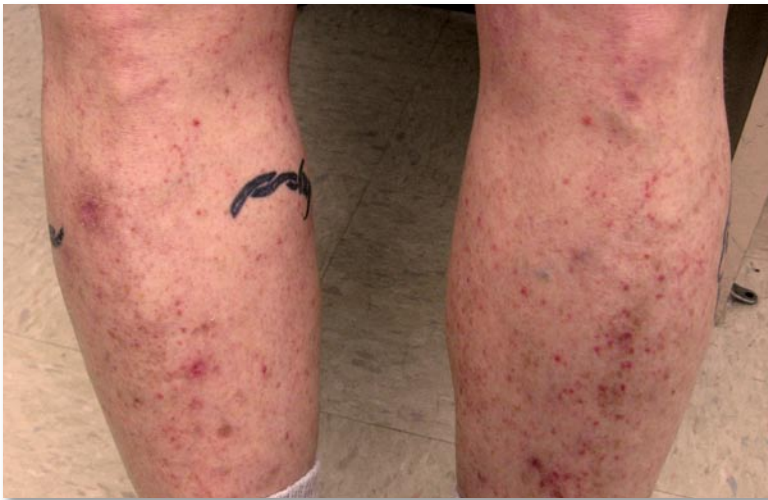


Subjects ranked Regenecare as having definite healing and soothing effects and a noticeable affect in reducing rash appearance. Preliminary results indicate Regenecare gel is a safe, and effective adjunct therapy for managing symptoms of EGFR inhibitors-induced grade 1 and 2 rash.

Two Erbitux Subjects (500mg weekly) with Grade 2 EGFR Rash are pictured below:



#1 – Patient Rates Regenecare Gel **Extremely Effective** for Reducing Pain and Itching



#2 – Patient Rates Regenecare Gel **Very Effective** for Reducing Itching and for Skin Healing

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Evaluation of Topical Gel (with 2% Lidocaine-HCl) for Treatment of Adverse Rash Symptoms Associated with HER1/EGFR Inhibitors

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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 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 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 initially 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 topical wound gel formulation containing marine collagen, aloe vera, sodium alginate and 2% lidocaine HCl (NDC 66977-100-03). 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-HCl (2%) is a safe proven topical anesthetic.^{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 trial of 10 patients was clinically assessed. Subjects evaluated effectiveness of Regenecare in reducing the primary discomfort of EGFR inhibitors induced rash symptoms of itching, pain, and effects of the gel formulation towards soothing, healing and reducing the appearance of the rash.

Background

The primary objective of the study is to evaluate the effect of Regenecare® topical gel 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 prospective, single-center observational study of outcomes in Erbitux (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 the collagen and aloe

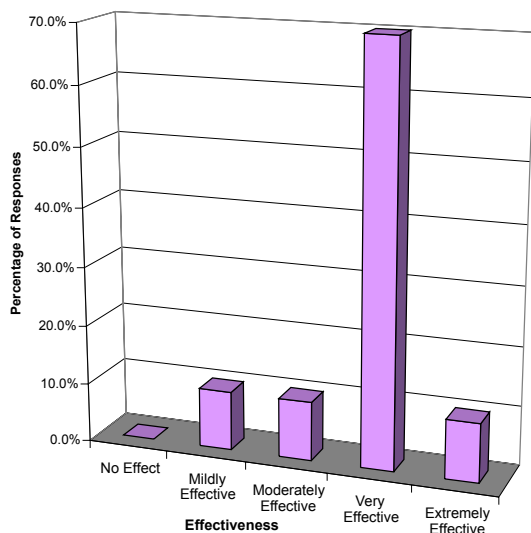
based gel with 2% lidocaine-HCl (Regenecare, MPM Medical Inc. Irving Tx), 4 times daily, to rash areas including face, hands, neck, back and feet. Typically, the acneform rash appears two weeks after initial administration of EGFR inhibitors drugs.

Every week patient rash was graded according to NCI CTC (National Cancer Institute Cutaneous Toxicity Criteria) 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 and soothing. 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.

