

# Topical Minoxidil Therapy for Androgenetic Alopecia

## A 30-Month Study

Judith A. Koperski, MD; Elaine K. Orenberg, PhD; David I. Wilkinson, PhD

● **Seventy-two adult male patients were entered into a double-blind, placebo-controlled investigation using 2% to 3% topical minoxidil solution for androgenetic alopecia. Fifty-nine patients completed the initial 12 months, and continued to use 3% topical minoxidil solution in an open study design. Hair regrowth (as measured by hair counts and bald-area diameters) was noted in all treatment groups at four months, and appeared to peak at approximately 12 months. At 30 months, mean hair counts had decreased from the 12-month level, but remained elevated over baseline counts, while mean bald-area diameters returned to baseline. However, 70% of the patients who did continue to use the drug for 30 months had 50% or more hairs than when they originally started the drug therapy. A subset of patients appeared to sustain a continued increase in hair counts after 12 months. No systemic side effects were noted.**

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**M**inoxidil (Loniten; Upjohn Co, Kalamazoo, Mich) is a potent peripheral vasodilator that has been used since the mid 1970s for treatment of refractory hypertension.<sup>1</sup> It acts preferentially on the arterioles to decrease peripheral resistance through mechanisms that are not entirely understood.<sup>2</sup> Systemic minoxidil therapy has been noted to cause hypertrichosis in nearly all patients treated for more than four weeks.<sup>2,3</sup> In 1980, Zappacosta<sup>4</sup> reported reversal of androgenetic alopecia in a patient receiving systemic minoxidil therapy for hypertension. Subsequent investigations using topical preparations of minoxidil for androgenetic alope-

cia have demonstrated statistically significant hair regrowth in selected patients.<sup>5,6</sup> Although several investigators have demonstrated a measurable short-term increase in the number of scalp hairs, no studies published to date have included data on patients using topical minoxidil therapy for greater than one year. The current study was designed to assess the long-term efficacy (objective and subjective) and safety of topical minoxidil when used for androgenetic alopecia.

### PATIENTS AND METHODS

#### Patient Selection

After informed consent was obtained, 72 adult male patients with androgenetic alopecia were entered into this study. Patients with hair loss patterns classified as III vertex, IV, V, Va, and VI according to the modified Hamilton scale<sup>7</sup> were selected. Patients with any scalp disease, hypertension, or history of significant cardiac, hepatic, renal, or endocrine disease were excluded, as were subjects taking antihypertensive medication. All patients were in good health, as documented by medical history, physical examination, and laboratory evaluation.

#### Laboratory Evaluation

Laboratory examinations were performed initially, and at four, 12, 18, 24, and 30 months. Studies included complete blood cell count, serum chemistry analyses, thyroid function tests, urinalysis, chest roentgenogram, and electrocardiogram. M-mode echocardiograms and serum minoxidil levels were obtained at four and 12 months.

Patients returned for clinic visits monthly for 12 months and subsequently at three-month intervals. At each visit, sitting blood pressure and pulse were recorded. Weight was recorded and ankles were examined for edema. Cardiac and pulmonary auscultation was performed and interval medical history taken.

#### Treatment Protocol

Each patient was initially assigned in a double-blind, randomized manner to one of three treatment groups. One

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From the Department of Dermatology, Stanford (Calif) University School of Medicine. Dr Koperski is now with Scripps Clinic and Research Foundation, La Jolla, Calif.

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group received placebo solution for four months followed by 3% minoxidil solution for the remainder of the study. Another group received 2% minoxidil solution for 12 months followed by 3% minoxidil solution. The final group received 3% topical minoxidil solution for the duration of the study.

The original 12-month portion of this study was designed as part of a multi-center study and utilized a placebo cross-over point at four months so that all patients were using minoxidil solution after the four-month point. The blind portion of the study ended at 12 months, and all patients then applied 3% minoxidil solution in an open study design.

