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Single ablative fractional resurfacing laser treatment for forearm actinic keratoses: six month follow-up data from an intrapatient comparison between treated and untreated sites

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Abstract

Introduction: Actinic keratoses (AK) are common precancerous lesions which are associated with ultraviolet light exposure and aging. Wounding therapies such as fractionated laser resurfacing have been previously demonstrated to effectively treat facial AK. However, the effectiveness of fractionated laser resurfacing (FLR) on other sites commonly afflicted with AK has not been studied in detail. Previously, our group has reported that treatment of aged skin with wounding therapies including dermabrasion and ablative fractionated resurfacing results in removal of senescent fibroblasts and normalizing the pro-carcinogenic acute ultraviolet B radiation responses associated with aged skin. The current studies were designed to test the effectiveness of FLR of forearm skin of subjects age 60 and older to remove AKs.

Methods: Between February 2018 and March 2019, 30 subjects were enrolled in a study in which they underwent a single FLR treatment of one extremity including dorsal forearm, wrist and dorsal hand. Numbers of AKs were recorded on both extremities at baseline, three and six months in blinded fashion. Side effects of the FLR were documented.

Results: A single FLR treatment resulted in a 62% reduction in absolute number of AK in the treated arm at 6 months post-treatment. The laser treatment was well-tolerated without major complications.

Conclusions: These studies demonstrate that FLR using settings which have been demonstrated to remove senescent fibroblasts and normalize the pro-carcinogenic UVB response of aged skin is

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a potentially effective and safe field therapy treatment that should be studied for long-term efficacy for use in treating upper extremity AKs.

INTRODUCTION

Actinic keratosis (AK) are common lesions [1–3] that are associated with chronic ultraviolet light exposure and increased age. Considered as precancerous lesions, a study has shown that 97% of SCCs were associated with AK as denoted by histologic changes of SCC in situ at the periphery of the lesion or within the tumor [4]. Thus, treatment of AK has important implications in prevention of non-melanoma skin cancer. Though the usual treatment of AKs is cryotherapy, field therapies using photodynamic therapy and 5-fluorouracil cream and other modalities are also employed for multiple AKs [5,6]. Fractionated resurfacing lasers (FLR) have been reported to be effective for field therapy of facial AKs [7,8]. Yet little is known regarding the safety and effectiveness of FLR on other sites.

It is known that age and UV are the major risk factors for actinic neoplasia. The incorporation of recent data from our laboratories has led our group to a new paradigm to explain non-melanoma skin carcinogenesis [9–13]. This new paradigm indicates that the accumulation of senescent fibroblasts in geriatric and photodamaged dermis leads to a silencing of insulin-like growth factor 1 (IGF-1) expression in the skin. There are at least three separate mechanisms by which IGF-1 receptor (IGF-1R) activation protects against keratinocyte malignant transformation, particularly in response to UVB. First, IGF-1R activation upregulates DNA repair enzymes [14]. Second, the temporary suppression of DNA synthesis following UVB, felt to be a protective mechanism to allow the cell to repair damaged DNA before proliferation, is mediated by IGF-1 [15]. Finally, IGF-1R activation promotes senescence of proliferating basal keratinocytes which cannot repair DNA damage, a process that protects the body against cells with fixed mutations [10,16]. Thus, aging results in a deficient activation of the IGF-1R in epidermal keratinocytes, causing an inappropriate UVB-response in these cells and leading to proliferation of these keratinocytes containing DNA damage (Ki67+thymine dimer+ basal keratinocytes), which ultimately results in photocarcinogenesis.

Consistent with this theory that fibroblast senescence with decreased levels of IGF-1 underlie these pro-carcinogenic effects, wounding of geriatric skin with dermabrasion or FLR removed senescent fibroblasts, increased IGF-1 levels to those found in young adult skin, and normalized acute UVB responses [11,12, 17]. However, these previous studies only treated a small (~5 x 5 cm) area of either forearm or buttock skin in geriatric volunteers. The safety and efficacy of a single treatment with ablative fractionated resurfacing laser on forearm/dorsal hand in aged individuals with multiple AKs is unknown.

The goal of the current pilot study is to define the safety and effectiveness of a single treatment with FLR on a larger area of upper extremity skin of an aged population as a field therapy for AKs. Using similar settings which have been reported to remove senescent fibroblasts, increase dermal IGF-1 levels and normalize the acute UVB responses [12], the current studies demonstrate that a single treatment with FLR is a potentially effective treatment for AK.

