Dermatol Ther (Heidelb) (2022) 12:29–40
https://doi.org/10.1007/s13555-021-00624-7

REVIEW

Dermatologic Events Associated with the Anti-CCR4 Antibody Mogamulizumab: Characterization and Management

Amy C. M. Musiek · Kerri E. Rieger · Martine Bagot · Jennifer N. Choi · David C. Fisher · Joan Guitart · Paul L. Haun · Steven M. Horwitz · Auris Onn-Lay Huen · Bernice Y. Kwong · Mario E. Lacouture · Sarah J. Noor · Alain H. Rook · Lucia Seminario-Vidal · Maarten H. Vermeer · Youn H. Kim

Received: July 2, 2021 / Published online: November 23, 2021
© The Author(s) 2021

ABSTRACT

The CCR4-directed monoclonal antibody mogamulizumab has been shown to significantly improve progression-free survival and overall response rate compared with vorinostat in adults with relapsed/refractory mycosis fungoides (MF) and Sézary syndrome (SS). One of the most common adverse events seen with mogamulizumab in MF/SS patients is rash. Because of the protean nature of MF/SS and the variable clinical and histopathological features of mogamulizumab-associated rash, healthcare providers may have difficulty distinguishing rash from disease, and may not be aware of appropriate treatment strategies for this generally manageable adverse event. The objective of this report was to combine results from published literature with experiences and recommendations from multiple investigators and institutions into clinical best practice recommendations to assist healthcare providers in identifying and managing mogamulizumab-associated rash. Optimal management, which includes biopsy confirmation and steroid treatment, requires a multidisciplinary approach among oncology, dermatology, and pathology practitioners.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13555-021-00624-7.

A. C. M. Musiek (✉)
Division of Dermatology, Washington University School of Medicine, 4901 Forest Park, Suite 502, Saint Louis, MO 63108, USA
e-mail: amusiek@wustl.edu

K. E. Rieger · B. Y. Kwong · Y. H. Kim
Stanford University, Stanford, CA, USA

M. Bagot
Hôpital Saint Louis, APHP, Inserm U976, Université de Paris, Paris, France

J. N. Choi · J. Guitart
Northwestern University, Evanston, IL, USA

D. C. Fisher
Dana-Farber Cancer Institute, Boston, MA, USA

P. L. Haun · A. H. Rook
University of Pennsylvania, Philadelphia, PA, USA

S. M. Horwitz · M. E. Lacouture · S. J. Noor
Memorial Sloan Kettering Cancer Center, New York, NY, USA

A. O.-L. Huen
MD Anderson Cancer Center, Houston, TX, USA

L. Seminario-Vidal
University of South Florida and H. Lee Moffitt Cancer Center, Tampa, FL, USA

M. H. Vermeer
Leiden University, Leiden, The Netherlands

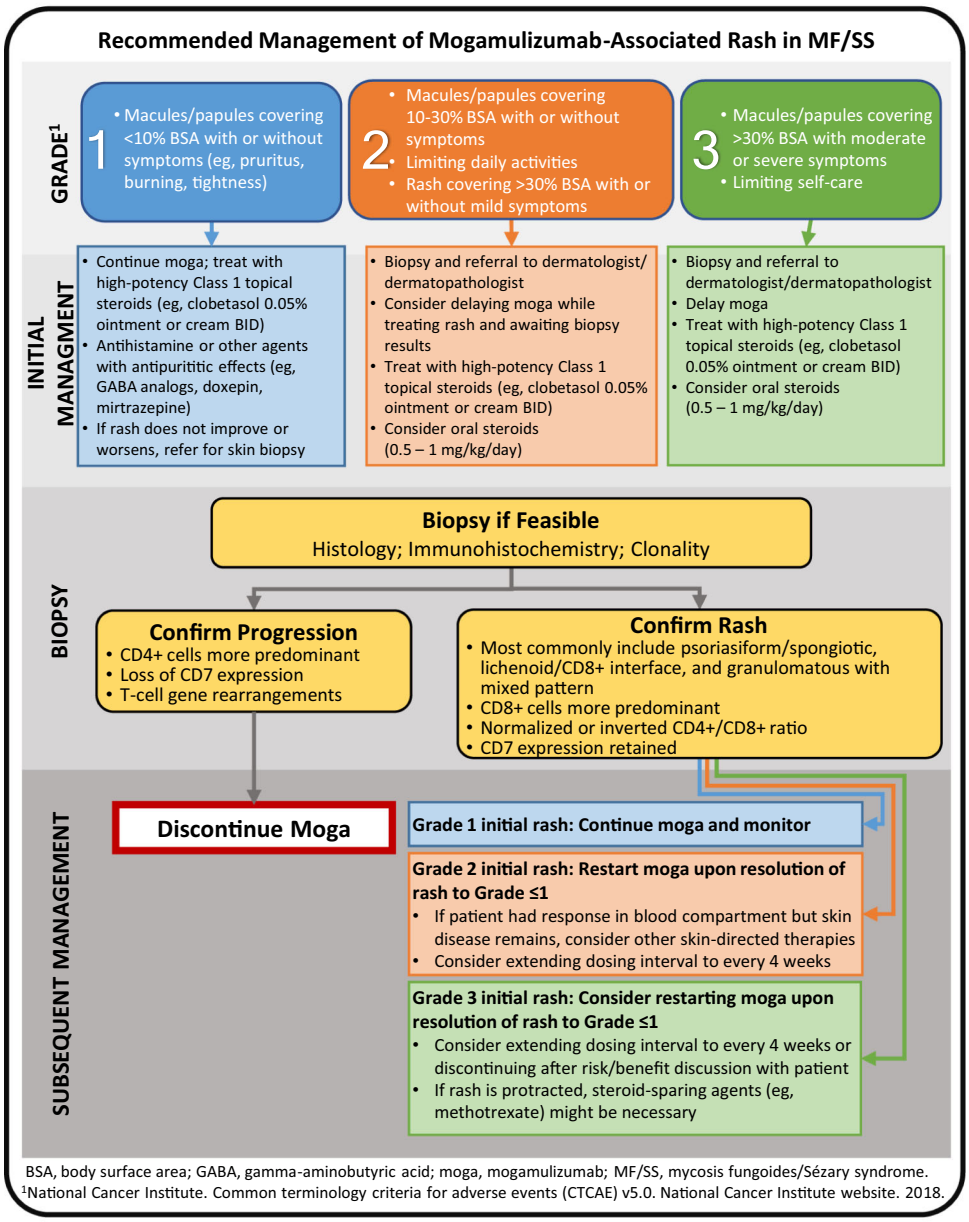
Infographic:

OPEN ACCESS

PEER-REVIEWED INFOGRAPHIC

Dermatologic Events Associated With the Anti-CCR4 Antibody Mogamulizumab: Characterization and Management

Amy C.M. Musiek, Kerri E. Rieger, Martine Bagot, Jennifer N. Choi, David C. Fisher, Joan Guitart, Paul L. Haun, Steven M. Horwitz, Auris Onn-Lay Huen, Bernice Y. Kwong, Mario E. Lacouture, Sarah J. Noor, Alain H. Rook, Lucia Seminario-Vidal, Maarten H. Vermeer, Youn H. Kim. Dermatology and Therapy (2021).



BSA, body surface area; GABA, gamma-aminobutyric acid; moga, mogamulizumab; MF/SS, mycosis fungoides/Sézary syndrome.
[1]National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v5.0. National Cancer Institute website. 2018.

Adis

The infographic represents the opinions of the authors. For a full list of declarations, including funding and author disclosure statements, please see the full text online. © The authors, CC-BY-NC 2021.

Keywords: Cutaneous T-cell lymphoma; Eruption; Mogamulizumab; Mycosis fungoides; Rash; Sézary syndrome

Key Summary Points

The US Food and Drug Administration (FDA) approval of the monoclonal antibody mogamulizumab in cutaneous T-cell lymphoma (CTCL) was based on the randomized, phase 3 MAVORIC trial, in which drug rash was found to be the second most common adverse event in the moga treatment group, occurring in 24% of patients, with most events of mild/moderate severity.

Mogamulizumab-associated rash may lead to unnecessary and premature discontinuation of treatment in patients who are receiving clinical benefit, because of the difficulty in distinguishing the rash from persistent or progressive disease and oncologists' limited experience in CTCL.

The objective of this report is to combine the knowledge gleaned from previous publications with the experiences from multiple investigators and institutions to develop clinical best practices for oncologists and other healthcare providers in identifying and managing mogamulizumab-associated rash.

Optimal management of mogamulizumab-associated rash, which includes biopsy confirmation and steroid treatment, requires a multidisciplinary approach among oncology, dermatology, and pathology practitioners.

DIGITAL FEATURES

This article is published with digital features, including an infographic, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.16677523.

INTRODUCTION

Mycosis fungoides (MF) and Sézary syndrome (SS) are two subtypes of cutaneous T-cell lymphoma (CTCL), which represents a rare group of non-Hodgkin lymphomas [1, 2]. Cutaneous manifestations of MF include patches, plaques, or tumors; patients can progress to extracutaneous disease in the blood, lymph nodes, or viscera [3]. SS is characterized by erythroderma with blood involvement and lymphadenopathy [3]. Beyond the mortality associated with advanced disease, MF and SS have substantial negative impacts on patients' quality of life, including intractable pruritus, sleep interference, and mood changes [4–8].

C–C chemokine receptor 4 (CCR4) is a transmembrane, cell-surface receptor for chemokines CCL17 and CCL22, which play a role in cell migration and trafficking of various lymphocyte subpopulations to the skin [9]. CCR4 is also expressed on malignant T-cells, including those in CTCL, peripheral T-cell lymphoma, and adult T-cell leukemia/lymphoma [10–13]. Moreover, CCR4 is expressed on regulatory T-cells, natural killer cells, and certain CD8+ cell populations [14, 15]. Mogamulizumab is a defucosylated, humanized anti-CCR4 monoclonal antibody with enhanced antibody-dependent cellular cytotoxicity (ADCC) activity [16].

Mogamulizumab has been approved in the US and European Union for adult patients with relapsed or refractory MF and SS after at least one prior systemic therapy (2018) and in Japan for CCR4-positive adult T-cell leukemia-lymphoma (2012, 2014), relapsed or refractory CCR4-positive peripheral T-cell lymphoma (2014), and relapsed or refractory CTCL (2014, 2018) [17–22]. The approval of mogamulizumab in MF and SS was based on the open-label, international, randomized, phase 3 MAVORIC trial (NCT01728805) in adults with relapsed/refractory disease after ≥ 1 systemic therapy [23]. In total, 372 patients were randomized 1:1 to receive mogamulizumab (1.0 mg/kg

administered as an intravenous infusion over at least 60 min once weekly for the first 28-days cycle, then on days 1 and 15 of subsequent cycles) or oral vorinostat (400 mg daily). Crossover from vorinostat to mogamulizumab was allowed upon disease progression or intolerable toxicity. In the randomized portion of the trial, mogamulizumab resulted in significantly longer progression-free survival (PFS) relative to vorinostat (median 7.7 versus 3.1 months; $P < 0.0001$). The overall response rate (ORR) was also significantly improved with mogamulizumab versus vorinostat in randomized patients (28% versus 5%; $P < 0.0001$); in crossover patients, the ORR was 31%.

