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REVIEW ARTICLE

Mechanism of action of chlormethine gel in mycosis fungoides

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Abstract

Mycosis fungoides (MF), the most common type of cutaneous T-cell lymphoma, is characterized by proliferation of malignant skin-tropic T cells. Progression from early-stage disease (skin patches and/or plaques) to more advanced stages (cutaneous tumours, erythroderma or extracutaneous involvement) occurs slowly and can be discontinuous. Prognosis is poor for the ~25% of patients who progress to advanced disease. Patients at any stage of MF may experience reduced health-related quality of life (QoL) via a spectrum of physically and psychologically debilitating symptoms that can impact many aspects of daily life. Allogeneic stem-cell transplantation is a curative treatment option for some patients with advanced disease, but otherwise there is currently no cure for MF; patients are often refractory to several treatments and require lifelong management. The goals of therapy are symptom control, prevention of disease progression, avoidance of treatment-related toxicity and maintenance/improvement of QoL. Although treatment regimens exist it can be difficult to know how to prioritize them, hence therapies are tailored according to patient needs and drug availabilities, following clinical recommendations. International consensus guidelines recommend skin-directed therapies (SDTs) as first-line treatment for early-stage disease, and SDTs combined with systemic therapy for advanced stages. Chlormethine (CL), also known as mechlorethamine, chlorethazine, mustine, HN2, caryolysine and embichin, is a synthetic deoxyribonucleic acid-alkylating agent that was used as a chemical weapon (mustard gas) during the First World War. Subsequent investigation revealed that survivors of mustard gas exposure had lymphocytopenia, and that CL could inhibit rapidly proliferating malignant T cells. CL has since been developed as a topical treatment for MF and prescribed as such for over 70 years. This review aims to summarize the current knowledge regarding the mechanism of action of CL in the cutaneous micro-environment, in the specific context of MF treatment.

INTRODUCTION

Mycosis fungoides (MF) is a primary cutaneous T-cell lymphoma (CTCL) that is characterized by clonal proliferation of malignant T cells in the skin.[1–4] MF is the most prevalent CTCL, accounting for 60% of all cases and nearly 50% of all cutaneous lymphomas.[2,5] MF typically affects older adults and has a chronic indolent, relapsing-and-remitting clinical course, progressing slowly from early-stage disease (stages IA–IIA) to more advanced stages (IIB–IVB) over a prolonged period, even decades.[2,6,7] Early-stage MF (~70% of patients) presents as patches and/or plaques on the skin (often in sun-protected areas), usually without extracutaneous involvement.[3,8,9] Progression to more advanced stages involves the development of cutaneous tumours or generalized erythroderma, sometimes with lymph node, blood and visceral organ involvement.[10,11] Although patients with stage IA MF generally have a normal life expectancy,[12] the prognosis for advanced disease is poor, with one study reporting a median survival of approximately 5 years and a 5-year survival rate of just 52%.[13] Disease prognosis is influenced by many factors, which are not yet fully defined, but the strongest known risk factors for poor survival are advanced tumour stage and presence of extracutaneous disease; male

sex, older age (>60 years), presence of plaques and lymph node stage >N1 and/or Nx may also portend poor survival.[14]

MF has a significant impact on a patient's health-related quality of life (QoL). Physical symptoms, such as pain, pruritus and alopecia, and other factors such as insomnia, anxiety, shame, embarrassment and depression can interfere with work, school and other daily activities.[15,16] Apart from allogeneic stem-cell transplantation, which may be appropriate for patients with advanced disease, MF is considered incurable and is often refractory to treatment (except stem cell transplantation); instead, patients generally require lifelong management.[6,17–19] The goals of treatment are to control symptoms, limit disease progression, avoid treatment-related toxicity and maintain or improve QoL.[6,12] The discontinuous nature of disease progression in MF is characterized by variable rates of tumour progression, from rapid (over a period of weeks) to being stable for protracted periods.[20] Numerous treatments and established guidelines are available,[21] but the relative scarcity of randomized, comparative studies in this area has led to heterogeneous treatment approaches[3,18,22,23] and hindered the development of clear, universally applicable treatment algorithms.[18,22,23] Hence, a 'one-size-fits-all' approach is not currently possible. This situation is compounded by different drug regulatory approval processes and varying access to new drugs and/or clinical trials in different geographical regions.[10,11] However, international consensus guidelines (European and US) have been developed to provide treatment recommendations according to disease stage, to update staging based on potential prognostic factors, diagnosis, and assessment methods, to standardize the criteria for clinical trial design, and facilitate the development and approval of novel and effective treatments for these patients.[12,24–26] These guidelines recommend skin-directed therapies (SDTs) as first-line treatment for patients with early-stage MF. In line with this, the PROspective Cutaneous Lymphoma International (PROCLIPI) study of patients with early-stage MF found that first-line SDTs were prescribed in the majority of cases (82%), versus 11% with systemic treatment and 7% with watchful waiting (expectant policy).[27] A combination of systemic therapy and an SDT is recommended for more advanced disease; the addition of an effective SDT to systemic therapy regimens in the later stages of MF may help to reduce response times and augment symptom improvement.[12,24,25]

