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ORIGINAL ARTICLE

Enhancing hair growth in male androgenetic alopecia by a combination of fractional CO_2 laser therapy and hair growth factors

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Abstract Laser therapy and growth factors have been used as alternative treatments for male androgenetic alopecia (MAA). The aim of this study is to determine the efficacy and safety of hair growth factors alone or combined with ablative carbon dioxide (CO_2) fractional laser therapy in MAA. Twenty-eight men were enrolled in this randomized half-split study based on a left-head to right-head pattern. Fractional CO_2 laser treatment was unilaterally performed; hair growth factors were bilaterally applied. Six sessions with 2-week intervals were performed. Global photographs and dermoscopy assessments were performed at the baseline and 4 months after first treatment. Global photographs underwent blinded review by three independent dermatologists. Scanning electron microscopy was used to compare changes in hair-follicle phase and hair-shaft diameter. Twenty-seven participants completed the 4-month treatment schedule. One patient was lost. Mean hair density increased from 114 ± 27 to 143 ± 25/cm^2 ($P < 0.001$) in the combined group and from 113 ± 24 to 134 ± 19/cm^2 in the growth factor group ($P < 0.001$). The mean change from baseline between two groups was also compared ($P = 0.003$). Global photographs showed improvement in 93% (25/27) patients in the combined group and 67% (18/27) patients in the growth factor group. Under scanning electron microscopy, hair follicles appeared to transition from telogen to anagen, and hair-shaft diameter increased in five randomly selected patients. Ablative fractional CO_2 laser combined with hair growth factors may serve as an alternative treatment for MAA in individuals unwilling/unable to undergo medical or surgical treatment.

Keywords Male androgenetic alopecia · Ablative fractional CO_2 laser · Hair growth factors

Introduction

Male androgenetic alopecia (MAA)—or hair loss—is the most common hair problem among men [1]. The overall prevalence of MAA in China was determined to be 21.3% in a community-based study conducted in six cities [2]. MAA has a genetic predisposition in which the disruption of proper androgen signaling results in a progressive decrease in anagen duration and a delay in the telogen-to-anagen transition. Eventually, the condition results in the decreased proliferation of hair follicle epithelium and progressive miniaturization of the terminal hairs on the scalp [3].

Conventional methods of treating hair loss include minoxidil, finasteride, and surgical transplantation [4]. However, the low efficacy and undesirable side effects of current medical treatments limit their use [5]. Moreover, although hair transplantation can be considered for severe hair loss, this treatment is limited by patient budgets and surgical burdens. Therefore, new and effective methods are needed for the treatment of hair loss.

In recent years, laser and light therapy have been used as alternative treatments for hair loss. In 2007, low-level laser therapy has been approved by the US Food and Drug Administration and appears to be safe and effective in treatment of male- and female-pattern hair loss [6, 7]. Moreover, the 1550-nm fractional laser may be useful for the treatment of human alopecia [8, 9]. Fractional CO_2 laser treatment has

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effectively induced hair regrowth through the wound-healing process in a murine model [10]. These new discoveries in hair follicle neogenesis suggest that laser irradiation might be useful for the treatment of alopecia.

Hair follicles are mini-organs that experience a life cycle consisting of anagen (growth phase), catagen (regression phase), and telogen (resting phase) [11]. Many cytokines and growth factors such as insulin-like growth factor (IGF)-1, transforming growth factor (TGF)-β, and vascular endothelial growth factor (VEGF) are involved in the regulation of hair morphogenesis and the hair growth cycle [12–14].

Hair growth factors used in our study, which are prepared using stem cells derived from the foreskin, contain several hair growth factors such as FGF-2 (7000 pg/ml), IL-3 (800 pg/ml), IL-6 (680 ng/ml), IL-7 (800 pg/ml), IL-8 (790 ng/ml), TGF-β1 (80 ng/ml), TGF-β2 (780 pg/ml), and TGF-β3 (825 pg/ml). In the present study, we aimed to determine the efficacy and safety of hair growth factors when used alone or in combination with fractional CO_2 laser treatment in order to explore an alternative therapy for hair regrowth in MAA.

