Reduced Number of Actinic Keratoses With Topical Application of DNA Repair Enzyme Creams

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ABSTRACT

Background: Actinic keratoses (AKs) are regarded as a carcinoma in situ by some dermatologists and its incidence continues to rise. Exposure to ultraviolet (UV) radiation is considered to be an important risk factor for developing these pre-malignant lesions. DNA repair enzymes have been shown to reverse sun-damage, resulting in reduced rates of actinic keratoses and non-melanoma skin cancers in specific patient populations.

Methods: Seventeen patients were evaluated for differences in actinic keratoses following topical application of T4N5 liposome lotion over 48 weeks.

Results: Compared to baseline, a statistically significant reduction in the number of actinic keratoses was seen following the treatment period.

Discussion: This study suggests that DNA repair enzyme creams effectively reduce the number of actinic keratoses in normal individuals with moderate-to-severe photodamaged skin.

INTRODUCTION

An increase in the number of actinic keratoses (AKs) has been seen within recent decades, globally. It is estimated that about 40 million United States (US) citizens have actinic keratoses. Furthermore, AKs are currently one of the most prevalent carcinomas in situ worldwide. It is widely accepted that AKs have the potential to progress to non-melanoma skin cancer. In a recent study by Criscione et al., the progression of AKs to either squamous cell carcinoma or basal cell carcinoma was more frequent than previously thought, with a progression rate of 0.6% or 0.5% in one year, respectively. Additionally, it is impossible to determine which individual AK will progress to a more invasive stage. Therefore, it is imperative to properly treat all clinically diagnosed AKs.

Current treatment of AKs involves ablative procedures or topical therapies. Yet, the most common method of treatment is cryotherapy. Despite the widespread use of cryotherapy, it has been reported that most patients prefer topical therapy to ablative procedures. Furthermore, cryotherapy can result in pain, pigmentation changes, scarring, and delayed healing of lesions. Alternative ablative procedures include surgical excision, dermabrasion and curettage, near-infrared laser treatment and chemical peels. All of these methods may cause pain, epidermal changes, and scarring as well. Topical therapies that are approved by the U.S. Food and Drug Administration (FDA) are 5-fluorouracil (5-FU), imiquimod cream, diclofenac gel and photodynamic therapy (PDT) with topical aminolevulinic acids. All of these topical therapies effectively and safely treat AKs. However, each has unpleasant side effects, some of which may interfere with patient compliance. Topical 5-FU may cause severe dermatitis with wound infections, pruritus, pain and ulceration. Imiquimod cream produces erythema, itching and burning at the site of application. It may also cause fevers with mucosal application or with treatment of larger areas. Diclofenac gel has similar side effects, including pruritus, erythema, dry skin and paraesthesia. PDT can selectively treat sub-clinical lesions, however, the costs of treatment can be high and there is a risk of photosensitivity.

As previously stated, all forms of current therapy effectively treat AKs; however, unpleasant side effects, medication regimens and costs may be an issue for certain patients. The purpose of this study is to determine if DNA repair enzyme cream (T4N5 liposome lotion) is a suitable alternative to the current topical therapies for the treatment of AKs. T4N5 liposome lotion contains the DNA repair enzyme T4-bacteriophage endonuclease V encapsulated within liposomes. With topical application, the enzyme is transported into skin cells, resulting in an increased rate of repair of sunlight-induced DNA damage. Studies have shown that liposome-encapsulated T4 endonuclease V increases removal of cyclobutane pyrimidine dimers from DNA, thereby reducing the incidence of skin cancer in UV-irradiated mice and in xeroderma pigmentosum patients. Furthermore, it has been shown that the presence of unrepaired cyclobutane pyrimidine dimers in DNA is a direct cause of cancer in mammalian skin.

In 2001, the Xeroderma Pigmentosum Study Group reported that topical T4N5 resulted in a 68 percent reduction in actinic keratoses and a 30 percent decrease in basal cell carcinomas.
when compared to placebo. In addition, reductions in the rate of new lesions remained stable during the six months following therapy and no significant adverse effects were noted as a result of therapy. Several studies have shown the effects of T4N5 in normal patients as well. Yarosh et al. demonstrated that T4N5 liposomes enhance DNA repair in the keratinocytes of skin cancer patients. Gilchrist et al. reported that T4N5 treatment enhances UV-induced melanogenesis in human melanocytes, which decreases damage from subsequent sun exposure by increasing the amount of epidermal melanin. Wolf et al. reported that the enzyme almost completely prevented UV radiation-induced upregulation of interleukin-1 and tumor necrosis factor-α mRNA, demonstrating the enzyme’s immunoprotective effects. However, no significant affects on erythema response and microscopic sunburn cell formation were seen. In addition, the chemopreventive properties of T4N5 in renal transplant recipients are currently under investigation.

**METHODS**

Seventeen subjects were evaluated for differences in actinic keratoses following topical application of T4N5 liposome lotion for a period of 48 weeks. All subjects included in the study had moderate-to-severe facial photodamage (determined by the Glogau scale), and one or more actinic keratoses (with an overall mean of 9.76). Subjects were aged 45–80 years old, were immunocompetent and in general good health, possessed Fitzpatrick Type I, II or III skin, and were not allergic to any component of the study topical medications. In addition, included subjects agreed to avoid natural and artificial ultraviolet (UV) light during the study. Subjects were excluded if they were pregnant or nursing, required to spend excessive time in the sun, had received topical drug therapy for actinic keratoses within the past three months or for photoaging within the past six months or had participated in a clinical testing study involving the face in the prior three months. Additionally, subjects were excluded if they had any facial skin disease that might interfere with the study treatments, including, but not limited to, rosacea, atopic dermatitis, psoriasis and seborrhea.

