Technological innovation for the treatment of hair loss*

Double-blind randomised clinical study

Fabio Rinaldi[1], Giammaria Giuliani[2]

[1]IHRF, Milan

[2]R&S, Giuliani SpA, Milan

Key words: Telogen effluvium; Anti-hair loss product; Modified release

INTRODUCTION

The human hair follicle is a unique mini-organ that has a life-cycle consisting of various phases: growth (anagen), followed by rapid involution driven by apoptosis (catagen) and a period of relative inactivity (telogen).

The cyclical process of transformation (the hair cycle) is induced by very complex mechanisms and specific signals that regulate the cycle itself like a clock (hair-cycle clock) (**1,2**). The hair-cycle clock is not synchronous for all the follicles; indeed, each cycle is usually independent so that the hairs on the scalp are in different stages of the cycle.

The marked independence of the hair-cycle clock is very obvious from the fact that each hair follicle, isolated and maintained *in vitro,* spontaneously undergoes the anagen-catagen transformation (**3,4**).

Unwanted changes in the hair cycle can cause alopecia (androgenetic alopecia, telogenic defluvium, alopecia areata); for example, in telogenic defluvium the passage from the anagenic phase to the telogenic one occurs prematurely (**5-7**).

Alopecia can affect individuals of either sex and of any age and may be caused by both intrinsic and extrinsic factors.

The *intrinsic factors* can be of various nature:

- oxidative stress due to dihydrotesterone (DHT);
- conditions of psychological stress (surgical interventions, high fever, chronic systemic diseases, blood loss);
- emotional stress (although a relation between this type of stress and alopecia is controversial, since it is difficult to demonstrate);
- medical conditions (hormonal, such as hypothyroidism, hyperthyroidism and chronic systemic pathologies);
- dietary factors (deficiencies of particular nutritional elements, such as zinc and biotin, or dietary regimes).

The *extrinsic factors* are related to continuous exposure of the hair follicles to environmental stress which increases oxidative damage and can accelerate ageing of the follicles.

Cosmetic topical lotions with an anti-hair loss effect, besides being more manageable to use and well appreciated by consumers, are particularly suited for treatment of parts of the head. Improving compliance is a fundamental part of scientific research in the field of trichological treatments.

For this reason we evaluated the efficacy of specific modified release technology as the vehicle for a lotion containing active ingredients of known efficacy (Biogenina®) to determine whether the same clinical results can be achieved as those obtained by the reference lotion, but with a reduction in the number of weekly applications.

**Bioscalin*® con *Biogenina*® in *Triactive3*®, developed and patented by Giuliani, Milan, www.bioscalin.it

MATERIALS AND METHODS

Rationale and aim of the study

The efficacy of Bioscalin® lotion containing Biogenina® (Calcium pantothenate, Spermidine HCl (**8**), Biotin; Giuliani SpA, Milan) has been documented in previous studies (**9**), demonstrating that daily application of the solution is clinically effective in controlling telogenic defluvium.

The new modified release technology with a phospholipid-based system (Triactive3®: Hydroxy-propyltrimonium hyaluronate, Lecithin (Glycinemax L.), Polyurethane-26; patent application n° MI-2011A000644), should ensure the efficacy of the traditional lotion containing Biogenina® even with a marked decrease in the number of applications, that is with only one application every 3 days.

To examine this hypothesis, we compared the two above-mentioned lotions with placebo.

Study design

The clinical study was performed in a double-blind, randomised manner versus daily treatment with placebo; given that the subjects using the new modified release technology were to apply the active product every 3 days, in the intervening days they were given the placebo lotion to apply.

The study population consisted of 90 male and female subjects, aged between 18 and 55 years old, who had telogen effluvium for at least 3 months. The subjects were divided into three treatment groups (Table 1):

1. traditional Biogenina® lotion (biosc f) (Giuliani SpA, Milan);

2. Biogenina® lotion with the new Triactive3® release technology (Giuliani SpA, Milan);

3. placebo lotion.

