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Hair Regrowth Following Topical HairUp™ Treatment in Subjects with Alopecia Totalis (AT) and Alopecia Universalis (AU): A Retrospective Analysis of Efficacy and Cosmetic Acceptability

Jaffe A[1], **Nir Y**[2*], **Zbar AP**[3], **Gonen-Shahar M**[4] **and Gonen S**[4]

[1]*Hillel Yaffe Medical Center, Hadera, Israel*

[2]*SPRIG Consulting LLC, Wilmette, IL, USA*

[3]*Department of Anatomy, University, Melbourne, Australia*

[4]*Shmuel Gonen Technologies, Ramat Gan, Israel*

[*]**Corresponding author:** Nir Y, 1020 Ashland Ave, Wilmette IL 60091, USA, E-mail: amiryael@gmail.com

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Abstract

Objective: Alopecia areata is a common disorder 5-30% of cases representing alopecia totalis (AT) or alopecia universalis (AU), the most severe forms of the disorder. In the absence of any FDA-approved treatments, topical Hair Up™ has shown promising results but has not been subject to formal study. The following study reports the initial use of a customized natural topical treatment-Hair Up™ in an unselected population of AT and AU patients. It includes a cohort of patients with an intention to treat and aims to serve as a pilot study to a prospective study.

Methods: A retrospective analysis of AT/AU patients treated with topical Hair Up™ was conducted. The study assessed type of hair growth and the percentage hair regrowth using the severity alopecia tool (SALT) scoring system with a subjective determination of the cosmetic acceptability of response over a 2 year follow-up period.

Results: Of 109 subjects, 53 with available data were eligible for analysis including 26 minors <18 years of age (mean age 10.8+4.7 years) and 27 adults (mean age 39.1+12.2 years). There were 34 subjects with AU and 19 with AT. Treatment appeared to be very safe with minimal contact reactivity. Almost all subjects achieved vellus hair growth (96%; 51/53) with 43% (23/53) developing full abundant hair and 81% (43/53) showing a return to quality vellus hair as early as 3 months after commencement of treatment. SALT scores exceeded 75% in 75% (21/28) of cases. Overall, 94% (17/18) of minors ultimately achieved a subjective cosmetically acceptable result compared with 58% (11/19) of adults (p=0.02).

Conclusion: Topical Hair Up™ treatment of subjects with Alopecia totalis (AT) and Alopecia universalis (AU) is effective and safe with a high rate of terminal hair regrowth and cosmetic acceptability, particularly in minors.

Keywords: Alopecia totalis; Alopecia universalis; Alopecia areata; SALT score; Hair regrowth; Severity alopecia tool; Topical treatment

Introduction

Hair loss is a common problem in the community affecting up to 50% of both men and women during their lives. It may occur anywhere on the body but is most common on the scalp, often being divided into scarring and non-scarring types or described as focal or diffuse [1]. Alopecia areata (AA) is one of the commoner non-scarring hair loss disorders with a genetic predisposition in 20% of cases and a prevalence rate of 2% in the overall population [2]. There is no gender predilection where about two-thirds of cases develop before 20 years of age. Severe forms of AA include Alopecia totalis (AT), a loss of all scalp hair and Alopecia universalis (AU), the loss of all scalp and body hair. Both AT and AU are less common than patchy AA accounting for only 5-30% of all treated alopecia cases [3]. Both AT and AU have a less favorable outcome than AA, with a reported cure rate around 10% overall. The prognosis of which is worse if there is an onset prior to puberty, or if there is a either a positive family history of AA or associated atopy [4,5]. Up to half of the AA patients with limited disease lasting up to one year, will recover although most patients will experience relapse with variable hair growth during follow-up with up to one-quarter progressing to a diagnosis of AT [6]. The pathogenesis of AA and its variants is controversial, reflecting a combined derangement of the normal hair cycle and an impairment of the status of protected immunological privilege enjoyed by the follicle [7]. On the one hand an unknown signal or injury results in a premature telogen phase with follicular arrest so that there is cycle shortening with repeated arrest of cells in the anagen (growth) phase. This disturbance occurs in tandem with an up regulation of MHC class I antigen expression in the proximal hair follicle epithelium probably triggered by an infectious focus, bacterial super antigens, skin micro trauma or psycho-emotional stressors and permits follicle destruction by nearby immunocompetent cytotoxic T cells [8].

