ORIGINAL RESEARCH ARTICLE

The PROVe Study: US Real-World Experience with Chlormethine/ Mechlorethamine Gel in Combination with Other Therapies for Patients with Mycosis Fungoides Cutaneous T-Cell Lymphoma

Ellen J. Kim[1] · Joan Guitart[2] · Christiane Querfeld[3] · Michael Girardi[4] · Amy Musiek[5] · Oleg E. Akilov[6] · James T. Angello[7] · William L. Bailey[7] · Larisa J. Geskin[8]

Abstract

Background Chlormethine/mechlorethamine gel is a skin-directed therapy for patients with mycosis fungoides cutaneous T-cell lymphoma. Currently, real-world data on chlormethine gel are lacking.

Objective Our objective was to analyze the effect of chlormethine gel in combination with other therapies on efficacy, safety, and health-related quality of life in a real-world setting.

Methods This prospective, observational study enrolled adult patients actively using chlormethine gel. Patients were monitored for up to 2 years during standard-of-care clinic visits. No specific visit schedules or clinical assessments, with the exception of patient-completed questionnaires, were mandated because of the expected variability in practice patterns. The primary efficacy endpoint was the proportion of patients with stage IA–IB disease receiving chlormethine + topical corticosteroids + other with ≥ 50% decrease in body surface area from baseline to 12 months. Response was assessed at each visit using by-time analysis, which investigates the trend to treatment response and allows assessment of response over time. Health-related quality of life was assessed with the Skindex-29 questionnaire.

Results In total, 298 patients were monitored. At 12 months post-treatment initiation, 44.4% (chlormethine + topical corticosteroids + other) and 45.1% (patients receiving chlormethine + other treatment) of efficacy-evaluable patients were responders. By-time analysis demonstrated that peak response occurred (chlormethine + other; 66.7%) at 18 months. There was a significant correlation between responder status and lower post-baseline Skindex-29 scores.

Conclusions This real-world study confirmed that chlormethine gel is an important therapeutic option for patients with mycosis fungoides and contributes to reducing the severity of skin lesions and improving health-related quality of life.

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Background

Chlormethine gel is a skin-directed therapy for mycosis fungoides, a subtype of cutaneous T-cell lymphoma.
It met all prespecified criteria for noninferiority to chlormethine ointment, but information on its real-world use is scarce.

The PROVe Study

Prospective observational study of **real-world** patients actively using **chlormethine gel with other therapies**

298 adults

From **46** US clinics

Followed up for up to 2 years

Mean age: 61.7 years
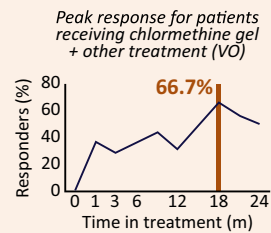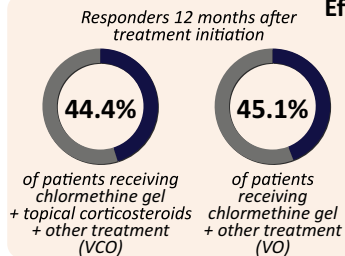Male: 60.1%
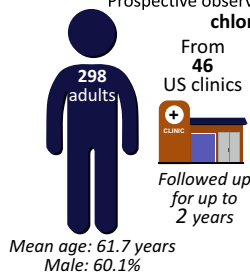
Primary efficacy endpoint

Proportion of patients:
- with stage IA-IB disease
- with ≥50% decrease in body surface area from baseline to 12 months
- receiving chlormethine + topical corticosteroids + other treatment

Other outcomes analyzed

Time to peak response

Safety

HRQOL (Skindex-29 questionnaire)

Key Findings

Efficacy

Responders 12 months after treatment initiation

44.4%
of patients receiving chlormethine gel + topical corticosteroids + other treatment (VCO)

45.1%
of patients receiving chlormethine gel + other treatment (VO)

Peak response for patients receiving chlormethine gel + other treatment (VO)

66.7%

Responders (%) vs Time in treatment (m): 0 1 3 6 12 18 24

Tolerability

The most common skin-related AEs were dermatitis (12.8%), pruritus (9.7%), skin irritation (7.4%), and erythema (5.0%)

HRQOL-improving effects

HRQOL was significantly better in responders than in non-responders

Main Limitations

Primarily a combination treatment; little data on chlormethine gel alone

Variable regimens and assessment measures

Conclusions

Chlormethine gel is an **important treatment option** for patients with mycosis fungoides

The observed **real-world** response patterns from **clinical practice** can inform patients and providers about typical response timelines, potential treatment combinations, and dosing schedules

HRQOL: Health-Related Quality of Life

Key Points

Treatment with chlormethine gel in combination with other therapies was effective and had a good tolerability profile in patients with mycosis fungoides in a real-world setting.

