Original Study

Evaluating Response Trends of Chlormethine/Mechlorethamine Gel in Patients With Stage I-IIA Mycosis Fungoides: Analysis of Individual Patient Data From a Randomized Controlled Phase II Study to Facilitate Optimal Treatment Experiences

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Abstract

This post hoc analysis of data from the pivotal trial investigating chlormethine gel in patients with mycosis fungoides assessed individual patient responses. Different response patterns were seen. Some patients had late or intermittent responses, or responded after initial progressive disease. Occurrence of dermatitis may be associated with early response. These results emphasize the need for continued treatment with chlormethine gel.

Introduction: Chlormethine (CL) gel was approved for treatment of mycosis fungoides based on the pivotal 201 trial (NCT00168064). Data visualization from individual patients is a powerful tool for discovery of hidden treatment trends. Here, we present a post hoc analysis of individual patient data from the pivotal trial to provide a more granular depiction of treatment and response changes over time, with an emphasis on end of treatment status. **Materials and Methods:** Individual patient response data were plotted over a 12-month treatment period to visualize patient experiences while using CL gel. Responder status was assigned according to end-of-treatment Composite Assessment of Index Lesion Severity (CAILS) score, and patients were classified as early (≤4 months) or late responders based on timing of response. Baseline and active treatment characteristics were compared between early and late responders, and baseline body surface area (BSA) was compared between responders and patients with stable or progressive disease. **Results:** Data from 123 patients with baseline and postbaseline results were included. At the end of treatment, 64.2%/55.3% were responders, 30.9%/34.1% had stable disease, and 4.9%/10.6% had progressive disease by CAILS and mSWAT, respectively. Among patients who responded to treatment, 64.6% and 35.4% were early and late responders, respectively. Response pattern analysis also identified patients with an intermittent response or initial progressive disease. Baseline BSA was not associated with responder status. Late responders had longer treatment duration and higher postbaseline plaque elevation, while early responders had a higher frequency of dermatitis. **Conclusions:** Results presented here can facilitate optimal treatment experiences for patients starting CL gel.

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Introduction

Chlormethine (CL) gel was approved for treatment of mycosis fungoides (MF) based on the pivotal 201 trial (NCT00168064).[1] In this randomized, controlled, observer-blinded study, the efficacy, and safety of CL gel was compared with equal-strength CL ointment. The main outcome measure was the overall response rate (ORR) of the intent-to-treat (ITT) population based on Composite Assessment of Index Lesion Severity (CAILS). The ITT population included 130 patients in each treatment arm. The ORR in the CL gel arm was 58.5%, with 76 responders who had a ≥50% reduction from baseline CAILS for at least 2 consecutive visits at any time during the 12-month treatment period.

In a post hoc by-time analysis of the 201 registrations data, response patterns over time were evaluated.[2] This by-time analysis showed the proportion of patients with a response at each visit. Results indicated that there was an increasing response rate over time, with peak response rates of 78.9% and 54.6% after 10 months of treatment for the patients with data and ITT populations, respectively. The analysis also demonstrated that individual patient treatment responses varied over time, with early, late, and intermittent responses observed. Similar results were seen in a by-time retrospective analysis of data from a center of excellence.[3] In this analysis, response rates increased from 45.8% after 180 days to 75% after 720 days.

Data visualization from individual patients is a powerful tool for discovery of hidden treatment trends. In the current post hoc analysis of the 201 study's data, we provide a more granular depiction of treatment and response changes over time with an emphasis on end of treatment status to obtain information on the final patient response disposition after up to 12 months of CL gel treatment. Results increase knowledge of the different patient experiences when treating MF with CL gel and provide insights into methods for optimizing treatment.

Material and Methods

Study Design and Patients

Details of the 201 study's including design, patient population, and interventions have been previously published.[1] The individual patient response data from the 201 study were plotted over the 12-month treatment period to visualize the spectrum of patient experiences while using CL gel.

Only patients with postbaseline CAILS/mSWAT results were included in the current analysis. Of the 130 patients enrolled in the CL gel arm during the 201 study, 2 were never treated with CL gel as they experienced disease progression between screening and baseline and were no longer eligible for the trial. In addition, no postbaseline CAILS/mSWAT data were collected for 5 patients.

