American Heart Journal Plus: Cardiology Research and Practice 9 (2021) 100049

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Adverse cardiovascular events in patients treated with mogamulizumab

Jennifer M. Kwan [a,1], Mariana L. Henry [a,1], Kirstin Cook [b,2], Angela Higgins [a,1], Jason Cuomo [a,1], Francine Foss [c,1], Lauren A. Baldassarre [a,*,1]

[a] Section of Cardiovascular Medicine, Yale University School of Medicine, New Haven, CT, United States of America
[b] Department of Neurosurgery, University of California, Los Angeles School of Medicine, Los Angeles, CA, United States of America
[c] Section of Hematology, Yale University School of Medicine, New Haven, CT, United States of America

ARTICLE INFO

Keywords:
Immunotherapy
Mogamulizumab
Cardiooncology
Cardiotoxicity
Lymphoma

ABSTRACT

Study objectives: Mogamulizumab is an important treatment for T-cell leukemia and lymphoma. Adverse cardiovascular events (ACE) after mogamulizumab therapy have not been investigated. The aim of the study is to investigate ACE occurrence after mogamulizumab therapy.

Methods: The International World Health Organization database, VigiBase, was analyzed from January 2013 to August 2019 for all adverse events, including ACE, that occurred after mogamulizumab treatment. ACE was defined as: cardiac death, myocardial infarction, heart failure, myocarditis, arrhythmia, vasculitis, thrombosis, palpitations and new hypertension.

Results: ACE after mogamulizumab therapy affected 28 out of 650 unique patients (4.3%). Heart failure (42.8%) and ventricular arrhythmias (17.85%) were most common. ACE accounted for 10% of all fatal adverse outcomes, and 25% of all ACE were fatal. Time to fatal outcome was significantly shorter for patients with ACE compared to non-cardiovascular events, with a mean of 7.7 days (SD 6.91) vs 73 days (SD 90.7), $p = 0.017$, respectively. There was an increased total number of adverse cardiovascular events in patients greater than 65 and in Asian countries.

Conclusions: Cardiovascular toxicity with mogamulizumab is a possible early occurring adverse outcome associated with high mortality.

1. Introduction

The traditional treatment regimens of cutaneous T-cell lymphomas are limited by systemic toxicities. The most common adverse side effects are infections due to the potent immunosuppression of these agents; however, heart failure has been described in some of these regimens, such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) [1–2]. Recent advances in immunotherapy have led to the development of newer agents to target cancers including immune checkpoint inhibitors (ICIs), chimeric antigen receptor (CAR) T-cell therapy, cytokines, immune cell related tyrosine kinase inhibitors and monoclonal antibodies [3–6]. These agents are revolutionizing the treatment of cancer patients.

Immune cell targeted therapies inhibit specific biomarkers or signal transduction pathways of immune cells that tumors depend upon for growth, proliferation, and survival. Mogamulizumab is an immune cell targeted therapy and monoclonal antibody that targets the CC chemokine receptor 4 (CCR4) on T cells [4]. In 2018, Mogamulizumab became the first FDA approved monoclonal antibody targeting CCR4 [4]. However, this agent was approved and used in countries outside of the United States in 2012 [7]. Mogamulizumab is used for the treatment of adult patients with T-cell leukemia or lymphoma, mycosis fungoides and Sezary syndrome [5,8–9].

Some immunotherapy, including agents targeting T-cell specific markers, can lead to potent immunosuppression and post marketing surveillance has shown that severe or even fatal adverse reactions can occur [10]. Specifically, cardiotoxicity is an important adverse reaction from ICIs, and myocarditis and fulminant heart failure are well documented complications, affecting 1-2% of patients [11–16]. In the randomized control trial that led to FDA approval, at least 20% of

* Corresponding author at: Department of Internal Medicine (Cardiology), Yale School of Medicine, 330 Cedar St, Boardman 110, P.O. Box 208056, New Haven, CT 06520-8056, United States of America.
E-mail address: lauren.baldassarre@yale.edu (L.A. Baldassarre).
[1] Current address: Yale University School of Medicine, 330 Cedar St, New Haven, CT, 06520-8056, United States of America.
[2] Current address: University of California, Los Angeles, School of Medicine, 10833 Le Conte Ave, Los Angeles, CA, 90095, United States of America.

https://doi.org/10.1016/j.ahjo.2021.100049
Received 15 May 2021; Received in revised form 17 August 2021; Accepted 2 September 2021
Available online 6 October 2021

Table 1
Demographics of patients who experienced adverse outcomes, stratified by cardiac vs non-cardiac adverse outcomes.

