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Topical Estrogen Therapy for Androgenetic Alopecia in Menopausal Females

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Key Words

Alopecia · Estradiol · Estrogens · Hormones

Androgenetic alopecia (AGA) is a common, cosmetically disfiguring and difficult-to-treat medical problem with a significant psychosocial impact. Until today, the treatment of AGA has most often been discouraging. The available topical or systemic modalities achieve only retardation of the hair loss process and, possibly, minimal regrowth [1]. An alternative approach in the management of AGA is the topical application of lotions containing estrogens (17 α - or 17 β -estradiol, estradiol benzoate or estradiol valerate), with or without the addition of corticosteroids.

In order to evaluate the efficacy and safety of topical estrogens, we studied 75 postmenopausal females (aged 48–71 years) with AGA, during a 3-year period (1998–2000). After they had given their informed consent, patients were randomized into three treatment groups. Evaluation for breast cancer was made before entry. Those at high risk were excluded from the study. Inclusion criteria included clinical diagnosis of AGA with a telogen rate >20% in a menopausal female; good general health, especially absence of other causes of alopecia, and no other treatment for AGA during the previous 3 months. Subjects of groups 1 (G1) and 2 (G2) received topical treatment with a lotion containing estradiol valerate 0.03%. In G1, the lotion was applied for 12 weeks, while in G2 it was applied for 24 weeks. Subjects of G3 received placebo treatment with a lotion containing only the vehicle for 24 weeks. Patients were instructed to apply 15 drops of the lotion on the affected area of the scalp, every evening for 4 weeks, and then every second evening until the end of the treatment period. Trichograms were taken at entry and again at the end of the treatment period. Improvement was defined as at least 30% improvement of the anagen to telogen ratio. Statistical analysis involved the χ^2 test (Yates' correction included) for the comparison of proportions. Patients were followed up clinically on a monthly basis and for 6 months after the completion of treatment.

Of the 75 women included, 65 were evaluable for safety. Ten (2 from G1, 3 from G2 and 5 from G3) were excluded due to poor compliance or were lost to follow-up. No significant topical adverse reactions were noted. Six patients, 2 out of 23 in G1 (8.7%), 4 out of 22 in

G2 (18.2%) and 2 out of 20 in G3 (10%), complained of mild pruritus, redness and/or scaling of the scalp. No systemic side effects were observed among patients of G1 and G3. In contrast, 2 subjects from G2 (9.1%) experienced postmenopausal uterine bleeding on weeks 17 and 22, respectively, and were withdrawn from the study. Both women had menopause of recent onset (less than 2 years). Histological examination of the endometrium revealed typical estrogen-induced proliferation. In both patients, estradiol serum levels were elevated, FSH and LH levels were suppressed, while androgen levels were normal. Within few weeks after discontinuation of the treatment, the estradiol levels returned to normal. Interestingly, a 53-year-old female patient developed breast cancer several months after the completion of the 6-month course with estradiol for AGA. Laboratory workup revealed an estrogen-dependent adenocarcinoma. It is unclear if this occurrence was coincidental or if there was any etiologic association.

Twenty-two patients of G1, 20 patients of G2 and 20 patients of G3 completed the treatment and were evaluable for efficacy. At baseline, the mean anagen/telogen ratio was 1.68 in G1 and 1.57 in G2 and rose to 2.33 and 2.27, respectively, after treatment. Accordingly, in G3, the mean anagen/telogen ratio dropped from 1.61 to 1.55. Improvement (decreased telogen rate and/or increased anagen rate) was observed in 14 G1 subjects (60.9%), in 13 G2 subjects (65%), and in 4 (20%) G3 subjects. One patient from G1 and 7 patients from G3 worsened (increased telogen rate), the rest remained stable. However, no hair regrowth was noted. A statistically significant difference in the improvement rate between G1 and G3 ($\chi^2 = 8.36$, $p < 0.01$), as well as between G1 and G3 ($\chi^2 = 8.43$, $p < 0.01$) was documented. No statistically significant difference was observed between G1 and G2. The results are summarized in table 1.