Materials and methods

Participants

In this pilot study, we enrolled 28 Chinese patients with MAA. The study was performed at the Department of Dermatology, Beijing Friendship Hospital, Capital Medical University, between September 2015 and October 2015. All participants provided written informed consent. Patients with a history of a systemic disease in the past 6 months, those who had undergone treatment with any medication that could affect the hair cycle within the past 3 months, and those who had undergone surgical treatment for alopecia (such as hair transplantation) were excluded. The use of other topical agents and the administration of any medication were not permitted during the study period.

Treatment protocol

This half-split study was approved by the ethics committee of Beijing Friendship Hospital. All patients received unilateral ablative fractional CO_2 laser treatment (Pixel CO_2, Alma Lasers Ltd., Esthetic Mode, Israel) on the alopecic scalp. In each patient, the right or left side of the scalp was randomly selected for laser treatment. We chose to use fractional CO_2 lasers based on the findings of our previous experiments in mice (data not shown). Fractional CO_2 laser with the following parameters was used: 50-mm tip, 12–18 mJ/spot, 361 spots/cm^2, one pulse, and 40% density. Ice cooling was applied for 20 min after the laser treatment.

Additionally, all patients underwent bilateral treatment with hair growth factors (AQ Skin Solutions®, USA, a company manufacturing medical cosmetic products and has been on the market). The entire alopecic scalp was covered with 2 ml of the hair growth factor solution by using acoustic-pressure ultrasound. Thereafter, the hair growth factors were regularly applied topically, once every other day for 2 weeks. The above treatment was considered as one session. A total of six sessions were performed at 2-week intervals during the study period. The side of the scalp that received both laser and hair growth factor treatment served as the combined group, and the other side served as the growth factor group.

Outcome evaluation

Three dermatologists, who were blinded to the study protocol, independently assessed global photographs taken at the baseline and at 4 months after first treatments. The photographs were scored using a 7-point global-assessment scale [9] as follows: significant deterioration, −3 points; moderate deterioration, −2 points; slight deterioration, −1 point; no change, 0 points; slight improvement, +1 point; moderate improvement, +2 points; and significant improvement, +3 points. In addition, to indicate their satisfaction with the overall treatment outcomes, patients scored their own photographs on the same 7-point scale.

Dermoscopy (Dermoscopy Image Diagnostic Workstation, Beijing; Dermat Speedy Recovery T&D Co. Ltd., Beijing, China) was also used to analyze the treatment outcomes. Bilaterally symmetrical areas in a region of severe alopecia, typically the vertex, were selected for the dermoscopy assessments. A 10-mm-wide circle was marked in the selected areas by signing a black tattooed dot at the center of the circle.

The hair density in the circle was evaluated under dermoscopy at the baseline and at 4 months after treatment. Also, the average diameter of the hair shaft and changes in hair follicles at the baseline and at 4 months after treatment were assessed in five participants with good outcomes using scanning electron microscopy (SEM; Hitachi TM3000, Hitachi, Tokyo, Japan). In each of these five patients, 10 hairs were pulled out from each shaved area on the scalp. Half of the hairs were used to determine the average hair-shaft diameter, and the other half were used to determine the stage of hair growth (anagen/telogen/catagen). Every 2 weeks, follow-up medical examinations were performed, and adverse effects related to the laser treatment (such as erythema, erosion, edema, seborrheic dermatitis, dryness, pruritus, and broken hair shafts) were noted if present.

Statistical analysis

The SPSS statistical package (SPSS v17.0) was used for statistical analyses. Changes in hair density before and after

treatment, and the differences between the two study groups were analyzed using the paired *t* test. Statistical significance was accepted for *p* values less than 0.05.