The most common treatment-emergent adverse events (TEAEs) with mogamulizumab were infusion-related reactions (33%), drug rash (i.e., drug eruption, defined as skin rashes that were assessed by the Investigator or sponsor as possibly, probably, or definitely related to study drug; 24%), diarrhea (23%), and fatigue (23%). Mogamulizumab-associated rash was the second most common TEAE of any cause or grade in patients randomized to mogamulizumab in the MAVORIC study. Events of grade 1–2 rash occurred in 20% of mogamulizumab-treated patients, whereas grade 3 events occurred in 4% (for grading, see Table 1). Similarly, in the 136 crossover patients evaluated for safety, mogamulizumab-associated rash occurred as grade 1–2 events in 21% and as grade 3 events in 4%.

Mogamulizumab-associated rash was the most common TEAE leading to treatment discontinuation, resulting in a discontinuation rate of 7% (13/184). It is important to note that patients in MAVORIC were permitted to have rash treated only with low-/medium-potency topical steroids. The use of systemic steroids was not permitted. Patient management outside the confines of the clinical study may allow better control of mogamulizumab-associated rash. In general, the etiology of dermatologic reactions may be misinterpreted as disease by health care providers, potentially leading to early treatment termination [24]. Given the relative rarity of MF/SS and the lack of specific guidelines, the objective of this report was to combine experiences and recommendations from multiple investigators and institutions into clinical best practices to assist healthcare providers in identifying and managing mogamulizumab-associated rash.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The patient gave consent for their photograph to be included in this publication.

PRIOR LITERATURE

There are limited publications that address the heterogeneous presentation or optimal management of mogamulizumab-associated rash in patients with MF/SS-type CTCL. Several publications have focused on single-institution experience with mogamulizumab-associated

Table 1 Grading for maculo-papular rash by the NCI-CTCAE

CTCAE term	Grade 1	Grade 2	Grade 3
Maculo-papular rash	Macules/papules covering < 10% BSA with or without symptoms (e.g., pruritus, burning, and tightness)	Macules/papules covering 10–30% BSA with or without symptoms (e.g., pruritus, burning, and tightness); limiting instrumental ADL; rash covering > 30% BSA with or without mild symptoms	Macules/papules covering > 30% BSA with moderate or severe symptoms; limiting self-care ADL

Based on the NCI-CTCAE v5.0 [41]

ADL activities of daily living, *BSA* body surface area, *CTCAE* Common Terminology Criteria for Adverse Events

rash, including two case studies, three case series of 7–19 patients, and a histopathologic analysis [25–30]. In previous reports, mogamulizumab-associated rash has been managed primarily with topical steroids, systemic steroids, methotrexate, and/or interruption or discontinuation of mogamulizumab therapy [25, 30]. A review article for nurses focused on practical considerations when administering mogamulizumab, including mogamulizumab-associated rash [31]. The incidence, impact, and management of immunotherapy-related rash and other toxicities have been reported previously, and guidelines from the National Comprehensive Cancer Network and the Society for Immunotherapy of Cancer are available; however, these publications and guidelines are not specific to CTCL or mogamulizumab and do not take into account the generally less severe and more manageable nature of mogamulizumab-associated rashes [32–37]. Overall, publications devoted to the identification, characterization, and management of mogamulizumab-associated rash in CTCL have been limited.

EXPERT SELECTION

The best practices provided in this manuscript are informed in large part by an advisory board meeting of dermatologists, oncologists, and pathologists that was held in November 2019 and sponsored by Kyowa Kirin Inc. Experts were selected for participation if they had experience treating patients with MF/SS using mogamulizumab, if they were experts in the histopathology of mogamulizumab-associated rash in MF/SS, or if they were dermatologists with experience managing oncology treatment-related cutaneous adverse events. Several additional expert treaters who were unable to attend the advisory board were also consulted based on their experience with mogamulizumab-associated rash. Consensus on treatment recommendations was reached based on a review of the participating institutions' clinical cases and of clinical trial data; specific recommendations were based on grading of the rash.

CLINICAL AND HISTOPATHOLOGICAL FEATURES OF MOGAMULIZUMAB-ASSOCIATED RASH AND TOOLS TO DISTINGUISH RASH FROM DISEASE

Differentiating mogamulizumab-associated rash from persistent/progressive MF/SS disease is essential to ensure that clinicians do not misinterpret rash as disease and discontinue mogamulizumab, thus preventing a possible response to mogamulizumab or contributing to loss of response when a partial or complete response has been achieved. However, the cutaneous manifestations inherent to MF/SS and the heterogeneous presentation of mogamulizumab-associated rash complicate the diagnosis.

The time to onset of mogamulizumab-associated rash is variable and, based on the authors' experience, can range from 2 to 6 months after start of treatment or even several months after treatment with mogamulizumab has ended. Overall in the MAVORIC study, mogamulizumab-associated rash had a median time to onset of approximately 15 weeks, consistent with the median time to onset of 4.6 months reported by Chen et al. (range 1.4–6.0 months) in their single-institution experience of 12 MAVORIC patients [18, 25].

Clinical presentations of mogamulizumab-associated rash may include erythematous macules or scaly erythematous plaques [25]. Mogamulizumab-associated rash may also present as a photo-distributed, pruritic rash. Masuda et al. reported mogamulizumab-induced photosensitive lesions in two patients with MF, occurring after 3 and 5 months of mogamulizumab treatment, respectively, following narrow-band ultraviolet B (nbUVB) exposure [26]. Eruptions in the scalp can sometimes lead to hair loss (localized or diffuse). In the MAVORIC study, the incidence of alopecia was 7.1% (13/184) in the mogamulizumab-treated group during the randomized portion of the trial [compared with 19.4% (36/186) in the vorinostat-treated group] and

7% (9/136) in the patients who crossed over to mogamulizumab [23].