The peak response with chlormethine gel was observed at 18 months post-baseline, and quality of life was better in patients who responded to treatment.

The described response patterns in real-world clinical practice can inform patients and healthcare practitioners regarding typical response timelines, potential treatment combinations, and dosing schedules when using chlormethine gel.

1 Introduction

Primary cutaneous lymphomas are non-Hodgkin lymphomas that present in the skin and include a heterogeneous group of cutaneous T-cell lymphomas (CTCLs). The most common type of CTCL is mycosis fungoides (MF), which is typically characterized by patches, plaques, and tumors and has an indolent clinical course during early disease stages [1, 2].

MF is a rare disease, and studies that detail its clinical course and how patients respond to treatment are scarce. The only curative option for MF is allogenic stem cell transplantation; current therapeutic strategies focus on local treatment of lesions, preventing progression of disease, minimizing long-term toxicity from treatment, and maintaining health-related quality of life (HRQOL). While numerous treatment choices are available, not all are specifically approved for MF. Recommended treatment options depend on disease stage. For patients with early-stage disease, skin-directed therapy is the main focus, including topical steroids, other topical treatments (imiquimod and retinoids), psoralen and ultraviolet A (PUVA), narrow-band ultraviolet B (nbUVB), and topical chemotherapy agents, such as chlormethine (also known as mechlorethamine) and carmustine [3–5].

Chlormethine is an alkylating agent that induces DNA damage and has been used as skin-directed therapy for MF for decades [6–9]. Early preparations of chlormethine were aqueous or ointment based and were only available as compounded agents. A chlormethine 0.016% w/w topical gel (mechlorethamine gel), equivalent to 0.02% chlormethine HCl, was approved in the USA for treatment of MF on the basis of results of the pivotal 201 study and 202 extension study (NCT00535470) [10–12]. Pharmacokinetic analysis has confirmed there is no systemic absorption of topically applied chlormethine gel [10, 11, 13, 14], so systemic drug interactions are unlikely.

In the pivotal registration trial, chlormethine gel met all prespecified criteria for noninferiority to chlormethine ointment. The primary endpoint of the study was response by Composite Assessment of Index Lesion Severity, and the response rates for chlormethine gel were higher than those for chlormethine ointment for both the intent-to-treat (58.5 vs. 47.7%) and efficacy-evaluable populations (76.7 vs. 58.9%). For the secondary endpoint, response per modified Severity-Weighted Assessment Tool, the response rates for chlormethine gel versus chlormethine ointment were 46.9 versus 46.2% for intent-to-treat and 63.3 versus 55.8% for efficacy-evaluable populations, respectively [11]. The PROVe (a PROspective, observational study assessing outcomes, adverse events [AEs], treatment patterns, and quality of life [QOL] in patients diagnosed with MF and treated with Valchlor and other therapies) study was designed to examine the real-world use of chlormethine gel in patients with MF in routine clinical practice across the USA. We have previously published patient clinical characteristics, treatment patterns, and preliminary safety data from the PROVe study [15]. Our preliminary results showed that chlormethine gel was used primarily in early-stage disease, often in combination with other therapies (the most common concomitant treatments were topical steroids, phototherapy, and oral bexarotene), and that treatment frequency varied [15]. Herein, we present final data regarding the clinical response, safety, and effect on HRQOL of chlormethine gel over a 2-year period.

2 Materials and Methods

2.1 Patients and Study Design

This was a multicenter, prospective, observational, US-based, noninterventional study with a total of 46 participating centers. All consecutive adult (≥ 18 years) patients with a diagnosis of MF who were being treated with chlormethine gel could enroll in the study. Patients who were using chlormethine gel for less than 1 month prior to enrollment were considered to be newly initiating treatment. Patients were included regardless of disease stage or previous and concomitant therapy received before or at the time of enrollment, and no exclusion criteria were applied.

Patients were monitored during routine clinical practice and prospectively followed for a maximum of 2 years regardless of whether chlormethine gel had been discontinued. Study end was defined as patient withdrawal of consent, loss to follow-up, death, physician's decision, study completion, or study discontinuation. Clinical characteristics, medical history, prior MF therapies, treatment patterns, concomitant

therapies, clinical response, and AEs were recorded when available. No specific visit schedules or clinical assessments were mandated because of the expected variability in practice patterns, with the exception of protocol-required patient-completed HRQOL questionnaires.

