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Lack of Systemic Absorption of Topical Mechlorethamine Gel in Patients With Mycosis Fungoides Cutaneous T-Cell Lymphoma

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To the Editor

Primary cutaneous T-cell lymphomas are a heterogeneous group of lymphoproliferative disorders. The most common type is mycosis fungoides (MF), which often presents with persistent patches and plaques (Willemze et al, 2019). The recommended therapeutic options for patients with MF are based on international guidelines. For patients with early stage (IA–IIA) MF, skin-directed therapies are recommended as first-line treatment. Mechlorethamine is a skin-directed therapy that has been used for MF for decades (Vonderheid et al, 1989). Early formulations of mechlorethamine were aqueous or ointment-based. More recently, a topical mechlorethamine 0.016% w/w gel was specifically developed for treatment of MF,

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DATA AVAILABILITY STATEMENT

All data from the bioanalytic assessments performed are present in the manuscript and supplementary files. There are no data sets in a repository. Individual patient-level data may be shared upon reasonable request.

and has been endorsed by international guidelines (Willemze et al, 2018; Trautinger et al, 2017; NCCN, 2020). Mechlorethamine gel was approved for treatment of patients with stage IA–IB MF in the US in 2013 on the basis of the 201 registration study (NCT00168064) and the 202 extension study (NCT00535470), in 2016 in Israel, and in 2017 in the EU (Valchlor prescribing information, 2020; Ledaga SmPC, 2018; Lessin et al, 2013; Kim et al, 2014).

The pivotal 201 study compared 0.02% mechlorethamine gel with equal-strength compounded ointment and demonstrated that the gel met all prespecified criteria for noninferiority compared with the ointment (Lessin et al, 2013). In total, 260 patients were enrolled and randomized 1:1 to receive 0.02% mechlorethamine gel or ointment. Treatment was applied once-daily for up to 12 months. Study 202 was an open-label extension of study 201 evaluating treatment with 0.04% mechlorethamine gel in patients who did not have a complete response during study 201. In total, 98 patients received 0.04% mechlorethamine gel once-daily for up to 7 months. No concomitant treatment was permitted during either study. The study protocols were approved by institutional review boards of participating centers; all patients provided written informed consent. Adverse events (AEs) reported in studies 201 and 202 were mainly skin related and manageable (Lessin et al, 2013; Valchlor prescribing information, 2020; Ledaga SmPC, 2018; Kim et al, 2014). The lack of systemic AEs occurring during treatment indicates mechlorethamine is unlikely to be systemically absorbed.

To confirm the lack of systemic absorption, bioanalytic assays were performed to determine mechlorethamine concentrations in plasma. During study 201, plasma samples were collected from 23 patients, 16 from the gel arm and seven from the ointment arm. Samples were collected predose at the baseline visit, 1, 3, and 6 hours after first application of mechlorethamine, and prior to application at the month 1 visit. Mechlorethamine concentrations were analyzed by high-performance liquid chromatography with ultraviolet detector (Coldstream Laboratories, Inc., Lexington, KY) with a lower limit of detection of 41.5 ng/mL. During study 202, plasma samples were collected from 15 patients before and 1 hour after gel application at the baseline visit (or month 2 or 4 if the patient had already started the trial), and prior to or 1 hour after application at the next visit (after 4 or 6 months of exposure). Fully validated high-performance liquid chromatography with tandem mass spectrometry methods (Frontage Laboratories, Inc., Exton, PA) were used to quantify levels of mechlorethamine and its primary degradation product (half-mustard); this more sensitive method had a lower limit of detection of 5.0 ng/mL. Hematologic and serum chemistry parameters were assessed at baseline and months 4, 8, and 12 (or at the termination visit) during study 201, and at baseline and final (or termination) visit for study 202. There was no overlap between the cohorts from study 201 and 202. The demographics and clinical characteristics for all patients are summarized in Table 1.

Bioanalytic results indicate lack of systemic absorption of mechlorethamine in plasma samples from study 201; all samples tested negative (<41.5 ng/mL). Similarly, plasma samples from study 202 did not show measurable systemic absorption (<5.0 ng/mL) (Table 2). These results were consistent regardless of gender, race, disease stage, or whether patients were using localized or full-body application (Supplementary Tables S1–2). There

was no pattern of change over time nor any abnormalities in the laboratory parameters (data on file).

