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SYSTEMATIC REVIEW

Clinicopathological definition, management and prognostic value of mogamulizumab-associated rash and other cutaneous events: A systematic review

G. Avallone[1,2,3] | G. Roccuzzo[1] | A. Pileri[4,5] | C. Agostinelli[6] | C. A. Maronese[2,3] | C. Aquino[1] | G. Tavoletti[2,3] | F. Onida[7] | P. Fava[1] | S. Ribero[1] | A. V. Marzano[2,3] | E. Berti[2,8] | P. Quaglino[1] | S. Alberti-Violetti[2,3]

[1]Department of Medical Sciences, Dermatology Clinic, University of Turin, Turin, Italy

[2]Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[3]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

[4]Dermatology Unit, IRCCS of Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

[5]Dermatology, Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, Italy

[6]Hematopathology Unit, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy

[7]Hematology-BMT Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

[8]Inter-Hospital Pathology Division, IRCCS MultiMedica, Milan, Italy

Correspondence
Gianluca Avallone, Section of Dermatology, Department of Medical Sciences, University of Turin, Via Cherasco 23, 10121 Turin, Italy.
Email: gianluca.avallone2@gmail.com

Abstract

Mogamulizumab is a first-in-class IgG1k monoclonal antibody that selectively targets the chemokine receptor type 4. The drug has received Food and Drug administration authorisation for mycosis fungoides and Sézary syndrome following failure of at least one previous course of systemic therapy and now is available in Europe. One of the most common treatment-related side effects observed has been the mogamulizumab-associated rash (MAR), which affects up to a quarter of patients and is the most frequent adverse event leading to drug discontinuation. The aim of this study is to perform a systematic review of the literature on patients diagnosed with MAR and other mogamulizumab-related cutaneous events to describe the clinical and histological characteristics, the management in clinical practice and to assess whether these events have prognostic implications. In total, 2073 records were initially identified through a literature search, 843 of which were duplicates. After screening for eligibility and inclusion criteria, 49 articles reporting mogamulizumab-associated cutaneous events were included. Totally, 1516 patients were retrieved, with a slight male prevalence as for the available data (639 males and 570 females, i.e. 52.9% vs. 47.1%). Regarding the reported clinicopathological findings of the cutaneous reactions, the five most common patterns were spongiotic/psoriasiform dermatitis (22%), eruptions characterized by the presence of papules and/or plaques (16.1%), cutaneous granulomatosis (11.4%), morbilliform or erythrodermic dermatitis (9.4%) and photodermatitis (7.1%). Our results highlight how the majority of the reported cutaneous adverse events on mogamulizumab are of mild-to-moderate entity and generally manageable in clinical practice, though prompt recognition is essential and case-by-case assessment should be recommended. Future research will need to focus on the MAR prognostic implications and to identify genomic and molecular markers for a more rapid and accurate diagnosis.

INTRODUCTION

Mogamulizumab is a first-in-class IgG1k monoclonal antibody that selectively targets the chemokine receptor type 4 (CCR4), an essential chemotaxis mediator for T-helper (Th) 2 lymphocytes, regulatory T cells (Tregs) and cutaneous lymphocyte-associated antigen-positive skin homing cells.[1] Malignant cutaneous T cells, including those in primary cutaneous T-cell

G. Avallone and G. Roccuzzo contributed equally to this article and share first authorship.

P. Quaglino and S. Alberti-Violetti contributed equally to this article and share senior authorship.

lymphoma (CTCL) and adult T-cell leukaemia-lymphoma (ATLL), are typically of Th2 phenotype and express CCR4 ubiquitously[2]; therefore, the targeting of CCR4 by mogamulizumab leads to a therapeutic antitumour effects.[3,4] The drug was first originally approved in Japan for relapsed or refractory CCR4-positive ATLL in 2012.[5] Thereafter, it has received Food and Drug administration (FDA) authorisation for mycosis fungoides (MF) and Sézary syndrome (SS) following failure of at least one previous course of systemic therapy on the basis of an international, open-label, randomized controlled phase III trial versus vorinostat (MAVORIC),[6] and now is available in Europe. One of the most common treatment-related side effects observed has been the mogamulizumab-associated rash (MAR), which affects up to a quarter of patients and is the most frequent adverse event leading to drug discontinuation (i.e. 7% of patients in the mogamulizumab group, according to the MAVORIC trial).[6] Since then, the following four predominant clinical patterns have been described in relation to MAR: folliculotropic MF-like scalp plaques with alopecia, papules and/or plaques, photodermatitis and morbilliform or erythrodermic dermatitis (Figures 1 and 2).[7] These clinical entities need to be distinguished from the progression of the underlying disease in order to prevent potentially premature drug discontinuation.[8] The development of MAR has been suggested as a possible favourable prognostic factor associated with a significant overall survival benefit in ATLL and greater durable responses in MF/SS.[9–11] According to a recently published consensus of experts in the field, MAR severity can be clinically classified as Grade 1 (i.e. macules-papules covering <10% body surface area (BSA) with or without symptoms), Grade 2 (i.e. macules-papules covering 10%–30% BSA with or without symptoms, limiting daily activities, rash covering >30% BSA with or without mild symptoms) and Grade 3 (i.e. macules-papules covering >30% BSA with moderate or severe symptoms, limiting self-care activities of daily living).[12] In terms of histological features, three main patterns have been described: psoriasiform/spongiotic, lichenoid/CD8+ interface and granulomatous, with mixed patterns often seen.[12] As the number of patients treated with mogamulizumab has grown rapidly worldwide, it has become clear that MAR has a more complex spectrum of clinicopathological presentations and other cutaneous events, with clinical and histological features different from the 'classic' MAR, have been reported in single-centre experiences. Several trials are currently assessing the efficacy of mogamulizumab in treating advanced or metastatic solid tumours, therefore there is the possibility that this drug will be used in an increasing number of diseases and broader geographical areas.[13–17]

