Letter to the Editor

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Ciclosporin A Initiates Active Hair Growth in Mice

A.	Atsumichi	Urabe
J.	Jean	Kanitakis
J.	Jean	Thivolet

Clinique Dermatologique, INSERM U-209, Hôpital Ed.-Herriot, Lyon, France

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Atsumichi Urabe, INSERM U-209, Clinique Dermatologique, Hôpital Ed.-Herriot, F-69437 Lyon Cedex 03 (France)

Dear Sir,

Hypertrichosis observed in ciclosporin A (CsA)-treated patients has been known to be a major side effect of this drug. Recent reports showed that unequivocal hypertrichosis occurring on the face and body is observed in about 80% of 67 bone marrow-transplanted patients [1] and 94.6% of 56 insulin-dependent diabetics [2]. Furthermore, recent clinical trials for the treatment of alopecia areata with CsA were reported to be partly successful [3–9]. However, the mechanism of hair growth after treatment with CsA is still unknown. Hormone studies in patients did not reveal substantial changes [5]. In this study we histologically investigated the effects of CsA on the hair growth of Balb/c mice (whose hair is in the spontaneous resting phase) and observed that CsA activates the resting phase of hair (telogen hair) and induces the shift to anagen hair. The study was carried out in summer. Eight-week-old Balb/c male mice weighing approximately 20 g were fed tap water and food ad libitum. No particular precautions were taken in the animal house during this study. Using a micropipeter 4 randomly chosen mice were given orally a daily dosage of

50 mg/kg CsA (Sandoz Inc., Basel, Switzerland) diluted in olive oil on 10 consecutive days. Mice of the control group were given an equivalent volume of olive oil. Before treatment and at the end of the study a skin biopsy was taken from the right and left dorsal region, respectively, and processed for routine histological examination. No pre-treatment for the initiation of hair growth (i.e. hair plucking) was done. The number of anagen hairs was counted under a light microscope and the results were expressed as the number of anagen hairs per unit length of epidermal surface of each section; the latter was measured with a semiautomatic image analyzer (Kontron, Videoplan, Munich, FRG). On macroscopical inspection there was no difference in the appearance between CsA-treated and control mice. Histologically, all skin sections obtained before CsA and olive oil administration revealed only telogen (resting) hair follicles consisting of club hairs, small germ area and a dermal papilla (fig. 1a). No anagen (active) hair was detected in any of the biopsies. After administration of CsA, variable stages (anagen II-IV) of anagen hair with increased area of

Fig. 1. Histological findings of Balb/c mouse skin, a Before examination. $\times 100$. b After CsA administration for 10 days (skin taken from the same mouse as in a). $\times 100$. Before treatment, all hair follicles are in the telogen phase. Numerous anagen hairs are observed after CsA administration.

Table 1. Number of anagen hair/cm length of epidermal surface

hair germ enveloping the dermal papilla were observed in the dermis and subcutaneous tissue (fig. 1b). The number of anagen hairs observed was different according to the animal studied (table 1). In control mice, all hair follicles were still in the telogen phase.

In contrast with what occurs in guinea pig and man, the hairs of small mammalian species are replaced not simultaneously but in a patterned sequence [10]. In the male albino rat, hair growth of the first wave, forming the second coat (G2 anagen hair), begins at about 5 weeks of age and is completed at 8 weeks. For the third coat (G3 anagen hair), resting follicles first become active in a limited ventral area at 8.5 weeks of age, and this follicular activation gradually spreads over the whole skin in a wave-like manner during 12–14 weeks [11]. Using this spontaneous hair cycle, Johnson [12] demonstrated that ultraviolet light initiates an active hair growth in telogen skin, and Silver et al. [13] carried out comparative studies of mitotic activity in plucking-induced and spontaneous anagen hairs. The results of our study show that a short treatment (10 days) with CsA activates resting hair follicles and induces anagen hairs. Indeed, histologically it was observed that the hair cycle of non-treated Balb/c mice is in the spontaneous telogen phase, while after treatment a dramatic

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increase in the number of anagen hair occurred. The variation in the number of CsA-induced anagen follicles observed in treated mice may depend on the difference of the drug absorption from the gastrointestinal tract or the variable sensitivity of their hair follicles to CsA.