Responder status was assigned for each patient according to their end-of-treatment CAILS/mSWAT score. Patients with ≥50% reduction from baseline CAILS/mSWAT were deemed responders, those with <50% reduction to <25% increase in baseline CAILS/mSWAT were considered to have stable disease, and those with ≥25% increase from baseline CAILS/mSWAT were considered to have progressive disease.

In addition, patients were classified based on the timing of response; patients who had a response ≤4 months from treatment start were deemed early responders and those who responded by month 5 or later were considered late responders. The study had a total of 9 visits with most responders occurring early, therefore, the middle month 5 visit and the remaining 4 visits were designated as late responders. This cut-off increased the sample size for the late responders group allowing for a more substantial group comparison. Patients who achieved a response, then lost it for some time, and regained it were classified as intermittent responders.

Statistical Analysis

The proportion of patients with a response, stable disease, or progressive disease were tabulated at each timepoint for the full cohort and for the subgroups of early and late responders using both CAILS and mSWAT separately. Responder status according to the current end-of-treatment response (EOTR) analysis was compared with the study 201 ORR analysis, in which patients were required to have 2 consecutive reductions in CAILS at any time to be considered a responder.

To evaluate if response to CL gel was dependent on baseline disease severity, baseline body surface area (BSA) of disease was used as a surrogate for disease severity. A comparative analysis of baseline BSA of disease was performed between patients with a response, stable disease, or progressive disease using both CAILS and mSWAT separately. Patients with a response, stable disease, or progressive disease were compared using a 2-tailed independent *t* test with equal variance.

Baseline and active treatment analyses of early and late responders' subgroups were performed to evaluate clinical differences between the subgroups. Assessed parameters included age, sex, baseline CAILS/mSWAT score, baseline and postbaseline plaque elevation, baseline BSA of disease, disease stage, treatment length, and adverse events experienced during treatment. Comparisons between early and late responders were analyzed using a 2-tailed independent *t* test with equal variance, a 2-tailed independent *t* test with unequal variance, or a 2-tailed Fisher's exact test, depending on the variable assessed.

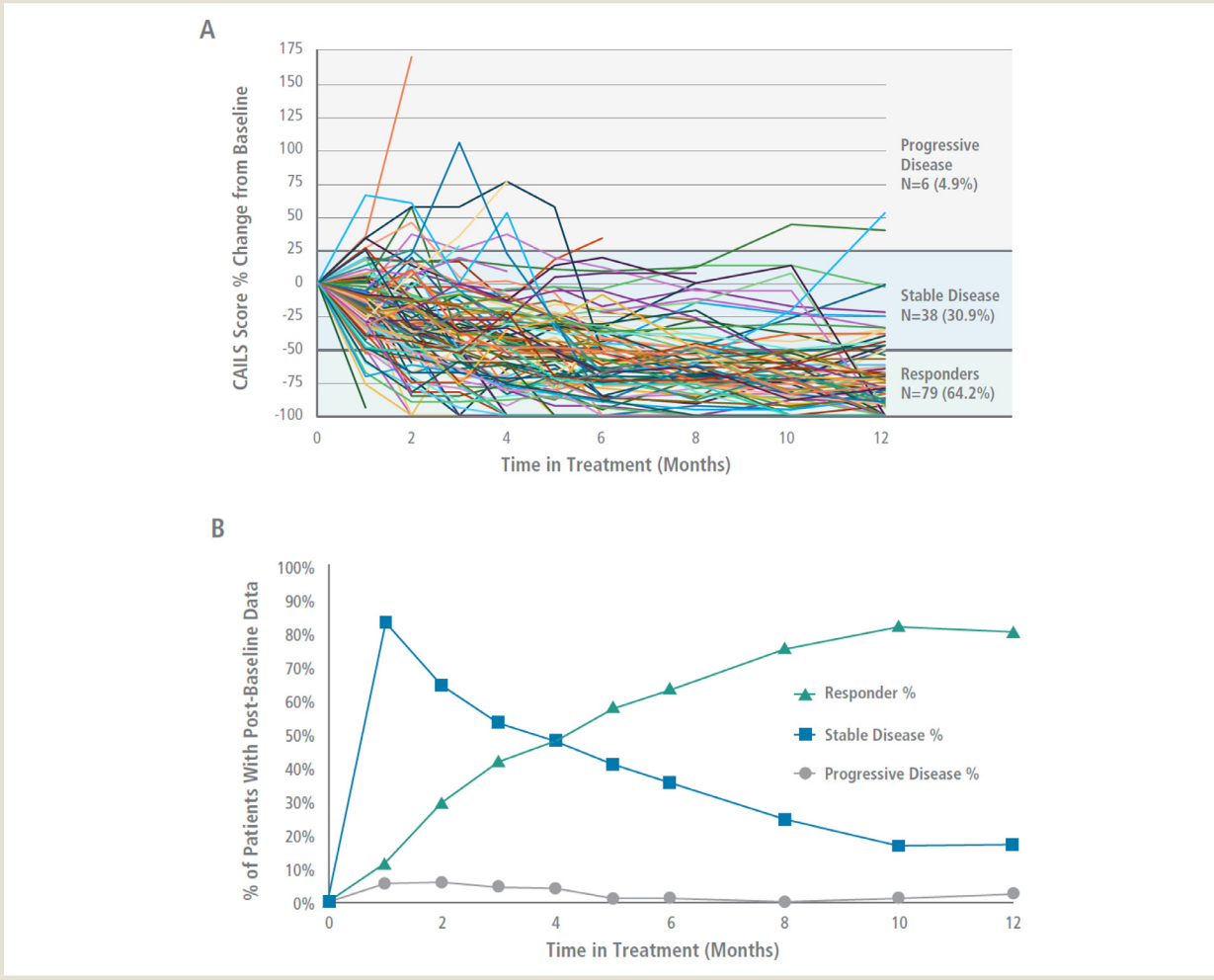
The primary data for this study was CAILS based, therefore, all responder trend graphics are presented using CAILS data. Comparative analyses of early versus late responders and baseline disease severity were completed using both CAILS and mSWAT data separately.

