Tumor recurrence or progression on the cases included in this review.

All cases selected in this systematic review reported a permanent ICI discontinuation after appearance of immune-related myocarditis. These results agree with recommendations of current SITC and ASCO guidelines (25,26), which suggest a permanent ICI termination for any grade of cardiac toxicity, due to high mortality rate and severity.

Allouchery *et al* (59) performed a review about safety of ICI resumption after irAEs, which showed that almost half of the patients –46%– who resumed ICI therapy after an adverse event reported recurrence of any irAE, often different and no more severe than the one reported in first place. Heterogenous results were observed when attending differences on severity and organ or system involved on the first irAE. This study suggests, accordingly to the current guidelines and recommendations, that ICI should be permanently discontinued in cases of cardiac toxicity or another grade 4 or potentially fatal irAEs. It suggests a different attitude on cases of less severe irAEs, always after a careful assessment of the benefit/risk ratio, the oncologic situation and patient's motivation.

CONCLUSION

Myocarditis is an uncommon although highly hazardous complication of ICIs which pathophysiology comprehension is crucial to provide an accurate diagnosis and therapy, as well as adequate prevention from cardiac adverse toxicities that impede the continuation of the cancer treatment, not to mention compromised efficacy. A need of increased awareness of immune related myocarditis must be raised among oncologists and other physicians in order to come up with an adequate strategy of prevention, diagnosis and treatment of this potentially lethal adverse event.

The treatment of myocarditis remains uncertain following the failure of high-dose glucocorticoids, which appear to be of little benefit in the event of MACE. Current oncological guidelines recommend the use of other immunosuppressive agents in cases of corticoid-resistant or severe myocarditis. On this behalf, data on the efficacy of treatment with abatacept (a CTLA-4 fusion protein that elicits global T-cell anergy) in this setting are scarce and based on a handful of case reports, with an absence of prospective studies or randomized trials. However, based on the mechanism of action and reported results, abatacept appears to have passed the proof of concept. These results need to be validated through multicenter collaborative efforts due to the rarity, albeit extremely serious, of these side effects, as well as to establish the optimal dose, schedule and combination of treatment.

AKNOWLEDGEMENTS

I would like to show my most sincere and deep gratitude to my parents and my family, for providing me with the chance of receiving this education and for their constant love and support day after day.

Also, I would like to thank my tutor, Dr. Luis Ángel León Mateos, and my cotutor, Dra. María José Villanueva Silva for their help and guidance during the whole process of writing this project.

Lastly, I want to briefly mention and thank my closest friends and colleagues that I found during my university education for their support and help in every field of my personal and educational life since the first moment.

REFERENCES

1. Yousif LI, Tanja AA, de Boer RA, Teske AJ, Meijers WC. The role of immune checkpoints in cardiovascular disease. Front Pharmacol. 2022 Oct 3;13:989431.
2. Hata H, Matsumura C, Chisaki Y, Nishioka K, Tokuda M, Miyagi K, et al. A Retrospective Cohort Study of Multiple Immune-Related Adverse Events and Clinical Outcomes Among Patients With Cancer Receiving Immune Checkpoint Inhibitors. Cancer Control J Moffitt Cancer Cent. 2022 Dec;29:10732748221130576.
3. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012 Mar 22;12(4):252–64.
4. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. Longo DL, editor. N Engl J Med. 2018 Jan 11;378(2):158–68.
5. Iranzo P, Callejo A, Assaf JD, Molina G, Lopez DE, Garcia-Illescas D, et al. Overview of Checkpoint Inhibitors Mechanism of Action: Role of Immune-Related Adverse Events and Their Treatment on Progression of Underlying Cancer. Front Med. 2022 May 30;9:875974.
6. Granier C, De Guillebon E, Blanc C, Roussel H, Badoual C, Colin E, et al. Mechanisms of action and rationale for the use of checkpoint inhibitors in cancer. ESMO Open. 2017;2(2):e000213.
7. Bajwa R, Cheema A, Khan T, Amirpour A, Paul A, Chaughtai S, et al. Adverse Effects of Immune Checkpoint Inhibitors (Programmed Death-1 Inhibitors and Cytotoxic T-Lymphocyte-Associated Protein-4 Inhibitors): Results of a Retrospective Study. J Clin Med Res. 2019 Apr;11(4):225–36.
8. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. N Engl J Med. 2016 Nov 3;375(18):1749–55.
9. Bertrand A, Kostine M, Barnetche T, Truchetet ME, Schaeverbeke T. Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis. BMC Med. 2015 Sep 4;13:211.
10. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. JAMA Oncol. 2018 Dec 1;4(12):1721.
11. Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. N Engl J Med. 2018 May 31;378(22):2093–104.
12. Michel L, Rassaf T, Totzeck M. Cardiotoxicity from immune checkpoint inhibitors. IJC Heart Vasc. 2019 Dec;25:100420.
13. Moslehi JJ, Salem JE, Sosman JA, Lebrun-Vignes B, Johnson DB. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. The Lancet. 2018 Mar;391(10124):933.
14. Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin

Oncol. 2019 Sep;16(9):563–80.
15. Shalata W, Abu-salman A, Steckbeck R, Mathew Jacob B, Massalha I, Yakobson A. Cardiac Toxicity Associated with Immune Checkpoint Inhibitors: A Systematic Review. Cancers. 2021 Oct 18;13(20):5218.
16. Zhou YW, Zhu YJ, Wang MN, Xie Y, Chen CY, Zhang T, et al. Immune Checkpoint Inhibitor-Associated Cardiotoxicity: Current Understanding on Its Mechanism, Diagnosis and Management. Front Pharmacol. 2019 Nov 29;10:1350.
17. Hu JR, Florido R, Lipson EJ, Naidoo J, Ardehali R, Tocchetti CG, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors. Cardiovasc Res. 2019 Apr 15;115(5):854–68.
18. Ganatra S, Neilan TG. Immune Checkpoint Inhibitor-Associated Myocarditis. The Oncologist. 2018 Aug 1;23(8):879–86.
19. Touat M, Maisonobe T, Knauss S, Ben Hadj Salem O, Hervier B, Auré K, et al. Immune checkpoint inhibitor-related myositis and myocarditis in patients with cancer. Neurology. 2018 Sep 4;91(10):e985–94.
20. Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. J Am Coll Cardiol. 2018 Apr;71(16):1755–64.
21. Escudier M, Cautela J, Malissen N, Ancedy Y, Orabona M, Pinto J, et al. Clinical Features, Management, and Outcomes of Immune Checkpoint Inhibitor–Related Cardiotoxicity. Circulation. 2017 Nov 21;136(21):2085–7.
22. Champion SN, Stone JR. Immune checkpoint inhibitor associated myocarditis occurs in both high-grade and low-grade forms. Mod Pathol. 2020 Jan;33(1):99–108.
23. Matzen E, Bartels LE, Løgstrup B, Horskær S, Stilling C, Donskov F. Immune checkpoint inhibitor-induced myocarditis in cancer patients: a case report and review of reported cases. Cardio-Oncol. 2021 Dec;7(1):27.
24. Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, et al. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation. J Am Coll Cardiol. 2018 Dec;72(24):3158–76.
25. Brahmer JR, Abu-Sbeih H, Ascierto PA, Brufsky J, Cappelli LC, Cortazar FB, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer. 2021 Jun;9(6):e002435.
26. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018 Jun 10;36(17):1714–68.
27. Herrero-Beaumont G, Martínez Calatrava MJ, Castañeda S. Mecanismo de acción de abatacept: concordancia con su perfil clínico. Reumatol Clínica. 2012 Mar;8(2):78–83.
28. Glatigny S, Höllbacher B, Motley SJ, Tan C, Hundhausen C, Buckner JH, et al. Abatacept Targets T Follicular Helper and Regulatory T Cells, Disrupting Molecular Pathways That Regulate Their Proliferation and Maintenance. J Immunol. 2019 Mar 1;202(5):1373–82.
29. Jespersen MS, Fanø S, Stenør C, Møller AK. A case report of immune checkpoint

