Post hoc Analysis of a Randomized, Controlled, Phase 2 Study to Assess Response Rates with Chlormethine/Mechlorethamine Gel in Patients with Stage IA–IIA Mycosis Fungoides

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Abstract

Background: Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma. Patients can be treated using chlormethine gel, a skin-directed therapy developed and approved for MF. In the randomized, controlled 201 trial, chlormethine gel was found to be noninferior to equal-strength chlormethine ointment. However, there remains a need to gain more insight into outcome measures after treatment. Objective: The aim of this study was to further investigate the potential of chlormethine gel treatment through a novel post hoc analysis of the 201 trial data (NCT00168064). Methods: Patients were randomized to chlormethine gel or ointment; response assessments included Composite Assessment of Index Lesion Severity (CAILS) and total body surface area (BSA). In this post hoc analysis, additional subgroup response analyses were performed for stage IA/IB–IIA MF. Very good partial response (75 to <100% improvement) was included as an additional response category. Time to response and overall response trends were determined. Finally, multivariate time-to-event analyses were performed to determine whether associations were observed between treatment frequency, response, and adverse events. Results: Response rates were significantly higher for patients with stage IA MF for CAILS (intent-to-treat [p = 0.0014] and efficacy-evaluable [EE; p = 0.0036] populations) and BSA (EE population [p = 0.0488]) treated with gel versus ointment. Time to first CAILS response and response trends were better for all-stage gel-treated patients overall. No association was seen between treatment frequency and response or occurrence of adverse events at the following visit. An association was observed between the occurrence of contact dermatitis and improved clinical response at the next visit (p = 0.0001). Conclusion: This post hoc analysis...
shows that treatment with chlormethine gel may result in higher and faster response rates compared with chlormethine ointment, which confirms and expands results reported in the original analysis. The incidence of contact dermatitis may potentially be a prognostic indicator for clinical response; this needs to be confirmed in a larger population.

Introduction

Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma, which represents a heterogeneous group of lymphoproliferative diseases [1]. MF is characterized by malignant T-cell proliferation in the skin; these are generally CD4+ memory T cells that express skin-homing receptors [2, 3]. Early stage (IA–IIA) MF can be difficult to diagnose, and diagnosis is delayed in the majority of patients (86%) for a median of 36 months [4].

Treatment for MF is generally focused on control of cutaneous lesions, preventing disease progression, and improving quality of life [5–7]. For patients with early-stage disease, international guidelines recommend using skin-directed therapies (SDTs), while for more advanced stages a combination of SDT and systemic therapy is advised [5–7], although there is substantial treatment heterogeneity in advanced MF [8].

Chlormethine (also known as mechlorethamine) is an SDT currently included in international guidelines [5–7] for use in adult patients with MF as first-line therapy. Chlormethine functions as an alkylating agent and induces DNA damage resulting in the inhibition of proliferating cells [9]. A topical chlormethine 0.016% w/w gel (equivalent to 0.02% chlormethine HCl) was developed and approved on the basis of results from the 201 registration study (NCT00168064) and the 202 extension study (NCT00535470) [10–12]. It is currently approved in the USA (since 2013) [10] and Israel (since 2016) for treatment of patients with stage IA–IB MF who have received prior SDT. Chlormethine gel was also approved for treatment of MF in the EU in 2017 [13].

Earlier formulations of chlormethine were aqueous or compounded ointment based [14, 15], had limited stability and lacked rigorous quality control, and presented challenges for patients with regard to application and preparation. In addition, there are only a limited number of compounding pharmacies, and the resulting formulations may vary in the concentration of active drug. In contrast, chlormethine gel is an optimized, stable, nongreasy, quick-drying formulation that allows for convenient, simple at-home administration, thereby encouraging patient compliance.

