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ORIGINAL RESEARCH

Treatment of male androgenetic alopecia with topical products containing *Serenoa repens* extract

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ABSTRACT

Background/Objectives: Male androgenetic alopecia (AGA) is a common hair problem. *Serenoa repens* extract has been shown to inhibit both types of 5-α reductase and, when taken orally, has been shown to increase hair growth in AGA patients. The aim of this study was to assess the efficacy of topical products containing *S. repens* extract for the treatment of male AGA.

Methods: This was a pilot, prospective, open, within-subject comparison limited to 24 weeks using no placebo controls. In all, 50 male volunteers aged between 20 and 50 years received topical *S. repens* products for 24 weeks. The primary end-point was a hair count in an area of 2.54 cm^2 at week 24. Secondary end-points included hair restoration, investigators' photographic assessment, patients' evaluation and discovering adverse events.

Results: The average hair count and terminal hair count increased at weeks 12 and 24 compared to baseline. Some of these positive results levelled off at week 24, presumably because the concentrated topical product containing *S. repens* extract was stopped after 4 weeks. The patients were satisfied with the products and the side-effects were limited.

Conclusions: The topical application of *S. repens* extract could be an alternative treatment in male pattern baldness in male patients who do not want or cannot tolerate the side-effects of standard medications, but the use of a concentrated *S. repens* product beyond 4 weeks may be necessary for sustained efficacy.

Key words: 5-alpha reductase, androgenetic alopecia treatment, Biothymus-M, Canfield, male pattern baldness treatment, *Serenoa repens*.

INTRODUCTION

Androgenetic alopecia (AGA) is a common hair problem affecting both sexes. This is seen in an ageing population, with an incidence in Caucasians of at least 80% in men and 40% in women.[1] Although baldness is not physically debilitating, it can significantly affect the patients' quality of life.[2] Currently, treatments cleared by the US Food and Drug Administration (FDA) for AGA include medications (topical minoxidil and oral finasteride)[3] and a medical device (low-level laser therapy).[4]

Topical minoxidil, at 5%, has been shown to increase the hair count by 12% on average at 12 months.[5] Irritation from propylene glycol, its vehicle, is common and a different preparation in a propylene glycol-free foam vehicle can be substitute to reduce the potential of irritation.[6]

Oral finasteride, an 5-α reductase inhibitor, is another FDA-approved medication for the treatment of male pattern baldness. At 1 mg/day, the increase in hair count at 12 months was 22% on average.[7] Direct comparison between oral finasteride and topical minoxidil at 12 months show the

Abbreviations:

AGA	androgenetic alopecia
FDA	Food and Drug Administration

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Conflict of interest: medications and patient compensation were provided by Rottapharm Madaus, Monza, Italy. The company was not involved in the design and conduct of the study.

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superiority of the former, with an increase in hair count of 29% versus 15% of the latter.[8] According to a very large prospective study, the effect of finasteride on sexual functioning is minimal for most men and should not impact on the decision to prescribe or take finasteride,[9] although in a small subset of patients altered sexual functions such as erectile dysfunction and diminished libido have been reported.[10]

A low-level laser therapy comb is another FDA-approved treatment for AGA. It emits beams at a wavelength of 655 nm. In a multicentre 6-month trial, this device has been shown to increase hair count by 16% on average.[11] Many other products to treat male pattern baldness are available, but the level of evidence is not as strong as it is for the aforementioned therapy.[12]

The treatment of AGA is costly, requires a lifelong commitment and may have side-effects. Thus, topical, over-the-counter, non-pharmocological cosmetic haircare products that are effective for male pattern baldness could be more acceptable and provide alternatives for men suffering from hair loss.

