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Original Article

Pharmacovigilance study for the identification of mogamulizumab-induced immune-related adverse events using a real-world database

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Abstract

Background: Mogamulizumab is a humanized anti-CCR4 monoclonal antibody used for relapsed/refractory adult T-cell leukemia, cutaneous T-cell lymphoma, and/or Sézary syndrome. Reports of immune-related adverse events (irAEs) in these patients are increasing, and the association between irAEs and mogamulizumab remains to be elucidated. This study aimed to evaluate the association between mogamulizumab and immune-related adverse events (irAEs), as well as to characterize the irAEs associated with mogamulizumab using data from a large-scale spontaneous reporting system.

Methods: We performed an exploratory hypothesis-generating analysis of patients from 1967 to September 2023 using VigiBase, a World Health Organization spontaneous adverse event reporting system database. We performed a disproportionality analysis and determined the reporting odds ratios and information components between the drugs of interest and each irAE.

Results: Mogamulizumab was associated with some irAEs, including myocarditis, severe cutaneous adverse reactions, hepatitis, and myositis. Mogamulizumab exhibited significantly higher reporting rates of these 4 irAEs compared to the anticancer agents other than mogamulizumab. Conversely, the reporting rate of other irAEs, including endocrine autoimmune diseases induced by immune checkpoint inhibitors, was not significant in patients who received mogamulizumab.

Conclusions: Mogamulizumab is associated with irAEs, including myocarditis, severe cutaneous adverse reactions, hepatitis, and myositis.

Key words: irAEs; mogamulizumab; VigiBase; disproportionality analysis; sézary syndrome.

Implications for Practice

Mogamulizumab is an effective treatment for relapsed/refractory adult T-cell leukemia, cutaneous T-cell lymphoma, and Sézary syndrome. However, it can induce immune-related adverse events (irAEs). As the risk of rare adverse events is difficult to assess in clinical trials owing to limitations in follow-up periods and population size, this study used VigiBase, a spontaneous adverse event reporting system database, to confirm the association between mogamulizumab and irAEs. Four mogamulizumab-associated irAEs—myocarditis, severe cutaneous adverse reactions, hepatitis, and myositis—were identified, and their clinical characteristics were described. This study suggests that physicians should be aware of irAEs to make a prompt diagnosis.

Introduction

Mogamulizumab is a humanized anti-CCR4 monoclonal antibody and one of the few effective treatments for relapsed/refractory adult T-cell leukemia (ATL), cutaneous T-cell lymphoma (CTCL), and Sézary syndrome. Mogamulizumab exerts antitumor effects through antibody-dependent cellular cytotoxicity by targeting CCR4 expression in T-cell lymphoma, leading to improved clinical outcomes in patients in the MAVORIC trial.[1] Mogamulizumab also suppresses regulatory T-cells (Tregs), and its application in treating other cancers, such as solid tumors, has been evaluated.[2-4] Given

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that the availability of mogamulizumab and the potential indications for its use may increase in the future, clinicians must recognize the adverse events associated with its use to ensure successful cancer therapy.

Dermopathies, including skin rashes, are common mogamulizumab-induced adverse events attributed to immune activation.[5-7] Recently, in addition to dermopathies, there have been increasing case reports of other immune-related adverse events (irAEs), including myocarditis and myositis, following treatment with mogamulizumab.[8,9] These autoimmune adverse events have been reported in clinical trials.[1,10] Notably, irAEs are induced by immune checkpoint inhibitors (ICI), with lethal adverse events such as myocarditis and myositis serving as examples of ICI-induced irAEs that can manifest in various systemic organs.[11,12] Given the risk of lethal ICI-induced irAEs, it is important to recognize the association between irAEs and mogamulizumab in cancer therapy.

There have been limited reports on the adverse events of mogamulizumab shared with ICIs, and the features of autoimmune adverse events associated with mogamulizumab remain unknown. Studies on larger populations are warranted to clarify the association between these rare adverse events and mogamulizumab. We have previously investigated the features of rare irAEs, such as myocarditis and myasthenia gravis, using adverse event reporting databases.[13,14] The use of big data, such as pharmacovigilance databases, has effectively characterized irAEs in clinical practice.[15] In the present study, we aimed to identify irAEs associated with mogamulizumab administration and determine their features using VigiBase, a global database of adverse event reports provided by the World Health Organization (WHO).