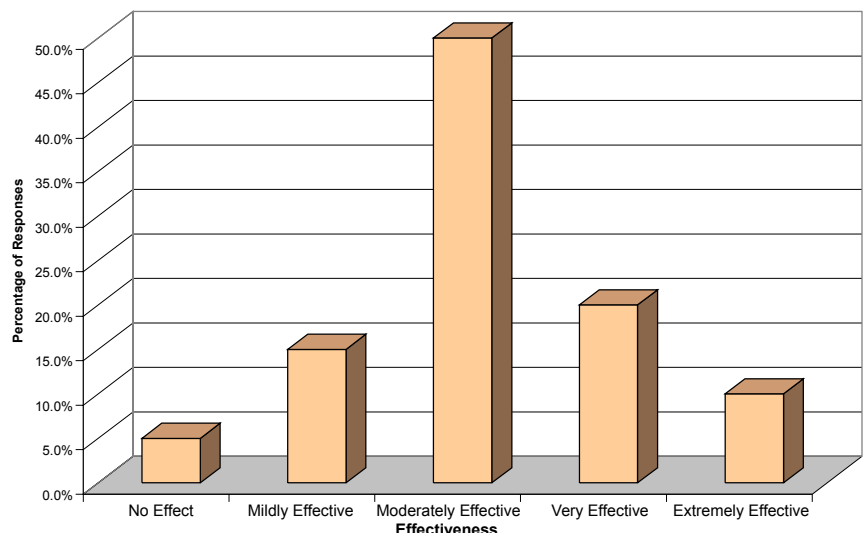
A comprehensive product evaluation was administered to each subject at the end of their EGFR treatment cycle which included a total of four weeks of rash management with Regenecare. These ordinal data were calculated.

Overall Rating Response	Appearance	Reduce Itching	Reduce Pain	Healing	Sooth Skin
No Effect	5.0%	0.0%	0.0%	0.0%	0.0%
Mildly Effective	15.0%	0.0%	0.0%	20.0%	10.0%
Moderately Effective	50.0%	12.5%	0.0%	20.0%	10.0%
Very Effective	20.0%	50.0%	80.0%	60.0%	70.0%
Extremely Effective	10.0%	37.5%	20.0%	0.0%	10.0%

Regenecare Rated for Ability to Soothe (n=10)



Regenecare Rated for Reducing Rash Appearance (n=10)



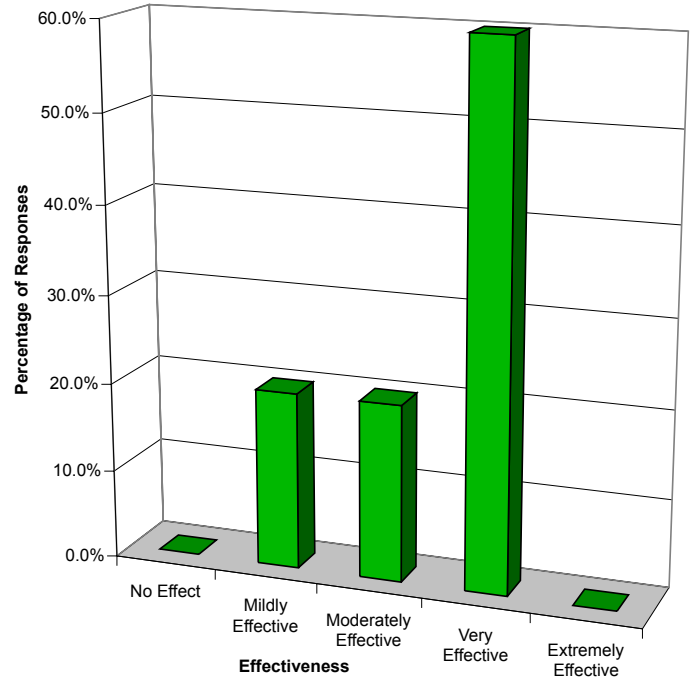
Results

Ten subjects meeting study criteria completed evaluation after 4 weeks of Regencare application for cutaneous toxicity with NCI CTC grade 1 or 2 rash. Three patients did not complete the study due to complications of grade 3 rash symptoms needing medical treatment for skin toxicity beyond the scope of the protocol.