	Whole dataset	% total	Adverse cardiovascular outcomes n (% total cardiovascular outcomes) 28 (4.3%)	No Adverse cardiovascular outcomes n (% total non-cardiovascular outcomes) 622 (95.6%)	Total 650 (100%)	P value
Number of unique patients	650	100	28 (100)	622 (100)		
Gender						P = 0.72
Number of male	326	50.15	13 (46.43)	313 (50.32)		
Number of female	239	36.77	11 (39.29)	228 (36.60)		
Number of unknown gender ("-")	85	13.08	4 (14.29)	81 (13.02)		
Counts of age groups:						*P* = 0.99
18 - 44 years	22	3.38	0 (0.00)	22 (3.54)		
45 - 64 years	187	28.77	6 (21.43)	181 (29.10)		
65 - 74 years	211	32.46	12 (42.86)	199 (31.99)		
≥ 75 years	109	16.77	3 (10.71)	106 (17.04)		
Unknown	121	18.62	7 (25.00)	114 (18.33)		
World regions counts						P = 0.99
Western Pacific Region	529	81.38	23 (82.14)	506 (81.35)		
European Region	38	5.85	1 (3.57)	37 (5.95)		
Region of the Americas	83	12.77	4 (14.29)	79 (12.71)		

mogamulizumab recipients experienced adverse reactions including rash, infusion-related reactions, fatigue, diarrhea, musculoskeletal pain, and upper respiratory tract infection [8].

At our institution, a case of acute myocarditis associated with mogamulizumab treatment in a patient with T-cell Lymphoma was documented [17]. However, to date, no study has examined cardiotoxicity arising from mogamulizumab. In this study, VigiBase, the World Health Organization (WHO) Global Individual Case Safety Reports (ICSR) Database System, was used to determine the total number of reported cardiovascular toxicities associated with mogamulizumab therapy.

2. Materials and methods

2.1. Data sources and study population

VigiBase, the WHO Global ICSR Database System, which is maintained by the Uppsala Monitoring Centre (UMC) (www.who-umc.org), was analyzed for adverse outcomes, including ACE. VigiBase collects data on adverse drug reactions from more than 110 member countries, and its central aim is to provide rapid surveillance on medicine-related safety issues. How the data is curated and validated has been previously described [18–19]. Data available included age range (45-64, 65-74, 50-64, ≥75 years, unknown), gender (male, female, and unknown), reporting year (2013-2019), reporting health professional (physician, pharmacist, other health professional, consumer/non health professional), adverse outcome (not recovered/resolved, recovering/resolved, recovered/resolved, fatal, unknown), indication (adult t cell lymphoma/leukemia, cutaneous t cell lymphoma, Sezary syndrome, unknown), geographic region (Asia Western Pacific Region, European region, Regions of the Americas), drugs and medications, and drug dosing.

All adverse drug reactions reported in VigiBase in patients who had received mogamulizumab between January 2013 and August 2019 were identified. All unique patients from VigiBase who had adverse reactions, including ACE, were included. All ACE were stratified by demographics, time to outcome, and type of outcome. ACE was defined as: cardiac

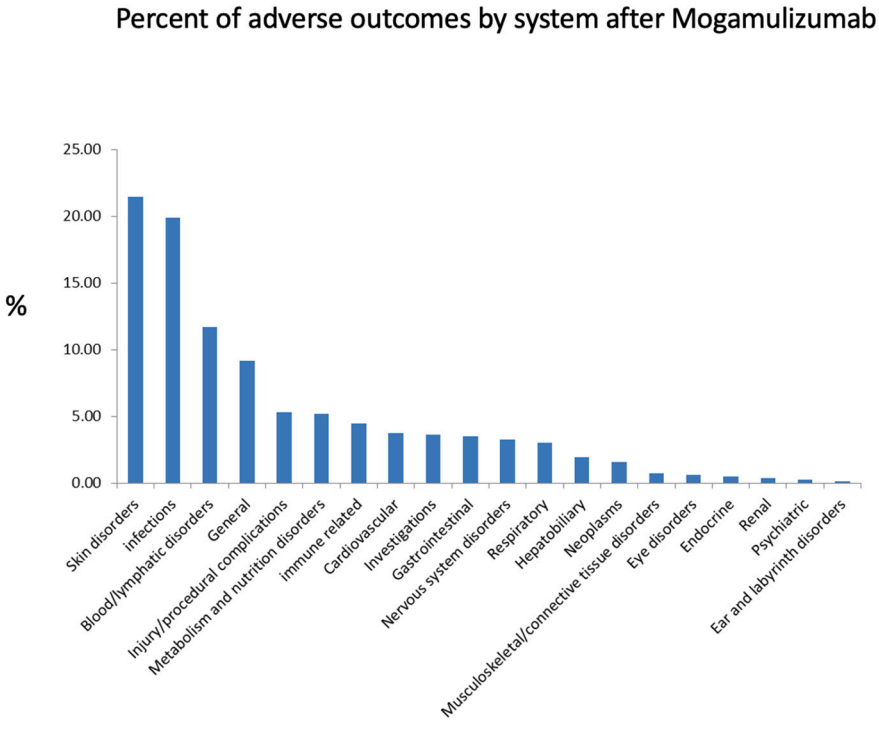

Fig. 1. Percent of adverse outcomes by system.

