CLINICAL EVALUATION OF A TRICHOLOGICAL PHYTOEXTRAC IN MOST FREQUENT FORMS OF HAIR LOSS. RESULTS OF A META-ANALYSIS STUDY.

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ABSTRACT

Ricapil® is a mousse containing substances of natural origin, for scalp application. Its use is intended for the most common forms of hair loss like androgenetic alopecia (AGA), telogen effluvium (TE) and alopecia areata (AA). The objectives, to halt hair loss, to strengthen hair and to help natural hair regrowth, are pursued by restoring hair shaft, dermal papilla and terminal hair favourable functional conditions.

Three clinical studies, carried out in four dermatological centres in Italy, report very promising results. Therefore we deemed interesting to reconcile the data of these trials, adopting the meta-analysis technique, to substantiate the results from the perspective of a larger controlled population of alopecic patients.

According to the pooled results, in TE and in AA the rate of success was 97% and 75% respectively, after 1-3 weeks of scalp application. In AGA, hair follicle reactivation and terminal hair re-growth was detected in 49% of treated cases, after 4-5 months of use, that is, less than the half of the one generally preconized in AGA (e.g., for minoxidil: 12 months).

An aim for future trials then should be to exploit the actual product success rate in AGA, at present already very positive but probably underestimated. In the total population of 200 studied cases, evaluated with the meta-analysis, 119 (59.5%) showed a significant ($p<0.001$) positive response as far as the three mentioned end points are concerned. In each type of hair loss a significant ($p<0.001$) difference was found between responder and non or poorly responder groups. The success rate is well above the data reported in literature for a placebo effect (9-20%). Product tolerability and acceptability resulted very good. This natural product appears to be promising and working in most frequent forms of hair loss like AGA, TE and AA, in men and women, with a very favourable benefit/risk ratio.

INTRODUCTION

The medical term for hair loss is alopecia. Alopecia is classified in: cicatricial and not cicatricial. The cicatricial alopecia is characterized by the atrophy or destruction of hair follicle (e.g.: chemicophysical agents, neoplasms). Hair follicles are replaced by fibrous tissue and hair loss becomes permanent. Not cicatricial alopecia is largely the most represented type and can be caused by many factors from genetics to environment. The most common forms are: androgenetic alopecia (AGA), telogen effluvium (TE), alopecia areata (AA).

AGA is an hereditary thinning of the hair induced by the effects of androgens on hair follicles in genetically susceptible men and women. Hair follicles become smaller, producing shorter, finer hair that cover scalp poorly. AGA is synonymous for male or female pattern baldness.

TE happens when there is a change in the num-

ber of hair follicles growing hair. If it drops significantly in the resting phase (telogen) there will be a huge increase in hair follicles in the telogen stage. The result is shedding or TE hair loss. TE is caused by an environmental shock influencing hair follicles. Classic short term TE often happens to women soon after giving birth (post-partum alopecia). Similarly, TE can be caused by vaccinations, strict diets, psychological stress, physical trauma, surgery, intake of some drugs, e.g.: antidepressants.

AA is the third most common form of hair loss. It is at present considered an autoimmune disease in which individual's own immune system attacks hair follicles.

Hair follicle, hair shaft and sebaceous gland constitute the pilosebaceous unit, a complex, dynamic, 3-D structure, site of unique biochemical, metabolical and immunological events. Thus the pilosebaceous unit represents a unique cell-rich microcosmos, staminal cells included, that is able to regenerate itself, based on the interactions of its epithelial and mesenchimal components. The pilosebaceous unit is the target for hormones but also the site of hormonal synthesis through the local aromatases. Its physiological activity is strictly linked with the functionality of the vessel supply, through the local microcirculatory system. The anagen phase is indeed accompanied by an increase in skin perfusion due to a rearrangement of the skin vasculature and angiogenesis.

Ricapil® is a product, for scalp application, addressed for a three way intervention in the most common forms of alopecia: to halt hair loss, to strengthen hair and to favour natural hair regrowth. This mousse has to be applied once a day, for 3 to 12 months according to the type of alopecia and the desired end-point. The dosage varies according to the extension of hair loss: one nut of mousse/hair loss area, till a total of 4 nuts of mousse a day.

