A randomized, placebo-controlled trial of 5% and 2% topical minoxidil solutions in the treatment of female pattern hair loss

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Background: Topical minoxidil solution 2% stimulates new hair growth and helps stop the loss of hair in men with androgenetic alopecia and women with female pattern hair loss. Results can be variable, and historic experience suggests that higher concentrations of topical minoxidil may enhance efficacy.

Objective: The purpose of this 48-week, double-blind, placebo-controlled, randomized, multicenter trial was to compare the efficacy and safety of 5% topical minoxidil with 2% topical minoxidil and placebo in the treatment of female pattern hair loss.

Methods: A total of 381 women (18-49 years old) with female pattern hair loss applied 5% topical minoxidil solution (n = 153), 2% topical minoxidil solution (n = 154), or placebo (vehicle for 5% solution; n = 74) twice daily. Primary efficacy variables were change in nonvellus hair count at week 48, and patient and investigator assessments of change in hair growth/scalp coverage at week 48.

Results: After 48 weeks of therapy, 5% topical minoxidil was superior to placebo for each of the 3 primary efficacy measures. The 2% topical minoxidil group demonstrated superiority over placebo for hair count and investigator assessment of hair growth/scalp coverage at week 48; differences in patient assessment of hair growth at week 48 were not significantly different from placebo. The 5% topical minoxidil group demonstrated statistical superiority over the 2% topical minoxidil group in the patient assessment of treatment benefit at week 48. Both 5% and 2% topical minoxidil helped improve psychosocial perceptions of hair loss in women with female pattern hair loss. An increased occurrence of pruritus, local irritation, and hypertrichosis was observed with 5% topical minoxidil versus 2% topical minoxidil and placebo.

Conclusion: In this 48-week study of 381 women with female pattern hair loss, 5% topical minoxidil was superior to placebo on each of the 3 primary efficacy end points: promoting hair growth as measured by change in nonvellus hair count and patient/investigator assessments of hair growth and scalp coverage. Application of 2% topical minoxidil was superior to placebo for assessments of nonvellus hair counts and investigator assessment of hair growth/scalp coverage at week 48; differences in patient assessment of hair

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growth at week 48 were not significantly different from placebo. At week 48, the 5% topical minoxidil group demonstrated statistical superiority over the 2% topical minoxidil group in the patient assessment of treatment benefit. Both concentrations of topical minoxidil were well tolerated by the women in this trial without evidence of systemic adverse effects. With the introduction of numerous herbal remedies for hair loss, of which most have not been tested in randomized, double-blind, placebo-controlled trials, it is important to describe well-controlled trials that demonstrate the efficacy and safety of topical drugs. (J Am Acad Dermatol 2004;50:541-53.)

Female pattern hair loss is the most common type of hair loss, affecting approximately 50% of women older than 40 years.[1] Female pattern hair loss has also been referred to as androgenetic alopecia (AGA), but the former designation is now preferred for women.[2,3] Topical minoxidil solution was developed as a treatment for AGA after the discovery that minoxidil caused hypertrichosis when taken orally for the treatment of hypertension. Topical minoxidil solution 2% (over-the-counter Rogaine for men and women, Pfizer Inc, formerly Pharmacia Corp) has been shown to stimulate new hair growth and help prevent further hair loss in affected areas in both men and women.[4] Historic experience (including data from clinical trials, pharmacokinetic trials, postmarketing surveillance, and worldwide drug surveillance) suggests that applying higher concentrations of topical minoxidil may enhance its therapeutic efficacy without an increased safety risk.[5,6] A recently published randomized, controlled trial demonstrated that topical minoxidil solution 5% was well tolerated, but more effective than the 2% formulation in men with AGA.[7] Thus, a clinical trial was conducted in women with female pattern hair loss to compare the efficacy and safety of 5% topical minoxidil (over-the-counter Rogaine for men extra strength [Pfizer Inc, formerly Pharmacia Corp]) with 2% topical minoxidil and placebo (vehicle for 5% solution) in promoting hair growth, which was determined by a hair count technique along with patient and investigator assessment of changes in hair growth/scalp coverage.

METHODS

Patient population

Women eligible for inclusion in the trial were 18 to 49 years old with naturally dark hair and female pattern hair loss characterized as gradual and conspicuous hair loss observed as diffuse thinning over the frontoparietal area of the scalp, with or without frontal hairline recession. They had to have a hair density rating of 4 to 7 on the basis of the Savin Female Density Scale,[8,9] with nonvellus hair present throughout the area of hair loss. The patient's hair loss was also categorized according to the Ludwig scale,[10] although this grading scale was not used as an inclusion criterion. Patients were in good general health with no evidence of systemic illnesses (eg, cardiac, psychiatric, or scalp disease). Women who were pregnant, at risk for pregnancy, less than 12 months postpartum, or breast feeding were excluded, as were patients known to be hypersensitive to minoxidil or who concomitantly used hair restorers or systemic drugs (steroids, cytotoxic agents, vasodilators, antihypertensives, anticonvulsant drugs, β-blockers, diuretics, or any of the following specific agents: spironolactone, cimetidine, diazoxide, cyclosporine, ketoconazole, or replacement hormonal therapy).

Study design

This was a 48-week, randomized, double-blind, placebo-controlled trial conducted at 9 investigative sites in the United States from May 1992 to 1993. The protocol and informed consent form were approved by institutional review boards, and written informed consent was obtained from each patient before enrollment in the trial. Randomization occurred in a 2:2:1 design: 5% topical minoxidil (n = 153); 2% topical minoxidil (n = 154); or placebo (vehicle for 5% solution, which contained more propylene glycol [50%] and less ethanol [30%] than the vehicle for the 2% solution (20% and 60%, respectively]) (n = 74). Patients applied 1 mL of assigned solution twice daily at approximately 12-hour intervals (total daily dose of 2 mL) for 48 weeks. The investigational medications were provided to each trial site in identically appearing, prepackaged, and prelabeled bottles, which were coded according to a predetermined, computerized randomization plan. Each trial site was provided with a unique list of randomization code numbers, and numbers were assigned sequentially in the order in which patients were enrolled. After the baseline visit (week 0), patients returned to the clinic for efficacy evaluation, safety evaluation, or both every 4 weeks through week 32, then every 8 weeks through the end of the 48-week trial.

