

Evaluation of Regenecare™ Topical Gel in the Treatment of Skin Rash Associated with Cetuximab (Erbix®), Tarceva® and Other EGFR Inhibitors-Treated Cancer Patients

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Introduction

Epidermal growth factor receptor (EGFR) inhibitors drugs such as cetuximab (Erbix®), gefitinib (Iressa®) and erlotinib (Tarceva®) are among this group of monoclonal antibody agents used for treating colorectal, lung, and head and neck cancers.^{1,4} EGFR drugs target epidermal derived tissues including capillaries, sebaceous cells, hair shaft and hair follicles. A common, often severe adverse side effect, is the appearance of an acneform skin rash in about 88% of treated cetuximab patients.^{4,5} Rash appearance although unpleasant and symptomatic for the patient, indicates a positive response to the drug's effectiveness.³ Patients need an understanding of why the rash appears and support in tolerating the side effect. The maculopapular rash often appears on the face, upper chest, back, hands, legs and feet.^{4,5} Although the rash is acneform in appearance it is not true acne because it is not the result of bacterial infection but the reaction of the drug to epidermal antigens.³

Rash management is important to promote optimal use of EGFR agents as patients may want to discontinue or reduce dosages due to rash unsightliness and irritation. Patients with grade 1 or 2 rash most often report physical discomforts of pruritis (itching), pain and sensitive skin. The skin often shows erythema, pustules, eruptions, lesions and dryness.^{5,6} Secondary skin infection can occur from scratching.

Practitioners are presently without an evidence-based topical product to treat this specific rash with its unique etiology and symptoms. An adjunct therapy that reduces pain and itching and has ingredients known to support healing would be beneficial for patients' quality of life and for clinicians managing this side effect.

Regenecare™ (MPM Medical Inc. Irving TX) is a collagen and aloe vera based wound care gel with 2% lidocaine HCl. The product ingredients have shown scientific evidence for wound healing and for pain management. Marine collagen, a natural humectant provides high substantivity to the skin surface and has shown benefit to wound healing.^{7,8} Aloe vera gel improved healing in animal wound repair models by stimulating fibroblasts, increasing

microcirculation, and has anti-inflammatory and emollient effects.^{9,10,11} Lidocaine is a safe anesthetic, widely used and proven effective.^{12,13} The combination of ingredients may be beneficial for the management of HER1/EGFR inhibitor-induced acneform rash.

Siu-Fun Wong et al. has presented preliminary results of a pilot crossover study evaluating the use of Regenecare topical gel with cutaneous toxicity caused by epidermal growth factor receptor (HER1/EGFR) inhibitors. Six patients with CTC grade 2 EGFR inhibitors-induced rash were evaluated, with one side of face receiving gel treatment and other side no gel treatment. The mean difference scores for self assessed reporting of severity of itching and pain were evaluated by a t test. Mean difference of scores for the Regenecare treated side vs. non treated side was $p=0.019$ for itching relief and $p=0.033$ for pain relief indicating symptom relief ($p\leq 0.05$) with application of product as compared to no treatment.¹⁴

A pilot clinical trial evaluating Regenecare for safety and efficacy is ongoing at Ingalls Memorial Hospital Cancer Research Center and will include at least 20 patients. Results of eight completed patients are reported.

Objectives

The primary objective of the study is to evaluate the effect of Regenecare™ towards alleviating pain and itching from the rash while the patient is undergoing EGFR inhibitors treatment. Secondary objectives include evaluating the effect of Regenecare in reducing the rash severity, helping reduce the appearance of the inflamed skin and assessing patient tolerability of topical Regenecare application.

Study Design

This is a randomized, prospective, single-center observational study of outcomes in Erbix (cetuximab) and Tarceva treated-patients receiving Regenecare™ for cutaneous toxicity management.

Methods

Patients selected met criteria of over 18 years of age, to be started on cetuximab or other EGFR inhibitors therapy, having no serious concomitant skin disorders that would interfere with skin assessment, and likely to comply. After obtaining signed informed consent, patients were instructed to apply RegeneCare, 4 times daily, to rash areas including face, hands, neck, back and feet.

Every week patient rash was graded according to NCI CTC (National Cancer Institute Common Toxicity Criteria- table 1) by clinical nurses. Nurses instructed each patient weekly to rank rash symptoms by answering a questionnaire that evaluated gel application as to its affectivity to reduce rash appearance, reduce itching, reduce pain, and rated the product for skin healing. Patients rated gel application towards each symptom as 1.) “no” effect, 2.) “mildly” effective, 3.) “moderately” effective, 4.) “very” effective and 5.) “extremely” effective. Nurses took weekly pictures of patient’s rash. It was of clinical importance to observe degree of rash manifestation and body areas affected.

A final product evaluation was administered to each subject at the end of their EGFR treatment cycle which included a total of four weeks of rash management with RegeneCare. Typically, the acneform rash appears approximately two weeks after initial administration of EGFR inhibitors drug.