Ricapil® contains natural substances extracted from 9 officinalis plants: *Carthamus Tinctorius, Prunus Persica, Zingiber Officinalis, Panax Ginseng, Salvia Officinalis, Cuscuta Epithimum, Carum Petroselinum, Angelica Archangelica, Capsicum Annuum*. The choice of these components was driven by the different targets in pilosebaceous unit: 1) dermal papilla: to increase blood flow and nutrients supply, to decrease local inflammatory status (*Capsicum A., Carthamus T., Panax Ginseng, Zingiber, Angelica A.*); 2) hair root: antioxidant effect, decrease in local pH, control of local bacterial overgrowth, improved sebum rheology, hydration (*Panax Ginseng, Prunus P., Salvia, Zingiber, Carthamus T. Cuscuta E.*); 3) hair shaft: hydrating, softening and shining actions (*Prunus P. Carthamus T., Carum P. Cuscuta E.*).

The Institute of Environmental Health of the Chinese Preventive Academic Mdicine, authorized by Chinese Ministry of Health, has evaluated the product local irritative potential both in animal and in man. It was not observed any sensitization or photosensitization or mutagenetic potential.

Per oral route acute toxicity levels resulted in a DL_{50} > 5 g/kg; repeated dermal irritation test in rabbit skin showed no irritative effects; acute eye irritation test in rabbit, with instillation without washing the eye for 24 hours, showed a light irritation only. The skin tolerability study carried out in 200 subjects showed no adverse cutaneous events after a 2 months scalp application.

Moreover, a clinical experience with 8,324 Chinese outpatients with alopecia, classified as limited, complete and ordinary hair losing, reported a rate of total effectiveness of 98,3%, 97,7% and 94,1% respectively. Given these premises, the availability of data from three clinical studies carried out in 4 dermatological centres in Italy with homogeneous methodologies, stimulated us to reconcile the results of the individual trials pooling their data in order to judge the product profile on a larger controlled population of subjects with hair loss.

MATERIALS AND METHODS

The main reason for conducting a meta-analysis is to reconcile previously carried out studies when the sample size of individual studies is too small to find consistent results. We have thus chosen to perform a re-analysis of individual data based on primary studies. With the individual data available this statistical re-analysis can be performed. This includes same inclusion criteria, a unified definition of the variables and a new statistical modelling. New hypotheses may be formulated with these types of pooled analysis and specific subgroups, such as age groups, may also be analysed.

STUDY OBJECTIVES

The primary objective was to determine if the studied formulation is able to exert a detectable effect against hair loss and in favour of follicle reactivation (anagen phase) together with a reduction or a complete stop in hair loss.

OVERALL STUDY DESIGN AND PLAN

The trial was a national multicentre study in patients with several degrees of the most common types of hair loss. Patients fulfilling the entry criteria were treated with the product once daily for at least 3 month and till a maximum of 12 months (average 4-5 months).

PROTOCOL OUTLINES

The formulation was applied once a day on the scalp, gently massaging. The total amount used per day was related with the extension of alopecic areas (1-2 to a maximum of 3-4 doses) in each individual. The subjects have been evaluated by the investigators before and after the treatment' end, with controls every month. The evaluated parameters consisted in macroscopic and microscopic examination of the hair, rating of AGA stage by Hamilton (males) and Ludwig (female) scales. In each subjects routinary hematochimic tests have been performed to exclude any systemic interference exerted by product application on the scalp.

STUDY POPULATION

Two hundred subjects (121 m, 79 f) completed the studies as outpatients. Two hundred and twenty four subjects were enrolled but 24 did not return to the scheduled control visits and have then been excluded from the evaluation by the investigators.

INCLUSION CRITERIA

To be eligible for inclusion each patient was required to fulfill each of the following criteria: provision of written informed consent; subjects of either gender and aged 12-60 years; presence of different degrees of AGA, AA, TE; subjects not treated with topical or systemic therapy for alopecia within six months of study entry; if female and of child bearing potential, the patient must be non-nursing and practicing an effective method of contraception through the study duration. All females of child bearing potential must have a negative serum or urine pregnancy test prior the start of study medication.