Results

Responder Status and Trends

Data from 123 patients who had both baseline and postbaseline results recorded while receiving treatment with CL gel during the 201 study were included in the analysis. At the end of treatment, 79 (64.2%)/68 (55.3%) patients were clinical responders, 38 (30.9%)/42(34.1%) had stable disease, and 6 (4.9%)/13 (10.6%) had progressive disease by CAILS and mSWAT, respectively. Initial observations of disposition density throughout the treatment interval showed an increase in responder density, along with a decrease in stable and progressive disease density (Figure 1A). This trend was confirmed when results were grouped based on responder status, the percentage of responders increased over time while the proportion

Figure 1 Response trends over time in all patients. Time in treatment versus the change in CAILS score from baseline was plotted for A) each individual patient and B) proportion of patients with a response, stable disease, and progressive disease. CAILS = Composite Assessment of Index Lesion Severity.



of patients with stable disease or progressive disease decreased over time (Figure 1B).

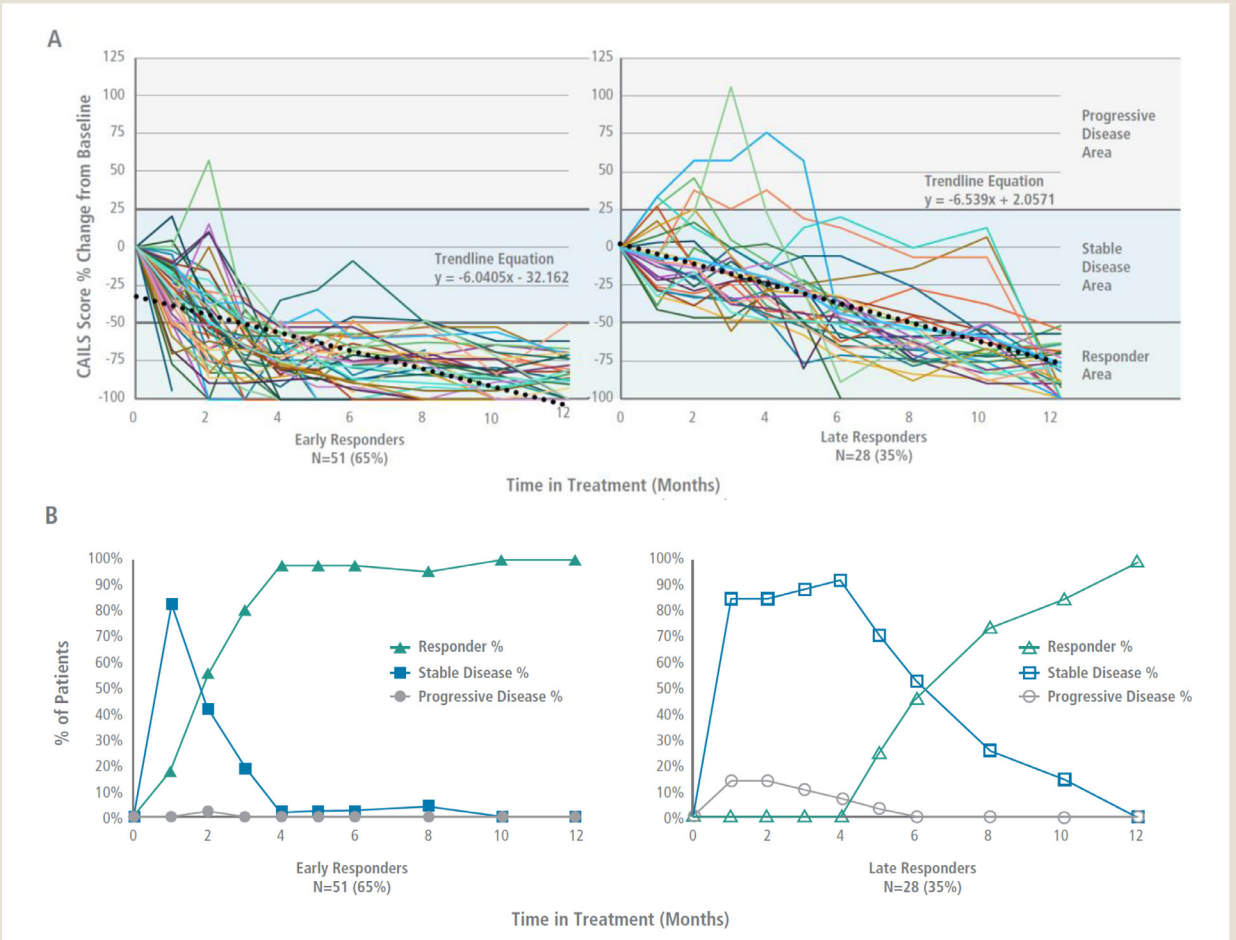
There were nearly twice as many early responders as late responders. Of the 79 patients classified as responders at the end of treatment, 51 (64.6%) and 28 (35.4%) met the definitions for early and late responders, respectively. There were 8 (10.1%) patients who met the definition for intermittent responders; 5 were early responders and 3 were late responders. The early responders spent less time in the stable and progressive disease areas during their treatment course (Figure 2A), indicating that early responders generally kept their response status once reached. This point is further illustrated in Figure 2B, which shows the proportion of patients who were in the responder, stable disease, and progressive disease categories at each timepoint during the study for both the early and late responder subgroups.

