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

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.

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
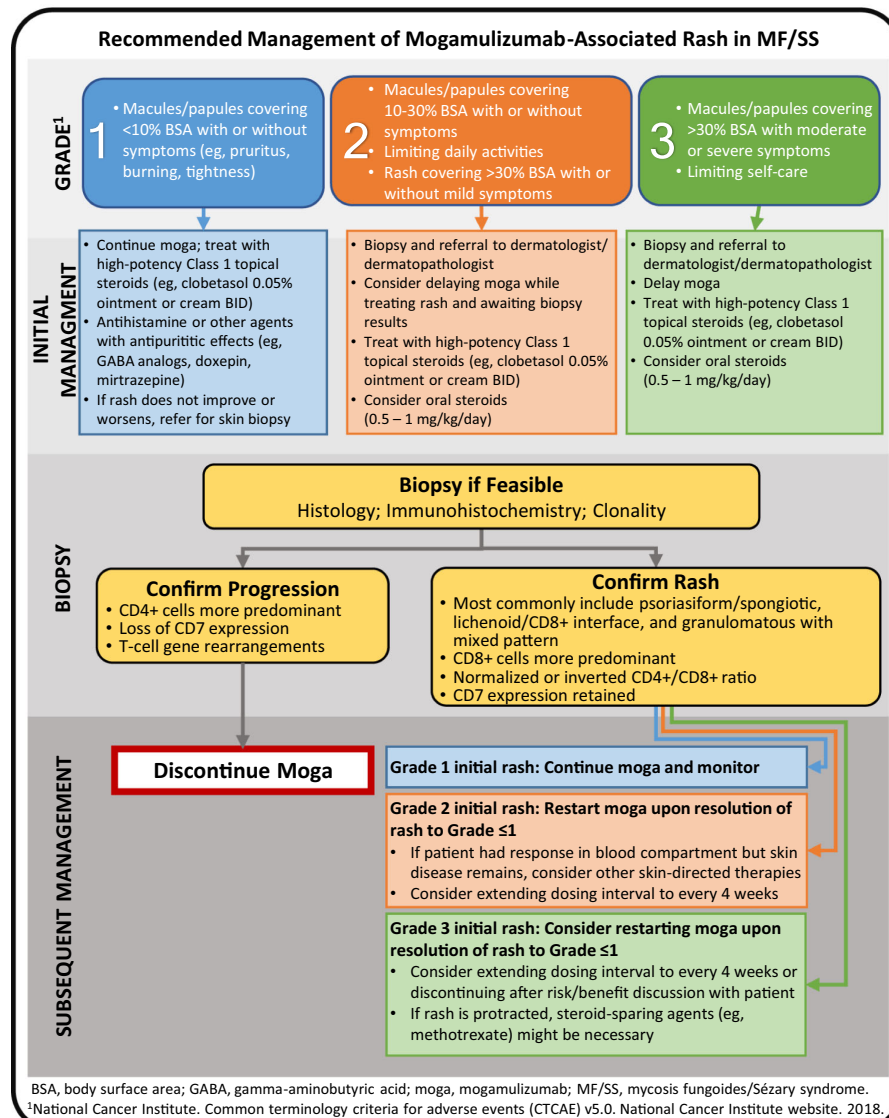University of South Florida and H. Lee Moffitt Cancer Center, Tampa, FL, USA

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

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Recommended Management of Mogamulizumab-Associated Rash in MF/SS

GRADE[1]

1
- Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness)

2
- Macules/papules covering 10-30% BSA with or without symptoms
- Limiting daily activities
- Rash covering >30% BSA with or without mild symptoms

3
- Macules/papules covering >30% BSA with moderate or severe symptoms
- Limiting self-care

INITIAL MANAGMENT

- Continue moga; treat with high-potency Class 1 topical steroids (eg, clobetasol 0.05% ointment or cream BID)
- Antihistamine or other agents with antipurititic effects (eg, GABA analogs, doxepin, mirtrazepine)
- If rash does not improve or worsens, refer for skin biopsy

- Biopsy and referral to dermatologist/dermatopathologist
- Consider delaying moga while treating rash and awaiting biopsy results
- Treat with high-potency Class 1 topical steroids (eg, clobetasol 0.05% ointment or cream BID)
- Consider oral steroids (0.5 – 1 mg/kg/day)

- Biopsy and referral to dermatologist/dermatopathologist
- Delay moga
- Treat with high-potency Class 1 topical steroids (eg, clobetasol 0.05% ointment or cream BID)
- Consider oral steroids (0.5 – 1 mg/kg/day)

BIOPSY

Biopsy if Feasible
Histology; Immunohistochemistry; Clonality

Confirm Progression
- CD4+ cells more predominant
- Loss of CD7 expression
- T-cell gene rearrangements

Confirm Rash
- Most commonly include psoriasiform/spongiotic, lichenoid/CD8+ interface, and granulomatous with mixed pattern
- CD8+ cells more predominant
- Normalized or inverted CD4+/CD8+ ratio
- CD7 expression retained

SUBSEQUENT MANAGEMENT

Discontinue Moga

Grade 1 initial rash: Continue moga and monitor

Grade 2 initial rash: Restart moga upon resolution of rash to Grade ≤1
- If patient had response in blood compartment but skin disease remains, consider other skin-directed therapies
- Consider extending dosing interval to every 4 weeks

Grade 3 initial rash: Consider restarting moga upon resolution of rash to Grade ≤1
- Consider extending dosing interval to every 4 weeks or discontinuing after risk/benefit discussion with patient
- If rash is protracted, steroid-sparing agents (eg, methotrexate) might be necessary

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.