There are currently no FDA-approved topical treatments for AA with many management alternatives but no definitive curative or preventative therapies [9-11]. Different options have included intra-lesional or topical corticosteroids, topical Minoxidil, contact Anthralin, topical sensitizer immunotherapies (such as squaric acid dibutylester-SADBE or diphenylcyclopropenone-DPCP) and topical psoralen-UVA

phototherapy [12]. Hair Up™ (Ramat Gan, Israel) is an ointment composed of 100% natural active ingredients (as defined by the US Personal Care Products Council) and approved for use by the Israeli Ministry of Health since 1980 (approval number 1/90954/16) and the governor of the prefecture of Saga, Japan.

The composition of Hair Up™ is shown in Table 1. It is suggested that hair follicles are strengthened by an ability of some of the components to reduce local sebum secretion, whereas others have anti-inflammatory or anti oxidative properties and some change the nutrient milieu [13-15]. Hair Up™ has been used by a single dedicated specialized clinic treating more than 20,000 subjects since 1993 where approximately 16% of our patients suffer from Alopecia areata (AA). Our previous findings with Hair Up™ (not published) have led to the impression that it reduces hair loss and promotes the growth of new hair when follicles are still alive, resulting in an improvement in hair appearance, hair thickening and an enhancement of hair vitality. Its use appears to be safe in both sexes as well as when indicated in minors. There are currently limited data concerning the long-term outcome of AT/AU cases. A recent study with a mean follow-up of 17.7 years showed a direct relationship between the severity of Alopecia and the long-term prognosis. The study showed that despite the long follow up, among 11 patients with AT, 5 still had AT and one developed AU at the end of the study. Among the 27 patients with AU, 23 maintained their disease, while 2 developed AT; none of these patients achieved total regrowth of hair. Out of 5 children with AU in this study, this level of severity of the disease continued in 4 patients without significant improvement [16].

Water (Aqua)
SD Alcohol 40
Carbomer
Foeniculum vulgare seed extract
Triethanolamine
Euxyl PE 9010
Myrtus communis flower extract
Myrtus communis leaf extract
Melissa officinalis whole plant extract
Rosmarinus officinalis leaf extract
Salvia officinalis leaf extract
Achillea millefolium leaf extract
Glycyrrhiza glabra root extract

Table 1: Component list of Hair Up™ constituents.

Our study reports the initial use of Hair Up™ in an unselected population of subjects with AT or AU objectively assessing their hair regrowth response.

Methodology

The study retrospectively analysed data concerning Hair Up™ use in patients diagnosed with AT/AU between January 1993 and January 2014. All clinic files were manually scanned with the AU/ AT files targeted and extracted. Approval for analysis was provided by the local Hillel Yaffe Medical Centre Ethics Committee. At the first consultation, subjects completed a questionnaire incorporating demographic data, disorder history and progression, general medical history, the use of concomitant medications, family history regarding hair loss and any prior history of autoimmune disorders. Study exclusion criteria were subjects using a wig attached with glue (unable to be taken off daily), subjects previously treated with parenteral corticosteroids or those without a follow-up of at least 3 treatment sessions. Following a cleansing shampoo, Hair Up™ was applied once daily over the entire scalp to include affected areas with removal after 2-3 hours. In some cases, Hair Up™ may be left on overnight and then rinsed off in the morning. Follow-up visits were performed monthly until vellus hair growth was achieved (also noting return of eyebrow and/or eyelash hair with follow-up photography) and then tapered accordingly to every alternate month or until such time that there was cosmetically acceptable hair growth. Delayed reviews were then conducted twice yearly. The last treatment date and an overall compliance measure were recorded. If the treatment was adjudged as ineffective over a period of 6 months, it was discontinued.

The study used 4 methods of evaluation during follow-up. The methods used are the standard methods used in the literature. To minimize bias, 4 different methods of evaluation were used. Determination of the type of hair regrowth labeled as vellus, intermediate, terminal (androgenic) or full abundant. Full abundant regrowth was defined as hair that was terminal in type and covered the whole scalp area. This end point was recorded as the composite of the clinic personnel's assessment together with the patient's response.

