

ORIGINAL ARTICLE

A prospective randomized trial of topical pimecrolimus for cetuximab-associated acnelike eruption

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Background: Clinical trials addressing the acneiform rash associated with epidermal growth factor receptor inhibitors are lacking.

Objective: We evaluated the ability of topical pimecrolimus to reduce the severity of cetuximab-related facial rash.

Methods: In all, 24 patients with metastatic colorectal cancer with cetuximab facial rash received twice daily pimecrolimus application for 5 weeks to half of the face. At baseline, week 2, and week 5, a dermatologist performed facial lesion counts, patients reported perceived severity of rash-related symptoms, and standardized facial photographs were obtained for blinded evaluation of global rash severity.

Results: Treatment sides had greater decrease in lesion counts than observation sides of face at weeks 2 ($P < .001$) and 5 ($P = .02$). However, there were no significant differences in patients' assessment of symptoms and in review of facial photographs for rash severity between treatment and observation sides.

Limitations: This study was not placebo controlled.

Conclusions: Pimecrolimus application did not translate into clinically meaningful benefit for patients with cetuximab-related facial rash. (J Am Acad Dermatol 10.1016/j.jaad.2009.03.046.)

Key words: acnelike rash; cetuximab; clinical trial; pimecrolimus.

Epidermal growth factor receptor (EGFR) inhibitors are being increasingly used for cancer therapy. There are two classes of anti

EGFR drugs: monoclonal antibodies against the extracellular, ligand-binding domain of the receptor (eg, cetuximab, panitumumab) and small molecular tyrosine kinase inhibitors that compete with the intracellular adenosine triphosphate-binding domain of the receptor. Cetuximab (Erbix, IMC-C225, ImClone Systems Inc, Branchburg, NJ) is an IgG1 chimeric monoclonal antibody type of EGFR inhibitor currently Food and Drug Administration (FDA) approved for EGFR-expressing metastatic colorectal carcinoma.^{1,2} Cetuximab, like other EGFR inhibitors of both classes, has been consistently associated in up to 86% of patients with a specific papular and pustular acneiform rash that affects mainly the face, scalp, and upper aspect of torso.^{2,3} Treatment breaks and dose reduction are needed in 5% to 18% of patients on EGFR inhibitors because of this rash.²⁻⁴ In addition, the facial involvement is often cosmetically distressing to patients and may compromise their compliance to the chemotherapy.⁵ Thus, the rash is a therapeutically limiting side effect for a class of drugs that has an otherwise favorable safety profile.

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We have recently reported a prospective, randomized trial showing that prophylactic treatment with systemic minocycline appears to significantly decrease the severity of the acneiform rash during the first month of cetuximab therapy.⁶ In the same study, topical tazarotene showed no clinical benefit in the management of cetuximab-related rash.⁶ Currently, additional formal clinical trials addressing the EGFR acneiform rash have been lacking. Rather, multiple anecdotal reports of using systemic antibiotics and antihistamines and various topical agents in an attempt to ameliorate the acneiform rash have been published,⁷ none of which provide true evidence-based support for the usefulness of any topical agents in the management of this rash.

Herein, we report a prospective randomized study of the efficacy of topical pimecrolimus (Elidel 1% cream, Novartis, Basel, Switzerland) in reducing the severity of facial cetuximab-related facial rash in patients with metastatic colorectal cancer.

METHODS

The study was designed as a single-institution, prospective, randomized trial, and approved by our institutional review board. Informed consent was obtained from each participant.

Patients

Patients, 18 years or older, with metastatic colorectal cancer, who were on cetuximab treatment with or without additional chemotherapy, were eligible. Study exclusion criteria included pregnant or lactating patients, patients with known hypersensitivity to pimecrolimus or tacrolimus, patients using topical prescription therapy for rash on the face in the previous 2 weeks, or patients already using systemic anti-inflammatory drugs for other conditions.

Treatment

Eligible patients were randomized to receive open-label pimecrolimus 1% cream to one side of the face for 5 weeks. Patients were instructed to apply the pimecrolimus cream twice a day at morning and bedtime. Patient compliance to pimecrolimus use and side effects were monitored by patient study diary and physician questioning during study visits.