Subjects were clinically evaluated at baseline, and then instructed to apply DNA Repair Formula™ to the entire face twice daily at 2 mg/cm². The effects of differences in facial cleansing products were controlled by having all subjects use Olay® Beauty Bar, Sensitive Skin version, for all facial cleansing. Subjects were then re-evaluated at weeks 2, 4, 12, 24, 36 and 48. The two-week visit served only as an assessment of compliance to dosing and as an adverse event check.

All subjects were evaluated by the same trained dermatologists (DK, RM, WF) throughout the entire study. From the baseline visit to week 48 (a total of seven visits), the number of actinic keratoses within the treatment area was recorded at each visit, with the exception of the second and fourth visits.

Subject compliance was determined by diary sheets, upon which daily application of the study product was recorded and by weighing all product containers prior to dispensal and again upon return. Any discrepancies were discussed with the subject.

**RESULTS**

Tables 1 and 2 describe the analysis results for the change across time (across visits 1, 3, 5, 6 and 7) in the 17 study patients. Table 1 summarizes the result for each individual visit, while Table 2 summarizes the change from visit 1 to each subsequent visit. Note that each change in Table 2 involves only the patients who had data for both of the visits. In summary, a statistically significant reduction has been detected at the 0.05 significance level for the change from visits 1–5 (Wilcoxon signed rank P=0.038) and the change from visits 1–7 (Wilcoxon signed rank P=0.044). The Wilcoxon test has been used rather than the more standard paired t test due to the presence of distributional non-normality.

**TABLE 1.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Wilcoxon</th>
<th>Signed Rank</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Visit 1</td>
<td>17</td>
<td>9.76</td>
<td>7.38</td>
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<tr>
<td>Visit 3</td>
<td>16</td>
<td>9.31</td>
<td>8.51</td>
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<tr>
<td>Visit 5</td>
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<td>6.07</td>
<td>4.40</td>
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<tr>
<td>Visit 6</td>
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<td>6.54</td>
<td>5.83</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 7</td>
<td>12</td>
<td>5.17</td>
<td>7.59</td>
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**TABLE 2.**

<table>
<thead>
<tr>
<th>Change from Baseline (visit_1)</th>
<th>N</th>
<th>Mean Reduction of AKs</th>
<th>Std Dev</th>
<th>Wilcoxon Signed Rank</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Visit 5 15</td>
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<td>0.038</td>
<td></td>
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<tr>
<td>Visit 6 13</td>
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<td>7.69</td>
<td>0.413</td>
<td></td>
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</tr>
<tr>
<td>Visit 7 12</td>
<td>-4.42</td>
<td>10.88</td>
<td>0.044</td>
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</tbody>
</table>

*Statistically significant, P<0.05*
In addition, repeated measures analysis of variance has also been used to evaluate the change across all five visits simultaneously. The resulting $P$ value of 0.025 indicates that a statistically significant overall change across time has been detected at the 0.05 significance level. The data from each visit was square root transformed for this repeated measures analysis of variance modeling due to the presence of distributional non-normality.

**CONCLUSION**

In vitro and in vivo studies show that topical T4N5 enhances repair of DNA damage induced by UV irradiation. It has successfully repaired damaged DNA within murine models, xeroderma pigmentosum patients, and in normal patients.\(^5,6,8\)

The results of this study suggest that topical application of T4N5 liposome lotion can effectively reduce actinic keratoses in normal patients who have moderate to severe photodamaged skin. Furthermore, differences in the number of actinic keratoses, from baseline, following treatment were statistically significant.

There are several advantages to T4N5 liposome lotion, including its ability to enhance DNA repair and to protect skin following exposure to the sun.\(^9\) In addition, unlike current modalities in the treatment of actinic keratosis, no significant adverse effects have occurred with the use of T4N5 during in vivo studies.\(^5,8\)

This is likely explained by the fact that liposome encapsulated T4 endonuclease V is localized to the epidermis.\(^7\) Furthermore, a significant decrease in the repair rates of both thymine dimers and photoproducts is evident with aging,\(^11\) which may be reversed by usage of DNA repair enzyme creams. Finally, as mentioned previously, the majority of patients prefer topical chemotherapeutics, as opposed to ablative procedures.\(^1\)

In order to appreciate the full benefits of therapy with T4N5 liposome lotion, this research should be repeated with a larger group of subjects in a randomized, controlled study. Therefore, the effects of T4N5 can be compared against a placebo, in order to rule out spontaneous resolution of actinic keratoses, rather than improvement secondary to treatment. In turn, it may be helpful to assess the long-term results of treatment. The Xeroderma Pigmentosum Study Group reported that the rates of new actinic keratoses and basal cell carcinomas did not increase even six months after discontinuation of therapy.\(^1\) Thus, it would be sensible to determine whether a similar effect is seen in normal individuals as well.

The authors foresee a future in which DNA repair cream will be another modality in skin cancer chemoprevention in normal individuals, providing adequate results with minimal to no adverse effects.

**DISCLOSURES**

The authors have no relevant conflicts of interest to disclose.

**REFERENCES**


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