STUDY

Topical Fluorouracil for Actinic Keratoses and Photoaging

A Clinical and Molecular Analysis

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Objective: To examine clinical and molecular changes after topical fluorouracil treatment of photodamaged human facial skin for actinic keratoses.

Design: Nonrandomized, open-label 2-week treatment with fluorouracil cream, 5%, followed by clinical and molecular evaluation.

Setting: Academic referral center.

Patients: Twenty-one healthy volunteers, 56 to 85 years old, with actinic keratoses and photodamage.

Interventions: Twice-daily application of fluorouracil cream for 2 weeks and biopsies and clinical evaluation at baseline and periodically after treatment.

Main Outcome Measures: Gene and protein expression of molecular effectors of epidermal injury, inflammation, and extracellular matrix remodeling 24 hours after fluorouracil treatment; clinical improvement measured by evaluators, photography, and patient questionnaires.

Results: One day after the final fluorouracil treatment, gene expression of the effectors of epidermal injury (keratin 16), inflammation (interleukin 1β), and extracellular matrix degradation (matrix metalloproteinases 1 and 3) was significantly increased. Types I and III procollagen messenger RNA were induced at week 4 (7-fold and 3-fold, respectively). Type I procollagen protein levels were increased 2-fold at week 24. Actinic keratoses and photoaging were statistically significantly improved. Most patients rated photoaging as improved and were willing to undergo the therapy again.

Conclusions: Topical fluorouracil causes epidermal injury, which stimulates wound healing and dermal remodeling resulting in improved appearance. The mechanism of topical fluorouracil in photoaged skin follows a predictable wound healing pattern of events reminiscent of that seen with laser treatment of photoaging.

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FLUOROURACIL IS AN ANTIMETABOLITE chemotherapeutic agent that inhibits the synthesis of thymine, a critical building block of DNA. Fluorouracil is preferentially incorporated into the DNA of cancers of the bone marrow, intestine, liver, and other tissues and leads to cell death. It is used systemically to treat cancers of the colon, head and neck, pancreas, and other organs.[1-5]

In early studies of cutaneous changes associated with systemic fluorouracil in patients with cancer, Falkson and Schulz[2] observed photosensitivity, erythema, pigmentation, alopecia, and nail changes. Specifically, they noticed that a patient with light skin, red hair, and keratoses developed erythema after systemic fluorouracil treatment, especially around the keratoses. The keratoses were then noted to disappear after therapy, sometimes without preceding erythema. More recent observations of systemic fluorouracil therapy describe a similar finding of an erythematous, papulosquamous eruption resembling a drug eruption on sun-exposed sites.[6]

On the basis of these early observations, Dillaha et al[7,8] pioneered the use of a topical formulation of fluorouracil for the treatment of actinic keratoses (AKs), with a 20% ointment applied to facial skin for 4 weeks, which resulted in selective inflammation, erosion, and resolution of AKs with little effect on normal skin without sys-

temic absorption. Other early pioneers in topical fluorouracil therapy described its application for premalignant and invasive skin cancers.[9-11] Topical fluorouracil has become a standard treatment of AKs along with cryotherapy, curettage, topical imiquimod, topical diclofenac sodium gel, and other superficial destructive procedures. It is associated with a predictable, characteristic reaction of erythema, desquamation, erosion, crusting, and sometimes pain, which typically resolve after discontinuation of the therapy. Although the mechanism of action of fluorouracil in rapidly proliferating solid tumors is well described, its mechanism of action in AKs is not well understood.

Interestingly, early observers of cutaneous reactions to systemic fluorouracil commented on the softening and smoothing of the skin's texture,[2] and others noted that patients' skin texture was restored to what it had been 2 decades earlier but that there was no effect on seborrheic keratoses, wrinkles, or hyperpigmentation.[12] Sturm and Scott[13] noted marked reduction in wrinkling after treatment, leading to an excellent cosmetic as well as therapeutic response. In our collective years of experience with topical fluorouracil, we, too, have noted improved appearance and texture of photoaged skin in patients treated for AKs.

Although topical fluorouracil is well established in many clinical trials as a therapy for the eradication of AKs,[7-9,12-15] softening and smoothing of the skin's texture and the wrinkle reduction effect have not been formally studied. In this study, we set out to determine whether patients treated with a standard course of topical fluorouracil for AKs have improvement of wrinkles, texture, and pigmentation measured by clinical and biochemical variables.

METHODS

This study was approved by our institutional review board, and written informed consent was obtained from all study patients before entry. In all, 21 patients recruited from the Department of Dermatology at the University of Michigan (13 men and 8 women) aged 56 to 85 years, with clinically evident moderate to severe photodamage and AKs involving the face, were enrolled for the 24-week study. We specifically selected patients who had a few AKs rather than those with numerous AKs so that we would be able to clearly evaluate photodamaged skin without AKs. The AKs served as "target lesions" to confirm that topical fluorouracil was exerting the expected effect.

