Demonstrated Improvement of Prematurely Aged Skin by oral intake of TA-65®

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Abstract

Telomere attrition is the central hallmark of cellular senescence. TA-65® is a small molecule that has been shown to prevent telomere attrition. The main objective of the current study is to evaluate cosmetic benefits of oral intake of TA-65® in subjects with prematurely aged skin (photo-aged skin). Randomized, double-blind and placebo-controlled study was carried out on 35 photo-aged subjects for sixteen weeks. Clinical assessments were performed at baseline and following 4, 8 and 16 weeks of use. VISIA® complexion analysis system (Canfield Scientific, Fairfield, NJ) revealed that TA-65® may reduce pre-clinical damage and uneven pigmentation and wrinkles after eight weeks' application. Histological analyses of biopsies revealed that the expression of inflammatory cytokines declined, whereas elastin level increased after 16 weeks' intake of TA-65® capsule, demonstrating the improvement of pre-maturely aged skin by TA-65® capsule.

Introduction

Repeated exposure of ultra violet light results in what is called photo-aging. In aging and photo-aging, human skin accumulates senescent keratinocytes and fibroblasts. Senescence not only limits replicative potential of cells but also fuels inflammation associated with aging and photo-aging (Lasry and Ben-Neriah 2015). Thus anti-senescence compounds have tremendous potential as novel therapeutics. TA-65® is a small molecule telomerase activator derived from the Astragalus plant identified in an empirical screen based on its ability to upregulate basal telomerase activity and has been shown to reduce telomere attrition (Harley, Liu et al. 2011). The current study is designed to test cosmetic skin improvement following the oral intake of TA-65®.

Objective

The main objective of this study is to evaluate the cosmetic benefits of TA-65® capsule in skin in subjects with prematurely aged skin.

Methodology

Randomized, double-blind, placebo-controlled study of 35 photo-aged subjects was carried out for 16 weeks with clinical assessment performed at baseline and following 4, 8 and 16 weeks of use.

The subjects were randomly assigned to either placebo group or treatment group. The placebo group took two placebo capsules per day for 16 weeks. The treatment group took two TA-65 capsules (250 Units each) per day for 16 weeks. The placebo capsule was identically formulated and packed to that of TA-65® capsule, but lacks the active ingredient, TA-65®.

VISIA® complexion analysis system

VISIA® complexion analysis system (Canfield Scientific, Fairfield, NJ) has been used to objectively measure (Goldsberry, Hanke et al. 2014) wrinkles and brown spots at all indicated visits (Figure 1).

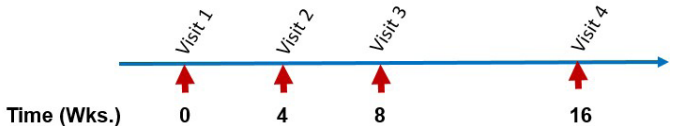

Figure 1: *Visits at different time during study period*

Punch biopsy

One subject from each group underwent punch biopsy procedure, wherein a small skin tissue were taken at the beginning and end of the trial (16 weeks). The biopsy samples (3mm) were sent to Development Engineering Sciences, LLC (Flagstaff, AZ) which analyzed the molecular markers suggestive of the skin's health by nuclear counting, histology and Real Time – Polymerase Chain Reaction (RT-PCR). Following parameters have been tested on the punch biopsies.

Nuclear counting

The nuclear counting algorithm was used to count the number of cells present in the stratum basale and spinosum of the H&E stained sections. The algorithm was tuned as per Aperio's algorithm user guide for nuclear quantification. Images acquired from the Hamatsu Nanozoomer digital slide scanner were analyzed using Aperio algorithms.

Immunohistochemistry (IHC) analysis

Collagen 1, elastin and filaggrin presence in the dermis and epidermis, respectively, were quantified using a color deconvolution algorithm from digitally-scanned IHC slides. Collagen 1 was analyzed at a depth of 200µm below the stratum basale, into the dermis. Elastin was analyzed at a depth of 200 µm above the hypodermis into the dermis. Filaggrin was measured in the stratum granulosum layer.