Results

General information

The mean age of the participants was 32 years (range 21–49 years). Of the 28 patients, 27 completed the entire treatment schedule. One patient was lost to follow-up. The Hamilton–Norwood stages of hair loss were determined as follows: stage II, 1 participant; stage III, 2 participants; stage IV, 10 participants; stage V, 12 participants; and stage VI, 2 participants (Table 1).

After topical hair growth factors under the acoustic-pressure ultrasound and laser treatments, definite erythema developed at the treatment sites in all participants. Slight edema was also noted in the area of laser irradiation. No topical anesthetics were required during the treatment phase.

Assessment of global photographs

Clinical improvement was observed in most participants. Evaluation of global photographs by the dermatologists revealed an improvement in 93% (25/27) patients. The outcomes of the combined group were as follows: significant improvement, 19% (5/27); moderate improvement, 15% (4/27); slight improvement, 59% (16/27); and no change, 7% (2/27).

In the growth factor group, the outcomes were as follows: significant improvement, 0 patients; moderate improvement, 22% (6/27); slight improvement, 44% (12/27); and no change, 33% (9/27). Self-evaluation of the global photographs by the participants was also performed to determine the subjective satisfaction with the treatment outcomes.

According to this evaluation, the results of the combined group were as follows: significant improvement, 15% (4/27); moderate improvement, 22% (6/27); slight improvement, 56% (15/27); and no change, 7% (2/27). In the growth factor group, the results were significant improvement, 7% (2/27); moderate improvement, 15% (4/27); slight improvement, 41% (11/27); and no change, 37% (10/27; Table 2, Fig. 1).

Importantly, 59% (16/27) participants reported an improvement in hair texture and quality on both sides of the scalp. The outcomes were significantly better in the combined group than in the growth factor group alone (patient assessment, $p = 0.009$; investigator assessment, $p = 0.018$).

Table 1 Characteristics of 27 men with male androgenetic alopecia

Characteristic	
Age, mean ± SD (range)	32.44 ± 8.25 years (21–49 years)
Familial history of hair loss, *n* (%)	17/27 (63%)
HN stage of hair loss, *n* (%)	
II	1/27 (4%)
III	2/27 (7%)
IV	10/27 (37%)
V	12/27 (44%)
VI	2/27 (7%)
Duration, mean ± SD (range)	6.93 ± 4.26 years (2–22 years)

HN Hamilton-Norwood

Dermoscopy assessments

An improvement in hair density was observed on dermoscopy. The mean hair density in the combined group significantly increased from 114 ± 27/cm^2 at the baseline to 143 ± 25/cm^2 4 months after treatment ($p < 0.001$; Table 3, Fig. 2). In the growth factor group, hair density increased from 113 ± 24 to 134 ± 19/cm^2 ($p < 0.001$; Table 3, Fig. 2). Hair density did not differ between the two groups at the baseline ($p = 0.694$) but was significantly higher in the combined group than in the growth factor group at 4 months after the first treatment ($p = 0.002$). More importantly, the mean change from baseline was also higher in the combined group than in the growth factor group ($p = 0.003$).

SEM examination

Changes in hair follicles were observed throughout the treatment. The hair follicles collected from the occiput area appeared as long, twisty, sharply tapered structures with a curly cuticle at the distal part of the hair root (Fig. 3a), indicating that the hair follicles were in the anagen phase. In fact, 80% of the hairs in this area appeared to be in the anagen phase. These hairs were therefore used as the control.

In both groups, hair samples taken from the vertex area at the baseline appeared dull-edged and tapering, with large scales covering the entire surface of the proximal end of the hair shaft and few hair cuticles on the surface of the hair shaft. These findings suggested miniaturization of the hair follicles and indicated that the hairs were in the telogen phase (Fig. 3b). At 4 months after the treatment, most hair follicle samples from the combined therapy area appeared to be in the anagen phase (Fig. 3c). Some samples from the growth factor group showed similar improvement.

