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Improvement in Atrophic Acne Scars Using Topical Synthetic Epidermal Growth Factor (EGF) Serum: A Pilot Study

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ABSTRACT

BACKGROUND: Atrophic acne scars are a common and psychologically devastating sequela of acne vulgaris that are refractory to the vast majority of topical treatments.
OBJECTIVE: We evaluated the efficacy of a topically applied synthetic epidermal growth factor (EGF) serum in reducing the appearance of atrophic acne scars.
METHODS: A single-center clinical trial was performed on nine self-selected male and female patients with Goodman &Baron grade II-IV atrophic acne scars. Subjects followed a standardized treatment regimen, including twice-daily application of EGF serum to scarred areas over 12 weeks. Subject progress was evaluated at baseline and 4-week intervals by clinical photography, Investigator Global Assessment (IGA), Goodman grade and patient self-assessment. Final patient perceptions were shared by written self-assessment at the end of the study. Before and after photographs were also evaluated by a blind investigator.
RESULTS: Eight subjects completed the trial. Compared to baseline, there was an improvement in mean IGA score from 2.875 (SEM= .327) to 2.38 (SEM = .375). Mean Goodman grade was reduced from 3.00 (SEM = .309) to 2.75 (SEM = .25). Of the eight pairs of before and after photographs given to a blind investigator, five were correctly chosen as the post-treatment image. Two were assessed as “excellent” (76-100%) improvement and three were assessed as "good" (50-75%) improvement. A one-tailed paired student t-test (α = .05) using blind investigator ratings of scar severity for each before and after photograph yielded a P-value of .0019, confirming the difference as statistically significant. On final self-assessment, all but one patient reported “good” to “excellent” improvement in their scars compared to baseline. 75% of patients who received alternative treatments in prior years reported EGF serum to be more efficacious.
CONCLUSION: These results suggest that topical EGF may improve the appearance of atrophic acne scars, though further study and more objective evaluation measures are required for definitive conclusions to be drawn.

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INTRODUCTION

Acne remains the most common dermatologic condition in the United States, affecting roughly 80% of people between the ages of 11 and 30.[1] It is well recognized as a major source of stress and insecurity among its sufferers, both adolescents and adults. However, often overlooked is the considerable psychosocial impact of residual scarring. Nearly 30% of individuals who experience acne at some point in their lives are left with scars ranging from mild to severe and which, in a majority of cases, are permanent.[2,3] For many, severe

scars contribute to depression, anxiety, body image alterations and generally low self-esteem.[4] It may also be a risk factor for suicide.[5]

Acne scars are typically classified into three different types: atrophic, hypertrophic and keloidal, the former being the most common.[3] Atrophic scars can be further subdivided into icepick, boxcar and rolling types. Though all are depressed, thin and often discolored secondary to tissue loss, severity is variable. Deep, punctiform icepick scars are considered the most severe, and, unfortunately, represent roughly 60-70% of cases.[6]

The pathogenesis of atrophic acne scars remains incompletely understood. The most accepted hypothesis points to dysregulated inflammation that culminates in collagen deficiency and tissue atrophy. This theory is supported by recent findings that activator protein (AP)-1, a transcription factor involved in inflammation, is over-expressed in inflammatory acne lesions.[7] This abnormality is thought to underlie the increased levels of MMP-1 (collagenase-1) and other matrix metalloproteinases (MMPs) also found in areas of active acne.[7] The well-recognized role of MMPs in collagen matrix degradation explains the tissue atrophy characteristic of depressed scars.[7] Consequently, acne scar formation is highly correlated with delay in initiating treatment and, therefore, the duration of the inflammatory response.[2]

Given the psychological burden, patients are often desperate to see any improvement and turn to one of several invasive procedures. Some of the most effective methods are chemical peels, dermabrasion, resurfacing lasers, and percutaneous collagen needling, all of which share the common endpoint of promoting collagen synthesis. Despite their variable success, however, the tissue damage they cause leads to variable degrees of peri- and post-treatment pain and an array of side effects ranging from mild and reversible to potentially severe and irreversible.[5,6,8] Despite their improved tolerability, less invasive topical creams have not been shown to be very effective when used alone. Topical retinoids, for example, can be used to treat keloidal, hypertrophic, and superficial atrophic scars, though evidence of its success in treating more aggressive atrophic scars is lacking.[9,10] Improved efficacy is generally reliant on adjuvant therapy with sequential chemical peels or combining treatment with iontophoresis.[11,12]

"These findings suggest EGF serum has the potential to be a modern, noninvasive treatment for an otherwise highly refractory condition."