The 8 (10.1%) patients with an intermittent response and the 7 (8.9%) patients who initially had progressive disease but became responders by end of treatment are shown in Figure 3. The patients with initial progressive disease made the transition to responder status by month 4 (n = 1), 6 (n = 4), 8 (n = 1), or 12 (n = 1).

Six patients who were counted as confirmed responders in the original study 201 ORR analysis,[1] were considered nonresponders in the current EOTR analysis, while 9 patients who were nonresponders in the study 201 ORR analysis were considered responders in the EOTR analysis (Table 1). All 9 of the patients considered responders in the EOTR analysis were cases of last visit improvements, with 6 of the 9 patients exceeding an 80% improvement in CAILS score from baseline at time of their last visit. The 6 cases considered nonresponders in the EOTR analysis included 4 patients who dipped just below the 50% threshold of a responder by the final visit, 1 patient who was in the stable disease area with a final CAILS change of zero from baseline, and 1 patient who responded initially but had progressive disease by the end of treatment.

Mean baseline BSA was 12.8%/13.6% for responders, 9.4%/8.9% for patients with stable disease, and 15.2%/12.7% for patients with progressive disease using CAILS and mSWAT

Figure 2 Response trends over time in early and late responders. Time in treatment versus the change in CAILS score from baseline was plotted for A) each individual patient and B) proportions of patients with a response, stable disease, and progressive disease. CAILS = Composite Assessment of Index Lesion Severity.



ratings, respectively (Table 2). There was no consistent trend in baseline BSA between the groups, when moving from responders to stable disease and to progressive disease. There were also no significant differences between the groups based on baseline BSA when using CAILS ratings, and a significantly larger BSA for responders versus stable disease patients when using mSWAT ratings ($P = .046$; Table 2).