Saw palmetto (*Serenoa repens*) extract has been shown to inhibit dihydrotestosterone in human prostate tissue *in vivo*.[15] *S. repens* extract also contains β-sitosterol. The latter can reduce steroid hormone synthesis, especially testosterone. A recent study has also demonstrated that its extract can inhibit both types of 5-α reductase.[14] However, according to a Cochrane Review, saw palmetto extract could not improve urinary flow measures or prostate size in men with lower urinary tract symptoms consistent with benign prostatic hyperplasia.[15] *S. repens* 320 mg/day, when taken orally, could increase hair growth in AGA patients.[16] *S. repens*, when used topically, could increase hair number and hair weight in patients with AGA, as shown by hair clipping method.[17] However, to the best of our knowledge,

Table 1 Inclusion and exclusion criteria for participants in this trial

Inclusion criteria	Exclusion criteria
Male	Coexisting systemic diseases
Age 20–50	Scars or ulcers on the scalp
Norwood–Hamilton types III, IIIv, IV and V	Hair loss other than from androgenetic alopecia
	Hair transplantation within 6 months
	Received any other treatment that could affect hair loss within 6 months, such as 5-α reductase inhibitors, minoxidil, hormones, corticosteroids or cytotoxic drugs

Table 2 Active ingredients of *Serenoa repens* products

Serum	Lotion	Shampoo
Saw palmetto Green tea extract Peony root extract Piroctone-olamine Oligopeptides	Same as serum but not as concentrated	Oligopeptides Multivitamins (B3, B5, zinc, biotin)

Table 3 Androgenetic alopecia (AGA) stage. The median of AGA stage changed from Norwood IV to Norwood IIIv at the 24th week compared to the baseline

Friedman's test		Q	*P* value
		8.375	0.015184*
Week	AGA stage median	Compared	*P* value
0	5	0 *vs* 12 weeks	0.000982**
12	3.5	0 *vs* 24 weeks	0.000196**
24	3	12 *vs* 24 weeks	0.067889

Norwood–Hamilton AGA stages were numerically converted for statistical calculations. III = 1, IIIa = 2, IIIv = 3, IV = 4, IVa = 5, V = 6, Va = 7, Vv = 8, VI = 9, VII = 10. *Significant, **highly significant.

Table 4 Patients' baseline characteristics

Category	Value
Mean age ± standard deviation (years)	35.12 ± 6.2487
Minimal age (years)	23
Maximum age (years)	49
AGA staging (%)	
III	22
IIIa	6
IIIv	10
IV	26
IVa	6
V	18
Va	2
VI	10

Table 5 Primary efficacy end-point analyses: average hair count

ANOVA repeated measures		F	*P* value
		17.2937	4.02E-07** values
Post hoc analysis			
Week	Mean hair count (95% CI)	Compared	*P* value
0	1,736.369 (1,666.325, 1,806.341)	0 *vs* 12 weeks	1.18E-05**
12	1,795.854 (1,725.86, 1,865.848)	0 *vs* 24 weeks	1.19E-06**
24	1,821.715 (1,751.721, 1,891.71)	12 *vs* 24 weeks	0.130756

*Significant, **highly significant.

Table 6 Secondary efficacy end-point analyses: average hair width

ANOVA repeated measures		F	*P* value
		7.904348	0.000672**
Post hoc analysis			
Week	Mean hair width (μm) (95% CI)	Compared	*P* value
0	45.174 (41.619–48.755)	0 *vs* 12 weeks	0.000518**
12	48.316 (44.877–52.014)	0 *vs* 24 weeks	0.117434
24	46.291 (42.759–49.896)	12 *vs* 24 weeks	0.021473*

*Significant, **highly significant.

standardised macrophotographic hair analyses have never been performed.

The aim of this study was to assess the efficacy of a topical products containing *S. repens* extract for the treatment of male AGA using a standardised validated macrophotographic technique and questionnaire.

MATERIALS AND METHODS

The study was approved by the Institute's Research and Ethics Review Board and was performed in accordance with the World Medical Association's Helsinki Declaration and its amendment. Written informed consent was obtained from all paricipants, who were recruited by advertisement.

Subject and study design

This study was a pilot, prospective, open, within-subject comparison conducted at the Institute of Dermatology, Bangkok. A screening period of 3 weeks was followed by a 24-week study period and a 4-week follow up.

Study participants

Eligible male volunteers were aged between 20–50 years and had mild-to-moderate hair loss, classified as Norwood–Hamilton types III, IIIv, IV, V and VI.[18] Fifty participants were enrolled by consultant dermatologists if they fulfilled the criteria laid down in the study design (Table 1).

