J. Appl. Cosmetol. **29**, 167-180 (October/December 2011)

Use of a Cosmetic Caffeine Lotion in the Treatment of Male Androgenetic Alopecia

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Received: *September, 2011.*

Key words: *Androgenetic alopecia; Caffeine; Cosmetic lotion;*

Summary

Androgenetic alopecia (AA) is the most common form of hair loss in men, affecting more than 50% of the male population over 50 years, and it often causes psychological and social distress to those affected, in addition to being one of the most common reasons why a patient consults a dermatologist. There are several cosmetic substances that can complement the medical treatment of this widespread disease, in order to obtain better results.

In the past few years caffeine has been used; this molecule, applied topically in the form of shampoos and lotions, has shown good efficacy in the treatment of AA.

We report the results of a study to test efficacy, safety and cosmetic qualities of a caffeine containing lotion used daily for four months by 40 men with AA.

Riassunto

L'alopecia androgenetica (AA) è la forma più frequente di alopecia nel sesso maschile, colpisce più del 50% della popolazione maschile oltre i 50 anni, ed è spesso causa di disagio psicologico e sociale per i soggetti affetti, oltre a rappresentare uno dei motivi più frequenti per cui un paziente si rivolge al dermatologo.

Esistono diverse sostanze cosmetiche che possono affiancare la terapia medica di questa diffusa patologia, per ottenere dei risultati complessivamente migliori.

In particolare negli ultimi anni è stata utilizzata la caffeina che, applicata localmente sottoforma di shampoo o lozioni, ha dimostrato una buona efficacia nel trattamento dell'AA.

Riportiamo i risultati di uno studio per testare l'efficacia, la sicurezza e le qualità cosmetiche di una lozione contenente caffeina utilizzata quotidianamente per quattro mesi da 40 uomini affetti da AA.

INTRODUCTION

Androgenetic alopecia (AA) is the most common form of hair loss in men, affecting more than 50% of men over 50 years. (1) The hair starts thinning in the temporal area, then continues on the frontal region and to the vertex, to finally involve the entire scalp; the disease progression has been described and classified for the first time in 1975 by Hamilton, whose scale is still used to define the severity of this condition (2).

Behind this widespread disease, there is definitely a genetic predisposition, transmitted with a polygenic inheritance, which explains the widespread familiarity observed in cases of AA.

In this setup we must add the role of testosterone; in fact it has been demonstrated that in patients with AA there is an increase in 5-alpha-reductase, the enzyme that catalyzes, in the hair follicle, the transformation of testosterone to its active metabolite, 5-alpha-dehydro-testosterone (DHT).

DHT binds to the androgen receptor, and this specific binding triggers a series of cellnlar processes that lead to the reduction of the anagen phase of hair cycle. The increased activity of the enzyme 5-alpha reductase is genetic, and depends on a polymorphism of the androgen receptor (3).

There are now only two FDA-approved drugs for the treatment of AA: finasteride (inhibitor of the synthesis of DHT) and minoxidil (a drug that acts nonspecifically on the opening of potassium channels) (4).

But 20-30% of patients with AA does not respond to these drugs; as well as non-responders, we must also consider the contraindications and side effects associated with use of finasteride (oligospermia, teratogenicity, ...) and minoxidil (hirsutism, hypertrichosis, hypotension, tachycardia ...), which limit their use in some patients.

Caffeine is a methylxanthine belonging to the alkaloids family, a group of compounds widely present in many plants.

This substance is mainly extracted from coffee (Coffea arabica, Rubiaceae family ...), belongs to the group of purine alkaloids such as theophylline (extracted from tea, Camellia sinensis, fam. Theaceae), and theobromine (extracted from cocoa, Theobroma, family Sterculiaceae). While the effects on the CNS, cardiovascular system and general metabolism resulting from its oral intake are well known, the effect of its topical use on hair growth cycle is not yet well defined.

The effect of caffeine is biologically mediated by cyclic AMP increase in cells with a combined action on two levels: increased synthesis of cAMP (caffeine blocks the inhibitor of adenylate cyclase enzyme, which converts ATP into cAMP) and slowing of the cAMP degradation (caffeine inhibits the phosphodiesterase enzyme, which converts cAMP to AMP); in this way caffeine promotes proliferation by stimulating the cellular metabolism, a mechanism that could connteract the miniaturization of the hair follicle induced by testosterone and DHT(5).

