



REVIEW

Chlormethine Gel for Patients with Mycosis Fungoides Cutaneous T Cell Lymphoma: A Review of Efficacy and Safety in Clinical Trial and Real-World Settings

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ABSTRACT

Mycosis fungoides (MF) is a rare disease and is the most common form of cutaneous T cell lymphoma. Topical chlormethine (CL) gel is the first cytotoxic chemotherapy gel that was specifically developed for treatment of MF. In this review, we provide an overview of all available data on the use of CL gel for treatment of patients with MF. On the basis of the current data collected, CL gel is highly effective, with good response rates observed both in clinical trial and real-world settings. While the gel is approved for monotherapy, it is also used in

combination with concomitant skin-directed or systemic therapies in clinical practice. Responses to CL gel treatment can be rapid, but they also frequently occur with a delayed onset of up to 6 months. This indicates that continued treatment with CL gel is important. CL gel has a manageable safety profile, with most adverse events being mild and skin related. Contact dermatitis is one of the more common skin-related adverse events to occur with CL gel treatment that can potentially lead to treatment discontinuation. The data from the literature indicate that patients being treated with CL gel should be monitored carefully, and that dermatitis must be managed effectively to allow

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patients to continue treatment and achieve the best possible response to treatment.

Keywords: Chlormethine gel; CL gel; Mycosis fungoides; MF

Key Summary Points

Herein we provide an overview of all available data on the use of chlormethine (CL) gel in adults with mycosis fungoides (MF).

CL gel, which primarily targets malignant T cells, is the first topical chemotherapy that was specifically developed for treatment of MF, with no evidence of systemic absorption.

CL gel is highly effective, with better response rates observed with the gel formulation compared with ointment in both clinical trial and real-world settings.

In real-world clinical practice, CL gel is often used at variable or lower treatment frequencies compared to product label indication (once daily), and combination therapy with other agents is common.

CL gel has a manageable safety profile, with most adverse events being mild and skin related—contact dermatitis being the most common.

INTRODUCTION

Mycosis Fungoides

Mycosis fungoides (MF) is the most common form of cutaneous T cell lymphoma, accounting for approximately 60% of cases [1, 2]. MF is characterized by malignant T cell infiltration in the skin [3, 4] and in most patients it initially presents as patches and/or plaques on the skin. It can be difficult to diagnose MF, in part

because of its resemblance to other inflammatory skin conditions, such as eczema or contact dermatitis [5, 6]. Early diagnosis of MF is complicated by the fact that the histology can also look quite similar to various other inflammatory skin disorders [7]. Modern molecular testing modalities, such as T cell receptor clonality assessments through polymerase chain reaction or next-generation sequencing, can be helpful but do not always enable a definitive diagnosis [8, 9]. In most cases, it takes several years to diagnose a patient with MF [10].

Staging of MF is based on tumor–node–metastasis–blood (TNMB) classification [11, 12]. Stages IA–IIA MF are generally considered early-stage disease, which is often indolent and can remain stable for many years [5, 6]; however, the quality of life (QOL) of patients can be severely affected [13]. When the disease progresses, patients may develop tumors, erythroderma, and blood or organ involvement [5].

Treatment guidelines for MF are based on disease stage and are mainly aimed at reducing symptoms, preventing progression of disease, and improving QOL. The guidelines recommend skin-directed therapies for patients with early-stage MF, and suitable systemic agents, alone or in combination with skin-directed therapies, for patients with more-advanced disease. Currently, topical chlormethine (CL) is recommended by the National Comprehensive Cancer Network and all major national guidelines as a first-line treatment option for stage IA–IIA MF [1, 12, 14, 15].

CL for Treatment of MF

CL (also known as mechlorethamine) has been used as treatment for MF for decades [16–19]. The initial preparation of topical CL was aqueous based [18], and since the 1980s, compounded ointment-based formulations of CL have been used for treatment of MF [20, 21]. Neither the aqueous nor ointment formulation of CL was approved by the US Food and Drug Administration, despite positive clinical results [18, 20]. In addition, both formulations could lead to preparation and application challenges

for patients. To address these issues, a novel CL gel formulation was developed. The CL 0.016% w/w topical gel formulation (equivalent to 0.02% CL HCl) has since been approved as monotherapy for treatment of patients with stage IA–IB MF who received prior skin-directed therapy in the USA [22] and Israel [23], and for the treatment of adult patients with early-stage MF in the EU [24]. CL gel is currently under consideration for approval in multiple different countries worldwide.

The release rate profiles of CL gel and ointment and permeation of CL gel have been assessed using in vitro release testing and in vitro permeation testing, respectively. CL gel had a higher mean release rate over 5 h compared with CL ointment (5.7 vs 2.4 $\mu\text{g}/\text{cm}^2/\sqrt{\text{h}}$), indicating that this formulation is better in terms of drug delivery (data on file, Helsinn Healthcare SA). The permeation study evaluated permeation of CL gel through harvested barrier-competent skin, which was either dermatomed to 500- μm thickness or separated into epidermal membranes. In vitro results showed permeation of CL through both the epidermal membranes and dermatomed skin, with a higher mean CL flux rate through epidermal membranes. After 24 h, close to 5% of applied CL had permeated the epidermal membrane and 2.5% of the applied dose permeated the dermal layer [25]. Currently, it remains unclear how high the concentration of CL must be to induce effects in deeper dermal layers, where, after in vitro experiments, only a minimal amount of CL was able to pass through. These findings do appear to correlate with the lack of systemic absorption after topical application of CL [26]. Since MF plaques can respond well clinically to topical treatment strategies, it seems highly likely that even low amounts of CL can potentially induce a clinical effect in plaque stage MF.