Despite the array of treatments, literature suggests no single modality is capable of achieving complete resolution of atrophic acne scars.[6] Aware of the paucity of successful topical agents currently in use, we evaluated the efficacy of a serum containing epidermal growth factor (EGF), which has never before been studied for this indication. Given the well-documented role of epidermal growth factor (EGF) in collagen synthesis, we believed that twice-daily application of this serum would counteract tissue atrophy in a similar manner to currently available treatments, while circumventing the need to induce inflammation through traumatic methods. This hypothesis was reinforced by soon-to-be published ultrasound findings that twice-daily topical application of EGF serum thickened forearm skin and reduced ecchymoses in senile purpura patients. In the end, our study demonstrated that topical EGF was, as we suspected, also beneficial in improving the appearance of atrophic acne scars. These findings suggest EGF serum has the potential to be a modern, noninvasive treatment for an otherwise highly refractory condition.

METHODS

A single-center clinical trial was performed on nine patients (5 women, 4 men) with evidence of grade II-IV atrophic facial acne scars as determined by the Goodman &Baron qualitative grading system (Figure 1). Patients ranged in age from 23 to 54 (mean age, 37.8) and were of diverse racial background (4 Hispanic, 2 Caucasian, 1 African-American, 1 South Asian, and 1 East Asian patient). Six of the nine patients personally rated

FIGURE 1. Goodman & Baron qualitative global acne scar grading system.[13]

Grade	Level of disease	Characteristics	Examples of scars
1	Macular disease	Erythematous, hyper-or hypopig-mented flat marks visible to patient or observer irrespective of distance.	Erythematous, hyper-or hypopig-mented flat marks
2	Mild disease	Mild atrophy or hypertrophy that may not be obvious at social distances of 50cm or greater and may be covered adequately by makeup or the normal shadow of shaved beard hair in males or normal body hair if extra facial.	Mild rolling, small soft papular
3	Moderate disease	Moderate atrophic or hypertrophic scaring that is obvious at social distances of 50cm or greater and is not covered easily by makeup or the normal shadow of shaved beard hair in males or body hair if extrafacial, but is still able to be flattened by manual stretching of the skin.	More significant rolling, shallow "box car," mild to moderate hypertrophic or papular scars
4	Severe disease	Severe atrophic or hypertrophic scaring that is obvious at social distances of 50cm or greater and is not covered easily by makeup of the normal shadow of shaved beard hair in males or body hair(if extrafacial) and is not able to be flattened by manual stretching of the skin.	Punched out atrophic(deep "box car"), "ice pick", bridges and tunnels, gross atrophy, dystrophic scars significant hypertrophy or keloid

their scars as “moderately severe,” one rated them as “moderate” and two as “mild.” When asked the patients to grade the degree of impact their scars had on their self-esteem, one patient said “very significantly,” four replied “significantly,” one said “somewhat,” and three replied “a little.” Four patients reported prior treatments for their scars (dermabrasion, glycolic acid peels, and topical retinoids). The remainder of subjects denied any intervention prior to study start. Informed consent of the same format used by the Western Institutional Review board was obtained from all patients. Standard Operating Procedures for Clinical Research in accordance with the Moy-Fincher-Chipps oversight committee and Good Clinical Practice were observed.

Inclusion criteria were healthy men and women aged 21-45 years of all racial backgrounds with evidence of grade II-IV atrophic acne scars on the face as determined by the Goodman &Baron qualitative grading system. It was additionally required that patients be able and willing to comply with the treatment regimen and follow-up obligations.

Patients were excluded on the basis of pregnancy, lactation, presence of active acne, concurrent use of systemic retinoids or discontinuation less than one year prior to study start, concurrent use of topical retinoids or discontinuation less than four weeks prior to study start, history of facial surgery or any procedure for acne scars within six months prior to study start, history of skin cancer, history of allergic or hypersensitivity reaction to any active ingredients in the treatment regimen, presence of an active skin infection, presence of deeply fibrotic lesions, and history of immunosuppressive disorder(s).

The trial involved twice-daily application of a 5 ppm barley-derived, human synthetic EGF serum (DNA Regeneration Serum, DNA EGF Renewal, Los Angeles, CA) to the areas of atrophic acne scarring over 12 weeks. All subjects were given a basic

facial cleanser (Neutrogena Ultra Daily Gentle Cleanser, Neutrogena Corp., Los Angeles, CA) for use during the course of treatment. All subjects refrained from the use of tretinoin, retinol and other vitamin A derivatives, as well as all other treatments, topical or otherwise, to the face. Clinical photography using standard Canfield equipment and standardized facial positioning was performed at each visit.