Efficacy evaluation

The 3 primary efficacy parameters were change from baseline nonvellus hair count at 48 weeks,

patient assessment of hair growth/scalp coverage at 48 weeks, and investigator assessment of hair growth/scalp coverage at 48 weeks. Hair counts were obtained from computer-assisted scans of macrophotographs of clipped hair in a 1-cm^2 target evaluation site within an area of thinning in 1 of 4 quadrants of the frontoparietal/occipitoparietal scalp, permanently defined by 2 diagonally placed tattoos to ensure reproducibility. Macrophotographs, taken at baseline and weeks 8, 16, 32, and 48, were converted into dot maps, a process of attaching a clear acetate sheet overlaid onto the macrophotograph and marking all visible nonvellus (pigmented) hairs with a black dot. This was done by a trained technician, who was blinded as to patient, treatment, and time point. The same technician produced all dot maps for the trial. Dot maps were converted into hair counts by analyzing the acetate overlay using computer-based scanners and imaging software.[11] The resulting hair counts per square centimeter were used to calculate mean change from baseline.

Patient self-assessment and investigator assessment of hair growth/scalp coverage were conducted with hair growth questionnaires. Patients' responses at each visit were on the basis of their perception of their current hair loss condition. Aids used in this assessment were instant Polaroid (The Polaroid Corporation, Waltham, Mass) photographs of the patient's scalp (frontal and occipital views with center part) taken at baseline and each evaluation time point that patients could compare with current scalp hair growth through mirror viewing. The investigator assessments were on the basis of a visual examination of the patient's scalp without reference to any photographs and primarily focused on changes in scalp coverage and central part width. Secondary efficacy parameters included patient and investigator assessments of quality of life, global benefit, hair growth, and hair styling measures.

Safety evaluation

Safety monitoring was designed to detect potential local intolerance and systemic cardiovascular effects of topical minoxidil. Before starting treatment, patients underwent an extensive initial interview and physical examination including evaluation of the scalp for signs of dermatitis; measurement of blood pressure, pulse rate, and weight; auscultation of the chest; evaluation of extremities for signs of peripheral edema; electrocardiography; pregnancy testing; menstrual cycle characterization; examination for extraneous hair growth; hematology and blood chemistry assays; urinalysis; and serum samples for determination of minoxidil concentrations. These tests and procedures were repeated at periodic intervals during the trial.

Statistical analysis

Sample size was determined a priori with adequate power (0.80) to detect an arbitrarily defined difference of 9 hairs/cm^2 between treatment groups with regard to mean change in nonvellus hair counts. Planned enrollment was intended to be equally distributed among the 9 trial sites. One site was only able to enroll 6 patients; therefore, these patients were combined with the next smallest enrollment site for purposes of statistical analyses. Continuous variables were assessed using analysis of variance models. At baseline, comparisons of treatment means were done using the 1-way analysis of variance model with treatment group as the independent variable. After baseline, the 2-factor, fixed effect analysis of variance model was used, including effects of treatment group, investigator, and treatment-by-investigator interaction.

Treatment-by-investigator interaction represents the potential for any 1 or several participating investigative sites to produce confounding responses or effect modification when treatments are administered across many sites in a multicenter trial. In this study, appropriate analyses across the individual sites sought to determine if there was any evidence of treatment response bias because of data clustering, unanticipated, and, therefore, uncontrolled, confounding factors or response heterogeneity across sites. Interaction effects were considered significant if the P value was $\leq .1$. When the overall treatment comparison P value was $\leq .1$, pairwise comparison of treatment groups was done using Fisher's protected least significant difference procedures. For treatment effects, tests with P values of $< .05$ were considered statistically significant and tests with P values between .05 to .10 were considered marginally significant. Questionnaire variables from visual analog scales and ordinal categorical variables with 5 or more categories were treated as continuous variables and analyzed as such. The remaining categorical variables were analyzed by the chi-square test for homogeneity of proportions. Efficacy analyses were done on the evaluable patient population (ie, those patients who completed the 48-week treatment period without violating the study exclusion criteria). Safety analyses were done on all randomized patients who received at least 1 dose of study medication.

RESULTS

Baseline characteristics

A total of 381 patients were enrolled in this trial. Patient demographic and hair loss features at base-

Table I. Demographic and hair loss features at baseline

Variable	5% Minoxidil (N = 153)	2% Minoxidil (N = 154)	Placebo (N = 74)	Treatment *P* value
Hair density score (investigator)*				
No. (%) of patients:†				.391
4	58 (38.9)	70 (45.8)	29 (39.2)	
5	58 (38.9)	61 (39.9)	35 (47.3)	
6	28 (18.8)	21 (13.7)	9 (12.2)	
Mean (SD)	4.8 (0.7)	4.7 (0.7)	4.7 (0.7)	
Pattern of hair loss (Ludwig scale)[7]				
No. (%) of patients:				.670‡
Grade I (mild)	55 (35.9)	56 (36.4)	27 (36.5)	
Grade II (moderate)	92 (60.1)	96 (62.3)	44 (59.5)	
Grade III (severe)	6 (3.9)	2 (1.3)	3 (4.1)	
Nonvellus hair count at baseline§				.207
Mean (SD)	141.3 (47.0)	150.4 (46.1)	138.4 (44.9)	
No. of patients	101	108	51	

Because the majority of the patients were Caucasian, race categories were collapsed to form the dichotomy of Caucasion and non-Caucasion for analysis.

*Savin Female Density Scale.[5,6]

†Nine density scores were missing in the 5% topical minoxidil group (n = 144), 2 were missing in the 2% topical minoxidil group (n = 152), and 1 was missing in the placebo group (n = 73).

‡Chi-square analysis.

§Data are presented for the efficacy-evaluable population.