Inclusion criteria were age greater than 50 years, presence of several AKs, and moderate to severe photoaging judged by presence of rhytids, dyspigmentation, poikiloderma, lentigines, skin thinning, and/or telangiectases. Patients needed to be in general good health and willing to undergo skin biopsies from the face. Exclusion criteria were previous systemic treatment with fluorouracil; oral retinoid therapy within 2 months of study entry; topical fluorouracil, retinoid, imiquimod, or diclofenac therapy within 2 months of study entry; and previous laser resurfacing or chemical peels for AKs or aging skin. Pregnant or nursing patients were excluded, as were individuals who did not adhere to the treatment regimen and those with a known history of allergy to lidocaine, fluorouracil, or any other known components of the product used (Efudex; Valeant Pharmaceuticals International, Costa Mesa, California).

The study design was a nonrandomized, non–vehicle-controlled, open-label study of a 2-week course of topical fluorouracil. At baseline, patients underwent clinical photography of the face with close-up photographs of target AKs, which were observed throughout the duration of the study. Baseline 3-mm punch biopsy specimens were taken of photodamaged facial skin excluding the central face. Specifically, specimens were taken from preauricular and/or forehead sites. Patients applied topical fluorouracil cream, 5%, to the entire face twice daily for 2 weeks according to the US Food and Drug Administration labeling indications for the treatment of AKs. Subsequent 3-mm punch biopsy specimens were obtained at 2 weeks (24 hours after the last fluorouracil application), 4 weeks, 10 weeks, and 24 weeks from clinically inflamed skin. If skin inflammation was no longer present, biopsy specimens were taken from the same general region where specimens from inflamed skin were taken.

Participants were clinically assessed at baseline, 1 week, 2 weeks (24 hours after the last fluorouracil application), 4 weeks, 6 weeks, 10 weeks, and 24 weeks. Evaluation visits included a global assessment of overall photoaging severity, coarse wrinkling, fine wrinkling, lentigines, mottled hyperpigmentation, sallowness, and tactile roughness. The AKs were counted at baseline and subsequent visits.

Facial photographs were obtained by our department's medical research photographer using a digital camera (Nikon D1x; Nikon Corp, Tokyo, Japan). Face front and left and right profile views were obtained. Photographs were taken with standardized studio lighting and subject positioning. Images were obtained at baseline and weeks 1, 2, 4, 6, 10, and 24. The photographs were subsequently evaluated by a panel of 3 dermatologists (Y.H., D.K., and J.O.), who were not involved in patient evaluations during the study. Evaluators were asked to distinguish pretreatment from posttreatment photographs of patients. Two groups of images from 2 time points were presented in random order to the panel. The first group of images were randomly ordered pretreatment and posttreatment images from baseline and week 10. The second group of images were randomly ordered baseline and week 24 images. The panel independently assigned a score for each photograph based on the 9-point global assessment of photoaging described by Griffiths et al.[16] The patients' impressions of the treatment and the associated results in terms of AK severity and photoaging severity were surveyed at week 10 of the study.

Messenger RNA (mRNA) levels for tumor necrosis factor; interleukin 1β (IL-1β); keratin 16; matrix metalloproteinases (MMPs) 1, 3, and 9; and type I and type III procollagen were quantified by reverse-transcriptase real-time polymerase chain reaction technology.[17] Protein levels of type I procollagen were determined by enzyme-linked immunosorbent assay.[18]

Changes in clinical and biochemical end points during the course of the study were statistically evaluated by means of repeated-measures analysis of variance. Individual pairwise comparisons of values at each subsequent time with baseline levels were made with the Dunnett test. The type I error rate was set at .05. When necessary, logarithmic transformations of the data were made before analysis to achieve normality, and, when appropriate, the data are depicted on figures with logarithmic scaled axes. Summary statistics include means and standard errors. The data were analyzed with SAS statistical software (SAS Institute Inc, Cary, North Carolina).

RESULTS

Twenty-one patients qualified and were enrolled in the study. Nineteen patients completed the study, the photographic requirements, and the clinical evaluations. Twenty patients completed the questionnaire at week 10.