Each patient applied 1 mL of the test medication twice daily to the balding vertex of the scalp, and the medication was allowed to dry. The placebo solution was equivalent to the vehicle base of the prepared minoxidil solutions, and was composed of 10% propylene glycol, 20% water, and 70% ethyl alcohol. Minoxidil and placebo solution were supplied in 60 mL bottles with droppers marked at 1 mL.

### Evaluation of Hair Growth

Before beginning treatment, the diameter of each patient's bald or thin area of the scalp vertex was recorded. This was obtained by measuring the bald spot in the plane that connected the midpoints of the ears. The edge of the bald spot was defined as the point at which there was a discernible visual change in hair density. Subsequent diameters were recorded at 12, 21, and 30 months.

Photographs of each patient's bald or thin area were obtained initially, monthly for the first 12 months, then at three-month intervals.

Hair counts were obtained in a 2.5-cm diameter area of the scalp vertex initially and at four, 12, and 30 months. The circle was traced on the patient's scalp using a plastic template and skin marking pen. This area was carefully measured to be in the same location each time a count was performed by repeated measurements using the tops of the ears and base of the nose as landmarks. Hairs were initially classified as vellus, indeterminate, and terminal, but the total hair counts were found to be more reliable and are used in this analysis. Hair counts performed after 12 months, while presented as total hair counts, essentially represent the total number of nonvellus hairs (indeterminate plus terminal), since few vellus hairs were present (ten hairs). All hair counts and diameter measurements were performed by the same experienced individual throughout the course of the study.

In an attempt to define the patients' opinions and self-perceived response to treatment, a questionnaire was designed. This was answered by all 33 patients who completed the entire 30 months of the study.

### Statistical Analysis

A two-tailed, unpaired Student's *t* test was used to compare differences in hair counts and diameters of bald areas between treatment groups and at various time intervals. A paired *t* test statistic was calculated for paired observations from one time point to another in subjects completing the entire 30-month study. A natural logarithmic transformation of the hair counts was done prior to calculating the *t* test statistics.

### RESULTS

Of the 72 patients enrolled, 59 patients (82%) completed 12 months and 33 patients (46%) completed the entire 30 months of study. At the 12-

month point patients were given the option to continue in the study. Some discontinued because of difficulty in keeping appointments, relocation, or dissatisfaction with cosmetic results. Fifty-five percent of those continuing and 32% of those who dropped out had greater than a twofold increase in hair counts. This suggests that increase in hair counts is a measure of an acceptable cosmetic effect. No patients left the study due to side effects. The initial, randomized treatment groups were evenly divided, with 24 patients in each group. There was no significant difference between groups in terms of age or duration of baldness of participants.

### Safety Evaluation

Analysis of laboratory data revealed no evidence of systemic side effects. Minoxidil blood levels ranged from 0 to 2.5 mg/dL. One patient using 2% minoxidil solution developed a transient scalp dermatitis following extensive sun exposure. This resolved spontaneously in several days and did not recur when the medication was resumed. One patient using 3% minoxidil solution died from suicide. A retrospective analysis of this patient's data revealed no evidence of medical problems prior to his death.

### Bald-Area Diameter Analysis

As shown in Table 1, the mean ( $\pm$ SEM) initial bald-area diameter was  $9.2 \pm 0.32$  cm. There were no significant differences in balding diameters among treatment groups at the beginning of the study. At 12 months, when all patients had been on topical minoxidil therapy for at least eight months (ie, eight months after the four-month cross-over point), a decrease in mean diameter was noted, but was not significant. At 21 months, when all patients had been using minoxidil at least 17 months, bald-area diameters decreased significantly ( $P < .05$ ). Surprisingly, this trend reversed itself by 30 months, resulting in a significant increase ( $P < .01$ ) in mean diameter to  $10.0 \pm 0.44$  cm, which was not significantly different from the initial diameter. No differences between groups were consistently present.