These bioanalytic data indicate that systemic absorption was not observed with mechlorethamine gel (0.02% or 0.04%) or mechlorethamine ointment (0.02%) in patients with MF. Samples were collected and tested up to 6 months after treatment initiation, indicating there was sufficient time for the gel to have penetrated the skin if it could. The patients included in the current analysis also presented with the typical skin-related AEs associated with MF and mechlorethamine treatment. These AEs, which included folliculitis, dermatitis, erythema, and eczema, can damage the integrity of the skin. In addition, there may be skin alterations due to symptoms of MF. Despite the potential skin alterations or damage, no systemic absorption of mechlorethamine was detected. Laboratory monitoring also confirmed that hematologic parameters, including numbers of white blood cells, neutrophils, platelets, and lymphocytes, showed no systematic pattern of change over time. This is consistent with historic data, where no abnormalities related to systemic absorption of mechlorethamine following treatment with the aqueous or ointment formulations have been reported (Lindahl et al, 2014; Kim et al, 2003).

With a number of other skin-directed therapies used for MF, systemic absorption of the agents has been linked to occurrence of AEs. For example, topical carmustine has been shown to be systemically absorbed (Nguyen et al, 2015), which may predispose patients to myelosuppression (Lovgren et al, 2019). There are also reports that topical corticosteroid treatment can result in systemic absorption, which in turn can lead to Cushing syndrome, hyperglycemia, and unmasking of latent diabetes mellitus (Nguyen et al, 2015).

In conclusion, we found no measurable evidence of mechlorethamine in plasma samples from patients with MF after topical once-daily application of 0.02% gel or ointment or 0.04% gel. This lack of systemic absorption also suggests that systemic drug-drug interactions are unlikely to occur when mechlorethamine gel is used concomitantly with other agents. These data, together with the lack of hematologic and systemic toxicity, confirm mechlorethamine gel is a valuable treatment option for patients with MF that does not require blood monitoring or hospital visits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CONFLICT OF INTEREST

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Abbreviations:

AE	adverse event
BQL	below quantification limit
H	hour
M	month
MF	mycosis fungoides
NA	not available

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Table 1.

Demographics and clinical characteristics for patients from studies 201 and 202 included in bioanalytic testing

	Study 201		Study 202
Characteristic	**Mechlorethamine gel (N=16)**	**Mechlorethamine ointment (N=7)**	**Mechlorethamine gel (N=15)**
Age, mean (range)	55 (31–78)	64 (41–75)	53 (27–79)
Gender, n (%)			
Male	9 (56.3)	6 (85.7)	9 (60.0)
Female	7 (43.8)	1 (14.3)	6 (40.0)
Race, n (%)			
White	14 (87.5)	6 (85.7)	10 (66.7)
Asian	2 (12.5)	0	0
African American	0	1 (14.3)	3 (20.0)
Hispanic	0	0	2 (13.3)
MF stage at baseline, n (%)			
IA	9 (56.3)	5 (71.4)	9 (60.0)
IB-IIA	7 (43.8)	2 (28.6)	6 (40.0)
Body surface area of disease, mean (range), %	11 (1–31)	9 (2–22)	11 (1–46)
Dose application, n (%)			
Localized treatment of affected lesions	9 (56.3)	5 (71.4)	9 (60.0)
Full-body application	7 (43.8)	2 (28.6)	6 (40.0)
Application frequency, n (%)			
Daily	15 (93.8)	7(100)	4 (26.7)
1–3 times/wk	1 (6.3)	0	0
4–6 times/wk	0	0	9 (60)
Multiple regimens over time	0	0	2 (13.3) *

* Patient 1: daily at month 2, 4–6 times/wk at month 4; patient 2: 4–6 times/wk at month 4, daily at month 6.

MF, mycosis fungoides.

Table 2.

Bioanalytic testing results from studies 201 and 202

	Study 201		Study 202
	Mechlorethamine gel (N=16)	**Mechlorethamine ointment (N=7)**	**Mechlorethamine gel (N=15)**
Lower limit of analyte quantification in plasma samples, n (%)			
5.0 ng/mL *	0	0	15 (100)
41.5 ng/mL	16(100)	7(100)	0
Analytic results for plasma samples taken at initial application and after 1 month (range)			NA
H0	BQL (BQL-BQL)	BQL (BQL-BQL)	
H1	BQL (BQL-BQL)	BQL (BQL-BQL)	
H3	BQL (BQL-BQL)	BQL (BQL-BQL)	
H6	BQL (BQL-BQL)	BQL (BQL-BQL)	
Ml	BQL (BQL-BQL)	BQL (BQL-BQL)	
Analytic results for plasma samples taken at months 2–6 (range)	NA	NA	
M2/H0			BQL (BQL-BQL)
M2/H1			BQL (BQL-BQL)
M4/H0			BQL (BQL-BQL)
M4/H1 †			BQL (BQL-BQL)
M6/H0			BQL (BQL-BQL)

* Two analytes were tested: mechlorethamine and half-mustard;

† One patient sample was taken at hour 3.

BQL, below quantification limit; H, hour; M, month; NA, not available.