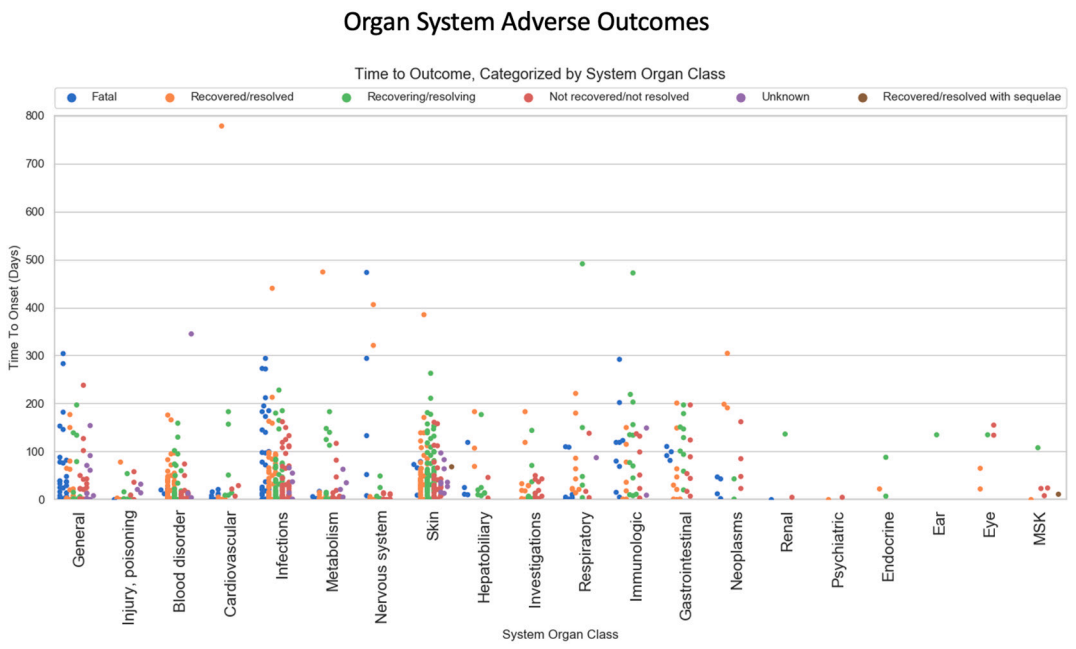

Fig. 2. Organ System Adverse Outcomes. Color plot of adverse outcomes across all systems by time to onset, and stratified by whether the adverse event was fatal, recovered, recovering, not recovered or unknown.

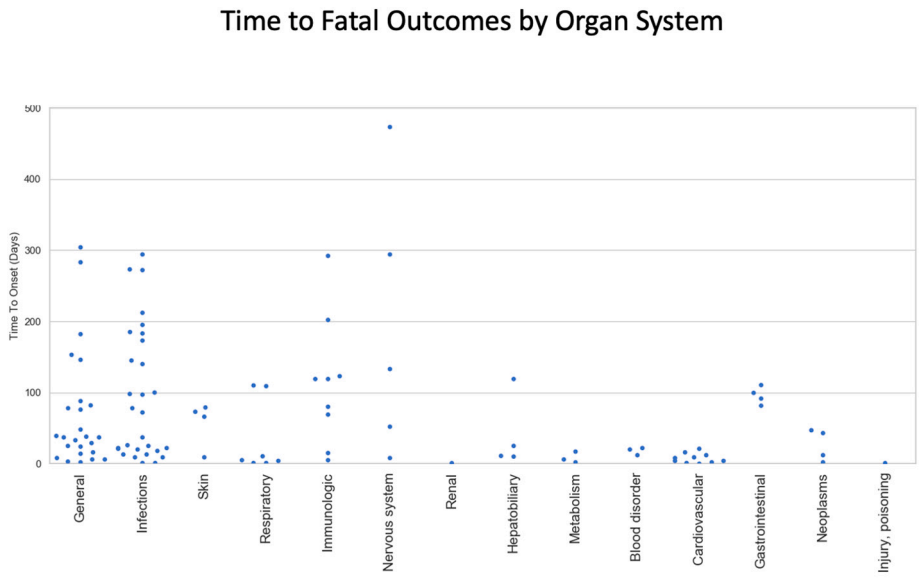

Fig. 3. Time to Fatal Outcomes by Organ System. Plot of all fatal systemic outcomes by time to onset.

death, myocardial infarction, heart failure, myocarditis, arrhythmia, vasculitis, thrombosis, palpitations and new hypertension. Non-cardiovascular events were grouped by organ system.