If we select out the group of patients who completed the entire 30 months of this study and whose diameter measurements were taken at each time point (Table 2), analysis by paired Student's *t* test reveals a significant decrease in bald-spot diameter at 12 months and a further decrease in size at 21 months. At 30 months, however, there was an increase in mean diameter ( $P < .001$ ) to  $9.78 \pm 0.40$  cm, which was not significantly different from the initial diameter.

### Hair Count Analysis

As shown in Fig 1, there was no difference in hair counts among groups initially, with a mean baseline hair count of  $115.8 \pm 6.6$  (total, 72 patients). At the four-month placebo cross-over point, a significant increase (range,  $P < .01$  to  $P < .001$ ) in hair counts was seen in all groups. The mean value for all subjects ( $n = 68$ ) was  $170.0 \pm 9.7$ . Although the mag-

Table 1.—Diameter of Bald Area in Each Minoxidil Treatment Group\*

Time Elapsed, mo	Diameter, cm (No. of Patients)			
	2% Solution	3% Solution	Placebo, Then 3% Solution	Total
0	8.7 ± 0.54 (20)	9.4 ± 0.58 (20)	9.4 ± 0.54 (20)	9.2 ± 0.32 (62)
12	8.8 ± 0.60 (19)	8.3 ± 0.50 (20)	9.2 ± 0.66 (16)	8.7 ± 0.33 (55)
21	8.1 ± 0.55 (11)	7.2 ± 0.56 (13)	8.8 ± 0.75 (14)	8.0 ± 0.38†(38)
30	10.4 ± 1.05 (8)	10.7 ± 0.67 (9)	9.1 ± 0.59 (10)	10.0 ± 0.44‡(27)

\*Values expressed as mean ± SEM.

†Significantly different ( $P < .05$ ) from initial diameter.

‡Significantly different ( $P < .01$ ) from 21-month diameter.

nitude of the increase in mean hair count was slightly less in the group that had received only placebo up to that point, counts were significantly elevated ( $P < .01$ ). At 12 months, when all patients had been receiving minoxidil therapy for at least eight months, the hair count increases were significant in all treatment groups ( $P < .001$ ). No difference in responses was noted between the 2% and 3% groups. The mean value for all subjects was  $324.2 \pm 20.3$  ( $n = 59$ ). At 30 months, when all patients had been receiving minoxidil for at least 26 months, the hair counts in all groups decreased, but remained elevated over the initial counts by approximately twofold. The mean count for all subjects ( $n = 33$ ) was  $249.8 \pm 35.6$ , significantly less ( $P > .02$ ) than mean counts for all subjects at 12 months.

When we selected out the 33 patients who completed the entire 30 months of the study (Table 3), the same trends were evident, with significant increases observed in counts at four and 12 months ( $P < .001$ ), followed by a significant decrease at 30 months ( $P < .001$ ).

In an attempt to classify the responses over the study period, patients were divided into groups according to their hair count at 30 months. Each patient was grouped according to percent of change in hair count as compared with his initial hair count. Patients with an outcome of  $-50\%$  to  $+50\%$  change in hair count were grouped. A second group was composed of those patients who experienced a  $50\%$  to  $100\%$  increase in hair count by 30 months, and the final group included those patients who had at least a  $100\%$  increase in hair count by 30 months. Graphic representation reveals different patterns of response (Fig 2). The best responders ( $>100\%$  change at 30 months), representing one third of all subjects, showed the highest hair counts at 12 months and slightly higher counts at 30 months. This subgroup with sustained responses contained four men who had received 3% minoxidil solution, four who had received 2% minoxidil, and four who had received placebo at the beginning of the study. Another subgroup of one third had a 30-month hair count that was approximately 70% greater than baseline, while the remaining subjects had counts approximating baseline counts. The mean age of the sustained responders was 38.3 years (range, 30 to 45 years) with a mean duration of baldness of 13.9 years (range, 10 to 14 years). Neither age, duration of baldness, nor pattern

Table 2.—Diameter of Bald Area in Patients Completing 30-Month Minoxidil Study\*

Time Elapsed, mo	Diameter, cm	P†
0	9.70 ± 0.5	<.001
12	8.13 ± 0.4	<.05
21	7.67 ± 0.4	<.001
30	9.78 ± 0.4	

\*Values expressed as mean ± SEM.