Materials and methods

Data sources

This study used the WHO database, VigiBase, which is managed by the Uppsala Monitoring Center in Sweden. VigiBase contains more than 30 million individual case safety reports (ICSRs) collected from various sources, such as physicians, other healthcare professionals, and non-healthcare professionals from over 130 countries. The ICSR includes information on patient background (age, sex, reporting year, and reporting regions), drug information (indications, anatomical therapeutic chemical classification, and dosage), and adverse drug reactions. As this information originates from multiple sources, the likelihood that a suspected adverse reaction is drug-related is not the same for all cases. This study compiled VigiBase ICSRs from its inception in 1967 to September 1, 2023. As VigiBase contains duplicate reports, potential duplicates were excluded from the analysis to avoid bias. The downloaded data were processed using SQLite databases 3.30.1 (SQLite Consortium, Charlotte, NC, USA). The need for informed consent was waived because anonymized data from VigiBase were used.

Procedures

Sixteen adverse events reported as irAEs induced by ICIs were extracted.[12,14,16,17] Terms related to adverse events (AEs) were systematically identified using the preferred terms in the Medical Dictionary for Regulatory Activities/Japanese (MedDRA/J) version 26.0, which was developed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). The AEs and drugs are listed in Supplementary Tables S1 and S2. Anticancer drugs and COVID-19 vaccines were defined using anatomical therapeutic chemical codes L01 and J07BN. The main outcome was the reporting rate of each irAE. This study used the definitions of age, sex, region, reporting source, and outcome groups as classified and provided as

Table 1. The characteristics of patients with mogamulizumab.

Characteristic	*n* = 1684*
Age group	
18-44 years	50 (3.0)
45-64 years	315 (18.7)
65-74 years	352 (20.9)
≥75 years	200 (11.9)
Unknown	767 (45.5)
Sex	
Male	577 (34.3)
Female	449 (26.7)
Unknown	658 (39.1)
Report year	
2013	123 (7.3)
2014	95 (5.6)
2015	43 (2.6)
2016	99 (5.9)
2017	90 (5.3)
2018	67 (4.0)
2019	210 (12.5)
2020	157 (9.3)
2021	282 (16.7)
2022	363 (21.6)
2023	155 (9.2)
Report region	
Eastern Mediterranean region	1 (0.1)
European region	471 (28.0)
Region of the Americas	650 (38.6)
Western Pacific region	562 (33.4)
Report type	
Spontaneous	878 (52.1)
Report from study	805 (47.8)
Other	1 (0.1)
Outcome	
Death	79 (4.7)
Life threatening	14 (0.8)
Caused/prolonged hospitalization	129 (7.7)
Disabling/incapacitating	2 (0.1)
Other	232 (13.8)
Unknown	1228 (72.9)
Report source	
Physician	1023 (60.7)
Pharmacist	36 (2.1)
Other health professional	571 (33.9)
Consumer or other non-health professional	54 (3.2)
Combination of ICIs	20 (1.2)

*n (%).
Abbreviations: ICIs, immune checkpoint inhibitors.

