

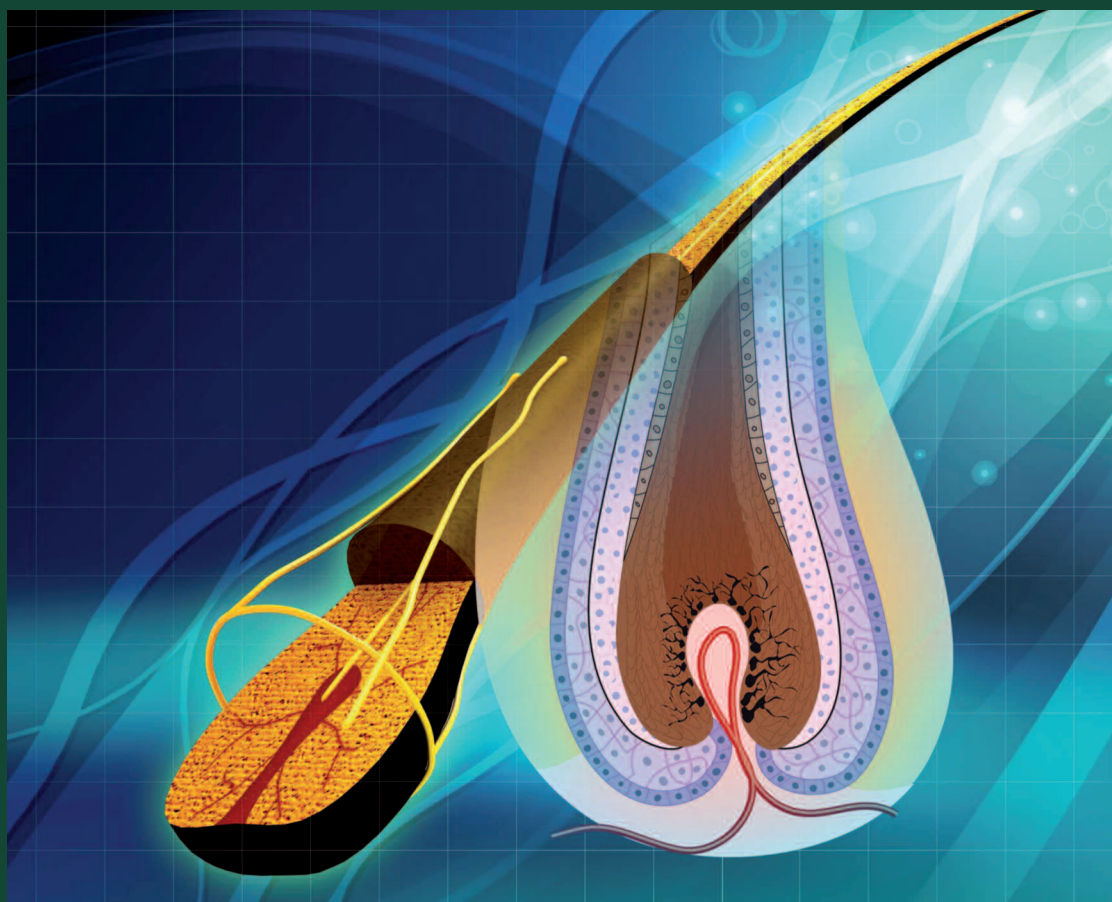


Sudden, temporary hair loss

2015 | Suppl. 4
| volume 3
| september

The benefits of RF80 ATP ENERGIE

M. Lévêque, MS. Dardé, N. Castex-Rizzi, C. Merial-Kieny



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The official journal of the **Fédération Française de Formation Continue et d'Évaluation en Dermatologie Vénéréologie (FFCEDV)**