Table II. Disposition of patients

Disposition	Patients, No. (%)		
	5% Minoxidil (N = 153)	2% Minoxidil (N = 154)	Placebo (N = 74)
Evaluable patients at week 48	102	108	51
Completion of 48-week trial	101 (66)*	108 (70.1)	51 (68.9)
Did not complete trial	52 (34.0)	46 (29.9)	23 (31.1)
Reasons for not completing trial			
Patient request	14 (9.2)	13 (8.4)	8 (10.8)
Adverse events			
Nonserious	19 (12.4)	15 (9.7)	3 (4.1)
Serious	2 (1.3)	1 (0.6)	0 (0)
Lost to follow-up	10 (6.5)	9 (5.8)	7 (9.5)
Ineligible after medication started	1 (0.7)	2 (1.3)	3 (4.1)
Protocol noncompliance/violation	4 (2.6)	3 (1.9)	0 (0)
Other	2 (1.3)	3 (1.9)	0 (0)
Lack of efficacy	0 (0)	0 (0)	2 (2.7)

*One patient dropped out because of a nonserious adverse event at her last visit (week 48), but was included in the efficacy evaluable population. The number completing planned treatment reflects this dropout.

line were similar among the treatment groups (Table I). The average age of the population was 37 years, and 74% of the patients were Caucasian. Patients had hair loss for an average of 10 years (range: 0-35 years). On the basis of the Savin Female Density Scale,[8,9] the mean density score was 4.8, 4.7, and 4.7 in the 5% topical minoxidil, 2% topical minoxidil, and placebo groups, respectively. Most (97%) patients had hair loss patterns of grade I or II on the basis of the Ludwig classification.[10]

A total of 260 patients completed the entire 48-week trial, and 261 were included in the efficacy evaluable population (Table II, Fig 1). One patient in the 5% topical minoxidil group dropped out because of a nonserious adverse event at her last clinic visit (week 48), but was included in the efficacy evaluable population. All patients enrolled were included in the safety analyses (intent to treat). In all, 52 (34%) of the 153 patients in the 5% topical minoxidil group, 46 (30%) of the 154 patients in the 2% topical mi-

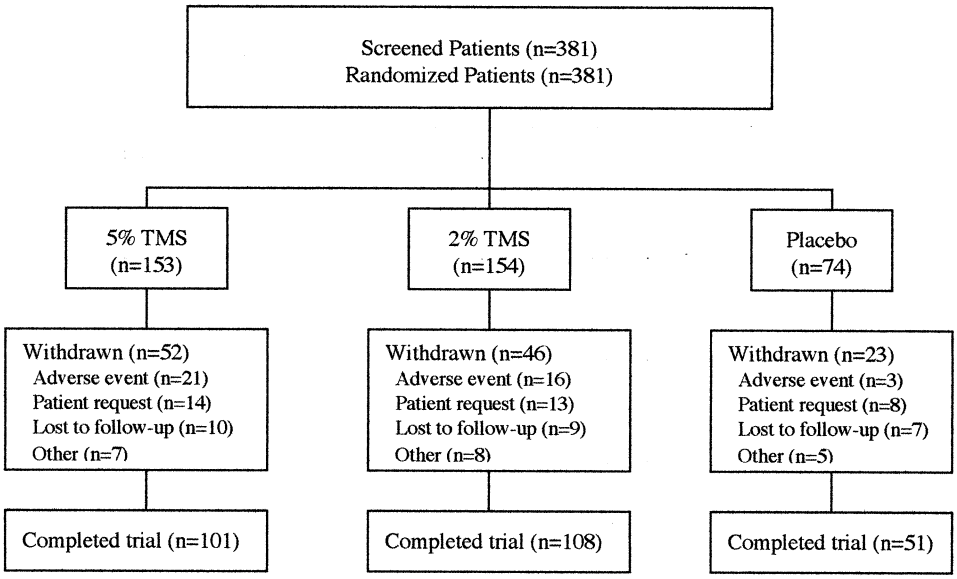

Fig 1. Profile of randomized controlled trial. *TMS*, Topical minoxidil solution.

noxidil group, and 23 (31%) of the 74 patients in the placebo group did not complete the trial. The most common reasons for discontinuation from the trial were patient request, nonserious adverse events, and becoming lost to follow-up (Table II).

Protocol deviations

The trial was conducted as planned with relatively few protocol deviations reported. Specific to efficacy end points, a total of 30 target area hair counts were missing for 19 patients during the 48-week trial period. Also, questionnaire information was unavailable in some instances because the patients missed a clinic visit or the patient or investigator skipped questions. Consequently, the number of patients in the evaluable population varies over time for the affected end points. A total of 21 patients used protocol-prohibited concomitant medications (mostly systemic corticosteroids of short duration with tapering doses) during the trial: 13 (8%) of the 153 patients in the 5% topical minoxidil group; 5 (3%) of the 154 patients in the 2% topical minoxidil group; and 3 (4%) of the 74 patients in the placebo group. None of these deviations was thought to have an impact on the trial results and conclusions.

Efficacy

Nonvellus hair count. Change from baseline nonvellus hair count at 48 weeks was a primary efficacy variable. The mean change from baseline in target area nonvellus hair counts at week 48 (Table III) showed that the 5% and 2% topical minoxidil groups were significantly superior to the placebo group. In addition, the mean change in target area nonvellus hair counts in the 5% and 2% topical minoxidil groups was significantly superior to the placebo group beginning at week 8 and continuing throughout the trial (Table IV, Fig 2).

No statistically significant difference was found between the 5% and 2% topical minoxidil groups for the mean change from baseline in target area nonvellus hair counts at week 48. A treatment-by-investigator interaction effect was found for this end point and 1 trial site was identified as the principal source for this interaction. At that site, 2 patients in the 5% topical minoxidil group had an inordinate loss of hair at week 48 (43 and 50 hairs, respectively). Reanalysis of the nonvellus hair count data excluding these 2 patients showed that the 5% topical minoxidil group was significantly superior to the 2% topical minoxidil and placebo groups at week 48 (Table III, Fig 3). The statistical significance tests for treatment effects reported in Table III, which included this site, represent a conservative estimate of the effects attributable to topical minoxidil solution.

Patient evaluation. Patient evaluation of hair growth/scalp coverage at week 48 was a primary efficacy variable. The 5% topical minoxidil group was significantly superior to the placebo group, but not to the 2% topical minoxidil group for change in hair growth/scalp coverage at week 48 (Table III). The change in scalp coverage for the 5% topical minoxidil group was significantly superior to the 2% topical minoxidil and placebo groups at weeks 16 and 32 ($P < .05$), although at the latter week there was a significant treatment-by-investigator interaction effect.