All *S. repens* (Biothymus-M) products were produced by Rottapharm Madaus, Monza, Italy. Volunteers used one 3.3 mL vial of concentrated serum daily by applying it to the thinning areas on the scalp for the first 4 weeks in accordance to the company's instructions. Two mL of lotion was applied daily to the whole scalp throughout the study period, the first a few minutes after the use of serum at 4 weeks. Shampoo was used to clean the patients' hair as needed. The ingredients of the products are listed in Table 2.

Outcome measurement

The primary efficacy end-points were a hair count within the area of 2.54 cm^2 at the vertex of scalp at weeks 12 and 24, compared to the baseline count, using a validated macrophotographic technique using the Canfield photography system.[19]

Secondary end-points included hair restoration and investigator assessments. Hair restoration means changes in average hair size and terminal hair count at week 12 and 24 compared to the baseline. Hair was classified as vellus if the width was less than 30 μm, intermediate if the width was between 30–60 μm and terminal if the width exceeded 60 μm. Macrophotographic pictures were collated at the end of the study and hair counts and measurements of each photograph were done separately by three investigators blinded to both the participants' names and time-points at which the photographs were taken. Investigator assessments included the change in AGA stage and patients' satisfaction with the treatment. A global photographic assessment of each participant was done separately by three physicians blinded to the time-points at the end of the study period. Norwood–Hamilton grading of these pictures was numerically converted for statistical calculations (Table 3). Satisfaction with the treatment was measured using the

Table 7 Secondary efficacy end-point analyses: vellus, intermediate and and terminal hair count

Terminal hair-ANOVA repeated measures		F	*P* value
		37.62822	9.89E-13**
Post hoc analysis			
week	Mean hair count (95% CI)	Compared	*P* value
0	433.25 (340.9253, 525.5747)	0 *vs* 12 weeks	0.000261**
12	526.0347 (433.7101, 618.3594)	0 *vs* 24 weeks	1.08E-10 **
24	754.1736 (661.8489, 846.4983)	12 *vs* 24 weeks	1.8E-05**
Medium-size hair; ANOVA repeated measures		F	*P* value
		5.303949	0.006569**
Post hoc analysis			
week	Mean hair count (95% CI)	Compared	*P* value
0	776.5278 (703.6628, 849.3927)	0 *vs* 12 weeks	0.165625
12	748.5278 (675.6628, 821.3927)	0 *vs* 24 weeks	0.001077**
24	696.2639 (623.3989, 769.1228)	12 *vs* 24 weeks	0.096847
Vellus hair: ANOVA repeated measures		F	*P* value
		16.99396	5.01E-07**
Post hoc analysis			
week	Mean hair count (95% CI)	Compared	*P* value
0	546.6389 (457.7988, 635.479)	0 *vs* 12 weeks	0.973424
12	545.9375 (457.0974, 634.7776)	0 *vs* 24 weeks	2.16E-06**
24	409.0069 (320.1668, 497.8471)	12 *vs* 24 weeks	0.000176**

**Highly significant.

Table 8 Investigator photographic assessment questionnaire. A photographic evaluation by the investigators confirmed there was a slight improvement in hair appearance from the 12th week compared to the baseline

Friedman's test			Q	*P* value
Anterior			52.57291667	3.83651E-12**
Vertex			52.71875	3.56672E-12**
Wilcoxon–signed rank test				
Area	Time (week)	Median*	Compared	*P* value
Anterior	0	4	0 *vs* 12	1.79E-06**
	12	5	0 *vs* 24	5.18E-09**
	24	5	12 *vs* 24	0.001377**
Vertex	0	4	0 *vs* 12	4.77E-07**
	12	5	0 *vs* 24	5.18E-09**
	24	5	12 *vs* 24	0.005418**

*Median 4 = no change, 5 = slight increase. **Highly significant.

investigator photographic assessment questionnaire.[20] It uses a seven-point rating scale, ranging from 'greatly decreased hair growth' to 'greatly increased hair growth,' centred at 'no change'.

Patients assessed their hair change at weeks 0, 12 and 24 by using validated, self-administered seven-point scale hair growth questionnaires[20,21] consisting of questions regarding therapeutic efficacy (hair thinning, coverage, and appearance) and satisfaction with appearance of scalp hair (overall, scalp appearance, coverage, amount of hair in the thinning areas, hair growth in the thinning areas).