MATERIALS AND METHODS

Human Volunteers

The study evaluated the safety and effectiveness of a single treatment with FLR on upper extremity skin of aged subjects with extensive AK. Thirty non-diabetic male volunteers (aged >60 years old and older) with Fitzpatrick Types I and II skin with at least 5 AKs on each forearm/wrist were recruited from patients at the Dayton Veterans Administration Medical Center dermatology clinics. All of the AKs were small < 3 mm (Grades I or II) [18]. The studies have the approval of both the Dayton VA and Wright State University Institutional Review Boards in accordance with the Declaration of Helsinki Principles. Specific requirements for inclusion and exclusion criteria were identical to our previous study which tested FLR to a small (5 x 5 cm^2) area of forearm skin [12]. Briefly, potential subjects were excluded if they had diabetes mellitus, wound healing or scarring disorders (eg, keloids), or were on any topical or oral immunomodulators. None of the subjects had a recent (6 months or less) history of significant commercial or medical UV exposure, any cryotherapy in the past year to the areas, nor any field treatment to upper extremities by topical 5-fluorouracil, topical NSAIDs, imiquimod or topical photodynamic therapy.

Fractionated Laser Resurfacing

Preparation.—All subjects were thoroughly briefed on the risks and benefits of participating in the study and they signed an informed consent statement attesting to their willful participation. Volunteers who met the criteria for inclusion in this study had the AKs mapped, counted and graded (Grades I and II) [18] on the bilateral dorsal forearms/wrists and dorsal hands (excluding digits—see Figure 1 A). The subjects were divided into two cohorts, one group was treated with FLR on to left side, the other on right side (based upon odd/even Social Security number).

Treatment.—Thirty subjects were enrolled in the study; fifteen subjects underwent treatment to the right arm and fifteen subjects underwent treatment to the right arm. Following shaving to remove hair from the planned laser treatment site, and cleaning with isopropyl alcohol, 4% xylocaine cream was placed for 30 minutes for anesthesia. The area was then treated with one pass (16% coverage) using 120 mJ of energy per microspot with the largest coverage (~1 x 2 cm) (Pearl Fractional Laser; Cutera, Brisbane, California). The Pearl Fractional Laser is a 2,790-nm yittrium scandium gallium garnet ablative fractional resurfacing device that thermally ablates microscopic columns of epidermal and dermal tissue in regularly spaced arrays. White petrolatum was placed on the wounded skin and the area was covered with clear plastic wrap until the subject could remove when returned home. All subjects were also reminded to avoid significant sun exposure and to use sun protection/sunscreen.

Follow up.—Subjects were given written wound care instructions to include white petrolatum and asked to return in 3 and 6 months. At these times, the areas on both arms were photographed, and AKs counted/mapped in blinded fashion with the measurer unaware of which arm had been treated with FLR. The subjects were also questioned as to any adverse effects of the laser treatment.

RESULTS

Of the 30 subjects, all completed the 3 and 6 month visits. The numbers of AKs on extremities were similar (Left= 6.9 +/− 0.6 [Mean +/− SE]; Right= 6.4+/− 0.7) at enrollment. Though the treatments resulted in differing levels of wounding (see Fig 1 B–C for examples), minimal discomfort and no scarring was noted in the subjects. One subject experienced a localized wound infection necessitating oral doxycycline and topical mupirocin. This individual mistakenly left the clear plastic wrap on his arm for three days without removing. The forearm skin healed completely without any residual changes by 1 month. Side effects from laser treatment were obtained by self-report. Pain, crusting, and epidermal change all resolved within two weeks following treatment. Erythema resolved within one month following treatment.

Average numbers of pretreatment AKs were slightly higher on the treated vs untreated arm at baseline (7.6 +/− 0.7 for treated, 5.7 +/− 0.5 on untreated arm-not significant by students T test). As noted in Figures 2 A and 2B, we noted statistically decreased numbers of AKs on the treated area in comparison to pre-treatment values at both three months (2.9 +/− 1.7 for treated vs 9.2 +/− 3.2 for untreated; $P < 0.001$) and at six months (3.1 +/− 2.0 for treated vs 9.5 +/− 4.2 for untreated; $P < 0.001$). At 6 months, the average percentage decrease of total AKs in the treated arm was 60%; In contrast, the average total numbers of AKs on the untreated arm increased by 167%.