2.2. Statistical analysis

The SPSS statistical package version 26 (Armonk, NY: IBM Corp) and GraphPad Prism version 8 were used for biostatistical analyses. Characteristics of cases were described in terms of percentages and means (± standard deviation). Tests for significance included chi-square for categorial variables and *t*-tests for comparison between groups. Statistical tests were 2-sided, and significance was defined as a p value of <0.05.

3. Results

3.1. Patient characteristics and outcomes for all adverse events in Vigibase

There were 650 patients (50% male, 37% female) who experienced adverse outcomes associated with mogamulizumab, as reported in VigiBase from 2013 to 2019. Most patients fell into the 65-74 age group (32.46%), followed by 45-64 (28.77%), and >75 years (16.77%). Most patients were from the Western Pacific Region (81.38%), followed by the Americas (12.77%) and the least came from Europe (5.85%) (Table 1). There were 830 total adverse events reported, as each patient could have more than one adverse outcome. The most common adverse events were skin disorders (21%, $n = 178$), followed by infectious outcomes (19.8%, $n = 165$), with adverse cardiovascular events occurring

Table 2
Demographic table of patients who developed adverse cardiac outcomes by type of cardiac outcome.

	Heart failure N = 12 (%)	Ventricular Fibrillation/ Ventricular Tachycardia N = 5(%)	Arrhythmia + Hypertension *N* = 1(%)	Vasculitis *N* = 3(%)	Atrial Fibrillation N = 1(%)	Acute myocardial infarction N = 2(%)	Hypertension *N* = 2(%)	Palpitations N = 1(%)	Thrombosis N = 1(%)	Total N = 28(%)
Age										
45-64	3(25.0)	2(40.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(100.0)	1(100.0)	7 (25.0)
50-64	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
65-74	6(50.0)	2(40.0)	0(0.0)	1(33.3)	1(100.0)	1(50.0)	1(50.0)	0(0.0)	0(0.0)	12 (42.9)
≥ 75 years	3(25.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	3 (10.7)
Unknown	0(0.0)	1(20.0)	1(100.0)	2(66.7)	0(0.0)	1(50.0)	1(50.0)	0(0.0)	0(0.0)	6 (21.4)
Gender										
Male	5(41.7)	5(100.0)	0(0.0)	0(0.0)	1(100.0)	1(50.0)	1(50.0)	1(100.0)	0(0.0)	14 (50.0)
Female	7(58.3)	0(0.0)	1(100.0)	2(66.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(100.0)	11 (39.3)
Unknown	0(0.0)	0(0.0)	0(0.0)	1(33.3)	0(0.0)	1(50.0)	1(50.0)	0(0.0)	0(0.0)	3 (10.7)
Outcome										
Not recovered/ Not resolved	3(25.0)	0(0.0)	0(0.0)	2(66.7)	0(0.0)	1(50.0)	0(0.0)	0(0.0)	0(0.0)	6 (21.4)
Recovering/ Resolving	4(33.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(50.0)	1(100.0)	0(0.0)	6 (21.4)
Recovered/ Resolved	3(25.0)	0(0.0)	1(100.0)	1(33.3)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	6 (21.4)
Fatal	1(8.3)	5(100.0)	0(0.0)	0(0.0)	0(0.0)	1(50.0)	0(0.0)	0(0.0)	0(0.0)	7 (25.0)
Unknown	1(8.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(50.0)	0(0.0)	1(100.0)	3 (10.7)
Indication										
Adult T-cell Lymphoma/ Leukemia	12 (100.0)	4(80.0)	0(0.0)	0(0.0)	1(100.0)	1(50.0)	1(50.0)	1(100.0)	1(100.0)	21 (75.0)
Cutaneous T-cell Lymphoma	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(50.0)	1(50.0)	0(0.0)	0(0.0)	2(7.1)
Sezary Syndrome	0(0.0)	0(0.0)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(3.6)
Unknown	0(0.0)	1(20.0)	0(0.0)	3(100.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4 (14.3)
Region										
Asia-Western Pacific Region	12 (100.0)	5(100.0)	0(0.0)	2(66.7)	1(100.0)	1(50.0)	1(50.0)	1(100.0)	1(100.0)	24 (85.7)
European Region	0(0.0)	0(0.0)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(3.6)
Region of the Americas	0(0.0)	0(0.0)	0(0.0)	1(33.3)	0(0.0)	1(50.0)	1(50.0)	0(0.0)	0(0.0)	3 (10.7)

as the 8th most frequent (3.4%, $n = 28$) (Fig. 1).

The overall mean time to adverse event from starting mogamulizumab was 25 days (SD 74). Time to event stratified by outcome (fatal, recovered, recovering, not recovered, unknown) for all adverse events is shown in Fig. 2. The mean times to fatal event for all organ systems is given in S1 Table. Overall, 13% of events were fatal. Time to fatal event stratified by organ system is shown in Fig. 3.