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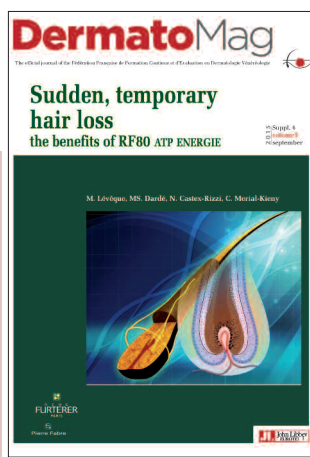
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Quote for institutions: institutions@jle.com
Member of the SPEPS (healthcare professionals' press and publications syndicate)
CCPAP: 0316 T 92203
ISSN : 2271-8273
ISSN (on line) : 2272-057X
4 issues per year



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Sudden, temporary hair loss

The benefits of RF80 ATP ENERGIE

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Sudden hair loss

We see our hair as an essential part of our appearance, especially women for whom a healthy head of hair is an important element of seduction [1, 2]. This is why hair loss can have a major psychological impact on our self-esteem. Sudden hair loss is a temporary and diffuse condition that occurs 2-3 months after a trigger event, such as giving birth, the pre-menopause or menopause, a nutritional deficiency (dieting), overwork, depression, general fatigue, or even the use of certain medications.

The hair follicle and cycle regulation

We now know that dermal papilla (DP) cell dysfunction can trigger an imbalance in the follicle growth cycle and a loss of hair.

The **hair follicle** is a complex organ, made of multiple layers of epithelial cells and mesenchymal cells (the dermal papilla cells located at the base of the follicle) [3].

The **signals from the dermal papilla** to the bulge and matrix cells play a central role, in particular during the initiation and maintenance of the anagen phase [4]. These signals are mediated by factors secreted by the DP cells, which act on the epithelial shaft cells of the bulge (initiation of the anagen phase) or on the matrix cells of the bulb (maintenance of the anagen phase) and induce their proliferation and differentiation.

Although the underlying mechanisms of the hair cycle are not fully understood, numerous studies have demonstrated the involvement of factors from the Bone Morphogenetic Protein (BMP) family. Of these signals, BMP-6, which is secreted by the DP cells, stimulates the transmembrane receptor type 1A (BMP-R1A) which is expressed in all compartments of the follicle. When BMP-R1A is activated, it triggers phosphorylation of the SMAD family of proteins, followed by their heterodimerization and nuclear translocation, where they activate the target

genes [5]. Recently, several researchers have reported that blocking the BMP signal by deleting the BMP-R1A receptor causes hair loss [6, 7]. It has also been found that BMP-6 increases the capacity of the DP cells to induce the formation of a new hair follicle [8]. Factor BMP-6 therefore plays a key role in anagen cycle initiation.

Finally, of the **growth factors** involved in the hair cycle, KGF (Keratinocyte Growth Factor) plays a central role in hair follicle development by stimulating the growth of the hair shaft and helping maintain the anagen phase [3]. It belongs to the Fibroblast Growth Factor (FGF) family.

Sudden, temporary hair loss

Sudden hair loss, or telogen effluvium, is caused when numerous hair follicles in the anagen phase enter the telogen phase at the same time, triggering an extensive loss of hair across the whole head. This sudden switch from the anagen phase to the telogen phase, which lasts between 2 and 3 months, explains why the hair loss occurs around 3 months after the trigger event. Regrowth is usually spontaneous and complete, but it can cause a certain amount of anxiety for the patient. This is because the hair loss is extensive, sometimes up to 30% of hair in the telogen phase. It can also be aggravated by two factors.

Vascularization

Although the vascular network is highly developed during the hair's active growth phase, it virtually disappears during shedding. There are various growth factors involved in regulating the hair cycle, including a potent angiogenic factor, VEGF (Vascular Endothelial Growth Factor).

Nutrient supply

This drastic reduction in vascularization of the hair follicle entails the depletion of its supply of nutrients and energy (especially vitamins), trace elements and other factors which induce hair regrowth.

Any effective treatment for sudden, temporary hair loss must therefore primarily target the rapid reactivation of a new hair cycle leading to the formation of new hair. This early initiation of the anagen phase is encouraged by certain growth factors. The secondary mechanism of action should therefore target the two aggravating factors of sudden hair loss (i.e. inducing revascularization and restoring the nutrient supply) in order to promote hair growth.

