Evaluation of Oral Minoxidil in the Treatment of Alopecia Areata

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• **A dose-response effect has previously been demonstrated in topical minoxidil treatment of alopecia areata. Limitations in minoxidil solubility and percutaneous absorption have impaired the development of more effective topical therapy. Oral minoxidil (5 mg every 12 hours), a dose demonstrated to be relatively well tolerated if a 2-g sodium diet is strictly followed, was given to 65 patients with severe, treatment-resistant alopecia areata in an attempt to bypass the limitations of topical treatment and increase efficacy. Although hair regrowth progressed more rapidly and was more extensive with oral than topical 5% minoxidil, cosmetic response was seen only in 18% of the patients. Neither serum nor tissue levels of minoxidil correlated with response. These findings suggest that improved preparations of topical minoxidil, when used as a single therapeutic agent, are unlikely to be cosmetically effective in the majority of patients with severe alopecia areata.**

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Topical minoxidil has been shown to elicit hair regrowth in alopecia areata (AA).[1-3] The data suggest a dose-response effect for topical minoxidil (1% vs 5%) treatment of AA.[2] Despite these encouraging results, cosmetic regrowth was ultimately achieved only in six (13%) of 47 patients with severe AA who were treated with topical 5% minoxidil.[3] Patients who achieved cosmetically acceptable regrowth showed a steady increase in hair growth at each visit. The majority of patients discontinued 5% minoxidil at the termination of the protocol because of lack of significant progress in the preceding three to six months.[3]

Thus far, 5% is the approximate maximum concentration of minoxidil that can be formulated for topical use. The possibility that higher tissue levels and greater efficacy might be achieved with oral minoxidil remains to be examined. We report in this study our results of oral minoxidil treatment of severe AA.

PATIENTS AND METHODS

After giving signed, informed consent, 65 patients were entered into a study to determine safety and efficacy of low-dose (5 mg every 12 hours) oral minoxidil in the treatment of severe AA. Patients included were 27 men and 38 women, ranging in age from 13 to 55 years (mean, 31 years). The mean duration of the current episode of hair loss was 5.9 years (range, one to 26 years). Extent of scalp hair loss at baseline was 75% to 100% in 44 (68%) patients, 25% to 74% in 19 (29%), and 0% to 24% in two (3%).

Before enrollment in the study, patients were evaluated by history, physical examination, and electrocardiogram to exclude those with hypertension, cardiovascular disease, or severe systemic illness. Any patient who was judged to be noncompliant was also excluded. Patients were seen at baseline, one month, and every three months thereafter.

Table 1.—Comparison of Response to Minoxidil* (Topical 5%† vs Oral‡)

Hair Loss, %	Begin Topical, No. (%)	End Topical-Begin Oral, No. (%)	Oral, No. (%)
0 to 24	0 · · ·	1 (3)	11 (32)
25 to 74	7 (21)	10 (29)	7 (21)
75 to 99	12 (35)	16 (47)	11 (32)
100	15 (44)	7 (21)	5 (15)

*Thirty-four patients treated in both studies.

†Topical 5% minoxidil applied every 12 hours for 12 to 15 months.

‡Oral minoxidil, 5 mg every 12 hours for six months.