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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-

Fig. 2 Non-photo-distributed rash

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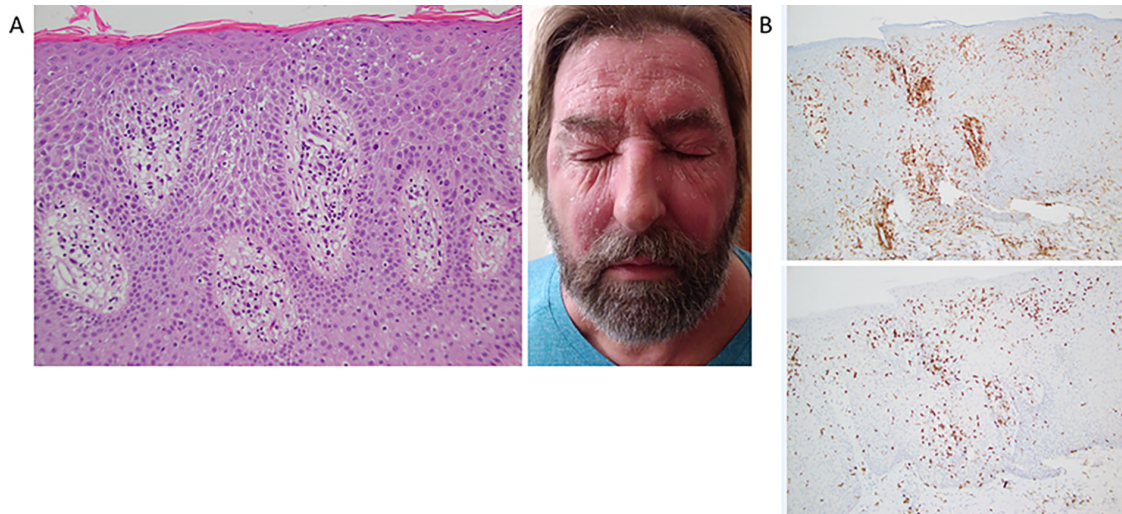
Fig. 1 A Psoriasiform spongiotic dermatitis with rare superficially located necrotic keratinocytes (arrow); B the infiltrate is composed of CD4 (top image) and CD8 (bottom image) lymphocytes that are morphologically mature and display a normal CD4:CD8 ratio of 2

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
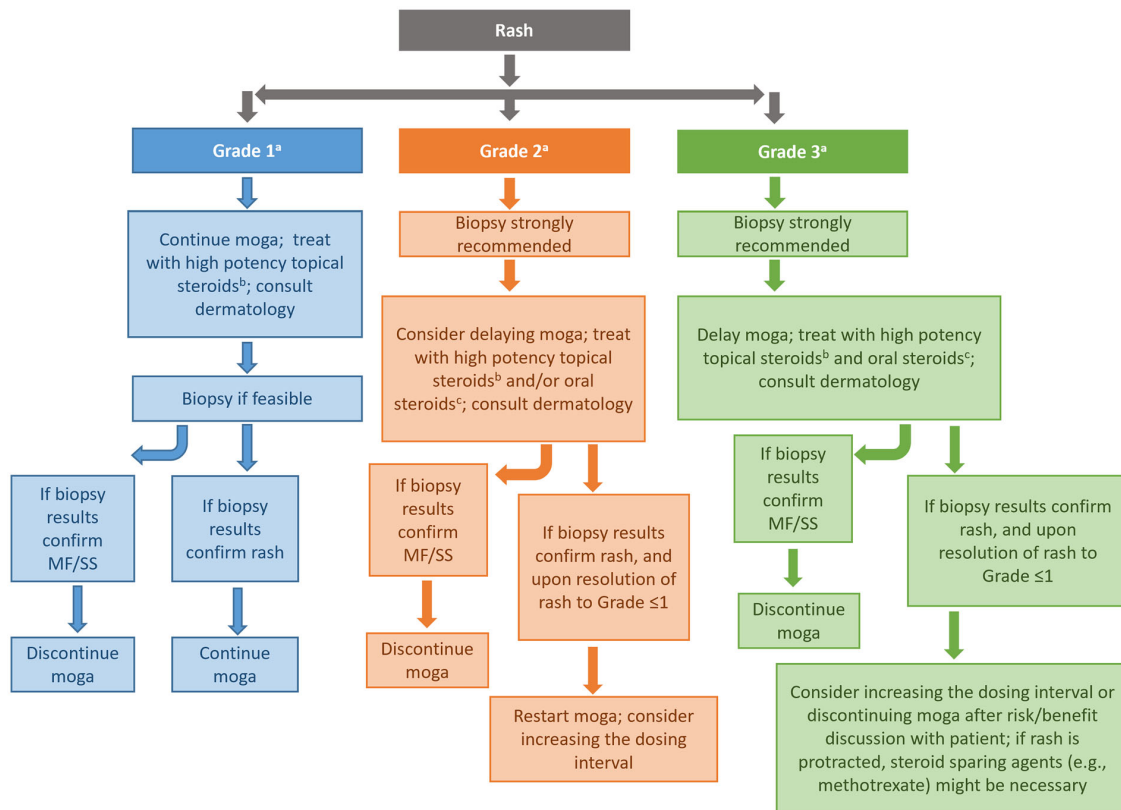
Fig. 3 Flow diagram on management of mogamulizumab-associated rash. *MF/SS* mycosis fungoides/Sézary syndrome, *moga* mogamulizumab. Permanently discontinue mogamulizumab for life-threatening (grade 4) rash or for any Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). For possible SJS/TEN, 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 moga-mulizumab. Decisions on restarting should be made on an individualized basis and informed, in part, by patient symptoms. Some moga-mulizumab-associated rashes are asymptomatic, thus making the decision to continue moga-mulizumab 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.

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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.

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