RF80 ATP ENERGIE : benefits of ATP for sudden, temporary hair loss

In 1980, René Furterer launched an anti-hair loss lotion called RF80, aimed at individuals suffering from sudden hair loss.

Thanks to ongoing research advances at Pierre Fabre, the lotion's performance has been optimized with the addition of essential oils and complementary natural active ingredients which act on the aggravating factors of sudden hair loss:

- **Revascularization**, thanks to the VEGF-targeted action of a *Pfaffia paniculata* extract combined with sage and lemon essential oils, arginine and vitamin B3, to encourage cutaneous microcirculation around the hair bulb.
- **Nutrient supply**, thanks to a combination of nutritional and energy-rich ingredients: methionine, plant peptides, vitamins B5 and B8, zinc, and copper, to provide the hair bulb the elements it needs to generate strong, healthy hair.

A new generation of RF80 has now been launched, with the **addition of ATP** (nucleotide adenosine 5'-triphosphate), and rebranded as **RF80 ATP ENERGIE**.

ATP, a nucleotide from the purine family, plays a determining role in cell function. It is the primary molecule of energy transport and storage in living cells. It acts on numerous tissues by binding to purinergic receptors. In the human hair follicle, P2Y and P2X receptor expression has been demonstrated in the different compartments during the anagen phase [9, 10], suggesting a role of ATP in the physiology of the hair follicle.

The aim of this article is to present first the results of *ex-vivo* studies demonstrating the benefits of ATP for an anti-hair loss product indicated for sudden

hair loss, and second the results of safety and efficacy studies of RF80 ATP ENERGIE lotion in patients with sudden, temporary hair loss.

Ex-vivo effect of ATP on hair follicles

The aim of this *ex-vivo* study (*in-vitro* for DP cell protein quantification) on cultured hair follicles was **to evaluate the effect of ATP on two key factors of the anagen phase, BMP-6 and KGF**.

Also, factor BMP-6 was detected in an isolated hair follicle culture model developed by *Philpott et al.* in 1990 [11].

Method

A first test was designed to study the effect of ATP on gene expression of factor BMP-6 in the hair follicles of two different donors, obtained by microdissection. These follicles were cultured in complete William's Medium E, with and without (control) ATP at 500 µM. After 6 and 48 hours in culture, the RNA was extracted, measured, and reverse transcribed to cDNA in preparation for real-time quantitative PCR (polymerase chain reaction).

A second test was conducted using primary cultures of dermal papilla cells from three different donors. These cells were cultured for 24 hours in complete DMEM, then for 24 hours with and without (control) ATP at 30 µM. The BMP-6 and KGF proteins were then measured in the culture supernatant using the ELISA technique. Prior to this, the dermal papilla cells underwent a cytotoxicity test (reduction in MTT and morphological observations under a microscope) in order to confirm the viability of the cells in culture conditions.

In order to determine the location of factor BMP-6 in the hair shaft, hair follicles in the anagen phase were cultured for 13 days. Immunohistochemistry was then used to detect factor BMP-6.

Results

• BMP-6 expression study:

ATP **stimulates BMP-6 expression** in the hair follicles and increases the production and secretion of the protein into the dermal papilla cells, suggesting an ability to stimulate the anagen phase *in vivo* (Figure 1).

Detecting BMP-6 using the method developed by *Philpott et al.* shows that this factor is primarily expressed at the base of the hair follicle and in the keratinization zone (Figure 2).

• **KGF expression study:**

ATP stimulates KGF expression in the hair follicle and increases the production and secretion of the KGF protein into the dermal papilla cells, suggesting its role in hair growth (Figure 3).

We conclude that ATP stimulates the expression of two essential factors for the anagen phase in cultured hair follicles: BMP-6 (anagen phase induction) and KGF (anagen phase maintenance). These results suggest that it could therefore re-initiate the anagen phase directly and more rapidly, and stimulate hair growth; these effects need to be confirmed by clinical studies of the end product.