Evaluation

Baseline evaluation (week 0) included: (1) brief clinical history—demographic data, medical history, current medications, history of drug reactions, and history of acne or rosacea; (2) complete skin examination by participating dermatologists; and (3) standardized digital photography of the face. Follow-up clinical assessment, including questionnaires and skin examination, were performed at the end of the second and fifth weeks of pimecrolimus therapy. An additional assessment was performed 2 weeks after completion of pimecrolimus therapy (ie, week 7) to observe potential posttreatment effects such as duration of response and rebound. At each study time point, patients were asked about presence and perceived severity of rash-associated symptoms including itch, burning, erythema, and dryness on either side of the face. Response categories to the question-

naire were categorized into none, mild, moderate, and severe. In addition, a dermatologist performed a skin examination that included counts of facial lesions on right versus left sides and assessment of facial erythema. At baseline, this dermatologic assessment was done before randomization of treatment to one side of the face. In some cases, the facial rash consisted of confluent plaques. However, one could usually appreciate multiple small pustules or follicular accentuation overlying the confluent plaque. These follicular lesions overlying a plaque were counted as individual lesions. Digital photography using the same standard poses as baseline was repeated at weeks 2, 5, and 7.

The images of both sides of the face were reviewed by two dermatologists blinded to treatment status. The reviewers assessed rash severity on each side of the face, categorized into none, mild, moderate, and severe, according to a predefined qualitative scheme (Fig 1).

Statistical analysis

The primary outcome was assessed as difference in lesion counts between treated and observation sides of the face at completion of topical therapy (week 5). In addition, we explored differences in lesion counts at other time points, patient subjective

CAPSULE SUMMARY

- Clinical trials addressing EGFR inhibitors—associated acneiform rash have been lacking.
- In a prospective randomized study, 24 patients with cetuximab-related facial rash applied pimecrolimus to half the face for 5 weeks whereas the other half was only observed.
- Pimecrolimus application did not translate into clinically meaningful benefit for patients with cetuximab-related facial rash.
- Unrelated to pimecrolimus, we observed a trend toward bilateral decreasing severity of the facial rash over time.

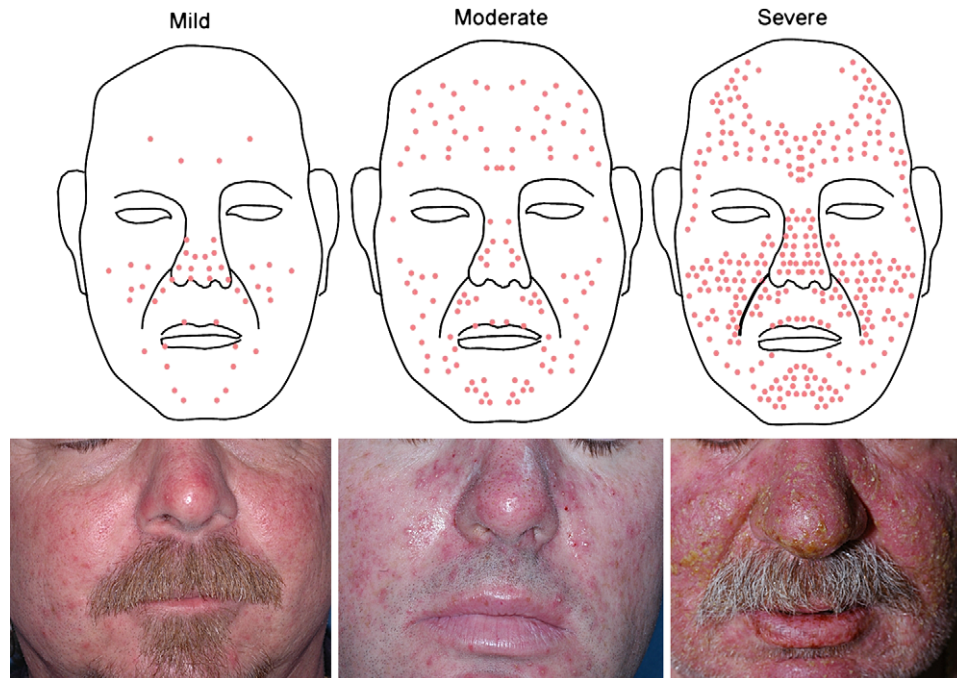


Fig 1. Schematic developed as visual scale to assess severity of cetuximab-related acneiform facial rash, graded from mild to severe.

report of itch and burn severity at study follow-up points, and differences in observer assessment of global rash severity at study follow-up points.