Percentage regrowth was calculated based upon the photographic evidence obtained during the follow-up visits over the period of time during which the patient was treated at the clinic. This information was evaluated for each visit by study research personnel and divided into 4 discrete stages of growth namely, <25%, (noticeable) 25-50% (moderate), 50-75% (obvious) and >75% (marked).

The Severity Alopecia Tool (SALT) score. This score was originally reported by Olsen et al. in 2004 and represents a mathematical approach to the determination of hair loss and regrowth [17]. Briefly, the percentages of hair loss on each of the sides (18% each), back (24%) and top (40%) of the scalp are determined independently and each is multiplied by the percentage scalp covered in that area. The products of each section are then summated for a final percentage hair loss. Comparisons were made between the baseline and the photograph at the last follow-up visit in responding cases. A percentage change from baseline was recorded such that:

$$SALT_{baseline} - SALT_{final} \times 100\ \%/SALT_{baseline} = \%\ Change$$

The score was determined by two evaluators.

An assessment by the two evaluators of a cosmetically acceptable or unacceptable result obtained by reviewing the last photograph obtained at the clinic. All adverse events were recorded during the conduct of the study noting any specific local effects such as redness of the scalp, pain or itching in the application area and any allergic reaction.

Statistical analysis

Statistical analyses were performed using the SAS® version 9.3 software (NC, USA). Means, medians, standard deviations and interquartile ranges are presented where appropriate along with 95%

confidence intervals. The comparisons of baseline characteristics between minors and adults were carried out using the Fisher's exact test. The Kaplan-Meier method was used to determine the time to each of the hair regrowth stages. P values <0.05 are considered significant.

Results

A total of 109 files of subjects diagnosed with AT/AU were retrieved. Of these, 56 subjects were ineligible, and excluded from analysis including 13 (23.2%) with insufficient follow-up by January 2014, 31 (55.4%) who were non-compliant with the treatment, 11 (19.6%) previously treated with intravenous steroids and one subject who used a wig that was not removed for regular scalp assessment. Fifty-three subjects fulfilled the inclusion criteria and were included in following analysis (Figure 1).

The baseline characteristics of the study subjects according to their age group are presented in Table 2. Thirty-four subjects (64%) suffered from AU with 19 (33.9%) suffering from AT.

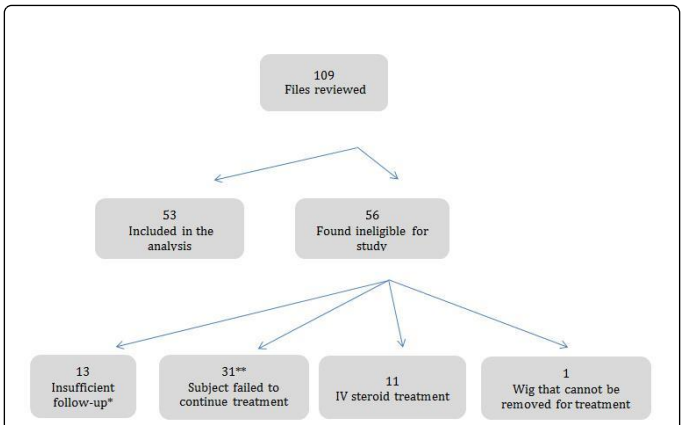

Figure 1: Flowchart showing the eligibility of patients for analysis. *Patients who began treatment during 2014 and therefore did not have a sufficient follow up period. **This group of 31 subjects who failed to continue treatment was not statistically different with respect to age and sex from the group of 56 subjects eligible for the study.

There were 26 (44.1%) subjects who were minors <18 years (Mean age 10.84+4.7 years) and 27 (48.2%) adults (Mean age 39.1 ± 12.2 years). In the cohort, 35 (66%) of the subjects were female. The time to the commencement of treatment in the clinic was shorter for minors than for adults (3.9 *vs.* 9.5 years, respectively). The mean age of onset of hair loss for minors and adults was 6.9 ± 4.3 years and 29.6 ± 15.6 years, respectively. Steroid treatment was the most common therapy previously administered to 37 subjects (70%) with 21/37 receiving local steroid injection.