The efficacy of CsA on patients with alopecia areata is known [3–8]. A recent study demonstrated that the number of hairs observed in the skin of CsA-treated alopecia patients was significantly higher than that in untreated skin, under the condition of grafting onto nude mice [14]. Histologically, telogen hairs are present in the lesional skin of alopecia patients [15].

Therefore, this strongly suggests that CsA activates the resting hair follicles and induces the anagen hair growth in the lesional skin of alopecic patients. Furthermore, the mechanism of hypertrichosis observed in nonalopecia patients treated with CsA is also strongly suggested to be the same with that observed in our studies; i.e. hair follicles sensitive to CsA are activated and remain in the anagen phase during treatment. After discontinuation of CsA therapy, their normal (pretreatment) hair cycling pattern may be reestablished. Wysocki and Daley [2] reported that the hair grown in excess in patients is lost soon after the cessation of CsA therapy.

References

- Harper JI, Kendra JR, Desai S, et al: Dermatological aspects of the use of cyclosporin A for prophylaxis of graft-versus-host disease. *Br J Dermatol* 1984;110:469–474.
- Wysocki GP, Daley TD: Hypertrichosis in patients receiving cyclosporine therapy. *Clin Exp Dermatol* 1987;12:191–196.

- de Prost Y, Teillac D, Paquez F, et al: Placebo-controlled trial of topical cyclosporin in severe alopecia areata. *Lancet* 1986;ii:803–804.
- Thomson AW, Aldridge RD, Sewell HF: Topical cyclosporin in alopecia areata and nickel contact dermatitis. *Lancet* 1986;ii:971–972.
- Gebhart W, Schmidt JB, Schemper M, et al: Cy-closporin-A-induced hair growth in human renal allograft recipients and alopecia areata. *Arch Dermatol Res* 1986;278:238–240.
- Parodi A, Rebora A: Topical cyclosporine in alopecia areata. *Arch Dermatol* 1987;123:165–166.
- Picascia DD, Roenigk HH Jr: Effects of oral and topical cyclosporine in male pattern alopecia. *Transplant Proc* 1988;20(suppl 4): 109–111.
- Gupta AK, Ellis CN, Tellner DC, et al: Cyclosporine A in the treatment of severe alopecia areata. *Transplant Proc* 1988;20(suppl 4): 105–108.
- Mauduit G, Lenvers P, Barthélémy H, et al: Traitement des pelades sévères par applications locales de cyclosporine A. *Ann Dermatol Vénéréol* 1987;114:507–510.
- Ebling FJ, Hale PA: Hormones and hair growth; in Goldsmith LA (ed): *Biochemistry and Physiology of the Skin*. New York, Oxford University Press, 1983, pp 522–552.
- Johnson E: Quantitative studies of hair growth in the albino rat. 1. Normal males and females. *J Endocrin* 1958;16:337–350.
- Johnson BE: Potentiation of hair growth by ultraviolet light. *Nature* 1960;187:159–160.
- Silver AF, Chase HB, Arenault CT: Early anagen initiated by plucking compared with early spontaneous anagen; in Montagna W, Dobson RL (eds): *Hair Growth: Advances in Biology of Skin*. Oxford, Pergamon Press, 1967, vol 9, pp 265–286.
- Gilhar A, Krueger GG: Hair growth in scalp grafts from patients with alopecia areata and alopecia universalis grafted onto nude mice. *Arch Dermatol* 1987;123:44–50.
- Lever WF, Schaumburg-Lever G: *Histopathology of the Skin*. Philadelphia, Lippincott Company, 1983, pp 202–203.