The study was designed to detect a mean lesion count difference of 5 with greater than 80% power and $\alpha = 0.05$. Differences in lesion counts between treatment and control sides of the face were calculated at each time point for all study participants. The observation sides of the face were used as control. Frequencies and relative frequencies were used to describe the study populations. To further assess lesion differences across study time points, and to account for the correlated nature of the data, linear regression models were used. For the analysis, subjective itch and burning responses were dichotomized into none/mild and moderate/severe. Similarly, for analysis of the photographic global assessment of facial rash severity, responses were dichotomized into none/mild and moderate/severe. McNemar chi-square analyses were performed at each study time point to assess the association between treatment arm and rash/itch response. To assess rash and itch across the study time points, logistic regression models using generalized estimating equations were used. All analyses were performed with software (Stata SE Version 9.1, Stata Corp, College Station, TX).

RESULTS

Between October 2006 and October 2007, 24 patients with stage IV colorectal cancer on

cetuximab therapy with acneiform facial rash were randomly assigned to receive half-face application of pimecrolimus 1% cream for 5 weeks. The mean age of patients was 52.5 years (SD = 12.6, range 23-75) and 17 patients (70.8%) were male. The median length of cetuximab treatment before enrollment in the study was 2 weeks (range 1-52 weeks).

Details of patient attrition during the study follow-up are shown (Fig 2). The main reason for cetuximab discontinuation during the first 5 weeks of the study was disease progression, seen in 3 patients (12.5%). In addition, cetuximab treatment was terminated in two patients (8.3%) because of grade III rash. Three patients (12.5%) had week-long cetuximab treatment interruptions because of severity of the rash. One patient (4.1%) withdrew study consent and prematurely discontinued pimecrolimus because of perceived lack of efficacy.

At baseline, the assessment of facial lesion counts before randomization shows that the median lesion count was significantly higher for the side of the face that was assigned to pimecrolimus treatment than for the observation side. The investigator assessment of lesion counts for pimecrolimus and observation sides of the face during the 5-week treatment period is presented (Fig 3). After controlling for baseline differences in lesion counts, there was a statistically significantly greater decrease in lesion counts for the treatment than observation sides of the face by study week 2 ($P < .001$), that was also maintained at week 5