Twenty-four (45%) subjects routinely used a wig with 10 (19%) regularly wearing a cap. Most subjects 43 (81%) could not attribute any cause to their alopecia, although 10 subjects (19%) linked its onset to a traumatic episode.

For the purposes of definition, traumatic events were considered if they occurred prior to the onset of hair loss and included any injury/disease or death of a close relative, exposure to war, involvement in a car accident and/or financial difficulties.

	Total	Minor	Adult	p-value
Age, years, mean ± SD	25.2 ± 17.0	10.8 ± 4.7	39.1 ± 12.2	NR
Females, % (n/N)	66 (35/53)	50 (13/26)	81 (22/27)	0.0214
Years since onset of hair loss, mean ± SD	6.8 ± 7.6	4.0 ± 3.7	9.6 ± 9.4	0.0073
Alopecia Totalis	36(19/53)	31 (8/26)	41 (11/27)	0.5694
Alopecia Universalis	64 (34/53)	69 (18/26)	59 (16/27)	0.5694
Prior treatment: Steroid (cream, local injection, oral) % (n/N)	70 (37/53)	58(15/26)	81 (22/27)	0.0772
Prior treatment: Other (DCP, Minoxidil) % (n/N)	42 (22/53)	35 (9/26)	48 (13/27)	0.4064
Wig, % (n/N)	55(24/44)	35 (7/20)	71 (17/24)	0.0324
Cap, % (n/N)	23 (10/43)	42 (8/19)	8 (2/24)	0.0131
Trauma, % (n/N)	19 (10/53)	23 (6/26)	15 (4/27)	0.5007
Family history of Alopecia, % (n/N)	24 (4/17)	29 (2/7)	20 (2/10)	1.0000

Table 2: Shows the baseline characteristics of the study subjects. Trauma is considered if it occurred prior to the onset of hair loss and included any injury/disease or death of a close relative, exposure to war, involvement in a car accident and/or financial difficulties. Abbreviations: NR–not relevant, DCP Diphenylcyclopropenone.

Treatment outcomes

Quality of hair regrowth: Almost all subjects (96%; (51/53)) achieved vellus hair with 43% (23/53) were able to achieve full abundant hair by the end of the study (Table 3). Although most subjects achieve vellus hair the growth itself is often patchy in nature.

Percentage regrowth: Moderate improvement (25-50%) was found in 53% (28/53) with marked improvement (above 75%) in 42% (22/53) subjects. 53% of subjects (28/53) showed a return of eyebrow hair and 36% (19/53) had a return of eyelash hair. The overall regrowth of scalp hair or quality growth did not show differences between minors and adults (Table 3).

The SALT score: The salt score was available for 28 of the 53 patients for whom images before and after treatment were taken. The score was above 75% in 75% (21/28) of subjects and in 57% (16/28) subjects it was 95% or higher (Table 3).

The cosmetic result: It is a binary record (either cosmetically acceptable or unacceptable) based upon assessment of the last available photograph by 2 reviewers blinded to each other's response. Overall, 53% (28/37) of the subjects experienced a good cosmetic result-acceptable with 17% (9/37) considered cosmetically unacceptable. In 30% (16/53) no suitable photographs were available for adequate determination (Table 3). Consensus between the two reviewers was achieved in all cases. The follow-up series of photographs of representative subjects (an adult and a minor) showing a good response with the development of full and abundant regrowth are

shown in Figure 2. Overall 94% (17/18) of minors experienced a cosmetically acceptable result compared with 58% (11/19) of adults (P=0.02).