The pivotal 201 trial, one of the largest randomized, controlled, phase 2/3 studies ever conducted in patients with MF (n = 260), compared chlormethine gel with equal-strength compounded ointment. The primary efficacy endpoint was the Composite Assessment of Index Lesion Severity (CAILS) score, and chlormethine gel met all prespecified criteria for noninferiority to chlormethine ointment [11]. CAILS response rates for chlormethine gel were consistently higher than for ointment in both the intent-to-treat (ITT) and efficacy-evaluable (EE; patients who were treated for ≥6 months) populations [11].

There is still an unmet need to understand the efficacy and response patterns of chlormethine gel in more detail and to evaluate how to best manage patients with MF receiving chlormethine gel. The original study 201 analysis did not directly compare response rates for gel and ointment since it was designed to determine noninferiority of the gel compared to the ointment only. To provide further insight into the potential of chlormethine gel treatment, a set of post hoc analyses was designed. In the original 201 study analysis, response rates were defined per standard oncology criteria; complete response (CR) was defined as 100% skin clearance, with a CAILS or Modified Severity-Weighted Assessment Tool (mSWAT) score of 0, and partial response (PR) as 50 to <100% reduction from the baseline score [16]. Although these classic definitions of CR and PR are widely used in clinical practice, a more detailed assessment of PR would allow for more precise evaluation of patients who achieve relevant clinical improvement. In the new post hoc analyses presented here, an additional response category of very good partial response (VGPR) was also considered, defined here as 75 to <100% reduction from the baseline score [17].

The examination of response over time in the original 201 analysis required that the confirmed response lasted for 2 or more consecutive visits over at least 4 weeks. This requirement highlighted the stable responses over time but did not allow for full appreciation of the response rate over time, since patients who had a response at the end of the study period may have been excluded from the analysis.

Only responses that were confirmed over 2 consecutive visits during the 12-month study period were included. In addition, while the original 201 analysis touched on assessing CAILS response rates by disease stage, expanding these analyses may provide further understanding of the efficacy of chlormethine gel compared with ointment. To better understand the relationship between the fre-
Frequency of gel application and adverse events (AEs) or CAILS responses, analyses were performed with the aim of providing useful insights for physicians involved in treatment management.

Consequently, we performed a post hoc analysis of the 201 study focused on analyzing the efficacy data in more detail. Different statistical approaches were applied to the data, reporting each visit outcome as a separate time point. Furthermore, the post hoc analysis compared CAILS, mSWAT, and total body surface area (BSA) involvement for patients with stage IA or IB–IIA MF treated with chlormethine gel or ointment. Patients were recategorized as having CR, VGPR, or PR and time-trend analyses were performed to highlight the responses with chlormethine gel and ointment. In addition, this post hoc analysis investigated whether associations were observed between chlormethine gel treatment frequency and clinical response or the occurrence of any skin-related AEs, or between the occurrence of contact dermatitis and response.

### Materials and Methods

**Patients and Study Design**

The randomized, controlled, observer-blinded, multicenter 201 trial compared daily treatment with 0.02% chlormethine gel to equal-strength chlormethine ointment in 260 patients with MF. Study design details have been previously published [11]. The primary endpoint of study 201 was response as defined by ≥50% improvement in baseline CAILS for 2 or more consecutive visits. Secondary endpoints included ≥50% improvement in mSWAT scores and the time to CAILS response.

Chlormethine gel or ointment was applied once daily for up to 12 months. In case of skin-related AEs, treatment frequency was reduced temporarily as per protocol. When patients experienced grade 3 AEs, treatment frequency could be temporarily reduced or suspended. If the AE improved to grade 2 or lower, treatment frequency could be increased again as tolerated. When patients experienced grade 4 AEs, treatment was discontinued until the AE improved to grade 2 or lower, after which treatment could be restarted at a decreased frequency and increased as tolerated.