Skin biopsy should be performed whenever possible to distinguish rash from disease. In the authors' experience, histological patterns of mogamulizumab-associated rash most commonly include psoriasiform/spongiotic, lichenoid/CD8+ interface, and granulomatous, with mixed pattern often seen (Figs. 1 and 2). The granulomatous type is characterized by granulomatous infiltrates consisting of epithelioid histiocytes [25]. In the authors' clinical experience, this granulomatous/histiocytic type is not pruritic or photo-distributed. Preliminary research suggests that the presence of granulomatous/histiocytic type rash may correlate with response to mogamulizumab in some patients with CTCL [25].

Immunohistochemical analyses indicate that, while CD4+ cells are predominant in MF lesions, CD8+ cells are more common in mogamulizumab-associated rash samples, yielding a normalized or inverted CD4+ / CD8+ ratio [25, 26]. In addition, while loss of CD7 expression is common in MF lesions, CD7 expression is generally retained in mogamulizumab-associated rash [25]. Clonality can also be helpful in identifying mogamulizumab-associated rash, with molecular studies showing polyclonal T-cell receptor gene rearrangements [25]. In the photo-distributed type rash, one histopathological pattern that has been

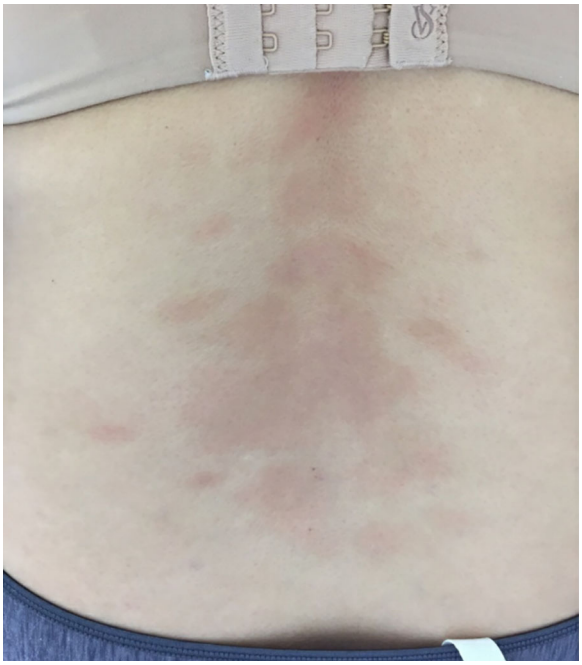


Fig. 2 Non-photo-distributed rash

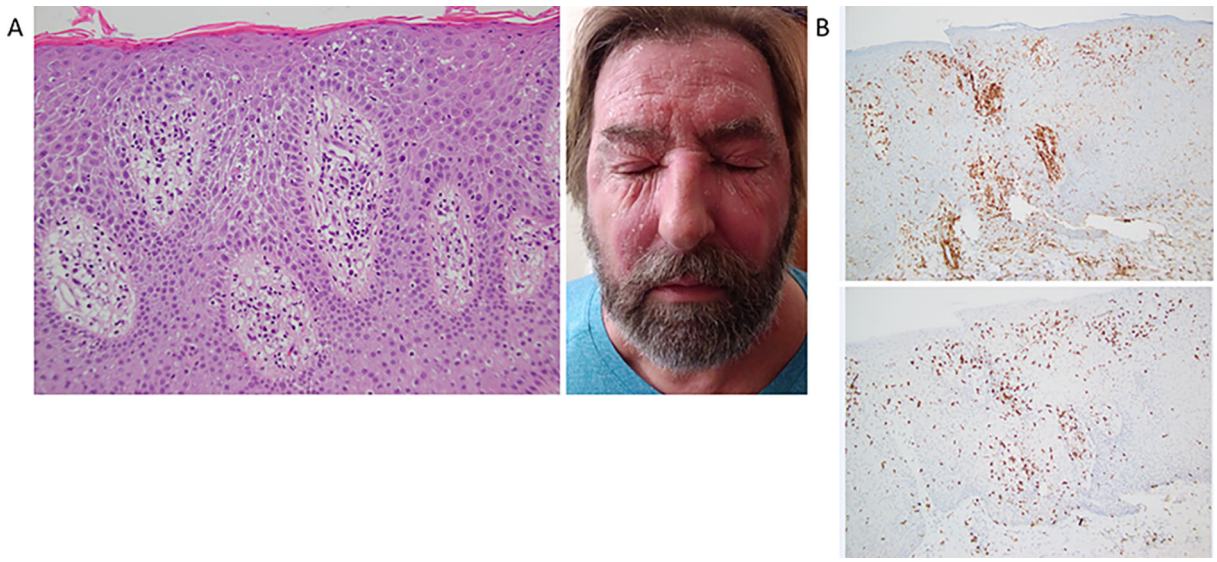


Fig. 1 **A** Psoriasiform spongiotic dermatitis with rare superficially located necrotic keratinocytes (arrow); **B** the infiltrate is composed of CD4 (top image) and CD8 (bottom image) lymphocytes that are morphologically mature and display a normal CD4:CD8 ratio of 2

reported is lichenoid tissue reaction with a CD8+ T cell-dominant infiltrate [26, 38].

Clinicians should be aware that mogamulizumab-associated rash can mimic MF with features such as follicular involvement, tagging at dermoepidermal junction, psoriasiform, histiocytic, and lamellar fibroplasia. Given that mogamulizumab-associated rash can closely mimic progression of MF/SS, the diagnosis of rash should be made with caution, particularly in patients with progressive disease in the blood, lymph nodes, or viscera.

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been observed in Japanese patients with mogamulizumab (monotherapy or combination therapy), predominantly in patients with adult T-cell leukemia/lymphoma (data on file) [18, 39, 40]. Based on the MAVORIC trial and the authors' clinical experience at the time of publication, in patients with MF/SS, mogamulizumab has thus far not resulted in any serious drug hypersensitivity reactions, such as anaphylaxis, SJS/TEN, or drug rash with eosinophilia and systemic symptoms (DRESS).