At the study start, the chief investigator completed an evaluation of scar severity using the Goodman &Baron Qualitative Grading System. This system was chosen given its widespread acceptance as a simple and

effective means of normalizing objective appearances among patients.[13] Each subject was assigned a baseline grade and, per recommendation by the system's creators, the investigator defaulted to the more severe disease pattern when a mixture was present.[13] An Investigator's Global Assessment (0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, 5 = extremely severe) was also noted. Subjects were asked to complete an initial personal assessment that rated the severity of scarring (1 = very mild, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe) and evaluated the psychosocial impact of their condition.

Subjects were followed at four-week intervals. At each evaluation, the chief investigator again assigned an IGA score. Patients completed a questionnaire that allowed them to share their experience with the product and any side effects in free-form answers. At the final visit, subjects were asked to complete a supplemental questionnaire that allowed them to share personal perceptions of scar improvement. Subjects rated improvement as poor (0-24% improvement), good (25-49% improvement), very good (50-75% improvement), or excellent (76-100% improvement). The patients who had received prior treatment for their acne scars were additionally asked to rate the EGF serum as 'significantly better," "better," "the same," "worse," or "significantly worse" in comparison. A blinded investigator, who was given before and after photographs for each subject and asked to select the treated image, provided additional evaluation. If chosen correctly, they were asked to quantify the degree of improvement seen in the image as poor (0-24%), good (25-49%), very good (50-75%), or excellent (76-100%).

RESULTS

Eight of the nine originally enrolled patients completed the trial in its entirety. At the study start, three patients were assessed by IGA as severe (4), two as moderate (3), two as mild (2) and one as very mild (1), resulting in an average initial IGA of 2.875 (SEM= .327). By Goodman qualitative grading system (Figure 1), three patients received a grade of 4 (severe), two patients received a grade of 3 (moderate), and three patients received a grade of 2 (mild), resulting in an average grade

TABLE 1.

Comparison of Mean Investigator Global Assessment (IGA) Scores and Mean Goodman Grade for All Patients at Baseline and Final Visit

	Baseline	Final Visit
Mean IGA	2.875 (SEM= .327)	2.38 (SEM = .375).
Mean Goodman grade	3.00 (SEM = .309)	2.75 (SEM = .25)

of 3.00 (SEM = .309). At the end of the trial, 50% of patients demonstrated improvement in IGA, with a final average IGA of 2.38 (SEM = .375). Compared to baseline, 25% of patients demonstrated an improvement in Goodman grade, with a final average grade of 2.75 (SEM = .25). A summary of these statistics can be seen in Table 1.

When asked to choose the treated image for each patient, a blinded investigator correctly selected the post-treatment photograph for five of the eight subjects. For three pairs, the post-treatment image was not correctly identified. The investigator quantified the degree of improvement as "excellent" (76-100% improvement) for two of the images and "good" (25-49% improvement) for the remaining three. Investigator ratings of scar severity in the before and after images for each correctly chosen pair are shown in Table 2. A one-tailed paired student t-test ($\alpha = .05$) performed on this data yielded a statistically significant P-value of .0019.

There were no reports of adverse reactions or side effects during the course of the 12-week period. When asked to rate the degree of improvement they saw in their acne scars at the final visit, one subject reported excellent (76-100%) improvement, four reported very good (50-75%) improvement, two reported good (25-59%) improvement, and only one subject reported poor (0-24%) improvement. Figure 2 illustrates what one subject perceived as "excellent" improvement. The mean time at which improvement was first perceived was 7.5 weeks. Of the four subjects who reported prior treatments for their acne scars, only three were able to complete the comparison evaluation owing to a loss of one subject to follow-up. Two subjects who had tried

dermabrasion and Retin-A in the past reported that EGF serum worked “significantly better.” One subject reported EGF serum efficacy as the “same” as dermabrasion. When asked whether they would recommend topical EGF serum to others suffering from atrophic acne scars, all subjects in the trial but one said yes.

DISCUSSION

The pathogenesis of atrophic scarring following acne vulgaris remains poorly understood, though most agree that inflammatory mediators are involved, which trigger the degradation of collagen.[6,14] The role of inflammation is evident in a study that examined biopsy specimens of acne lesions from patients with and without severe scars and found the inflammatory reaction

TABLE 2.