Tumor response and AEs were assessed every month between months 1–6 and every 2 months between months 7–12. Response was assessed using CAILS, mSWAT, and BSA involvement. CAILS is a method of index lesion scoring for patch/plaque disease considering erythema, scaling, plaque elevation, hypo- or hyperpig-

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*BSA results were collected in the case report forms in the original 201 study report. AE, adverse event; BSA, body surface area; CAILS, Composite Assessment of Index Lesion Severity; CR, complete response; GEE, generalized estimating equation; GLIMs, generalized linear models; mSWAT, Modified Severity-Weighted Assessment Tool; PR, partial response; VGPR, very good partial response.*
mentation, and lesion size [16]. For all patients, up to 5 index lesions were identified at baseline and assessed throughout the study. The mSWAT is calculated by multiplying the BSA of each lesion type in 12 different areas of the body with a weighting factor (patch = 1, plaque = 2, and tumor = 4) [16]. Total BSA involvement can also be determined without weighting factors.

**Statistical Methods**

The main outcome measures for the original study 201 analysis and the post hoc analysis are listed in Table 1. Details of the applied statistical methods are presented in online supplementary Table S1 (see www.karger.com/doi/10.1159/000516138 for all online suppl. material).

**Subgroup Analyses**

Subgroup analyses for CAILS, mSWAT, and BSA response data were done for patients with stage IA and stage IB–IIA MF in both the ITT and EE populations. The response variable used in this analysis was the proportion of response, defined as PR or better, at the final study visit. CR was defined as 100% improvement (with a score of 0), PR as a 50 to <75% reduction from the baseline score, and VGPR as a 75 to <100% reduction from the baseline score. The subgroup analyses were performed using generalized linear models (GLIMs) with logit link function and binomial distribution [18]. Treatment, disease stage, and treatment-by-disease-stage interaction were used as fixed effects. Missing values were imputed using 50-fold multiple imputation by fully conditional specification methods. Each of the 50 imputed datasets was analyzed by GLIM models and final estimates were combined with Rubin’s rule using the MI and MIANALYZE procedures of SAS software (SAS Institute, Inc., Cary, NC, USA) [19].

**Time-to-Response Analysis**

The time to response in the ITT population was estimated using Kaplan-Meier curves with an event being defined as the first occurrence of a CAILS response; for these analyses, different curves were produced on the basis of response being defined as either “CR only,” “at least VGPR” (i.e., CR or VGPR), or “at least PR” (i.e., CR or VGPR or PR). Patients treated with chlormethine gel and ointment in the ITT population were compared with the log-rank test by using the LIFETEST procedure of SAS software [20].

**Time-Trend Analyses**

Trend analysis was performed in both the ITT and EE populations using generalized estimating equation (GEE) models with logit link function and binomial distribution. Baseline scores, treatment, visit, and treatment-by-visit interaction were applied as model fixed effects. The variance-covariance matrix of the GEE model, which takes into account correlation across repeated measures, was parameterized using the first-order autoregressive form. The weighted GEE method was applied to accommodate missing responses. The estimates of the linear component of the response time profiles were computed using proper contrasts applied on the treatment-by-visit interaction and were used to test the differences between the treatment arms. Quasimaximum likelihood estimates of the model parameters were obtained with the GEE procedure of SAS software [21]. Results are reported as model-based estimates with standard errors. The CAILS response trend over time was compared between patients treated with chlormethine gel and ointment; response was defined as CR only, at least VGPR, or at least PR.

**Multivariate Time-to-Event Analysis**

Multivariate time-to-event analyses were employed to test the association between potential predictors (covariates) and events of interest that may occur multiple times in the same patient (e.g., occurrence of AEs or response) and were performed using the safety population of the chlormethine gel arm (n = 128). Multivariate time-to-event data were analyzed using the semiparametric proportional means model [22] implemented in the PHREG procedure of SAS software. This statistical model is also able to accommodate so-called time-dependent covariates (e.g., treatment frequency or occurrence of dermatitis), that is, dynamic covariates that can change value or status over time within the same patient. Results are reported as hazard ratios with associated 95% confidence intervals.