The diameter of the hair shaft also remarkably increased after the treatment. The mean diameter of five hairs from each of the five participants was determined at the baseline and at 4 months after the treatment. In the combined group, the mean hair-shaft diameter increased from 44.32 ± 3.89 to 58.39 ± 9.29 μm, while in the growth factor group, it increased from 44.32 ± 6.04 to 54.74 ± 7.88 μm (Table 4 and Fig. 4).

Table 2 Differences in post-treatment (4 months) and pretreatment global photographs

	Patient assessment (questionnaire)		Investigator assessment (GPA)	
	Combined treatment	Growth factors	Combined treatment	Growth factors
Improvement (+1, +2, +3)	25/27 (93%)	17/27 (63%)	25/27 (93%)	18/27 (67%)
No change (0)	2/27 (7%)	10/27 (37%)	2/27 (7%)	9/27 (33%)
Worsening (−1, −2, −3)	0	0	0	0
P value	0.009[a]		0.018[a]	

GPA global photography assessment

[a] Significant difference between the groups ($p < 0.05$)

Adverse effects

None of the participants complained about transient hair shedding after the laser treatment. Slight pain feeling was common during treatment in most participants. Side effects such as mild post-treatment erythema (n = 27), edema (n = 7), pruritus (n = 8), dryness (n = 3), seborrheic dermatitis (n = 2), and dandruff (n = 7) were also observed. All patients showed good tolerance to treatment-related pain, and their discomfort resolved within 2 or 3 days.

Post-treatment SEM revealed blunt damage to the hair cuticles and splitting of the cortex (Fig. 5). Occasionally, breakage of the hair shafts after irradiation was observed.

Fig. 1 Significant clinical improvement in hair growth is seen at 4 months after the treatments, as compared with the baseline

Table 3 Dermoscopy assessment of hair density

	Combined group	Growth factor group	*P* value
Baseline	114 ± 27/cm^2	113 ± 24/cm^2	0.694[b]
4 months after treatment	143 ± 25/cm^2	134 ± 19/cm^2	0.002[a]
Mean change from baseline	29 ± 22/cm^2	21 ± 20/cm^2	0.003[a]
P value	<0.001[c]	<0.001[c]	

[a] Significant difference between the groups ($p < 0.05$)

[b] No significant difference between the groups ($p > 0.05$)

[c] Significant difference between the baseline and 4 months after treatment ($p < 0.05$)

Discussion

Alopecia or hair loss is a common condition in which the decreased amount of hair fails to adequately cover the scalp; it can cause psychosocial and emotional distress in affected people [15]. Androgenic alopecia, in particular, is characterized by miniaturization of hair follicles, shortened anagen, and prolonged telogen [16]. There has been a growing demand among affected individuals for treatments that not only prevent hair loss but also induce hair regrowth. The reported efficacy of finasteride and minoxidil for MAA ranges from 40 to 60% [3]. Thus, it is necessary to find a supplementary treatment or alternative therapy.

The relationship between skin wounding and hair regrowth has been a popular topic of research. The possibility of hair-follicle regeneration secondary to wounding was raised in studies on rabbits [17], mice [10, 18, 19], and even humans [9, 20]. According to this theory, fractional lasers, which create numerous microscopic thermal injury zones, could induce the growth of new hair follicles. Furthermore, the microscopic thermal injury zones are surrounded by normal skin tissue, allowing for the rapid repair of laser-induced thermal injury [21].