DISCUSSION

Non-melanoma skin cancer and precursor AK are a source of considerable morbidity including cost. Moreover, NMSC (especially SCC) can occasionally metastasize, especially in immune-suppressed populations such as transplant patients [19,20]. The importance of NMSC has resulted in the adoption of field therapies for treatment of precursor AKs [5,6]. Though effective, therapeutic options such as topical 5-fluorouracil cream or topical photodynamic therapy are designed to remove precancerous lesions, but, not generate long-term changes in the aged skin which could result in a sustained protection from actinic neoplasia. In contrast, there is a volume of literature suggesting that wounding therapies used for cosmetic purposes appear to protect the recipient from AK and NMSC [21–24]. The concept that wounding therapies could protect against NMSC fits with the hypothesis that dermal fibroblast senescence with lack of IGF-1 mediates the increased incidence of actinic neoplasia [25].

The current pilot study tested the potential utility of a single FLR treatment as a field therapy to treat AKs on dorsal forearm skin in aged subjects using settings that we have previously demonstrated remove senescent fibroblasts and upregulate dermal IGF-1 levels [12]. The resultant improvement of total numbers of AK was found to be 62% at 3 months and 60% at 6 months following a single FLR treatment. There are a paucity of studies in the literature examining the effectiveness of FLR to treat AK on forearm skin. In contrast, there are several studies which have tested FLR for facial AK field therapy. For example, use of up to four treatments of the fractionated 1927-nm non-ablative thulium laser resulted in an 86.6% decrease in pre-treatment AK numbers at six months [7]. However, in this study [7], the

population ranged from 30-80 years of age. In contrast, another use of five treatments (at 2-4 week intervals) of the nonablative 1550-nm fractionated erbium-doped laser on facial skin of a cohort of 14 men aged 59 to 79 years resulted in a reduction of total AK counts of 55.6% at 6 months [8]. Thus, the results of the current studies with a single treatment with an ablative fractionated laser appear to be in the range of multiple facial non-ablative FLR treatments. More importantly, the side effect profile of the 2,790-nm yittrium scandium gallium garnet ablative fractional resurfacing device on forearm skin used is similar to those described using multiple nonablative FLR treatments. An advantage of use of forearm skin is the ability to use a control untreated arm, which is more acceptable to the subject than split facial treatment studies.

There are several limitations of the current pilot study. First is the use of only men in these studies which took place at a Veterans Administration dermatology clinic. Second limitation is the lack of confirmation of the dermal improvement of the fibroblast IGF-1 levels following FLR wounding. Regarding the latter issue, our group has ongoing studies which are examining the dermal IGF-1 levels and acute UVB responses in geriatric skin treated with FLR, which suggest that wounding improvement which we reported at 3 months [12] is still present by two years post-wounding (*data not shown*). Finally, a limitation of this study is that, similar to previously reported facial FLR studies [7,8], only six month data was recorded. Unfortunately, selecting a high-risk population of 5 or more AKs per arm does not allow long-term studies because of the concerns of not treating these pre-cancerous lesions might result in development of skin cancers via malignant transformation. Consistent with this concept, even with the sun screen/sun protection education provided, the numbers of AKs in the untreated arm in our current cohort increased by 167% over the six month time frame studied.

In summary, the present pilot studies indicate that a single FLR treatment appears to be a potential option in treating and possibly preventing Grade I/II AKs on the forearm/wrist in high-risk subjects aged 60 and older. Inasmuch as FLR treatment can increase IGF-1 and normalize abnormal UVB responses associated with aged skin, future studies could allow characterization of the long-term effects of FLR treatment on the acquisition of actinic neoplasia.]

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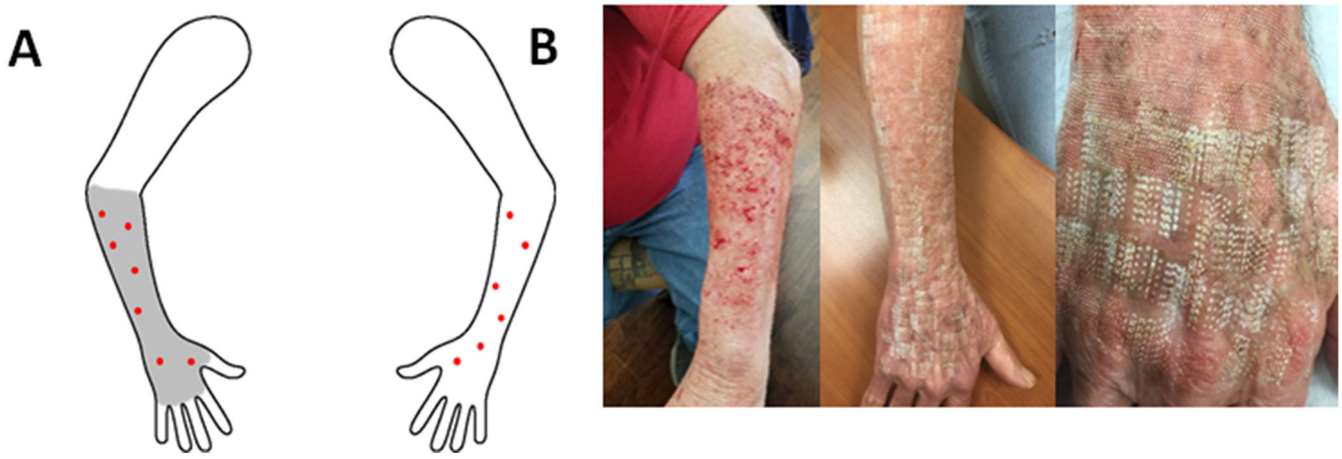