**Results**

**Patients**

In total, 260 patients were enrolled in study 201; 130 were randomized to the chlormethine gel and ointment arms each. The ITT population in the post hoc analysis included 129 patients from the gel arm and 127 patients from the ointment arm; 4 patients did not receive chlormethine treatment and were excluded. The EE population consisted of 90 patients from the gel arm and 95 from the ointment arm.

**Response by Disease Stage**

During study 201, chlormethine gel or ointment was applied once daily for up to 12 months. Tumor response was assessed every month between months 1–6 and every 2 months between months 7–12 using 3 response measures: CAILS, mSWAT, and BSA involvement. For CAILS, the response rates in the ITT population were higher in patients treated with chlormethine gel compared with ointment for both stage IA and stage IB–IIA patients (Table 2); this difference was significant only for patients with stage IA MF, with response rates of 79.8% for chlormethine gel versus 49.2% for ointment (p = 0.0014). Similar results were seen for CAILS in the EE population, with chlormethine gel-treated patients showing higher response rates than patients treated with ointment. The difference was significant for stage IA patients (p = 0.0036), with response rates of 82.3 and 51.4% for chlormethine gel and ointment, respectively. The CAILS response distribution for each visit is listed in online supplementary Table S2.
The post hoc analysis mSWAT response rates were higher for stage IA patients treated with chlormethine gel compared with ointment for both the ITT and EE populations, although these differences were not significant (Table 2). mSWAT results for patients with stage IB–IIA were comparable between gel and ointment.

The post hoc analysis showed that BSA response rates were higher with chlormethine gel compared with ointment in patients with stage IA in both the ITT and EE populations. The difference was significant for the EE population ($p = 0.0488$; Table 2).

**Table 2. Clinical response (≥50% improvement in skin score) by MF stage in the original and post hoc analyses of the 201 study data**

<table>
<thead>
<tr>
<th></th>
<th>ITT population</th>
<th></th>
<th>EE population</th>
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<tr>
<td></td>
<td>CL gel</td>
<td>CL ointment</td>
<td>$p$ value</td>
<td>CL gel</td>
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<td><strong>CAILS, %</strong></td>
<td></td>
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<tr>
<td>Original analysis*</td>
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<tr>
<td>Stage IA</td>
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<td>40.0</td>
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<tr>
<td>Stage IB–IIA</td>
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<td>55.4</td>
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<td>73.2</td>
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<tr>
<td>Post hoc analysis</td>
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<tr>
<td>Stage IA</td>
<td>79.8</td>
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<td>82.3</td>
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<tr>
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<td>59.6</td>
<td>0.0785</td>
<td>79.5</td>
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<tr>
<td><strong>mSWAT, %</strong></td>
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<tr>
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<td>36.9</td>
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<tr>
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<td>55.4</td>
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<td>36.9</td>
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<td>58.9</td>
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<tr>
<td><strong>BSA, %</strong></td>
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<tr>
<td>Post hoc analysis</td>
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<tr>
<td>Stage IA</td>
<td>49.5</td>
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<td>0.0934</td>
<td>56.4</td>
</tr>
<tr>
<td>Stage IB–IIA</td>
<td>47.2</td>
<td>50.3</td>
<td>0.7648</td>
<td>49.4</td>
</tr>
</tbody>
</table>

* The original study 201 analysis was based on noninferiority. BSA, body surface area; CAILS, Composite Assessment of Index Lesion Severity; CL, chlormethine; EE, efficacy-evaluable; ITT, intent-to-treat; MF, mycosis fungoides; mSWAT, Modified Severity-Weighted Assessment Tool; N/A, not available.

**Time to Response**

When comparing the time to CAILS response between chlormethine gel and ointment in the ITT population, a difference was evident in the time-to-response curves when response was defined as CR only; the time to response appeared to be shorter for chlormethine gel-treated patients, but this difference was not statistically significant ($p = 0.2678$; Fig. 1a). When response was defined as at least VGPR, the difference between chlormethine gel- and ointment-treated patients was significant ($p = 0.0107$; Fig. 1b), in favor of patients treated with chlormethine gel. The difference in time to response was also significant when response was defined as at least PR ($p = 0.0419$; Fig. 1c).