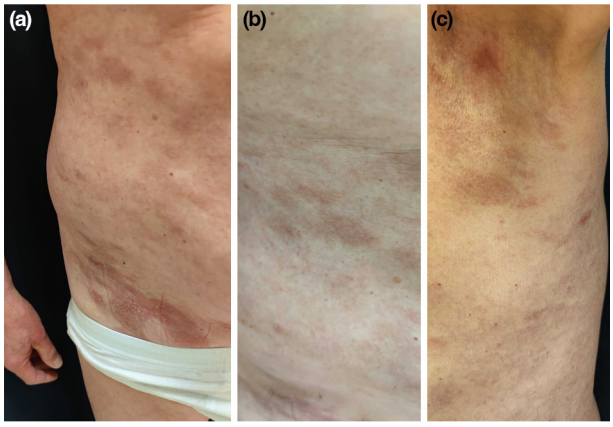

FIGURE 1 An 84-year-old man developed a skin rash on the trunk 3 months after starting mogamulizumab. The patient at the time of the consultation was in complete response for his Sézary syndrome. (a) Erythematous patches and plaques in abdomen, (b) back and (c) in left axillary region.

To date, no systematic review on mogamulizumab-associated cutaneous events, including MAR, has been conducted and the current data available are based largely on case reports and case series. The aim of this study is to perform a systematic review of patients diagnosed with MAR and other mogamulizumab-related cutaneous events to identify which are their clinical and histological characteristics, how they are managed in daily practice and whether their development has prognostic implications.

PROTOCOL AND REGISTRATION

The protocol for this review was defined a priori and registered online in the PROSPERO international prospective register of systematic reviews (CRD42023388458). This review was conducted in accordance with PRISMA and the Cochrane Handbook for Systematic Reviews.[18]

Eligibility criteria

Studies were included if (i) patients' mogamulizumab-associated cutaneous reactions were diagnosed either clinically, histologically or both; (ii) the studies were randomized controlled trials, cohort studies, case–control studies, cross-sectional studies, case series, case reports or letters; (iii) the papers were published in the English language and (iv) they reported at least one outcome of treatment. Therapy cycles were defined according to the commonly used schedule (administration of intravenous mogamulizumab, at the dosage of 1.0 mg/kg, on Days 1, 8, 15 and 22 of the first 28-day cycle, then on Days 1 and 15 of each subsequent 28-day cycle).[6] Studies were excluded if (i) a diagnosis of MAR or other mogamulizumab-related cutaneous events was not made; (ii) they were reviews, abstract or poster presentations. No restrictions were set on the number, age and ethnicity of patients included in the studies.

Information sources

The MEDLINE, Embase and Cochrane databases were searched from inception from 10 March 2010 to 2 January 2023 using the only search term 'mogamulizumab'. Restriction to the English language was set. The reference lists of the shortlisted studies were then screened. The PRISMA statement was followed, and the checklist was completed.