EXCLUSION CRITERIA

Subjects unwilling to give an approved informed consent form; female of child bearing potential and lactating; subjects treated with topic or systemic therapy for alopecia within six months of study entry; known allergy or known intolerability to any component and/or excipient of the product; subjects with any significant medical condition which might interfere with the evaluation of safety and efficacy of the tested treatment.

STUDY PROCEDURES

The study procedures are reported below in Figure 1.

Figure 1. Study procedures.

Figure 1 – Study procedures

Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Month	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Written informed consent	*												
Demography	*												
Inclusion and exclusion criteria	*												
Administration and dispensing of study medication	*												
Clinical assessment	*	*	*	*	*	*	*	*	*	*	*	*	*
Assessment of efficacy		*	*	*	*	*	*	*	*	*	*	*	*
Assessment of tolerability		*	*	*	*	*	*	*	*	*	*	*	*
Adverse Events		*	*	*	*	*	*	*	*	*	*	*	*

PRIMARY EFFICACY VARIABLE

The primary efficacy variable was the score for response to treatment measured at last visit. The score was assigned as follows:

0. Not valuable re-growth (= negative result: absent)
1. Appearance of fine vellus (= first stimulation result on inactive follicles: poor)
2. Initial re-growth of terminal hair (= good)
3. Re-growth of terminal hair (= very good)

SAFETY VARIABLE

The safety variable was tolerability to the treatment evaluated on the following parameters: itching, irritation and burning sensation.

STATISTICAL METHODS

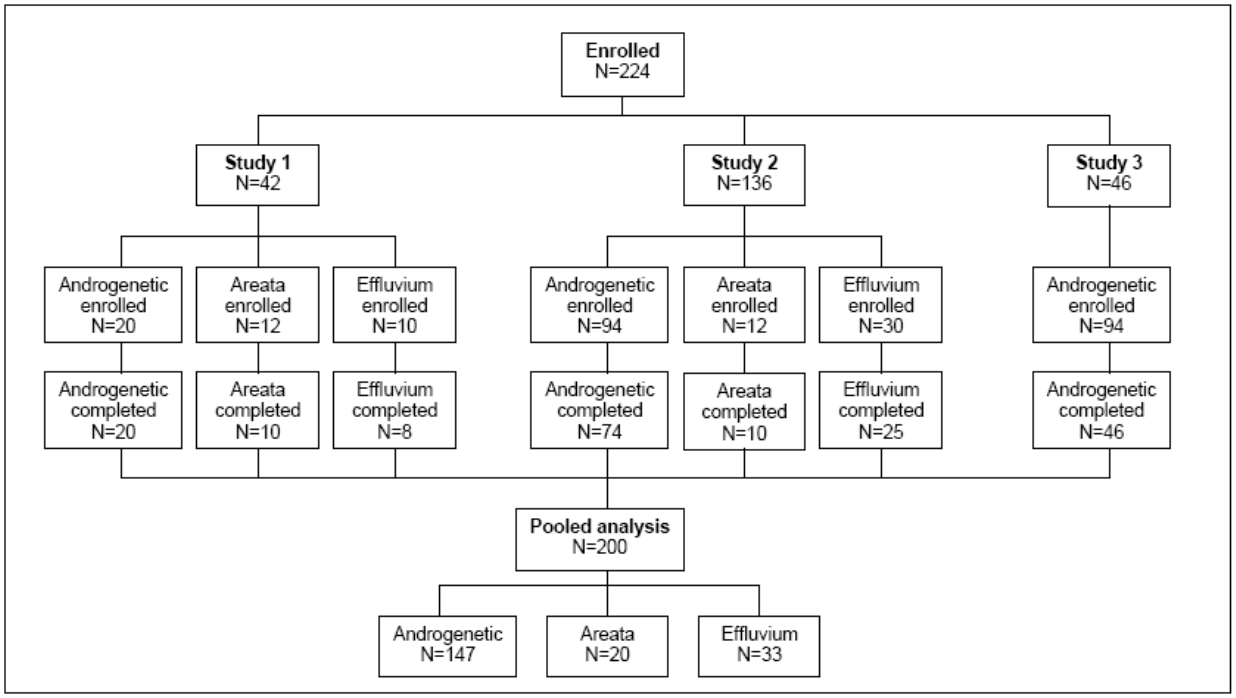
The pooled analysis for efficacy was performed on intention-to-treat (ITT) population including all randomized subjects who started treatment and which have a post-baseline measurement of the primary efficacy variable after three month of treatment.