CL gel is the first cytotoxic chemotherapy gel that was specifically developed for MF [27]. The formulation is optimized, stable, non-greasy, and quick drying. These attributes make it convenient for patients to apply the gel at home, which can help encourage compliance. In clinical practice, CL gel is used in various settings, sometimes beyond the approved indication, including as monotherapy in early-stage

MF, in combination with systemic therapy in advanced-stage disease, and as maintenance treatment [11, 19, 28–30].

Mechanism of Action of CL

CL is a bifunctional alkylating agent that inhibits rapidly proliferating cells. Alkylating agents can interfere with DNA replication and lead to the disruption of nucleic acid function through different mechanisms [18, 31]. The precise antitumor mechanisms of CL were assessed using cancerous T cells extracted from skin samples of patients with MF. The in vitro impact of CL on malignant skin T cells was investigated, with a focus on treatment susceptibility, DNA double-stranded breaks, and expression of alkylated nucleotide excision repair genes. Lymphoma cell lines were shown to be more susceptible to CL than healthy T cells. T cells isolated from MF lesions showed downregulation of multiple DNA-repair pathways, and exposure to CL suppressed the expression of genes related to DNA repair further. This reduces the ability of T cells to repair their damaged DNA and results in increased killing of cancerous T cells. Exposure to CL also induced significant double-stranded breaks in malignant MF skin T cells and increased the expression of the apoptotic gene *CASP3*. These data provide a rationale for the use of CL as an early and valuable treatment for patients with MF [32].

Aim of the Review

The efficacy and safety of CL gel has been evaluated in multiple studies since its development. Initial results with CL gel were obtained in clinical trials, which can often include conditions that do not reflect daily clinical practice. For example, variable dosing and the use of concomitant therapies are often seen, and a more diverse patient population, including those with comorbidities, may be targeted in clinical practice. Thus, real-world studies and patient cases can provide valuable additional data on how to manage patients with MF using CL gel. In this review, we provide an overview of

all available data on the use of CL gel for patients with MF, both in clinical trial and real-world settings. 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.

EFFICACY OF CL GEL TREATMENT

The efficacy of CL gel has been investigated in several clinical trials and real-world studies. Details on these studies and their design are summarized in Table 1 [33–45]. In addition, several case reports have been published detailing the response to CL gel treatment in individual patients with MF (Table 2) [30, 46–51].

Clinical Trials

The efficacy of CL gel was first assessed in the pivotal registration study, commonly referred to as the “201 trial” (NCT00168064). This randomized, observer-blinded, controlled, non-inferiority trial compared CL gel with equal-strength CL ointment [33]. The Composite Assessment of Index Lesion Severity (CAILS) response rate with CL gel was 59% (76/130), including 18 patients with a complete response (CR) and 58 with a partial response (PR). Of the patients who had a response, 86% (65/76) maintained their response until the end of the 12-month trial. Comparable results were seen with the modified Severity-Weighted Assessment Tool (mSWAT), with a response rate of 47%. While the response rates seen with CL gel were numerically higher than those with CL ointment, the 201 trial was designed to investigate non-inferiority of the gel only, which was established. On the basis of a post hoc approach of switching from non-inferiority to superiority testing, the 95% CI of the CAILS score in the efficacy-evaluable population exceeded the non-inferiority threshold (≥ 0.75), consistent with superiority ($p < 0.05$) findings for CL gel. The response rates increased over time, indicating that longer treatment with CL gel increased the likelihood of response. For CL gel, the time to a 50% response rate was 26 weeks,

which was shorter than the 42 weeks to 50% response for CL ointment [33].

Two post hoc analyses of the 201 trial data were undertaken to gain more information about the response rates and patterns over time. The first of these, from Geskin et al. [34], used a by-time analysis to investigate timelines and durability of response. Overall response rates (ORR) after 1 month of treatment were 8.5% for CAILS, 5.9% for mSWAT, and 5.0% for body surface area (BSA). The ORR rose steadily over time until the peak response at 10 months (CAILS, 78.9%; mSWAT, 54.4%; BSA, 51.1%). Different patterns of response were observed during the study, including early responses, intermittent responses, and late responses (≥ 6 months after initiation). Illustration that the peak response with CL gel treatment can occur with a delay of more than 6 months was a significant finding of this study [34].

A second post hoc analysis of the 201 trial data by Querfeld et al. [35] analyzed the response obtained at each individual time point. A very good partial response (VGPR; $\geq 75\%$ improvement from baseline) category was included in the analysis. Response rates for CL gel-treated patients with stage IA MF were 79.8% for CAILS, 48.9% for mSWAT, and 49.5% for BSA involvement. The response rates for patients with stage IB–IIA disease were similar: 77.0% for CAILS, 55.2% for mSWAT, and 47.2% for BSA. At the month 10 visit, 71 patients (55%) had achieved at least 50% improvement from baseline by CAILS; of these, 31 had PR, 24 VGPR, and 16 CR. The CAILS response rates for patients with stage IA disease were significantly higher for CL gel compared with ointment (79.8% vs 49.2%, $p = 0.0014$). In addition, the time to response was shorter for patients treated with CL gel than for those treated with ointment when response was defined as PR or better, or as VGPR or better. Trend analyses showed that overall responses were higher in patients who received CL gel vs ointment; this difference was statistically significant when response was defined as at least VGPR ($p = 0.0420$) or as at least PR ($p = 0.0013$). No association was found between the frequency of CL gel application and occurrence of a CAILS response at the next visit ($p = 0.8850$). These results show that CL gel