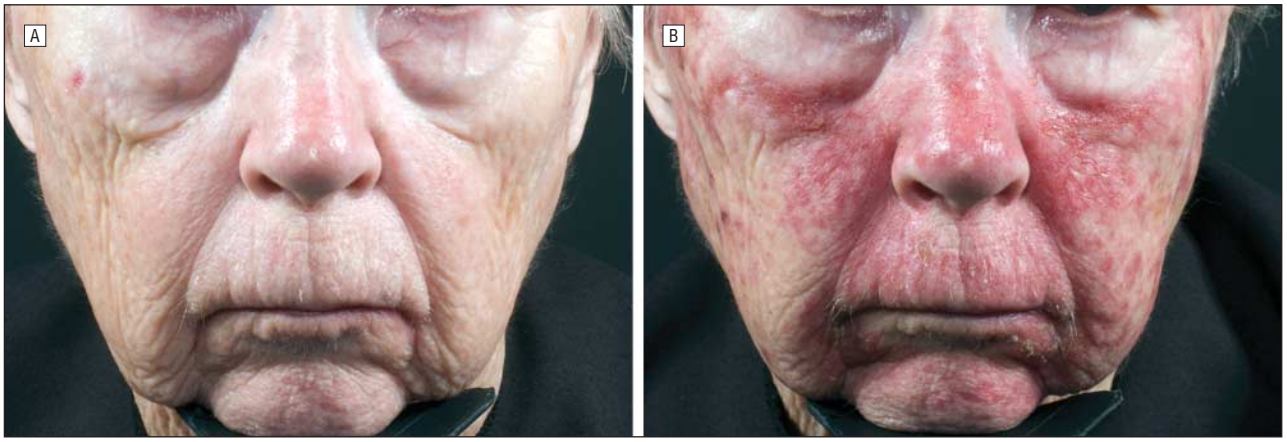

Figure 1. Appearance of a patient before and after topical application of fluorouracil cream, 5%, to the entire face twice daily for 2 weeks. A, Baseline photodamage and actinic keratoses before treatment. B, Appearance 24 hours after the last application of topical fluorouracil, demonstrating erythema, scaling, and desquamation over most of the face.

Topical fluorouracil treatment was generally well tolerated during the 2-week application phase. One patient had severe inflammation after 1 week and therefore ended the treatment phase at day 7 but completed the remainder of the study. All patients developed the characteristic erythema and irritation with enhancement of clinically apparent AKs to varying degrees (**Figure 1**). Some developed confluent erythema, scaling, and swelling, whereas others had more patchy involvement.

CLINICAL EVALUATION

As expected, topical fluorouracil treatment significantly reduced AK counts. The mean number of AKs per patient at baseline was 11.6, and, at the end of the study, the mean number had decreased to 1.5 ($P<.05$) (**Figure 2**).

Wrinkling, tactile roughness, lentigines, hyperpigmentation, and sallowness were rated on a scale of 0 to 9 by dermatologists performing clinical evaluations. Coarse wrinkling was noted to be improved from a baseline mean of 5.76 to a mean of 5.26 at week 24 ($P<.05$) (**Figure 3**A), while fine wrinkling was improved from a baseline mean of 5.10 to 4.53 at week 24 ($P<.05$) (Figure 3B). Fine wrinkling improvement was initially noted at week 6 ($P<.05$) and remained improved at weeks 10 and 24 ($P<.05$). Tactile roughness was improved at week 10 from a baseline of 3.48 to 2.25 ($P<.05$) and continued to improve, with a mean score of 2.11 ($P<.05$) at week 24 (Figure 3C).

Mottled hyperpigmentation was improved from 4.86 at baseline to 4.20 ($P<.05$) by week 4, and this measure continued to improve until week 24, at which time the mean was 3.74 ($P<.05$) (Figure 3D). Lentigines were improved from a baseline mean of 4.52 to 4.05 at week 6, and to 3.60 at week 24 ($P<.05$) (Figure 3E). Sallowness, best defined as a yellow cast seen in photoaged skin, was noted to be improved from a baseline mean of 4.29 to 3.52 by week 2 ($P<.05$) (Figure 3F), but this may be an effect of the erythema created by the therapy and not a true reflection of improvement. However, when inflammatory erythema was no longer present at week 24, sallowness had still decreased to a mean score of 3.00 ($P<.05$).

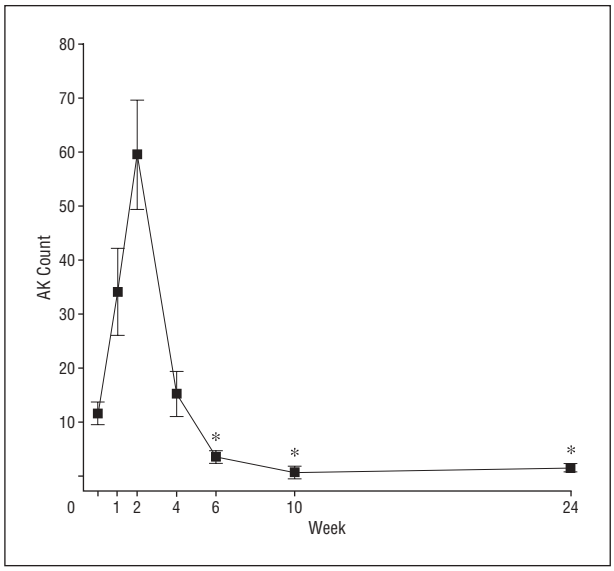

Figure 2. Mean number of actinic keratoses (AKs) in 19 patients at baseline and throughout the study period. The number of AKs was significantly decreased at weeks 6, 10, and 24 when data were analyzed with a logarithmic transformation to account for variability. *$P<.05$.