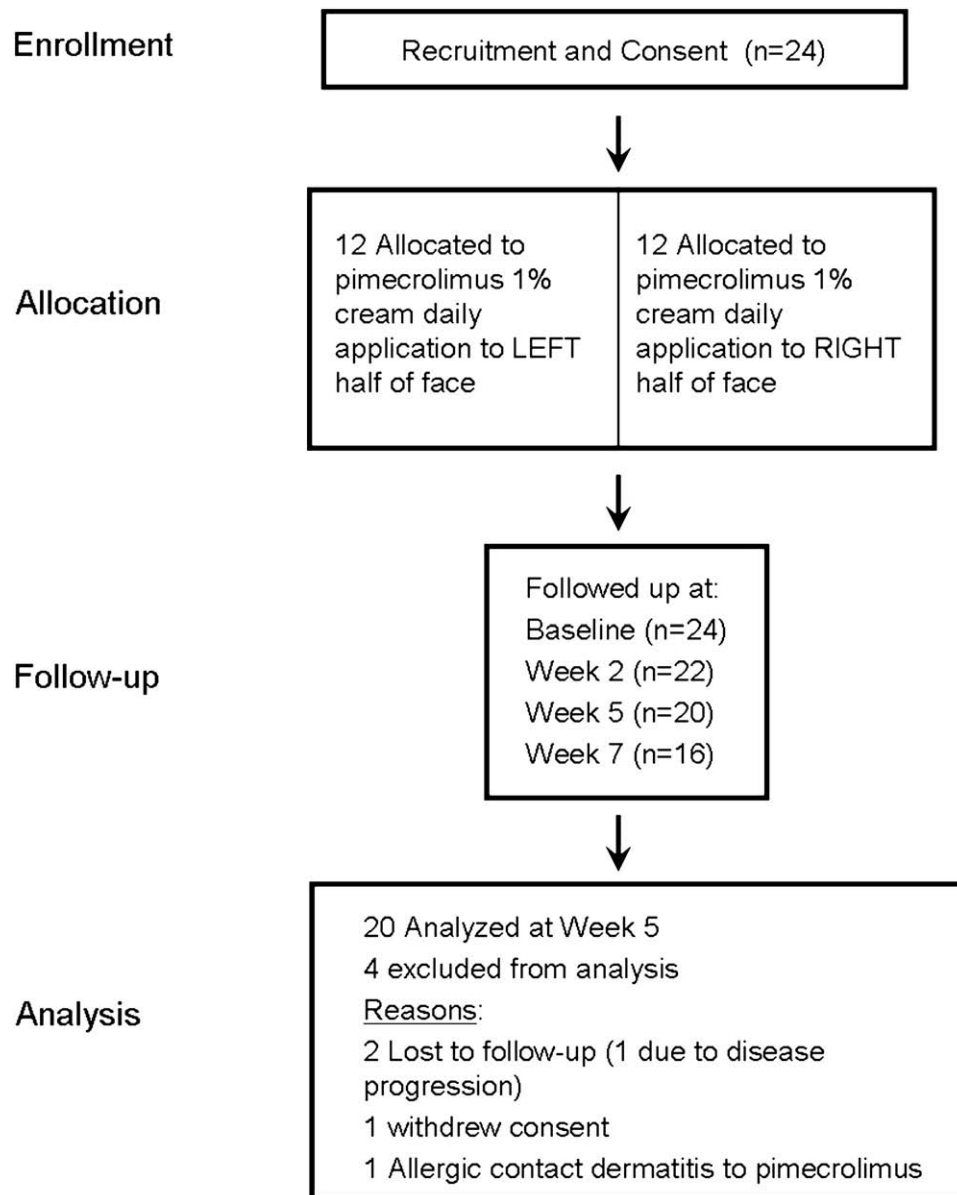


Fig 2. Study schema, patient disposition, and attrition data by study week. Values represent number of patients assessed at follow-up.

($P = .02$). These differences became nonstatistically significant after discontinuation of pimecrolimus therapy (study week 7).

Rash severity was also evaluated by blinded photographic global assessment by study dermatologists and by patient self-assessment. There were no statistically significant differences between treatment and observation sides of the face for either of these measurements.

Although the vast majority demonstrated no significant differences in global visual assessment or symptoms, in 4 patients (17%), differences were observed with milder rash ($n = 3$) and/or less erythema ($n = 3$) on the pimecrolimus-treated side

of the face. In 3 of the 4 patients, this difference was evident by week 2; these patients also reported a lesser severity of rash-associated symptoms (itching, burning, and redness) on the treatment side. In two patients (8.5%) the rash was found to be worse on the pimecrolimus side. In one of these patients pimecrolimus was discontinued because of an adverse effect, with redness and swelling on the treated half of the face after a single application; a contact allergic reaction to pimecrolimus was confirmed by patch testing. In the other patient, the treated side was found on the photographic assessment to be worse than the observational side at week 5. Notably, this patient reported worse symptoms

(itching, burning, and redness) on the treated side at weeks 2 and 5, but remained compliant with pimecrolimus treatment. We did not observe an increased risk of skin infections on the treated compared with the observation side of the face.