Early and Late Responder Subgroups

There were no statistically significant differences between the early- and late responder groups with regards to baseline characteristics of age, sex, disease stage, CAILS score, percentage of BSA, and plaque elevation (scored from 0 to 3) using CAILS data. However, there was significantly higher baseline mSWAT ($P = .025$) scores and BSA ($P = .043$) in early versus late responders (Table 3). Patients with a late response had a mean treatment duration that was 13.6%/17.3% longer versus early responders ($P = .008$/$P = .003$; CAILS/mSWAT). Another difference between early and late responders was the postbaseline plaque elevation, which was 45.8%/20.2% higher in the late responder's subgroup compared with early responders ($P = .0004$/$P = .1423$; CAILS/mSWAT). There were no significant differences in the occurrence of pruritus in patients with an early or late response. The proportion of patients with dermatitis was more than 2-fold greater in early responders (49%) versus late responders (21%) ($P = .0181$) using CAILS data, however, this difference was not seen by mSWAT. Another disparity between CAILS and mSWAT data was seen in the erythema differences between early and late responders with a 4-fold greater rate of erythema in late versus early responders by mSWAT ($P = .0269$) with no significant difference by CAILS.

Discussion

Classic ORR analysis for studies with patients with MF, divides the number of patients who have a confirmed response (2 consecutive reductions from baseline in CAILS or modified Severity-Weighted Assessment Tool score of ≥50%) during their treatment course with the number of randomized patients for an ITT analysis, or patients with a minimum amount of postbaseline treatment and

Figure 3 Response trends over time in intermittent responders and patients with initial progressive disease who became responders. Time in treatment versus the change in CAILS score from baseline for each individual patient with an intermittent response (left panel) or with initial progressive disease turned responder (right panel).
CAILS = Composite Assessment of Index Lesion Severity.

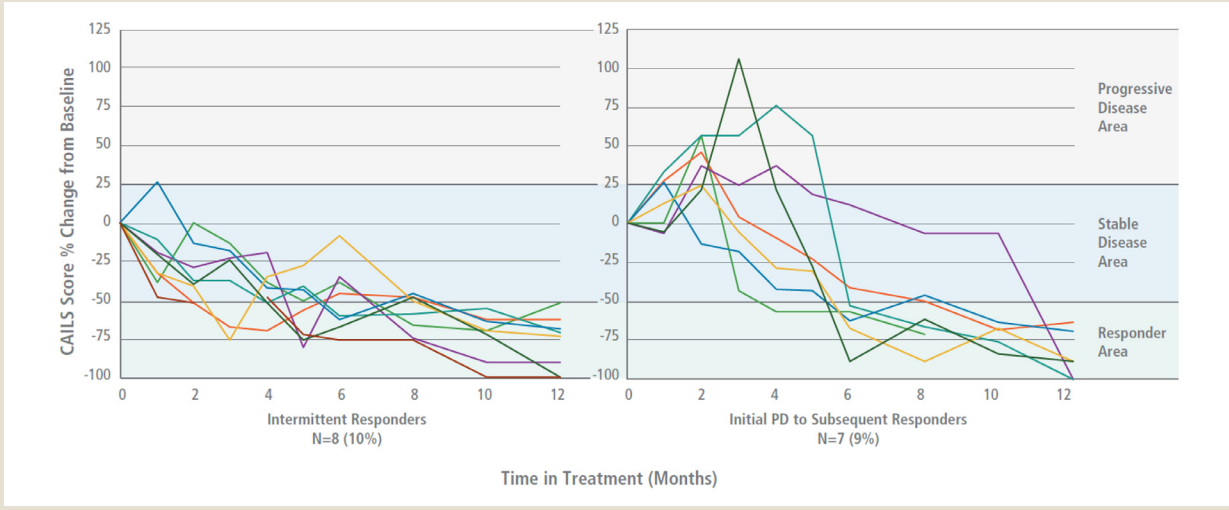


Table 1 Current EOTR Analysis Versus Study 201 ORR Analysis: Responder Status Results