Recently, non-ablative 1550-nm fractional Erbium-glass laser was reported to have some success in treating female-pattern hair loss based on a C57BL/6 mouse model [8, 9, 19]. The results in this model showed that anagen entry was associated with the combination of laser-beam energy and density. Additionally, high levels of interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-1β were associated with high beam density. Moderate inflammation within a short period can induce premature anagen entry without inducing ulcers. Ito et al. found that cells making up newly formed hair follicles were derived from the interfollicular epidermis and not existing hair bulges [18]. This provided further proof that proper wounding (by ablative fractional lasers) can induce hair regrowth. In the

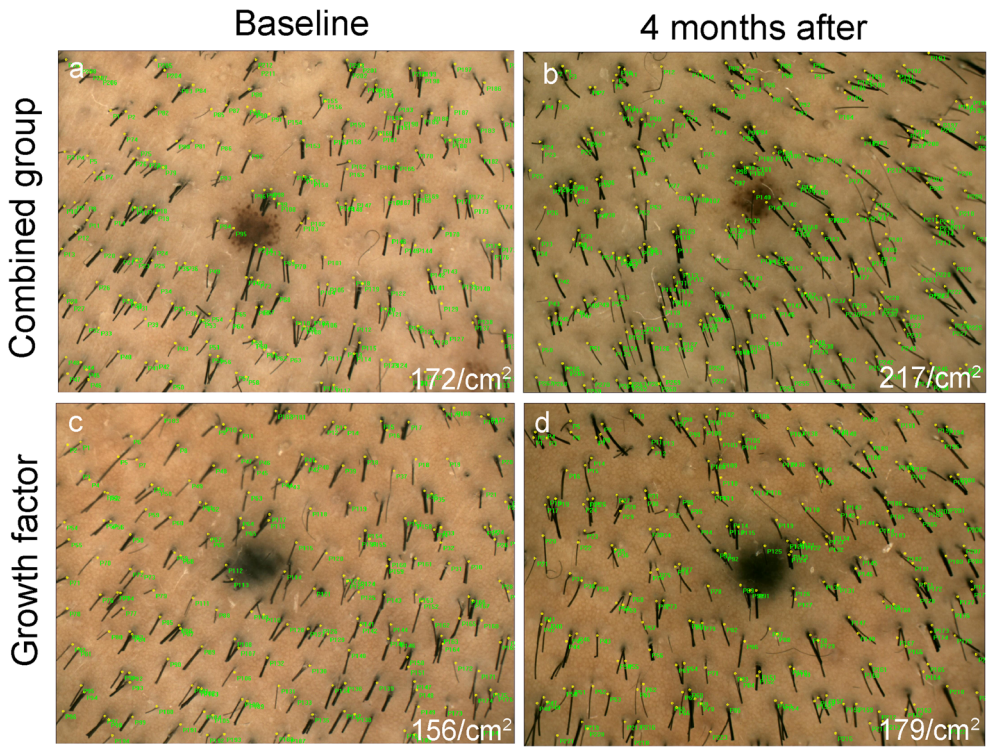

Fig. 2 Significant improvement in hair density is seen at 4 months after the treatments **(b, d)**, as compared with the baseline **(a, c)**