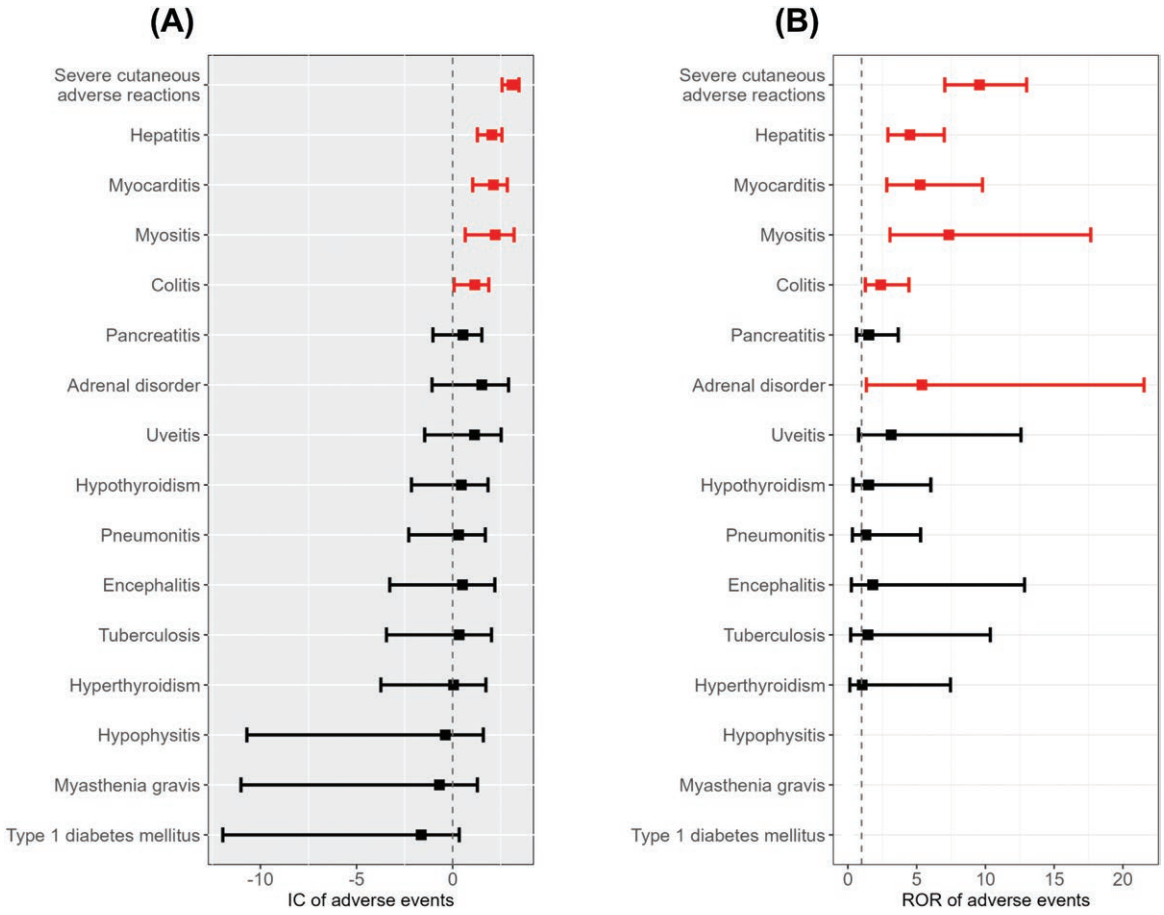

Figure 1. Disproportionality analysis of mogamulizumab and immune-related adverse events (irAEs). Information components (IC) (A) and reporting odds ratios (ROR) (B) of mogamulizumab for immune-related adverse events (irAEs) compared to the overall database. RORs of irAEs not reported in mogamulizumab reports are not displayed. The plots and lines represent the ROR and IC with 95% confidence intervals. A significantly high ROR or IC of the irAE is defined as the lower limit of the 95% confidence interval exceeding the dotted line, and the dotted line indicates ROR = 1 or IC = 0.

categorical variables by VigiBase. Missing values were defined as "unknown."

Statistical analysis

Disproportionality analysis was performed to detect an adverse event signal. The risk of adverse events was evaluated using signal detection with 2 indicators: reporting odds ratios (ROR) and information components (IC).[18] To calculate the ROR, cases were classified into the following 4 groups: (A) patients who used the drug of interest and reported an AE of interest; (B) patients who used the drug of interest and did not report an AE of interest; (C) patients who did not use the drug of interest and reported an AE of interest; and (D) patients who did not use the drug of interest and did not report an AE of interest. The ROR was calculated using the following equation:

$$ROR = (A/B)/(C/D)$$

The signal of the ROR was considered significant if the lower limit of the 95% CI for the ROR exceeded 1. The IC was calculated using the number of expected reports for specific AEs for the drug of interest (Nexpected), and the number of actual reports on a specific AE for the drug of interest (Nobserved), as follows:

$$IC = \log_2([Nobserved + 0.5] / [Nexpected + 0.5])$$

The signal of IC was considered significant when the IC025, the lower limit of the 95% CI for IC, exceeded zero.[19] The present study used ROR and IC for disproportionality analyses of the entire database (Dataset 1), while ROR was used only for sensitivity analyses using subgroups. To improve the accuracy of the signals and eliminate false-positive signals, we defined significant signals when they met all criteria simultaneously in analyses, including 2 indicators for disproportionality analysis. All analyses were performed using R statistical software version 4.1.2 (R Foundation, Vienna, Austria).

Sensitivity analyses

We performed sensitivity analyses of AEs to account for confounders and bias as follows: (1) To account for any reporting bias, the ROR of mogamulizumab from post-2013 data (after mogamulizumab reporting started; Dataset 2) was evaluated; (2) To mitigate the impact of the COVID-19 pandemic on spontaneous reporting, COVID-19 vaccines were excluded, and the ROR of mogamulizumab was evaluated (Dataset 3)[20]; (3) As patients with cancer (not limited to T-cell lymphoma) often have specific physiological profiles due to cancer therapy, cachexia, and analgesic drugs, the ROR of mogamulizumab compared to other anticancer drugs (Dataset 4) was evaluated; (4) To minimize confounding due to indications, the ROR and IC for each AE of vorinostat and romidepsin, which are used for similar indications of mogamulizumab, were investigated in Dataset 1.