Patient	% Change From Baseline CAILS[a] Scores Per Month									Study 201 ORR Status	EOTR Status
	1	2	3	4	5	6	8	10	12		
	EOTR Responders/ORR Nonresponders										
1	−25.8	−30.3	−24.2	−45.5	−48.5	−43.9	−27.3	−37.9	***−54.5***	NR	R; PR
2	−41	−46.2	−46.2	−30.8	−48.7	***−100***				NR	R; CR
3	−10	***−60***								NR	R; PR
4	17.2	−10.3	***−55.2***	−27.6	−24.1	−20.7	−13.8	6.9	***−93.1***	NR	R; PR
5	−6.3	37.5	25	37.5	18.8	12.5	−6.3	−6.3	***−100***	NR	R; CR
6	−41	15.4	***−51.3***							NR	R; PR
7	33.3	13.3	0	−13.3	13.3	20	0	13.3	***−100***	NR	R; CR
8	***−94.2***									NR	R; PR
9	−29.2	***−83.3***								NR	R; PR
	EOTR nonresponders/ORR responders										
1	4.8	−9.5	***−52.4***	−38.1	***−52.4***	***−85.7***	***−90.5***	***−71.4***	−46.7	R	NR; SD
2	−8.3	−41.7	***−50***	***−50***	−33.3	−33.3	0			R	NR; SD
3	66.7	60	0	53.3	−33.3	***−66.7***	***−60***	−20	53.3	R	NR; PD
4	***−50***	***−55.7***	***−64.3***	***−61.4***	***−70***	***−64.3***	***−57.1***	***−51.4***	−47.1	R	NR; SD
5	−31.3	***−50***	***−50***	−31.3	−37.5	−37.5	−37.5	***−50***	−43.8	R	NR; SD
6	−39.1	−43.5	***−52.2***	−21.7	***−69.6***	***−73.9***	***−73.9***	***−60.9***	−43.5	R	NR; SD

CR = complete response; EOTR = end-of-treatment response; NR = nonresponder; ORR = overall response rate; PD = progressive disease; PR = partial response; R = responder; SD = stable disease.
Bold values represent timepoints when a ≥50% reduction in CAILS was reached.
[a] Results in bold/italics indicate changes where there was a reduction of baseline CAILS of ≥50% (responder status).

data for a typical per protocol analysis. Using the ITT approach can often result in an underestimation of clinical response by including patients who did not receive any treatment and/or had no postbaseline data in the analysis. This was the case for 7 patients who were included in the ORR calculation for the ITT CL gel arm in study 201. In addition, whether an ORR is based on an ITT or per protocol approach, it provides a measure of a patient's best response during the whole treatment interval without insight into whether the best response occurred early or late and if it was maintained or lost.

The present analysis focused on the changing response status of patients with MF treated with CL gel, with an emphasis on the

Table 2 Analysis of Baseline BSA and CAILS/mSWAT Response Categories

	Responders (CAILS N = 79) (mSWAT N = 68)	Stable Disease (CAILS N = 38) (mSWAT N = 42)	Progressive Disease (CAILS N = 6) (mSWAT N = 13)	*P* Value[a]
Baseline BSA percentage, mean/median (range) with CAILS response categories	12.8/7.0 (1-61)	9.4/7.5 (1-34)	15.2/11.0 (2-41)	R vs. SD: $P = .146$
				R vs. PD: $P = .671$
				SD vs. PD: $P = .161$
Baseline BSA percentage, mean/median (range) with mSWAT response categories	13.6/8.5 (1-61)	8.9/5.0 (1-34)	12.7/9.0 (1-41)	**R vs. SD: $P = .046$**
				R vs. PD: $P = .824$
				SD vs. PD: $P = .208$

BSA = body surface area; CAILS = Composite Assessment of Index Lesion Severity; PD = progressive disease; R = responder; SD = stable disease.
Bold values represent timepoints when a ≥50% reduction in CAILS was reached.
[a] Calculated with independent t-test, 2-tailed, equal variances.

end of treatment disposition. The EOTR CAILS analysis resulted in 79 responders, compared with 76 in the original study 201 ORR CAILS analysis. Nine patients who were considered nonresponders in the ORR analysis were responders in the EOTR analysis, and 6 patients considered responders in the ORR analysis were nonresponders in the EOTR analysis. Most noteworthy among these status changes were the 2 patients in the original ORR analysis counted as responders, with 1 returning to baseline and another becoming progressive disease by the end of the study. The EOTR analysis puts these patients more appropriately in stable and progressive disease categories, respectively. In addition, the 6 patients with end of treatment ≥80% improvements in CAILS that went undetected in the original analysis, and are appropriately credited as responders using the EOTR method. These results emphasize that design of clinical trial endpoints can sometimes conceal important findings at the end of treatment. The current data visualization technique could be an informative and complementary secondary endpoint to an ORR analysis, to evaluate the dynamic response behavior to treatment for MF.