Thanks to these results from *ex-vivo* studies, ATP has been added to the new generation RF80 ATP ENERGIE. The efficacy and safety of this product have been tested in two dermatologically controlled clinical trials:

- one single-center, open-label, in-use tolerability study;
- one single-center, open-label, biometry study to evaluate product efficacy

In-use tolerability study of RF80 ATP ENERGIE

STUDY PROTOCOL

Subjects

This single-center, open-label study assessed female subjects aged 18 and over with all types of hair and scalp, who were, if possible, occasional users of topical anti-hair loss lotions.

Subjects were instructed to use René Furterer RF80 ATP ENERGIE at home for three consecutive weeks, in normal conditions i.e. apply once weekly to clean, damp hair then massage.

Evaluation

The study endpoints were:

- objective endpoints: cutaneous erythema, cutaneous dryness, desquamation, and roughness assessed by a dermatologist at D1 and D21
- subjective endpoints: tingling skin, itching, burning sensation, discomfort and tightness rated by the subjects using a questionnaire.

Adverse effects were recorded, either when spontaneously reported by the volunteer or observed by the investigator. The cosmetic properties of the product were also scored from 1 to 10 (1: not very pleasant; 10: very pleasant).

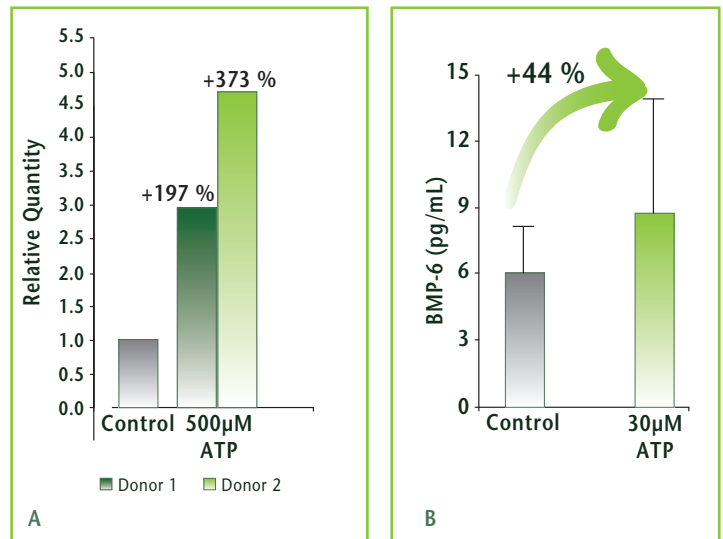


Figure 1: *In vitro* effect of ATP on BMP6 expression in the hair follicle mRNA is assessed using quantitative PCR (A) and proteins measured using the ELISA procedure (B).

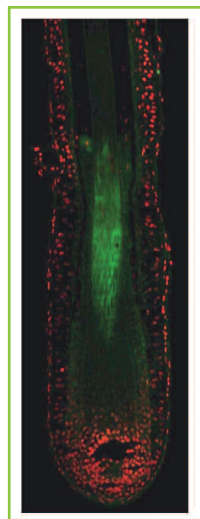


Figure 2: Immunohistochemical analysis of the BMP-6 expression site (in green) in the hair follicle during the anagen phase.

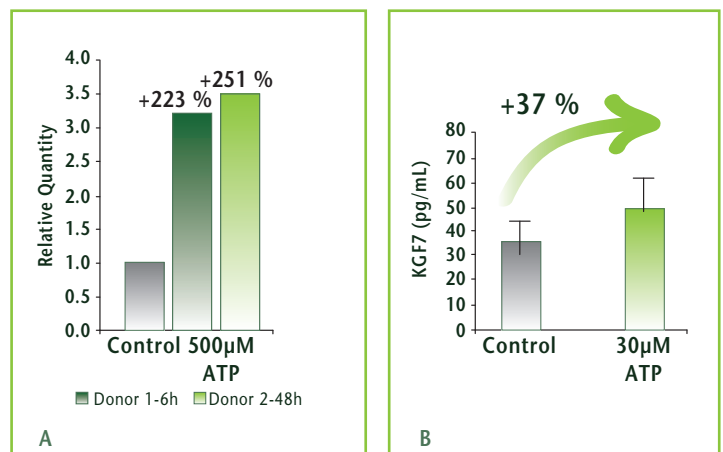


Figure 3: *In vitro* effect of ATP on KGF expression in hair follicle mRNA is assessed using quantitative PCR (A) and proteins measured using the ELISA procedure (B).