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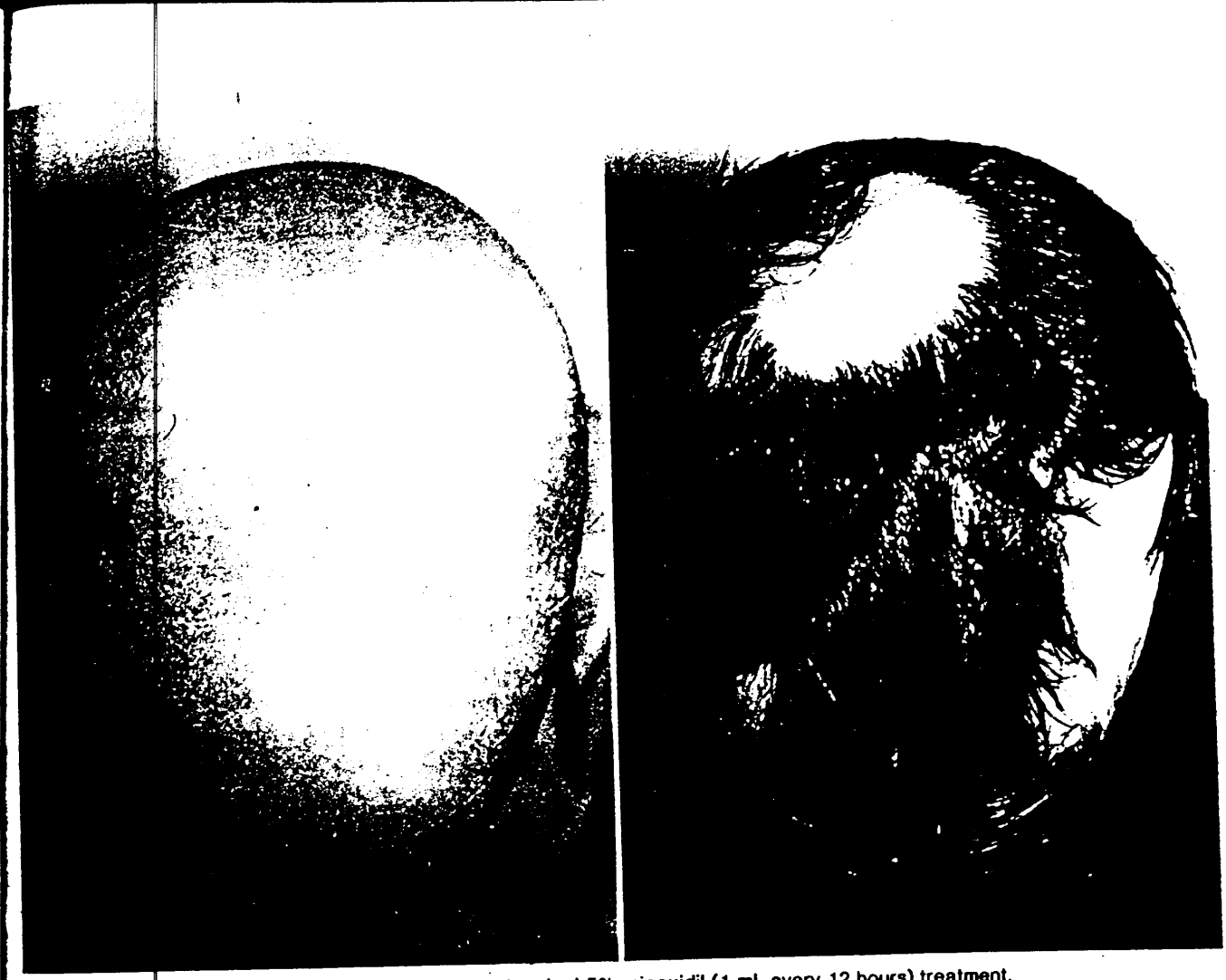

Left, Patient after 15 months of topical 5% minoxidil (1 mL every 12 hours) treatment. Right, Same patient after four months of oral minoxidil (5 mg every 12 hours) treatment.

At each visit, pulse, blood pressure, and weight were monitored; cardiac auscultation was performed; evidence of edema, headaches, depression, or lethargy was sought. Laboratory studies obtained at each visit included a complete blood cell count, serum electrolyte values, liver enzyme levels, serum creatinine concentration, and gross and microscopic urinalysis. Electrocardiograms were obtained at baseline and every six months. Echocardiograms were obtained at baseline, six months, and 12 months, and thereafter only as indicated by physical examination or electrocardiographic changes. Scalp biopsies were performed at baseline and at six months. Serum minoxidil levels were monitored at each visit for the first 12 to 18 months of treatment. Minoxidil assays of serum and scalp biopsy tissue were performed as previously described.[4]

Photographic documentation was obtained at each visit. Cosmetic response was defined as sufficient terminal hair regrowth such that the patient no longer needed a wig or cap to conceal any residual alopecia. Fair response was defined as extensive, but not cosmetic, regrowth. Slight response was defined as sparse terminal hair regrowth. Nonresponse was defined as vellus or no regrowth.

Strict adherence to a 2-g sodium diet was required for the duration of treatment. Minoxidil, 5 mg every 12 hours, was prescribed. This dosage was chosen, in part, because higher doses are not uniformly well tolerated. The mean duration of treatment was 53 weeks (range, 20 to 115 weeks).

Table 2.—Serum and Tissue Levels of Minoxidil*

Hours After Dose	Serum Level† (No. of Determinations)	Tissue Level‡ (No. of Determinations)
1	64.0 (6)	...
2	43.5 (47)	98.1 (6)
3	29.5 (63)	137.9 (7)
4	14.8 (43)	14.4 (3)
5	15.2 (25)	60.0 (1)
6	4.5 (1)	...
7	...	...
8	0.7 (1)	...
9	2.8 (3)	...
10	0.0 (2)	5.0 (1)
11	0.6 (2)	...
12	1.3 (6)	117.5 (1)

*Minoxidil dose, 5 mg administered orally every 12 hours.
†Mean values, nanograms per milliliter.
‡Mean values (nanograms per gram) obtained from scalp biopsy tissues after six months of chronic treatment.