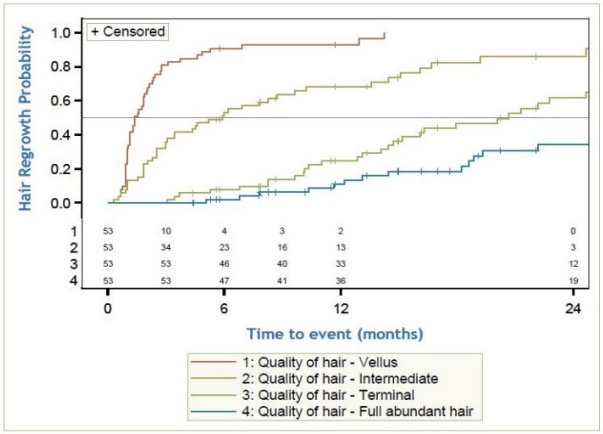

Figure 2: Quality of hair over treatment time up to 2 years following treatment.

Quality of hair and percent regrowth over treatment time

Most subjects (81%) showed a return of quality vellus hair as early as 3 months after the commencement of treatment and all subjects achieved vellus hair regrowth over a 2 year follow-up period (Table 4). Moderate regrowth (25-50%) was evident at 6 months in 23% of the subjects and was extended to 55% at 2 years.

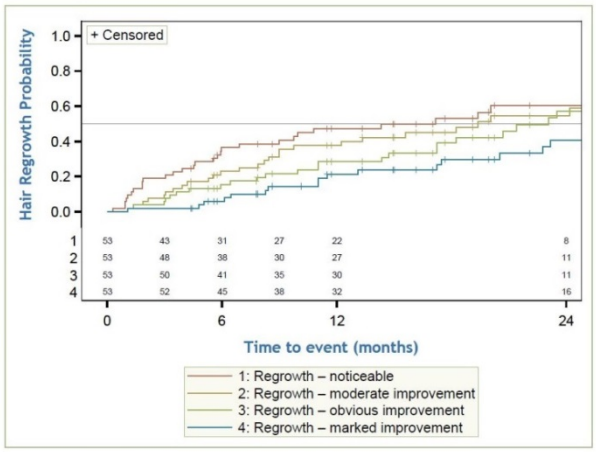

Figure 3: Percent regrowth over treatment time up to 2 years following treatment.

Stress and hair regrowth

We examined the effect of stress on hair regrowth and its quality defining stress as the experience of situations including divorce in adults, or cases where a grandparent became a guardian for a child as well as financial difficulties that necessitated the receipt of receiving the treatment either at a reduced price or free.

		Total	Minor	Adult	p-value
A-Quality of hair, % (95% CI) (n/N)	Vellus	96 (87-100) (51/53)	100 (87-100) (26/26)	93 (76-99) (25/27)	0.4906
	Intermediate	83 (70-92) (44/53)	92 (75-99) (24/26)	74 (54-89) (20/27)	0.1415
	Terminal	72 (58-83) (38/53)	81 (61-93) (21/26)	63 (42-81) (17/27)	0.2238
	Full abundant hair	43 (30-58) (23/53)	54 (33-73) (14/26)	33 (17-54) (9/27)	0.1704
B-Regrowth,% (95%CI)(n/N)	Noticeable (>0%)	53 (39-67) (28/53)	58 (37-77) (15/26)	48 (29-68) (13/27)	0.5857
	Moderate Improvement (>25%)	53 (39-67) (28/53)	58 (37-77) (15/26)	48 (29-68) (13/27)	0.5857
	Obvious Improvement (>50%)	49 (35-63) (26/53)	58 (37-77) (15/26)	41 (22-61) (11/27)	0.2763
	Marked Improvement (>75%)	42 (28-56) (22/53)	50 (30-70) (13/26)	33 (17-54) (9/27)	0.2709
Return of eyebrows		53 (39-67) (28/53)	62 (41-80) (16/26)	44 (25-65) (12/27)	0.2749
Return of eye lashes		36 (23-50) (19/53)	42 (23-63) (11/26)	30 (14-50) (8/27)	0.3983
C- SALT	Score >75%, % (n/N)	75 (21/28)	93 (14/15)	54 (7/13)	0.0286
	Score >95%, % (n/N)	57 (16/28)	73 (11/15)	39 (5/13)	0.1248
D- Cosmetic result	Acceptable, % (n/N)	76 (28/37)	94 (17/18)	58 (11/19)	0.0188
	Un-acceptable, % (n/N)	24 (9/37)	6 (1/18)	42 (8/19)	0.0188

Table 3: Shows the treatment outcome according to 4 evaluation methods at the end of follow-up time; A-quality (type) of hair growth, B- Regrowth, return of eyebrows and eye lashes, C-SALT score, D-cosmetic acceptability. The comparison was made between minors and adults. Full abundant regrowth was defined as hair that was terminal in type and which covered the whole scalp area. Regrowth is cumulative and adds up to more than 100%. Abbreviations: SALT Score-Severity of Alopecia Tool score.