Table III. Summary of efficacy at week 48 (efficacy evaluable population)

Efficacy end points	Mean ± SD			Pairwise comparison *P* value*		
	5% Minoxidil	2% Minoxidil	Placebo	5% vs 2%	5% vs placebo	2% vs placebo
Primary						
Nonvellus hair count (mean change from baseline)	24.5 ± 21.9	20.7 ± 17.6	9.4 ± 14.6	.129	<.001	<.001
Nonvellus hair count (mean change from baseline) excluding outlier patients	26.0 ± 19.5	20.7 ± 17.6	9.4 ± 14.6	.031	<.001	<.001
Change in hair growth/scalp coverage (patient)*	68.1 ± 17.9	62.9 ± 16.7	58.3 ± 18.2	.062	<.001	.057
Change in hair growth/scalp coverage (investigator)	11.7 ± 17.2	10.3 ± 17.0	2.2 ± 17.9	.608	.001	.004
Secondary						
Benefit from treatment (patient)†	60.0 ± 27.6	50.5 ± 32.5	41.8 ± 29.9	.029‡	<.001‡	.092†
Benefit from treatment (investigator)†	42.0 ± 27.1	37.4 ± 30.1	30.2 ± 27.0	.331‡	.022‡	.124†
Treatment benefit S/E ratio (patient)§	1.13 ± 2.65	0.73 ± 0.56	0.56 ± 0.41	NA	NA	NA

NA, Not applicable; *S/E,* satisfaction/expectation.
Pairwise comparisons are displayed when the overall treatment *P* value was ≤.1.
*Based on a 100-mm visual analog scale (VAS) in which a score of 0 = much less scalp coverage, 50 = same scalp coverage, and 100 = much more scalp coverage.
†Based on a 100-mm VAS in which a score of 0 = no benefit, 50 = moderate benefit, and 100 = great benefit.
‡Interaction of treatment and investigator effects at *P* = .10.
§Calculated from patient perspectives before and after treatment. A score of 1 is an indication of equal expectation and satisfaction.

Table IV. Efficacy results at all evaluation time points (efficacy evaluable population)

End point/Time point	Mean (± SD) change from baseline			Treatment Comparison *P* value	Pairwise comparison *P* value		
	5% Minoxidil	2% Minoxidil	Placebo		5% vs 2%	5% vs Placebo	2% vs Placebo
Nonvellus hair count							
Week 8	21.7 ± 18.8	18.3 ± 19.0	11.1 ± 18.6	.010	.286	.002	.024
Week 16	36.0 ± 22.5	35.9 ± 21.7	20.0 ± 19.8	<.001	.936	<.001	<.001
Week 32	27.1 ± 23.1	26.7 ± 20.3	15.2 ± 16.8	.004	.928	.002	.002
Week 48	24.5 ± 21.9	20.7 ± 17.6	9.4 ± 14.6	<.001	.129	<.001	<.001
Scalp coverage (investigator rating)*							
Week 16	4.0 ± 16.8	4.1 ± 14.6	−5.4 ± 18.8	.003	.937	.002	.001
Week 32	9.1 ± 20.1	7.7 ± 17.2	−0.4 ± 17.4	.007	.708	.003	.006
Week 48	11.7 ± 17.2	10.3 ± 17.0	2.2 ± 17.9	.004	.608	.001	.004
Center part width (investigator rating)†							
Week 16	5.8 ± 17.9	7.2 ± 14.7	0.2 ± 15.8	.066‡	.464‡	.092‡	.020‡
Week 32	11.2 ± 21.2	7.6 ± 16.1	0.9 ± 16.7	.003‡	.163‡	<.001‡	.020‡
Week 48	9.8 ± 18.3	10.3 ± 14.9	2.6 ± 17.1	.015	.834	.011	.006
Hair density (investigator rating)§‖							
Week 16	−0.4	−0.5	0.0	<.001	.743	.001	<.001
Week 32	−0.8	−0.6	−0.3	.002	.134	<.001	.016
Week 48	−0.8	−0.9	−0.4	.026	.961	.015	.012

*Calculated mean change from baseline based on a 100-mm visual analog scale (VAS) in which a score of 0 = no coverage, 50 = medium coverage, and 100 = complete coverage.
†Calculated mean change from baseline based on a 100-mm VAS in which a score of 0 = extremely wide, 50 = medium, and 100 = extremely narrow. Higher score indicates a more positive response.
‡Interaction of treatment and investigator effects at *P* ≤ .10.
§Calculated mean change from baseline based on the Savin Female Density Scale.[5,6] Lower score indicates a more positive response.
‖SD not calculated.

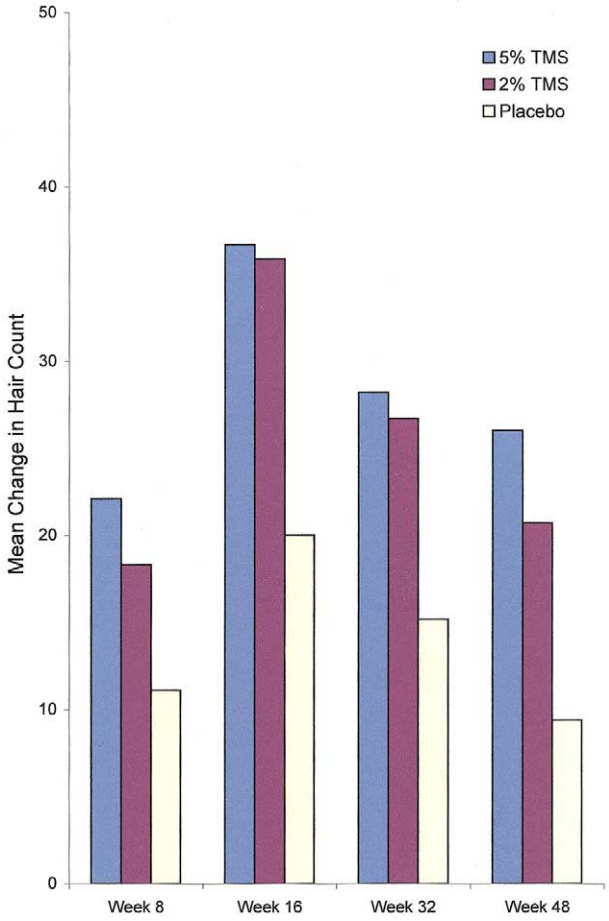

Fig 2. Change from baseline in nonvellus hair count. Both 5% and 2% topical minoxidil solution (*TMS*) groups were significantly superior ($P < .05$) to placebo group at each evaluation time point.