IMPORTANCE OF A MULTIDISCIPLINARY APPROACH

Given the heterogeneous nature of mogamulizumab-associated rash, a multidisciplinary approach is essential for optimal management of patients experiencing this adverse event. The primary doctor for patients receiving mogamulizumab, most often an oncologist or other advanced practitioner, should work with a dermatologist who can provide their expertise in determining the type and severity of the rash and whether to hold or discontinue mogamulizumab. The dermatopathologist or hematopathologist can help confirm rash versus disease through biopsies, immunostaining, and molecular studies.

MANAGING MOGAMULIZUMAB-ASSOCIATED RASH

Management should be tailored to the severity of rash and impact on life quality (Fig. 3). Grading of rash by the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) is listed in Table 1. For grade 1 suspected rash, clinicians are recommended to continue mogamulizumab while initiating treatment with high-potency Class 1 topical steroids (e.g., clobetasol 0.05% ointment or cream BID). Antihistamines or other agents with antipruritic effects (e.g., gamma-aminobutyric acid analogs, doxepin, mirtazapine) can be used with topical steroids for pruritus. For grade 1 rash, skin biopsies should be performed if feasible. If skin biopsies are not feasible, then the diagnosis can be based on the timing and clinical appearance of the rash. However, if grade 1 rash does not improve or worsens despite topical steroid treatment, we recommend referral to a dermatologist/dermatopathologist with biopsy.

For grade 2 rash, skin biopsies and referral to a dermatologist/dermatopathologist are strongly recommended. Clinicians should consider delaying mogamulizumab while treating the rash and awaiting biopsy results. Most cases of grade 2 rash can be treated with Class 1 topical steroids. In some cases, oral steroids (0.5–1 mg/kg/day) should be considered. If the biopsy results of the grade 2 rash confirm progressive disease, mogamulizumab should be discontinued, whereas if the biopsy results confirm drug rash, mogamulizumab can be resumed upon resolution of the rash to grade ≤ 1. In some cases, clinicians might consider other treatment changes; for example, if mogamulizumab has resulted in a response in the blood compartment but there is persistent skin disease, clinicians can try other skin-directed therapies. Clinicians could also consider extending the dosing interval of mogamulizumab from every 2 to every 4 weeks. In most patients with prior history of rash, mogamulizumab can be considered again, absent absolute contraindications (e.g., anaphylaxis, SJS, TEN). In patients with history of rash, it is

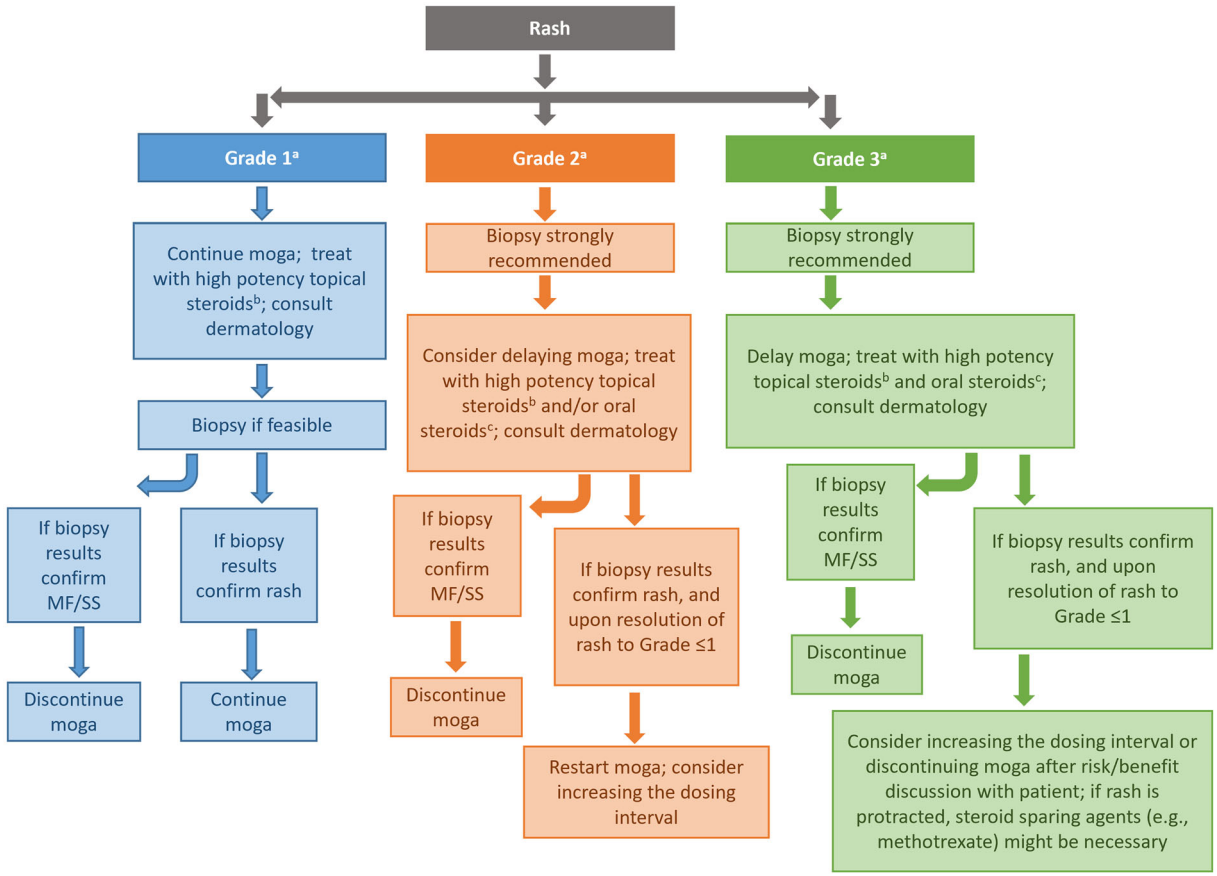


Fig. 3 Flow diagram on management of mogamulizumab-associated rash. *MF/SS* mycosis fungoides/Sézary syndrome, *moga* mogamulizumab. Permanently discontinue mogamulizumab for life-threatening (grade 4) rash or for any Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). For possible SJS/TEN, interrupt mogamulizumab and do not restart unless SJS/TEN is ruled out and the cutaneous reaction has resolved to grade ≤ 1 [18]. [a]Based on the NCI-CTCAE v5.0 [41]. [b]For example, clobetasol 0.05% ointment or cream BID, fluocinonide solution 0.05% BID. [c]0.5–1 mg/kg/day