inhibitor-related steroid-refractory myocarditis and myasthenia gravis-like myositis treated with abatacept and mycophenolate mofetil. Niederseer D, Melato GT, Kaufmann CC, Amin R, Kott K, editors. Eur Heart J - Case Rep. 2021 Nov 1;5(11):ytab342.
30. Kalapurackal Mathai V, Black A, Lovibond S, Binny S, Lipton J, Moldovan C. Use of abatacept in steroid refractory, immune checkpoint-induced myocarditis. Intern Med J. 2021 Nov;51(11):1971–2.
31. Nguyen LS, Bretagne M, Arrondeau J, Zahr N, Ederhy S, Abbar B, et al. Reversal of immune-checkpoint inhibitor fulminant myocarditis using personalized-dose-adjusted abatacept and ruxolitinib: proof of concept. J Immunother Cancer. 2022 Apr;10(4):e004699.
32. Ramayya T, Mitchell JD, Hartupee JC, Lavine K, Ridley CH, Kotkar KD, et al. Delayed Diagnosis and Recovery of Fulminant Immune Checkpoint Inhibitor-Associated Myocarditis on VA-ECMO Support. JACC CardioOncology. 2022 Dec;4(5):722–6.
33. Salem JE, Allenbach Y, Vozy A, Brechot N, Johnson DB, Moslehi JJ, et al. Abatacept for Severe Immune Checkpoint Inhibitor–Associated Myocarditis. N Engl J Med. 2019 Jun 13;380(24):2377–9.
34. Wakefield C, Shultz C, Patel B, Malla M. Life-threatening immune checkpoint inhibitor-induced myocarditis and myasthenia gravis overlap syndrome treated with abatacept: a case report. BMJ Case Rep. 2021 Nov;14(11):e244334.
35. Liu S, Chan J, Brinc D, Gandhi S, Izenberg A, Delgado D, et al. Immune Checkpoint Inhibitor-Associated Myocarditis With Persistent Troponin Elevation Despite Abatacept and Prolonged Immunosuppression. JACC CardioOncology. 2020 Dec;2(5):800–4.
36. Ruste V, Goldschmidt V, Laparra A, Messayke S, Danlos FX, Romano-Martin P, et al. The determinants of very severe immune-related adverse events associated with immune checkpoint inhibitors: A prospective study of the French REISAMIC registry. Eur J Cancer. 2021 Nov;158:217–24.
37. Kalinich M, Murphy W, Wongvibulsin S, Pahalyants V, Yu KH, Lu C, et al. Prediction of severe immune-related adverse events requiring hospital admission in patients on immune checkpoint inhibitors: study of a population level insurance claims database from the USA. J Immunother Cancer. 2021 Mar;9(3):e001935.
38. Lal JC, Brown SA, Collier P, Cheng F. A retrospective analysis of cardiovascular adverse events associated with immune checkpoint inhibitors. Cardio-Oncol. 2021 Dec;7(1):19.
39. Chennamadhavuni A, Abushahin L, Jin N, Presley CJ, Manne A. Risk Factors and Biomarkers for Immune-Related Adverse Events: A Practical Guide to Identifying High-Risk Patients and Rechallenging Immune Checkpoint Inhibitors. Front Immunol. 2022 Apr 26;13:779691.
40. Manne A, Mulekar MS, Escobar DE, Alsayed A, Sharma G, Prodduturvar P, et al. Clinical and Hematological Predictors of High-Grade Immune-Related Adverse Events Associated With Immune Checkpoint Inhibitors. J Clin Med Res. 2021 May;13(5):268–75.
41. Chhabra N, Kennedy J. A Review of Cancer Immunotherapy Toxicity: Immune Checkpoint Inhibitors. J Med Toxicol. 2021 Oct;17(4):411–24.
42. El Osta B, Hu F, Sadek R, Chintalapally R, Tang SC. Not all immune-checkpoint inhibitors are created equal: Meta-analysis and systematic review of immune-related adverse