The 5% topical minoxidil group was significantly superior to the 2% topical minoxidil group and placebo group for the patients' assessment of benefit of treatment at week 48 (primary efficacy measure) (Table III), although there was a significant treatment-by-investigator interaction effect. As with the nonvellus hair count data, the same trial site was identified as the principal source for this interaction. A reanalysis of the patients' assessment of benefit of treatment data excluding this 1 site eliminated the statistically significant interaction effect, and the 5% topical minoxidil group maintained its statistical superiority over the 2% topical minoxidil group.

The ratio of satisfaction/expectation with treatment (calculated from patient perspectives before and after treatment) was not statistically significant among the treatment groups (secondary efficacy measure) (Table III).

In addition, questions on the patient questionnaire were categorized to evaluate 4 aspects of hair growth: quality of life; global benefit; hair growth; and hair styling. A composite score was calculated for each category using all questions or selected questions within each category (Table V). The 5% topical minoxidil group was significantly superior to the 2% topical minoxidil group at week 48 for the global benefit composite score and significantly superior to the placebo group for all 4 composite scores, although for the hair growth composite score a significant treatment-by-investigator interaction effect was found.

Although 5% topical minoxidil did not achieve statistical superiority over 2% topical minoxidil or placebo for each individual patient questionnaire end point, there was a suggestion of increased efficacy with 5% topical minoxidil (Table VI). When considering the treatment means for 32 visual analog scale questions in the 4 hair growth categories (ie, hair growth, global benefit, hair styling, quality of life), the 5% topical minoxidil group had higher mean scores than the 2% topical minoxidil and placebo groups in most cases.

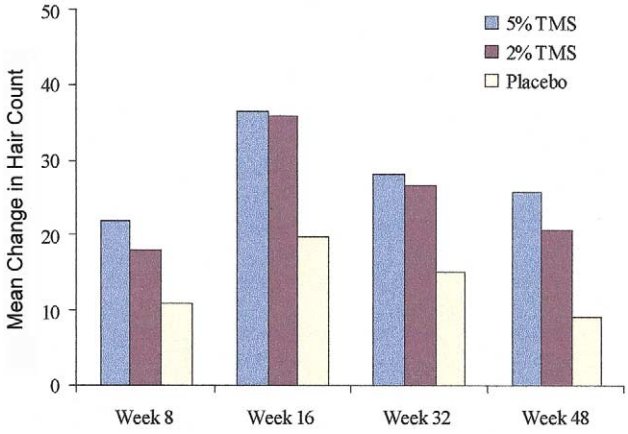

Fig 3. Change from baseline in nonvellus hair count (excluding 2 outlier patients). Group with 5% topical minoxidil solution (*TMS*) was significantly superior ($P = .031$) to 2% TMS group at week 48 (primary evaluation time point). Both 5% and 2% TMS groups were significantly superior ($P < .05$) to placebo group at each evaluation time point.

Table V. Patient questionnaire composite scores at week 48 (efficacy evaluable population)

	Mean composite score				Pairwise comparison *P* value		
Category	5% Minoxidil	2% Minoxidil	Placebo	Treatment comparison *P* value	5% vs 2%	5% vs Placebo	2% vs Placebo
Hair growth*	64.5	60.5	56.4	.006†	.095†	.002†	.061†
Global benefit‡	56.6	49.9	43.6	.002	.037	<.001	.053
Hair styling§	55.7	51.6	44.1	.001	.124	<.001	.013
Quality of life‖	54.4	52.1	46.5	.014	.280	.004	.035

*Composite score was calculated based on 8 of 8 hair growth questions.
†Interaction of treatment and investigator effects at $P \leq .10$.
‡Composite score was calculated based on 11 of 16 global benefit questions.
§Composite score was calculated based on 6 of 8 styling questions.
‖Composite score was calculated based on 6 of 6 quality of life questions.

The 5% topical minoxidil group was significantly superior to the 2% topical minoxidil group for 1 quality of life question (effect of hair loss condition on the patient's life) and significantly superior to the placebo group for all 6 quality of life questions (Table VII). The 2% topical minoxidil group was significantly superior to the placebo group for 2 quality of life questions (Table VII). The 5% topical minoxidil group was significantly superior to the placebo group for all global benefit and hair styling questions, but not to the 2% topical minoxidil group (Table VII). The 2% topical minoxidil group was significantly superior to the placebo group for all global benefit questions and 2 hair styling questions (Table VII).

Investigator evaluation. Investigator evaluation of hair growth/scalp coverage at week 48 was a primary efficacy variable. Both the 5% and 2% topical minoxidil groups were significantly superior to the placebo group for the investigators' rating of change in scalp coverage at week 48 (Table III) and at earlier time points (weeks 16 and 32) (Table IV). No statistically significant difference was found between the 5% and 2% topical minoxidil groups for this efficacy measure.

Table VI. Patient questionnaire outcome means (Visual analog scale responses only) showing a dose-related effect at week 48 (efficacy-evaluable population)

Questionnaire category	Total No. of VAS questions	No. of responses that showed a dose-related effect*
Hair growth	7	6 (86%)
Global benefit	14	14 (100%)
Hair styling	5	5 (100%)
Quality of life	6	5 (83%)

VAS, Visual analog scale.
*Dose-related effect = 5% topical minoxidil >2% topical minoxidil > placebo.