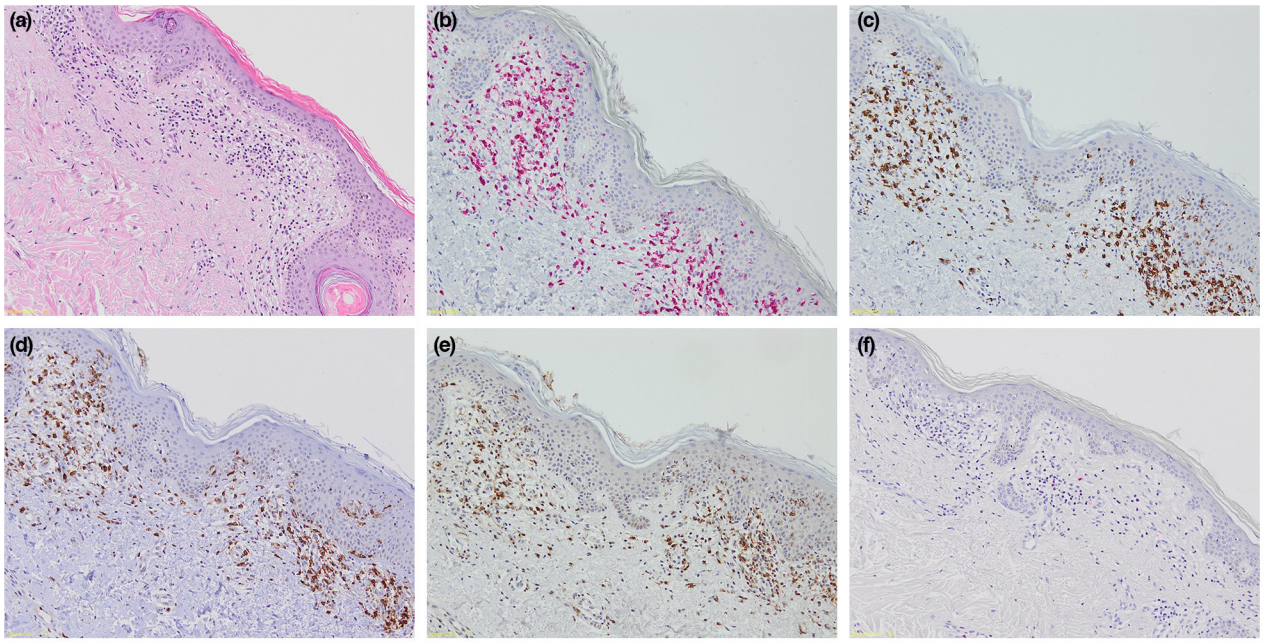

FIGURE 2 The skin biopsy performed revealed a (a) lympho-histiocytic infiltrate expressing (b) CD3, (c) CD8, (d) CD7, (e) PD1, (f) with few scattered CD 20 elements while the diagnostic biopsy was CD4+, CD7− and CD8− (not shown). A diagnosis of mogamulizumab-associated rash was made and topical steroid cream was started.

Study selection

Following the database search, studies were compiled into a single list with all duplicates removed. Titles and abstracts were then screened for initial eligibility by two reviewers independently (G.A. and C.A.) and conflicts were resolved by a third independent reviewer (S.A.V.). Full-text publications were retrieved and assessed using the complete eligibility criteria in a similar fashion. Reference lists of included publications were screened, and citation tracking was completed on Google Scholar. Figure 3 outlines the study selection process.

Outcomes

The primary outcome measures were (i) clinical and histological characteristics, (ii) therapy, (iii) response to mogamulizumab regimen defined as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Secondary outcomes measures were (i) time to skin reaction onset, (ii) number of infusions before onset, (iii) duration and (iv) treatment discontinuation.

Data collection, synthesis and management

Data were extracted independently by two authors (G.A. and C.A.) into a Microsoft Excel spreadsheet. The information extracted from eligible studies included general information (first author's name, year of publication and country), study characteristics (study type and number of patients), participant characteristics (age and sex), lymphoma type (MF/SS, ATLL or others) and primary or secondary outcome measures.

Quality and risk of bias in individual studies

Two reviewers (G.A. and G.T.) assessed the methodological quality of the evidence and the risk of bias of the included studies independently using the 20-item Quality Appraisal Checklist for Case Series Studies, developed by the Institute of Health Economics using the Delphi method[19] (Table S1). Any uncertainty was resolved through discussion with a third reviewer (S.A.V.).

Data analyses

All numeric variables were presented with mean and standard deviation (SD), whereas the categorical ones were summarized using absolute frequency and percentage values.

RESULTS

A total of 2073 records were initially identified through a literature search, 843 of which were duplicates. After screening for eligibility and inclusion criteria, 49 articles reporting mogamulizumab-associated cutaneous events were included[6–11,20–62] (Table 1). Most publications were case reports/letters to the editor ($n = 28$), followed by case series ($n = 14$), original articles ($n = 6$) and clinical trials ($n = 1$). A total of 1516 patients were retrieved, with a slight male prevalence as