Pre and Post-Treatment Severity Ratings of Patients for Which With Blind Investigator Correctly Chose the Treated Image

Patient	Severity rating (before)*	Severity rating (after)*
1	4 (moderate)	2 (very mild)
2	3 (mild)	2 (very mild)
3	3 (mild)	2 (very mild)
4	2 (very mild)	1 (none)
5	2 (very mild)	1 (none)

*P- value = .0019

at the pilosebaceous gland to be stronger and of a longer duration in patients with scars compared to those without.[15]

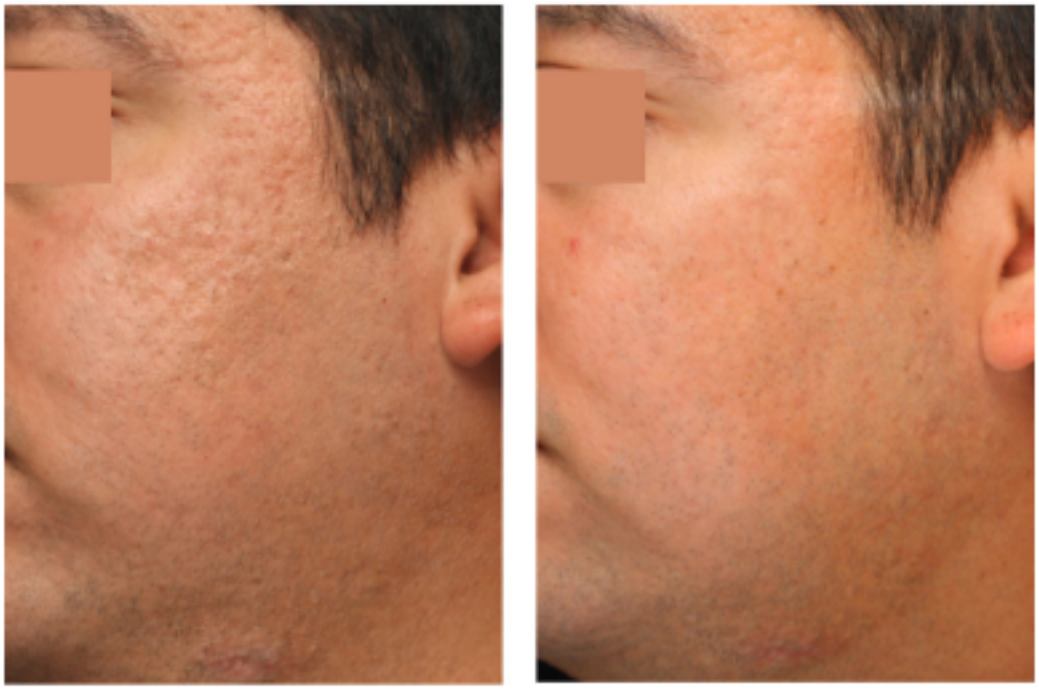
Acne scar formation is thought to occur during the final, third stage of inflammation and wound healing.[11] During this phase, fibroblasts and keratinocytes produce collagen-degrading matrix metalloproteinases along with their inhibitors, both of which act in concert to determine the architecture of the extracellular matrix.[11] Typically, collagen degradation by matrix metalloproteinases (MMPs) is regulated by a number of growth factors that ensure an adequate balance between collagen degradation and synthesis.

In inflammatory acne lesions, MMP-1, MMP-3, and MMP-9, all of which strongly degrade type III collagen, are elevated compared to uninvolved facial controls, owing to increased expression of AP-1, a transcription factor released during inflammation that regulates these enzymes.[7] Also elevated is MMP-8, a collagenase release by neutrophils that is highly specific for type I collagen, the primary structural component of dermal tissue.[7,16] Studies have also demonstrated that acne scar specimens express less than normal quantities of TGF-β, a growth factor that directly inhibits MMPs. TGF-β also maintains extracellular matrix homeostasis by inducing the proliferation of fibroblasts and thereby increasing their deposition of collagen during wound repair.[17,18] Therefore, increased MMP activity combined with reduced expression of TGF-β leads to uninhibited collagen degeneration and, ultimately, collagen deficiency. Quantitative confirmation of this matrix breakdown was provided by a recent study that found a 2.6 fold increase in degraded collagen in inflammatory acne lesions compared to non-lesional facial acne.[7] Increased expression of procollagens I and III in inflammatory acne lesions indicate that the process of dermal matrix degradation is followed by attempts at synthesis and repair. However, this process is imperfect and repetitive cycles, over time, are unable to compensate for tissue atrophy.[7] The result is focal areas of collagen loss, forming scars that are clinically noticeable.[7]

