Real-world experience with mechlorethamine gel in patients with mycosis fungoides-cutaneous lymphoma: Preliminary findings from a prospective observational study

To the Editor: Mechlorethamine (ie, nitrogen mustard) is a skin-directed therapy (SDT) for mycosis fungoides-cutaneous T-cell lymphoma (MF-CTCL) used since the mid-1900s, with response rates of 70% to 80%.[1-3] Mechlorethamine gel (MG) 0.016% (Valchlor; Helsinn Therapeutics, Iselin, NJ) was United States Food and Drug Administration approved in 2013 (stages IA/IB). PROVe (A PROspective, Observational, US-based Study Assessing Outcomes, Adverse Events, Treatment Patterns, and Quality of Life in Patients Diagnosed With Mycosis Fungoides Cutaneous T-cell Lymphoma and Treated With Valchlor®, ClinicalTrials.gov identifier: NCT02296164) was designed to study MG real-world use. This report describes study population baseline characteristics and preliminary safety analysis (efficacy, health-related quality of life data to be presented later).

In this cohort study, 301 adult patients with MF-CTCL actively using MG were enrolled at 41 United States sites (academic/private, March 2015-July 2017) after Investigational Review Board approval and patient informed consent. Patients were monitored for up to 2 years, regardless of MG discontinuation. Standard of care visit routine information (clinical characteristics, treatment patterns, response, adverse events, health-related quality of life) were collected.

At the time of this analysis (February 15, 2019), 298 patients were evaluable. The population was predominantly male and white, with a median age of 62 years (Table I). Disease stage at enrollment was recorded for 81% patients, of whom 78% were stage I/II and 4% were stage III/IV. MG in 41% was started <3 months before study enrollment ("newly initiated"), and 93% received prior therapy (84% SDTs, 36% systemics, 32% both).

During MG treatment, 48% used concomitant therapies comprising topical corticosteroids in 24%, phototherapy in 12%, or systemic retinoids in 10% (Table II). Median MG treatment duration was 23.7 months for newly initiated patients vs 32.0 months for those on MG ≥3 months at enrollment. Of the cohort, 79% continued MG at 12 months. Most (75%) applied MG once daily. A dose frequency change occurred during treatment in 63% because of physician decision in 26%, complete response in 7%, or adverse events (AEs) in 20%. Other treatment frequencies were every 2 days in 38%, every 3 days in 16%, once weekly in 9%, and daily Monday through Friday in 10%. Dosing interruption (<3 months) occurred in 29% (median, 10 days). At the time of this analysis, 39% of patients had discontinued MG due to AEs in 9%, complete response in 4%, or physician's decision in 7%.

At least 1 MG-related AE occurred in 44.6%, and 93% of these experienced "skin/subcutaneous tissue disorders" at application site. These included contact dermatitis (mild/moderate) in 12.8%, pruritus in 9.7%, skin irritation in 7.4%, and erythema in 5%. A serious AE occurred in 8%, but none were MG-related.

Our preliminary results for PROVe showed that MG is primarily used in early stage MF-CTCL, at various dosing frequencies, with concomitant therapies, and generally well tolerated. The dermatitis/skin irritation rates were lower than observed in the randomized pivotal trial (Study 201, 14.8% and 25% respectively for gel-treated arm),[4] possibly due to concomitant steroid treatment and/or dosing modifications. Study 201 prohibited topical corticosteroids, but permitted dosing modifications. Additionally, most PROVe patients had been using MG ≥3 months at time of enrollment and thus less likely to experience dermatitis/skin irritation during PROVe than the "newly-initiated." Our observational Phase IV study illustrates the dynamic nature of MG treatment patterns and its reasonable safety profile in the real-world management of MF/CTCL in the U.S.

We acknowledge and thank all patients who enrolled in the trial, the study investigators and coordinators, and Dr Youn Kim (Department of Dermatology, Stanford University, Stanford, CA), who contributed to the study concept and design.

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Table I. Patient characteristics at baseline

Characteristics*	Result (N = 298)		
	At diagnosis	Mechlorethamine gel initiation	PROVe enrollment
Age, y	57.0 (13.0, 88.0)	NC	62.0 (21.0, 90.0)
Male		179 (60.1)	
Race/ethnicity			
White		203 (68.1)	
African American		45 (15.1)	
Hispanic or Latino		29 (9.7)	
Asian		11 (3.7)	
Native Hawaiian/other Pacific Islander		2 (0.7)	
Unknown or ≥2 races/ethnicities		8 (2.7)	
Duration of MF-CTCL, y	NC	2.3 (0.0, 48.2)	2.9 (0.1, 48.3)
Body surface area involvement, %	10.0 (1.0, 33.0)	6.0 (1.0, 99.0)	5.0 (0.0, 90.0)
Disease stage			
IA	105 (35.2)	62 (20.8)	125 (41.9)
IB	75 (25.2)	39 (13.1)	78 (26.2)
IIA	6 (2.0)	5 (1.7)	9 (3.0)
IIB	15 (5.0)	13 (4.4)	19 (6.4)
III	5 (1.7)	4 (1.3)	5 (1.7)
IV	5 (1.7)	5 (1.7)	6 (2.0)
Unavailable	87 (29.2)	170 (57.0)	56 (18.8)
Prior therapies			
Skin-directed therapies		250 (83.9)	
Phototherapy		134 (45.0)	
Radiotherapy		44 (14.8)	
Topical			
Chemotherapy		35 (11.7)	
Corticosteroids		177 (59.4)	
Retinoids		43 (14.4)	
Imiquimod		18 (6.0)	
Other		46 (15.4)	
Systemic therapies		106 (35.6)	
Chemotherapy		27 (9.1)	
Retinoids		74 (24.8)	
HDAC inhibitors		22 (7.4)	
Extracorporeal photopheresis		10 (3.4)	
Other systemic		36 (12.1)	
Skin-directed and systemic therapies		95 (31.9)	