Table 1 Clinical trial and real-world studies assessing the efficacy of CL gel

Study	Study type	Patients	Treatment	Main study endpoints	Study details
Clinical trials					
Lessin et al. [33]	Randomized, controlled, observer-blinded, multicenter clinical trial (study 201)	$N = 260$	Daily 0.02% CL gel or ointment treatment for up to 12 months	The primary endpoint was response, defined as $\geq 50\%$ improvement in baseline CAILS for at least two consecutive visits over ≥ 4 weeks	Treatment efficacy was assessed every month for the first 6 months, and every 2 months thereafter
		$N = 130$ receiving CL gel	No concomitant therapy allowed per trial protocol	Secondary endpoints included $\geq 50\%$ improvement in mSWAT	CR was defined as 100% improvement with a score of 0, and PR as at least a 50% reduction from baseline scores
		$N = 130$ receiving CL ointment			
Geskin et al. [34]	Post hoc analysis of study 201	$N = 260$	Daily 0.02% CL gel or ointment treatment for up to 12 months	By-time analysis of clinical response data	The by-time analysis was performed to analyze proportions of patients with clinically responsive disease at each individual visit. This was determined by dividing the number of patients with a response by the total randomized population ($n = 130$)
		$N = 130$ receiving CL gel	No concomitant therapy allowed per trial protocol		VGPR was included as a response category; this was defined as $\geq 75\%$ improvement from baseline by CAILS, mSWAT, or BSA
		$N = 130$ receiving CL ointment			Each visit outcome was reported as a separate time point
Querfeld et al. [35]	Post hoc analysis of study 201	$N = 260$	Daily 0.02% CL gel or ointment treatment for up to 12 months	Response by CAILS, mSWAT, and BSA	Separate response analyses were done for patients with stage IA or IB–IIA MF
		$N = 130$ receiving CL gel	No concomitant therapy allowed per trial protocol	Time to first response and response trends	Relationship between the frequency of gel application and AEs or CAILS responses
		$N = 130$ receiving CL ointment			VGPR was included as a response category

Table 1 continued

Study	Study type	Patients	Treatment	Main study endpoints	Study details
Querfeld et al. [36]	Extension phase of study 201, using 0.04% CL gel (study 202)	$N = 98$	Daily CL gel 0.04% treatment for up to 7 months No concomitant therapy allowed per trial protocol	The primary endpoint was response, defined as $\geq 50\%$ improvement in baseline CAISL for at least two consecutive visits over ≥ 4 weeks	The same lesions as evaluated during study 201 were included; if fewer than five original lesions were available, additional lesions could be evaluated if they had been consistently treated during the study 201 period as well
Querfeld et al. [37]	Post hoc analysis of study 201/202	$N = 260$ from study 201 $N = 98$ from study 202 $N = 58$ who received CL ointment in study 201 $N = 40$ who received 0.02% CL gel in study 201	Daily 0.02% CL gel or ointment treatment for 12 months followed by CL gel 0.04% treatment for up to 7 months No concomitant therapy allowed per trial protocol	Response by CAISL Time-to-response and repeated measures analyses Relationship between the frequency of gel application and AEs or CAISL responses	Each visit outcome was reported as a separate time point VGPR was included as a response category Patients using CL gel since the beginning of study 201 were compared with those who used CL ointment during study 201 and subsequently switched to CL gel during study 202

Table 1 continued

Study	Study type	Patients	Treatment	Main study endpoints	Study details
Real-world studies					
Kim et al. [38]	Prospective, observational study with 46 participating centers (PROVe)	<i>N</i> = 298	CL gel (0.02%) treatment for up to 2 years Variable treatment frequency (daily to less than once per week) Concomitant therapy allowed; 77.9% of patients used other skin-directed therapies and 30.2% used systemic therapies	The primary endpoint was the proportion of stage IA–IB patients who received CL gel + topical corticosteroids + other therapies with a $\geq 50\%$ decrease in BSA from baseline to 12 months Secondary endpoints included BSA response at 12 months for all patients, and a by-time analysis of response	All adult (≥ 18) patients with MF who were treated with CL gel were invited to enroll in the study, regardless of how long they had been using the gel, concomitant therapy, or disease stage Patients were monitored during routine clinical practice visits and no specific clinical assessments were mandated BSA was analyzed to assess efficacy, as this was the most frequently used assessment
Prag Naveh et al. [39]	Single-center retrospective analysis of CL gel-treated patients	<i>N</i> = 66	CL gel (0.02%) application frequency was increased gradually to once daily or lower Over time, multiple dosing regimens were used in 13 patients (20%) Concomitant topical corticosteroids in 40% of patients; concomitant systemic treatment in 7% of patients	Time to response was based on assessment of BSA Response was categorized as CR, PR, SD, or PD; ORR was defined as CR + PR Differences between patients with stage IA and stage IB disease were analyzed	Time to response was based on assessment of BSA Response was categorized as CR, PR, SD, or PD; ORR was defined as CR + PR Differences between patients with stage IA and stage IB disease were analyzed

Table 1 continued

Study	Study type	Patients	Treatment	Main study endpoints	Study details
Papadavid et al. [40]	Retrospective analysis of CL gel-treated patients	<i>N</i> = 58	CL gel (0.02%) treatment once daily as monotherapy or in combination with other treatment		Efficacy was assessed through mSWAT scores, collected at each visit CR was defined as 100% clearance of skin lesions and PR as 50% to < 100% clearance; ORR4 was defined as all patients who maintained a response for at least 4 months ORR and ORR4 were compared between patients with different disease stages, lesion types, and treatment types
Correia et al. [41]	Retrospective analysis of CL gel-treated patients: focus on maintenance therapy	<i>N</i> = 25 active <i>N</i> = 23 maintenance	CL gel (0.02%) treatment 1–4 × per week, depending on disease severity Most patients alternated use of CL gel with topical steroids		Patients were divided into cohorts depending on active vs maintenance therapy Efficacy was assessed through mSWAT scores—two consecutive scores documented at 6-month intervals Change from baseline mSWAT scores over time (\geq 50% reduction was considered a response) Safety, PFS, and quality-of-life scores (DLQI) were also assessed