Reports of adverse events, if any, were collected at every visit (Fig. 1).

Statistical analyses

Statistical analyses were done using Microsoft Excel with an additional Real Statistics Resource Pack (http://real-statistics.com).

The reliability of the hair count by the three different raters was done using intraclass correlations. The analyses of objective measurements (hair count, hair size) were done using ANOVA repeated measures, followed by a post-hoc test Tukey honest significance difference. For subjective measurements, Friedman's test was used, followed by the Wilcoxon–signed rank test.

Table 9 Hair growth index (HGI), a validated, self-administered 7-point scale hair growth questionnaire. Patients' assessment showed a slight decrease (by one point) in hair thinning and a slight improvement in coverage and overall appearance from the 12th week onwards, compared to the baseline

Friedman's test			Q	*P* value
HGI1 (hair thinning)			22.875	1.07834E-05**
	Time (week)	Median	Compared	*P* value
Wilcoxon–signed rank test	0	4	0 *vs* 12	6.45838E-06**
	12	3	0 *vs* 24	3.73E-06**
	24	3	12 *vs* 24	0.465415
Friedman's test			Q	*P* value
HGI2 (coverage)			16.94791667	0.000208837**
	Time (week)	Median	Compared	*P* value
Wilcoxon–signed rank test	0	4	0 *vs* 12	0.015194691*
	12	5	0 *vs* 24	5.42E-05**
	24	5	12 *vs* 24	0.069377
Friedman's test			Q	*P* value
HGI3 (overall appearance)			40.53125	1.07834E-05**
	Time (week)	Median	Compared	*P* value
Wilcoxon–signed rank test	0	4	0 *vs* 12	6.79864E-07**
	12	5	0 *vs* 24	1.83E-07**
	24	5	12 *vs* 24	0.212211

*Significant, **highly significant.

RESULTS

One patient left the trial at the beginning for personal reasons and his incomplete data were not included in the analyses. In all, 49 patients completed the study. The paticipants' baseline characteristics are shown in Table 4 . A total of 147 macrophotographs were used (three each from 49 patients) in the efficacy assessment. The intraclass correlation of hair count between the raters was 0.866.

Table 10 Hair growth satisfaction scale (HGSS), a validated, self-administered 7-point scale hair growth questionnaire. Patients reported satisfaction in all categories from the 12th week compared to the baseline

Friedman's test			Q	*P* value
HGSS1 (Overall satisfaction)			52.54166667	3.89693E-12**
	Time (week)	Median	Compared	*P* value
Wilcoxon–signed rank test	0	3	0 *vs* 12	1E-08**
	12	5	0 *vs* 24	1.41E-08**
	24	5	12 *vs* 24	1
Friedman's test			Q	*P* value
HGSS2 (scalp appearance)			63.26041667	1.83305E-14**
	Time (week)	Median	Compared	*P* value
Wilcoxon–signed rank test	0	2.5	0 *vs* 12	1.12E-08**
	12	5	0 *vs* 24	3.52E-09**
	24	5	12 *vs* 24	0.269241
Friedman's test			Q	*P* value
HGSS3 (coverage)			61.54166667	4.32909E-14**
	Time (week)	Median	Compared	*P* value
Wilcoxon–signed rank test	0	4	0 *vs* 12	6.79864E-07**
	12	5	0 *vs* 24	1.83E-07**
	24	5	12 *vs* 24	0.212211
Friedman's test			Q	*P* value
HGSS4 (amount of hair in the thinning areas)			64.125	1.18969E-14**
	Time (week)	Median	Compared	*P* value
Wilcoxon–signed rank test	0	2	0 *vs* 12	4.59E-09**
	12	5	0 *vs* 24	3.52E-09**
	24	5	12 *vs* 24	0.253098
Friedman's test			Q	*P* value
HGSS5 (hair growth in the thinning areas)			62.09375	3.28483E-14**
	Time (week)	Median	Compared	*P* value
Wilcoxon–signed rank test	0	3	0 *vs* 12	7.62E-09**
	12	5	0 *vs* 24	5.18E-09**
	24	5	12 *vs* 24	0.758528

*Significant, **highly significant.