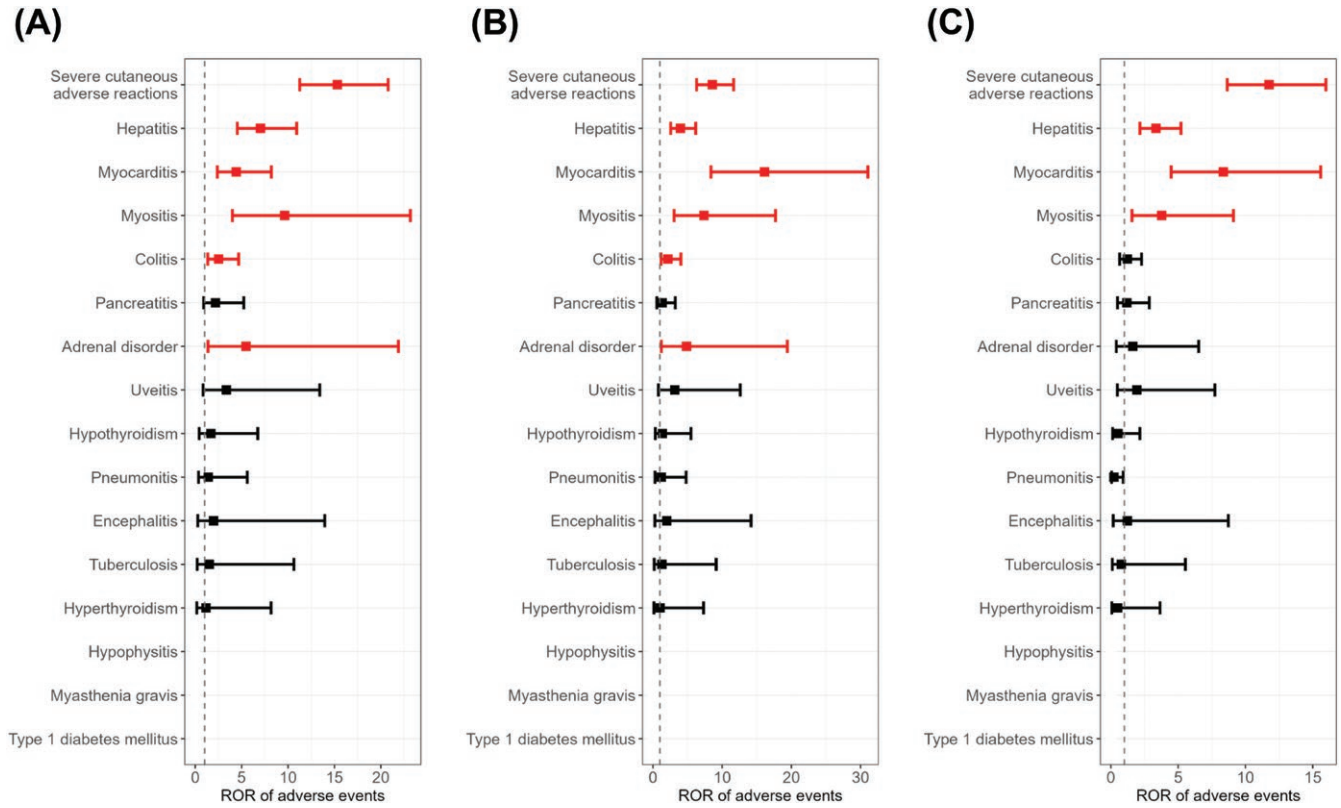

Figure 2. Disproportionality analysis of mogamulizumab and immune-related adverse events (irAEs) in the subgroup. Reporting odds ratios (ROR) of mogamulizumab for immune-related adverse events (irAEs) compared to post-2013 reports (Dataset 2) (A), Covid-19 vaccine-excluded reports (Dataset 3) (B), and anticancer drug-specific reports (Dataset 4) (C) are displayed. RORs of irAEs not reported in mogamulizumab reports are not displayed. The plots and lines represent ROR with 95% confidence intervals. The significant ROR of the irAE is defined as the lower limit of the 95% confidence interval exceeding the dotted line, and the dotted line indicates ROR = 1.

A summary of the datasets used for the disproportionality analysis performed in this study is presented in Supplementary Figure S1.

Results

Demographic data in VigiBase

Of the 35 159 260 reports registered in VigiBase, 1684 ICSRs were related to mogamulizumab use. These reports, first recorded in 2013, have gradually increased over time. Mogamulizumab ICSRs included 577 males (34.3%) and 449 females (26.7%). Although age information was missing in 767 reports, patients in reports with age-related data were older than 18 years. The most common age group was 65-74 years (n = 352, 20.9%). These reports originated mainly from the following 3 regions: 471 (28.0%) from the "European Region," 650 (38.6%) from the "Region of the Americas," and 562 (33.4%) from the "Western Pacific Region." There were 805 (47.8%) "Report from study" and 878 (52.1%) "Spontaneous" reports, and almost all originated from health professionals. Of the 1684 reports on mogamulizumab, 20 (1.2%) used concomitant ICIs. Detailed demographic data are presented in Table 1.