The vast majority of treatments for atrophic scars work by resurfacing the skin and inducing injury by one of several methods, of which chemical peels, dermabrasion, laser resurfacing and, more recently, percutaneous skin needling, are considered the most effective.[6,11] Though the mechanism and depth of injury varies with each treatment, all exploit the inflammatory response. Micro-injuries to the dermis stimulate the need for wound healing and activate an inflammatory cascade that includes fibroblast proliferation and the release of growth factors that promote neocollagenesis and dermal remodeling.[3,6,19] This process replaces fragmented collagen and elastin with more compact and favorably organized fibers, thereby compensating for the aftermath of dysregulated inflammation seen in acne lesions.[19] Owing to the nature of these treatments, a variable degree of discomfort is typically experienced. Associated risks include prolonged erythema, transitory and permanent pigmentary changes, infection, edema, and scarring.[6,20] To achieve satisfactory results, several treatments are typically required and, even when the recommended protocol is followed, no one currently available treatment can achieve complete scar resolution.[6]

One of the growth factors released during the inflammatory response is epidermal growth factor (EGF). Signaling between EGF and its receptor, EGFR, is critical for epidermal homeostasis and has been shown to stimulate the proliferation of keratinocyte stem cells in vivo as well as accelerate healing in damaged skin.[21,22] EGF is also pro-mitotic for fibroblasts, stimulating their

FIGURE 2. Visible improvement in atrophic acne scars following 12-week daily topical application of EGF serum.



proliferation and thereby their deposition of collagen, an action that occurs during wound healing as well as normal cellular development.[16,22-24] Evidence for this role was provided in a study by Laato et al, which found dose-dependent increases in the accumulation of collagen following EGF injections in rat wound models.[23] The resulting increase in collagen content of extracellular matrices explains improvements in dermal thickness following topical application of EGF in pharmacologic doses.[24]

The stimulatory effects of EGF likely underlie the improvements in acne scarring seen by the subjects in this study. Whereas resurfacing procedures rely on skin injury to trigger its release, direct topical application offers the effects of EGF without the associated discomfort and recovery time. The production of new collagen, which replaces residual, fragmented fibers resulting from inflammatory acne lesions, thickens the dermis and combats tissue atrophy.

While not the primary focus of this study, several subjects reported improvements in fine lines and general skin consistency. Because a majority of acne scar sufferers are adults, thin skin, the result of both age-dependent processes and cumulative UV exposure, is a common secondary complaint.[16,25] The ability of EGF to stimulate neocollagenesis and dermal thickening likely explains the reduction in fine lines and wrinkles and increased firmness reported by a majority of the subjects in our study. Patients with macular scarring and pigmentary abnormalities also noted an improvement in hyperpigmentation. These findings were similarly expected in light of the well-documented role of EGF in stimulating epidermal regeneration.[16,22,26] Similar results were documented by a recent study evaluating the efficacy of topical EGF in the treatment of photodamaged skin. All subjects in this study noted improvements in skin texture, fine lines, and wrinkles, while the vast majority also saw a reduction in brown and age spots.[16]

These results suggest that topical EGF may improve the appearance of atrophic acne scars. As the first study of its kind on acne scars using topical human growth factors and given the small sample size, however, further studies are necessary to investigate the ideal duration and frequency of application to maximize results. Additionally, these results could be sometimes strengthened by the use of a more objective means of

evaluation than clinical photography alone. For example, histologic analysis of collagen content in areas of atrophic scarring before and after the application of EGF serum may underscore the improved clinical results for a more unbiased assessment of efficacy. Histologic or quantitative methods of assessing collagen production, however, are difficult to accomplish in human volunteers given the need for biopsies that may cause facial scarring. Future studies with a larger number of patients comparing improvement between EGF serum and vehicle alone will be performed in the future.

Looking forward, we would also like to evaluate the prophylactic use of topical EGF in the prevention of atrophic scar formation in patients with active acne. We believe that, by counteracting collagen degradation during the course of the inflammatory response, significant tissue atrophy capable of causing visible scarring may be prevented. Knowing the role that MMPs play in the formation of these scars, pairing EGF serum with an agent capable of reducing MMP expression may generate better results than seen with EGF serum alone. The proven role of DNA repair enzymes in silencing MMP genes suggests they may be the proper agent.[27] Therefore, studying a combination of EGF serum with a cream containing DNA repair enzymes may optimize results by simultaneously inhibiting collagen breakdown and promoting its synthesis.

DISCLOSURES

Dr. Ronald Moy owns stock and is the scientific advisor of DNA EGF Renewal, which manufactures the serum studied in this trial.

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