Options for SDTs include topical corticosteroids, topical deoxyribonucleic acid (DNA)-alkylating agents, radiotherapy, total skin electron beam radiotherapy (TSEBT) and phototherapy.[11,28] Phototherapy (e.g. narrow-band ultraviolet B [nbUVB], psoralen and ultraviolet A [PUVA]) is commonly recommended as a first-line therapy for MF.[12,24,25] Most of these options provide good response rates for early, skin-limited disease. The PROCLIPI study reports an objective response rate (ORR) with SDTs of 73% overall (68% for topical corticosteroids, 74% for nbUVB and 83% for PUVA), versus 57% for systemic treatment.[27] However, high-certainty evidence supporting their use is somewhat limited. A recent Cochrane systematic review found just 20 randomized controlled trials with 1369 participants on local or systemic treatments in MF published up to 2019.[29] Complete response (CR) rates (CRRs)/ORRs were as follows: from 80%–90% to 100% for localized radiotherapy (evidence level: 4); from 45%–65% to 75%–95% for topical corticosteroids (evidence level: 3); from 45%–75% to 75%–95% for nbUVB (evidence level: 2); and from 50%–80% to 75%–100% for PUVA (evidence level: 2).[29] Moreover, the majority of these SDTs are not licensed for MF.[11] In addition, some may be associated with concerning side effects, particularly with long-term treatment (topical corticosteroids, phototherapy, radiotherapy, TSEBT), may be time consuming or difficult to access (topical corticosteroids, alkylating agents, radiotherapy and phototherapy), or are limited by dose and therefore may only be used as a palliative option.[11] Of note, there has been progress recently in the field of radiotherapy in oncology with the development of a protocol that delivers a single high dose of irradiation to the tumour over a very short time (<200 ms). This technique enables high-precision irradiation of tumour lesions while sparing of larger volumes of non-tumour tissue compared with conventional radiation therapy, and thus imposing fewer side effects on healthy tissue.[30,31] Preliminary clinical evidence from a single case report demonstrated the feasibility and tolerability of this treatment, with the patient experiencing a rapid, complete and durable (with a follow-up of 5 months) tumour response with minimal and transient adverse reactions in the surrounding non-tumour skin.[31] While it shows promise, research into the utility of this novel radiotherapy protocol in CTCL is currently nascent and studies are on-going. The calcineurin pathway is often activated in MF and the calcineurin inhibitor, pimecrolimus, was recently demonstrated to be active and well tolerated in patients with early-stage MF in a phase 2 trial,[32] although long-term follow-up data are needed to confirm the findings. Topical DNA-alkylating agents have a good safety profile with relatively benign side effects, the most common being dermatitis; however, evidence supporting their use is thus far predominantly retrospective.[11]

Chlormethine (CL), also known as mechlorethamine, chlorethazine, mustine, HN2, caryolysine, and embichin (among others),[33,34] is a synthetic bifunctional DNA-alkylating agent that was originally used as a chemical weapon (mustard gas) during the First World War. It was subsequently found to inhibit rapidly proliferating malignant skin-tropic T cells and developed as a topical treatment for MF. CL was first approved in the 1940s to treat various malignant lymphomas, and has been used as a topical primary therapy for MF and other lymphoid malignancies since the 1950s.[12,34–36] Early topical formulations of CL were available only as aqueous solutions (i.e. CL in water) or compounded ointments.[36,37] The efficacy of treatment with compounded formulations can be variable given the risks of incomplete mixing of the ingredients, unclear stability, inconsistent concentration of the active ingredient, and degradation or contamination of the ointment.[38] More recently, a topical CL gel formulation (CL 0.016% w/w, equivalent to 0.02% CL hydrochloride) was introduced as the first topical

therapy purposely developed and subsequently approved for the treatment of MF.[35,36,39] It is endorsed by European guidelines, and one of several endorsed by other major guidelines for first-line treatment in adult patients.[12,24,25] While the clinical use of CL gel is well established, recently published data are beginning to elucidate different aspects of its mechanism of action in the cutaneous micro-environment. Here, we will briefly summarize the role of CL gel in the treatment of MF before reviewing current knowledge regarding its mechanism of action, with reference (where available) to relevant clinical data.

