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A preliminary study on topical cetirizine in the therapeutic management of androgenetic alopecia.

A pilot study on topical cetirizine.

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ABSTRACT

Androgenetic alopecia (AGA) is a common form of scalp hair loss that affects up to 50% of males between 18-40 years old. Several molecules are commonly used for the treatment of AGA, acting on different steps of its pathogenesis (Minoxidil, Finasteride, Serenoa repens) and show some side effects.

In literature, on the basis of hypertrichosis observed in patients treated with analogues of prostaglandin PGF2α , was supposed that prostaglandins would have an important role in the hair growth: PGE and PGF2α play a positive role, while PGD2 a negative one.

We carried out a pilot study to evaluate the efficacy of topical cetirizine versus placebo in patients with androgenetic alopecia.

We found that the main effect of cetirizine was an increase of total hair density, terminal hair density and diameter variation from T0 to T1, while the vellus hair density shown an evident decrease.

The use of a molecule as cetirizine, with no notable side effects, make possible a good compliance by patients. Our results have shown that topical cetirizine 1% is responsible for a significant improvement of the initial framework of androgenetic alopecia.

Introduction

Androgenetic alopecia (AGA) is a common form of scalp hair loss that affects up to 50% of males between 18-40 years old. The onset of AGA is extremely variable and the physical aspect is characterized by progressive miniaturization of scalp hair follicles [1,2]. Even though this condition is a paraphysiological condition, the loss of hair leads to stressful events for the patients with considerable psychosocial consequences. Genetic factors and androgens play a major role in the pathogenesis of the disease. Polymorphism of the androgen receptor genes was first identified in association with androgenetic alopecia. Several studies in literature have confirmed the predominant involvement of androgens and especially of dihydrotestosterone (DHT). Testosterone is converted to DHT by the enzyme 5 alpha-reductase, which exists as two isoenzymes: type I and type II. The first one is predominant on the scalp (external epithelial sheath), trunk, liver, kidney, sebaceous glands and adrenal glands. The second one is located in the more internal part of external epithelial sheath, internal epithelial sheath and in the dermal papilla, in the beard and in the prostate [3-5].

Several molecules are commonly used for the treatment of AGA, acting on different steps of its pathogenesis (as minoxidil, finasteride, serenoa repens). In literature, on the basis of hypertrichosis observed in patients treated with analogues of prostaglandin PGF2α (i.e. latanoprost used for glaucoma), it was supposed that prostaglandins would have an important role in the hair growth. Their action is variable depending on

the class they belong to: PGE and PGF2α play a generally positive role on the hair growth, while PGD2 a inhibition of the hair growth [6].

On the basis of these evidences and lacking studies that confirm the effectiveness of cetirizine in AGA treatment, therefore, we carried out a pilot study to evaluate the efficacy of topical cetirizine in patients with androgenetic alopecia.

Materials and Methods

A sample of 85 patients (both male and female aged between 20 and 65 years) was recruited, of which 67 was used to assess the effectiveness of the treatment with topical cetirizine, while 18 were control patients (both male and female aged between 22 and 60). All the patients were in good health conditions and with different grades of AGA (we used the Hamilton classification, modified in order to evaluate also the quantity of the hairs in the vertex). All patients were asked to fill out the informed consent.

The aim of our report was to evaluate the efficacy and tolerability of a galenic lotion composed of cetirizine 1%, 16% cyclo-silicone-pentamer, 96°C of ethyl alcohol applied once a day on the scalp. In order to perform the study, the patients were divided in two groups: the first one characterized by the use of topical cetirizine 1% (1 application/daily = 1ml/daily) and a second one treated with placebo (16% cyclo-silicone-pentamer, 96 °C of ethyl alcohol , 1 application/daily= 1ml/daily). The exclusion criteria were: previous therapies for AGA, systemic diseases and pregnancy.

For each patient we evaluated the following variables: total hair density (D), vellus hair density (VD), terminal hair density (TD) and diameter (d). We have defined as vellus hairs the hairs with a diameter < 0.05 mm and terminal the ones ≥ 0.05 mm.

A first visit was performed at T0 and was repeated after 6 months of treatment at T1.

Macrophotograps at 20-70_X (Trichoscan Dermoscope Fotofinder®) were performed to collect photographical reports. The final score was obtained by averaging the evaluation given by a group of expert dermatologists.