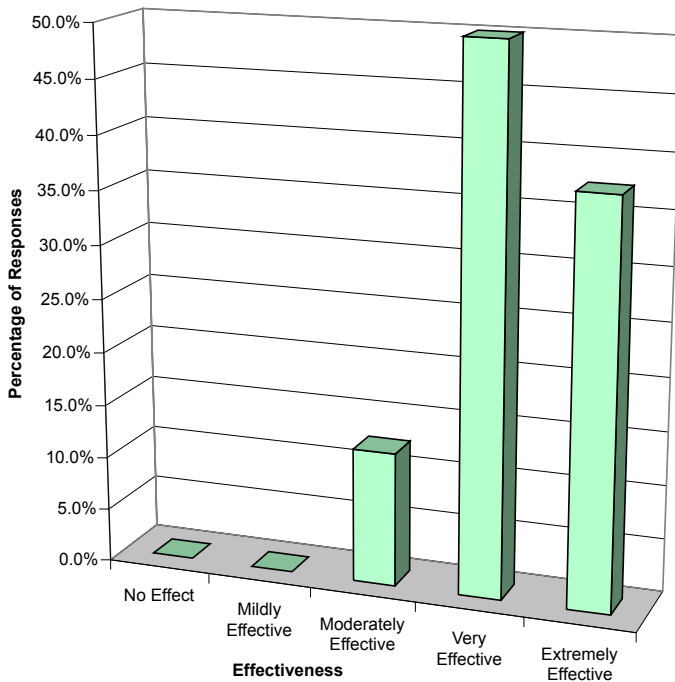
Six patients receiving Erbitux (cetuximab) and four patients receiving Tarceva experiencing presence of pustules, acneform rash, pruritis and pain were evaluated during EGFR inhibitors treatment completion (6 weeks). Weekly patient product evaluations and clinical assessment of rash were conducted by clinicians. The final product evaluations were analyzed by a statistician rating percentage of response to each question (Graphs Shown) as described in methods rating effectivity of each symptom managed by Regencare.

Patients were asked how soon itch and pain relief occurred after gel application and all subjects indicated relief within 15 to 30 minutes. Subjects were asked if they would recommend the gel to others as a remedy to rash symptoms, 100% said yes.

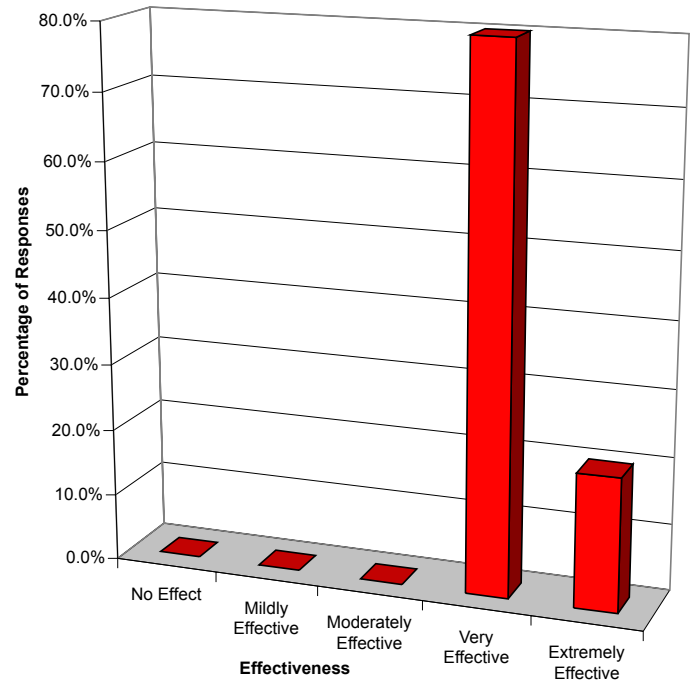
Regencare Rated for Perceived Healing (n=10)



Regencare Rated for Reduction of Itching (n=8)



Regencare Rated for Pain Reduction (n=5)



Conclusion

The evaluation study indicates Regencare effective in reducing itching, which clinicians consider one of the most uncomfortable side effects of EGFR inhibitors-induced rash. This ordinal ranking of each subject's description of effectiveness indicated all subjects received symptom relief from itching. Pain is not always a symptom in milder rash. Some patients responded to itching evaluation but not pain evaluation according to individual perception. The number of patients responding to

each question is noted in titles.

Overall product ranking showed substantial positive outcome towards reducing symptoms of pain and itching effectively in CTC grade 1 and 2 rash. Patients with grade 3 rash often require additional therapeutic intervention with corticosteroids or antibiotics and were not evaluated in this study design. The authors recommended conducting further studies evaluating combination therapies which would include Regencare for best treatment outcome of grade 3 rash.