Disproportionality analysis in VigiBase

To evaluate the irAEs associated with mogamulizumab, the following 16 adverse events were identified as representative irAEs: myocarditis, myasthenia gravis, type 1 diabetes mellitus, colitis, pneumonitis, tuberculosis, severe cutaneous adverse reactions, hypothyroidism, hyperthyroidism, pancreatitis, encephalitis, hepatitis, uveitis, hypophysitis, adrenal disorders, and myositis. Disproportionality analyses indicated that treatment with mogamulizumab exhibited significant signals for 5 irAEs, with IC and ROR indicating an association compared to the overall database: colitis (IC025 = 0.08, ROR = 2.38 [1.28-4.43]), hepatitis (IC025 = 1.29, ROR = 4.51 [2.90-7.01]), myocarditis (IC025 = 1.04, ROR = 5.25 [2.82-9.78]), myositis (IC025 = 0.65, ROR = 7.34 [3.05-17.66]), and severe cutaneous adverse reactions (IC025 = 2.58, ROR = 9.57 [7.04-13.00]). Adrenal disorders (IC025 = −1.07, ROR = 5.5 [1.37-22.01]) exhibited a significant ROR but a nonsignificant IC (Figure 1). The signals of these 5 irAEs remained when disproportionality analysis was performed on the dataset from 2013 (Dataset 2) or when reports of the COVID-19 vaccine were excluded (Dataset 3), as shown in Figure 2. None of the mogamulizumab reports involved myasthenia gravis, type 1 diabetes mellitus, or hypophysitis (Figures 1 and 2).

Patients with cancer exhibit specific features due to radiotherapy and cachexia. Therefore, we performed a subgroup analysis to evaluate the association between mogamulizumab and irAEs using only reports involving anticancer drugs (Dataset 4). Mogamulizumab treatment exhibited significant signals for ROR in 4 irAEs: myocarditis (ROR = 8.36 [4.49-15.98]), severe cutaneous adverse reactions (ROR = 11.75 [8.64-15.95]), hepatitis (ROR = 3.35 [2.16-5.22]), and myositis (ROR = 3.35 [2.16-5.22]), compared to other anticancer reports. Colitis (ROR = 1.23 [0.66-2.28]) did not exhibit a significant ROR in this analysis (Figure 2). This result

Table 2. RORs and ICs of drugs with different mechanisms of action but similar indications and irAEs associated with mogamulizumab in full reports.

Drugs	irAEs	Number of reports	ROR (95%CI)	IC (IC025-IC075)
Romidepsin				
	Adrenal disorder	1	4.58 (0.64 to 32.56)	1.06 (−2.72 to 2.75)
	Pneumonitis	5	5.64 (2.34 to 13.58)	1.98 (0.42 to 2.97)
	Hypothyroidism	1	1.28 (0.18 to 9.11)	0.23 (−3.55 to 1.92)
	Myasthenia Gravis	0	NA	−0.44 (−10.77 to 1.54)
	Hyperthyroidism	0	NA	−1.08 (−11.41 to 0.9)
	Encephalitis	1	3.08 (0.43 to 21.89)	0.86 (−2.92 to 2.55)
	Myocarditis	2	1.78 (0.45 to 7.14)	0.62 (−1.97 to 2.01)
	Type 1 diabetes mellitus	0	NA	−1.16 (−11.49 to 0.82)
	Uveitis	0	NA	−0.81 (−11.13 to 1.17)
	Myositis	1	2.49 (0.35 to 17.73)	0.74 (−3.05 to 2.42)
	Pancreatitis	3	1.55 (0.5 to 4.82)	0.52 (−1.55 to 1.73)
	Hypophysitis	0	NA	−0.24 (−10.56 to 1.74)
	Tuberculosis	0	NA	−0.85 (−11.18 to 1.13)
	Severe cutaneous adverse reactions	4	1.52 (0.57 to 4.05)	0.52 (−1.24 to 1.6)
	Hepatitis	4	1.52 (0.57 to 4.07)	0.52 (−1.24 to 1.6)
	Colitis	1	0.4 (0.06 to 2.87)	−0.99 (−4.77 to 0.7)
Vorinostat				
	Adrenal disorder	1	2.5 (0.35 to 17.79)	0.74 (−3.05 to 2.43)
	Pneumonitis	28	17.47 (12.02 to 25.38)	3.74 (3.11 to 4.19)
	Hypothyroidism	2	1.4 (0.35 to 5.61)	0.38 (−2.22 to 1.77)
	Myasthenia Gravis	1	3.04 (0.43 to 21.59)	0.86 (−2.93 to 2.54)
	Hyperthyroidism	0	NA	−1.61 (−11.93 to 0.37)
	Encephalitis	0	NA	−1.13 (−11.45 to 0.85)
	Myocarditis	0	NA	−2.35 (−12.68 to −0.37)
	Type 1 diabetes mellitus	2	1.77 (0.44 to 7.07)	0.61 (−1.98 to 2.01)
	Uveitis	0	NA	−1.24 (−11.57 to 0.74)
	Myositis	1	1.36 (0.19 to 9.69)	0.28 (−3.5 to 1.97)
	Pancreatitis	4	1.13 (0.42 to 3.02)	0.16 (−1.61 to 1.24)
	Hypophysitis	0	NA	−0.41 (−10.73 to 1.57)
	Tuberculosis	1	1.36 (0.19 to 9.65)	0.28 (−3.5 to 1.97)
	Severe Cutaneous Adverse Reactions	4	0.83 (0.31 to 2.21)	−0.24 (−2.01 to 0.84)
	Hepatitis	0	NA	−3.41 (−13.73 to −1.43)
	Colitis	31	6.95 (4.88 to 9.92)	2.65 (2.05 to 3.07)