The EOTR analysis showed higher CAILS/mSWAT response rates of 64.2%/55.3% for patients who had both baseline and postbaseline data and received treatment. The CAILS response patterns seen for patients with postbaseline data while on treatment with CL gel included early responders (65%), late responders (35%), intermittent responders (10%), and initial progressive disease to subsequent responders (9%). The time in treatment plots for these different patterns all emphasized the importance of maintaining patients on treatment longer term (≥6 months) before making a definitive evaluation of the response potential of CL gel in early stage MF patients. After 6 months of treatment with CL gel, the proportion of responders was higher than the proportion of combined stable and progressive disease across all reponse patterns seen in the CAILS analyses. This conclusion is consistent with the data from the current analysis as well as the by-time responder rate analyses previously reported.[2,3]

In order to evaluate if a response to CL gel was dependent on baseline disease severity, baseline BSA scores were compared between CAILS responder, stable disease, and progressive disease groups. No significant differences were detected. A similar analysis was conducted using mSWAT response data that showed a significantly larger BSA for responders versus stable disease patients ($P = .046$; Table 2). Overall, CL gel responder status remained neutral by CAILS and had a positive association by mSWAT in patients with larger baseline disease severity. These data support the use of CL gel for the full range of up to 79% BSA of disease for all IA and IB patients consistent with its labeling, and NCCN guidelines that recommend CL gel for generalized skin involvement.[4]

There were no differences between early and late responders with regards to baseline characteristics for CAILS, while there was significantly higher baseline mSWAT scores and BSA for early versus late responders (Table 3). In addition, mSWAT analysis showed significantly higher baseline BSA in the responders versus stable disease patients (Table 2). While there are differences in these CAILS and mSWAT results, taken together there is a neutral to positive association between responder status and baseline BSA in addition to earlier responder status. Thus, the data overall supports the use of CL gel in patients with a wide range of BSA. Late responders did have a significantly longer treatment duration and a higher postbaseline plaque elevation for both CAILS and mSWAT, emphasizing the need for longer duration of treatment with CL gel before realizing a patient's best response in patients with thicker plaques. Investigators appear to have selected thicker plaques for the CAILS index lesions giving more opportunity to observe a difference than with the overall plaque assessment captured by mSWAT. This may explain why there was a greater difference in late versus early plaque elevation scores for CAILS (45.8%) versus mSWAT (20.2%). In any case, both CAILS and mSWAT analyses of plaque elevation in early versus late responders moved in the same direction. The occurrence of pruritus during treatment was similar in early and late responders. Dermatitis occurred significantly more often in early responders than in late responders by CAILS, but not confirmed in the mSWAT data. While the reason for this discrepancy is unknown, the CAILS observation appears to be consistent with a prior report from Kim et al. in which patients with brisk local contact reactions were more likely to have earlier complete clearance.[5] In addition, this aligns with the concept of beneficial immunomodulation in the cutaneous microenvironment with exposure to topical CL.[6] Nonallergic contact dermatitis occurring with CL gel has been shown to be effectively managed with medium potency topical corticosteroids use without interfering with clinical response.[7] Erythema

Table 3 Baseline and Active Treatment Characteristics of Early and Late Responders (CAILS/mSWAT)

