A topical botanical lotion improves recovery from chemotherapy alopecia and persistent hair issues in cancer survivors through local modulation of apoptosis and inflammation.

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Introduction

CIA (chemotherapy induced alopecia), with an incidence of 65% [1], is considered by sufferers as the most distressing side effect of cancer therapies [2]. Cooling devices are meant to prevent CIA. Their efficacy is however variable [3] and they do not address hair recovery.

Chemo-agents attack fast-dividing cells, severely inhibiting hair matrix cells that prematurely undergo apoptosis [6]. This adverse event generally causes dystrophic anagen and dystrophic catagen hairs [4]. Dystrophic anagen hair follicles actually recover much more slowly than dystrophic catagen hair follicles. As anagen hair proportion represents 80 – 90%, CIA is not only an acute event; the hair recovery usually becomes a long-term issue.

p53 knock-out mice do not undergo CIA [5] suggesting that normalization of Bcl-2 expression level may be an appropriate strategy. In addition, massive apoptosis and secondary necrosis due to chemotherapies stimulate the production of pro-inflammatory mediators triggering and sustaining scalp micro-inflammatory conditions. In return, enhanced level of inflammation will favor further death of more hair follicular cells, resulting in persistent scalp inflammation [7-10]. Such a vicious cycle will impede normal hair cycle. Disturbed hair cycle materializes in delayed hair regrowth and thinner hair - the main clinical manifestations of chemotherapy long-term hair issues.

Therefore, to counteract cancer treatment related hair issues, it is crucial to tackle unwanted hair follicular cells death and to dampen scalp micro-inflammation, two key unresolved issues in the management of CIA and chemotherapy persistent hair disorders.

Objective

In order to assess the topical product potential for CIA and chemotherapy persistent hair issues, we conducted 4 studies aiming to show:

- **A** The ability of the topical botanical lotion to normalize the Bcl-2 level in scalp biopsies of AGA subjects who present low level of Bcl-2
- **B** The product's anti-inflammatory property (in vitro)
- **C** Clinical efficacy in reducing CIA baldness period (20 weeks on average [11, 12])
- **D** Clinical efficacy in the recovery from persistent hair issues, especially improvement of hair thinning and hair volume.

A

Apoptosis modulation & safety

Objective:

To demonstrate the molecular basis for proof of concept and safety through the assessment of the product's potential in modulating Bcl-2 towards normal level in AGA subjects.

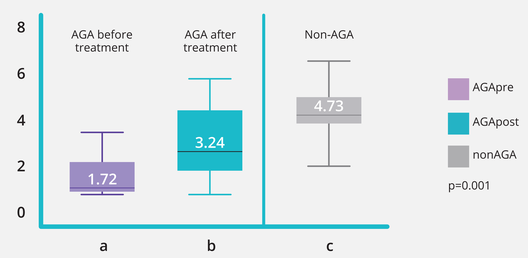
Method:

After 3 months' topical application, to analyze, via immunohistochemistry, Bcl-2 level in scalp biopsy of male AGA subjects (n=20), and compare with Bcl-2 in non-AGA volunteers (n=25).

Result:

In AGA subjects Bcl-2 level is depressed (1.7) (a). The product restored Bcl-2 (3.2) (b) towards normal level (4.73) (c), as shown below.

Fraction of epidermal BCL-2+ cells (%)



B

Anti-inflammation

Objective:

To test, in vitro, the anti-inflammatory potential of the product.

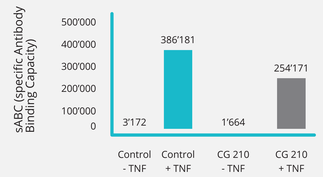
Method:

To evaluate TNFα-induced expressions of adhesion molecules (E-selectin and ICAM-1) in endothelial cells (HUVECs) using specific Antibody Binding Capacity technology, measured by flow cytometry.

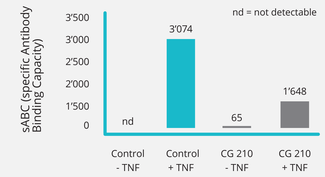
Result:

The product is able to inhibit TNFα-induced cell surface expression of the inflammatory markers E-selectin and ICAM-1 in HUVECs.

ICAM-1 (CD54) expression level in huvec



ELAM-1/E-selectin (CD62E) expression



C

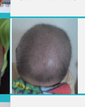
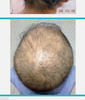
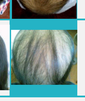
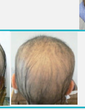
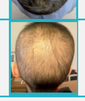
CARA - Open Label Assessment on Recovery from CIA

Objective & Method:

Assessment, in female subjects treated with taxanes, of the efficacy of the product on hair recovery subsequent to CIA, in terms of duration of baldness period, throught macrophotography compared to non-treated historical control [11, 12].
Note: baldness period, from maximum hair loss until first hair regrowth, lasts 20 weeks on average (n=9).

Result:

Topical application of the product in female cancer patients treated with chemo agents known to cause alopecia (docetaxel, etc.) allowed faster hair recovery (5-16 weeks quicker than historical control).
Compliance with product use (twice-daily) was good. No side effect was reported.

Ref.	Start of product use	Before start of chemo (or else)	During chemo	Week 0 = End of chemo	Week 1 after end of chemo	Week 2	Week 3	Week 5	Week 6	Week 8	Week 10	Week 12
Duvic et al. [11]	No hair loss treatment		Maximum hair loss is reached usually 6 weeks after start of chemo	Balding period with no hair loss treatment = 20 weeks							Expected first hair regrowth	
V. Kanti et al. [12]	No hair loss treatment			End of chemo (week 16 after start of chemo)								
CARA 02	At start of chemo			End of chemo (estimated)								
CARA 03	-14 weeks before start of chemo											
CARA 04	At start of chemo			End of chemo								
CARA 05	2 weeks after start of chemo			End of chemo								
CARA 01	1 week after start of chemo			End of chemo								

D

RELAC - Open Label Assessment on Recovery from Persistent Hair Issues

Objective & Method:

Assessment of the product efficacy on improvement of hair pattern in cancer survivors complaining from persistent hair issues, several years after chemotherapy (n=21) throught macrophotography and questionnaire.

Result:

First improvement was observed and/or reported in 33%, 52% and 76% of subjects after 1, 2 and 3 months, respectively.
Compliance with product use (twice-daily) was good.
No side effect was reported.

Ref.	Years since end of last chemo	Start	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Time to reach first improvement
RELAC 15	4.6 years								1 month
RELAC 17	12.6 years								1 month
RELAC 21	2 years								1 month
RELAC 09	3.6 years								2 months
RELAC 20	3.2 years								4 months

Conclusion and discussion

Although studies with larger sample size are needed, the initial results showed that topical application of this botanical scalp and hair lotion (CG428) reduced baldness period of cancer patients treated with chemo-therapy regimen known to cause alopecia.

Furthermore, the topical product application improved hair pattern in most subjects complaining from persistent hair issues due to chemotherapy, as early as 1-3 months.

These studies confirm the strategies of local modulation of apoptosis and anti-inflammation in the management of CIA and chemotherapy persistent hair issues.

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