important to note that the rash may recur on re-challenge; there is some evidence that the presentation is similar to the first episode of mogamulizumab-associated rash and is treatable with steroid-based therapy [30].

For grade 3 rash, mogamulizumab should be delayed, and the rash treated with Class 1 high-potency topical steroids and/or oral steroids. As with grade 2, skin biopsies and referral to a dermatologist/dermatopathologist are strongly recommended. Assuming that the biopsy results confirm rash, upon resolution of the rash to grade ≤ 1, clinicians and patients should discuss the risk/benefit of restarting treatment with mogamulizumab with possible changes to the dosing interval, but only in the absence of anaphylaxis, SJS, or TEN. Life-threatening rash should prompt discontinuation of mogamulizumab. Decisions on restarting should be made on an individualized basis and informed, in part, by patient symptoms. Some mogamulizumab-associated rashes are asymptomatic, thus making the decision to continue mogamulizumab treatment easier. A response in the blood compartment to mogamulizumab will also make the decision to continue treatment easier; however, with stable disease, the decision might be less clear. Clinicians should refer to the dermatologist when considering dose delays and/or discontinuations for grade ≥ 2

rash. Evidence suggests that resolution of mogamulizumab-associated rash is variable and might occur over the course of 1–8 months after mogamulizumab is discontinued [30].

A subset of mogamulizumab-associated rashes have been described as photo-exacerbated and pruritic. Photo-protection should be discussed with these patients, and nbUVB avoided or used with caution. Clinicians should review medication lists to exclude known drugs that cause photosensitive/toxic rash and investigate for an underlying autoimmune condition that may explain the photo-distributed rash.

The authors generally treat most cases of rash with an oral steroid dose from 0.5–1 mg/kg with a typically short taper over 1–2 weeks. If the rash rebounds, the authors recommend managing with topical steroids or a slower taper of oral steroids (e.g., 4–6 weeks). If the rash is protracted, clinicians should consider steroid-sparing treatments, such as methotrexate, that are acceptable in MF/SS. Primary immunosuppressive agents such as cyclosporine should be avoided. In cases of long-term steroid use, prophylaxis with antibiotics and/or bone protection should be considered.

Regardless of grade, after identifying mogamulizumab-associated rash, clinicians should continue to monitor and reassess for mogamulizumab-associated rash versus disease. In some cases, disease and mogamulizumab-associated rash may occur at the same time on the histological sample. In the case of a mixed-result biopsy, clinicians can consider continuing to treat the disease and the mogamulizumab-associated rash. Multiple biopsies may be beneficial in the event that one shows mixed results while others are clear.

CONCLUSIONS

Mogamulizumab-associated rash is heterogeneous in presentation and can be difficult to distinguish from MF/SS disease. Clinicians might discontinue mogamulizumab because of a misdiagnosis of disease progression, thus preventing a possible response to mogamulizumab. Given the cutaneous nature of the disease and the variability of the rash, skin biopsies are recommended for a definitive diagnosis. Mogamulizumab-associated rash is generally manageable, with steroids being the mainstay of treatment, but physicians should always assess the risk–benefit of interventions for rash. Optimal management requires a multidisciplinary approach among oncology, dermatology, and pathology practitioners.

ACKNOWLEDGEMENTS

Funding. The development of this report and the Journal's Rapid Service fee were funded by Kyowa Kirin, Inc. Drs. Horwitz, Lacouture, and Noor are supported in part by NIH/NCI Cancer Center Support Grant P30 CA008748.

Medical Writing, Editorial, and Other Assistance. The authors thank Rebecca D. Miles, PhD, and Anthony DiLauro, PhD, of MedVal Scientific Information Services, LLC (Princeton, NJ), for medical writing and editorial assistance, which were funded by Kyowa Kirin, Inc. (Bedminster, NJ). This manuscript was prepared according to the International Society for Medical Publication Professionals' "Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3."

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. Amy C.M. Musiek, Kerri E. Rieger, Jennifer N. Choi, David C. Fisher, Joan Guitart, Paul L. Haun, Steven M. Horwitz, Auris Onn-Lay Huen, Bernice Y. Kwong, Mario E. Lacouture, Sarah J. Noor, Alain H. Rook, Lucia Seminario-Vidal, Maarten H. Vermeer, and Youn H. Kim all participated in the expert panel advisory board meeting and contributed to the conception of the article. All authors contributed to the literature review and to the data analysis. All authors contributed to

the preparation of manuscript draft, made revisions, and approved the final manuscript.