Finally, an overall global severity rating was assigned to each patient at the start of the study and was evaluated at each subsequent visit on the basis of the previously published photonumeric scale of photoaging.[16] The baseline mean score of patients was 5.38, and this had decreased to 4.85 ($P<.05$) (Figure 3G) at week 6. Continued improvement was seen at week 24, with a mean of 4.63 ($P<.05$).

PHOTOGRAPHIC EVALUTION

Facial photographs obtained at baseline and weeks 10 and 24 were assessed by a panel of 3 dermatologists who were not involved in the clinical assessments of patients. The evaluators were presented with 2 pairs of images for each patient. In the first pair of images, they were asked to assign a global severity photoaging score based on the published Griffiths et al photoaging scale[16] to each image and to use that score to identify randomly ordered images of

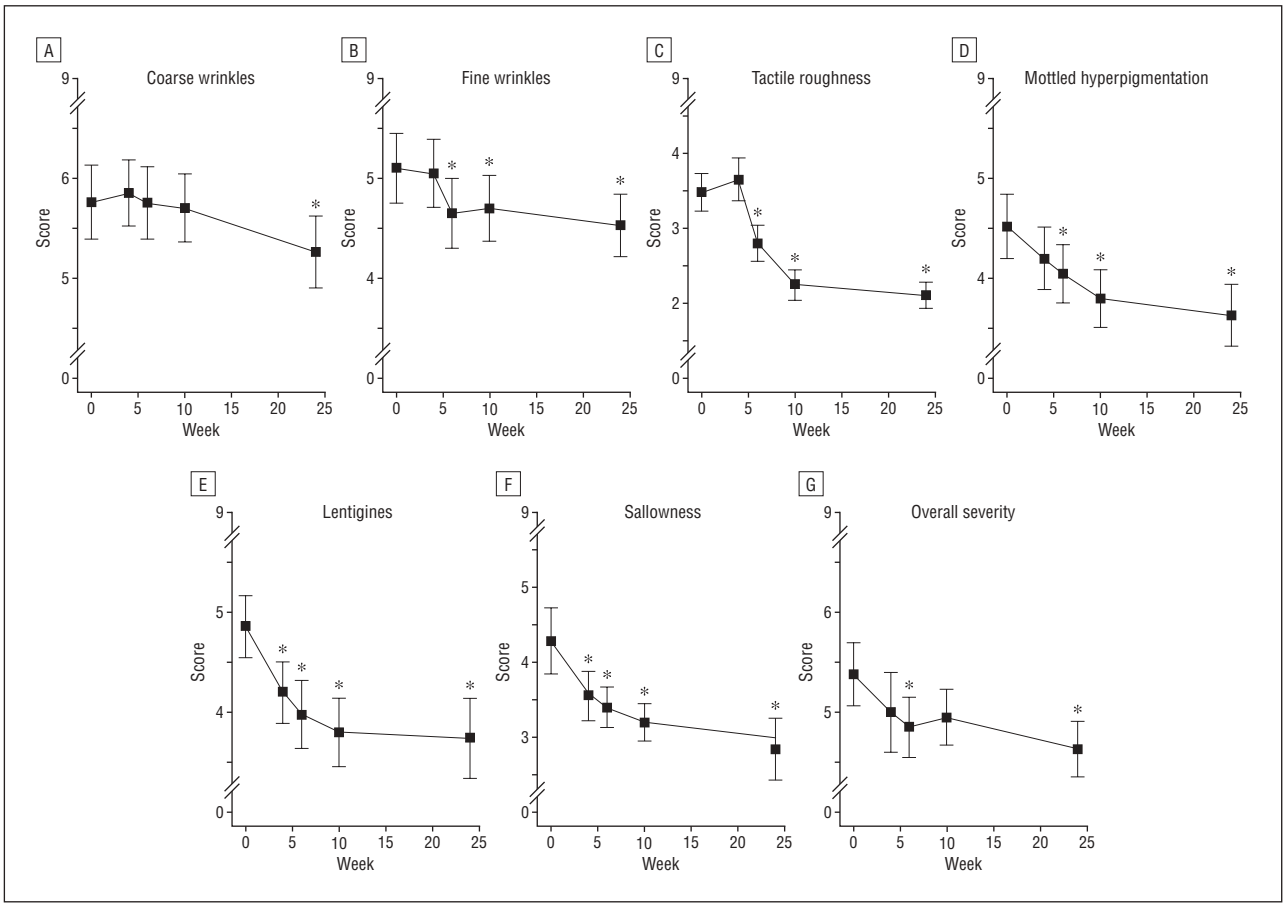

Figure 3. Mean scores of clinical photoaging measures after topical fluorouracil therapy over the course of the 24-week study. The measures were graded on a scale of 0 (none) to 9 (severe photoaging). *$P<.05$ compared with before therapy.

baseline and week 10 images. For the second pair of images, they were asked to assign the global severity photoaging score to randomly ordered images of baseline and week 24. For both pairs of images, the evaluators were asked whether the presence of AKs helped them to distinguish baseline images from week 10 or 24 images, to determine whether they were able to truly discern photoaging or whether the clearance of AKs helped them to make the distinction.