Thirty-four patients were treated in a previous study with topical 5% minoxidil. They had experienced either no response to treatment or no additional response in the

preceding three to six months. These patients were subsequently enrolled in the present study with oral minoxidil.

RESULTS

Response to oral minoxidil was seen in 52 (80%) of the 65 patients, in 21 (100%) of 21 patients with baseline scalp hair loss less than 75%, and in 31 (70%) of 44 patients with baseline scalp hair loss greater than or equal to 75%. Cosmetic response was seen in 12 (18%) of the 65 patients, in eight (38%) of 21 patients with less than 75% scalp hair loss, and in four (9%) of 44 patients with greater than or equal to 75% scalp hair loss. Cosmetic regrowth was maintained during treatment in all 12 patients, although minor episodes of hair loss occurred in some.

Mean time to response, when present, was 9.3 weeks (range, four to 32 weeks). Mean time to cosmetic response was 34.8 weeks (range, 12 to 61 weeks). Duration of the current episode of hair loss for responders ranged from one to 23 years (mean, 5.5 years); for cosmetic responders it ranged from one to 17 years (mean, 5.8 years); and for nonresponders it ranged from one to 26 years (mean, 7.5 years). Duration of the current episode did not correlate with response.

Data for the 34 patients treated sequentially with topical 5% minoxidil followed by oral minoxidil are found in Table 1. Hair regrowth with oral minoxidil was more rapid and more extensive than it was with topical 5% minoxidil (Figure).

Maximum serum levels of minoxidil were found at one hour after the oral dose. Serum levels were in the negligible range after six hours (Table 2). Maximum tissue levels of minoxidil apparently occur at about three hours (Table 2). Serum and tissue levels showed no correlation with each other or with response to treatment. The mean tissue level for fair and cosmetic responders was 88.01 ng/g of tissue vs 99.90 ng/g of tissue for slight and nonresponders.

Side effects of oral minoxidil were sodium and fluid retention when the 2-g sodium diet was not strictly adhered to; occasional episodes of headaches, depression, or lethargy in women; occasional episodes of palpitations or tachycardia after ingestion of caffeine, alcohol, or decongestants; and facial hypertrichosis in 11 (17%) of the 65 patients.

Thirty-three patients discontinued taking oral minoxidil, 19 because of lack of efficacy and 14 for personal reasons. Seven of these patients reported onset of hair loss within two to eight weeks after discontinuation of treatment.

COMMENT

Oral minoxidil and topical 5% minoxidil produ similar percentages of responders.[3] The mean tim regrowth was similar in both studies.[2] Comparison the 34 patients who were treated in both studi shows, however, that hair regrowth progressed mo rapidly and was more extensive with oral than wi topical 5% minoxidil. Cosmetic response w enhanced with oral minoxidil (12/65 [18%]) vs to cal 5% minoxidil (6/47 [13%]).[3] The mean time to cosmetic response was also shortened with oral (3 weeks [range, 12 to 61 weeks]) vs topical 5% mino idil (62 weeks [range, 16 to 158 weeks]).[3] As previous studies with topical 1% and 5% minoxidil the duration of the current episode of hair loss d not correlate with the response or cosmetic respon to oral minoxidil.

Peak serum levels were markedly higher with or vs topical minoxidil treatment.[1,2] Serum levels aft chronic application of topical 5% minoxidil we found to be low (mean, 2.1 ng/mL)[2] and relative constant over 24 hours following application.[3] Aft an oral dose of minoxidil (5 mg), a peak mean seru level of 64 ng/mL was obtained at one hour; after s hours, serum levels were low. Serum levels followin treatment with oral minoxidil did not correlate wi tissue levels or with response. The serum leve obtained in this study seem to correlate with sid effects noted. In this study, no side effects we serious enough to require discontinuation of mino idil.

Topical minoxidil slowly penetrates whole skin the stratum corneum represents over 99% of th total barrier to minoxidil diffusion.[4] Oral minoxidi at a dose demonstrated to be relatively well tole ated, was used in an attempt to bypass the barrier t percutaneous absorption and the limitations o minoxidil solubility. Although efficacy was en hanced, only 18% of the patients achieved a cosme ically meaningful response. Mean tissue levels o minoxidil were similar for fair and cosmeti responders vs slight and nonresponders. These dat suggest that even if topical minoxidil preparation are improved such that absorption and solubilit limitations are overcome, minoxidil as a single ther apeutic agent is expected to be cosmetically effectiv only in a minority of patients with severe AA.

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