CL GEL IN THE TREATMENT OF MF

Based on results from the pivotal registration study, Study 201 (NCT00168064),[36] CL gel was approved in the United States in 2013 for the treatment of adult patients with stage IA–IB MF who have received prior SDT,[39,40] and has since been registered in several countries worldwide for the treatment of adult patients with MF.[41–43] A retrospective study of 203 patients with MF found that treatment with CL aqueous formulation yielded an overall ORR of 83%, with 50% and 33% of patients achieving a CR and partial response (PR), respectively, after a median maintenance treatment duration of 6 months (range: 0–57 months). Responses were observed not only in patients with limited early-stage disease (T1, patches or plaques covering <10% of the skin surface; ORR: 93%; CR: 65%; PR: 28%), but also in those with more extensive involvement (T2, covering ≥10% of the skin surface; ORR: 72%; CR: 34%; PR: 38%). Survival rates at 5 years were 97% and 72%, respectively, for patients with T1 and T2 disease.[25,44]

Although CL aqueous and ointment iterations have a decades-long history of clinical use, they can present challenges in terms of preparation and application.[41] The non-aqueous CL gel contains an active solvent, Transcutol® (Sigma-Aldrich Solutions, Darmstadt, Germany [part of Merck KGaA]) and the excipient Klucel™ hydroxypropylcellulose (Ashland, Wilmington, DE, USA).[39] Transcutol promotes drug delivery to the epidermis, imparts high stability, is non-irritating for skin delivery and is non-toxic,[45–47] while Klucel hydroxypropylcellulose confers fast-drying, highly viscous and non-greasy properties to the formulation.[39] Thus, these additives may serve to augment the efficacy of CL gel and improve its convenience, making it easier to apply.[39,41] In addition, CL has intrinsic antimicrobial properties, which potentially obviates the need for antimicrobial preservatives and reduces the risk of allergy.[39,48] All international guidelines that we are aware of, including those of the National Comprehensive Cancer Network (NCCN), European Organisation for Research and Treatment of Cancer (EORTC), British Association of Dermatologists/UK Cutaneous Lymphoma Group (BAD/UKCLG) and European Society of Medical Oncology, recommend topical CL as a first-line treatment for MF stages IA, IB and IIA. NCCN guidelines extend this to stage IIB, and the EORTC also recommends topical CL for maintenance treatment after remission. The BAD/UKCLG guidelines state that SDT may be considered as a maintenance or adjuvant therapy for patients who achieved a response with chemotherapy,[12,24,25,49] although it should be noted that the indications, optimal treatment selection and benefits of maintenance therapy have not been fully characterized and remain uncertain.[12,24,25,49]

EXPERIMENTAL INVESTIGATIONS: MECHANISM OF ACTION

CL gel versus ointment-based formulations

Toward elucidating the mechanism of action of CL gel, the release profiles of CL 0.016% from the registered gel formulation and a compounded ointment-based formulation were compared using in vitro release testing.[50] CL gel and CL ointment were applied to a polytetrafluoroethylene (PTFE) membrane, sandwiched between a donor compartment and a receptor solution compartment in a vertical diffusion cell. The receptor solution was sampled regularly for 5 h after application of the CL formulations to the PTFE membrane. The mean ± standard deviation rate of CL release over the 5-h data-collection period was significantly higher for CL gel ($5.70 \pm 0.73\ \mu g/cm^2/\sqrt{h}$; coefficient of variation [CV], 12.80) than for the CL ointment-based formulation ($2.38 \pm 1.03\ \mu g/cm^2/\sqrt{h}$; CV: 43.36). The formulations were considered inequivalent according to Food and Drug Administration bioequivalence criteria.[50,51] Additional statistical analysis (*t*-test assuming unequal variances) confirmed that the CL release rate and cumulative amount of CL released were significantly greater (both $p < 0.0001$) for CL gel versus CL ointment.[50] The substantially higher CL release rate suggests that drug delivery from the gel is more efficient than from the ointment, and may explain the higher response rates seen with CL gel versus ointment in Study 201.[36] Study 201 was a randomized, observer-blinded, controlled, non-inferiority trial, comparing once-daily CL gel with CL ointment for 12 months in 260 patients with stage IA–IIA MF; use of corticosteroids was prohibited.[36] Response rates based on Composite Assessment of Index Lesion Severity (CAILS) scores were higher for CL gel than for CL ointment in both the intent-to-treat population (59% vs. 48%, respectively) and the efficacy-evaluable population (77% vs. 59%, respectively; $p = 0.011$). CL gel met prespecified criteria for non-inferiority; furthermore, in addition to exceeding the non-inferiority threshold of ≥0.75, the 95% confidence interval of the CAILS score in the efficacy-evaluable population was consistently >1.[36,39] Post hoc switching from non-inferiority to superiority testing revealed that this was consistent with superiority findings for CL gel versus CL ointment ($p < 0.05$).[39]