Evaluator 1 was correct in identifying baseline and week 10 images in 74% of cases (14 of 19; $P=.06$), and the presence of AKs was helpful to this evaluator in 42% of cases (8 of 19). When comparing baseline with week 24 images, this evaluator was correct in 94% of cases (17 of 18; $P<.001$), and AKs were helpful to this evaluator in distinguishing baseline from week 24 images in 44% of cases (8 of 18).

Evaluator 2 was correct in identifying baseline and week 10 images in 79% of cases (15 of 19; $P=.02$), and the presence of AKs was helpful to this evaluator in 26% of cases (5 of 19). When comparing baseline with week 24 images, this evaluator was able to correctly identify 89% of cases (16 of 18; $P=.001$), and AKs were helpful to this evaluator in 39% of cases (7 of 18).

Evaluator 3 was correct in identifying baseline and week 10 images in 79% of cases (15 of 19; $P=.02$), and the presence of AKs was helpful to this evaluator in 58% of cases (11 of 19). When comparing baseline with week 24 images, this evaluator was able to correctly identify 72% of cases (13 of 18; $P=.10$), and the presence of AKs assisted this evaluator in 67% of cases (12 of 18).

Overall global severity ratings for the 3 evaluators were averaged for the 2 sets of images. For the first set of images, baseline was scored at 5.19 and week 10 at 4.93 ($P=.005$). The second set of images was scored with a baseline of 5.06 and a week 24 score of 4.76 ($P=.002$). (**Figure 4**).

PATIENT QUESTIONNAIRE

Twenty patients completed a questionnaire at week 10 inquiring about their experience with topical fluorouracil therapy (although 4 questions were inadvertently skipped by 1 patient each). Of all 20 patients, 9 (45%) rated their precancerous lesions as being much improved compared with before treatment, 10 (50%) claimed that their AKs were mildly or moderately improved, and only 1 (5%) reported that there had been no change in precancerous lesions. Nineteen patients (95%) rated their sun damage as mildly (4 [20%]), moderately (7 [35%]), or much (8 [40%]) improved over baseline. Patients reported wrinkle improvement over baseline as mild (8 of 19 patients [42%]), moderate (5 [26%]), or much improved (3 [16%]). All 20 patients reported their skin tex-

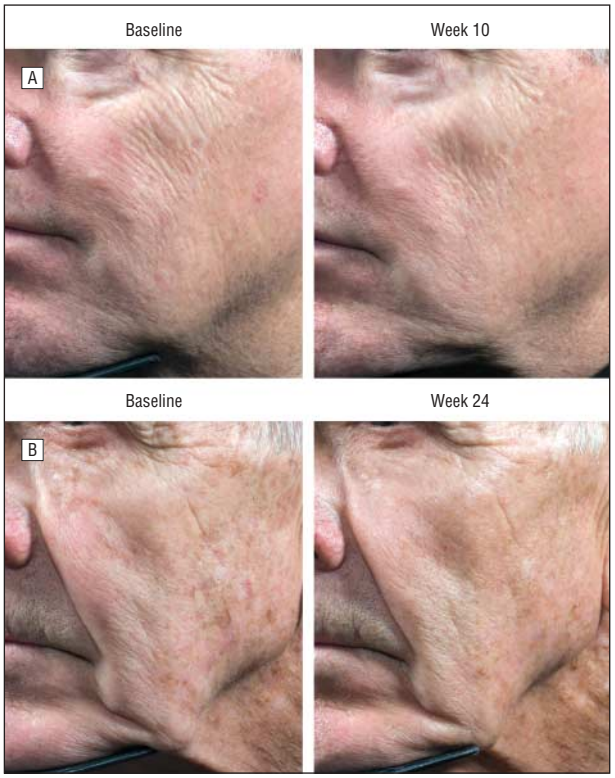

Figure 4. Two pairs of randomly ordered clinical images from each of 2 patients. Such images were presented to investigators not involved in the clinical assessment of patients to see whether they could distinguish between pretreatment and posttreatment photographs. A, At week 10, the investigators were able to distinguish between pretreatment and posttreatment photographs by the improvement in wrinkles and sallowness. B, At week 24, the investigators were able to distinguish between photographs by the improvement in actinic keratoses, wrinkles, and lentigines.