Disclosures. Amy Musiek reports serving on an advisory board for Kyowa Kirin during the conduct of the study and serving on an advisory board for Helsinn and Kyowa Kirin, as well as serving as an investigator for Pfizer, Menlo, Elorac, Soligenix, miRagen, and Connect outside the submitted work. Kerri Rieger reports personal fees from, and serving on an advisory board for, Kyowa Kirin during the conduct of the study. Martine Bagot reports personal fees from, and serving on an advisory board for, Kyowa Kirin during the conduct of the study and personal fees from, and serving on an advisory board for, Takeda, Innate Pharma, and Helsinn-Recordati outside the submitted work. Jennifer Choi reports serving on an advisory board for Kyowa Kirin outside the submitted work. David Fisher reports serving on an advisory board for Kyowa Kirin during the conduct of the study and outside the submitted work. Joan Guitart reports honoraria from Kyowa Kirin during the conduct of the study and grants from Soligenix, Galderma, and Elorac for serving as an investigator on clinical trials outside the submitted work. Paul Haun reports serving on an advisory board for Kyowa Kirin during the conduct of the study. Steven Horwitz reports grants and personal fees from Kyowa Kirin during the conduct of the study and grants and personal fees from Corvus, ADC Therapeutics, Affimed, Aileron, Celgene, Forty Seven Inc., Kyowa Kirin, Takeda, Portola, Seattle Genetics, and Trillium, Verastem, grants from Daiichi Sankyo, and personal fees from Acrotech Biopharma, Astex, BeiGene, miRagen, Merck, Innate Pharma, Bristol Myers Squibb, Mundipharma, C4 Therapeutics, Janssen, Kura Oncology, Myeloid Therapeutics, ONO Pharmaceuticals, and Vividion outside the submitted work. Auris Huen reports personal fees from, and serving on an advisory board for, Kyowa Kirin outside the submitted work. Bernice Kwong reports personal fees from, and serving on an advisory board for, Kyowa Kirin during the conduct of the study and personal fees from, and serving as a consultant for, Oncoderm outside the submitted work. Mario Lacouture reports personal fees from, and serving on an advisory board for, Kyowa Kirin during the conduct of the study and grants and personal fees from Berg, Lutris, Paxman, Novocure, Johnson & Johnson, US Biotest, AstraZeneca, Novocure, QED, Janssen, Novartis, Hoffmann-La Roche, EMD Serono, Genentech, Seattle Genetics, Lutris, OnQuality, Azitra, NCODA, and Apricity outside the submitted work. He is funded in part through NIH/NIAMS grant U01 AR077511 and NIH/NCI Cancer Center Support Grant P30 CA008748. Sarah Noor reports personal fees from, and serving on an advisory board for, Kyowa Kirin during the conduct of the study. Alain Rook has nothing to disclose. Lucia Seminario-Vidal reports grants and personal fees from Kyowa Kirin and Novartis, grants from Soligenix, Eisai, Innate Pharma, Eli Lilly, Amgen, Boehringer Ingelheim, Celgene, AbbVie, Bristol Myers Squibb, Pfizer, and Glenmark, and personal fees from Helsinn, and Aptis Partners outside the submitted work. Maarten Vermeer reports grants from Kyowa Kirin during the conduct of the study and grants from, and serving on an advisory board for, Kyowa Kirin and grants from Takeda outside the submitted work. Youn Kim reports grants and personal fees from, and serving on an advisory board for, Kyowa Kirin during the conduct of the study.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The patient gave consent for their photograph to be included in this publication.

Data Availability. Data sharing is not applicable to this article, as no new datasets were generated or analyzed during the current study.

Open Access. This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit

to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc/4.0/.

REFERENCES

1. Teras LR, DeSantis CE, Cerhan JR, et al. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin. 2016;66:443–59.

2. Olsen EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol. 2011;29:2598–607.

3. Foss FM, Girardi M. Mycosis fungoides and Sézary syndrome. Hematol Oncol Clin North Am. 2017;31:297–315.

4. Bhat TS, Herbosa CM, Rosenberg AR, et al. Current measures are not sufficient: an interview-based qualitative assessment of quality of life in cutaneous T-cell lymphoma. Br J Dermatol. 2021;184:310–8.

5. Semenov YR, Rosenberg AR, Herbosa C, Mehta-Shah N, Musiek AC. Health-related quality of life and economic implications of cutaneous T-cell lymphoma. Br J Dermatol. 2020;182:190–6.

6. Demierre MF, Gan S, Jones J, Miller DR. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: results of a 2005 National Cutaneous Lymphoma Foundation Survey. Cancer. 2006;107:2504–11.

7. Molloy K, Jonak C, Woei AJF, et al. Characteristics associated with significantly worse quality of life in mycosis fungoides/Sézary syndrome from the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study. Br J Dermatol. 2020;182:770–9.

8. Scarisbrick JJ, Prince HM, Vermeer MH, et al. Cutaneous Lymphoma International Consortium study of outcome in advanced stages of mycosis fungoides and Sézary syndrome: effect of specific prognostic markers on survival and development of a prognostic model. J Clin Oncol. 2015;33:3766–73.

9. Sokol CL, Luster AD. The chemokine system in innate immunity. Cold Spring Harb Perspect Biol. 2015;7: a016303.

10. Yoshie O, Fujisawa R, Nakayama T, et al. Frequent expression of CCR4 in adult T-cell leukemia and human T-cell leukemia virus type 1-transformed T cells. Blood. 2002;99:1505–11.

11. Ishida T, Utsunomiya A, Iida S, et al. Clinical significance of CCR4 expression in adult T-cell leukemia/lymphoma: its close association with skin involvement and unfavorable outcome. Clin Cancer Res. 2003;9:3625–34.

12. Ishida T, Inagaki H, Utsunomiya A, et al. CXC chemokine receptor 3 and CC chemokine receptor 4 expression in T-cell and NK-cell lymphomas with special reference to clinicopathological significance for peripheral T-cell lymphoma, unspecified. Clin Cancer Res. 2004;10:5494–500.

13. Ferenczi K, Fuhlbrigge RC, Pinkus J, Pinkus GS, Kupper TS. Increased CCR4 expression in cutaneous T cell lymphoma. J Invest Dermatol. 2002;119:1405–10.

14. Scheu S, Ali S, Ruland C, Arolt V, Alferink J. The C-C chemokines CCL17 and CCL22 and their receptor CCR4 in CNS autoimmunity. Int J Mol Sci. 2017;18:2306.