The faster release rates seen in vitro with CL gel may also explain the faster response times and stronger responses over time in patients treated with CL gel (vs. CL ointment) in Study 201. CL gel was associated with a faster time to response, attaining a 50% response rate approximately 16 weeks sooner

than CL ointment. Response rates at 52 weeks were higher for patients treated with CL gel (76% vs. 56% for CL ointment).[36] In a post hoc analysis of efficacy data from Study 201, patients treated with CL gel had significantly shorter times to at least PR or very good PR (VGPR) ($p = 0.0419$ and $p = 0.0107$, respectively, vs. CL ointment); time to CR was also numerically (non-significant) shorter with CL gel. Strength of response was higher over time with CL gel than with CL ointment; these differences were significant for responses defined as at least PR ($p = 0.0013$) and at least VGPR ($p = 0.0420$).[41]

CL gel targets the epidermis following topical administration, with no evidence of systemic absorption

In vitro evidence

In vitro permeation testing (IVPT) has been performed to evaluate the percutaneous absorption profile of CL gel in ex vivo human skin.[50] In those experiments, CL gel was applied at a dose of 10 mg/cm^2 to the upper surface of ex vivo skin samples (epidermal membranes or dermatomed skin [epidermis plus dermis]) mounted into the donor compartment of flow-through diffusion cells. The amount of CL gel permeating through the skin was measured by sampling the receptor solution that flowed continuously underneath the skin, every 2 h post dose for 24 h. Residual CL gel was also retrieved from the skin surface at the end of the experiment.[50] After 24 h, the mean cumulative amount of CL permeation through skin was greater for the epidermal membrane (73.3 ng/cm^2) than for the dermatomed skin (40.4 ng/cm^2), representing 4.6% and 2.5% of the applied dose, respectively. The mean peak CL flux values for epidermal membrane and dermatomed skin were 10.8 and 5.2 ng/cm^2/h, respectively. Mean residual CL retrieved from the surface of skin samples after 24 h was 21.0 ng (1.3% of the applied dose) for epidermal membrane and was undetectable for dermatomed skin. Overall, these data suggest that CL gel remains predominantly within the epidermal layer, where it can exert its clinical effects in MF skin lesions, with only minimal amounts passing through the epidermis to dermal tissue.[50] The concentration of CL required to induce its clinical effects in the dermal layer has yet to be established. However, since MF plaques have been shown to respond well to topical CL treatment,[25,44,52] it is possible that the minimal amounts of CL shown to reach the dermis in IVPT experiments may be sufficient to exert an effect, potentially by inducing cytotoxic inflammation, with cytokine or chemokine release from an associated influx of reactive T cells.

Pharmacokinetic data

Data from the IVPT study, which found negligible permeation of CL through the epidermis or dermatomed skin,[50] are consistent with pharmacokinetic data from clinical trials, which indicated no evidence of CL gel absorption into the systemic circulation.[53] In Study 201, CL gel ($n = 130$ patients) or ointment ($n = 130$) was applied once daily for 12 months.[36] During the extension study (Study 202), patients who had not achieved a CR after 12 months in Study 201 received CL gel once daily for a further 7 months using a double-strength formulation (0.02% to 0.04%).[54] Plasma CL concentration was quantified (by high-performance liquid chromatography) in samples collected from 31 patients in these two studies (Study 201 and 202) who received CL gel at baseline (predose), at 1, 3 and 6 h, after the first application of CL gel, and finally predose at the month 1 visit (16 patients from Study 201); and at predose and 1 h after first application at baseline and predose or 1 h at the next visit (4 or 6 months; 15 patients from Study 202).[53] All plasma samples from Study 201 tested negative for CL (<41.5 ng/mL), indicating a lack of systemic absorption; similarly, there was no measurable systemic absorption of CL in plasma samples from Study 202 (<5.0 ng/mL). These bioanalytic results are consistent with historical data showing a lack of systemic absorption following treatment with aqueous and ointment-based CL formulations.[44,53] The absence of systemic absorption of CL suggests that drug–drug interactions are unlikely when used concomitantly with other agents; for example, if used as an adjuvant therapy in patients with more advanced disease.