Table 1 continued

Study	Study type	Patients	Treatment	Main study endpoints	Study details
Koumourtzis et al. [45]	Single-center study of CL gel-treated patients with MF	<i>N</i> = 23	CL gel (0.02%) was initiated once daily and could be scaled down to three times per week		
Wehkamp et al. [42]	Retrospective analysis of CL gel-treated patients	<i>N</i> = 18	CL gel (0.02%) was initiated once daily (<i>n</i> = 7) or three to four times per week (<i>n</i> = 11)		Data on treatment regimen and photo documentation of skin findings were available Efficacy was assessed through mSWAT scores, collected every 3 months
Dugre et al. [43]	Retrospective observational analysis of medical records of CL gel-treated patients	<i>N</i> = 14	CL gel (0.02%) treatment three times per week (<i>n</i> = 12) or daily (<i>n</i> = 2)		Data collected for the retrospective observational analysis were BSA or BSA affected by disease, location of the lesions, therapeutic management, effectiveness, and treatment tolerance

Table 1 continued

Study	Study type	Patients	Treatment	Main study endpoints	Study details
Sidiropoulou et al. [44]	Prospective, single-center study of MF skin lesions of CL gel-treated patients	$N = 13$	CL gel (0.02%) treatment once daily as monotherapy	Histopathologic, immunophenotypic, and molecular changes from baseline to week 4–6 of treatment Potential correlations between clinical, histopathologic, and molecular skin responses were evaluated	Twelve of 13 patients were male; 85% had early stage (\leq IIA) at treatment initiation; 62% had classical MF Median follow-up time was 14 months (range 8–17) Paired skin biopsies were collected at baseline and at 4–6 weeks post-CL gel treatment

AE adverse event, *BSA* body surface area, *CAILS* Composite Assessment of Index Lesion Severity, *CL* chlormethine, *CR* complete response, *DLQI* Dermatology Life Quality Index, *MF* mycosis fungoides, *mSWAT* modified Severity-Weighted Assessment Tool, *ORR* overall response rate, *ORR4* all patients who maintained a response for at least 4 months, *PD* progressive disease, *PFS* progression-free survival, *PR* partial response, *SD* stable disease, *VGPR* very good partial response

treatment may result in greater and faster responses compared with the ointment formulation, in particular for patients with stage IA disease. In addition, they indicate that reducing the frequency of CL gel application may be possible without decreasing the likelihood for response.

An open-label extension phase of study 201, termed study 202 (NCT00535470), assessed the efficacy of a higher concentration of CL gel (0.032% w/w, equivalent to 0.04% chlormethine HCl) for those patients who did not achieve CR during the original 12-month trial [36, 52]. In total, 26 (26.5%) patients who did not have a CR during study 201 had a response during study 202 (6 CR, 20 PR) on the basis of CAILS scores. The ORR calculated from the original study 201 baseline CAILS scores was 81.6%, with 12 CR and 62 PR. For mSWAT, the ORR was 68.4% from the baseline of study 201 and 20.4% from the baseline of study 202. These results show that continued (and higher-concentrated) treatment with CL gel can result in further clinical benefit. However, a higher concentration of CL gel is not currently available on the market, and patients with MF are treated using the approved 0.02% CL gel.

A post hoc analysis of the 201 and 202 trial data compared patients who had used CL gel since the beginning of study 201 (switching from 0.02% gel to 0.04%) with those who used CL ointment during study 201 and subsequently switched to CL gel during study 202. Patients who had received the gel formulation during both studies had faster and more improved CAILS responses than patients who switched from ointment to gel. These results suggest that patients who initiate CL treatment with the gel may have additional benefit compared with those who start with other formulations [32, 53, 54].

Real-World Experience

Cutaneous lymphoma clinics have had good experiences with CL gel for patients with MF [55, 56], and several clinical studies have investigated CL gel treatment in a real-world setting. Here, cohort studies with more than ten

Table 2 Efficacy and safety results from small retrospective reviews and case series on real-world CL gel treatment

Study	Study type	Treatment	Efficacy	Safety	Treatment reduction, interruption, or discontinuation
Trager et al. [46]	Case series N = 10	CL gel treatment once daily (n = 2), three times per week (n = 7), or two times per week (n = 1)	Not reported	Ten patients developed lymphomatoid papulosis induced by CL gel	CL gel was discontinued by four (40%) patients
Jennings et al. [30]	Retrospective review N = 8	CL gel after TSEBT CL gel treatment two to five times per week CL gel could be initiated at a lower frequency and increased over time Concomitant topical steroids allowed	Patients had long-term responses, with median time to progression of 22.7 months (95% CI 10.7–24.7) One patient achieved CR One patient had a reduction in BSA involvement	Not reported	Not reported
Garcia-Saleem et al. [47]	Case series N = 4	CL gel + topical steroids (n = 2) CL gel + tacrolimus ointment (n = 2) CL gel was initiated at three times per week, and could be increased to max. once daily Topical steroids were started as needed A specialized skincare protocol was recommended	For one patient, BSA reduced from 8% to 1% after 9 months of treatment The second patient achieved a near CR, with BSA lessening from 6% to 0.1% The third patient had a reduction in BSA (20% to 1%) after 9 months, and CR after 21 months The final patient had a reduction in BSA and was stable at 0.7% BSA after 40 months	Superficial erosions in the left popliteal fossa (n = 1) applied twice daily for 2 weeks, after which CL gel was restarted at a decreased frequency	CL gel was paused, and tacrolimus 0.1% ointment applied twice daily for 2 weeks, after which CL gel was restarted at a decreased frequency