events in cancer trials. Crit Rev Oncol Hematol. 2017 Nov;119:1–12.
43. Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chávez A, Keegan N, Khamashta MA, et al. Immune-related adverse events of checkpoint inhibitors. Nat Rev Dis Primer. 2020 May 7;6(1):38.
44. Akturk HK, Alkanani A, Zhao Z, Yu L, Michels AW. PD-1 Inhibitor Immune-Related Adverse Events in Patients With Preexisting Endocrine Autoimmunity. J Clin Endocrinol Metab. 2018 Oct 1;103(10):3589–92.
45. Michailidou D, Khaki A, Morelli M, Diamantopoulos L, Singh N, Grivas P. Association of Blood Biomarkers and Autoimmunity with Immune Related Adverse Events in Patients with Cancer treated with Immune Checkpoint Inhibitors [Internet]. In Review; 2021 Jan [cited 2023 Apr 17]. Available from: https://www.researchsquare.com/article/rs-136849/v1
46. Menzies AM, Johnson DB, Ramanujam S, Atkinson VG, Wong ANM, Park JJ, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. Ann Oncol. 2017 Feb;28(2):368–76.
47. Wang C, Zhong B, He J, Liao X. Immune checkpoint inhibitor sintilimab-induced lethal myocarditis overlapping with myasthenia gravis in thymoma patient: A case report. Medicine (Baltimore). 2023 Apr 14;102(15):e33550.
48. Hao Y, Lin G, Xiang J, Wang W, Xu C, Wang Q, et al. Analysis of the efficacy and safety of immunotherapy in advanced thymoma patients. Cancer Med. 2023 Mar;12(5):5649–55.
49. Liu S, Ma G, Wang H, Yu G, Chen J, Song W. Severe cardiotoxicity in 2 patients with thymoma receiving immune checkpoint inhibitor therapy: A case report. Medicine (Baltimore). 2022 Nov 18;101(46):e31873.
50. Anquetil C, Salem JE, Lebrun-Vignes B, Johnson DB, Mammen AL, Stenzel W, et al. Immune Checkpoint Inhibitor–Associated Myositis: Expanding the Spectrum of Cardiac Complications of the Immunotherapy Revolution. Circulation. 2018 Aug 14;138(7):743–5.
51. Gürdoğan M. Myocarditis associated with immune check-point inhibitors: Practical considerations in diagnosis and management. Anatol J Cardiol [Internet]. 2020 [cited 2023 Apr 3]; Available from: https://anatoljcardiol.com/jvi.aspx?un=AJC-79584
52. Moslehi J, Lichtman AH, Sharpe AH, Galluzzi L, Kitsis RN. Immune checkpoint inhibitor–associated myocarditis: manifestations and mechanisms. J Clin Invest. 2021 Mar 1;131(5):e145186.
53. Sugano T, Seike M, Saito Y, Kashiwada T, Terasaki Y, Takano N, et al. Immune checkpoint inhibitor-associated interstitial lung diseases correlate with better prognosis in patients with advanced non-small-cell lung cancer. Thorac Cancer. 2020 Apr;11(4):1052–60.
54. Hsiehchen D, Naqash AR, Espinoza M, Von Itzstein MS, Cortellini A, Ricciuti B, et al. Association between immune-related adverse event timing and treatment outcomes. OncoImmunology. 2022 Dec 31;11(1):2017162.
55. Simon TA, Smitten AL, Franklin J, Askling J, Lacaille D, Wolfe F, et al. Malignancies in the rheumatoid arthritis abatacept clinical development programme: an epidemiological assessment. Ann Rheum Dis. 2009 Dec 1;68(12):1819–26.
56. Wadström H, Frisell T, Askling J, for the Anti-Rheumatic Therapy in Sweden (ARTIS)