CL gel induces DNA double-stranded breaks and impairs DNA repair machinery in malignant skin T cells in vitro (Figure 1)

CL reduces malignant T-cell viability

CL is known to inhibit rapidly dividing cells by inducing conformational changes in DNA. CL is rapidly metabolized to a highly reactive ethylene immonium derivative that alkylates DNA, DNA-to-DNA and DNA-to-protein cross-linking, inhibition of DNA replication and transcription, induction of double-stranded breaks (DSBs), and triggering apoptosis.[33,35,55,56] In order to characterize further the anti-tumour activity of CL gel against malignant CTCL/MF skin T cells at the DNA level, Chang and colleagues conducted a series of in vitro/ex vivo studies. The aim was to investigate the extent of CL treatment susceptibility, focusing on DNA damage-repair pathways, DNA DSBs, cell proliferation and apoptosis.[35] In vitro exposure to CL at various concentrations (0.0016%, 0.016%, and 0.16%) and at different time points (0.016% CL exposure at 6, 24 and 72 h) preferentially decreased the viability of two malignant T-cell lymphoma lines compared with healthy human T cells in a time- and dose-dependent manner.[35]

CL induces DNA DSBs and apoptosis in skin-homing malignant T cells

Analysis of γH2AX Ser139 expression (a specific marker for DNA DSBs), using flow cytometry, showed that CL exposure

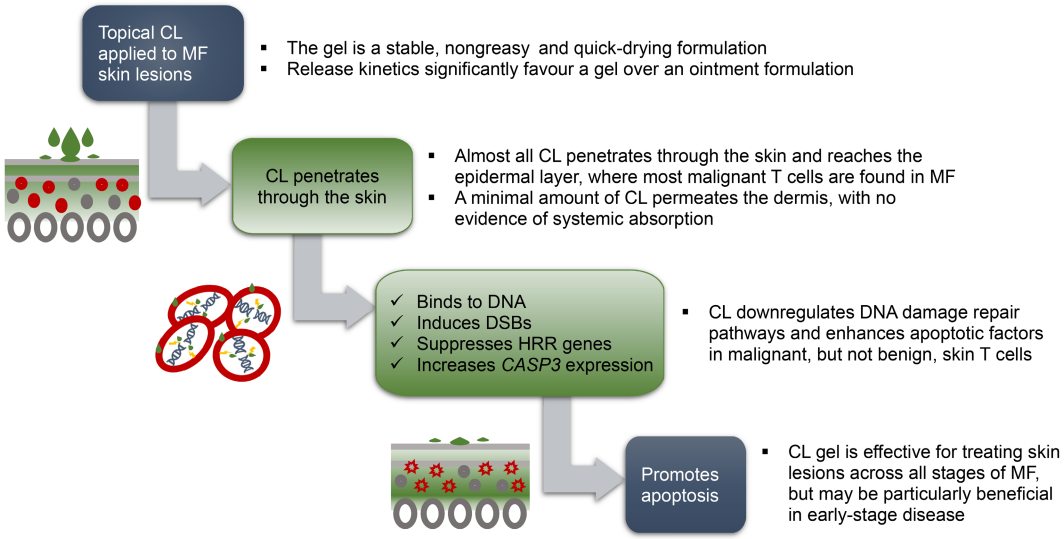

FIGURE 1 CL gel induces DNA DSBs and impairs DNA repair machinery in malignant skin T cells in vitro. CL gel may be an effective targeted SDT for the treatment of early MF. CL is released from the gel formulation at a faster rate than from the ointment, and its permeation profile appears optimum in that very little CL from the skin surface of epidermis (indicating that it has reacted there), and even less reaches the dermis (consistent with the observed lack of systemic absorption).[50] The available data suggest that where CL reacts in the epidermis (and to a lesser extent in the dermis), its mechanism of action involves induction of DSBs, increased expression of *CASP3*, and reduced expression of certain DNA repair genes in malignant skin T cells, rendering them more susceptible to apoptosis.[35] Adapted from Chang et al, 2022.[35] *CASP3*, gene-encoding caspase-3; CL, chlormethine; DNA, deoxyribonucleic acid; DSBs, DNA double-stranded breaks; HRR, homologous recombination repair; MF, mycosis fungoides.

induced significant DNA DSBs in MF clonal malignant skin T cells, but not in MF control T cells ($p = 0.0005$). Quantitative reverse transcription polymerase chain reaction (RT-qPCR) analysis demonstrated that CL exposure also significantly increased expression of the apoptotic caspase 3 gene (*CASP3*) in MF malignant versus MF bystander skin T cells. This upregulation in *CASP3* expression, resulting in a greater tendency toward apoptosis, is an expected functional consequence of the CL-induced increase in DNA DSBs.[35] However, while the response to DNA DSBs also typically includes cell-cycle arrest,[57] Chang and colleagues determined that proliferation of malignant T cells remains relatively unaffected by CL exposure,[35] a finding that warrants further investigation.