Abbreviations: CI, confidence intervals; IC, information component; irAEs, immune-mediated adverse events; ROR, reporting odds ratios.

indicates that the signals related to colitis in Figure 1 may not have been generated by the use of mogamulizumab but by the environment of the underlying cancer. Therefore, 4 irAEs other than colitis are considered to be associated with mogamulizumab. In contrast, in Dataset 1, vorinostat and romidepsin, which are used for the same indications as mogamulizumab, exhibited no significant ROR and IC values for the 4 irAEs identified as significant signals with mogamulizumab (Table 2).

Characteristics of patients with irAEs using mogamulizumab in VigiBase

To estimate the clinical features of mogamulizumab-associated irAEs, demographic information was collected from patients who developed myocarditis ($n = 10$), severe cutaneous adverse reactions ($n = 42$), hepatitis ($n = 20$), or myositis ($n = 5$). All data were reported by healthcare professionals. Serious outcomes (including "Death," "Life threatening," and "Caused/Prolonged Hospitalization") were reported in 6 (60%) cases of myocarditis, 4 (9.5%) cases of severe cutaneous adverse reactions, 5 (25%) cases of hepatitis, and 2 (40%) cases of myositis. One patient with myositis received nivolumab, an ICI, in addition to mogamulizumab. Thirty-four (81.0%) ICSRs of severe cutaneous adverse reactions and 4 (80.0%) ICSRs of myositis were from the "Western Pacific Region." The 10 cases of mogamulizumab-associated myocarditis were all "Spontaneous" reports; 7 (70%) originated from the "Region of the Americas" and 3 (30%) from the "European Region" (Table 3). Mogamulizumab was withdrawn in 3 patients (30.0%) with myocarditis, 11 (26.2%) with severe

Table 3. The characters of mogamulizumab-treated patients with 4 irAEs have a significant reporting rate.