All the participants in the study applied the topical single-dose product that they were assigned by massaging it with circular movements for a few minutes.

The inclusion criteria required that the subjects enrolled had not received either topical or systemic treatment for hair loss in the 3 months preceding the study.

Subjects with systemic or dermatological conditions or receiving treatment for them were excluded from the study.

Each participant was informed of the purpose, methods used, possible risks and duration of the study before giving their written consent.
The evaluations, including the dermatological assessment, measurement of the diameter of the hair shaft, the pull test and the wash test, were performed at the time of inclusion in the study (T0), after 1 month of treatment (T1), after 2 months of treatment (T2) and at the end of the study, after 3 months of treatment (T3).

Tests and evaluation criteria

The pull test evaluates the resistance of hairs to traction in different areas of the head (superior, frontal, occipital): the results are expressed on a scale from 0 (very high) to 3 (low).

The diameter of the hair shaft can be determined from a phototrichogram, using specific software to analyse the images.

The wash test consists of counting the number of hairs lost during hair-washing, which provides an evaluation of the hairs in the telogenic phase.

Statistical analysis

The statistical analysis was performed on an intention-to-treat basis, that is, on the whole population of study participants.

The analysis of the efficacy variables was performed on the values obtained at the planned study assessments. The comparisons between the three treatments for the 'Wash test' and 'Hair shaft diameter' variables were performed by analysis of variance (ANOVA) for repeated measures, followed by Tukey's test for pairwise comparisons at individual assessments, while the 'Pull test' results (difference with respect to the baseline assessment at T0) were analysed using the Kruskall-Wallis test, followed by Wilcoxon's test for pairwise comparisons (with statistical significance adjusted by applying Bonferroni's correction).

RESULTS

All 90 patients enrolled completed the study and no adverse events were notified.

Based on the mean values of the clinical evaluations performed at T0 in the 90 subjects, there were no statistically significant differences in the parameters evaluated between the groups.

In detail, the pull test showed a low resistance to traction in all the subjects, while an average of about 280 hairs were lost during the wash test. The mean shaft diameter was 0.048 cm.

The same parameters measured after 1 month of treatment showed that in the group of subjects who had applied the Biosc f lotion there was improvement in the pull test (+29.27%) (**Fig. 1**), a decrease in the number of hairs lost during the wash test (-24.24%) (**Fig. 2**) and an increase in the shaft diameter (+16.10%) (**Fig. 3**). In the group treated with Triactive3® the improvements were similar to those obtained with Biosc f (+19.30% for the pull test; -14.62% for the wash test and +14.49% for the shaft diameter).

No significant differences were seen between the results of treatment with Bioscalin f and the lotion containing the modified release lotion with regards to the pull test, shaft diameter and wash test.

Table 1 Products tested and their ingredients (INCI nomenclature)

Biogenina® (Biosc f)	Aqua, Alcohol denat., Calcium pantothenate, PEG-40 Hydrogenated Castor Oil, Parfum, Butylphenylmethylpropional, Limonene, Linalool, Spermidine HCl, Biotin.
Biogenina® and Triactive3® modified release	Aqua, Alcohol denat., Calcium pantothenate, PEG-40 Hydrogenated Castor Oil, PEG-15 Hydroxystearate, Polyurethane-26, Phospholipids, Parfum, Butylphenylmethylpropional, Limonene, Linalool, Octadecyl Di-t-butyl-4-hydroxyhydrocinnamate, Hydroxypropyltrimonium hyaluronate, Spermidine HCl, Biotin.
Placebo	Aqua, Alcohol denat., PEG-40 Hydrogenated Castor Oil, Parfum, Butylphenylmethylpropional, Limonene, Linalool.

In the placebo group, no significant changes were found in the parameters evaluated in the placebo group (pull test +3.57%; wash test -6.78%, shaft diameter +4.40%).