Real-time PCR (RT-PCR)

IL-6, IL-8, TNF-α, MMP-1 and MMP-12 were measured by RT-PCR. Samples were analyzed in triplicate to calculate fold change (increase or decrease) in gene expression.

Results and Discussion

VISIA® complexion analysis system analyzed wrinkles and brown spots. Compared to baseline, there was a significant reduction in the mean scores of wrinkles after taking TA-65 capsule for 8 weeks (33% decline; p=0.02). The mean scores (S.E) at baseline and after 8 weeks were 21±2 and 14±2 respectively (Figure 2A). This result indicate that oral intake of TA-65® capsule can effectively reduce facial wrinkles.

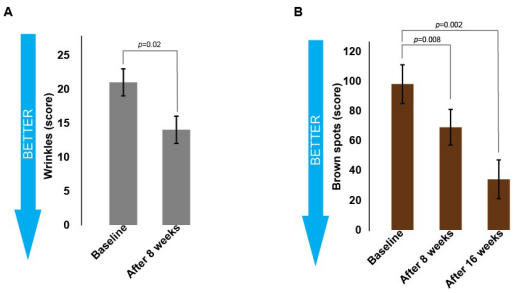

Figure 2: Cosmetic benefits of TA-65® capsule. *Daily intake of TA-65 capsule reduced wrinkles by 33% after 8 weeks (A). Brown spots declined by 30% after 8 weeks and 65% after 16 weeks compared to baseline (B). p-values are estimated by the t-test.*

There was a significant reduction in the mean scores of brown spots after the oral intake of TA-65® capsule for 8 weeks (30% decline; p=0.008) and 16 weeks (65% decline; p=0.002). The mean scores (S.E) at baseline, 8 weeks and 16 weeks were 98±13, 69±12 and 34±13, respectively (Figure 2B). These results indicate that oral intake of TA-65 capsule can diminish uneven pigmentation. Taken together, these results indicate that in addition to other health-benefits, oral intake of TA-65® capsule can also offer cosmetic benefits.

Histopathology Findings

Histopathology comparisons between active vs. placebo treatment sites at the 16 week time-point did not reveal any noticeable differences with respect to acanthosis, spongiosis, chronic inflammation, hyperkeratosis, epidermal mononuclear infiltration, or dermal edema. No trend change existed for prominence of any of these characteristics between active and placebo treated samples. Representative histopathology is shown in figure 3.

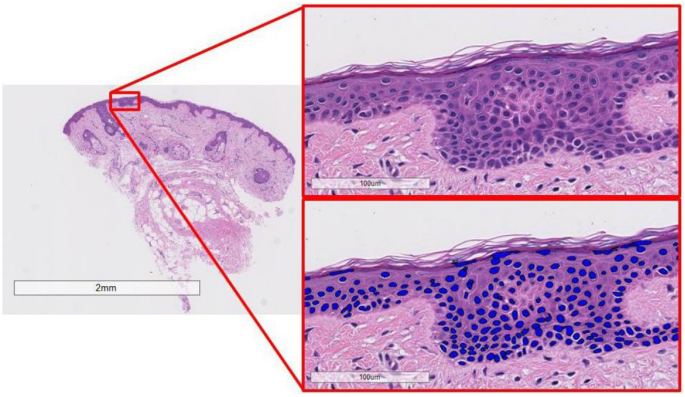

Figure 3: H&E staining of punch biopsy at baseline in TA-65® group. *No acanthosis, spongiosis, chronic inflammation, hyperkeratosis, epidermal mononuclear infiltration or dermal edema were observed at baseline. Left panel is the low magnification (scale bar = 2 mm) and right panel is the high magnification (scale bars = 100µm).*