Demographic data and all other significant parameters were summarized and described in order to characterize the study population. Descriptive continuous variables were reported as mean, SD, minimum and maximum, whilst categorical descriptive variables were reported as frequencies and percentages.

Baseline value for primary efficacy variable was the grade of alopecia measured before the start of treatment. The variation of alopecia compared to baseline was measured as a detectable effect

against not only hair loss but also in favor of hair follicle reactivation. The subjects who responded to treatment were defined according to the previously described score. The response to treatment has been analyzed using the chi-square test. The disposition of subjects is reported in Figure 2.

Figure 2. Disposition of subjects. Note: a) Study 1 (Bologna/Di Stanislao); Study 2 (Chimenti); Study 3 (Lucheroni/Gori); b) 224 enrolled subjects, 24 did not return to the foreseen control visits, pooled analysis: 200



RESULTS AND DISCUSSION

The difference between the responses after treatment for each type of hair loss are shown in Table 1, 2 and 3.

In telogen effluvium a response to treatment (halt in hair loss and initial/appreciable regrowth) was demonstrated in 97% of cases ($p<0.001$) (Table 1). In alopecia areata the response was found in 75% of studied cases ($p<0.001$) (Table 2).

In AGA the rate of success (hair follicle reactivation and terminal hair re-growth) resulted 49% ($p<0.001$), as shown in Table 3. A longer application time (10-12 months) is usually recommended in AGA than the one of the analyzed population (4-5 months), to allow the treatment displays its effects with a terminal hair regrowth. The observed rate, already very positive, is then probably underestimated.

The pooled response to treatment in all the 200 completed patients is reported in Figure 3. In the most frequent forms of hair loss, the scalp application of the product resulted in hair loss halt, hair follicle reactivation and hair regrowth in 119/200 cases (59,5%; pooled results).

Table 1. Telogen Effluvium - Comparison between responses (χ^2 test – significativity level 0.05).

Response	Observed N	Expected N	Residual
Absent	1	16,5	-15,5
Poor	-	-	-
Good + Very good	32	16,5	15,5
Total	33		
χ^2 = 29,121	Df = 2	p < 0.001	

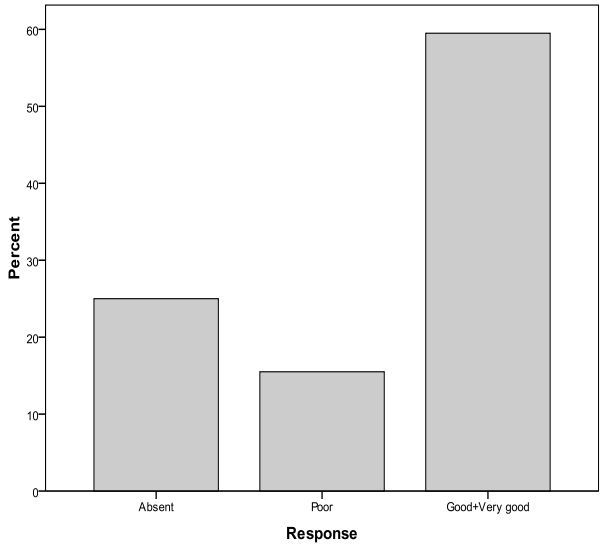
Table 2. Alopecia areata - Comparison between responses (χ^2 test – significativity level 0.05).