†Paired  $t$  test;  $n = 26$ .

of baldness of these individuals differed from those parameters in the other two groups.

#### Photographic Analysis

Sequential photographs were taken but proved to have limited value in illustrating the range of responses experienced by our study group. In the case of patients showing good response, the photographs did not always reflect the changes in hair counts. Sometimes it was felt that this was due to changes in patients' hair style or light hair color. On the whole, we felt the cosmetic improvements were not sufficiently dramatic in most patients to be recorded by photograph.

#### Questionnaire Analysis

When asked their opinion of hair growth at 30 months, 32 (96.9%) of the 33 patients felt that they had at least a little more hair than at the beginning of the study. When asked to categorize the effectiveness of minoxidil treatment in growing new hairs, most patients felt they had experienced minimal to moderate new hair growth (Table 4). Interestingly, most patients felt that they had more hair at 12 months than at 30 months, which parallels our hair count and diameter results.

Similarly, when asked to describe their rate of hair growth since beginning minoxidil therapy, most patients felt that they were still growing new hairs, but 45.2% thought that the rate of new hair growth had decreased since the initial response.

Forty-two percent of patients thought that their new hairs were somewhat different from other scalp hairs, especially noting that the new hairs appeared thinner or finer when compared with other scalp hairs.

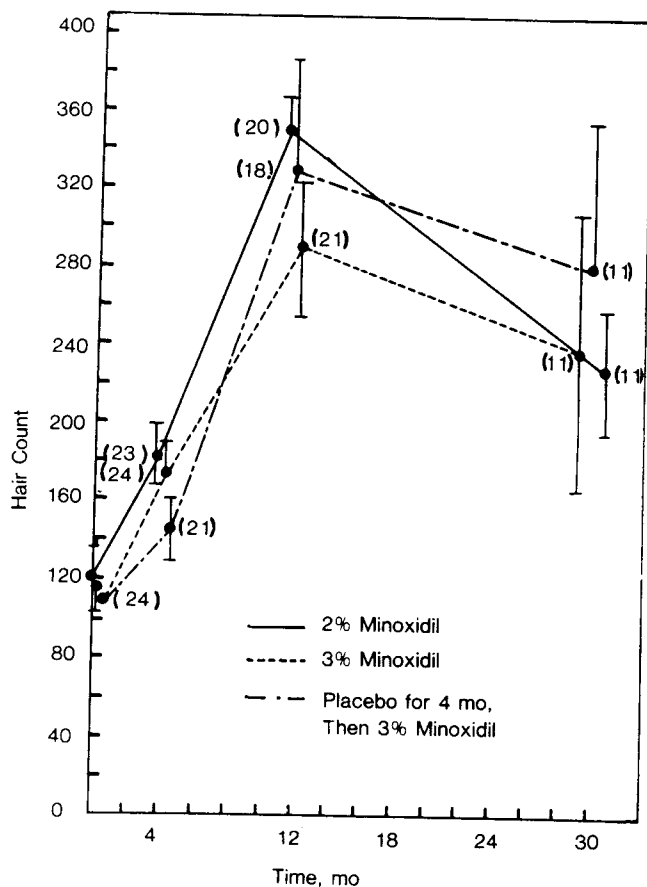


Fig 1.—Total hair counts (mean  $\pm$  SEM) in a 2.5-cm area of scalp vertex relative to each minoxidil treatment group. Number of subjects is shown in parentheses. All treatment group hair counts at four months are elevated significantly ( $P < .05$ ) above baseline, and 12-month counts are elevated significantly ( $P < .05$ ) above four-month counts. Thirty-month counts in group receiving 2% minoxidil solution decreased ( $P < .05$ ) in comparison with 12-month counts.