**Trend Analyses**

Trend analyses were performed in order to better understand the strength of response to chlormethine gel versus ointment. These comparisons take into account responses evaluated on all visits rather than requiring response to be defined as improvement over 2 consecutive visits. In the ITT population, responses with chlormethine gel were higher than those with chlormethine ointment (Fig. 2a) and this difference was statistically significant when response was defined as at least VGPR ($p = 0.0420$) or as at least PR ($p = 0.0013$). Similar results were observed in the EE population (Fig. 2b), where the difference between patients treated with gel and ointment was close to significant when response was defined as at least VGPR ($p = 0.0605$), and significant when response was defined as at least PR ($p = 0.0030$).
Fig. 1. Time to first occurrence of Composite Assessment of Index Lesion Severity (CAILS) response in patients in the intent-to-treat (ITT) population treated with chlormethine gel or ointment for patients with complete response (CR) (a), at least very good partial response (VGPR) (b), and at least partial response (PR) (c).
Multivariate Time-to-Event Analysis
The effect of treatment frequency on the occurrence of skin-related AEs at each following visit was determined by comparing patients using chlormethine gel on a daily basis with those using it less frequently. Skin-related AEs relevant for this post hoc analysis included contact dermatitis, erythema, folliculitis, pruritus, skin hyperpigmentation, and skin irritation. The total number of skin-related AEs that occurred in the analyzed population was 64; these occurred in 45 patients in total: 30 (67%) had 1
Fig. 3. Associations between chlormethine gel application frequency and the occurrence of adverse events (a), chlormethine gel application frequency and Composite Assessment of Index Lesion Severity (CAILS) response (b), and the occurrence of dermatitis and CAILS response (c). HR, hazard ratio; CI, confidence interval.
AE, 11 (24%) had 2 AEs, and 4 (9%) had 3 AEs. Eight cases of contact dermatitis occurred. The analysis did not demonstrate an association between the frequency of chlormethine gel application and the occurrence of skin-related AEs \((p = 0.8514; \text{Fig. 3a})\). The potential effect of application frequency of chlormethine gel on CAILS response at the following visit was also assessed. The analysis did not demonstrate an association between the frequency of chlormethine gel application and occurrence of a CAILS response \((p = 0.8850; \text{Fig. 3b})\). Finally, the association between the occurrence of contact dermatitis and CAILS response at the following visit was investigated. This analysis showed an association between the occurrence of contact dermatitis and an improved clinical response at the next visit \((p = 0.0001; \text{Fig. 3c})\).

**Discussion**

The presented post hoc analysis shows that treatment with chlormethine gel may result in higher response rates than treatment with chlormethine ointment in patients with stage IA MF. According to stage stratification, CAILS (ITT and EE populations) and BSA response rates (EE population) were significantly higher for chlormethine gel compared with ointment. BSA results were collected in the case report forms in the original 201 study report [11], but had not previously been reported. We chose to report the BSA response analyses here, as it is an important clinical indicator regularly recorded in clinical practice. A prospective observational study examining real-world experience with chlormethine gel (PROVe) [23] used the percentage change in BSA as a clinical outcome measure [24]. Overall, the stage stratification data reinforce the concept that chlormethine gel is a valid first-line treatment option, especially for early-stage MF.

The time to first CAILS response in the ITT population was shorter in patients treated with chlormethine gel compared with ointment; this difference was significant when CAILS response was defined as at least VGPR or at least PR. The time-trend analyses confirmed that higher CAILS response rates were seen over time with chlormethine gel.

PR as defined in the original 201 analysis included a broad range of responses between 50 and <100% improvement. In that analysis, only 18 patients in the ITT population had a CR, while 58 had PR after chlormethine gel treatment [11]. In this post hoc analysis, 24 patients had a VGPR and 31 had a PR at the month 10 visit. VGPR could be particularly interesting from a clinical point of view to further define the level of response in MF.