Characteristic	Myocarditis	Severe cutaneous adverse reactions	Hepatitis	Myositis
	n = 10*	*n* = 42*	*n* = 20*	*n* = 5*
Age group				
18-44 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
45-64 years	1 (10.0)	11 (26.2)	7 (35.0)	1 (20.0)
65-74 years	0 (0.0)	17 (40.5)	6 (30.0)	1 (20.0)
≥75 years	0 (0.0)	9 (21.4)	3 (15.0)	0 (0.0)
Unknown	9 (90.0)	5 (11.9)	4 (20.0)	3 (60.0)
Sex				
Male	3 (30.0)	21 (50.0)	8 (40.0)	1 (20.0)
Female	0 (0.0)	18 (42.9)	8 (40.0)	1 (20.0)
Unknown	7 (70.0)	3 (7.1)	4 (20.0)	3 (60.0)
Report year				
2013	0 (0.0)	4 (9.5)	2 (10.0)	0 (0.0)
2014	0 (0.0)	6 (14.3)	1 (5.0)	0 (0.0)
2015	0 (0.0)	5 (11.9)	0 (0.0)	0 (0.0)
2016	0 (0.0)	5 (11.9)	0 (0.0)	0 (0.0)
2017	0 (0.0)	4 (9.5)	3 (15.0)	1 (20.0)
2018	0 (0.0)	5 (11.9)	0 (0.0)	0 (0.0)
2019	0 (0.0)	6 (14.3)	2 (10.0)	1 (20.0)
2020	3 (30.0)	0 (0.0)	3 (15.0)	1 (20.0)
2021	2 (20.0)	1 (2.4)	5 (25.0)	0 (0.0)
2022	4 (40.0)	3 (7.1)	4 (20.0)	1 (20.0)
2023	1 (10.0)	3 (7.1)	0 (0.0)	1 (20.0)
Report region				
Eastern mediterranean region	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
European region	3 (30.0)	5 (11.9)	11 (55.0)	1 (20.0)
Region of the Americas	7 (70.0)	3 (7.1)	3 (15.0)	4 (80.0)
Western Pacific region	0 (0.0)	34 (81.0)	6 (30.0)	0 (0.0)
Report type				
Spontaneous	10 (100.0)	31 (73.8)	11 (55.0)	4 (80.0)
Report from study	0 (0.0)	11 (26.2)	9 (45.0)	1 (20.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Outcome				
Death	1 (10.0)	1 (2.4)	0 (0.0)	0 (0.0)
Life threatening	3 (30.0)	0 (0.0)	1 (5.0)	0 (0.0)
Caused/prolonged hospitalizatioN	2 (20.0)	3 (7.1)	4 (20.0)	2 (40.0)
Disabling/incapacitating	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	4 (40.0)	4 (9.5)	7 (35.0)	2 (40.0)
Unknown	0 (0.0)	34 (81.0)	8 (40.0)	1 (20.0)
Report source				
Physician	4 (40.0)	38 (90.5)	15 (75.0)	2 (40.0)
Pharmacist	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other health professional	6 (60.0)	4 (9.5)	5 (25.0)	3 (60.0)
Consumer or other non health professional	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Combination of ICIs	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)

*n (%).
Abbreviations: ICIs, immune checkpoint inhibitors.

cutaneous adverse reactions, 10 (50.0%) with hepatitis, and 3 (60.0%) with myositis (Table 4). Regarding the outcomes of patients who had mogamulizumab therapy withdrawn, "no effect observed" was reported in 2/11 (18.2%) patients with severe cutaneous adverse reactions, 2/10 (20.0%) with hepatitis, and 2/3 (66.7%) with myositis (Table 5).

Table 4. The actions to 4 irAEs extracted significant reporting rates with mogamulizumab are displayed.

Dechallenge action	Myocarditis	Severe cutaneous adverse reactions	Hepatitis	Myositis
	n = 10*	*n* = 42*	*n* = 20*	*n* = 5*
Dose increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dose not changed	1 (10.0)	0 (0.0)	0 (0.0)	1 (20.0)
Dose reduced	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Drug withdrawn	3 (30.0)	11 (26.2)	10 (50.0)	3 (60.0)
Unknown	6 (60.0)	31 (73.8)	10 (50.0)	1 (20.0)

*n (%).

Table 5. The outcome of the action to 4 irAEs extracted significant reporting rates with mogamulizumab are displayed.

Dechallenge outcome	Myocarditis	Severe cutaneous adverse reactions	Hepatitis	Myositis
	n = 3*	*n* = 11*	*n* = 10*	*n* = 3*
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No effect observed	0 (0.0)	2 (18.2)	2 (20.0)	2 (66.7)
Reaction abated	2 (66.7)	9 (81.8)	5 (50.0)	1 (33.3)
Unknown	1 (33.3)	0 (0.0)	3 (30.0)	0 (0.0)

*n (%).

Discussion

Immune-related AEs are systemic adverse events resulting from immune abnormalities induced by drugs targeting the immune system, such as ICI. Mogamulizumab may induce dermopathies through immune activation; however, reports of other mogamulizumab-associated irAEs are scarce, and comparative studies on these irAEs are lacking. Our study comprehensively evaluated the systemic irAEs associated with mogamulizumab using a large database. The results indicated that mogamulizumab exhibited a high reporting rate for the following 4 irAEs: myocarditis, severe cutaneous adverse reactions, hepatitis, and myositis. These adverse events have been reported in previous case reports, and myocarditis, myositis, and hepatitis were observed in 0.5%-1.1% of patients based on post-hoc analyses of the MAVORIC trial.[1,21] Zhang et al. reported an association between mogamulizumab and autoimmune diseases, including myocarditis.[22] In contrast, the reporting rate of other irAEs induced by ICI, including endocrine autoimmune diseases, was not significantly associated with mogamulizumab use.