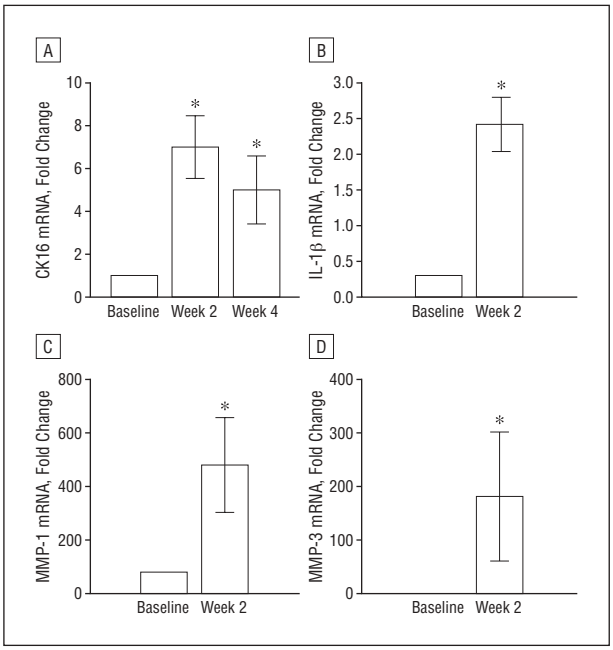

Figure 5. Messenger RNA (mRNA) levels in response to treatment with topical fluorouracil. Levels obtained were for markers of epidermal injury (keratin 16 [CK16]; A), inflammatory mediators (interleukin 1β [IL-1β]; B), and matrix metalloproteinases 1 and 3 (MMP-1 [C] and MMP-3 [D]). Levels were standardized to a baseline of 1, and increases or decreases are described relative to the baseline. Bars represent mean values; limit lines, standard error. *$P<.05$ compared with before therapy.

ture to be mildly, moderately, or much improved over baseline. Even though 12 of 19 patients (63%) reported the fluorouracil treatment to be very uncomfortable (8 [42%]) or moderately uncomfortable (4 [21%]), 17 patients (89%) were willing to undergo the treatment again for photoaging and 11 patients (58%) were willing to pay out of pocket for the treatment. Of all 20 patients, 15 (75%) were very satisfied (10 patients [50%]) or moderately satisfied (5 [25%]) with fluorouracil therapy, whereas 3 patients (15%) were only mildly satisfied and 2 (10%) were neither satisfied nor dissatisfied.

MOLECULAR RESPONSE TO FLUOROURACIL TREATMENT

Keratin 16 is not expressed in normal human interfollicular epidermis. However, keratin 16 expression is induced after epidermal injury and in certain hyperproliferative diseases such as psoriasis. Interfollicular epidermal expression of keratin 16 is a well-characterized marker of injury; its expression is associated with reepithelialization.[19] Keratin 16 mRNA was found to be significantly elevated from baseline to week 2 (24 hours after the final fluorouracil application) by 7-fold (n=16; $P<.05$) and at week 4 by nearly 5-fold (n=15; $P<.05$) (**Figure 5**A).

Tumor necrosis factor and IL-1β are primary inflammatory mediators, and acute induction of these cytokines is expected to occur rapidly after physical stress or wounding. At week 2, just after the completion of topical fluorouracil therapy, IL-1β mRNA levels more than doubled over baseline (n=16; $P<.05$) (Figure 5B). No change in tumor necrosis factor mRNA levels was observed (data not shown).

The MMPs degrade structural proteins that compose the dermal extracellular matrix.[20] Matrix metalloproteinase 1 (collagenase), MMP-3 (stromelysin 1), and MMP-9 (92-kDa gelatinase) are induced in human skin by various stimuli such as laser resurfacing[21] and UV irradiation.[22] Matrix metalloproteinase 1 initiates the cleavage of fibrillar type I and type III collagen, which are the major structural proteins in the dermis. Once cleaved by MMP-1, type I and III collagens are further degraded by MMP-3 and MMP-9. Immediately after topical fluorouracil therapy, marked induction of MMP-1 mRNA (480-fold; n=16; $P<.05$) was seen (Figure 5C) and remained elevated at week 4 (25-fold; n=15; $P<.05$). Matrix metalloproteinase 1 mRNA levels returned to near baseline by week 10 (n=16). Matrix metalloproteinase 3 mRNA was induced 180-fold at week 2 (n=16; $P<.05$), and levels returned to near baseline by week 10 (n=16) (Figure 5D). No change in MMP-9 mRNA levels was observed (data not shown).