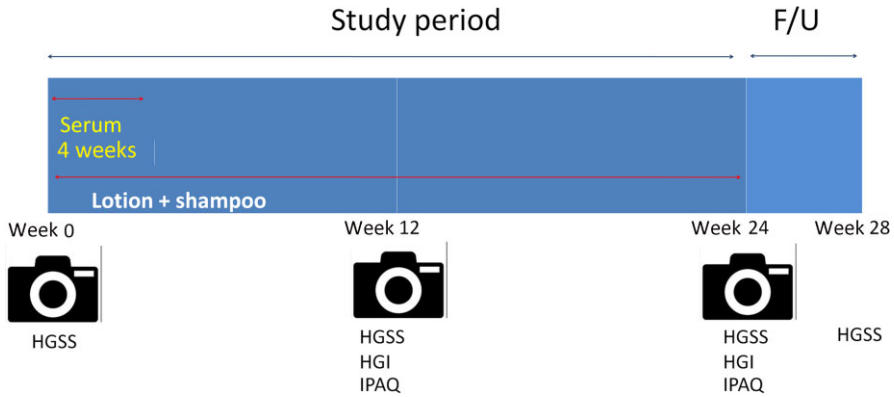

Figure 1 The trial consisted of a 24-week study period, during which patients used medication, and a 4-week follow-up (*F/U*) period of observation alone. Patients applied *Serenoa repens* serum daily for the first 4 weeks but used *S. repens* lotion daily throughout the study. *S. repens* shampoo was used as needed. Global and macro photographs were taken thrice: at the beginning and at 12th and 24th week. A hair growth satisfaction scale (*HGSS*) questionnaire was taken at the beginning and at 12, 24 and 28 weeks and a hair growth index (*HGI*) questionnaire were taken at weeks 12 and 24. IPAQ, investigator photographic assessment questionnaire.

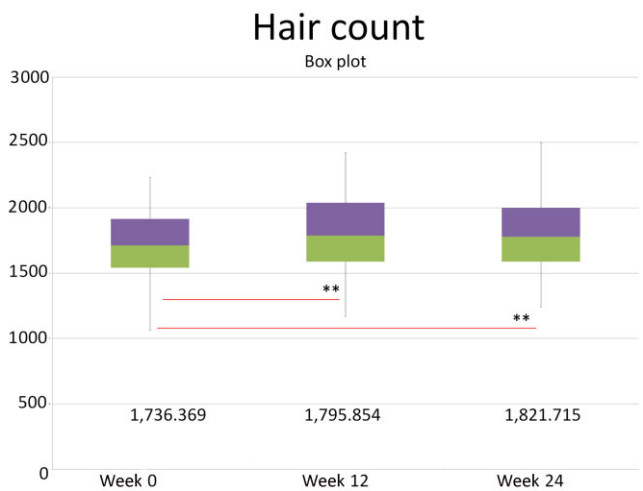

Figure 2 Primary end-point analyses. Box-whisker plot of average hair count at both week 12 and week 24 show an increase from baseline (week 0). There was no difference between week 12 and week 24. **Highly significant.

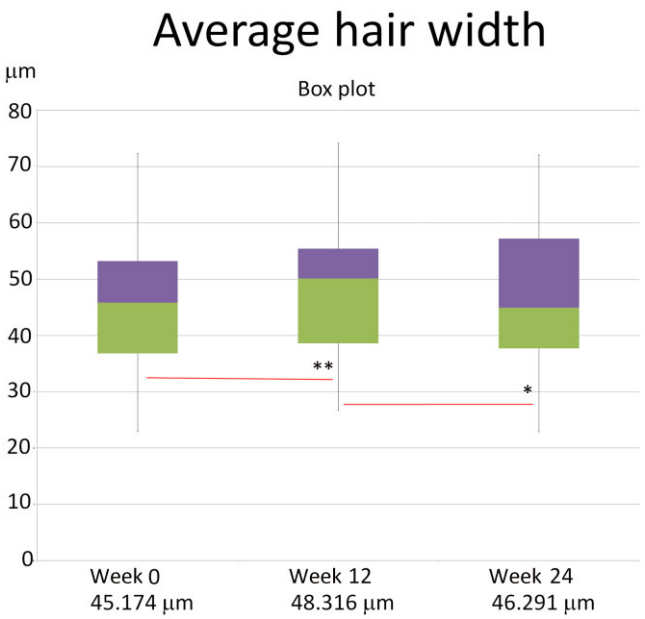

Figure 3 Secondary end-point analyses. Box-whisker plot of average hair width. Hair width at week 12 increased from the baseline (week 0) but was reduced at week 24. There was no difference between week 24 and the baseline. *Significant, **highly significant.