RESULTS

Study population

33 women (average age 35 years) were assessed for this study. Their scalp was normal (55% of volunteers), dry (21%) or greasy (24%).

Tolerability

In normal in-use conditions, RF80 is very well tolerated on the skin. No serious intolerance issues were reported, and 100% of subjects believed the product respected the natural balance of their scalp.

Cosmetic appeal

91% of women were happy with the condition of their hair after use.

Item	%
Convenient packaging (single doses)	91
Easy-to-open single doses	97
Easy to apply section by section	85
Light texture	97
Rapidly absorbed into the scalp	97
Pleasant fragrance	85

In conclusion, RF80 ATP ENERGIE demonstrates **good cutaneous tolerability** in normal in-use conditions and the cosmetic qualities of the product were also very popular, which is a factor in ensuring good treatment compliance.

Efficacy of RF80 ATP ENERGIE for sudden, temporary hair loss

STUDY PROTOCOL

Inclusion criteria

The subjects on this study were female volunteers aged at least 18, with Fitzpatrick phototype I to IV, a telogen hair percentage of at least 15% (or at least 12% with a clinical diagnosis of telogen effluvium), hair length at least 5 cm, who agreed to keep this minimum length for the duration of the study, with brown or black hair (no blonds or fair-haired subjects), and who signed the written consent form.

The subjects had to agree to the technical requirements of the phototrichogram i.e. for a 1.5-2 cm² area of their scalp to be shaved.

Women of childbearing age had to declare that they had not been exposed to pregnancy risk in the 3 months before the start of the study and agree to use an effective method of contraception starting at least 1 month before the study and until it ended.

Subjects were instructed to apply RF80 ATP ENERGIE once weekly over the whole scalp for 3 consecutive months, and for the first time at the study center (M0).

Exclusion criteria

The exclusion criteria were subjects with white or fair hair, those who were enrolled on another study protocol, and the administration of any oral or topical treatment likely to interfere with the growth, diameter or shedding of their hair in the two months prior to the start of the study.

Endpoints

The primary endpoint was the assessment of the anti-hair loss efficacy of the product after 4, 8, and 12 weeks of use. This assessment was performed using the method of choice, **the phototrichogram**, performed at baseline (M0), then after 1 month (M1), 2 months (M2), and 3 months (M3) of using the product.

The endpoints were anagen density (number of anagen follicles/cm² ± SDM), telogen density (number of telogen follicles/cm² ± SDM), telogen percentage (T%), and anagen/telogen ratio (A/T).

Secondary endpoints

- growth rate at M0 and M3
- an evaluation of product efficacy using clinical scores: total capillary density, volume (visible), mass

(by touch) assessed at M0, M1, M2, and M3 by the dermatologist using a 5-point scale (1= very light, 2= light, 3= moderate, 4=high, 5= very high), self-assessment questionnaires completed by the subjects at M0, M1, M2, and M3 and macrophotography at M0 and M3.

- change in density of anagen hairs and in total capillary density at M1, M2, and M3
- evaluation of cosmetic properties and the efficacy of the lotion using a questionnaire after 1, 2, and 3 months' use.

RESULTS

Subjects

This single-center clinical study enrolled 58 healthy female subjects aged 18-50 years who reported suffering from sudden hair loss (telogen effluvium). The results were calculated for the 51 subjects in the per protocol population.

57% (n=29) described their scalp skin as sensitive/reactive.

Primary endpoint: product efficacy

The phototrichogram assessments at M0, M1, M2, and M3 showed:

- a significant increase in the density of hair in the anagen phase between M0 and M3 (from 201 (± 7.44) hairs/cm² at M0, to 206.22 (± 7.33) at M3, $p < 0.0005$).
- a significant reduction in the density of hair in the telogen phase between M0 and M3 (from 42.85 (± 1.91) hairs/cm² at M0, to 35.99 (± 2.12) at M3, $p < 0.002$).
- a significant increase in the A/T ratio from the first month of using RF80 ATP ENERGIE ($p < 0.0005$) (Figure 4).