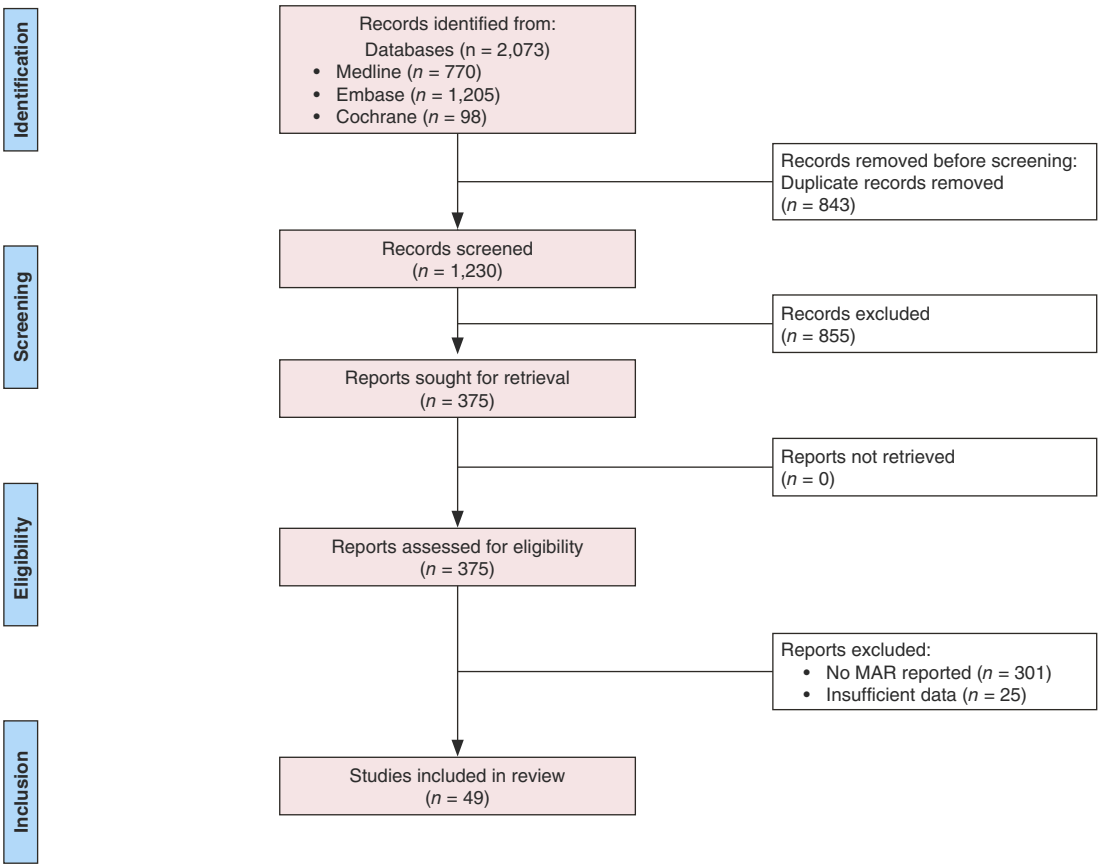

FIGURE 3 PRISMA flowchart of the study. The selection process for study inclusion in the systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

for the available data (639 males and 570 females, i.e. 52.9% vs. 47.1%). Sex distinction of the patients experiencing skin reactions in the different studies was detectable in 462 cases (30.5%) and this cohort displayed a mean age of 61.5 (SD: 13.73). The most common diseases were ATLL ($n = 279$) and MF/SS ($n = 124$), followed by Epstein–Barr virus-associated T-cell lymphoproliferative diseases (EBV T-LPD) ($n = 1$) and peripheral CD4+ T-cell lymphoma, not otherwise specified (PTL-NOS) ($n = 1$), for a total of 405 patients with analysable information.

Clinicopathological findings

Complete data on the clinicopathological presentation of the cutaneous reactions were accessible in 62.7% of the cases, for a total of 254 patients. As for the anatomical distributions of the cutaneous events, the trunk was the most involved site (30.3%), followed by the head/neck (28%), the upper limbs (22.3%) and the lower limbs (20.6%). The five most common findings were spongiotic/psoriasiform dermatitis (22%), eruptions characterized by the presence of papules and/or plaques (16.1%), cutaneous granulomatosis (11.4%), morbilliform or erythrodermic dermatitis (9.4%) and photodermatitis (7.1%). Folliculotropic–MF-like scalp plaques with alopecia and other alopecia phenomena accounted for 5.1% and 4.3% of the available cutaneous reactions. Severe forms of cutaneous reactions with systemic symptoms, such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), were reported in three (1.2%) and six cases (2.4%), respectively. As for the other ones, lichenoid reactions, interface dermatitis, vitiligo and generalized eruptive lentiginosis were reported in 5.1%, 5.1%, 1.6% and 0.8% of the analysed patients, respectively. Other occasional skin findings, encompassing a total of 11.8% patients in the analysed cohort, were facial oedema ($n = 5$), erythema multiforme ($n = 4$), mucosal involvement ($n = 3$), scaling of the scalp ($n = 2$), cutaneous CD8+ T-cell pseudo-lymphoma ($n = 1$), ecthyma gangrenosum ($n = 1$), eruptive sebaceous hyperplasia ($n = 1$), unspecific grade 3 skin reaction ($n = 1$), lupus miliaris disseminated faciei ($n = 1$), palmo-plantar hyperkeratosis ($n = 1$) and pustular eruption ($n = 1$). In terms of clinical description, papules and/or plaques were the most common cutaneous events encountered (28.7%), followed by

TABLE 1 Demographic and clinical characteristics.