Primary efficacy end-points

The increase in the hair count was significant at the 12th and 24th week compared to the baseline (Fig. 2 and Table 5). There was no difference between the 12th and the 24th week.

Secondary efficacy end-points

Average hair size increased significantly at the 12th week compared to the baseline but decreased significantly at the 24th week, so there was no difference when comparing the 24th week to the baseline (Fig. 3 and Table 6). The terminal hair count increased at both the 12th and 24th week, and the 24th week was superior to the 12th week (Fig. 4 and Table 7). There was also a significant decrease in vellus hair count (significant between 0 *vs* 24th week and 12th *vs* 24th week) and medium hair count (significant at 0 *vs* 24th week).

The median AGA stage changed significantly from stage IV to IIIv between 0 *vs* 12th week and 0 *vs* 24th week (Table 3). For photographic assessments, investigators reported a slight increase of the hair at anterior and vertex scalp, statistically significant at 0 *vs* 12th, 12th *vs* 24th and 0 *vs* 24th week time-points (Fig. 5, Table 8).

As per participants' self evaluation, hair growth index scores were significantly higher in all three categories at weeks 12 and 24 compared to the baseline, but by only one point out of seven (Table 9). From the hair growth satisfaction scale, median scores were significantly higher by two to

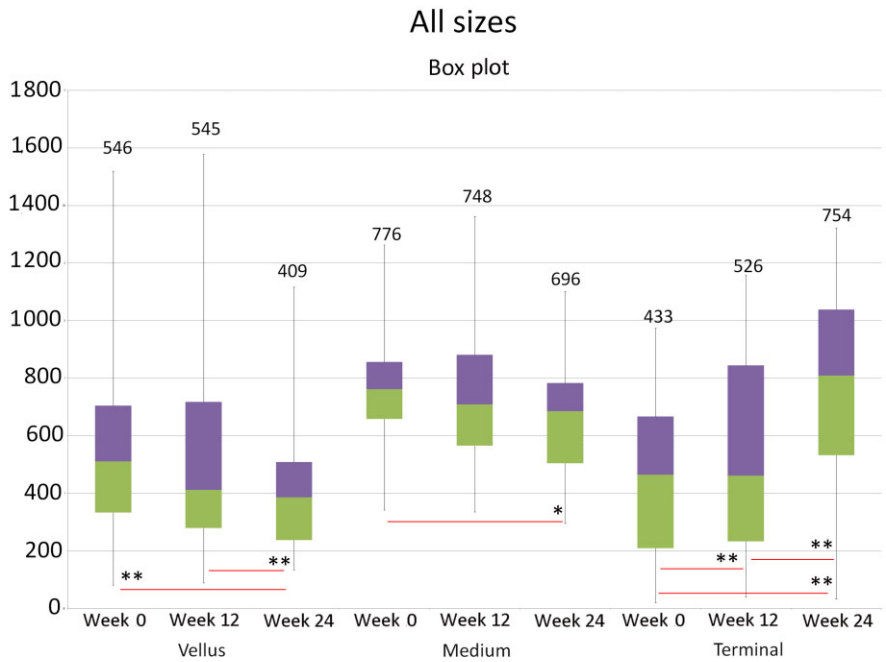

Figure 4 Secondary end-point analyses. Box-whisket plot of vellus, intermediate and and terminal hair count. Hair was classified as vellus if the width was less than 30 μm, intermediate if it was between 30–60 μm and terminal if it was more than 60 μm. Mean counts appear above the plot. Terminal hair increased in number at week 12 and 24 week compared to the baseline, but both vellus hair and intermediate hair count significantly decreased at week 24 compared to the baseline count. *Significant, **highly significant.