15. Al-Banna NA, Vaci M, Slauenwhite D, Johnston B, Issekutz TB. CCR4 and CXCR3 play different roles in the migration of T cells to inflammation in skin, arthritic joints, and lymph nodes. Eur J Immunol. 2014;44:1633–43.

16. Ishii T, Ishida T, Utsunomiya A, et al. Defucosylated humanized anti-CCR4 monoclonal antibody KW-0761 as a novel immunotherapeutic agent for adult T-cell leukemia/lymphoma. Clin Cancer Res. 2010;16:1520–31.

17. Subramaniam JM, Whiteside G, McKeage K, Croxtall JC. Mogamulizumab: first global approval. Drugs. 2012;72:1293–8.

18. Kyowa Kirin, Inc. Poteligeo® (mogamulizumab-kpkc) injection, for intravenous use [prescribing information]. US Food and Drug Administration website. 2018. https://www.accessdata.fda.gov/

drugsatfda_docs/label/2018/761051s000lbl.pdf. Accessed Aug 8, 2018.

19. Ollila TA, Sahin I, Olszewski AJ. Mogamulizumab: a new tool for management of cutaneous T-cell lymphoma. Onco Targets Ther. 2019;12:1085–94.

20. European Medicines Agency. Poteligeo (mogamulizumab). European Medicines Agency website. 2020. https://www.ema.europa.eu/en/medicines/human/EPAR/poteligeo. Accessed Apr 23, 2020.

21. Kyowa Hakko Kirin Co., Ltd. Kyowa Hakko Kirin receives the partial change approval of POTELIGEO® in Japan [press release]. Kyowa Kirin website. 2018. https://www.kyowakirin.com/media_center/news_releases/2018/e20180821_01.html. Accessed Jun 12, 2020.

22. Kyowa Hakko Kirin Co., Ltd. Approval for additional indication for chemotherapy-native CCR4-positive ATL of mogamulizumab [press release]. Kyowa Kirin website. 2014. http://www.kyowakirin.com/news_releases/2014/e20141218_02.html. Accessed Sep 5, 2017.

23. Kim YH, Bagot M, Pinter-Brown L, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Lancet Oncol. 2018;19:1192–204.

24. Hassel JC, Kripp M, Al-Batran S, Hofheinz RD. Treatment of epidermal growth factor receptor antagonist-induced skin rash: results of a survey among German oncologists. Onkologie. 2010;33:94–8.

25. Chen L, Carson KR, Staser KW, et al. Mogamulizumab-associated cutaneous granulomatous drug eruption mimicking mycosis fungoides but possibly indicating durable clinical response. JAMA Dermatol. 2019;155:968–71.

26. Masuda Y, Tatsuno K, Kitano S, et al. Mogamulizumab-induced photosensitivity in patients with mycosis fungoides and other T-cell neoplasms. J Eur Acad Dermatol Venereol. 2018;32:1456–60.

27. Trager MH, de Clippelé D, Ram-Wolff C, et al. Mogamulizumab-induced mucocutaneous lichenoid reaction: a case report and short review. Acta Derm Venereol. 2020;100: adv00158.

28. Wang JY, Hirotsu KE, Neal TM, et al. Histopathologic characterization of mogamulizumab-associated rash. Am J Surg Pathol. 2020;44:1666–76.

29. Breen ID, Brumfiel CM, Patel MH, et al. Mogamulizumab-induced interface dermatitis drug rash treated successfully with methotrexate and extracorporeal photopheresis in a patient with Sézary syndrome. JAAD Case Rep. 2021;9:24–7.

30. Hirotsu KE, Neal TM, Khodadoust MS, et al. Clinical characterization of mogamulizumab-associated rash during treatment of mycosis fungoides or Sézary Syndrome. JAMA Dermatol. 2021;157:700–7.

31. Tawa M, Kopp E, McCann S, Cantrell W. Cutaneous T-cell lymphoma: optimizing care in patients receiving anti-CCR4 monoclonal antibody mogamulizumab. Clin J Oncol Nurs. 2019;23:E73–80.

32. Phillips GS, Wu J, Hellmann MD, et al. Treatment outcomes of immune-related cutaneous adverse events. J Clin Oncol. 2019;37:2746–58.

33. Phillips GS, Freites-Martinez A, Wu J, et al. Clinical characterization of immunotherapy-related pruritus among patients seen in 2 oncodermatology clinics. JAMA Dermatol. 2019;155:249–51.

34. Santini FC, Rizvi H, Plodkowski AJ, et al. Safety and efficacy of re-treating with immunotherapy after immune-related adverse events in patients with NSCLC. Cancer Immunol Res. 2018;6:1093–9.

35. Chen CB, Wu MY, Ng CY, et al. Severe cutaneous adverse reactions induced by targeted anticancer therapies and immunotherapies. Cancer Manag Res. 2018;10:1259–73.

36. Thompson JA, Schneider BJ, Brahmer J, et al. Management of immunotherapy-related toxicities, version 1.2019. J Natl Compr Cancer Netw. 2019;17:255–89.

37. Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017;5:95.

38. Tatsuno K, Sano T, Fukuchi K, et al. Emergence of photosensitivity with decreased treg cells in a patient with mycosis fungoides treated with anti-CC chemokine receptor 4 antibody mogamulizumab. Acta Derm Venereol. 2016;96:420–1.

39. Ishida T, Joh T, Uike N, et al. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. J Clin Oncol. 2012;30:837–42.

40. Ishitsuka K, Yurimoto S, Tsuji Y, et al. Safety and effectiveness of mogamulizumab in relapsed or refractory adult T-cell leukemia-lymphoma. Eur J Haematol. 2019;102:407–15.

41. National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v5.0. National Cancer Institute website. 2018. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50. Accessed Dec 6, 2019.