Table 2 continued

Study	Study type	Treatment	Efficacy		Safety	
					Skin-related AEs	Treatment reduction, interruption, or discontinuation
Chase et al. [48]	Case series <i>N</i> = 4	CL gel (<i>n</i> = 3) CL gel + oral retinoids (<i>n</i> = 1) Three patients initiated CL gel once daily (one after patch testing) and one patient initiated at three times per week, increasing to daily	All patients responded to CL gel, with reductions in BSA involvement ranging from 3% to 30% MF patches faded, reduced in size, and became less inflamed, painful, and itchy One patient had complete resolution of lesions after 6 months of treatment and discontinued CL gel	Hyperpigmentation (<i>n</i> = 2) Severe dermatitis (<i>n</i> = 1)	CL gel was discontinued in the patient with dermatitis; after resolution, the patient restarted treatment	
Lampadaki et al. [49]	Case series <i>N</i> = 3	CL gel + clobetasol + IFN α (<i>n</i> = 2) CL gel + IFN α (<i>n</i> = 1) CL gel was initiated at a once-daily frequency	For one patient, the mSWAT score decreased from 11.6 to 2.5 after 12 months of treatment, and clear improvement in patches and plaques was observed The second patient achieved a PR with an mSWAT score of 0.8 The third patient had a CR with an mSWAT score of 0	Dermatitis (<i>n</i> = 1) Erythema, hyperpigmentation (<i>n</i> = 1) Skin irritation, hyperpigmentation (<i>n</i> = 1)	CL dosing was reduced in response to dermatitis (once every other day) and skin irritation (every 3 days)	
Gary et al. [50]	Case report <i>N</i> = 1	CL gel twice weekly	Not reported	Necrotic leg ulcers	CL gel was discontinued	

Table 2 continued

Study	Study type	Treatment	Efficacy	Safety	
				Skin-related AEs	Treatment reduction, interruption, or discontinuation
El Alami et al. [51]	Case report N = 1	CL gel + topical clobetasol	PR	Not reported	Not reported

AE adverse event, *BSA* body surface area, *CL* chlormethine, *CR* complete response, *IFN α* interferon- α , *MF* mycosis fungoides, *mSWAT* modified Severity-Weighted Assessment Tool, *PR* partial response, *TSEBT* total skin electron beam treatment

patients are discussed. Smaller retrospective chart reviews and case report series have also described good efficacy of CL gel in clinical practice; results from these studies are summarized in Table 2 [30, 46–51].

The PROVe study (a PROspective, observational study assessing outcomes, adverse events [AEs], treatment patterns, and QOL in patients diagnosed with MF and treated with Valchlor and other therapies) examined the use of CL gel in clinical practices across the USA over a 2-year period [38, 57]. In total, 298 patients were treated with CL gel. The majority of patients also used concomitant therapies during the study. Patients with different stages of MF were included (62.4% early MF [IA–IIA] and 8.4% advanced-stage MF [IIB–IV]) at enrollment. While 74.5% of patients used CL gel daily at some point during the study, lower frequencies of application were also common, and patients could change treatment frequency over time. The most common alternative treatment frequencies were every 2 (37.6%) or 3 (16.4%) days. The main reasons for dose frequency changes were physician decision (26%), AEs (20%), and CR (7%). Dosing interruptions occurred in 29.2% of patients and had a median duration of 9.7 days. The median treatment duration was 23.7 months for patients newly initiated on CL gel, and 32 months for patients who had been using CL gel for at least 3 months at time of enrollment. At 12 months into the study, 79% of the cohort continued treatment. For patients with stage IA–IB disease, the BSA ORR at 12 months was 44.5% (24/54) for those who received CL gel, corticosteroids, and other treatments, and 45.1% (37/82) for those receiving CL gel in combination with any other treatment. A by-time analysis of response indicated that the peak of response occurred at 18 months (66.7%) for patients receiving CL gel with any other treatment, although responses were also seen as early as 1 month after enrollment (36.7%). Patients who responded to CL gel treatment had significantly better QOL scores according to the Skindex-29. These results show the efficacy of CL gel in daily clinical practice, when used at variable treatment frequencies and in combination with other treatments. In addition, the peak of response occurring after

18 months highlights the importance of continued treatment with the gel [38, 57].

A single-center retrospective study by Prag Naveh et al. [39] analyzed 66 early-stage adult patients with MF who were treated with CL gel in Israel in 2016–2019. All patients had received prior topical corticosteroids before initiation of CL gel treatment. After an initial gradually increasing treatment frequency with CL gel, 52% of patients received CL gel at a once-daily frequency, while the remaining patients applied the gel at lower frequencies (four to six or two to three times per week). CL gel was combined with concomitant topical corticosteroids in 40% of patients, and with concomitant systemic therapy in 7%. The ORR was 50%, with three (4.5%) patients achieving CR and 30 (45.4%) achieving PR. The estimated median time to 50% improvement from baseline was 38.1 weeks. Efficacy results were similar for stage IA and IB patients [39].

A retrospective chart review of 58 patients in Greece (Papadavid et al. [40]) also evaluated the efficacy of CL gel treatment in real-world practice. Patients were included if they used CL gel for at least 1 month and were varied regarding disease stage (stage IA, IB, IIA, IIB), lesion type (patches, plaques, and tumors), and histologic disease type. Most patients had received more than one prior skin-directed (65.5%) and/or systemic (65.5%) treatment for MF. Results showed that the ORR increased over time to 80.8% after 9 months of treatment and 64.2% of patients were able to maintain their response for at least 4 months (ORR4). Median time to response was 12 weeks and median time to best response was 22 weeks. While CL gel was effective for treatment of different types of skin lesions in patients with early- and late-stage disease, a few differences were seen that suggest that patients with patch-stage early MF might benefit most from treatment. The ORR at month 3 was higher for patients with patches (69.7%) compared with plaques or tumors (15.5% each), and the ORR4 was higher for patients with early-stage disease (71.4%) vs late-stage disease (36.4%). Median mSWAT scores decreased significantly during the study, from 11.8 before treatment initiation to 1.7 after 9 months. The change in mSWAT scores during

the first 6 months of treatment was correlated with a change in Skindex-29 scores, indicating that QOL improved when skin disease scores decreased [40].