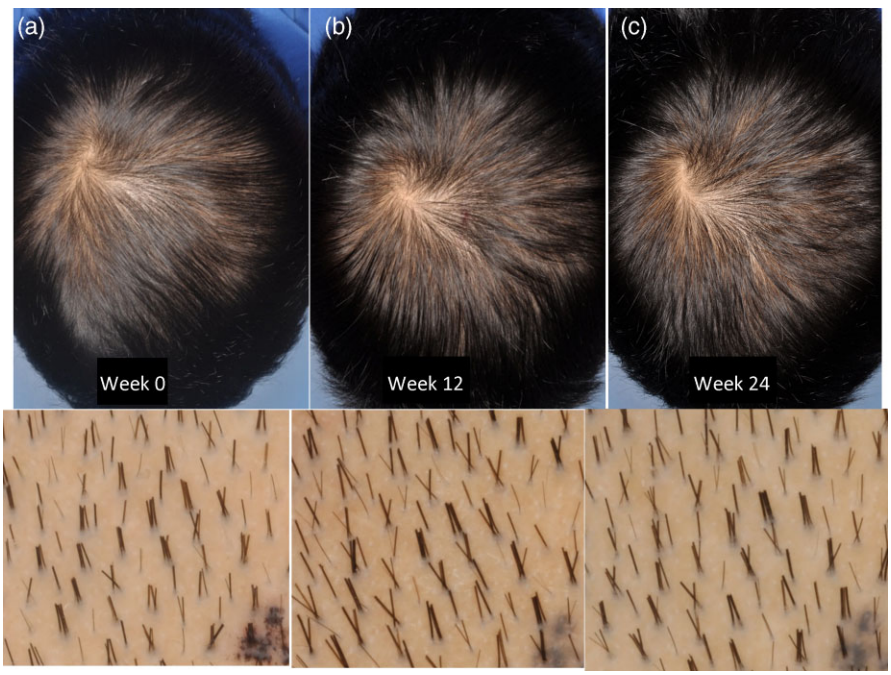

Figure 5 Example pictures of a typical patient with corresponding macro-photographs of the vertex scalp, showing (a)baseline, (b), week 12 and (c) week 24. The hair count and size improve at the week 12 but the beneficial effects waned at week 24.

three points out of seven in all categories at week 12 and 24, compared to the baseline (Table 10).

Adverse events

Side-effects were common but mild and none of the participants needed to stop using the products. They included a feeling of coldness (16%), mild burning (12%), an unpleasant smell (2%), an itchy scalp (2%), acne on the forehead (2%) and abrasion when using the finger that touched the products to scratch the scrotum (2%).

DISCUSSION

The normal course of male pattern baldness is progressive over time.[22] In this study, treatment with products containing *S. repens* was shown to significantly increase the numbers of total hair and especially that of terminal hair.

This translated into clinical benefits, as confirmed by investigators' evaluation showing the change in Norwood–Hamilton AGA grading and an increase hair growth in the photographic assessment. Volunteers also reported limited hair growth and increased satisfaction with the appearance of their hair, with no serious side-effects.

Not all improvements lasted until the end of the study. Average hair size improved only until the 12th week then declined at the 24th week until there was no difference from the baseline. The total hair count did not increase between the 12th and 24th week. Although the terminal hair count continued to improve until the 24th week, this coincided with a significant loss of medium size and vellus hair. The termination of the more concentrated serum containing *S. repens* after 4 weeks could be the reason for this and its continuation beyond 4 weeks may be advisable.

The main limitations of this study include the design and the short duration. This is an open, within-subject comparison pilot trial without controls thus the generalisation of these results should be made with care. The duration of the study was only 24 weeks. Thus, further research comparing *S. repens* products with standard medications, in a double-blinded manner and for a longer duration should be conducted to substantiate the findings of this study.

CONCLUSION

This present investigation has demonstrated the effects of the topical application of products containing *S. repens* for the treatment of AGA. Improvements in hair counts and sizes were found at week 12 week but the positive gains declined at week 24. The reason could be the termination of a more concentrated *S. repens*-containing serum after only 4 weeks. *S. repens*-containing products could be alternative medications used in male pattern baldness in male patients who do not want or cannot tolerate the side-effects of standard medications, but more prolonged use of the concentrated serum are advisable.

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