Subjects under stress tended to have a lower chance of achieving a marked improvement in hair growth when compared with those not experiencing stress (32% *vs.* 55% respectively), although this did not reach significance. This effect also translated to the quality of hair regrowth where those with stress (as defined) had a lesser chance of achieving abundant hair quality than those with no coincident stress (35% *vs.*55% respectively). Wearing a wig tended to lower the probability of achieving a cosmetically acceptable result with full abundant hair by the end of the treatment (40% success for wig users *vs.* 67% success with no wig use, respectively, P=N.S.).

Safety

Over the conduct of the entire study, 2 adverse events were recorded noting superficial lesions of the scalp both of which healed spontaneously. These lesions may potentially have been a result of product contact irritation.

Discussion

The topical treatment HairUp™ was utilized in 53 subjects (34 with AU and 19 with AT) showing improvement in half the subjects with a similar number showing regrowth of both eyebrow and eyelash hair. An objective improvement in the SALT score was achieved in 83% of cases with cosmetically acceptable results in just over half (where data were available). In general, minors appeared to have better results than adults with half the children showing marked improvement in hair regrowth compared with only one-third of adult subjects. This was also reflected in a higher return of eyebrow and eyelash hair in children compared with adults (42% *vs.* 30%, respectively) with an overall better chance of a cosmetically acceptable result in children compared with adults at the end of the treatment program (94% *vs.* 58%; P=0.02). A positive family history of alopecia in all forms appeared to be associated with an overall lower probability of achieving a cosmetically acceptable outcome or full abundant hair following treatment, although this did not reach statistical significance (data not shown).

The regrowth of facial hair in areas where the treatment was not applied suggests a systemic responsiveness. A regrowth of eyebrow hair in particular, appears to be crucial for the reversal of alopecia. Subjects report on facial hair not when the first eyebrow hair appears but rather when the process of regrowth is complete, suggesting that end parameters such as eyebrow and eyelash regrowth should be compared with the final cosmetic appearance. The objective assessment of hair regrowth is not straightforward. Often the quality of the hair is less important than its quantity (overall growth); a parameter characterized by determination of general cosmetic acceptability. Further, for many subjects, early growth which is uniform and covers more of the scalp may be considered a superior result to a very limited area of hair growth with terminal quality.

Almost all subjects in this study achieved vellus hair during the study period, with 81% reaching this goal within 3 months. Following the growth of vellus hair it takes a considerable amount of time and often a prolonged treatment period in order to achieve terminal hair, characterized by darkening and thickening of the hair [17,18]. In this regard, terminal hair was noted in 25% of the subjects at one year and in 62% by 2 years. Similarly, more prolonged use of the product improves the success rate for hair regrowth with 36% achieving noticeable and only 6% achieving marked hair regrowth at 6 months. This result rose to 60% and 41%, respectively by 2 years also suggesting advantage in treatment continuance and prolonged follow-up surveillance.

The literature shows that patients with Alopecia areata who have had the disease since childhood tend to have a less favorable outcome than adults. However, in patients with AT/AU age did not seem to affect the prognosis [19,20]. In our study, minors appeared to have better results than adults with regard to hair regrowth, return of eyebrow and eyelashes and a better chance of achieving cosmetically acceptable results. This perhaps reflects an effect of the time from disease onset to treatment rather than the age of the patient but it may also represent a better parental compliance with daily HairUpTM application. Future studies will need to address the correlation in younger patients between cosmetic outcome and treatment compliance.