After 2 months of treatment (**Fig 1-3**) the changes with respect to baseline confirmed the trend in improvement in the pull test (+40.25% and +51.82%), wash test (-39.30% and -42.38%) and shaft diameter (+31.39% and +36.45%) respectively for the group treated with Biosc f and that treated with Triactive3®. Again at this time, there were no statistically significant differences between the effects of the two active treatments. In the placebo group there was a +8.32% change in the pull test, -12.57% in the wash test and +11.11% for shaft diameter. These effects were statistically inferior to those obtained with the two active treatments (Bios f and Triactive3®).

At the end of the study (**Fig. 1-3**), the following improvements were recorded: for the pull test, -75.59% in the Biosc f group, -80.74% in the Triactive3® group and -28.57% in the placebo group; for the wash test, -53.38% in the Biosc f group, -62.95% in the Triactive3® group and -27.03% in the placebo group, while the shaft diameter increased by +44.47% in the subjects treated with Biosc f, +59.42% in those treated with Triactive3® and only +20.12% in those given the placebo.

Also after 3 months of treatment the results confirmed that there were no significant differences between the effects of the two treatments, whereas both were statistically significantly from the placebo.

An analysis of the data showed that there were no significant differences between the results achieved by the traditional lotion and that using the new technology, whereas both treatments were significantly more effective than the placebo, confirming the efficacy of the two treatment.

The lotion based on the new Triactive3® technology produced a clinically evident increase in shaft diameter in 87% of the subjects, whereas, based on the changes in the parameters at the end of the study with respect to those at the start of treatment, there was a 63% decrease in hair loss (compared with a decrease of 26% in the placebo group) and an 80% increase in resistance to traction (28% in the placebo group).

CONCLUSIONS

This double-blind, randomised controlled clinical study versus placebo, carried out in 90 individuals with telogen effluvium, not only confirmed the efficacy of the Bioscalin® lotion, but also demonstrated that the efficacy of the modified release Triactive3® product applied every 3 days is comparable to that of the traditional product which is, however, applied daily.

In the light of the results obtained from this clinical study, the new modified release technology (Triactive3®) technology could be used in lotions for the treatment of hair loss, alone or in more complex and specific formulations aimed at the treatment of pathological conditions in both males and females.

REFERENCES

1. **Krause K, Foitzik K (2006)**
   Biology of the hair follicle: the basics.
   Semin Cutan Med Surg **25**(1) 2-10

2. **Paus R, Cotsarelis G (1999)**
   The biology of hair follicles.
   N Engl J Med **341** 491-498

3. **Paus R, Foitzik K (2004)**
   In search of the 'hair cycle clock': a guided tour.
   Differentiation **72**(9-10) 489-511

4. **Stenn KS, Paus R (2001)**
   Controls of hair follicle cycling.
   Physiol Rev **81** 449-494

5. **Cotsarelis G, Millar SE (2001)**
   Towards a molecular understanding of hair loss and its treatment.
   Trends Mol Med **7** 293-301

6. **Botchkarev VA (2003)**
   Molecular mechanisms of chemotherapy-induced hair loss.
   J Investig Dermatol Symp Proc **8** 72-75

7. **Hendrix S, Handjiski B et al (2005)**
   A guide to assessing damage response pathways of the hair follicle: lessons from cyclophosphamide-induced alopecia in mice.
   J Invest Dermatol **125** 42-51

8. **Ramot Y, Tiede S, Bíró T et al (2011)**
   Spermidine promotes human hair growth and is a novel modulator of human epithelial stem cell functions.
   PLoS One **6**(7) e22564

9. **Rinaldi F, Sorbellini E, Bezzola P (2004)**
   Biogenina® topica nel defluvium telogenico. Studio clinico in doppio cieco.
   Cosmet Technol **7**(1) 9-14