The study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization guidelines. The appropriateness of the study protocol and all risks and benefits to participants were approved by institutional review boards. All patients provided written informed consent.

2.2 Evaluations

As specified in the statistical analysis plan, prior to conducting any analyses, four patient groups were identified on the basis that there were at least 30 patients per group who received a predominant concomitant MF therapy in combination with chlormethine gel. The numbers of patients on chlormethine gel monotherapy or chlormethine gel + topical corticosteroids only were too low to permit statistical analysis. Given this, the groups analyzed for response were as follows: chlormethine + topical corticosteroids + other (VCO; $n = 185$), chlormethine + phototherapy + other (VPO; $n = 76$), chlormethine + oral bexarotene + other (VOB; $n = 47$), and chlormethine + any other treatment (VO; $n = 298$). The term "other" encompassed multiple, overlapping therapies. This overlap exists as a result of patients frequently being treated with multiple therapies sequentially in real-world clinical practice and explains why the sum of the groups exceeds the total number of monitored patients ($n = 298$). The predominance of the first two concomitant treatments was the rationale for creating the VCO, VPO, and VOB subgroups for analysis, and VO was a catch-all group. The primary and other specific therapies (used in $\geq$ 10% of patients at enrollment) in the different groups follow. For the VCO group: chlormethine gel (100%), corticosteroids (100%), phototherapy nbUVB (42.2%), oral bexarotene (29.2%), PUVA (22.7%), local electron-beam therapy (EBT, 19.5%), topical bexarotene (14.1%), and imiquimod (10.3%). For the VPO group: chlormethine gel (100%), phototherapy nbUVB (77.6%), corticosteroids (71.1%), PUVA (32.9%), oral bexarotene (25.0%), UVB (22.4%), imiquimod (13.2%), and acitretin (13.2%). For the VOB group: chlormethine gel (100%), oral bexarotene (100%), corticosteroids (78.7%), phototherapy nbUVB (44.7%), local EBT (27.7%), PUVA (23.4%), total skin EBT (TSEBT, 21.3%), romidepsin (14.9%), imiquimod (12.8%), topical bexarotene (10.6%), and extracorporeal photopheresis (10.6%). For the VO group: chlormethine gel (100%), corticosteroids (73.8%), phototherapy nbUVB (38.6%), oral bexarotene (24.2%), PUVA (20.1%), topical bexarotene (15.8%), and local EBT (14.1%).

The primary efficacy endpoint was the proportion of patients in the VCO group with current stage IA–IB disease and evaluable clinical response data who responded to treatment, defined as a $\geq$ 50% reduction from baseline in the body surface area percentage (%BSA) at 12 months (365 $\pm$ 90 days). Patients who had discontinued chlormethine gel permanently were not included in the primary analysis. Secondary efficacy endpoints included %BSA response rates at 12 months in the VPO, VOB, and VO groups, and a by-time analysis of the %BSA response rates at 1, 3, 6, 9, 12, 15, 18, 21, and 24 months ($\pm$ 45 days) in all patient groups. In addition, the overall response rate (ORR)-2 was determined, defined as the proportion of patients with a $\geq$ 50% reduction from baseline in %BSA for two consecutive visits.

Safety was evaluated by recording AEs and serious AEs at every visit and determining their relation to chlormethine gel treatment. An on-study event was defined as occurring on the day of enrollment or later but prior to study discontinuation or completion. HRQOL was determined using the Skindex-29 questionnaire, which comprises results from three subscales: emotions, symptoms, and functioning (all scored 0–100) [16, 17]. Higher scores for the Skindex-29 indicate lower QOL.

2.3 Statistical Analysis

Separate analyses were conducted for patients with stage IA–IB disease, all staged patients, and all patients regardless of staging. Response over time was assessed using by-time analysis, a statistical approach where the number of patients exceeding the responder threshold of $\geq$ 50% reduction from baseline in %BSA score is divided by the number of patients providing clinical response data (patients with data) at each individual post-enrollment visit. As patient visits were variable, the by-visit analyses of changes from baseline were assigned to the closest time points and included data that fell within $\pm$ 45 days of each designated time point. Not all patients had data available for each time point, resulting in a variation in the number of evaluable patients for each time point and patient group. The by-time analysis of clinical response explores the treatment response trends over the course of the study. The aim of this analysis was to obtain information about response over time, which provides complementary data to the ORR and can help visualize the changing response rates during treatment.