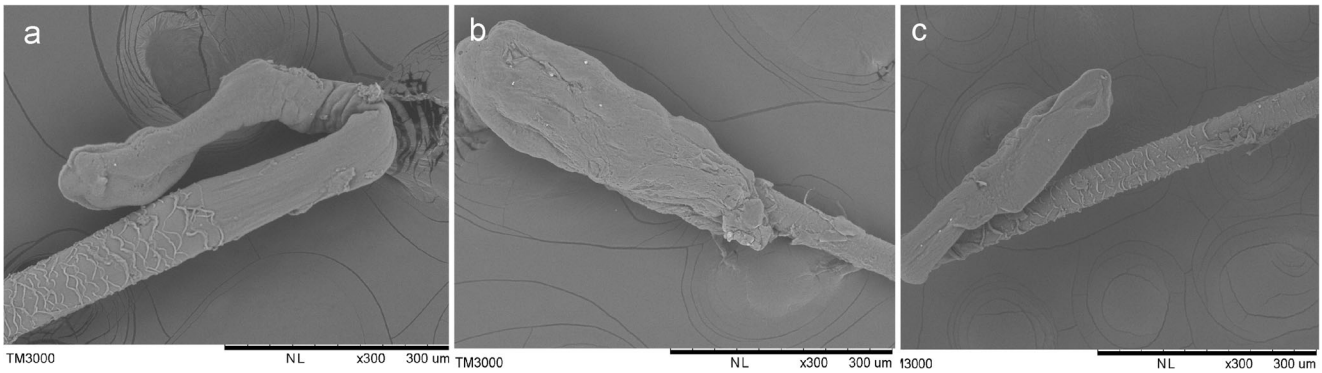

Fig. 3 **a** Scanning electron microscopic image of a hair root in a sample taken from the occiput area (control). **b** Before treatment, dull-edged, tapering hair shafts, with large scales covering the entire surface of the proximal end of the hair shaft, and a few cuticles on the surface were observed in both the combined and growth factor groups, indicating that the hairs were in the telogen phase. **c** After combined treatment, plenty of hair roots had long, twisty, or sharply tapering structures with curly cuticles, indicating that they were in the anagen phase

present study, hair growth factors alone or combined with ablative CO_2 fractional laser treatment were used to treat MAA. The creation of a wound by the ablative fractional laser may stimulate stem cell populations expressing known molecular markers of follicle differentiation to produce a hair shaft and progress through all stages of the hair follicle cycle through the Wnt/β-catenin/Lef-1 signaling pathway [18]. Many molecular manipulators in wound healing—including the fibroblast growth factor (FGF) family, epidermal growth factor (EGF), IGF, hepatocyte growth factor (HGF), VEGF, and ILs—have been reported as key factors for hair growth and the hair follicle cycle [22, 23]. Laser-induced wounds initiate inflammation, which promote anagen entry. Many inflammatory cells, especially macrophages and cytokines, may play an important role in this process [19]. Thus, changes in cytokines and growth factors might mediate the hair-growth stimulation and hair-cycle progression induced by fractional laser treatment. Ablative fractional lasers have two main effects: induction of moderate inflammation to promote anagen entry and creation of channel pathways for topically applied medicine whose molecular weight might otherwise be too large to bypass the skin barrier [24].

Acoustic-pressure ultrasound, which was used in our study, can further facilitate the absorption of growth factors. In each participant in this study, mild edema and erythema of the scalp was observed after the treatment. This phenomenon was much more apparent in the combined group and disappeared within 2 days. Hair density recovered in both groups, but the improvement was greater in the combined group than in the growth factor group. We speculated that fractional laser-induced wounds may initiate the expression of endogenous hair growth factors and inflammatory mediators, and provide delivery routes that enable exogenous growth factors to bypass the skin barrier and penetrate deep into the dermis. These molecular mechanisms may explain how fractional laser-assisted hair growth factor therapy induced anagen entry.

Table 4 Scanning electron microscopic assessment of hair-shaft diameter

	Combined group	Growth factor group
Baseline	44.32 ± 3.89 μm	44.32 ± 6.04 μm
4 months after treatment	58.39 ± 9.29 μm	54.74 ± 7.88 μm

In our present study, the density, thickness, and texture of hair were also enhanced in the growth factor group. This indicated that complex hair growth factors, such as FGF-2, TGF-β1, TGF-β2, TGF-β3, IL-3, IL-6, IL-7, and IL-8 can promote cell cycle progression and cell proliferation and may help rescue hair loss and facilitate hair cell regeneration in vivo. These findings are in accordance with the study by Lin et al. [23] and support the topical application of hair growth factors or cytokines for MAA treatment.