		ATLL (*N* = 279)	EBV T-LPD (*N* = 1)	MF/SS (*N* = 124)	PTL-NOS (*N* = 1)	Overall (*N* = 405)
Gender						
N. patients[a]	*n* (%)	39 (14%)	1 (100%)	95 (76.6%)	1 (100%)	136 (33.6%)
Male	*n* (%)	22 (56.4%)	1 (100%)	41 (43.2%)	1 (100%)	65 (47.8%)
Female	*n* (%)	17 (43.6%)	0 (0%)	54 (56.8%)	0 (0%)	71 (52.2%)
Age (total)						
N. patients[a]	*n* (%)	15 (5.4%)	1 (100%)	11 (8.9%)	1 (100%)	28 (6.9%)
	mean (SD)	68.8 (11.41)	74 (–)	54.7 (16.98)	76 (–)	63.7 (15.2)
Age (Pts skin react.)						
N. patients[a]	*n* (%)	18 (6.5%)	0 (0%)	18 (14.5%)	1 (100%)	37 (9.1%)
	mean (SD)	64.9 (18.91)	– (–)	57.3 (22.38)	76 (–)	61.5 (13.73)
Skin reaction onset (days)						
N. patients[a]	*n* (%)	21 (7.5%)	0 (0%)	12 (9.7%)	1 (100%)	34 (8.4%)
	mean (SD)	120.7 (154.63)	– (–)	236.6 (209.92)	730 (–)	195.1 (211.81)
Duration (days)						
N. patients[a]	*n* (%)	6 (2.2%)	0 (0%)	6 (4.8%)	1 (100%)	13 (3.2%)
	mean (SD)	87.8 (87.63)	– (–)	230.5 (145.75)	56 (–)	161.8 (138.6)
Infusions before onset						
N. patients[a]	*n* (%)	36 (12.9%)	0 (0%)	10 (8.1%)	0 (0%)	46 (11.4%)
	mean (SD)	7.6 (3.61)	– (–)	14.9 (14.71)	– (–)	9.7 (10.07)
Anatomical distribution[b]						
N. patients[a]	*n* (%)	46 (16.5%)	0 (0%)	86 (69.4%)	1 (100%)	133 (32.8%)
Trunk	*n* (%)	14 (30.4%)	0 (0%)	39 (45.3%)	0 (0%)	53 (30.3%)
Head/neck	*n* (%)	8 (17.4%)	0 (0%)	40 (46.5%)	1 (100%)	49 (28%)
Upper limb	*n* (%)	12 (26.1%)	0 (0%)	27 (31.4%)	0 (0%)	39 (22.3%)
Lower limb	*n* (%)	12 (26.1%)	0 (0%)	24 (27.9%)	0 (0%)	36 (20.6%)
Response rate						
N. patients[a]	*n* (%)	42 (15.1%)	0 (0%)	91 (73.4%)	0 (0%)	132 (32.6%)
CR	*n* (%)	19 (45.2%)	0 (0%)	41 (45.1%)	0 (0%)	59 (44.7%)
CR + PR	*n* (%)	15 (35.7%)	0 (0%)	6 (6.6%)	0 (0%)	21 (15.9%)
PR	*n* (%)	1 (2.4%)	0 (0%)	37 (40.7%)	0 (0%)	38 (28.8%)
SD	*n* (%)	1 (2.4%)	0 (0%)	3 (3.3%)	0 (0%)	4 (3%)
SD + PD	*n* (%)	5 (11.9%)	0 (0%)	0 (0%)	0 (0%)	5 (3.8%)
PD	*n* (%)	1 (2.4%)	0 (0%)	4 (4.4%)	0 (0%)	5 (3.8%)
Treatment discontinuation						
N. patients[a]	*n* (%)	13 (4.7%)	0 (0%)	100 (80.6%)	1 (100%)	114 (28.1%)
Yes	*n* (%)	6 (46.2%)	0 (0%)	61 (61%)	0 (0%)	67 (58.8%)
No	*n* (%)	7 (53.8%)	0 (0%)	39 (39%)	1 (100%)	47 (41.2%)
Reaction type						
N. patients[a]	*n* (%)	28 (10%)	1 (100%)	223 (179.8%)	2 (200%)	254 (62.7%)
Spongiotic/psoriasiform dermatitis	*n* (%)	2 (7.1%)	0 (0%)	54 (24.2%)	0 (0%)	56 (22%)
Papules and/or plaques	*n* (%)	3 (10.7%)	0 (0%)	38 (17%)	0 (0%)	41 (16.1%)
Cutaneous granulomatosis	*n* (%)	0 (0%)	0 (0%)	28 (12.6%)	1 (50%)	29 (11.4%)
Morbilliform or erythrodermic dermatitis	*n* (%)	7 (25%)	0 (0%)	17 (7.6%)	0 (0%)	24 (9.4%)

(Continues)

TABLE 1 (Continued)