Table VII. Patient questionnaire results at week 48 (efficacy evaluable population)

End points	Visual analog score*			Treatment comparison *P* value	Pairwise comparison *P* value		
	5% Minoxidil	2% Minoxidil	Placebo		5% vs 2%	5% vs Placebo	2% vs Placebo
Quality of life							
Effect of hair loss condition on life	49.2	43.7	39.9	.016	.038	.007	.298
Effect of hair loss condition on social life	51.1	51.5	42.9	.032	.876	.021	.013
Degree of self-confidence	62.4	59.0	52.3	.054	.343	.016	.092
Effect of treatment of hair loss condition on first impressions in social situations	55.2	52.9	47.1	.060	.454	.018	.073
Effect of hair loss condition on job	53.2	51.9	47.9	.067	.545	.022	.066
Effect of treatment of hair loss condition on first impressions made in job	55.3	54.1	49.0	.048	.669	.017	.038
Global benefit							
Feeling about present hair loss condition	55.2	48.3	40.9	.004	.126	.001	.034
Feeling of having control over hair loss†	47.5	42.8	33.8	.014‡	.505	.004	.017
Whether patient's expectations were met†	62.7	56.2	46.8	.006‡	.131	.001	.042
Hair styling							
Description of hair thickness	35.0	31.5	24.5	.026‡	.252	.007	.069
Satisfaction with amount of hair styling products used	59.7	58.4	46.4	.002	.672	<.001	.002
Satisfaction with amount of time spent daily on styling hair	62.9	58.2	49.0	.002	.130	<.001	.015

*Based on a 100-mm visual analog scale (VAS) in which a score of 0 = negative, 50 = neutral, and 100 = positive.
†Based on 100-mm VAS (increasingly positive, 50 not neutral).
‡Interaction of treatment and investigator effects at $P \leq .10$.

Similarly, no statistically significant difference was found between the 5% and 2% topical minoxidil groups for the investigators' assessment of benefit of treatment at week 48 (Table III). A significant treatment-by-investigator interaction effect was found for this end point, where the mean values for both active treatment groups at 1 trial site were very much below the means of the other sites. A reanalysis of the data excluding the 1 site resulted in elimination of the interaction effect and both the 5% and 2% topical minoxidil groups achieved significantly higher mean levels of investigators' assessment of benefit than the placebo group ($P = .007$ and $P = .019$, respectively); the difference between the 5% and 2% topical minoxidil groups, however, was not significant.

Other questions of interest on the investigator questionnaire included the change from baseline in the patient's center part width and hair density (Table IV). The 5% and 2% topical minoxidil groups were significantly superior to the placebo group at week 48 for both of these end points. No significant differences were found between the 5% and 2% topical minoxidil groups. An example of treatment response with 5% topical minoxidil, 2% topical minoxidil, and placebo is shown in Fig 4.

Safety

Adverse events. Drug-related adverse events of a dermatologic nature (eg, pruritus, dermatitis, hypertrichosis, scaling) were more prevalent in the 5% topical minoxidil group (22 of 153 patients; 14%) than in the 2% topical minoxidil group (10 of 154 patients; 6%) and the placebo group (3 of 74 patients; 4%). The most frequent drug-related dermatologic event was pruritus, affecting 8 (5%) of 153 patients in the 5% topical minoxidil group, 1 (0.6%) of 154 patients in the 2% topical minoxidil group, and 2 (3%) of 74 patients in the placebo group. In all, 7 patients in the 5% topical minoxidil group, 4 patients in the 2% topical minoxidil group, and 3 patients in the placebo group dropped out because of drug-related local intolerance (ie, itching, dryness, scaling, and other symptoms of dermatitis of the scalp).

Of the 153 patients in the 5% topical minoxidil group, 4 (3%) had hypertrichosis (facial hair growth) reported as a drug-related adverse event, which caused 3 patients to drop out of the trial. Serum minoxidil levels were low or nondetectable in all 4 patients. In reply to specific questioning by the investigator of any new hair growth in areas other than the scalp, 71 (46%) of the 153 patients in the 5%