3 Results

3.1 Patients

In total, 301 patients were registered, one was not enrolled and two were ineligible for the study; the remaining 298

patients were monitored. Baseline demographics and clinical characteristics are shown in Table 1. The mean age was 61.7 years, 60.1% of patients were male, and the mean MF duration was 5.5 years. At enrollment, 186 (62.4%) patients had early-stage disease (IA–IIA), 25 (8.4%) had advanced-stage disease (IIB–IV), and current staging information was not available for 87 (29.2%) patients. Most patients used chlormethine gel on a daily basis (74.5%), whereas others used chlormethine gel on a less frequent basis or used different dosing regimens over time (Table 2). The reasons for different dosing frequencies during treatment were physician decision, complete response, and AEs.

The study was completed by 188 (62.5%) patients. Reasons for early study termination were AEs ($n = 9$), loss to follow-up ($n = 5$), withdrawal of consent ($n = 20$), physician's decision ($n = 24$), and termination of the study by the sponsor ($n = 54$). During the study, 77.9% of patients used other skin-directed therapies in combination with chlormethine gel, and 30.2% of patients received systemic therapies. The most common concomitant skin-directed therapy was topical corticosteroids (60.1%); the most common systemic therapy was oral bexarotene (16.1%). The median duration of treatment with chlormethine gel was 24 months for newly initiated patients and 32 months for those who had been on chlormethine gel for ≥ 3 months at time of enrollment [14]. Chlormethine gel was continued for at least 12 months by 190 (63.8%) patients and for 24 months by 134 (45.0%) patients. In total, 87 patients (29.2%) had a dosing interruption during the study, with

Table 2 Dosing frequency and interruptions

Characteristic	PROVe ($n = 298$)
Dosing frequency[a]	
Daily	222 (74.5)
Five times a week	30 (10.1)
Every 2 days	112 (37.6)
Every 3 days	49 (16.4)
Once a week	26 (8.7)
Less frequent/unknown	34 (11.4)
Patients with dosing interruption[b]	87 (29.2)
Average duration of dosing interruption, days	9.7 (1.0–84.0)

Data are presented as n (%) or median (range)

[a]Percentages exceed 100% because patients could have multiple dosing regimens over time; patients with multiple records for dosing were counted in each relevant category

[b]Dosing interruption is defined as dosing that was stopped and restarted within 3 months

a median duration of 9.7 days (range 1–84). The cumulative exposure to chlormethine gel and other treatment is summarized in Table 3.

3.2 Efficacy

The study design did not mandate collection of specific response scores, and modified Severity-Weighted Assessment Tool scores were not documented universally during the study. As the most common response-assessment method

Table 1 Baseline demographics and clinical characteristics

Characteristic	VCO ($n = 185$)	VPO ($n = 76$)	VOB ($n = 47$)	VO ($n = 298$)
Age (years)	63.2 ± 12.6	62.5 ± 11.3	65.3 ± 12.4	61.7 ± 13.5
Sex				
Female	75 (40.5)	28 (36.8)	22 (46.8)	119 (39.9)
Male	110 (59.5)	48 (63.2)	25 (53.2)	179 (60.1)
Duration of MF (years)	5.2 ± 6.3	5.2 ± 6.0	4.3 ± 4.1	5.5 ± 6.8
Months from diagnosis to enrollment, mean (minimum; maximum)	36.6 (0.9; 210.2)	34.2 (0.9; 140.7)	42.6 (1.9; 210.2)	35.8 (0.6; 210.2)
TNMB classification				
IA	60 (32.4)	21 (27.6)	7 (14.9)	105 (35.2)
IB	49 (26.5)	27 (35.5)	12 (25.5)	75 (25.2)
IIA	1 (0.5)	3 (3.9)	2 (4.3)	6 (2.0)
IIB	11 (5.9)	5 (6.6)	6 (12.8)	15 (5.0)
III–IV	6 (3.2)	3 (3.9)	6 (12.8)	10 (3.4)
Missing/unknown	58 (31.4)	17 (22.4)	14 (29.8)	87 (29.2)

Data are presented as mean ± standard deviation or n (%) unless otherwise indicated

MF mycosis fungoides cutaneous T-cell lymphoma, *TNMB* tumor-node-metastasis-blood, *VCO* chlormethine gel + topical corticosteroids + any other treatment, *VO* chlormethine gel + any other treatment, *VOB* chlormethine + oral bexarotene + other, *VPO* chlormethine + phototherapy + other