To align the physiological conditions caused by cancer, we performed the disproportionality analysis limited to cases of anticancer drug use only (Figure 2C). Reports of mogamulizumab use had high reporting rates of myocarditis, severe cutaneous adverse reactions, hepatitis, and myositis compared to other anticancer agents. We also evaluated whether other ATL drugs, such as vorinostat, a histone deacetylase inhibitor used as a control drug in the MAVORIC trial, and romidepsin, another histone deacetylase inhibitor, are associated with irAEs.[1] These drugs exhibit pharmacological effects that differ from those of mogamulizumab. Notably, other ATL therapies were not associated with the 4 irAEs that exhibited significant signals in the mogamulizumab analysis. These results suggest that the signals of these irAEs were likely caused by mogamulizumab therapy rather than the underlying condition of T-cell lymphoma or leukemia in these patients. The mechanism underlying mogamulizumab-associated irAEs is believed to involve immune stimulation via CCR4 inhibition. CCR4 is a chemokine receptor expressed on Tregs, and its inhibition can suppress Tregs, activate the immune system, and induce irAEs. Following the administration of mogamulizumab, the percentage of Tregs decreases, whereas that of CD8 + T-cells increases in the peripheral blood of patients with CTCL.[23] In addition, cutaneous adverse reactions caused by immune activation may predict the therapeutic efficacy of mogamulizumab.[5,24]

In the present study, we described additional characteristics of the 4 irAEs with significant signals that were not highlighted in previous studies. As the risk of rare adverse events is difficult to assess in clinical trials owing to limitations in follow-up periods and population size, pharmacovigilance studies are a useful first step in validating potential adverse events. In this study, more than 50% of the ICSRs for the 4 irAEs were reported spontaneously. Although mogamulizumab ICSRs were reported relatively evenly across the 3 regions, the reporting region for the 4 irAEs was unbalanced. This imbalance is considered to be due to regional differences in the reporting and recognition of adverse events; however, based on the present analysis, the influence of racial differences cannot be completely ruled out. The subgroup analysis of the MAVORIC trial showed that there was no difference in safety signals for drug rash in Black vs. non-Black patients; however, verification of ethnic differences in rare adverse events, including myocarditis, was insufficient.[25] Future studies should carefully evaluate ethnic differences. Among numerous irAEs, myocarditis is one of the most lethal ICI-induced irAEs and has been detected as mogamulizumab-associated irAEs. Our results indicate that the outcomes of patients with myocarditis treated with mogamulizumab tended to be more severe than those of

patients experiencing the other 3 irAEs. In the MAVORIC trial, myocarditis that developed after mogamulizumab administration was classified as grade 3.[1] Moreover, Kwan et al. reported that a patient with myocarditis treated with mogamulizumab had a decreased left ventricular ejection fraction after treatment, which led to death.[8] These findings indicate that the outcomes of mogamulizumab-associated myocarditis may be as severe as those of ICI-induced myocarditis. Drug withdrawal is the first choice against severe adverse drug events and can provide a useful dechallenge effect. In this study, 81.8% of patients who discontinued mogamulizumab treatment due to severe cutaneous adverse events had a reduced reaction. However, drug withdrawal alone may not be sufficient in some cases. A few studies have reported that intravenous immunoglobulins and systemic corticosteroids may be useful in the treatment of mogamulizumab-associated adverse events.[9,26] Information on the treatment of adverse events associated with mogamulizumab remains limited, and further studies are needed for the specific management of mogamulizumab-induced irAEs.

Pharmacovigilance studies have several inherent limitations. First, it is not feasible to calculate the actual frequency of adverse events because all reports in VigiBase include only cases with adverse events, and the denominator of actual drug users is unknown. Second, in our study using data from spontaneous reporting databases, we did not account for the Weber effect, which describes the pattern of adverse event reporting for newly approved medications. Given that mogamulizumab is a relatively new medication, the reporting trend of mogamulizumab ICSRs shown in Table 1 may be influenced by the Weber effect. Third, VigiBase lacks information on other treatments or conditions in patients treated with mogamulizumab. In addition, the disproportionality analysis approach to generate hypotheses, which we employed in this study, is prone to high false-positive rates and does not rule out confounders or biases related to the use of mogamulizumab. Therefore, we performed sensitivity analyses and 2 signal extraction techniques to address the limitations of this study. Our findings provide useful hypotheses and information for future epidemiological studies.

In conclusion, we comprehensively evaluated the possible risk of irAEs associated with mogamulizumab in a real-world population. Using VigiBase, we identified 4 mogamulizumab-associated irAEs: myocarditis, severe cutaneous adverse reactions, hepatitis, and myositis. Other irAEs, including autoimmune endocrine diseases, were not associated with mogamulizumab. This study suggests that physicians prescribing mogamulizumab should be aware of the possibility of irAEs.

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Conflict of Interest Statement

Authors declare no competing interests.

Data Availability

The data underlying this article cannot be shared publicly but can be obtained from the WHO Uppsala Monitoring Center under license. Some subsets of the data will be shared upon request from the corresponding author after the proposal is approved.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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