In a model of male skin in culture, caffeine has been shown to counteract the inhibitory effect of testosterone on the proliferation of keratinocytes (6).

Similar results were obtained by testing the caffeine in an organic model of hair in culture (7), and in human hair follicles extracted ex vivo from male patients with AA (8).

With regard to the ability of topically applied caffeine to penetrate into the follicle, it has already been studied for a shampoo formulation, and good results were obtained (9); Otberg and collaborators have shown that caffeine penetrates the hair follicle and the stratum corneum after 2 minutes. In addition, it was observed that the penetration through the hair follicle is faster and higher than the interfollicular route and that hair

follicles are the only pathway for fast caffeine absorption during the first 20 minutes following application (10).

AIM OF THE STUDY

This clinical study was designed to test skin compatibility, efficacy and cosmetic quality of a cosmetic lotion for the treatment of male androgenetic alopecia after application under normal conditions of use for 4 consecutive months.

MATERIALS AND METHODS

This monocentric study was performed in open. 40 volunteers were included in the study, with age between 19 and 55 years (mean age 37 years), with following inclusion criteria:

- men suffering from androgenetic alopecia in the stages of Hamilton-Norwood II-IV
- age: 18 to 55 years old
- men suffering from an increased hair loss topically
- men showing a hair count of the "Hair Pull Test" of at minimum 15 (last shampoo 2 days before)
- men, who did not use any hair restorer (tablet, capsule, tonic nor shampoo) since the last 4 months
- with a phototype (Fitzpatrick) I, II, III or IV
- exhibiting no cardiovascular, pulmonary, digestive, neurological, genital, urinary, osteoarticular, psychiatric, haematological, immunological or endocrinal pathology which could interfere directly or indirectly with the study
- exhibiting no skin affection which could interfere with the study, for example: dermographism, seborrheic dermatitis, recurrent herpes, pityriasis versicolor, psoriasis, important pigmentary disorders (vitiligo, chloasma, chronic lupus erythematous .....).

The specific non inclusion criteria were the following ones:

- men suffering from a different cause of alopecia:
  - alopecia areata
  - psychosomatic alopecia ie Trichotillomania
  - hair loss due to medication (immunologics, chemo-therapy, etc.)
- men with an unhealthy condition of the scalp:
  - widely spread, highly expressed eczema (sparely stages can be included)
  - high grade of dandruff
  - allergy against an ingredient of the test product
- atopy
- long-term anti-inflammatory treatment stopped less than 4 months before the beginning of the study
- regular use of hair dye, bleaching products or products for permanent wave
- surgical correction of the alopecia performed before the study
- having received excessive or intensive exposure to sunlight (natural or artificial) within the month prior to the study or foreseeing UV exposures for the duration of the study
- under general or local medication such as anti-inflammatory, anti-histaminic or anti-allergic treatment or who have stopped one of this treatment less than 10 days before the beginning of the study.

All volunteers have expressed their consent to the study through a written informed consent.

The experimental conditions were as follows: once a day for four consecutive months, the volunteers had to apply the product on the scalp and massage it with fingers for about 2 minutes, allow to dry hair and do not rinse them, (in case of washing, the application had to be carried out immediately after washing).

During the study, volunteers were unable to use products similar to the one tested, would make the last shampoo at least 2 days prior to dermatological control, should not use products for colouring, hair bleaching, permanent wave,

alpha level of 0.05).
For the primary efficacy variable (hair pulled back to pull-test) mean, standard deviation, 25% - 50% - [average] and 75%-percentiles were calculated at baseline, after 2 months and 4 months after application of the Caffeine Lotion. For the secondary efficacy variables (evaluated using questionnaires, ordinal scales) frequencies and percentages were calculated.
The statistical analysis was performed using 'SPSS for Windows' (version 18.0).

RESULTS

About the skin compatibility,investigators described no clinical signs, nor any sense of discomfort related to the use of the lotion has been reported by volunteers.
Regarding the assessment of cosmetic effectiveness of the product, the results obtained showed that the investigational product has resulted in a reduction of the number of hairs extracted with the pull-test of 8.14% after 2 months and 15.33% after 4 months of treatment, indicating an increase in tensile strength of hair and a decrease in hair loss.
After 2 months of treatment, the percentage of ' positive' volunteers (for which the number of hair in pull test is decreased with treatment) was 75%, and after 4 months of treatment, of' 83%.
These data are represented in the graphs below:

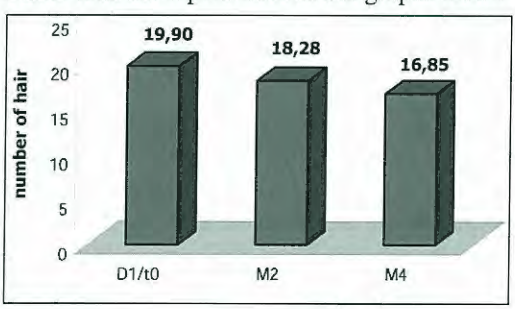

Fig. 1 number of hairs pulled in the pull-test at baseline, after 2 and 4 months of Caffeine Lotion application (means with 95% confidence intervals).

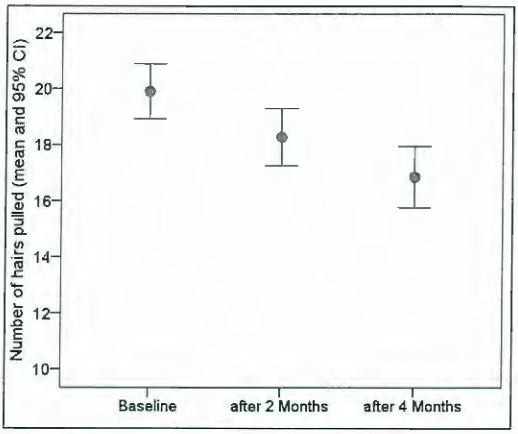

Fig. 2 Means with 95% confidence intervals of the number of hairs taken from the pull-test at baseline and after 2 and 4 months of treatment.

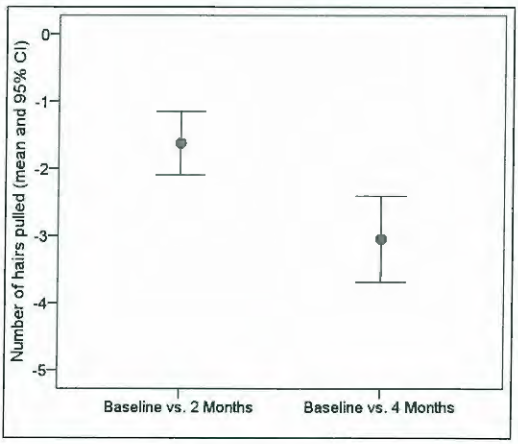

Fig. 3 Decreased hair pulled in the pull-test after 2 and 4 months of Caffeine Lotion application, compared to baseline (before applying the product); here are shown the means and confidence intervals of 95%.

About the assessment of the cosmetic efficacy in the dermatologic questionnaire, the results were as follows:

Items	How do you describe the scalp? Redness														
	At the beginning					After 2 months of treatment					After 4 months of treatment				
Score	absent	very slight	slight	mode-rate	strong	absent	very slight	slight	mode-rate	strong	absent	very slight	slight	mode-rate	strong
Number of vol.	30	4	4	2	0	30	5	5	0	0	32	5	3	0	0
Number and % of volunteers with a decrease in redness referred only to volunteers with redness at the inclusion						3/30%					7/70%				

Items	How do you describe the scalp? Scaling/dandruff														
	At the beginning					After 2 months of treatment					After 4 months of treatment				
Score	absent	very slight	slight	mode-rate	strong	absent	very slight	slight	mode-rate	strong	absent	very slight	slight	mode-rate	strong
Number of vol.	26	5	3	6	0	26	5	9	0	0	31	5	4	0	0
Number and % of volunteers with a decrease in scaling / dandruff referred only to volunteers with dandruff at the inclusion						6/43%					13/93%				

Items	How do you rate the strength of the hair?										
	At the beginning				After 2 months of treatment				After 4 months of treatment		
Score	strong	medium	thin	very thin	strong	medium	thin	very thin	strong	medium	
Number of vol.	0	4	25	11	0	7	24	9	1	14	
Number and % of volunteers with an increase in the strength of the hair					5/12%				21/53%		

Items	How do you describe the progression of the balding?											
	At the beginning				After 2 months of treatment				After 4 months of treatment			
Score	very slight	slight	mode-rate	severe	very slight	slight	mode-rate	severe	very slight	slight	mode-rate	severe
Number of vol.	1	18	16	5	3	18	14	5	9	18	9	4
Number and % of volunteers with a decrease in the progression of the balding					4/10%				17/43%			