The efficacy results seen in the current post hoc analysis indicate that there may be a benefit to using chlormethine gel over chlormethine ointment for patients with MF. Chlormethine gel may also be easier to apply for patients. Nonadherence to treatment has been observed with chlormethine ointment due to greasiness of ointment-based preparations [25, 26]. In contrast, chlormethine gel is nongreasy and quick to absorb.

The multivariate time-to-event analyses showed that there was no clear association between treatment frequency and the development of skin-related AEs or clinical response at the next visit. This indicates that reducing the frequency of chlormethine gel application might not affect the possibility of developing skin-related AEs. In addition, it might be possible to be more flexible with chlormethine gel treatment schedules, reducing the application frequency from once daily on the basis of individual patient characteristics and needs, without impacting the efficacy of the treatment. This should be investigated further to determine the effect of reduced treatment frequency on the overall response. The presence of stimulated T cells in the environment and background inflammation could be partially responsible for no clear association existing between lower treatment frequency and occurrence of AEs. This observation also fits with real-world evidence from the recent PROVe study, where patients had a greater variation in treatment schedules with chlormethine gel than study 201. Even with this dose flexibility, patients still had good responses during the PROVe study, and the peak of response (67%) was seen after 18 months of treatment [27]. In addition, differently from study 201, lower rates of AEs were seen in the PROVe study, although this could partly be due to the different dose regimen used, and to the concomitant use of corticosteroids in clinical practice, a method employed by clinicians to help manage skin reactions [23]. These results could suggest that, independently of treatment frequency, continued use of chlormethine gel over time may still be beneficial in many cases [28]. An association was observed between the occurrence of contact dermatitis at the previous visit and response at the following visit, which may imply that development of contact dermatitis after chlormethine gel treatment may be a predictor of response. A similar observation has been made with topical chlormethine previously, where patients who had a brisk local contact reaction could have earlier complete clearance [25]. This association between contact dermatitis and response is of interest to clinicians and warrants

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further investigation. It will be explored in the REACH study (NCT04218825), which will compare response rates in patients with and without skin-related reactions after chlormethine gel application. Future research on the link between contact dermatitis and response should also analyze the etiology of the dermatitis in more detail.

The current results were analyzed post hoc as well as found within the context of a controlled clinical trial. Therefore, the data presented here have the limitation of only referring to the specific criteria of the 201 study, such as patients not being allowed concomitant treatment, including corticosteroids; a controlled treatment application schedule; and limited duration of patient monitoring (12 months). A real-world study of chlormethine gel usage has shown that it is often used together with other treatment options and can be used less frequently than once daily [23, 27].

In conclusion, results from the post hoc analysis of the 201 study data described herein suggest that treatment with chlormethine gel may result in higher and faster response rates than treatment with chlormethine ointment. These data confirm and expand on the noninferiority results reported in the original 201 study analysis [11]. Moreover, our data suggest that contact dermatitis might be a prognostic factor for clinical response to chlormethine gel. Finally, preliminary results indicate that within the present set of analyses, the frequency of gel application was not directly associated with the incidence of skin-related AEs (including contact dermatitis) or clinical response; this is an intriguing sign that warrants further exploration. While these last results were found within the limits of a controlled clinical trial, they are an interesting observation that could help improve treatment efficacy for patients with MF.

Key Message

Chlormethine gel treatment for mycosis fungoides may result in higher/faster response rates compared with chlormethine ointment.

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Statement of Ethics

Institutional review board approval of the 201 study was obtained at all study sites, and the study complied with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent prior to enrollment.

Conflict of Interest Statement

C. Querfeld: research grant: Celgene; clinical investigator: Celgene, Trillium, miRagen, Bioniz, Kyowa Kirin; advisory board: Helsinn, miRagen, Bioniz, Trillium, Kyowa Kirin.

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Post hoc Analysis of Response Rates with Chlormethine Gel in MF

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