In the combined group, proper energy parameters are very important for the effective stimulation of hair growth. The parameters were flexible and chosen from 12 to 18 mJ/pixel based on the content of hair covering the scalp and the presence of edematous-erythematous plaques. A high-energy laser irradiation protocol may increase the incidence of hair-shaft breakage by damaging the hair cuticle and cortex. Frequent treatment (>two times/week) may induce fibrotic changes around the hair follicle [8]. A low-energy, high-density protocol with treatments at 2-week intervals is thought to be the most appropriate MAA protocol. Participants who had little hair to cover the scalp and developed highly transient edematous-erythematous plaques after laser treatment showed satisfactory outcomes; this was consistent with the finding reported by Wu et al. [19]. We speculated that moderate inflammation induced by fractional laser treatment may be associated with anagen entry.

Surprisingly, hair regrowth was also observed in MAA participants with stage V–VI hair loss at 4 months after therapy. As we know, conventional therapy with oral finasteride will take at least half a year to induce visible hair regrowth. In

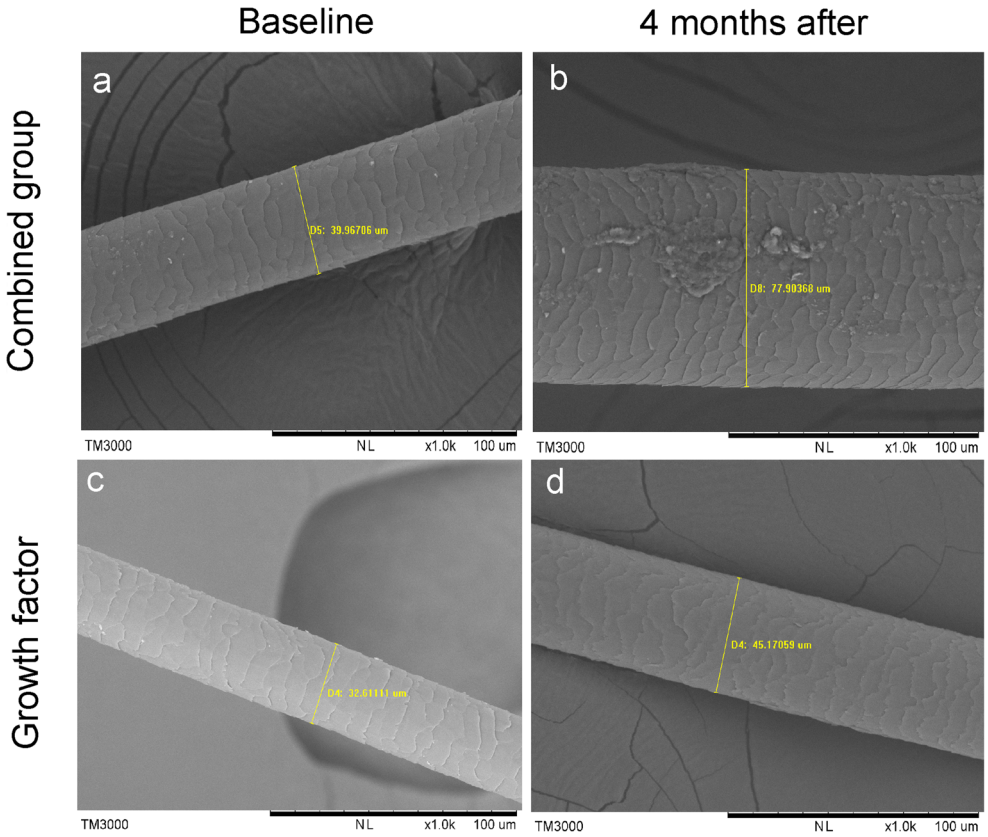

Fig. 4 Improvement in diameter of hair shaft at 4 months after the treatments **(b, d)**, as compared with the baseline **(a, c)**

a recent study, four MAA patients with stage V–VII hair loss showed no new hair growth after treatment with oral finasteride and topical minoxidil for more than 2 years [25]. However, all four patients showed hair regrowth after