The phototrichogram results are statistically significant for all endpoints and demonstrate the anti-hair loss efficacy of RF80 ATP ENERGIE, right from the first month of use.

Secondary endpoints

The dermatologist's assessment :

- A significant increase ($p < 0.0005$) in capillary density was seen from the first month of use, as was a significant increase ($p < 0.05$) in apparent hair volume and touchable mass after the second month of use.

- For the responder subjects, a continued and significant increase in the number of anagen phase hairs was observed at M1 (+7,140 anagen hairs), M2 (+7,920 anagen hairs), and M3 (+10,380 anagen hairs).

- Hair growth rate rose significantly after 3 months of using the product, from 0.755 (± 0.755) at M0 to 0.818 (± 0.111) at M3 ($p < 0.005$).

Perceived efficacy measured by the subjects using self-assessment questionnaires:

- A significant reduction in hair loss after washing and brushing, on the towel ($p < 0.0005$), or on clothes ($p = 0.001$), and in perceived hair loss was observed after the first month of use.
- Subjects rated the volume and thickness of their hair using a visual analog scale from 0 to 10, and the

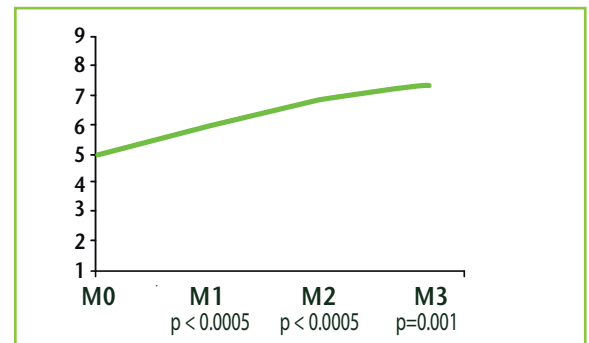


Figure 4: Growth coefficient (anagen/telogen ratio) after phototrichogram analysis



Figure 5: Self-assessment

results reveal a significant increase in volume ($p=0.008$) and thickness ($p=0.001$) from the first month (Figure 5).

- Anti-hair loss efficacy was confirmed from the first month of treatment by 84% of subjects questioned.

The cosmetic properties of the product were particularly popular

RF80 ATP ENERGIE lotion was very well liked by 90% of participants after 1 month of use, and by 98% after 3 months.

After applying the product, 92% of subjects were happy with the condition of their hair. They described their hair as soft (92%), supple (88%), non sticky (90%), and non greasy (88%).

At the end of the study, after 3 months of using the product:

90% of subjects thought their hair was strengthened, 92% healthier, and 94% denser.

CONCLUSION

The new formula RF80 ATP ENERGIE, incorporating the new anti-hair loss active ingredient ATP, targets the two factors involved sudden hair loss (vascularization and nutrition).

Ex-vivo studies have demonstrated the benefits of ATP as an active ingredient in treating sudden hair loss, thanks to its effective action on inducing the anagen phase which allows the hair to re-enter the growth phase faster.

This efficacy has been confirmed with the product RF80 ATP ENERGIE, thanks to a program of dermatologically-controlled clinical studies which have provided objective evidence of the anti-hair loss efficacy of RF80 ATP ENERGIE from the very first month of use.

This statistically significant anti-hair loss efficacy was demonstrated using the method of choice, the phototrichogram, but also using dermatologist evaluations and a self-assessment by study subjects.

As well as demonstrating clinical efficacy, these clinical studies have confirmed the tolerability of RF80 ATP ENERGIE lotion as a sudden or seasonal hair loss treatment for women, when applied once weekly for three months.

RF80 ATP ENERGIE therefore combines statistically proven results **from the 1st month** with a **simple dose regime** (1 application per week) and **ease of use**. All of which are factors likely to ensure good treatment compliance.

Conflicts of interest to disclose : the authors were or are employees of Pierre Fabre Dermo-Cosmétique

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