Table 3 Cumulative exposure duration to chlormethine gel and other treatments ≥5% post-enrollment (*n* = 298)

Treatment received by patients	For any time	For ≥3 months	For ≥6 months	For ≥12 months	For ≥24 months
Chlormethine gel	298 (100)	264 (88.6)	234 (78.5%)	190 (63.8)	134 (45.0)
Skin-directed therapy	232 (77.9)	216 (72.5)	206 (69.1)	198 (66.4)	155 (52.0)
Corticosteroids, topical	179 (60.1)	168 (56.4)	160 (53.7)	156 (52.3)	120 (40.3)
Other topical	31 (10.4)	26 (8.7)	24 (3.0)	24 (8.1)	17 (5.7)
Phototherapy	61 (20.5)	54 (18.1)	54 (18.1)	50 (16.8)	36 (12.1)
Retinoids, topical, bexarotene	17 (5.7)	14 (4.7)	14 (4.7)	12 (4.0)	7 (2.3)
Systemic therapy	90 (30.2)	82 (27.5)	78 (26.2)	66 (21.8)	48 (16.1)
Other systemic	25 (8.4)	14 (4.7)	13 (4.4)	11 (3.7)	8 (2.7)
Retinoids, systemic, bexarotene	48 (16.1)	44 (14.8)	41 (13.8)	35 (11.7)	25 (8.4)

Data are presented as *n* (%)
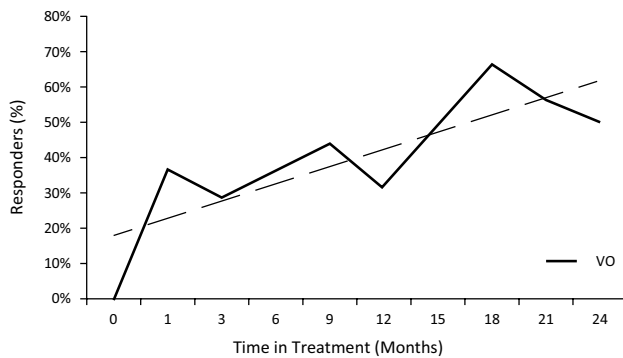
Fig. 1 Clinical response in patients with mycosis fungoides cutaneous T-cell lymphoma. By-time analysis of the percentage body surface area response rate (proportion of patients with ≥50% reduction from baseline) of patients with stage IA–IB disease receiving chlormethine gel + any other treatment (VO) with trend line

Table 4 Skin-related adverse events occurring in ≥ 3% of patients

Adverse event	All patients (*n* = 298)	
	All	Chlormethine gel related
Dermatitis	38 (12.8)	37 (12.4)
Pruritus	29 (9.7)	22 (7.4)
Skin irritation	22 (7.4)	21 (7.0)
Erythema	15 (5.0)	12 (4.0)
Skin burning sensation	11 (3.7)	10 (3.4)
Rash	10 (3.4)	4 (1.3)

Data are presented as *n* (%)

used during this observational study, %BSA was analyzed as a surrogate measurement of response. The %BSA does not take severity of lesions into account and can result in significant underestimation of the response rate. Limited clinical differences were observed between the different analysis groups; therefore, only data from patients with stage IA–IB disease in the VO and VCO groups are reported. In patients with stage IA–IB disease who had %BSA data recorded, the ORR at 12 months was 44.4% (24/54) in the VCO group and 45.1% (37/82) in the VO group. The ORR2 for patients with stage IA–IB disease was 43.5% (67/154) in the VO group.

A by-time analysis of the %BSA response data showed that clinical responses occurred as early as 1 month (36.7%) after treatment, and the peak response occurred at 18 months for patients with stage IA–IB disease in the VO group (66.7%) (Fig. 1).

For the Skindex-29 analysis, all patients were included (*n* = 298) and results were compared between responders and nonresponders at 24 months post-baseline. The mean Skindex-29 subscale scores indicated mild (symptoms and

functioning) and mild to moderate (emotions) impairment of HRQOL. The post-baseline weighted mean subscale scores for responders (emotions 26.6; symptoms 25.3; functioning 13.3) showed a better HRQOL than for nonresponders (emotions 36.2; symptoms 34.4; functioning 21.2). The differences between responders and nonresponders were statistically significant ($p < 0.001$ for each subscale).