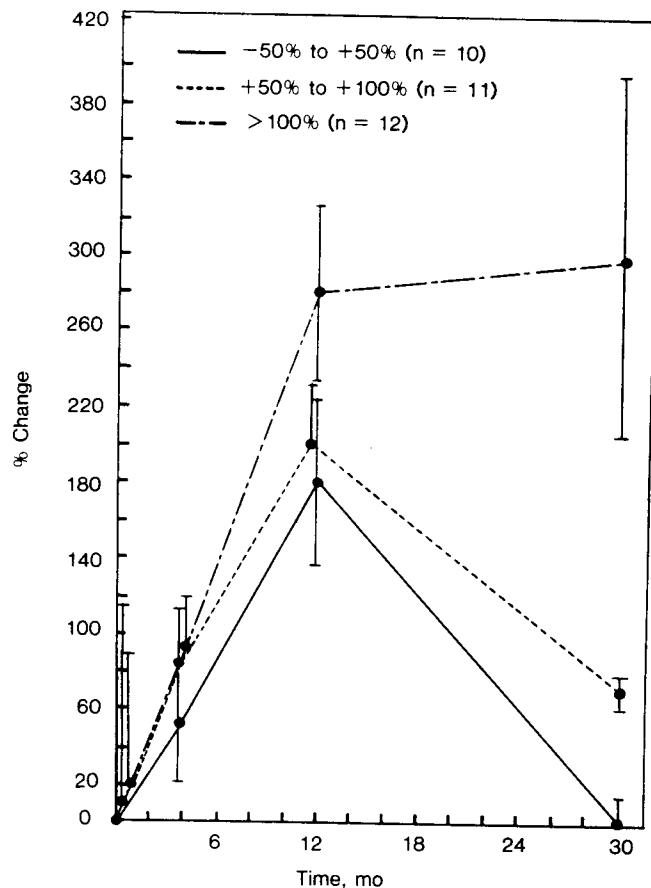


Fig 2.—Percent change (mean  $\pm$  SEM) of total hair count over 30-month study period.

Table 3.—Total Hair Counts in Target Bald Area in Patients Completing 30-Month Minoxidil Study

Time Elapsed, mo	Hair Count, Mean $\pm$ SEM	P*
0	118.8 $\pm$ 8.9	<.001
4	188.5 $\pm$ 14.0	<.001
12	352.6 $\pm$ 25.6	<.05
30	249.8 $\pm$ 35.6	<.05

\*Paired *t* tests; n = 33.

Table 4.—Patient Evaluations of How Effective Minoxidil Therapy Was in Growing New Hair\*

Time Elapsed, mo	Very, %	Moderate, %	Minimal, %	None, %	Not Sure, %
4	9.4	28.1	37.5	15.6	9.4
12	9.4	43.8	37.5	0	9.4
30	3.1	37.5	46.9	6.2	6.2

\*Values expressed as percent of patients.

Some patients (43.3%) felt that their new scalp hairs grew more slowly than other scalp hairs, while 36.7% thought they grew at the same rate, and 6.7% thought the new hairs grew faster than other scalp hairs.

The perceived pattern of new hair growth within the bald area (eg, edges, center, or all over) was not consistent, since 30% of patients indicated the initial growth response occurred at the edges, 10% all over, and 6.7% in the center. Twenty percent of patients felt that their fine hairs just became thicker.

Some patients (33.3%) thought that some of their new hairs were falling out even while they continued to use minoxidil.

Many patients (87.1%) felt that their overall rate of hair loss had decreased since beginning minoxidil therapy, with 48.4% reporting less hair loss than initially, and 38.7% indicating that they thought they were no longer losing hair at the 30-month point.