It is difficult to achieve successful treatment in people with severe sustained hair loss such as AT and AU [21]. There are very few available treatment options of topical therapies available. Topical steroid treatment as well as topical minoxidil has not proven to be very effective for these patients and treatment with intralesional steroids has been reported as unsuitable for AT/AU [22]. Diphenylcyclopropenone (DPCP) is considered the most effective topical immunotherapy for refractory or extensive Alopecia areata. In a retrospective study of 50 patients with a median treatment period of 3 years the success in terminal hair growth was similar to the 62% found in our study at 2 years. The study defined treatment success as 50% terminal hair regrowth which was reached in 71% of AT patients 56% of AU patients [23].

Our study was limited by its retrospective nature and by the method of data collection which was not adjusted to the end points. Since the HairUp™ clinic comprised only 2 clinicians there was no established photographic protocol which although taken at various angles were not adjusted for SALT score evaluation. This affected score calculation in some cases leading to inadequate records: an effect which can be improved in the future with photographic standardization. An additional limitation is that the methods used in the literature as well as in our study are subjective to a large extent. To minimize bias in this study we used several methods used in the literature (rather than just one) to review the data and report the treatment results. In addition for subjective measures such as SALT score and acceptability, two independent reviewers analyzed the data.

Our study population is not significantly different from other similar studies in this field, although we included a comparatively large number of minors. Despite the exclusion from analysis of a considerable number of subjects due to treatment non- compliance, there were no age or sex differences between the excluded and the analyzed cases which would likely influence results. Concerning this point, our patients represent a non-naïve group of cases who often come to the clinic for treatment as a last resort. Many have been disappointed with the results of previous treatments provided at no cost through the public insurance system and they will often choose to discontinue therapies (particularly those private treatments which incur out of pocket expenses), especially if they do not perceive rapid effectiveness.

From 1993 until 2014, the clinic has treated over 20,000 patients with the Hair Up™ product for a variety of hair loss diagnoses including hypothyroidism, stress-related alopecia, hormonal-related cases (including post-partum alopecia) and alopecia associated with specialized diets and medications. Approximately 16% of our patients

suffer from Alopecia areata. The management in this study of AT and AU patients reflects the nature of the referral process and shows effectiveness in an unselected cohort of patients 70% of whom had received prior unsuccessful steroid therapy.

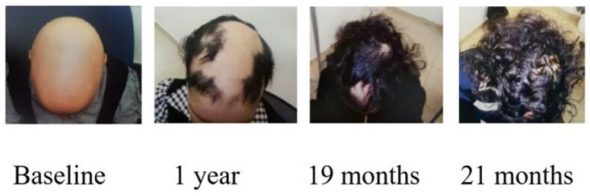

Figure 4a: Image of a 14 year old female with AU following failed steroid (PO) therapy prior to Hair Up™ treatment at baseline and at 21 months.

Subjects under stress trended (although not reaching significance) towards a lower probability of achieving more hair or a better degree of hair quality. In our cohort, wearing a wig tended to lower the probability of achieving a cosmetically acceptable result, perhaps reflecting the deleterious effect of local glues and adhesives used for their attachment, a lower compliance to treatment and potentially a higher degree of stress in this group related to baldness. Although these stress-related findings were not significant, the study was insufficiently powered for these specific analyses.

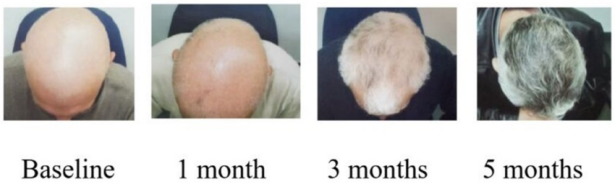

Figure 4b: Image of a 33 year old male with AT following failed steroid (PO) therapy prior to Hair Up™ treatemnt at baseline and at baseline and 5 months.

Conclusions

This retrospective study assessed an unselected group of Alopecia subjects presenting with AT or AU, 70% of whom had received prior unsuccessful steroid therapy. It showed that topical HairUp™ treatment was safe and effective with almost all subjects achieving vellus hair regrowth. Early development of vellus hair and continuation of treatment through the first 2 years of follow-up assessment resulted in a high rate of cosmetic acceptability particularly in minors. This data would support the implementation of a prospective, double-blind randomized controlled trial of topical HairUp™ use.

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