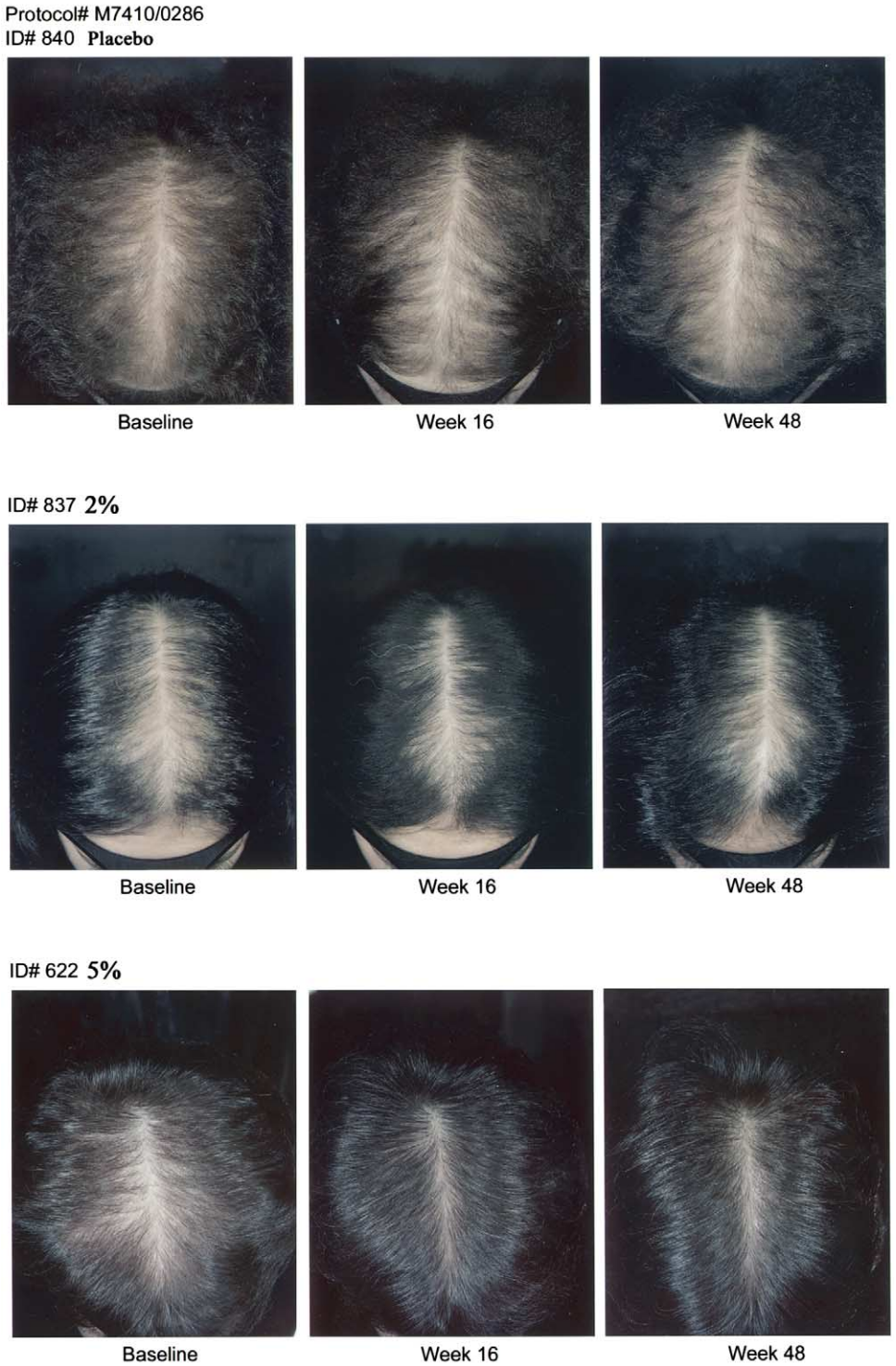

Fig 4. Clinical photographs of patients treated with placebo (*top*), 2% topical minoxidil solution (TMS) (*middle*), and 5% TMS (*bottom*).

topical minoxidil group, 34 (22%) of the 154 patients in the 2% topical minoxidil group, and 12 (16%) of the 74 patients in the placebo group noted this observation. In most cases, the hair growth was on the face (ie, sideburns, forehead, cheeks, chin, upper portion of lip); there were no reports of generalized hypertrichosis. The high occurrence of hair growth in areas other than the scalp in all treatment groups was not unexpected because this information was solicited by the investigator.

Headache was the next most commonly reported drug-related adverse event, affecting 3 (2%) of the 153 patients in the 5% topical minoxidil group and 6 (4%) of the 154 patients in the 2% topical minoxidil group; no patients in the placebo group reported headache. One patient in the 5% topical minoxidil group and 3 patients in the 2% topical minoxidil group dropped out because of headaches.

Drug-related cardiovascular adverse events (ie, palpitations, chest pain) were reported for 2 (1%) of the 153 patients in the 5% topical minoxidil group, 2 (1%) of the 154 patients in the 2% topical minoxidil group, and 2 (3%) of the 74 patients in the placebo group. One patient in the 5% topical minoxidil group dropped out because of palpitations. She experienced several episodes of palpitations from week 7 through 22, at which time she dropped out of the trial. The palpitations did not seem to coincide with application of the study medication. She had no history of cardiovascular disease and her vital signs were normal at each evaluation time point, as were electrocardiograms taken at weeks 12 and 22. A serum minoxidil level obtained at week 12 was 2.1 ng/mL. One day after she dropped out, she was seen in the emergency department for palpitations. A physical examination was normal as were 2 electrocardiograms. One week later the patient reported she had been free of palpitation episodes for 48 hours. Given the patient's low level of systemic absorption after topical administration, it appears unlikely the palpitations were a result of minoxidil.

Other drug-related adverse events that caused patients to drop out included abdominal bloating in 1 patient in the 5% topical minoxidil group and dizziness/lightheadedness in 1 patient in the 2% topical minoxidil group.

Nondrug-related adverse events that caused patients to drop out in the 5% topical minoxidil group included 2 cases of pregnancy (1 women delivered a live infant with no obvious abnormalities; the outcome was unknown for the other woman) and 1 case each of motor vehicle accident, gallbladder attack, atrial septal defect, operation for removal of a breast tumor, and rash (erythema annulare centrifugum). Nondrug-related adverse events that caused patients to drop out in the 2% topical minoxidil group included 2 cases of pregnancy (both women delivered live infants with no obvious abnormalities) and 1 case each of menopausal symptoms, broken leg, exacerbation of heel pain, and cluster headache/dizziness.

The occurrence of serious adverse events, all unrelated to study medication, was similar among the treatment groups: 6 (4%) of 153 patients in the 5% topical minoxidil group; 5 (3%) of 154 patients in the 2% topical minoxidil group; and 2 (3%) of the 74 patients in the placebo group. Two patients in the 5% topical minoxidil group dropped out, one because of a motor vehicle accident and the other as a result of a gallbladder attack. Two patients in the 2% topical minoxidil group dropped out, one because of acute depression and the other as a result of pregnancy with resultant miscarriage. Other serious adverse events, not resulting in discontinuation from the trial, included fibrocystic tumors, gastroenteritis, cholelithiasis/cholecystitis, infection (cellulitis) of the leg, broken ankle, planned operation, breast reduction operation, and cholecystitis.

Local tolerance. On the basis of the investigators' assessment of signs and symptoms of contact dermatitis (ie, stinging/burning, itching, dryness/scaling), scalp symptoms were fairly similar across all treatment groups except for a slightly increased occurrence of mild stinging/burning and severe itching in the 5% topical minoxidil group. Mild and moderate dryness/scaling were reported in a large number of patients in all treatment groups; however, this was particularly noteworthy in the 5% topical minoxidil and placebo groups. This finding may be related to the higher percentage of propylene glycol in the vehicle for both of these groups. A total of 4 patients had patch tests done: 2 in the 5% topical minoxidil group; 1 in the 2% topical minoxidil group; and 1 in the placebo group. All 4 patients tested positively to 2% and 5% topical minoxidil formulations, 1 patient per group tested positively to ethanol (vehicle component), and 1 patient in the placebo group tested positively to propylene glycol (vehicle component). All 4 of these patients dropped out because of adverse events associated with itching/irritation of the scalp.