Response	Observed N	Expected N	Residual
Absent	4	6,7	-2,7
Poor	1	6,7	-5,7
Good + Very good	15	6,7	8,3
Total	20		
χ^2 = 16,300	Df = 2	p < 0.001	

Table 3. Response to treatment – Androgenetic alopecia - Comparison between responses (χ^2 test – significativity level 0.05)

Response	Observed N	Expected N	Residual
Absent	45	49,0	-4,0
Poor	30	49,0	-19,0
Good + Very good	72	49,0	23,0
Total	147		
χ^2 = 18,490	Df = 2	p < 0.001	

Figure 3. Response to treatment – Pooled data



The difference between the responses after treatment resulted statistically significant (p< 0.001), as shown in Table 4. The response to treatment according to the type of hair loss is reported in Table 5.

Table 4. Comparison between responses (χ^2 test – significativity level 0.05)

Response	Observed N	Expected N	Residual
Absent	50	66,7	-16,7
Poor	31	66,7	-35,7
Good + Very good	119	66,7	52,3
Total	200		
χ^2 = 64,330	Df = 2	p < 0.001	

Table 5. Response to treatment – type of alopecia.

	Alopecia					
	Androgenetic		Areata		Effluvium	
Response	N	%	N	%	N	%
Absent	45	30,61	4	20,00	1	3,03
Poor	30	20,41	1	5,00	-	-
Good + Very good	72	49,98	15	75,00	32	96,97
Total	147	100	20	100	33	100

CONCLUSIONS

Hair loss is in most of cases a disorder but deeply influences affected individuals' quality of life. The curative approach has then to consider not only the possible benefit but also its tolerability and practicality.

The psychological attitude of many subjects urges to the use of pharmacological options that, in reality, increase the side of the risks more than the one of the benefits. The search for products with a negligible risk of adverse events, local and systemic, together with an appreciable degree of effect on hair loss and hair regrowth has a long tradition.

A huge amount of products in this field claims for efficacy but clinical documentation is not available, apart for drugs like minoxidil and finasteride. Claims of efficacy sometimes lay on simple questionnaires on customer's subjective satisfaction, where physicians or dermatologists are not involved. In our meta-analysis we have evaluated the data of 200 patients who have completed trials carried out in four Italian dermatological centres.

In TE the stop in hair loss and initial regrowth was observed in 97% of cases ($p<0.001$) within the first month. In AA the responders (= stop in hair loss and initial re-growth) were 75% ($p<0.001$). In AGA 49% of subjects showed a significant ($p< 0.001$) hair follicle reactivation/hair regrowth versus the non/poorly responder groups (4-5 months of application). The pooled analysis on all 200 cases showed a significant ($p<0.001$) difference between the responder groups (59,5%) and the poor (15,5%) or non responder (25%) groups. The percentage of telogen phase before and after the treatment in AGA changed from 35% to 27% (-23%).

The value of placebo effect in hair loss, extrapolated from literature data for a drug like minoxidil, ranges from 9% to 20% after 24 and 48 weeks of treatment; the percentage of success in AGA for topical minoxidil 5% was 28% after 48 weeks. Minoxidil 3% showed no efficacy in chronic alopecia areata. The actual success rate in AGA of the presently evaluated product would be probably even more significative with a more prolonged application (4-5 months in comparison with twelwe months of minoxidil).

The importance of a constant and adequate application period seems then to be stressed. In conclusion, from the results of this meta-analysis, the scalp application of this product is able to achieve till to 97% of success results in hair loss, with a

significant difference between the responder and non/poorly responder groups. In any type of alopecia the reported success rate is placed well above the level of placebo effect and results superior to the one a drug like topical minoxidil, 5%.

During scalp application the product has shown a very good tolerability. Only rare cases of transient mild itching and erythema at beginning of application were reported, linked with product activity. Product acceptability for its cosmetic and practical characteristics was also very good.

To the studied formulation has now been joined a further plus, a technology exerting a gentle mechanical massage to the scalp during the application and able to speed the penetration of the components within the epidermal strata, where hair follicle is located. In conclusion, from the results of our meta-analysis, the product appears to be effective and promising in most frequent forms of hair loss like AGA, TE and AA, in men and women, with a very favourable benefit/risk ratio.

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