In Table 1 we show the results of analysis, in particular the mean and standard deviation of the parameters variation ($<|\Delta P|>\pm\sigma$) and of the variation normalized to the initial value ($<|\Delta P/P(T0)|>\pm\sigma$) where P = D, DV, DT, d.

Results

In order to quantify the improvement of the estimated parameters, we compute the mean and standard deviation of variation $<|\Delta P|> = <|P(T1)-P(T0)|>$ where T1 and T0 represent the times taken into account to compute the averaged parameters variation. After six months of treatment with cetirizine the patients show an increase of the average $<|\Delta D|> = 30.31$ that represents $<|\Delta D/D(T0)|>= 11\%$ variation relative to initial total density. This can be seen in Figure 1 where an evident improvement of total density is clearly visible. Similar results were obtained for the diameter (see Table 1) while for the terminal density we found a significant improvement of $<|\Delta TD/TD(T0)|>= 18\%$. The vellus density show an decrease of $<|\Delta VD/VD(T0)|>=$

15%. On the contrary in the control group we observed variations of 1% for the total density and 3% for the terminal density as shown in the table 2.

Discussion

Androgenetic alopecia (AGA) is a common form of scalp hair loss that affects up to 50% of males 18-40 years old. The onset of AGA is extremely variable and the physical aspect is characterized by progressive miniaturization of scalp hair follicles [1,2].

Up to date, the role of prostaglandins in AGA is rarely reported in literature.

Garza et al. found elevated levels of prostaglandin D2 synthase (PTGDS) at the mRNA and protein levels in bald scalp versus haired scalp of men with AGA; as well as the enzymatic product of PTGDS, prostaglandin D2 (PGD2), is generally elevated in bald human scalp tissue. Furthermore, Garza et al. provided functional data indicating that PGD2 and its no enzymatic metabolite, 15-deoxy-Δ12,14-prostaglandin J2 (15-dPGJ2), inhibit hair growth in both mouse and human hair follicles. In addition, in mice and human models, hair growth inhibition requires the PGD(2) receptor G protein-coupled receptor 44 (GPR44), but not the PGD(2) receptor 1 (PTGDR) [6-8].

All these results implicate PGD2 in the pathogenesis of AGA and may suggest new receptor targets for its treatment. In fact, recent evidences highlighted a role for prostaglandins in regulating hair growth. For example, the PGF2α analogous latanoprost is Food and Drug Administration (FDA)–approved and routinely used clinically to enhance hair growth of human eyelashes [9]. PGE2 has been proposed to

protect from radiation-induced hair loss in mice and both PGE2 and PGF2α have been shown to enhance hair growth in mice. These studies confirm that prostaglandins are deregulated in AGA, the most common type of hair loss in men.

In front of these evidences, the aim of our study was that to evaluate the efficacy and tolerability of a topical lotion containing cetirizine 1% for the treatment of androgenetic alopecia in male and female patients. To our knowledge, this is the first report in literature that evaluate the efficacy of cetirizine in AGA.

Cetirizine is a safe and selective, second-generation histamine H1 receptor antagonist, widely used in daily practice. Charlesworth EN et al. showed that cetirizine causes a significant reduction in both the inflammatory cell infiltrate and PGD2 production. However, these effects apparently are not related to its anti-H1 activity [10].

Cetirizine hydrochloride is a racemic mixture composed of equal amounts of two enantiomers, R -levocetirizine and S -dextrocetirizine, which do not undergo interconversion and therefore maintain configuration stability in the body. Cetirizine has been shown to have highly favorable pharmacological properties. In particular, cetirizine is a zwitterion, with high binding to mainly serum albumin and low apparent volume of distribution, as well as low brain uptake, which are indicative of a low affinity for lean tissues such as the myocardium (thus low cardiotoxicity) and low/lack of sedative effects, respectively. Cetirizine has also been shown to be absorbed extensively and rapidly from the gut, leading to high bio-availability and rapid onset of action of the drug, and unlike many other second generation antihistamines, it does not undergo hepatic metabolism to any appreciable extent, but

is excreted mostly unchanged in the urine, equally well in both healthy volunteers and patients with chronic liver disease. The lack of hepatic metabolism demonstrates a low potential for drug-drug interactions, which avoids any exaggerated pharmacological or toxicological effects with drugs that are subject to metabolism by P450 enzymes and to transmembrane transport. Similarly, H1 receptor binding studies have demonstrated that compared with many other commonly used 2nd-generation H1 antihistamines, cetirizine has a relatively higher and more favorable affinity and selectivity for H1 receptors, which confers a more potent, faster onset and longer duration of action. Studies investigating the anti-inflammatory/anti-allergic effects of cetirizine have indicated that it may exhibit anti-inflammatory properties independent of its H1 effects [11].