CL suppresses expression of DNA repair genes in MF malignant skin T cells

A detailed gene-expression analysis confirmed that MF malignant skin T cells show substantial messenger RNA downregulation of several genes important for base excision repair, nucleotide excision repair, homologous recombination repair (HRR) and direct enzymatic DNA repair.[35] Exposure to CL produces further significant reductions in the expression of three major HRR genes (Fanconi anaemia, complementation group I, breast cancer susceptibility gene 2 and flap structure-specific endonuclease 1) in MF malignant T cells, as demonstrated by RT-qPCR analysis. These reductions were also evident (although less pronounced) in healthy and bystander T cells.

Clinical efficacy

The IVPT data suggesting that CL gel acts predominantly within the epidermis[50] are also supported by efficacy data from clinical studies. In MF, skin infiltration of malignant T cells predominantly affects the epidermis.[3] Therefore, the possibility that CL gel mainly exerts its activity in the epidermal layer may help to explain the efficacy observed in clinical trial data[36,41] and real-world studies.[39,42,58] Current clinical practice suggests that CL gel is effective for treating skin lesions across all stages of MF, including when used as adjunctive therapy in advanced disease.[39,42,58] However, restriction of its clinical activity to the epidermis[50] may mean that it is particularly effective when used in early-stage disease, as indicated by a post hoc analysis of data from Study 201.[41] The maximum response obtained with CL gel in Study 201 occurred 10 months from the start of treatment,[59] highlighting that continued treatment with close follow-up may maximize the response potential with this agent. The potential value of continued treatment is reinforced by the findings of Study 202, in which the efficacy of a higher dose (0.04%) of CL gel was evaluated in patients from Study 201 who had received either CL gel (0.02%) or CL ointment but did not achieve a CR.[54] Among patients in Study 202, 27% had a confirmed response to CL gel 0.04%,[54] some of which occurred as late as 16 months after the start of treatment in Study 201, with no signals of increased toxicity. These data also suggest that patients with recalcitrant lesions may receive particular benefit from prolonged treatment with CL gel.

CLINICAL SAFETY

The lack of systemic CL absorption supported by in vitro and pharmacokinetic data[50,53] is further corroborated by clinical safety data, which have consistently shown a lack of abnormalities that would indicate systemic absorption. In Study 201, most adverse events were local skin reactions. These reactions were commonly local dermatitis (skin irritation), which occurred in 25% and 14% of patients receiving CL gel and ointment, respectively.[36] There were no changes in haematology or serum chemistry parameters and no evidence of systemic toxicity.[36,53] Local skin reactions are also reported to be the most common adverse event related to CL gel in real-world practice.[39,42,58,60] Depending on their severity, these localized skin reactions can usually be managed with a reduced CL dose and/or frequency/temporary dose suspension or use of topical interventions (e.g. emollients, steroids, antihistamines [oral or topical]).[36,39,42,60]

The Mechlorethamine-Induced Contact Dermatitis Avoidance Study (MIDAS)