Items	How do you rate the extent of the out falling hairs? (comb the hair several times and make a semiquantitative rating)											
	At the beginning				After 2 months of treatment				After 4 months of treatment			
Score	very slight	slight	mode-rate	severe	very slight	slight	mode-rate	severe	very slight	slight	mode-rate	severe
Number of vol.	0	17	18	5	4	18	16	2	13	20	7	0
Number and % of volunteers with a decrease in the extend of the out falling hairs					12/30%				34/85%			

Items	What is your clinical opinion of the efficacy of the test product?			
	The test product has reduced the premature hair loss	The test product has reduced the balding	The test product has improved the scalp condition	The test product has improved the structure of the hair
Number of vol.	17	17	5	21
% of volunteers	43%	43%	13%	53%

Items	Do you recommend the test product as a daily treatment of hereditary hair loss to reduce the number of out falling hairs?	
Score	yes	no
Number of volunteers	34	6
% of volunteers	85%	15%

Items	Please evaluate personally the intensity of your hair loss											
	At the beginning				After 2 months of treatment				After 4 months of treatment			
Score	very slight	slight	mode-rate	severe	very slight	slight	mode-rate	severe	very slight	slight	mode-rate	severe
Number of vol.	0	9	20	11	2	18	12	8	7	20	12	1
Number and % of volunteers which referred a decrease in the intensity of the hair loss					16/40%				32/80%			

Items	Does your hair-loss decrease or normalize with the treatment?							
	After 2 months of treatment				After 4 months of treatment			
Score	quite agree	agree	fairly disagree	disagree	quite agree	agree	fairly disagree	
Number of volunteers	0	16	11	13	10	22	8	
Number and % of satisfied volunteers quite agree / agree	16/40%				32/80%			

Items	During daily combing, do you count a high number of hairs in the basin?										
	At the beginning				After 2 months of treatment				After 4 montbs of treatment		
Score	very few	few	some	many	very few	few	some	many	very few	few	
Number of vol.	0	6	23	11	2	15	15	8	8	18	
Number and % of volunteers which referred a decrease in the number of hair in the basin					16/40%				32/80%		

Items	Please evaluate your scalp condition - Itching														
	At the beginning					After 2 months of treatment					After 4 months of treatment				
Score	absent	very slight	slight	mode-rate	strong	absent	very slight	slight	mode-rate	strong	absent	very slight	slight	mode-rate	strong
Number of vol.	25	2	8	4	1	25	6	8	1	0	28	7	5	0	0
Number and % of volunteers which referred a decrease in itching referred only to volunteers with itching at the inclusion						8/20%					12/30%				

Items	Please evaluate your scalp condition – Tension/dryness														
	At the beginning					After 2 months of treatment					After 4 months of treatment				
Score	absent	very slight	slight	mode-rate	strong	absent	very slight	slight	mode-rate	strong	absent	very slight	slight	mode-rate	strong
Number of vol.	20	6	10	4	0	21	10	9	0	0	25	12	3	0	0
Number and % of volunteers which referred a decrease in tension/dryness referred only to volunteers with tension/dryness at the inclusion						10/25%					17/43%				

Items	Please evaluate the strength and the thickness of your hair											
	At the beginning				After 2 months of treatment				After 4 months of treatment			
Score	bouncy	strong hair	soft, weak	fine hair	bouncy	strong hair	soft, weak	fine hair	bouncy	strong hair	soft, weak	fine hair
Number of vol.	0	1	11	28	4	2	7	27	7	14	5	14
Number and % of volunteers which referred an improve in the strength and/or in the thickness of hair					5/12%				20/50%			

Items	Are you satisfied with the product?							
	After 2 months of treatment				After 4 months of treatment			
Score	very high	high	low	very low	very high	high	low	very low
Number of volunteers	2	14	18	6	11	21	5	3
Number and % of satisfied volunteers Very high / high	16/40%				32/80%			

Items	Do you like to continue with the test product?		Do you like to recommend the test product?	
Score	yes	no	yes	no
Number of volunteers	32	8	32	8
% of volunteers	80%	20%	80%	20%

Items	How do you feel about the use of the bottle, i.e. the dosing?				How do you feel about the viscosity of the test product?		
Score	precisely to dose	simple, comfortable	unprecisely	uncomfortable	exactly right	too thin	too viscous
Number of vol.	10	16	8	6	35	5	0
% of volunteers	25%	40%	20%	15%	88%	12%	0%