Study Group. Malignant Neoplasms in Patients With Rheumatoid Arthritis Treated With Tumor Necrosis Factor Inhibitors, Tocilizumab, Abatacept, or Rituximab in Clinical Practice: A Nationwide Cohort Study From Sweden. JAMA Intern Med. 2017 Nov 1;177(11):1605.
57. Montastruc F, Renoux C, Dell'Aniello S, Simon TA, Azoulay L, Hudson M, et al. Abatacept initiation in rheumatoid arthritis and the risk of cancer: a population-based comparative cohort study. Rheumatology. 2019 Apr 1;58(4):683–91.
58. Simon TA, Boers M, Hochberg M, Baker N, Skovron ML, Ray N, et al. Comparative risk of malignancies and infections in patients with rheumatoid arthritis initiating abatacept versus other biologics: a multi-database real-world study. Arthritis Res Ther. 2019 Dec;21(1):228.
59. Allouchery M, Beuvon C, Pérault-Pochat MC, Roblot P, Puyade M, Martin M. Safety of Immune Checkpoint Inhibitor Resumption after Interruption for Immune-Related Adverse Events, a Narrative Review. Cancers. 2022 Feb 14;14(4):955.

APPENDIX

Prospero-like protocol according to PRISMA guidelines

ADMINISTRATIVE INFORMATION

Tittle	Abatacept for the treatment of immune checkpoint inhibitor induced myocarditis, a systematic review.
Registration	The protocol of this systematic review will not be recorded.
Authors	Iago Lázaro Saiz supervised by the cotutor, María José Villanueva Silva.
INTRODUCCTION	
Rationale	Abatacept is a fusion protein binding to costimulatory molecules B7 (also known as CD80 and CD86) on antigen presenting cells, blocking interaction with CD-28 on T cells, thereby preventing T cell activation. Treatment with Abatacept has been shown to be effective in patients with various autoinflammatory diseases, including rheumatoid arthritis and could potentially reverse immune Checkpoint inhibitors-derived T cell activation.
Objectives	To perform a systematic review that gathers all scientific evidence on Abatacept for the treatment of immune checkpoint inhibitors induced myocarditis.
METHODS	
Eligibility criteria	Inclusion criteria published articles on abatacept for the treatment of immune checkpoint induced myocarditis between January 2000 and December 2022. There will be abstract language restriction to English, Spanish and French publications.
Information sources	An electronically search will be performed in PubMed, Embase, Web of Science.
Search strategy	Search strategy will include a combination of broad terms related to abatacept AND immune myocarditis AND a combination of broad terms related to immune checkpoint inhibition (“anti-PD1” OR “AntiPDL-1” OR “AntiCTLA-4” OR “pembrolizumab” OR “nivolumab” OR “avelumab” OR “atezolizumab” OR “ipilimumab”. In addition, a comprehensive manual search of the Reference section as well as the Appendix section, when available, is meant to be undertaken.
Exclusion criteria	(i) immune myocarditis not related to checkpoint inhibition (ii) non-myocarditis immune checkpoint toxicity, (iv) immunosuppressor agent other than abatacept, (v) letters, editorials, news articles or commentaries (vi) In the event of multiple publications reporting the study or trial, only the most recent data were considered (vii) Preference prospective articles over retrospective review was applied.

DATA

Data items	From each included article the following information was extracted, with close attention to AMSTAR checklist for systematic review evaluation, including: age, gender, underlying autoimmune disease (yes/no; type; severity), cardiac comorbidity (yes/no; type; severity), cardiovascular risk factors (smoking habit, hypertension, diabetes, dyslipidemia), lung comorbidity (yes/no; type; severity), renal comorbidity (yes/no; type; severity), other comorbidities (yes/no; type; severity), tumor type, tumor stage, tumor burden (1 or 2 metastatic sites versus > 2 metastatic sites), performance status, prior chemotherapy (yes/no; number of lines); prior radiotherapy (yes/no; field location), immune checkpoint employed (drug, monotherapy or combination), number of courses delivered, myocarditis associated signs and symptoms, myocarditis diagnostic criteria fulfilled, myocarditis diagnostic test performed, timing of myocarditis, circulating blood counts, troponin I, NT-proBNP, other serum biomarkers performed (autoantibodies, cytokines, HLA genotypes, microRNA, gene expression profiling, and serum proteins), myocarditis treatment (corticoid, other immunosuppressor treatments, timing), abatacept treatment (dose, schedule, timing), outcome.