HDAC, Histone deacetylase; *MF-CTCL*, mycosis fungoides-cutaneous T-cell lymphoma; *NC*, not collected; *PROVe*, PROspective, Observational, US-based Study Assessing Outcomes, Adverse Events, Treatment Patterns, and Quality of Life in Patients Diagnosed With Mycosis Fungoides Cutaneous T-cell Lymphoma and Treated With Valchlor®.
*Continuous data are presented as the median (range) and categorical data as number (%).

Ireland[g]; and Helsinn Therapeutics (US), Inc, Iselin, NJ.[b]

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Conflicts of interest: Dr Kim has received grant funding from Helsinn, Galderma, Kyowa Kirin, Medimmune, and Soligenix; consulted for Helsinn and the PROVe Scientific Committee, Galderma, and WebMD; and served on an advisory board for Seattle Genetics. Dr Geskin has received grant funding and has consulted for Helsinn. Dr Guitart has received grant funding and had consulted for Helsinn, received grant funding from Galderma, Medivir, and Soligenix, and has consulted for Miragen and LEO Pharma. Dr Querfeld has consulted for Miragen, Helsinn, Mallinckrodt, Medivir, and Kyowa Kirin and received grant funding from STOP Cancer, the Leukemia & Lymphoma Society, Trillium, and Celgene Corp. Dr Girardi has

Table II. Concomitant therapies, treatment frequency, and adverse events

Concomitant therapy*	During mechlorethamine gel treatment (N = 298)
Skin-directed therapies	124 (41.6)
Phototherapy	35 (11.7)
Radiotherapy	12 (4.0)
Topical	
Chemotherapy	2 (0.7)
Corticosteroids	70 (23.5)
Retinoids	10 (3.4)
Imiquimod	9 (3.0)
Other	21 (7.0)
Systemic therapies	48 (16.1)
Chemotherapy	11 (3.7)
Retinoids	30 (10.1)
HDAC inhibitors	6 (2.0)
Extracorporeal photopheresis	1 (0.3)
Other	19 (6.4)
Dosing frequency†	
Daily	222 (74.5)
5 times a week	30 (10.1)
Every 2 days	112 (37.6)
Every 3 days	49 (16.4)
Once a week	26 (8.7)
Less frequent (monthly, prn, unknown)	34 (11.4)
Patients with dosing interruption‡	87 (29.2)
Average duration of dosing interruption, d	9.7 (1.0, 84.0)
Adverse events	
At least 1 related adverse event reported	133 (44.6)
Dermatitis (all grades)	38 (12.8)
Mild	18 (6.0)
Moderate	14 (4.7)
Severe	6 (2.0)
Not assessed	4 (1.3)
Pruritus	29 (9.7)
Skin irritation	22 (7.4)
Erythema	15 (5.0)
Infections	12 (4.0)

HDAC, Histone deacetylase.

*Categorical data are presented as number (%) and continuous data as median (range).

†Percentages exceed 100% because patients could use a different number of tubes each month or have multiple dosing regimens over time, or both; patients with multiple records for dosing were counted in each relevant category.

‡Dosing interruption is defined as dosing that was stopped and restarted within 3 months.

consulted for Helsinn, Mallinckrodt, Transimmune, and Sanofi and received grant funding from Helsinn, Soligenix, and AbbVie. Dr Musiek has received grant funding and consulted for Helsinn, Elorac, Kyowa Kirin, Soligenix, and Pfizer; served on advisory board for Helsinn, Kyowa Kirin, and Seattle Genetics, and served on a speakers bureau for Helsinn. Mr Mink and Dr Williams are employed by ICON Commercialization & Outcomes. Dr Angello and Dr Bailey are employed by Helsinn Therapeutics (US), Inc.

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Relationship between sociodemographic factors and geographic distribution of pharmacies dispensing isotretinoin in Washington, DC

To the Editor: Prescription of isotretinoin, the standard treatment for severe acne, is regulated by the United States Food and Drug Administration iPLEDGE program, requiring registration by the patient, physician, and pharmacy. Studies demonstrate that iPLEDGE has promoted health care disparities: racial minorities and women are underprescribed isotretinoin and more likely to face delays in treatment.[1] One barrier to treatment is proximity to an iPLEDGE-participating pharmacy. This study analyzed the distribution of iPLEDGE pharmacies in the District of Columbia (DC) and its correlation with sociodemographic factors.

A list of non-iPLEDGE and iPLEDGE pharmacies in DC was obtained from DC.gov and iPLEDGE. Inpatient pharmacies were excluded. To confirm