There was an overall trend of decreasing facial rash density bilaterally during the study period, with statistically significant decrease in lesion counts on both sides of the face at weeks 2, 5, and 7 compared with the baseline assessment (Fig 3). Photographic global assessment showed significant bilateral decreases in rash and erythema. At baseline, 47.8% of patients had moderate to severe rash and 30.4% had moderate to severe erythema. By study week 5 these proportions decreased to 19.4% and 23.7%, respectively ($P < .001$). Patient subjective assessment of facial rash-related symptoms followed a similar trend (Fig 4). Patients reported a lower proportion of moderate to severe itch, burning, dryness, and redness from baseline to study week 5 ($P < .001$).

DISCUSSION

In addition to expression and overexpression in various cancers, EGFR is expressed by the normal epidermal and follicular epithelium.⁸ EGFR inhibition has been shown to involve abnormalities in the follicular epithelium together with inflammation, without an infectious cause. Histologic findings range from an infiltrate of T lymphocytes surrounding the follicular infundibulum to suppurative folliculitis.^{9,10}

Pimecrolimus (Elidel 1% cream, Novartis) is a topical immunomodulator developed for the treatment of inflammatory skin diseases. Pimecrolimus' mechanism of action is blockage of T-cell activation. Pimecrolimus binds to the cytosolic receptor immunophilin macropophilin-12.¹¹ This pimecrolimus-macropophilin complex effectively inhibits the protein phosphatase calcineurin by preventing calcineurin from dephosphorylating the nuclear factor of activated T cells. This results in the blockage of signal transduction pathways in T cells and the inhibition of the synthesis of proinflammatory cytokines.¹¹ The systemic immunosuppressive potential of pimecrolimus is low and pharmacokinetic studies have shown very low blood levels of pimecrolimus after topical application, with no accumulation after repeated applications.¹² Occasional transient irritation may be experienced at the application site. Recently, the FDA posted a "black box" warning for pimecrolimus and tacrolimus, raising safety concerns because of reports of lymphomas and solid organ tumors in patients taking systemic tacrolimus as an immunosuppressive agent after organ transplantation. Although the applicability of the FDA warning

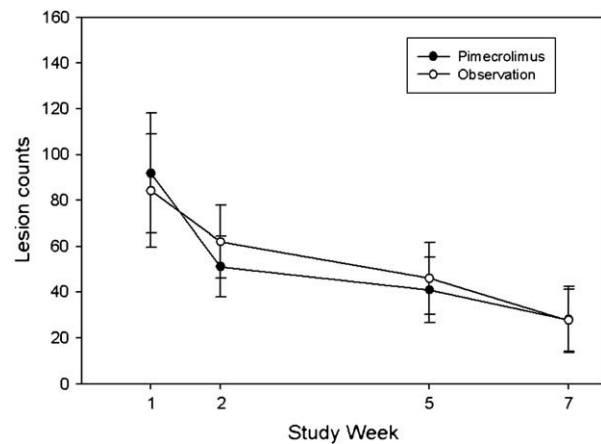


Fig 3. Plot of log lesion counts for pimecrolimus-treated and observation sides of face for each study time point.

to topical applications has been debated in the literature, the short duration of treatment in this protocol and limiting the application to the face precluded significant cancer risk.

Unlike topical steroids, pimecrolimus does not inhibit epidermal growth or collagen synthesis and shows no risk of epidermal atrophy or striae distensae.¹¹ Because the acneiform rash of EGFR inhibitors is typically pronounced on the face, prolonged treatment with topical steroids may result in unacceptable adverse effects such as atrophy, hirsutism, and pigmentary changes. Based on the role of inflammation in the acneiform rash and the favorable toxicity profile of pimecrolimus, it seemed rational to evaluate pimecrolimus' efficacy for cetuximab-associated facial rash.

We found an overall decrease in the investigator-assessed density of the acneiform lesions on the pimecrolimus-treated side of the face that reached statistical significance. There was no difference in the frequency of the patient-assessed itch, burning, and dryness sensation, or in the perceived degree of facial erythema between the treated and observation sides of the face. Furthermore, assessment by two blinded dermatologists who reviewed images of the face obtained at each study point and compared overall rash and erythema severity between treated and observation sides of the face revealed no statistically significant, clinically significant differences between the two sides of the face. In 4 patients (17%) there was an objective response to pimecrolimus treatment with reduction in facial rash severity and erythema that was consistent with a reduction in patient-reported symptoms in 3 of the 4 patients. In two patients there was evidence of worsening on the pimecrolimus side, and one of these patients required cessation of pimecrolimus.