		ATLL (*N* = 279)	EBV T-LPD (*N* = 1)	MF/SS (*N* = 124)	PTL-NOS (*N* = 1)	Overall (*N* = 405)
Photodermatitis	*n* (%)	1 (3.6%)	1 (100%)	16 (7.2%)	0 (0%)	18 (7.1%)
Folliculotropic–MF-like scalp plaques with alopecia	*n* (%)	0 (0%)	0 (0%)	13 (5.8%)	0 (0%)	13 (5.1%)
Interface dermatitis	*n* (%)	2 (7.1%)	0 (0%)	11 (4.9%)	0 (0%)	13 (5.1%)
Lichenoid	*n* (%)	0 (0%)	0 (0%)	12 (5.4%)	1 (50%)	13 (5.1%)
Alopecia	*n* (%)	0 (0%)	0 (0%)	11 (4.9%)	0 (0%)	11 (4.3%)
Vitiligo	*n* (%)	0 (0%)	0 (0%)	4 (1.8%)	0 (0%)	4 (1.6%)
Generalized eruptive lentiginosis	*n* (%)	0 (0%)	0 (0%)	2 (0.9%)	0 (0%)	2 (0.8%)
Others	*n* (%)	13 (46.4%)	0 (0%)	17 (7.6%)	0 (0%)	30 (11.8%)
TEN[c]	*n* (%)	6 (46.2%)	0 (0%)	0 (0%)	0 (0%)	6 (20%)
Facial oedema	*n* (%)	0 (0%)	0 (0%)	5 (29.4%)	0 (0%)	5 (16.7%)
EM[c]	*n* (%)	4 (30.8%)	0 (0%)	0 (0%)	0 (0%)	4 (13.3%)
Mucosal involvement[c]	*n* (%)	0 (0%)	0 (0%)	3 (17.6%)	0 (0%)	3 (10%)
SJS[c]	*n* (%)	3 (23.1%)	0 (0%)	0 (0%)	0 (0%)	3 (10%)
Scaling of the scalp[c]	*n* (%)	0 (0%)	0 (0%)	2 (11.8%)	0 (0%)	2 (6.7%)
Cutaneous CD8+ T-cell pseudolymphoma[c]	*n* (%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	1 (3.3%)
Ecthyma gangrenosum[c]	*n* (%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	1 (3.3%)
Eruptive sebaceous hyperplasia[c]	*n* (%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	1 (3.3%)
Aspecific grade 3 skin reaction[c]	*n* (%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	1 (3.3%)
Lupus miliaris disseminated faciei[c]	*n* (%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	1 (3.3%)
Palmo-plantar hyperkeratosis[c]	*n* (%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	1 (3.3%)
Pustules[c]	*n* (%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	1 (3.3%)
Therapy[b]						
N. patients[a]	*n* (%)	43 (15.4%)	0 (0%)	65 (52.4%)	1 (100%)	109 (26.9%)
Systemic corticosteroids	*n* (%)	31 (72.1%)	0 (0%)	16 (24.6%)	0 (0%)	47 (43.1%)
Topical corticosteroids	*n* (%)	5 (11.6%)	0 (0%)	38 (58.5%)	0 (0%)	43 (39.4%)
Methotrexate	*n* (%)	0 (0%)	0 (0%)	6 (9.2%)	0 (0%)	6 (5.5%)
Dupilumab	*n* (%)	1 (2.3%)	0 (0%)	1 (1.5%)	0 (0%)	2 (1.8%)
Others	*n* (%)	6 (14%)	0 (0%)	4 (6.2%)	1 (100%)	11 (10.1%)
IVIg[c]	*n* (%)	3 (42.9%)	0 (0%)	0 (0%)	0 (0%)	3 (15%)
Dupilumab[c]	*n* (%)	0 (0%)	0 (0%)	2 (18.2%)	0 (0%)	2 (10%)
Azathioprine[c]	*n* (%)	1 (14.3%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Ceftazidime[c]	*n* (%)	0 (0%)	0 (0%)	1 (9.1%)	0 (0%)	1 (5%)
Ciprofloxacin[c]	*n* (%)	0 (0%)	0 (0%)	1 (9.1%)	0 (0%)	1 (5%)
Doxycycline[c]	*n* (%)	0 (0%)	0 (0%)	1 (9.1%)	0 (0%)	1 (5%)
ECP[c]	*n* (%)	0 (0%)	0 (0%)	1 (9.1%)	0 (0%)	1 (5%)
Fluconazole[c]	*n* (%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	1 (5%)
Hydroxychloroquine[c]	*n* (%)	0 (0%)	0 (0%)	1 (9.1%)	0 (0%)	1 (5%)
Ketoconazole[c]	*n* (%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	1 (5%)
Oral tacrolimus[c]	*n* (%)	1 (14.3%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)

TABLE 1 (Continued)

		ATLL (*N* = 279)	EBV T-LPD (*N* = 1)	MF/SS (*N* = 124)	PTL-NOS (*N* = 1)	Overall (*N* = 405)
Phototherapy[c]	*n* (%)	1 (14.3%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Plasma exchange[c]	*n* (%)	1 (14.3%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Topical metronidazole[c]	*n* (%)	0 (0%)	0 (0%)	1 (9.1%)	0 (0%)	1 (5%)
Topical tretinoin[c]	*n* (%)	0 (0%)	0 (0%)	1 (9.1%)	0 (0%)	1 (5%)
Topical urea[c]	*n* (%)	0 (0%)	0 (0%)	1 (9.1%)	0 (0%)	1 (5%)
Watch-and-wait[c]	*n* (%)	0 (0%)	0 (0%)	1 (9.1%)	0 (0%)	1 (5%)

Abbreviations: ATLL, adult T-cell leukaemia/lymphoma; CR, complete response; EBV T-LPD, Epstein–Barr virus-associated T-cell lymphoproliferative disease; ECP, extracorporeal photopheresis; EM, erythema multiforme; IVIg, Intravenous immunoglobulins; MF, mycosis fungoides; PD, progressive disease; PR, partial response; PTL-NOS, peripheral CD4+ T-cell lymphoma, not otherwise specified; SD, stable disease; SD, standard deviation; SJS, Stevens–Johnson syndrome; SS, Sézary syndrome; TEN, toxic epidermal necrolysis.

[a]Percentage values are calculated by taking the total number of patients for each lymphoma type as the denominator.

[b]For Anatomical distribution and Therapy variables, records considered NA if more than one patient was included in the study and more than one category was indicated without the distribution of patients within category.

[c]Percentages values are calculated considering number of *Other* as denominator.

morbilliform or erythrodermic dermatitis (16.8%), photodermatitis (12.6%), follulotropic-MF like scalp plaques with alopecia (9.1%), alopecia (7.7%), vitiligo (2.8%) and generalized eruptive lentiginosis (1.4%). All the other cutaneous presentations together account for 21% of cases (Table S2). A further data analysis encompassing studies with specified histological findings showed as spongiotic/psoriasiform dermatitis represents the most common pattern found (50.5%), followed by granulomatous pattern (26.1%) and interface/lichenoid dermatitis (23.4%). At last, data on T-cell receptor clonality and CD4+/CD8+ ratio in the histopathology report of the MAR were available in 10 and 11 studies, respectively, with normal-inverted CD4+/CD8+ ratios in all cases (100%).