Another retrospective chart review was conducted at Thomas Jefferson University by Correia et al. [41] that focused on a novel protocol using CL gel as maintenance therapy for patients in remission. Forty-four patients received either maintenance or active treatment and had two consecutive mSWATs documented. The study found that patients on maintenance therapy had a 65.22% progression-free survival rate with a median time to progression of 29.45 months. Importantly, this study also found that responders on active and maintenance CL gel therapy showed an increased response over time and experienced improved quality-of-life scores [41].

A recent study by Koumourtzis et al. [45] investigated the efficacy of CL gel in everyday clinical practice at a single center in Greece. It included 23 patients with stage IA–IIB MF who initiated CL gel once daily, either as monotherapy ($n = 12$) or in combination with systemic treatments (methotrexate and peginterferon alfa-2a; $n = 11$). ORRs at 3, 6, and 9 months were 43.5%, 56.5%, and 65.2%, respectively. Five patients (21.73%) achieved near CR at a mean time of 6 months.

Another study, by Wehkamp et al. [42], retrospectively evaluated 18 patients with MF treated in two dermatologic centers specialized in cutaneous lymphoma in Germany. This study included three cases of folliculotropic MF and one of syringotropic MF. Most patients had received more than five ($n = 8$) or two to four ($n = 7$) lines of treatment prior to receiving CL gel; one patient was treatment naive. The majority of patients ($n = 11$) initiated CL gel treatment at a reduced frequency of three to four times per week, while the remaining seven patients initiated treatment at a once-daily frequency. The median mSWAT score decreased from 4 at the start of CL gel treatment to 0.75 after 9 months of follow-up. In total, six of 16 evaluable patients experienced a CR, four patients had a PR, five had stable disease, and one had progressive disease [42].

Table 3 Safety of CL gel treatment in clinical trial and real-world studies

Study	Study type	Skin-related AEs	Treatment reduction, interruption, or discontinuation
Clinical trials			
Lessin et al. [33]	Randomized, controlled, observer-blinded, multicenter clinical trial (study 201)	In the CL gel arm: skin irritation (25%), pruritus (19.5%), erythema (17.2%), contact dermatitis (14.8%), skin hyperpigmentation (5.5%), and folliculitis (5.5%)	Twenty-six (20.3%) patients in the gel arm withdrew from the trial because of protocol-defined treatment-limiting skin AEs
Querfeld et al. [36]	Extension phase of study 201, using 0.04% CL gel (study 202)	Total skin-related AEs: skin irritation (17.3%), erythema 13.3%, and pruritus 8.2% Treatment-related AEs: skin irritation (11.2%), erythema (10.2%), and pruritus (6.1%)	Eight (8.2%) patients reduced dosing frequency, five (5.1%) temporarily suspended treatment, and four (4.1%) discontinued CL gel treatment
Gilmore et al. [58]	Non-randomized, open-label, split-face, two-arm study (MIDAS)	Nine patients (34.6%) developed dermatitis. Of these, eight were ACD and one ICD	Two of nine (22%) patients were unable to restart CL therapy
Real-world studies			
Kim et al. [38]	Prospective, observational study with 46 participating centers (PROVe)	Total skin-related AEs: dermatitis (12.8%), pruritus (9.7%), skin irritation (7.4%), erythema (5.0%), skin burning sensation (3.7%), and rash (3.4%) Treatment-related AEs: dermatitis (12.4%), pruritus (7.4%), skin irritation (7.0%), erythema (4.0%), skin burning sensation (3.4%), and rash (1.3%)	Dosing frequency could be changed in response to AEs Eighty-seven (29.2%) patients had a dosing interruption, with an average duration of 9.7 days (range 1.0–84.0)

Table 3 continued

Study	Study type	Skin-related AEs	Treatment reduction, interruption, or discontinuation
Prag Naveh et al. [39]	Single-center retrospective analysis of CL gel-treated patients	Cutaneous side effects occurred in 37 (56%) patients, including irritant or allergic contact dermatitis (36%), unmasking effect (9%), hyperpigmentation (14%), and pruritus (9%)	Management of mild to moderate dermatitis consisted of topical corticosteroids and/or a reduction in the frequency of CL gel application. If necessary, CL gel was interrupted or discontinued. Reinitiation of CL gel, when possible, was gradual, and combined with topical corticosteroids if needed In total, 19.6% of patients withdrew from the study because of side effects; 15% for contact dermatitis
Papadavid et al. [40]	Retrospective analysis of CL gel-treated patients	In total, 42 patients (72.4%) experienced dermatitis; 22 (37.9%) cases were categorized as mild-moderate and 20 (34.5%) as severe	CL gel tapering in 23 patients (39.7%) Treatment discontinuation in nine patients (15.5%) by month 9 of the study
Koumourtzis et al. [45]	Single-center study of CL gel-treated patients with MF	AEs were recorded in 43.47% of patients	Treatment was discontinued because of dermatitis in three (13.0%) patients
Wehkamp et al. [42]	Retrospective analysis of CL gel-treated patients	Seven (38.9%) patients developed dermatitis	All patients had a treatment interruption and addition of topical steroids Five of seven patients reinitiated treatment after the skin reaction resolved One patient had a severe recurrence of dermatitis and permanently discontinued treatment
Dugre et al. [43]	Retrospective observational analysis of medical records of CL gel-treated patients	Seven patients (50%) presented with at least one AE, including irritant dermatitis and erosive toxicity ($n = 5$), rash ($n = 2$), and telangiectasia ($n = 2$)	Five patients (36%) discontinued treatment and two (14%) interrupted treatment temporarily