In the literature, there is limited experience regarding the efficacy and safety of local application of estrogens in AGA. In a controlled, randomized, double-blind study, topical use of 17 α -estradiol 0.025% for at least 6 months produced an increased anagen and decreased telogen rate and a reduction in hair shed [2]. Another study in females of reproductive age showed that a 32-week trial of topical estradiol benzoate, combined with prednisolone and salicylic acid, achieved minimal hair regrowth in 33.3% and moderate hair regrowth in 7.1% [3].

A literature review revealed two studies in which the safety of local estrogen application in AGA was assessed. In a clinical trial of 51 patients, no significant side effects were seen [2]. In another study of 30 male patients, the total urinary estrogen level was estimated before and after topical treatment with dienestrol diacetate 0.05% [4]. No differences were found between treated patients and controls and no clinical side effects were recorded. There is one report of postmenopausal bleeding in a 74-year-old female following the application of an estrogen-containing hair lotion [5]. In addition, a male was reported with persistent gynecomastia resulting from scalp inunction of estradiol [6].

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Table 1. Synopsis of the efficacy and safety of topical estradiol valerate 0.03% for 3 months (G1) or for 6 months (G2) compared with placebo (G3)

| | Group 1 (3 months) | Group 2 (6 months) | Group 3 (placebo) |
|------------------------------------|-----------------------|-----------------------|----------------------|
| Patients enrolled | 25 | 25 | 25 |
| Patients excluded | 2 | 3 | 5 |
| Evaluable for safety | 23 | 22 | 20 |
| Frequency of topical side effects | 2/23 (8.7) | 4/22 (18.2) | 2/20 (10) |
| Frequency of systemic side effects | 0/23 (0) | 2/22 (9.1) | 0/20 (0) |
| Evaluable for efficacy | 23 | 20 | 20 |
| Anagen/telogen (baseline) | 1.68 | 1.57 | 1.61 |
| Anagen/telogen (endpoint) | 2.33 | 2.27 | 1.55 |
| Responders | 13/23 (60.9) | 14/20 (65) | 3/23 (15) |

Figures in parentheses indicate percentages.

At present, it is still unclear how estrogens mediate their beneficial effect on AGA-affected hair follicles. Estrogens appear to be a much weaker inhibitor of 5 α -reductase than finasteride [7]. It has been shown that 17 α -estradiol is able to diminish the amount of dihydrotestosterone (DHT) formed by human hair follicles after incubation with testosterone, while increasing the concentrations of weaker steroids such as estrogens [7]. Furthermore, a time-dependent increase in aromatase activity, an enzyme involved in the conversion of testosterone to estrogens, was found in 17 α -estradiol-incubated female hair follicles [8]. It has been suggested that under the influence of 17 α -estradiol, an increased conversion of testosterone to 17 β -estradiol and of androstenedione to estrone takes place, diminishing the amount of testosterone available to be converted to DHT [7, 8].

Our results suggest that topical estrogen therapy was significantly more effective than placebo in AGA of menopausal females, as far as the improvement of the anagen to telogen ratio and reduction of the hair shed are concerned. Furthermore, a 3-month course of estradiol valerate 0.03% did not differ significantly in efficacy from a 6-month course. However, a study to evaluate to what extent the duration of treatment affects the duration of its beneficial effect and the recurrence rate is warranted. AGA is a continuing process and all available treatments only halt the progress of hair thinning. As a result, repeated courses of therapy are necessary. In this context, 3-month courses of topical estrogen therapy would be safer and more cost effective than 6-month courses. Despite previous experience, the topical application of estrogens for the treatment of AGA is not devoid of side effects that are most probably associated with systemic penetration. Side effects may be more prominent in females with menopause of recent onset and they are probably dose dependent, mostly depending on the duration of the treatment. They may also depend on the estrogen form used. On the basis of evidence for systemic penetration, the possible association of topical estrogen application with breast cancer development should be kept in mind. Therefore, careful selection of patients to be treated and limitation of the treatment period to the shortest possible is strongly recommended. In our opinion, a 12-week treatment achieves considerable therapeutic value with minimal side effects.

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