Timing and responses

Regarding the timing of the mogamulizumab-associated cutaneous reaction, very few details were available, as the reporting rates of skin reaction onset, duration and prior number of infusions were retrievable in only 8.4%, 3.2% and 11.4% of the analysed patients, respectively. Overall, cutaneous reactions were seen after a mean time of 195.1 days and 9.7 infusions, with an average duration of 161.8 days. Response rates to mogamulizumab therapy were reported in 32.6% of the patients, with favourable outcomes in most of the cases, as complete (CR) and partial (PR) responses accounted for up to 83.3% in ATLL patients and 92.4% in MF/SS patients whose outcome was clearly specified in the reports. Mogamulizumab-associated cutaneous reactions led to therapy discontinuation in little more than half of the analysed subjects (i.e. 58.8%), with similar trends in both ATLL and MF/SS subsets of patients. Therapy restart after temporary drug discontinuation was described in 68.8% of the studies. Among cases with available data, a recurrence of MAR was detected in 4 (30.7%) out of the 13 patients in whom mogamulizumab was reintroduced after withdrawal.[8,25,31,49,62]

Management

Data regarding the management of the cutaneous reactions were available in only 26.9% of the patients, with higher reporting rates in the MF/SS (i.e. 52.4%) compared to the ATLL (i.e. 15.4%) subset of patients. The most prescribed treatments were systemic (43.1%) and topical (39.4%) corticosteroids, followed by methotrexate (5.5%). Intravenous immunoglobulins (IVIg) and dupilumab were also mentioned to be useful in few cases (2.8% and 1.8% of the patients, respectively).

DISCUSSION

This systematic review collects the currently available data regarding mogamulizumab-associated cutaneous events in the scientific literature and a multitude of clinical and histopathological presentation of cutaneous adverse reactions events have emerged. Overall, the key element emerged is the crucial need of a clear distinction between MARs and disease progression, being a misinterpretation one of the potential reasons of incorrect mogamulizumab's effectiveness assessment and unnecessary drug discontinuation.[12] The outlined clinical manifestations appear more frequently of mild–moderate severity and reversible, while severe cutaneous reactions, such as SJS and TEN, have been reported only in few cases.[9,35,38,41,42,54,60] The manifestation in the same patient of two distinct cutaneous events with different temporal onset is uncommon,[46] though the presence of more than one histopathologic pattern in different biopsy specimens has been described.[25,27] From a histological point of

view, there are three most frequent patterns of MAR: spongiotic/psoriasiform dermatitis, interface/lichenoid dermatitis, and granulomatous dermatitis. Based on our results, spongiotic/psoriasiform dermatitis represents the most frequent MAR and this agrees with what has been previously reported.[27] As for the putative mechanisms behind the occurrence of MAR, the mogamulizumab-related Treg cells depletion seems to result in an increased activation of CD8+ which presumably targets autoantigens on epidermal keratinocytes.[33] Treg cells also regulates the peripheral checkpoint to avoid the autoantibody production: their consequent depletion has been shown to elicit the production of autoantibodies directed again keratinocytes and melanocytes.[63,64] As stated by several studies speculating on the potential positive role of mogamulizumab-associated cutaneous events and the patients' prognosis, our results showed that most subjects experiencing any skin events achieved a response to mogamulizumab. According to Yonekura et al., the tumour infiltrating CD8+ lymphocytes, promoted by the reduction of Treg cells, are indicative of enhanced antitumour immunity.[10] Treatment continuation in cases of biopsy-proven CD8+ lymphocyte-rich lesions following mogamulizumab has been therefore recommended.[9,10,35] A higher frequency of MAR appears to be noticeable in SS compared to MF patients, probably due to the different underlying pathophysiology of the two entities.[8,62] As higher blood disease burden seems to be related to more frequent MAR development and concomitant better overall response, Trum et al. speculated that the depletion of both functional immunomodulatory and dysfunctional tumour Tregs in these CTCL patients may be associated with greater T-cell dysregulation in peripheral blood and skin.[8] Outside of clinical trials, few cutaneous adverse events have been described so far in patients who received mogamulizumab to treat a lymphoma other than MF/SS or ATLL such as a *malessezia*-driven head and neck dermatitis occurred in a patient with peripheral CD4+ T-cell lymphoma,[34] a photodermatitis in a patient with EBV T-LPD,[33] and a grade II skin event in a patient with refractory/relapsed angioimmunoblastic lymphoma.[61] These are only a negligible proportion of cutaneous adverse events that have been encountered, and this is likely due to the rarity and aggressiveness of these forms as well as the few reports describing the use of mogamulizumab in these types of disease.[61,65–72] Concerning the therapeutic management of MAR by healthcare providers, a relatively high degree of heterogeneity has emerged, especially prior to the 2022 expert consensus recommendations.[12] As thoroughly outlined by Musiek et al., clinical grading of MAR should guide the proper management.[12] Specifically, Grade 1 events can be managed without recurring to drug discontinuation nor skin biopsy, with the support of high-potency Class 1 topical steroids and anti-pruritic agents (e.g. antihistamines, or GABA analogs, doxepin and mirtazapine). Conversely, a biopsy should be considered in cases of non-resolving Grade 1, and all cases of Grade 2 or 3 MARs, to obtain a histopathologic proof of the clinical suspect.[12] In the latter two scenarios, in which symptoms tend to be more intense and have an impact on patients' daily life, delaying mogamulizumab and administering oral steroids (0.5–1 mg/kg/day) should be considered as first options.[12] In our review, topical steroids, systemic steroids and methotrexate were the most common primary therapeutical strategy used.[7,8,10,11,20–25,28,29,32,33,35,38–43,44,46,47,49,51,52,54,57–59,62] Few patients have been treated with dupilumab, including a case of treatment-refractory MAR in whom a short course of seven dupilumab injections—preferred over a more protract regimen to minimize any potential risk of CTCL exacerbation—successfully treated the eruption. However, the exact mechanism by means of dupilumab could be effective in the treatment of MARs has not established yet.[8,20] Doxycycline and hydroxychloroquine resulted in no improvement in mogamulizumab-induced granulomatous dermatitis of the scalp,[22] whereas azathioprine was a suitable therapeutic option in a case of toxicoderma-like eruption and autoimmune hepatitis.[21] IVIg therapy combined with pulse methylprednisolone achieved complete responses in TEN following mogamulizumab.[41,42,45] Little is known about the risk of relapse upon drug re-challenge. According to the available data, it appears that recurrent MAR arises in a limited subset of patients. Nevertheless, these insights are based on limited evidence, and it remains unclear whether the recurrent MAR exhibits similarities to its original occurrence.[8,25,31,49,62] This review encompasses several types of studies, with differences in terms of specialty fields (i.e. haematology vs. dermatology), levels of evidence (i.e. single-centre vs. multicentre experiences) and statistical power. Several limitations have emerged across the studies and warrant attention. First, there were remarkable differences in reporting clinical and morphological features of the mogamulizumab-induced cutaneous reactions between the ATLL and MF/SS clusters of studies. For instance, anatomical distribution and response rates were reported in 16.5% and 15.1% of the cases in the former group of studies, while up to 69.4% and 73.4% in the latter. These findings are likely relatable to a different approach in describing the characteristics of cutaneous reactions and their relationship with disease outcomes among different specialists (i.e. haematologists and dermatologists), yet they may be also attributable to the growing attention throughout the years towards mogamulizumab-associated cutaneous events, as the drug has received approval for CTCL few years after ATLL.[1,5] Second, most data on MARs occurring in ATLL come from haematological facilities in Japan, a geographical area where the human T-cell leukaemia virus type 1 (HTLV-1) is endemic.[73] Conversely, data on MARs occurring in CTCLs mainly derive from Northern American and European institutions, areas in which ATLL is significantly less represented.[74] Third, the small cohort size, along with the retrospective nature of the studies, poses most case reports at a weak level of scientific evidence, preventing to establish any certain causal relationship between the evaluated cutaneous event and the drug administration. Moreover, the analysed cohorts included patients treated both in clinical trials and in real-life settings, and these populations are