Characteristic	*CAILS*			*mSWAT*		
	Early Responders (N = 51)	Late Responders (N = 28)	*P* Value[a]	Early Responders (N = 44)	Late Responders (N = 24)	*P* Value[a]
Baseline characteristics						
Age (years), mean/median (range)	53/55 (24-83)	52/53 (25-80)	$P = .636^1$	55/58 (24-83)	55/55 (25-80)	$P = .935^1$
Sex, n (%)			-			-
Male	29 (57)	14 (50)		25 (57)	11 (46)	
Female	22 (43)	14 (50)		19 (43)	13 (54)	
Disease stage, n (%)			-			-
IA	29 (57)	17 (61)		20 (45)	18 (75)	
IB	22 (43)	11 (39)		24 (55)	6 (25)	
CAILS/mSWAT score, mean/median (range)	33.6/36.0 (2-68)	40.0/33.5 (15-74)	$P = .100^1$	19.8/12.0 (1-104)	10.8/7.0 (2-46)	**$P = .025^2$**
BSA percentage, mean/median (range)	13.4/7.0 (1-61)	11.4/7.5 (2-36)	$P = .468^2$	15.7/11.0 (1-61)	9.7/6.5 (2-32)	**$P = .043^2$**
Plaque elevation score (0-3), mean/median (range)	0.477/0 (0-3)	0.409/0 (0-3)	$P = .405^1$	0.506/0 (0-3)	0.351/0 (0-2)	$P = .104^1$
Active treatment characteristics						
Treatment length (days), mean/median (range)	317/363 (27-403)	360/366 (198-397)	**$P = .008^2$**	312/364 (27-403)	366/365 (350-397)	**$P = .003^2$**
Postbaseline plaque elevation score (0-3), mean/median (range)	0.120/0 (0-3)	0.175/0 (0-2)	**$P = .0004^1$**	0.114/0 (0-3)	0.137/0 (0-2)	$P = 0.1423^1$
Patients with pruritus, n (%)	14 (27.5)	7 (25.0)	$P = 1.000^3$	8 (18.2)	4 (25.0)	$P = 0.5415^3$
Mild	10 (19.6)	3 (10.7)		6 (13.6)	2 (16.7)	
Moderate	4 (7.8)	2 (7.1)		2 (4.5)	2 (8.3)	
Moderately severe	0	2 (7.1)		0	0	
Severe	0	0		0	0	
Patients with dermatitis, n (%)	25 (49.0)	6 (21.4)	**$P = .0181^3$**	13 (29.5)	7 (29.2)	$P = 1.000^3$
Mild	9 (17.6)	5 (17.9)		9 (20.5)	5 (17.9)	
Moderate	5 (9.8)	1 (3.6)		3 (6.8)	1 (3.6)	
Moderately severe	10 (19.6)	0		0	0	
Severe	1 (2.0)	0		1 (2.3)	0	
Patients with erythema, n (%)	12 (23.5)	8 (28.6)	$P = .7873^3$	3 (6.8)	7 (29.2)	**$P = .0269^3$**
Mild	5 (9.8)	2 (7.1)		2 (4.5)	5 (20.8)	
Moderate	1 (2.0)	3 (10.7)		1 (2.3)	2 (8.3)	
Moderately severe	6 (11.8)	3 (10.7)		0	0	
Severe	0	0		0	0	

BSA = body surface area; CAILS = Composite Assessment of Index Lesion Severity; mSWAT = Modified Severity Weighted Assessment Tool.
[a] Calculated with 1: independent *t* test, 2 tailed, equal variances; 2: independent *t* test, 2-tailed, unequal variance; 3: Fisher's exact test, 2-tailed.

occurred more frequently in late responders by mSWAT, but not confirmed by CAILS, so overall erythema may be of greater concern with longer duration of treatment.

The main limitation of the current analysis was its retrospective nature. Several changes in responder's status was seen at the end of treatment or end of study. Longer follow-up duration could have provided a clearer image of response over time.

Conclusions

The data presented here increase knowledge of different patient experiences when treating MF with CL gel and provide insights into methods for optimizing treatment. Different response patterns were seen when treating patients with CL gel. Time in treatment plots for the full set of patients with post baseline data or various subgroups of early and late responders, intermittent responders and initial progressive disease to responders show the importance of maintaining patients on treatment longer term (≥6 months) before making a definitive evaluation of the response potential of CL gel in early stage MF patients. CL gel was an effective treatment even for patients with high baseline BSA involvement consistent with product labeling and NCCN guidelines for patients with stage IA/IB MF. Dermatitis may be seen more commonly in early responders. Proper management of dermatitis is vital to maintain patients on treatment.

Clinical Practice Points

- Treatment with chlormethine gel was effective and had a good safety profile in patients with early-stage mycosis fungoides, as seen in the pivotal 201 study.
- Individual patient response data assessed in the current study showed varied response patterns. While the majority of patients were early responders (within 4 months of treatment), others responded late, had intermittent responses, or had progressive disease early during treatment before responding.
- The adverse event of dermatitis may be seen more commonly in patients with an early response, while erythema may be seen more commonly in patients with a later response.
- In patients with larger baseline disease severity using BSA as a surrogate, CL gel responder status remained neutral by CAILS, but had a positive association and occurred earlier by mSWAT, supporting the use of CL gel in patients with a wide range of BSA.
- Continued treatment ≥6 months with chlormethine gel is important to achieve the best possible response to treatment.
- Together the observations presented herein can facilitate optimal treatment experiences for patients initiating chlormethine gel treatment.

Disclosure

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