Table 3 continued

Study	Study type	Skin-related AEs	Treatment reduction, interruption, or discontinuation
Sidiropoulou et al. [44]	Prospective, single-center paired-biopsy study of MF skin lesions before and after CL gel administration	Ten patients (77%) developed contact dermatitis, including one case of pseudotumor formation	Two of 13 patients discontinued treatment because of drug-related cutaneous intolerance

ACD allergic contact dermatitis, *AE* adverse event, *CL* chlormethine, *ICD* irritant contact dermatitis

Dugre et al. [43] conducted a retrospective observational analysis of medical records of CL gel-treated patients that examined several factors including BSA, lesion location, and effectiveness of treatment. Fourteen patients were treated in total; 12 patients applied CL gel three times per week and two applied it daily. Of these patients, 10 (71%) achieved CR or PR, and one had stabilization of MF [43].

Recently, a prospective single-center, paired-biopsy cohort study by Sidiropoulou et al. [44] was the first to evaluate the histopathologic, immunophenotypic, and molecular profiles of MF skin lesions before and after 4–6 weeks of daily CL gel application. Biopsies from 13 treated lesions showed that (1) all cases with epidermotropic features displayed loss (50%) or lower degrees of (50%) epidermotropism; (2) dermal infiltrate density was decreased (69%); and (3) T cell receptor-gamma (TCR- γ) analysis by PCR in previously tested positive lesions became negative (56%) [44]. CR or PR was achieved in 92% of patients after 1 month of treatment, and ORR was 61.5% at 12 months. No safety concerns beyond contact dermatitis were reported [44].

SAFETY OF CL GEL TREATMENT

AEs with CL Gel Treatment

Most AEs observed with CL gel treatment are mild and skin related (Table 2 [30, 46–51] and Table 3 [33, 36, 38–40, 42–45, 58]). During study 201, most patients (61.7%) experienced an AE that was related to CL gel treatment;

none of these were severe. The majority of the AEs were skin related, and these included skin irritation (25%), pruritus (19.5%), erythema (17.2%), contact dermatitis (14.8%), skin hyperpigmentation (5.5%), and folliculitis (5.5%) [33]. While 11 patients (three in the CL gel arm) developed non-melanoma skin cancer, none of these cases were considered related to CL gel use.

The higher concentration of CL gel used in study 202 did not appear to lead to an increased occurrence of skin-related AEs [36]. During the study, 72.4% of patients experienced an AE, and for 32.7% of patients the AEs were deemed related to CL gel treatment. The most frequently occurring treatment-related AEs were skin irritation (11.2%), erythema (10.2%), and pruritus (6.1%).

Safety was also examined during the real-world PROVe study where CL gel was used in combination with concomitant therapies [38]. During the study, 41.9% of patients experienced at least one AE. The most frequent skin-related AEs were dermatitis (12.8%), pruritus (9.7%), skin irritation (7.4%), and erythema (5.0%); for 27.9% of patients, the AEs were considered related to treatment. Compared with study 201, the rate of dermatitis was similar, but other skin-related AEs occurred at a lower frequency. This difference could be due to the concomitant use of corticosteroids, which was allowed in the PROVe study. In addition, treatment schedules were more flexible during the PROVe study and most patients were already using CL gel prior to study enrollment.

During both study 201 and 202, serum samples were collected from patients to determine

whether CL gel was systemically absorbed [26]. No systemic absorption of CL was detected, with all samples testing below the detection limits (< 41.5 ng/mL for samples from study 201; < 5.0 ng/mL for samples from study 202). Lack of systemic absorption of the gel could represent the reason systemic AEs are not usually seen after CL gel treatment. This also highlights the unlikelihood of any systemic drug–drug interactions occurring with concomitant therapy and confirms that CL gel-treated patients would not require any blood monitoring.

Contact Dermatitis

Contact dermatitis is frequently experienced following topical CL gel treatment; it can be divided into allergic contact dermatitis (ACD), which is a hypersensitivity reaction to allergens, and irritant contact dermatitis (ICD), a non-specific skin reaction. Patch testing can be used to distinguish ACD and ICD. Although patch testing was not routinely used during study 201, the estimated incidence of ACD was 16.4%. In total, 26 patients (20.3%) had to withdraw from the study because of protocol-specified treatment-limiting skin AEs [33]. The incidence and type of contact dermatitis in patients with MF treated with CL gel have been assessed in the Mechlorethamine Induced Contact Dermatitis Avoidance Study (MIDAS; NCT03380026). In this non-randomized, open-label, split-face, two-arm study, patients were treated once nightly with CL gel for 4 months, and half of the lesions were also treated with 0.1% triamcinolone. Patch testing was undertaken to determine the type of dermatitis, and contributing allergens were analyzed [58–60]. Preliminary data indicated that nine (34.6%) of 26 enrolled patients developed contact dermatitis after treatment initiation, and most cases ($n = 8$) were ACD. Two patients were unable to restart CL gel. The addition of the topical corticosteroid triamcinolone could potentially reduce the severity of dermatitis.

The different degrees of dermatitis that can occur after CL gel treatment should be managed differently [61]. In any case of occurrence of a

skin reaction to CL gel, a treatment break should be considered. Patients with mild to moderate dermatitis are often able to continue therapy after reductions in treatment frequency and the addition of emollients or topical steroids. In the case of severe dermatitis, the best course of action after initial treatment discontinuation may depend on the type of dermatitis. Patients with severe ICD can often successfully restart treatment at a lower frequency after the dermatitis has resolved, while patients who have severe ACD can still try to restart treatment to test tolerance, but some of these patients may have complete intrinsic intolerance to CL gel treatment.