3.2. Patient characteristics and outcomes for adverse cardiovascular events in Vigibase

Out of 650 patients with adverse events, 28 (4.3%) had adverse cardiac events (Table 2). Of these patients, 46% were male, 39% were female, and 14% were unknown gender. Most patients (42.86%) were in the 65-74 age group, with the next most abundant age group being 45-64 (28.57%). Compared with patients who had non-cardiac adverse events, there were no significant gender or age differences (Table 1).

Most ACE were reported in 2013 (25%), followed by 2017 and 2019 with 17.9% each. In those with ACE, the most common indication for mogamulizumab use was T-cell cancers, most being T-cell lymphoma/leukemia (75%), followed by cutaneous T cell lymphoma at (7.1%) and Sezary syndrome at (3.6%). Most of these ACE were reported by a healthcare professional (96.4%), specifically a physician (85.7%), pharmacist (3.6%) or other healthcare professional (7.1%).

Of these 28 patients, the most common adverse cardiac event was heart failure ($N = 12$, 42.8%) followed by ventricular tachycardia or ventricular fibrillation ($N = 5$, 17.85%). Three (10.7%) had non-ventricular arrhythmias (1 supraventricular arrhythmia, 1 atrial fibrillation, 1 palpitations), 2 developed new hypertension (7.14%), 3 developed vasculitis (10.71%), 2 developed acute myocardial infarctions (7.14%), and 1 developed thrombosis (3.57%). Of note, one patient had both a supraventricular arrhythmia and new HTN (3.57%).

Seven of 28 (25%) had fatal outcomes, 6 (21%) did not recover, 12 (42.87%) recovered or were recovering and 4 (14.29%) had unknown outcomes in terms of recovery. The time to fatal ACE was a mean of 7.7 days (SD 6.91) compared to 73 days (SD 90.7 days) for all other disorders combined ($p = 0.017$). The time to ACE stratified by type of event and outcome (fatal, recovered, recovering, not recovered, unknown) is shown in Fig. 4.

Mean time to fatal outcome trended earlier for females at 5.66 days

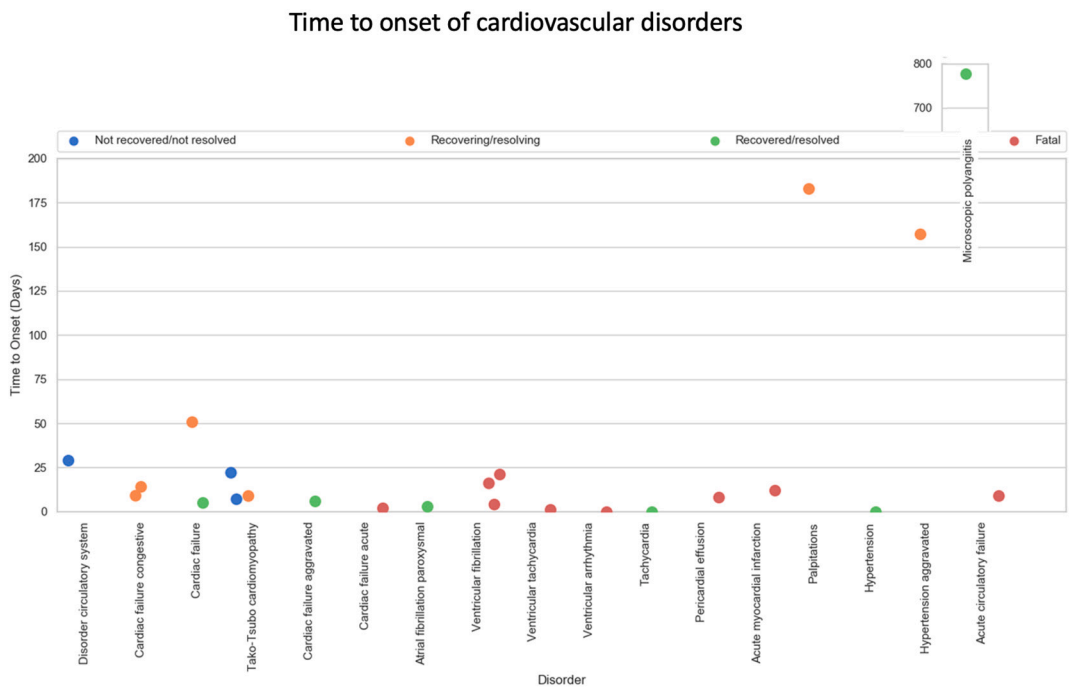

Fig. 4. Time to onset of cardiovascular disorders. Plot of adverse cardiovascular outcomes with mogamulizumab therapy, time to onset, and whether it was fatal, not recovered, or recovered.