Type I procollagen mRNA was induced by more than 7-fold at week 4 (n=15; $P<.05$) (**Figure 6**A), and type III procollagen mRNA was significantly elevated at week 4 by nearly 3-fold (n=15; $P<.05$) (Figure 6B). Consistent with the mRNA data, procollagen protein levels were

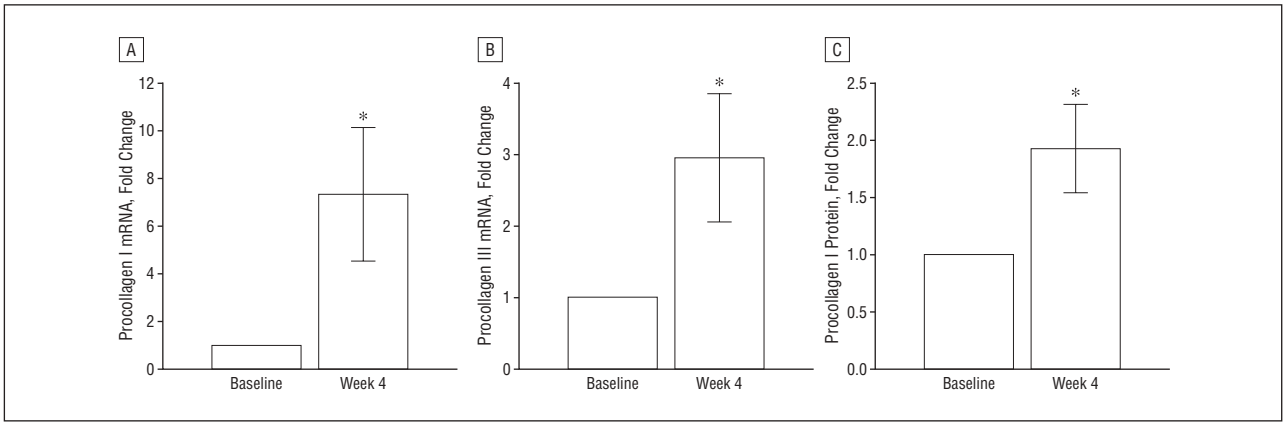

Figure 6. Changes in type I and III procollagen messenger RNA (mRNA) and type I procollagen protein after treatment with topical fluorouracil. A, Type I procollagen mRNA is increased at week 4. B, Type III procollagen mRNA is increased at week 4. C, Type I procollagen protein is increased at week 24. Bars represent mean values; limit lines, standard error. *$P<.05$ compared with before therapy.

significantly elevated at week 24 by nearly 2-fold (n=10; $P<.05$) (Figure 6C). These data suggest that there may be a sustained effect on collagen deposition after fluorouracil therapy.

COMMENT

Topical fluorouracil has been used for more than 4 decades for the treatment of AKs. Although subjective improvements in photodamaged skin have been observed,[2,12,13] formal studies are lacking in quantifying the changes associated with improved skin appearance. Our study evaluated the improvement in photodamaged skin with AKs and disclosed some of the underlying mechanisms of this repair.

The clearance of AKs after a course of topical fluorouracil was significant and predictable. The presence of AKs was an end point for our study as a positive control to demonstrate that topical fluorouracil was exerting its known effect and to ensure that patients were using the drug properly. We used a logarithmic transformation of the data for AKs because of the large range in the number of AKs that each patient had at the start of the study. A significant decrease was seen in AKs at the end of the study with this type of analysis.

Interestingly, at the end of the application period at 2 weeks, the average number of AKs was significantly increased from 11.6 to 59.5 ($P<.05$) per patient. The increase in AKs immediately after therapy raises the issue of the quantification of AKs. It is well known that AK counts, even when performed by expert dermatologists, are unreliable.[23] It is also known that "subclinical" AKs are unmasked after fluorouracil therapy. However, we believe that significant amounts of the red, scaly, confluent areas that were judged to be AKs were, in fact, areas of inflamed skin. It may be that fluorouracil is less selective for AKs than previously reported and is actually exerting an inflammatory effect on photodamaged skin in general rather than just on AKs. There is controversy in the literature regarding AK clearance in relation to inflammation and irritation. A study of 10 patients in 1991 who applied topical fluorouracil once or twice weekly for 6 to 10 weeks concluded that AKs were cleared in 98% of patients without significant irritation,[24] but this regimen may have induced clearance of AKs through subclinical inflammation. Epstein[25] attempted to replicate this study but found that topical pulse fluorouracil (once weekly for 10 weeks) did not clear AKs in two-thirds of patients compared with daily topical fluorouracil. He proposed that this discrepancy in the findings may be attributable to the quantification of AKs. A more recent study's results supported Epstein's findings; it compared twice-daily topical fluorouracil to once-weekly topical fluorouracil and found that twice-daily application was more effective at clearing AKs than once-weekly treatment and also concluded that inflammation is likely to be required to achieve the therapeutic effect.[26] Our work concurs with this premise that inflammation is needed for AK clearance. Furthermore, our study suggests that remodeling of the dermal matrix, which follows the inflammatory phase of wound healing, is the mechanism for the improved appearance of photodamaged skin.