Items	Do you like the perfume of the test product?		How do you think about the intensity of the perfume?		
Score	I like it very much	I dislike it	exactly right	too much	too low
Number of vol.	29	11	15	25	0
% of volunteers	73%	28%	38%	63%	0%

Items	How do you feel your dried hair after the hair wash?					Has your hair styling been changed by the test product?		
Score	light	smooth	strong	greasy	uncomfortable	easier than before	unchanged	more difficult than before
Number of vol.	11	19	0	4	7	5	35	0
% of volunteers	28%	48%	0%	10%	18%	12%	88%	0%

Items	How do you think about the bounciness of your hair?			How do you think about the combing of your hair?		
Score	very good	quite normal	bad, very low	very easy	normal	very bad
Number of vol.	7	33	0	5	35	0
% of volunteers	18%	82%	0%	12%	88%	0%

Items	What is the best you like in this test product?					
Score	hair strengthening effect	application	perfume	scalp care, fit for sensitive scalp	feel of hair	freshening
Number of vol.	17	1	11	16	6	2
% of volunteers	43%	3%	28%	40%	15%	5%

Items	What should be improved in this test product?					
Score	hair strengthening effect	application	perfume	scalp care, fit for sensitive scalp	feel of hair	freshening
Number of vol.	8	13	16	0	10	0
% of volunteers	**20%**	**33%**	**40%**	**0%**	**25%**	**0%**

Items	Do you like to continue with the test prodnct?		
Score	yes, it is fit for my daily hair care	yes, but only in case trouble (time-limited)	no, not fit for my scalp and hair care
Number of volunteers	18	14	8
% of volnnteers	**45%**	**35%**	**20%**

DISCUSSION

Male androgenetic alopecia (AA), or more commonly 'baldness', is the most common cause of hair loss or thinning in men; this condition, while having a purely aesthetic and not pathological meaning, significantly affects the social life and the psychology of individuals who are affected, especially if young and of childbearing age. Its development is mainly androgen-dependent and modulated by dihydrotestosterone (DHT) and by the expression of the androgen receptor of the hair follicle. The available medical treatments (topical minoxidil and oral finasteride), prevent the progression of disease in many patients with moderate and severe AA, but there is still a rather high percentage (20-30%) of non-responders.

For this reason, considering the widespread of this imperfection, the cosmetics industry is devoted to finding alternatives that can assist or replace medical treatment, acting on mechanisms unrelated to androgens, or synergistically with the anti-androgen drugs.

Caffeine is one of the substances considered by the cosmetic industry for the treatment of AA; its ability to inhibit the negative effects of testosterone on keratinocyte proliferation has been shown in culture models of male skin as well as in hair follicle models extracted ex vivo from men with AA and cultivated *in vitro*.

In addition, caffeine has shown a high and fast penetration through the hair follicle, and so it was possible to formulate a product containing Caffeine such as shampoo*, which showed a good cosmetic efficacy (9).

In this experimental study, we tested a lotion containing caffeine** for daily use, that accor-

* *Trade name: Alpecin® Caffeine Shampoo*
** *Trade name: Alpecin® Liquid*

ding to the experimental conditions showed a very good skin compatibility after application under normal conditions of use, and a good cosmetic efficacy in the treatment of androgenetic alopecia.

Specifically, the results of the pull-tests showed an increase in tensile strength of hair and a decrease in hair loss in 75% of volunteers after 2 months and in 83% of volunteers after 4 months of treatment.

The dermatological control confirmed the good efficacy of the product; in particular there was an important reduction in premature hair loss hair in 43% of the volunteers, an improvement in hair texture (force, tensile strength) in 53%, an improvement of the conditions of the scalp (erythema, dandruff, dryness) in most of the volunteers who showed abnormalities of the scalp at enrollment.

The subjective evaluation of the cosmetic effectiveness showed that 80% of volunteers were satisfied with the product; in particular they reported, after 4 months of treatment, a decrease in hair loss and an improvement in the hair and scalp conditions.

In addition, the product was also appreciated for its cosmetic qualities (smell, viscosity, ease of dosing, combing hair, etc..).

Ultimately, we can say that this daily use lotion is an effective and well tolerated cosmetic complement, and that caffeine contained in the lotion is an interesting and promising substance for cosmetic treatment of androgenetic alopecia.

ACKNOWLEDGEMENTS

The authors thank Dr.Kurt Wolff GmbH - Germany for the product samples given for the study.

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