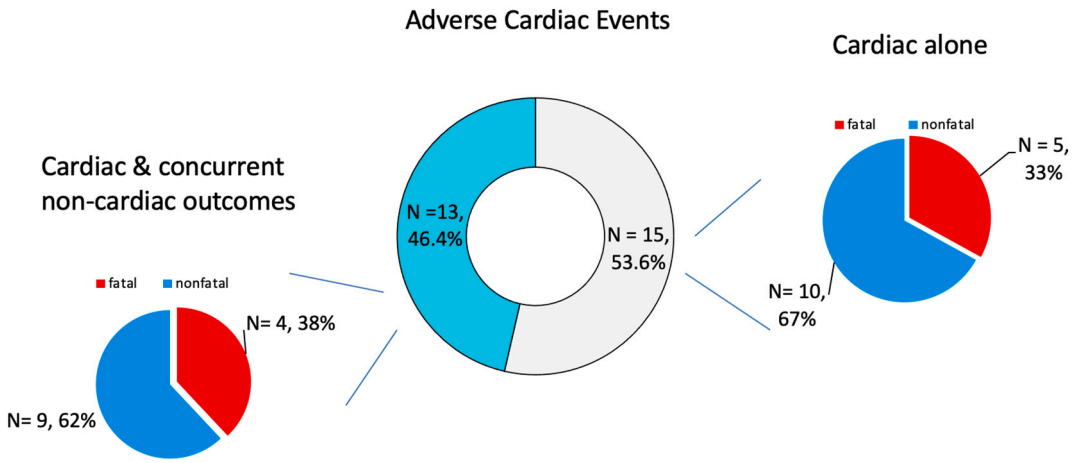

Fig. 5. Adverse Cardiac Events. Percent of cardiovascular events in isolation versus combined with non-cardiovascular events, and proportion of fatal events in each group.

(SD 4.93) than for males at 10 days (SD 8.33) ($p = 0.310$). However, males tended to have more fatalities (46%) than females (9%), although this difference also did not reach statistical significance ($p = 0.720$).

Of all those who had adverse cardiac outcomes, 53.6% had cardiac outcomes alone and 46.4% had a combination of adverse cardiac and non-cardiac outcomes. Of the 15 patients who had stand-alone adverse cardiac outcomes, 33.3% had fatal outcomes compared with 38.5% of patients with concomitant non-cardiac adverse events ($p = 0.890$). Of the fatal outcomes in those with concomitant cardiac and non-cardiac events, 15.4% were from cardiac causes, 15.4% were from infectious causes and 7.7% was multifactorial (Fig. 5).

4. Discussion

This is the first study to document cardiovascular toxicities that occurred after mogamulizumab therapy, using an international database of reported adverse drug reactions. It is important to note that this study may hold bias due to the nature of the reporting system used, as all adverse events, especially those which may have been clinically less severe, may not have been reported. Additionally, no direct causation between ACE and mogamulizumab therapy can be established from such an analysis.

This study revealed that ACE make up 4.3% of total adverse outcomes, but are disproportionately associated with fatal outcomes, occurring in 10.0% of all mortalities. Additionally, ACE occur early, at a mean of 7.7 days (SD 6.91).

The high occurrence of isolated ACE in 54% of reported cases suggests that mogamulizumab may cause cardiotoxicity directly, rather than as just cardiac sequalae of another organ toxicity. Moreover, taken alongside the high mortality associated with ACE, these considerations highlight the need to identify baseline factors that might increase risk of adverse cardiovascular outcomes. The available Vigibase data did not

include baseline cardiovascular comorbidities, and the only classic cardiovascular risk factor data available was age and gender, which did not differ significantly with respect to ACE or fatalities. A trend toward greater mortality was noted among males, and women tended to present earlier, but these differences did not achieve statistical significance, likely due to the small number of subjects. It is possible that this difference may potentially be attributed to increased cardiovascular risk factors in men, such as hypertension, hyperlipidemia, and type 2 diabetes. However, data about such comorbidities are not available in Vigibase for analysis.

In congruence with other findings on cardiotoxicity arising from immunotherapies, this was a moderately common adverse event, affecting 28 patients of the 650 patients with reported events associated with Mogamulizumab worldwide between 2013 and 2019. Heart failure was the most common cardiovascular adverse reaction. Of note, in more than half of these cases, the cardiovascular conditions were classified as fatal or not recovered/resolved. Additionally, most ACE occurred early, within 60 days post mogamulizumab administration. This suggests that cardiac function should be monitored, particularly in the first few months in patients receiving mogamulizumab therapy.

Of note, differences were seen in the frequency of mogamulizumab use by country. The increased utilization in the Western Asian region may be due to mogamulizumab's original approval in Japan in 2012. Thus, it may be a more integrated part of cancer treatment in the Asian-Western Pacific Region, and so this region would have had more time to accumulate adverse event occurrences. Therefore, the higher reporting of ACE in this region does not necessary mean that this patient population is at greater risk for ACE in the setting of mogamulizumab use as compared to other regional populations.