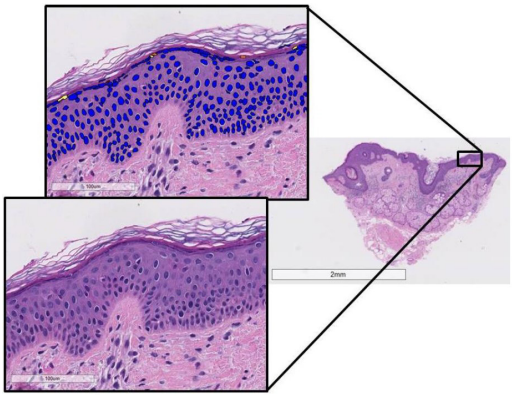

Figure 4: H&E staining of punch biopsy after 16 weeks' intake of TA-65® capsule. *No acanthosis, spongiosis, chronic inflammation, hyperkeratosis, epidermal mononuclear infiltration or dermal edema were observed with 16 weeks' use of TA-65® for Skin. Right panel is the low magnification (scale bar = 2mm) and left panel is the high magnification (scale bars = 100µm).*

Immunohistochemistry and RT-PCR

Expression of pro-inflammatory molecules IL-6 and IL-8 increased in the skin of the subject who took placebo capsule, whereas oral intake of TA-65 capsule reduced them within 16 weeks (Figure 5A). A 2 fold reduction in the IL-6 and 6 fold reduction in the IL-8 were observed after 16 weeks' intake of TA-65® capsule; in placebo group, there is a 10 fold increase in IL-6 and 30 fold increase in IL-8. No improvement in the molecular markers TNF-α, MMP-1 and MMP-12 were observed following the oral intake of TA-65® capsules.

Elastin is a structural protein found in the dermis that provides flexibility to the skin and allows for it to elastically return to its native resting architecture. Figure 5B shows that the oral intake of TA-65® capsule increases the level of elastin by 93% after 16 weeks. No improvement in the molecular markers collagen and filaggrin were observed following the oral intake of TA-65® capsule.

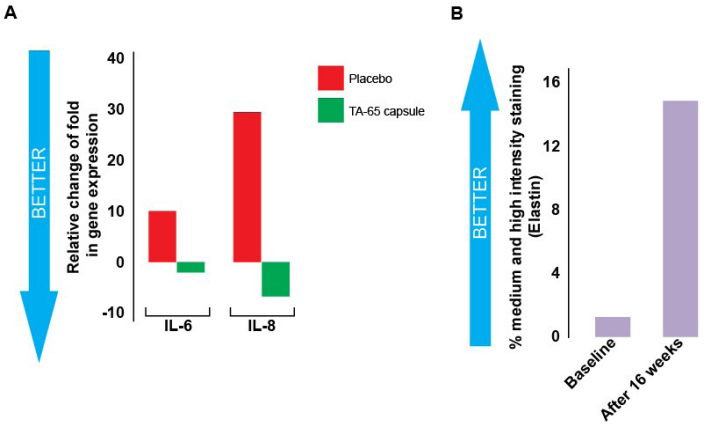

Figure 5: Expression of inflammatory cytokines declines after 16 weeks' use of TA-65® for Skin. *IL-6 and IL-8 declines by 2 fold and 7 fold after 16 weeks' oral intake of TA-65® capsule. (A). Elastin level increases by 93% after 16 weeks' oral intake of TA-65® capsule (B).*

References

Goldsberry, A., C. W. Hanke and K. E. Hanke (2014). "VISIA system: a possible tool in the cosmetic practice." J Drugs Dermatol 13(11): 1312-1314.

Harley, C. B., W. Liu, M. Blasco, E. Vera, W. H. Andrews, L. A. Briggs and J. M. Raffaele (2011). "A natural product telomerase activator as part of a health maintenance program." Rejuvenation Res 14(1): 45-56.

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