Contact dermatitis is frequently experienced following treatment with topical CL gel.[36,61] Contact dermatitis 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 between ACD and ICD.[62] Although patch testing was not routinely used during Study 201, the estimated incidence of ACD was 16.4% in patients treated with CL gel (vs. 12.6% in the ointment arm). In total, 26 patients (20.3%) withdrawn from the CL gel arm (vs. 17.3% in ointment group) due to protocol-specified treatment-limiting skin adverse events.[36] MIDAS (NCT03380026) was conducted to determine whether cotreatment with topical triamcinolone 0.1% ointment (henceforth triamcinolone) could reduce the development of CL-gel-induced contact dermatitis in patients with early-stage MF.[63,64] In this randomized, open-label, split-face, two-arm trial, patients with at least two similar MF lesions were administered CL gel alone to selected lesions and CL gel in conjunction with triamcinolone to others, once nightly for 4 months. Patch testing was undertaken in patients with severe reactions to the CL gel to identify the type of dermatitis and contributing allergens.[63–65] The primary endpoint was the ability of triamcinolone to prevent CL gel-induced dermatitis. Quantification of the severity of dermatitis was achieved using SCORD, a modification of an established tool for measuring dermatitis reactions: the Scoring of Atopic Dermatitis scale (SCORD).[65,66] Secondary endpoints included identification of the type of dermatitis, which was achieved through pathologic evaluation, patch testing and examination of T-cell clones/diversity. The efficacy of both treatment arms was determined by measuring the CAILS score and genetic T-cell clonality.[65] Of the 28 enrolled patients (17 males and 11 females), 25 completed the 12-month follow-up. SCORD was shown in this study to be able to differentiate between patients with no or mild dermatitis ($n = 11$) and those with moderate-to-severe dermatitis ($n = 16$) from around month 2 of treatment, with a trend toward identifying those with moderate-to-severe dermatitis at month 1. Compared to treatment with CL gel alone, CL gel plus triamcinolone was associated with a reduction in SCORD score throughout the 4-month treatment period. The difference between the two treatment arms reached statistical significance at month 3, coinciding with the time at which the worst severity of CL gel-related dermatitis was observed in the CL monotherapy arm. CAILS assessment revealed that the addition of triamcinolone was also associated with increased tolerability of CL gel without impacting its efficacy. Moreover, there was no increase in the number of malignant clones in patients who experienced contact dermatitis.[65] Interestingly, this analysis also showed a posttreatment improvement in CAILS clinical response for all patients at month 5 after the per-protocol discontinuation of treatment at month 4.[65] One possible explanation for this improvement is resolution of inflammation (i.e. mild erosions, ulcerations); however, a cytotoxic, antitumour T-cell response cannot be ruled out, as suggested by the corresponding large quantitative reduction in the malignant clone count in baseline versus month 5 posttreatment lesion biopsy samples in a representative patient. This observation appears to fulfil a previously documented justification for disease modification: 'sustained improvement in disease state, continuing after treatment discontinuation.'[67] However, further research is needed to confirm these findings. Such long-lasting effects have also been demonstrated in patients with early-stage MF treated with first-line topical nbUVB, PUVA or TSEBT.[68–70]

Dermatitis can occur after CL gel treatment and should be managed according to its severity.[52,60] If treatment with CL gel results in a skin reaction, physicians should consider pausing treatment. In patients with mild to moderate dermatitis, treatment with CL gel may be continued at a reduced frequency and in combination with emollients or topical steroids. However, the best option for patients with severe dermatitis is treatment discontinuation. Subsequent therapy may depend on the type of dermatitis. For example, in patients with severe ICD, resolution of the dermatitis may be followed by reinstitution of CL gel therapy; however, patients with severe ACD may be intrinsically intolerant to CL gel, although it is worth rechallenging to establish unequivocally that this is the case.[60]

ADDITIONAL MECHANISMS OF ACTION FOR CL GEL

While the current data suggest that the main mechanism by which CL gel exerts its antitumour effects in MF is by impeding DNA damage repair and triggering apoptosis,

there are other potential mechanisms. There is evidence to suggest that DNA-alkylating agents are not only directly antineoplastic, but also immunostimulatory, which may enhance antitumour immunity by counteracting the tumour-protective immunosuppressive micro-environment.[71–74] The cytotoxic effect of CL gel on malignant T cells in MF, with upregulation of pro-apoptotic *CASP3* expression,[35] may be potentiated by its ability to induce an inflammatory tumour micro-environment (via either ACD or ICD). In addition, the induction of apoptosis by CL gel could lead to a dendritic cell-driven epidermal immunotherapeutic response. Combination treatments with CL gel and immunotherapies may thus provide additional benefit. However, more research is needed to highlight the role of the antitumour environment, given that (for instance) MIDAS findings argue against a contact dermatitis-induced antitumour response, since mitigation of the associated inflammation by 0.1% triamcinolone ointment in patients with early-stage MF did not reduce the efficacy of CL gel.[65] That said, the immune system may still be key, and although triamcinolone may effectively reduce inflammation, it may have been too weak to suppress the immunostimulatory impact of CL gel.