Mogamulizumab has a narrower indication when compared to some other immunotherapies, such as ICIs; however, this study shows that adverse cardiotoxicities can occur. The mechanism of its cardiotoxicity is not known. However, since it can inhibit T regulatory cells, which have immunosuppressive properties, inhibition of these inhibitor cells could lead to activation of the immune system to attack other organs, including the heart. In fact, it has been shown that there are T regulatory cells in the heart and they have been shown to be protective against and to modulate cardiovascular disease due to their anti-inflammatory properties [20]. Additional mechanistic studies may reveal the underlying pathway of toxicity as well as strategies for preventing adverse cardiovascular effects associated with mogamulizumab. One major limitation of this study is the lack of information on baseline cardiovascular comorbidities in Vigibase, not allowing for assessment of comorbidities predictive of ACE. Additionally, this database only allows for the assessment of reported adverse events and, therefore, does not capture all adverse events from mogamulizumab. Similarly, it does not supply the total number of patients treated with this therapy, and therefore does not provide a denominator from which to derive a true prevalence of adverse cardiovascular events.

Mogamulizumab remains a promising T cell cancer treatment, and our study shows that cardiotoxicity is a possible early side effect that physicians should be aware of, particularly in patients who may have received prior cardio-toxic oncologic agents (Central illustration). Monitoring with electrocardiogram, serum biomarkers and cardiac imaging before and early after starting mogamulizumab may help identify early signs of cardiovascular toxicities. Baseline and serial imaging with echocardiogram or CMR with strain assessment may be helpful in some patients and is especially indicated with any concern of symptoms of heart failure. Treatment for ACE in the setting of mogamulizumab should likely be tailored to the specific clinical presentation, and no current data or guidelines exist for management of these scenarios. However, specifically for the presentation of myocarditis, steroids may be of benefit, as was demonstrated in the case published from our institution [17]. Future studies should include monitoring for cardiotoxicity from mogamulizumab, most likely using a serum biomarker and a multi-modality cardiac imaging approach, including the use of CMR for detection of myocarditis [21]. A larger, multicenter study with information on comorbidities would be helpful to correlate preexisting cardiac conditions and risk for adverse cardiac outcomes with mogamulizumab. Additionally, genetics, pharmacogenomics and microbiome have been shown to influence response to immunotherapy [22–25]. Thus, obtaining molecular data in parallel could allow for personalization of risk identification in patients. In general, further prospective study of cardiovascular risk and events in this patient population may help to predict who may be at risk for cardio-toxicity and hopefully lead to the development of strategies to monitor and mitigate this risk.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2021.100049.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None to report.

Funding

This work was supported by American Heart Association (Dallas, TX) grant #18CDA34110361 (LAB, 2018).

Disclaimer from VigiBase

(i) 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' is the source of the information for part of our study
(ii) The information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases
(iii) The information does not represent the opinion of the Uppsala Monitoring Centre or the World Health Organization

References

[1] S. Limat, E. Daguindau, J.Y. Cahn, V. Nerich, A. Brion, S. Perrin, M.C. Woronoff-Lemsi, E. Deconinck, Incidence and risk-factors of CHOP/R-CHOP-related cardiotoxicity in patients with aggressive non-Hodgkin's lymphoma, J. Clin. Pharm. Ther. 39 (2) (2014 Apr) 168–174.
[2] S. Limat, K. Demesmay, L. Voillat, Y. Bernard, E. Deconinck, A. Brion, A. Sabbah, M.C. Woronoff-Lemsi, J.Y. Cahn, Early cardiotoxicity of the CHOP regimen in aggressive non-Hodgkin's lymphoma, Ann. Oncol. 14 (2) (2003 Feb 1) 277–281.
[3] D. Jagadeesh, M.R. Smith, Novel targeted therapies in peripheral T cell lymphoma, Discov. Med. 15 (85) (2013 Jun 27) 367–378.
[4] T. Poggio, J. Duyster, A.L. Illert, Current immunotherapeutic approaches in T cell non-Hodgkin lymphomas, Cancers 10 (9) (2018 Sep) 339.
[5] S.K. Barta, J. Zain, A.W. MacFarlane IV, S.M. Smith, J. Ruan, H.C. Fung, C.R. Tan, Y. Yang, R.K. Alpaugh, E. Dulaimi, E.A. Ross, Phase II study of the PD-1 inhibitor pembrolizumab for the treatment of relapsed or refractory mature T-cell lymphoma, Clin. Lymphoma Myeloma Leuk. 19 (6) (2019 Jun 1) 356–364.
[6] E. Gorshein, S. Devata, Immunotherapy Emerges as Treatment for T-Cell Lymphoma. ASCO-SITC Clinical Immuno-Oncology Symposium, 2018.
[7] A. Beck, J.M. Reichert, Marketing approval of mogamulizumab: a triumph for glyco-engineering, in: MAbs, vol. 4, No. 4, Taylor & Francis, 2012 Jul 1, pp. 419–425.
[8] Y.H. Kim, M. Bagot, L. Pinter-Brown, A.H. Rook, P. Porcu, S.M. Horwitz, S. Whittaker, Y. Tokura, M. Vermeer, P.L. Zinzani, L. Sokol, Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial, Lancet Oncol. 19 (9) (2018 Sep 1) 1192–1204.
[9] T.A. Ollila, I. Sahin, A.J. Olszewski, Mogamulizumab: a new tool for management of cutaneous T-cell lymphoma, OncoTargetsTher. 12 (2019) 1085.
[10] K.A. Thursky, L.J. Worth, J.F. Seymour, H. Miles Prince, M.A. Slavin, Spectrum of infection, risk and recommendations for prophylaxis and screening among patients with lymphoproliferative disorders treated with alemtuzumab, Br. J. Haematol. 132 (1) (2006 Jan) 3–12.