Figure 1. Fractionated laser resurfacing of forearm skin.

(A) Cartoon of treatment site (grey area), with left vs right side treatment based upon odd/even Social Security Number. Subjects had AKs (red dots) counted and sites mapped on dorsal forearms/wrists, then following use of topical xylocaine (4%) anesthesia, underwent a single pass of the Pearl Fractional 2,790nm yittrium scandium gallium garnet ablative fractional resurfacing device. **(B)** Examples of post-FLR treated skin.

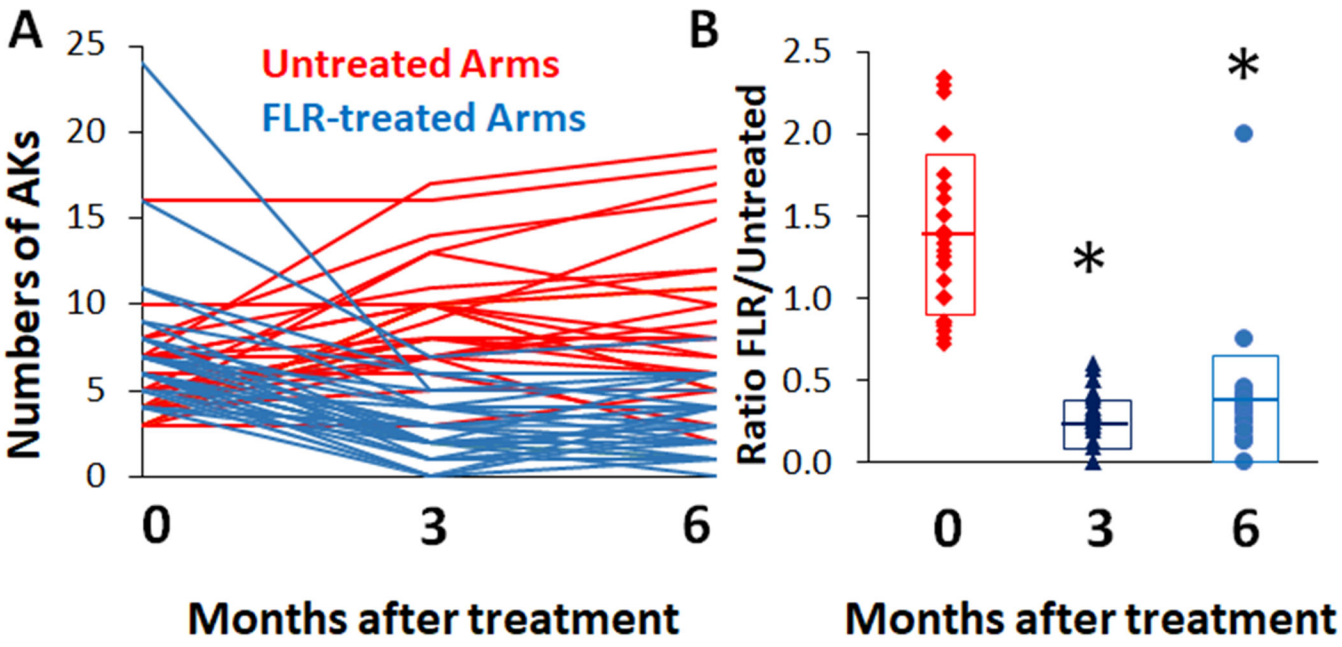

Figure 2. Fractionated laser resurfacing results in decreased numbers of AKs.

(A) Changes in numbers of AKs in treated (blue) vs untreated (red) sites at 0 (pre-treatment), 3 and 6 months post-treatment. **(B)** Ratio of AKs in FLR-treated versus – untreated sites. Asterisk (*) denotes statistically significant ($P < 0.001$) differences from pre-treatment values.