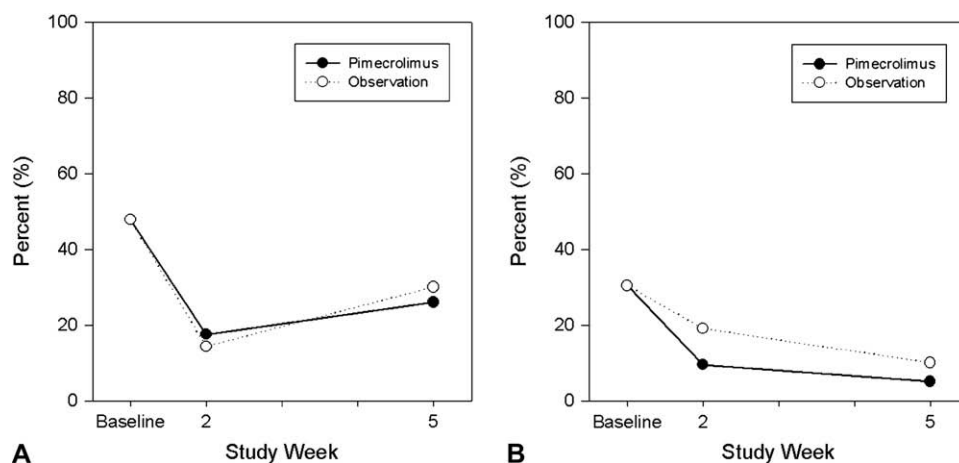


Fig 4. Line plots of subjective patient assessment showing proportion of patients reporting moderate to severe facial itch (**A**) and burning (**B**) for pimecrolimus-treatment and placebo sides of face across study assessment time points.

Unrelated to pimecrolimus, we observed a trend toward bilateral decreasing severity of the facial rash over time. During the 7-week follow-up period, there was a significant gradual decrease in lesion counts on both sides of the face, in the proportion of patients reporting moderate-severe symptoms or erythema, and in the proportion of moderate-severe facial rash and erythema on the investigator-blinded assessment of the facial photographs. This trend of improvement in the rash over time is concordant with our previous study⁶ in which we saw an improvement in the facial rash severity and patient-reported symptoms in both the minocycline-treated and placebo groups. We previously attributed this trend to the natural history of the cetuximab-related rash during the first 2 months of therapy. Of note, despite the current trial's design of accrual of patients already experiencing rash on cetuximab therapy, most patients in fact were in the initial stages of therapy, with median duration of 2 weeks of cetuximab treatment at study enrollment.

During the study period, 21% of patients had cetuximab treatment discontinuation or interruption because of the acneiform rash. This observation reiterated the need to find an effective therapy for the rash associated with EGFR inhibitors. More prospective randomized trials are warranted to test the efficacy of systemic and topical therapies for the rash. Given the documented bilateral improvement in the rash over time, it is clear that studies of topical agents can only have validity and interpretability if they use the approach of treating one side only that we used in this trial. Uncontrolled reports of improvement are impossible to distinguish from the natural history of the rash.¹³

Our study has several limitations. First, the study is small as it was powered to detect differences in lesion counts between two sides of the face, each patient serving as his or her own control. Although a larger study may be powered to detect significant clinical differences between treatment and controls, our results are not conducive for launching a large trial using pimecrolimus as a single agent. Secondly, the trial was not placebo controlled or blinded to the application side of pimecrolimus. This may bias investigators in counting facial lesions and subjective assessment by patients. To counterbalance such inherent bias, we added an objective assessment of facial photographs by blinded investigators. Finally, although the study was conducted specifically on cetuximab, a monoclonal antibody, similarity of the rash across the two classes of EGFR inhibitors suggests that our results are generalizable to other EGFR inhibitors.

In conclusion, pimecrolimus application did not translate to clinically significant benefit in patients with cetuximab-related facial rash.

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