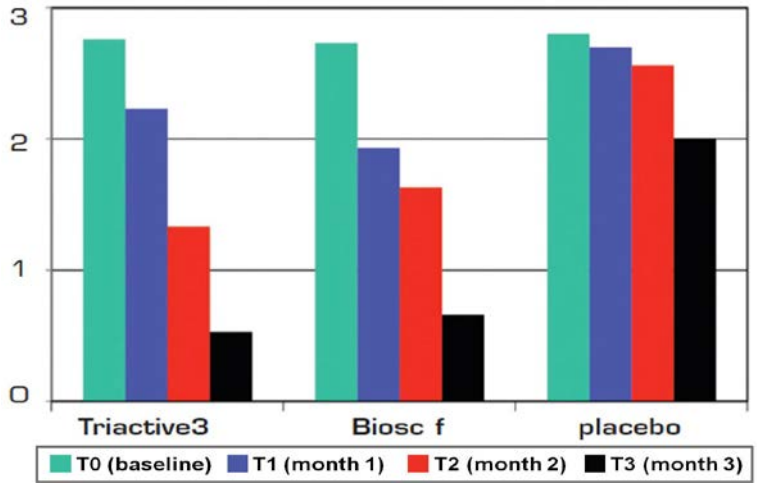

Figure 1 *Effects of 3 months of treatment with the modified release lotion (Trimatrix3®, every 3 days), traditional lotion (Biosc f, every day) and placebo on the Pull test (average)*

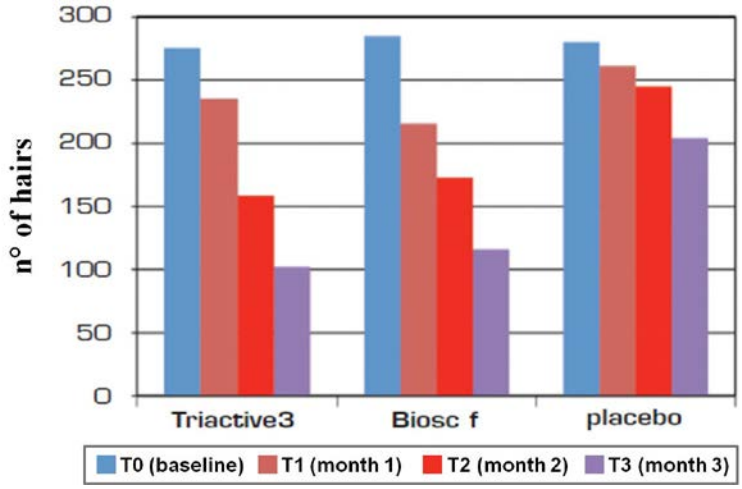

Figure 2 *Effects of 3 months of treatment with the modified release lotion (Trimatrix3®, every 3 days), traditional lotion (Biosc f, every day) and placebo on the Wash test (average)*

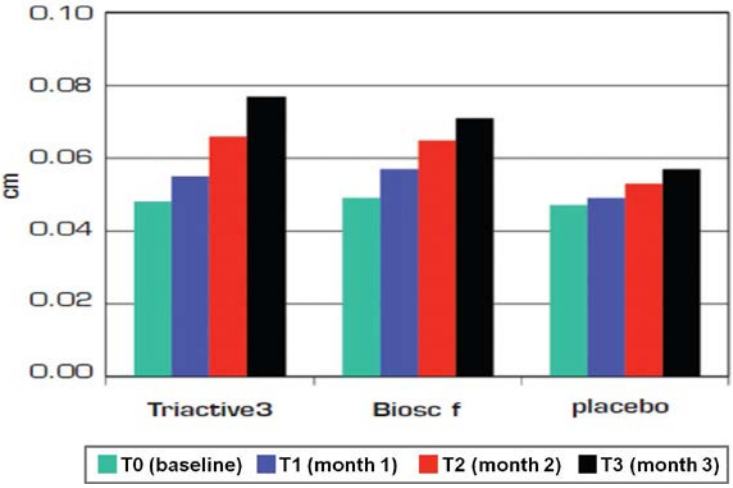

Figure 3 *Effects of 3 months of treatment with the modified release lotion (Trimatrix3®, every 3 days), traditional lotion (Biosc f, every day) and placebo on hair shaft diameter (average)*