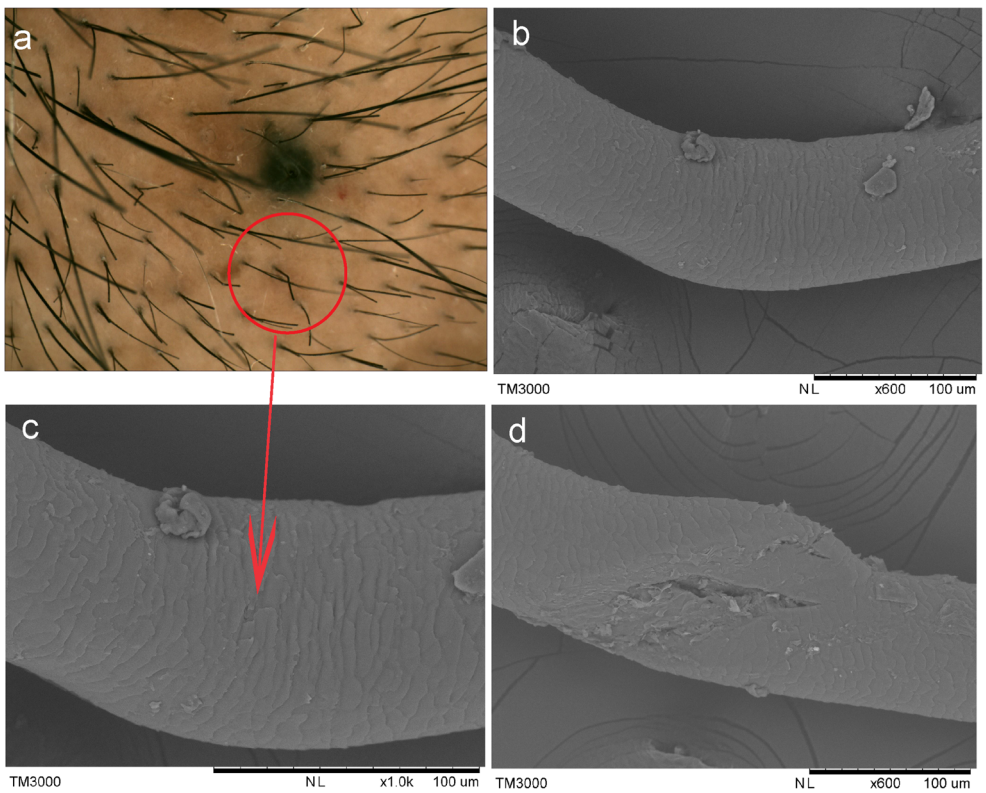

Fig. 5 Dermoscopy and scanning electron microscopy showed blunt damage to the hair cuticle and cortex after irradiation **(a–c)**. Occasionally, breakage of the hair shafts after irradiation was observed **(d)**

additional microneedling treatment [25]. These results indicate that multiple factors are implicated in the pathogenesis of MAA. The condition involves not only dihydrotestosterone but also inflammation, genes, signaling pathways, growth factors, activation of stem cells of the hair bulge, and improvement in vascularity. The existing conventional therapies (i.e. finasteride and minoxidil) do not target all of these factors. Both microneedling and ablative CO_2 fractional laser treatment create skin wounds. Thus, inflammation, growth factors, and the activation of stem cells by laser-induced wounds may all play a role in promoting anagen entry. However, hair complex growth factors alone could partially rescue hair loss in our study.

This study has some limitations. It is necessary to prolong the course of treatment and evaluate suitable maintenance treatment courses. The present observation and treatment periods were relatively short. Additionally, a fractional laser-assisted drug system can be used to provide supportive care for patients with MAA, but it cannot completely replace traditional treatment methods. Rather, the technique could potentially be used in combination with conventional treatments.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Beijing Friendship Hospital, Capital Medical University research committee and with the declaration of Helsinki.

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Conflict of interest The authors declare that they have no conflict of interest.

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