Patients did not perceive any side effects except for the single case of scalp dermatitis following extensive sun exposure.

Self-rated compliance was excellent in this study, with 67% of patients applying the medication twice daily at least 90% of the time, and 90% of patients applying it twice daily at least 75% of the time.

## COMMENT

The use of 2% and 3% topical minoxidil solution in this patient group provided a significant increase in hair counts and significant decrease in bald-area diameter over the initial 12 months. These findings are consistent with those reported by others using similar treatment protocols.<sup>6,7,9-12</sup> Within the limitations of this study, there was no dose-dependence of the response between 2% and 3% solution.

One article has suggested that placebo treatment alone may lead to an increase in vellus hairs,<sup>9</sup> but this has not been confirmed.<sup>10,12</sup> At any rate, the relative proportion of vellus hairs is very low, especially on minoxidil-treated areas; Savin<sup>9</sup> found that numbers fall to ten to 20 per circle. We found ten or fewer vellus hairs per circle, and decided that the error in counting these low numbers was very large.

After four months, the increase in hair counts in the placebo group, although lower than the increases recorded for groups receiving 2% or 3% minoxidil solution, was not significantly different from the latter. Similar findings have been reported,<sup>10</sup> although some investigators found that nonvellus hair counts in placebo-treated areas remained near baseline.<sup>9</sup> After the cross-over, counts in the group formerly receiving placebo rapidly increased, and counts in all groups apparently reached plateau values at about 12 months.<sup>7,9-12</sup> Data from this and our own study suggest that a true placebo effect may exist, or that there is actual stimulation of hair growth by placebo ingredients. Distinction between these possibilities will require further studies.

The decrease in hair count at 30 months has not been previously reported, although Olsen et al<sup>11</sup> have shown that loss can occur between 12 and 31 months if treatment is reduced to a single daily application; hair counts are maintained (but not increased) by the normal regimen.<sup>11</sup> This suggests the development of tolerance to the medication, or the existence of a coordinated wave of hair growth initiated by the drug therapy and ending somewhere between 12 and 30 months after start of therapy. If hair counts had been taken on a monthly basis, it would have been possible to establish whether there was a gradual loss of hair between 12 and 30 months, or a precipitate loss at a certain time. Another unknown factor is the normal rate of hair loss in a controlled population of individuals not receiving minoxidil

therapy or vehicle. In Figs 1 and 2 we would expect the actual baseline at 30 months to be appreciably lower than at the start of the study. The increase in bald-area diameter at 30 months is associated with a concomitant fall in hair count.

Because of the possible significance of patient compliance to the understanding of our data, we evaluated questionnaire responses and conducted personal interviews. A lack of compliance was not a predisposing factor in the decrease in hair counts since, with the exception of one patient who used minoxidil only once daily after month 12, all patients continued to use the drug twice daily as prescribed for the duration of study.

The in-depth analysis of those patients who completed the entire 30-month study suggests that there is a subgroup of patients who may sustain their response to topical minoxidil therapy. Because this group comprised excellent responders at 12 months, it may be possible to predict at that time which patients would be more likely to have a continued hair growth response.

In summary, our results indicate that therapy with 2% and 3% topical minoxidil solutions stimulated some hair regrowth in all patients with androgenetic alopecia. The mean diameter of the bald area initially decreased. This was accompanied by an increase in hair count, which in our study had maximum values at 12 months but subsequently decreased with a concomitant increase in bald-area diameter. Expressed quantitatively, approximately 80% of patients experienced a 100% or more increase in number of scalp hairs at 12 months, but only 36% of patients maintained this level of hair increase at 30 months. Despite the fall in hair counts after 12 months, 70% of the patients remaining in the study had at least 50% more hairs at 30 months than at the start of the study. It is not known whether there may be a further cycle of hair growth with sustained use of the drug.

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