CONCLUSIONS

Taken together, the combination of in vitro, ex vivo and in vivo research provides new evidence supporting the use of topical CL gel for the treatment of early MF lesions as a potentially disease-modifying agent. The demonstration of preferential apoptosis of malignant T-cell clones by a variety of methods provides evidence of changes to the cutaneous micro-environment. The MIDAS in vivo research not only provided the first clinical quantitative finding of malignant T-cell clone reduction in early-stage MF lesions treated with CL gel, but also the first controlled results showing a sustained, posttreatment improvement in clinical response (i.e. further reductions in CAILS at month 5, 1 month after discontinuation of CL gel treatment).[65] The clinical pharmacodynamic data highlight both the magnitude of reduction in the proliferation of cutaneous malignant T-cell clones in early MF disease, and the corresponding posttreatment improvement in clinical response in the same patients. These targeted reductions in malignant clones, along with posttreatment improved responses, appear to reflect an impact on the underlying pathophysiology in patients with early-stage MF. The antitumour effects of CL gel on malignant skin T cells in MF are exerted predominantly by reducing the ability of T cells to repair damaged DNA and triggering apoptosis via several mechanisms, including induction of DNA DSBs, overexpression of the apoptotic gene, *CASP3*, and reduced expression of key genes involved in DNA damage-repair pathways.[35] These in vitro and ex vivo pharmacodynamic effects of topical CL gel in the cutaneous micro-environment demonstrate mechanistically how CL gel preferentially inhibits cutaneous malignant T-cell lines that are known to drive early MF disease.[2,3,35,39] Topical CL may therefore provide some early-stage disease modification via preferential induction of apoptosis in the malignant T-cell infiltrate within MF skin lesions. Regarding the formulation of topical CL, release kinetics favour the gel over its ointment-based counterparts in vitro, indicating that it may offer more efficient drug delivery to the cutaneous micro-environment.[50] Furthermore, the demonstrated lack of systemic absorption with CL gel[53] suggests that treatment may not require blood monitoring or hospital visits. One hypothetical mechanism of action for the benefit of topical CL is that it induces inflammation and an antitumour response.[65] This hypothesis raised the possibility that coadministration with triamcinolone aimed at reducing the development of CL gel-induced contact dermatitis would dampen this inflammation, and thus the antitumour response. The MIDAS findings indicated that this is unlikely to be the case, demonstrating no adverse impact of coadministration with triamcinolone 0.1% ointment on the efficacy of CL gel. In fact, conversely, an improvement in the CAILS score was observed, even during the study washout period (1 month washout period after 4 months treatment) requiring treatment discontinuation, suggesting that CL gel affects the evolution of MF. In addition, the immune response driving CL gel-induced contact dermatitis appears to be distinct from that driving lymphoma.[65] Contact dermatitis-induced inflammation is thus unlikely to exacerbate lymphoma.[65] Finally, given the known antiproliferative and pro-apoptotic properties of calcineurin inhibitors in vitro and the recent positive clinical findings with pimecrolimus,[32,75] combination therapy with CL gel and pimecrolimus may represent a rational option in patients with MF.

The growing body of evidence supports CL gel as an effective and valuable targeted SDT for the treatment of early MF and suggests that extended periods of use, with close follow-up, may confer additional clinical benefit without concomitant increased toxicity.

AUTHOR CONTRIBUTIONS

Professor Guenova had full access to all the materials in the article and takes responsibility for the integrity of the work as a whole, from inception to published article. All authors take responsibility for the content, contributed to the interpretation, and reviewed and approved all manuscript drafts, including the final draft.

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CONFLICT OF INTEREST STATEMENT

Prof Guenova has received consulting fees, payment or honoraria from Helsinn, KIOWA Kirin, Mallinckrodt Pharmaceuticals, Novartis, Recordati Rare Diseases, Sanofi and Takeda, has a patent on diagnostic method for blood disease, has been involved in a leadership role for EADV and EORTC, and has stock/stock options for Scailyte AG. Prof Ortiz-Romero has served on advisory boards for 4SC, Actelion, Helsinn, Innate Pharma, Kyowa Kirin, Recordati Rare Diseases and Takeda, received support for attending meetings for Almirall, Kyowa and Leo Pharma, has a patent for PLC gamma 1, and has received research support from MEDA. Dr Poligone has served as advisor/consultant for Bioniz, Helsinn, Kyowa Kirin and Soligenix, and as an investigator with grant support from Astex, Biogen, Bioniz, Eli Lilly, Helsinn, Innate Pharma, Kyowa Kirin, miRagen Therapeutics and Soligenix. Prof Querfeld has served on advisory board/scientific committees for Citius Pharmaceuticals, Helsinn, Kyowa Kirin and Mallinckrodt Pharmaceuticals, sits on a Board of Directors for the International Society for Cutaneous Lymphoma, and has received research funding from Celgene and Helsinn.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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