After a 2-week course of topical fluorouracil, the observed biochemical changes are typical of a wound-healing response. Keratin 16 is expressed in squamous epithelia undergoing abnormal regenerative hyperplasia as in the case of epidermal injury and irritation.[19] Keratin 16 expression was significantly elevated by fluorouracil therapy and remained so for several weeks. Enhanced keratin 16 expression is a marker of injury, and fluorouracil predictably induced clinical injury manifested by erythema, inflammation, and desquamation. Levels of the proinflammatory cytokine IL-1β were significantly elevated by fluorouracil treatment early on. This proinflammatory cytokine is known to induce MMPs. Shortly after IL-1β induction, MMP-1 (collagenase 1) and MMP-3 (stromelysin) levels were elevated. The MMP-1 catalyzes the first step of collagen degradation and MMP-3 further degrades partially degraded collagen as well as other matrix proteins. Levels of these MMPs reverted to near baseline at week 6. Although the changes seen after topical fluorouracil therapy are not as dramatic as those after carbon dioxide laser resurfacing, the pattern of biochemical changes seems to closely follow them, suggest-

ing that fluorouracil may be inducing a wound-healing response after damage.[21]

Type I and type III collagen mRNA were induced at week 4 and remained elevated at 6 months, which was the end of the study. Consistent with increased mRNA levels, protein levels of procollagen I were elevated at study's end by 2-fold, indicating long-lasting effects of fluorouracil on dermal extracellular matrix.

We chose to study a dosing regimen (approved by the US Food and Drug Administration for the treatment of AKs) of twice daily for 2 weeks, which produces significant and predictable irritation and inflammation. Had we chosen a regimen producing less irritation and inflammation, such as a pulse-dose regimen, it is unclear whether the same biochemical changes would have been seen. If epidermal damage is the mechanism by which topical fluorouracil exerts its effects, then it would be expected that any agent producing equivalent damage would exhibit such effects.

We designed our study without randomization or placebo because it is not possible to randomize patients to topical fluorouracil therapy or vehicle alone, as it would be readily apparent to the patient and the study team which therapy was being used from the vigorous and predictable inflammatory response from topical fluorouracil. We did not set out to compare topical fluorouracil with drugs known to improve photoaging, so the option of a topical retinoid as a control was not investigated. Nor did we believe that comparison with a topical retinoid could simulate the same degree of irritation and inflammation seen with topical fluorouracil. A split-face study would not have been a practical undertaking given that patients often do not adhere to this study design and that studies have shown that migration of topical preparations across the face is known to occur (James Leyden, MD, written communication, September 19, 2008), obviating this design. We used blinded evaluators to score resolution of AKs and subjective improvement in photoaging to compensate for the study design.

The changes seen in photodamaged skin in response to a course of topical fluorouracil are consistent with a wound-healing response. Perhaps it is best to think of topical fluorouracil as being selective for photodamaged skin rather than just for AKs. Its mechanism in photodamaged skin seems to be that damage to the epidermis triggers a cascade of fibrogenic activities of the dermis. For patients in whom a course of topical fluorouracil is indicated for the treatment of AKs, there will likely be the additional benefit of a restorative effect from sun damage; this may provide further motivation for these patients to undergo the rigorous treatment. It is possible that for some patients topical fluorouracil may have an important role against photoaging. For others, however, it may not be cosmetically acceptable given that a standard course of therapy may last 2 to 3 weeks and the ensuing reaction can persist for several more weeks. Undoubtedly, there will be patients who desire a therapy such as topical fluorouracil for cosmetic purposes given the relatively low cost of this therapy compared with ablative laser resurfacing. It may not, however, achieve the same degree of improvement.

Evidence is accumulating that even minimal epidermal injury, such as that from nonablative laser resurfacing, microdermabrasion, and now topical fluorouracil, can lead to mild to moderate clinical improvement.[27,28] It is likely that other topical agents such as diclofenac gel or imiquimod that have similar skin-injuring properties in photodamaged skin may have a similar restorative effect.

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Author Contributions: Drs Sachs, Hammerberg, and Fisher had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Sachs, Kang, Johnson, Fisher, and Voorhees. *Acquisition of data*: Sachs, Hammerberg, and Fisher. *Analysis and interpretation of data*: Sachs, Kang, Hammerberg, Helfrich, Karimipour, Orringer, and Fisher. *Drafting of the manuscript*: Sachs and Kang. *Critical revision of the manuscript for important intellectual content*: Kang, Helfrich, Karimipour, Orringer, Johnson, Fisher, and Voorhees. *Statistical analysis*: Hamilton. *Obtained funding*: Voorhees. *Administrative, technical, and material support*: Hammerberg. *Study supervision*: Sachs, Hammerberg, Hamilton, Fisher, and Voorhees.
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