Laboratory tests. Application of study medication was not associated with any clinically important adverse effects on blood pressure, pulse rate, body weight, electrocardiograms, or laboratory assays. The mean serum minoxidil level for all posttreatment samples in the 5% topical minoxidil group was 1.8 ng/mL, which was 2.6 times higher than the level seen in the 2% topical minoxidil group (0.7 ng/mL). Among all 381 patients, serum minoxidil levels were less than 10 ng/mL in all but 3 (2%) of the 153 patients in the 5% topical minoxidil group. These 3 patients were examined for signs of systemic effects of minoxidil. The minor, fluctuating changes seen in blood pressure and pulse rate were well within expected physiologic limits. The highest serum minoxidil concentration reported was 18.2 ng/mL, which is below the level (21.7 ng/mL) that minor hemodynamic effects (pulse rate changes) have been first reported.[12] This patient completed the trial

and was asymptomatic for cardiovascular problems throughout the duration of the trial.

DISCUSSION

This 48-week trial showed that 5% topical minoxidil was consistently statistically superior to placebo in promoting hair growth in women with female pattern hair loss for all 3 primary efficacy measures of hair count and patient/investigator assessment of hair growth/scalp coverage. In contrast, 2% topical minoxidil achieved statistical superiority for 2 of the 3 efficacy measures (change from baseline in nonvellus hair count and investigator rating of hair growth/scalp coverage). A consistent statistical advantage of 5% topical minoxidil over 2% topical minoxidil was not demonstrated. There was statistical superiority of 5% topical minoxidil over 2% topical minoxidil in the patient assessment of benefit of treatment at week 48, even in the presence of a negative treatment-by-investigator interaction effect.

Interpretation of the results from this trial is markedly confounded by a number of factors including a high dropout rate (approximately 30% in all treatment groups), significant treatment-by-investigator interaction effects for many week-48 efficacy measures, and an unexplainable report of excessive hair shedding at week 48 in 2 patients at 1 site in the 5% topical minoxidil group.

The high patient dropout rate (Table II) may have significantly affected the overall statistical power and, thereby, affected the treatment effects. The most common reasons for discontinuation from the trial were patient request (eg, could not keep scheduled appointments, relocation, family- and work-related problems), nonserious adverse events, and becoming lost to follow-up. The significant treatment-by-investigator interaction effects for 2 important efficacy end points (target area nonvellus hair counts and patients' assessment of benefit of treatment) were primarily because of 1 trial site where the results differed considerably from those of the other sites. The lack of statistical superiority for target area hair counts may be explained by the fact that 2 patients in the 5% topical minoxidil group at 1 site had an inordinate loss of hair at week 48. When these 2 patients were excluded in a reanalysis of the target area hair counts at 48 weeks, the 5% topical minoxidil group achieved statistical superiority over the 2% topical minoxidil group. Similarly, when the patients' assessment of treatment benefit data were reanalyzed after exclusion of the data obtained at this site, the interaction effect was eliminated and the 5% topical minoxidil group maintained its statistical superiority over the 2% topical minoxidil group. The statistical significance tests for treatment effects reported in Table III, which included this site, represent a conservative estimate of the effects attributable to topical minoxidil solution.

The finding of increased target area hair counts over the course of the 48-week trial provides evidence that both 5% and 2% topical minoxidil not only reverse hair loss but also slow the progression of hair loss. This effect is further supported by findings from other 2% topical minoxidil clinical trials in women with female pattern hair loss,[13,14] and from a 5% topical minoxidil trial in male patients with AGA, which used a precise measure to demonstrate efficacy (ie, hair weight) and the standard hair count measures.[15] In this latter trial, a minimal placebo effect was apparent, which was unlike the placebo response seen in this current trial and other topical minoxidil clinical trials.

Unlike previous clinical trials, this trial used an extensive patient questionnaire to evaluate aspects of quality of life, global benefit, hair growth, and hair styling. These data showed that 5% and 2% topical minoxidil helped improve psychosocial perceptions of hair loss in women with female pattern hair loss.

The mean change in the patient's center part width and hair density, as assessed by the investigator, demonstrated that both the 5% and 2% topical minoxidil groups were significantly superior to the placebo group. No significant differences were found between the active treatment groups. Although these were not main efficacy measures in this trial, both of these end points are important in the diagnosis of female pattern hair loss and determination of efficacy in clinical trials, as recently reported by Olsen.[9]

Drug-related adverse events of a dermatologic nature (eg, pruritus, dermatitis, hypertrichosis, scaling) were more prevalent in the 5% topical minoxidil group than in the 2% topical minoxidil and placebo groups. The patient dropout rate because of local intolerance, however, was fairly similar among the treatment groups, as was the occurrence of scalp symptoms of contact dermatitis (eg stinging/burning, itching, dryness/scaling) except for a slight increased occurrence of mild stinging/burning and severe itching in the 5% topical minoxidil group. Facial hypertrichosis was reported by 4 patients, all in the 5% topical minoxidil group, and 3 of them dropped out because of the adverse event. The hypertrichotic effect on scalp and other sites is reversible, and it can disappear despite continued use of the product.[4]

The mechanism by which topical minoxidil induces hair growth in AGA and female pattern hair loss has not been fully characterized. Topical minoxidil is postulated to increase hair density either by induction of anagen or an increase in anagen

duration. Hair diameter is also increased by topical minoxidil.[16,17] The net result is reversal of the miniaturization process, slowing the progression of hair loss, or both.

In conclusion, both 5% and 2% topical minoxidil were superior to placebo in promoting hair growth in women with female pattern hair loss. Although a consistent statistical advantage of 5% topical minoxidil over 2% topical minoxidil was not demonstrated, trends in the data may support an enhanced efficacy of the higher concentration when considering the confounding factors in this trial. A statistically significant difference between 5% and 2% topical minoxidil was demonstrated when 2 patients with a sudden, unexpected decrease in hair counts at their last visit (week 48) were eliminated from the hair count analysis. Psychosocial perceptions of hair loss in women with female pattern hair loss were improved with 5% and 2% topical minoxidil. Both concentrations of topical minoxidil were well tolerated by the women in this trial without evidence of systemic adverse effects. An increased occurrence of pruritus, local irritation, and hypertrichosis was observed with 5% topical minoxidil versus 2% topical minoxidil and placebo. With the introduction of numerous herbal remedies for hair loss, of which most have not been tested in randomized, double-blind, placebo-controlled trials, it is important to describe well-controlled trials that demonstrate the efficacy and safety of topical drugs.

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