[11] G. Varricchi, G. Marone, V. Mercurio, M.R. Galdiero, D. Bonaduce, C.G. Tocchetti, Immune checkpoint inhibitors and cardiac toxicity: an emerging issue, Curr. Med. Chem. 25 (11) (2018 Apr 1) 1327–1339.
[12] S. Upadhrasta, H. Elias, K. Patel, L. Zheng, Managing cardiotoxicity associated with immune checkpoint inhibitors, Chronic Dis.Transl. Med. 5 (1) (2019 Mar 1) 6–14.
[13] A.R. Lyon, N. Yousaf, N.M. Battisti, J. Moslehi, J. Larkin, Immune checkpoint inhibitors and cardiovascular toxicity, Lancet Oncol. 19 (9) (2018 Sep 1) e447–e458.
[14] H. Läubli, C. Balmelli, M. Bossard, O. Pfister, K. Glatz, A. Zippelius, Acute heart failure due to autoimmune myocarditis under pembrolizumab treatment for metastatic melanoma, J. Immunother. Cancer 3 (1) (2015 Dec 1) 11.
[15] D.B. Johnson, J.M. Balko, M.L. Compton, S. Chalkias, J. Gorham, Y. Xu, M. Hicks, I. Puzanov, M.R. Alexander, T.L. Bloomer, J.R. Becker, Fulminant myocarditis with combination immune checkpoint blockade, N. Engl. J. Med. 375 (18) (2016 Nov 3) 1749–1755.
[16] J.J. Moslehi, J.E. Salem, J.A. Sosman, B. Lebrun-Vignes, D.B. Johnson, Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis, Lancet 391 (10124) (2018 Mar 10) 933.
[17] J.M. Kwan, N. Odanovic, A. Arbune, A. Higgins, D. Greif, F. Foss, M.L. Henry, L. A. Baldassarre, Mogamulizumab-associated acute myocarditis in a patient with t-cell lymphoma, JACC Case Rep. 3 (7) (2021 Jun) 1018–1023.
[18] M. Lindquist, VigiBase, the WHO global ICSR database system: basic facts, Drug Inf. J. 42 (5) (2008 Sep) 409–419.
[19] K. Star, L. Sandberg, T. Bergvall, I. Choonara, P. Caduff-Janosa, I.R. Edwards, Paediatric safety signals identified in VigiBase: methods and results from Uppsala Monitoring Centre, Pharmacoepidemiol. Drug Saf. 28 (5) (2019 May) 680–689.
[20] X. Meng, J. Yang, M. Dong, K. Zhang, E. Tu, Q. Gao, W. Chen, C. Zhang, Y. Zhang, Regulatory T cells in cardiovascular diseases, Nat. Rev. Cardiol. 13 (3) (2016 Mar) 167–179.
[21] A. Soufer, L.A. Baldassarre, The role of cardiac magnetic resonance imaging to detect cardiac toxicity from cancer therapeutics, Curr.Treat. Options Cardiovasc. Med. 21 (6) (2019 Jun 1) 28.
[22] T.E. Keenan, K.P. Burke, E.M. Van Allen, Genomic correlates of response to immune checkpoint blockade, Nat. Med. 25 (3) (2019 Mar) 389–402.
[23] J.R. Conway, E. Kofman, S.S. Mo, H. Elmarakeby, E. Van Allen, Genomics of response to immune checkpoint therapies for cancer: implications for precision medicine, Genome Med. 10 (1) (2018 Dec 1) 93.
[24] J. Gong, A. Chehrazi-Raffle, V. Placencio-Hickok, M. Guan, A. Hendifar, R. Salgia, The gut microbiome and response to immune checkpoint inhibitors: preclinical and clinical strategies, Clin. Transl. Med. 8 (1) (2019 Dec 1) 9.
[25] V. Matson, J. Fessler, R. Bao, T. Chongsuwat, Y. Zha, M.L. Alegre, J.J. Luke, T. F. Gajewski, The commensal microbiome is associated with anti–PD-1 efficacy in metastatic melanoma patients, Science 359 (6371) (2018 Jan 5) 104–108.