Contact dermatitis has also been reported in real-world studies on CL gel treatment in clinical practice. In the PROVe study, dermatitis was the most commonly reported AE, with an incidence of 12.8%. As seen in this study, many clinicians already use topical steroids in combination with CL gel treatment, which may help reduce the incidence [38]. The retrospective study in Israel by Prag Naveh et al. [39] saw ICD or ACD in 36% of patients. While most cases were mild to moderate and could be managed accordingly, 15% of patients withdrew from the study because of dermatitis. Patch tests were not available for this study and contact dermatitis was diagnosed on the basis of clinical judgment. Diagnosis of ICD was based on enhanced erythema at the start of treatment in CL-naive patients that was associated with localized burning or stinging in the treated areas. Diagnosis of ACD was based on the appearance of dermatitis at least 2–4 weeks after initiation of CL gel in CL-naive patients that was associated with pruritus that could extend beyond the treated areas [39]. In the retrospective chart review from Greece, a higher rate of dermatitis was observed; 20 (34.5%) patients had severe/generalized dermatitis and 22 (37.9%) had mild to moderate dermatitis. Through close monitoring and reducing the treatment frequency to two or three times per week in response to dermatitis, most patients were able to continue treatment. Only nine (15.5%) patients discontinued because of dermatitis by month 9; the majority of these had severe dermatitis [40]. In the retrospective study

in Germany, seven patients (39%) developed dermatitis, and five of them were categorized as severe; CL gel was paused, and topical steroids treatment applied to control the skin reaction. After resolution of the dermatitis, five patients could reinitiate treatment [42].

In the post hoc analyses of the study 201 and study 202 data, the association between contact dermatitis and a clinical response per CAIS was investigated through multivariate time-to-event analyses. Results showed an association between the occurrence of contact dermatitis and clinical response at the next visit [35, 37]. This result suggests that patients who experience contact dermatitis may be more likely to have an improved skin response at the following visit compared with those patients who did not have dermatitis. The retrospective study in Germany also reported a higher response rate (five of seven patients, 71%) in patients who experienced dermatitis compared with those who did not (five of nine patients, 56%) [42].

These data from the literature emphasize the importance of evaluating and managing contact dermatitis after CL gel treatment, to maximize the chance for patients to remain on treatment.

Rare AEs Seen in Case Reports

While some case reports have also described similar skin-related AEs and contact dermatitis after treatment with CL gel [48, 49], others have detailed uncommon adverse reactions (Table 2) [30, 46–51]. A retrospective observational analysis observed telangiectasia in patients treated with CL gel. This is not an AE usually reported with CL gel treatment, and the authors suggested that applying too large a volume of the gel could potentially lead to more AEs [43]. A case series examined 10 patients who experienced lymphomatoid papulosis after treatment with CL gel [46]. The authors hypothesized that an immune reaction caused by CL gel treatment could induce CD30 expression in malignant T cells, resulting in lymphomatoid papulosis lesions. Finally, anecdotally, an elderly patient with MF suffered a local trauma and developed necrotic ulcers on the lower limbs 1 month after

initiation of CL gel. This was suspected to be a CL gel-induced ulcer, on the basis of the treatment schedule [50]. Each of these AEs has only been described in a single case report, and thus may be considered very rare, and it has not been fully established whether they are directly attributable to CL gel treatment.

SUMMARY

CL gel is the first CL formulation that has been developed and approved for treatment of patients with MF, with no evidence of systemic absorption [26]. Recent data on the CL mode of action have shown that CL predominantly inhibits rapidly proliferating malignant skin T cells [62]. The gel is effective for treatment of MF, with high response rates seen both in clinical trial and real-world settings. While some patients have a quick response to CL gel treatment, others do not have a response for up to 18 months after treatment initiation [33, 38], indicating that it is important for patients to continue treatment long-term, when possible. Good responses were also seen in real-world clinical practice, where CL gel was often used at variable or lower treatment frequencies and in combination with other therapies [38]. Currently, no studies have directly compared the use of topical ultrapotent corticosteroids with chlormethine gel in patients with MF.

CL gel may be used with a multitude of concomitant therapies [30, 38, 49], and real-world studies and case reports have illustrated the variety of patients with MF, with different stages and presentation of disease, who benefit from CL gel treatment [30, 40, 48, 49, 51]. In addition, positive responses can be achieved with CL gel monotherapy in clinical practice [40, 48].

CL gel has a manageable safety profile, with mainly mild, skin-related AEs, although patients may discontinue treatment, often as a result of contact dermatitis [33]. Dermatitis may be resolved after treatment interruption, reduction of the frequency of treatment application, and the addition of emollients and topical steroids; patients who experience dermatitis can still have positive responses to CL

gel treatment [33, 61]. In fact, in some instances patients who experienced contact dermatitis could achieve earlier lesion resolution [21]. Post hoc analyses of study 201 and 202 found that dermatitis may even be a prognostic factor for response [35, 37]. While this association needs to be confirmed in larger prospective studies, it highlights the importance of managing contact dermatitis and restarting patients on CL gel treatment whenever possible. The REACH study (NCT04218825) will further investigate the relationship between skin-related reactions and response in CL gel-treated patients with stage IA–IB MF.

In conclusion, the efficacy and safety of CL gel, in combination with the ease of self-application by instructed patients at home, makes it a valuable treatment option for patients with MF. Indeed, CL gel was also designated as a low-risk treatment in a recent recommendation for cutaneous lymphoma treatment during the COVID-19 pandemic [63]. A high proportion of patients respond well to CL gel, although continued treatment is of the utmost importance. For some patients, a higher concentration of CL gel may also lead to improved responses. According to real-world data, CL gel may also be used effectively and safely in combination with different concomitant therapies for MF. Patients do need to be well-instructed, be monitored carefully, and CL gel-associated dermatitis must be managed effectively to allow patients to continue treatment and achieve the best possible response of MF lesions.

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