TABLE 1
NCI CTC Version 3.0 Determining the Grade of Acneform Rash/Desquamation

Grade 1	Grade 2	Grade 3	Grade 4
Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritis or other associated symptoms; localized desquamation or other lesions covering <50% of body surface	Severe, generalized erythroderma or macular, papular, vesicular eruption; desquamation covering >50% of body surface area	Generalized exfoliative, ulcerative or bullous dermatitis

Results

Of eleven subjects meeting study criteria eight completed evaluation after 4 weeks of RegeneCare application for cutaneous toxicity with NCI CTC grade 1 or 2 rash. Three patients did not complete the study because of grade 3 rash symptoms needing medical treatment for skin toxicity beyond the scope of the protocol.

Five patients receiving Erbitux (cetuximab) and three patients receiving Tarceva experiencing presence of pustules, acneform rash, pruritis and pain were evaluated during EGFR inhibitors treatment completion (6 weeks). Weekly patient evaluations and the final product evaluation were analyzed by a statistician rating percentage of response to each question. Results are shown in table 2.

TABLE 2

Overall rating Response	Reduce Appearance	Reduce Itching	Reduce Pain	Moisturizing	Heal Skin	Sooth
No Effect	6.3%	0.0%	0.0%	50.0%	0.0%	0.0%
Mildly Effective	6.3%	0.0%	0.0%	0.0%	12.5%	12.5%
Moderately Effective	62.5%	16.7%	0.0%	12.5%	25.0%	12.5%
Very Effective	12.5%	66.7%	100.0%	37.5%	62.5%	62.5%
Extremely Effective	12.5%	16.7%	0.0%	0.0%	0.0%	12.5%

In a final product evaluation, patients also scored gel effects similar to weekly questionnaires but with additional questions. Patients were asked how soon itch and pain relief occurred after gel application (i.e. 15 minutes, 30 minutes, 1 hour, etc.) (table 3).

Subjects were asked if they would recommend the gel to others as a remedy to rash symptoms and to state why. Five patients responded. Information was included for these individuals as to rash location and drug administered. (table 4).

Conclusion

The study from patient ordinal descriptive data indicates Regenecare effective in reducing itching, which clinicians consider one of the most uncomfortable side effects of EGFR inhibitors-induced rash. Total subjects reported the effect of Regenecare on rash itching with 16.7% reporting “extremely,” effective, 66.7% “very” effective, and 16.7% “moderately” effective in reducing symptom. None of the subjects reported Regenecare use as to “no” effect or only “mildly” effective in reducing itching. This ordinal ranking of each subject’s description of effectiveness indicated all subjects received symptom relief from itching.

TABLE 3

Would you recommend this product to others?	How soon did you experience relief from pain and itching after applying gel to rash?
Yes 100%	15 minutes 60%
No 0%	30 minutes 40%

Patient with grade 2 rash scores Regenecare as extremely effective in reducing itching and very effective in reducing pain



**Tarceva®
Treated Patient**



Patient with Grade 2 rash, scores Regenecare as very effective in reducing itching.

Back



**Erbix®
Treated Patient**



Chest



In Summary

- Collectively 100% of subjects ranked Regenecare as either “very,” “extremely,” or “moderately” effective in reducing rash itching. No subjects ranked Regenecare with “no” effect, or “mild” effect towards reducing itching.
- 100% of subjects reported Regenecare as “very” effective in reducing pain.
- Collectively, 87.5% of subjects ranked Regenecare as “very,” “extremely,” or “moderately” effective for reducing rash appearance.
- Collectively, 87.5% of subjects rated Regenecare as “very,” “extremely,” or “moderately” effective in ability to sooth skin.
- Collectively, 87.5% of subjects rated Regenecare as “very,” and “moderately” effective towards skin healing.
- 50% of subjects observed no moisturizing effect while 37.5% rated it as “very” and 12.5% rated it as “moderately” effective.

Overall product ranking showed substantial positive outcome towards reducing symptoms of pain and itching effectively in CTC grade 1 and 2 rash. Collectively a total of 87.5% of subjects ranked gel application effective (all responses in categories of “extremely,” “very,” and “moderately” effective) towards reducing rash appearance, skin healing and skin soothing. There were no untoward side effects associated with continued use of Regenecare.

This preliminary study indicates that Regenecare is effective towards subjects’ assessment of considerable reduction of rash itching and pain. Subjects ranked Regenecare as having definite healing and soothing effects and a noticeable affect in reducing rash appearance. Preliminary results indicate Regenecare gel is a safe, and effective adjunct therapy for managing symptoms of EGFR inhibitors-induced grade 1 and 2 rash. These positive results warrant further study.

TABLE 4

Why would you recommend this product to others for skin rash or itching?	CTC Rash Grade (Rash Eruption Areas)
“It provides relief.”	Grade 1 Eribitux subject. (Face, upper chest, scalp.)
“It worked well for me.”	Grade 2 Tarceva subject. (Face, upper chest.)
“It helped.”	Grade 2 Tarceva subject. (Face, upper chest, back, arms, legs, fingers.)
“It relieved the redness.”	Grade 2 Tarceva subject. (Face, upper chest, back, arms, legs.)
“It works great.”	Grade 1 Eribitux subject. (Face, upper chest, back of neck.)

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