3.3 Safety

Overall, 125 (41.9%) patients experienced at least one AE, and 83 (27.9%) experienced treatment-related AEs. The most common skin-related AEs were dermatitis (12.8%), pruritus (9.7%), skin irritation (7.4%), and erythema (5.0%) (Table 4). No treatment-related serious AEs or deaths were reported.

4 Discussion

This 2-year observational study examined the use of chlormethine 0.016% w/w gel in real-world clinical practice in the USA. The study revealed that chlormethine gel was

primarily used in early-stage MF, often in combination with other topical and systemic MF therapies; treatment frequency varied from once per week to daily, with frequent treatment interruptions.

The most commonly coadministered therapies were corticosteroids, phototherapy, and oral bexarotene. The use of chlormethine gel in combination with other therapies resulted in clinical improvement as measured by a ≥ 50% reduction from baseline in %BSA scores, with an ORR in patients with stage IA–IB disease of 43.5%. In addition, the by-time analysis revealed a response rate of 36.7% after 1 month of treatment and a peak response rate of 66.7% at 18 months post-baseline. A post hoc analysis of the pivotal registration study found an ORR of 44.4% by %BSA, a response rate of 5% at 1 month, and a peak response of 55.7% at 12 months post-baseline (Helsinn Healthcare SA, data on file). The delay in peak response observed in the current study may be due to a more gradual dose increase during the PROVe study. However, no direct comparison can be made between the results from the current study and the pivotal study because of the differences in study design; the registration study was a randomized controlled trial examining chlormethine gel monotherapy, whereas PROVe was a real-world study that allowed concomitant therapy. Regardless, these data highlight the importance of continued chlormethine treatment.

While chlormethine gel is indicated for patients with stage IA–IB disease in the USA, the results of the PROVe study show that, in clinical practice, it is used across all stages. At least 31 of 298 patients enrolled in the study had stage IIA–IV MF. These patients were likely using chlormethine gel for local control of patches and plaques.

No unexpected or serious chlormethine gel-related AEs occurred during the study. The reported skin-related AEs appeared to be manageable in this real-world setting, and 63.8 and 45.0% of patients were able to continue chlormethine gel treatment for 12 and 24 months, respectively. The percentage of patients experiencing skin-related AEs of pruritus, skin irritation, and erythema were generally lower, at 9.7%, 7.4%, and 5.0% in PROVe versus 19.5%, 25%, and 17.2%, respectively, in the pivotal study; dermatitis rates were similar (12.8% in PROVe vs. 14.8% in the pivotal study) [11]. These differences may be due to coadministration of corticosteroids, the flexibility in the dosing schedule, or the fact that the majority of patients (85.2%) were using chlormethine gel for > 30 days prior to start of the study.

Chlormethine gel treatment also had an impact on HRQOL. The Skindex-29 results showed a significant correlation between clinical responder status and improved HRQOL scores. Patients who responded to treatment had significantly lower mean scores post-baseline in all subscales of the Skindex-29, indicating a lower impact of skin disease compared with nonresponders.

The real-world setting of the PROVe study does carry a number of limitations. As no specific assessments were mandated, a limited number of patients had both pre-enrollment and post-baseline %BSA data available for analysis. In addition, the clinical responses reported herein likely also reflect the use of concomitant therapies. Treatment schedules and frequency of chlormethine gel use varied, and patients could also have multiple dosing regimens over time, which can complicate data analysis but is representative of chlormethine gel use in daily clinical practice.

5 Conclusion

The PROVe study showed that chlormethine gel is effective and has a good tolerability profile in a real-world setting, where it was coadministered with other therapies in patients with early and advanced disease. Peak response occurred at 18 months, emphasizing the importance of continued treatment. HRQOL was higher in patients who responded to treatment, as indicated by lower Skindex-29 subscale scores. The chlormethine gel formulation offers patients with MF access to an important therapeutic option that can be safely applied at home and contributes to improving HRQOL by reducing the severity of skin lesions and symptoms.

Declarations

Conflict of Interest E.J. Kim has received research support from and/or acted as principal investigator for Actelion, Galderma, MedImmune, and Soligenix; has received consultant, speaking, or travel support from Actelion, Galderma, Helsinn, and Soligenix; and has served on a scientific advisory board for Helsinn and Kyowa Kirin. J. Guitart has received research support from Galderma and Soligenix and served on a scientific advisory board for Helsinn, Kyowa Kirin, miRagen, and Leo Pharma. C. Querfeld has received a research grant from Celgene; acted as clinical investigator for Celgene, Trillium, miRagen, Bioniz, and Kyowa Kirin; and served on a steering committee

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