known to have different characteristics and outcomes, due to specific inclusion criteria. At last, a thorough assessment of the histologic, immunohistochemical and clonal features of the cutaneous events, such as CD4+/CD8+ ratio, CD7 expression, and TCR rearrangements were rarely reported in the published manuscripts, because not yet recognized as key elements of MAR definition.[12] In conjunction with the lack of a standardized classification prior to the study by Musiek et al., all these factors contribute to the inability to establish a defined clinicopathological correlation in most of the cases reported in this study.[12] As thoroughly described by Wang and colleagues, the combined use of immunohistochemistry, through the individualisation of an inverted or normalized CD4:CD8 ratio within the intraepidermal lymphocytes, and TCR-HTS, which have a higher sensitivity and specificity than polymerase chain reaction techniques, could be valid tools in distinguishing MAR from CTCL.[27,75,76] However, considering the costs and the low availability of next generation sequencing in many clinical settings, the authors did not wish to portray TCR-HTS as critical to the routine diagnosis of MAR, but rather as an ancillary study providing further support for the overall clinicopathologic impression.[27] The findings of our review are in line with this conclusion, as T-cell clonality of mogamulizumab-induced cutaneous events was rarely assessed in clinical practice and indeed may be unfeasible on a routine basis in most facilities.

CONCLUSIONS

The landscape of MAR and other cutaneous events displays heterogenous clinical and histological features. Our results highlight how the majority of the reported cutaneous adverse events on mogamulizumab are of mild-to-moderate entity and generally manageable in clinical practice, though prompt recognition is essential and case-by-case assessment should be recommended. It cannot be excluded that new emerging events will be observed and a better understanding of the characteristics of previous established ones will be possible. Consequently, knowledge of the mogamulizumab-associated MAR and other cutaneous events is likely to be of increasing interest for a larger number of healthcare providers. Albeit Tregs lymphocytes depletion are one of the most frequently involved factors along with an altered disease background, the mechanisms which drive the onset of the adverse events remain unclear. Future research will need to focus on the MAR prognostic implications and to identify genomic and molecular markers for a more rapid and accurate diagnosis.

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The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT
The patients described in this paper have given their written informed consent to the publication of their case details.

ORCID
G. Avallone https://orcid.org/0000-0001-7253-2370
G. Roccuzzo https://orcid.org/0000-0001-7126-5506
C. A. Maronese https://orcid.org/0000-0002-9449-849X
G. Tavoletti https://orcid.org/0000-0001-8901-318X
S. Ribero https://orcid.org/0000-0002-0098-1406
A. V. Marzano https://orcid.org/0000-0002-8160-4169
P. Quaglino https://orcid.org/0000-0003-4185-9586

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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