According to reports about the effect of various types of prostaglandins on hair follicle cycling, it has been showed that the E and F types (PGE and PGFα) stimulate the hair growth, while the D types (in particular PGD2) favor the progression of baldness[6]. Indeed, PGD2 inhibits hair growth, favoring the miniaturization. In this regard we can state that inhibition of PGD2 (as di-hydroxy-testosteron) through the use of cetirizine is a further pathogenic clue in AGA, resulting to be a new and promising target treatment for AGA. Finally, the lower number of potential side effects if compared with other drugs commonly used for AGA, as minoxidil (often cause of hypertrichosis, contact allergic dermatitis, headache and hypotension), can promote a wider use of cetirizine in the future for the treatment of AGA.

Conclusions

The use of a molecule as cetirizine, with no notable side effects, make possible a good compliance by patients. In fact patients often alarmed by media campaigns, do not follow faithfully the therapy required by the physicians. It's therefore primary patient adherence to treatment, by which obviously depends the effectiveness of the drug. Another advantage of this therapy is the possible use in female compared to other drugs yet used.

Our results have shown how the topical application of a 1ml / day of a solution containing cetirizine 1% is responsible for a significant improvement of the initial framework of androgenetic alopecia. Further studies are needed to better investigate the role of cetirizine in AGA, starting from the current first observation.

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Table 1

Results of analysis for patients treated with cetirizine. From first column: total density, vellus density terminal density and diameter variation. For each parameters the mean and standard deviation and minimum and maximum value of the parameters variation, mean and standard deviation and minimum and maximum value of the variation normalized to the initial value.

<|ΔD|>±σ	<|ΔVD|>±σ	<|ΔTD|>±σ	<|Δd|>±σ
30.31 ± 4.21	9.14 ± 1.99	31.68 ± 3.74	3.30 ± 0.27
|ΔD|	|ΔVD|	|ΔT|	|Δd|
[2.30, 142.90]	[0.5 , 67.4]	[1.5, 105.2]	[0, 7]
<|ΔD/D(T0)|>±σ	<|ΔVD/VD(T0)|>±σ	<|ΔTD/TD(T0)|>±σ	<|Δd/d(T0)|>±σ
0.11 ± 0.02	0.15 ± 0.02	0.18 ± 0.02	0.05 ± 0.01
|ΔD/D(T0)|	|ΔVD/VD(T0)|	|ΔTD/TD(T0)|	|Δd/d(T0)|
[0.01, 0.51]	[0.02, 0.69]	[0.01, 0.54]	[0.0, 0.1]

Table 2

Results of analysis for the control group.

<|ΔD|>±σ	<|ΔVD|>±σ	<|ΔTD|>±σ	<|Δd|>±σ
2.59 ± 0.55	0.59 ± 0.13	5.69 ± 1.39	1.83 ± 0.53
|ΔD|	|ΔVD|	|ΔT|	|Δd|
[0.70, 5.90]	[0.20, 1.20]	[0.60, 14.40]	[0, 5]
<|ΔD/D(T0)|>±σ	<|ΔVD/VD(T0)|>±σ	<|ΔTD/TD(T0)|>±σ	<|Δd/d(T0)|>±σ
0.01 ± 0.01	0.02 ± 0.01	0.03 ± 0.01	0.04 ± 0.01
|ΔD/D(T0)|	|ΔVD/VD(T0)|	|ΔTD/TD(T0)|	|Δd/d(T0)|
[0.00, 0.02]	[0.01, 0.04]	[0.00, 0.08]	[0.00, 0.12]

Fig. 1 Global photography of patients treated with Cetirizine at T0 (a, c, e, g) and at T1 (b, d, g, h).