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A randomized clinical trial of 5% topical minoxidil versus 2% topical minoxidil and placebo in the treatment of androgenetic alopecia in men

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Background: Topical minoxidil solution 2% stimulates new hair growth and helps stop the loss of hair in individuals with androgenetic alopecia (AGA). Results can be variable, and historical 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 5% topical minoxidil with 2% topical minoxidil and placebo in the treatment of men with AGA.

Methods: A total of 393 men (18-49 years old) with AGA applied 5% topical minoxidil solution (n = 157), 2% topical minoxidil solution (n = 158), or placebo (vehicle for 5% solution; n = 78) twice daily. Efficacy was evaluated by scalp target area hair counts and patient and investigator assessments of change in scalp coverage and benefit of treatment.

Results: After 48 weeks of therapy, 5% topical minoxidil was significantly superior to 2% topical minoxidil and placebo in terms of change from baseline in nonvellus hair count, patient rating of scalp coverage and treatment benefit, and investigator rating of scalp coverage. Hair count data indicate that response to treatment occurred earlier with 5% compared with 2% topical minoxidil. Additionally, data from a patient questionnaire on quality of life, global benefit, hair growth, and hair styling demonstrated that 5% topical minoxidil helped improve patients' psychosocial perceptions of hair loss. An increased occurrence of pruritus and local irritation was observed with 5% topical minoxidil compared with 2% topical minoxidil.

Conclusion: In men with AGA, 5% topical minoxidil was clearly superior to 2% topical minoxidil and placebo in increasing hair regrowth, and the magnitude of its effect was marked (45% more hair regrowth than 2% topical minoxidil at week 48). Men who used 5% topical minoxidil also had an earlier response to treatment than those who used 2% topical minoxidil. Psychosocial perceptions of hair loss in men with AGA were also improved. Topical minoxidil (5% and 2%) was well tolerated by the men in this trial without evidence of systemic effects. (J Am Acad Dermatol 2002;47:377-85.)

Pattern hair loss (androgenetic alopecia [AGA] in men and female pattern hair loss in women) is the most common type of hair loss, affecting approximately 50% of men and women older than 40 years.[1] Topical minoxidil solution was developed as a treatment for AGA after the discovery that the active ingredient (minoxidil) caused hypertrichosis (excessive growth of hair)

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when taken orally for the treatment of hypertension. Topical minoxidil solution 2% (Rogaine for Men and Women; OTC, Pharmacia Corp, Peapack, NJ) has been shown to stimulate new hair growth and to help prevent further hair loss in affected areas in both men and women with AGA.[2] Historical 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.[3,4] Thus, we performed a clinical trial in men with AGA to compare the efficacy and safety of 5% topical minoxidil (Rogaine for Men Extra Strength; OTC, Pharmacia Corp) with those of 2% topical minoxidil and placebo (vehicle for 5% topical minoxidil).

METHODS

Patient population

Men eligible for inclusion in the trial were 18 to 49 years old with naturally dark hair and AGA characterized as vertex pattern 3, 4, 5, or 6 with a density rating of 4 to 7 according to the Savin Male Pattern and Density Scale.[5] Patients were in good general health with no evidence of systemic illnesses (eg, cardiac, psychiatric, or scalp disease). Patients known to be hypersensitive to minoxidil were excluded, as were patients who concomitantly used hair restorers or systemic drugs (steroids, cytotoxic agents, vasodilators, antihypertensive agents, anticonvulsant drugs, β-adrenergic receptor blockers, diuretics, or any of the following specific agents: spironolactone, cimetidine, diazoxide, cyclosporine, or ketoconazole).

Study design

This was a 48-week, randomized, double-blind, placebo-controlled trial conducted at 6 investigative sites in the United States. 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 = 157), 2% topical minoxidil (n = 158), or placebo (vehicle for 5% topical minoxidil solution*; n = 78).

Patients applied 1 mL of assigned solution twice daily at approximately 12-hour intervals (total daily dose of 2 mL) to the frontoparietal and vertex areas of the scalp 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 and safety evaluations every 4 weeks through week 32, then every 8 weeks through the end of the 48-week trial.

Efficacy evaluation procedures (protocol-specified)

Hair counts were obtained from computer-assisted scans of macrophotographs of clipped hair in a 1 cm^2 target evaluation area in the balding vertex 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 (any pigmented) hair 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 with computer-based scanners and imaging software.[6] The resulting hair counts per square centimeter were used to calculate mean change from baseline.

Patient self-assessment and investigator assessment of hair growth were done by using validated hair growth questionnaires. Patients' responses at each visit were based on their perception of their current hair loss condition. Aids used in this assessment were instant photographs, obtained with Polaroid film, of the patient's scalp (frontal and occipital views with a center part), taken at baseline and each evaluation time point that patients could compare with current scalp hair growth through mirror viewing. The investigators' assessment was based on 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. Three primary and 3 secondary efficacy measures were analyzed in this trial, as well as other patient questionnaire data relating to quality of life, global benefit, hair growth, and hair styling.

Retrospective efficacy evaluation procedures

After the trial was completed, 2 reviewers (board-certified dermatologists with expertise in hair), blinded to treatment, rated the baseline and week 48 clinical global Polaroid photographs of patients' scalp hair. Two sets of photographs were used (a

* The vehicle for the 5% solution contains more propylene glycol (50%) and less ethanol (30%) than the vehicle for the 2% solution (20% and 60%, respectively).

front view and a vertex view), and each set was scanned and provided as optical images. The Picture Comparison Viewer (PictComp) was used to display the baseline and week 48 photographs side by side on the same screen. The reviewers independently graded the photographs on a 7-point scale as showing "dense growth," "moderate growth," "minimal growth," "no change," "minimal loss," "moderate loss," or "dense loss." Those photographs in which technical problems occurred and those of poor quality that precluded assessment were marked as "unable to rate." For analysis purposes, the minimal loss, moderate loss, and dense loss categories were collapsed into one category defined as hair loss.

Safety evaluation

Safety monitoring was designed to detect potential local intolerance and systemic cardiovascular effects of topical minoxidil. Patients underwent an extensive initial interview and physical examination before treatment was started, including evaluation of the scalp for signs of dermatitis; measurement of blood pressure, pulse rate, and body weight; auscultation of the chest; evaluation of extremities for signs of peripheral edema; electrocardiography; hematology and blood chemistry assays; and urinalysis; and determination of minoxidil concentrations in serum samples. 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 a difference of 9 hairs/cm^2 between treatment groups with regard to mean change in nonvellus hair counts. Continuous variables were analyzed by using analysis of variance models. At baseline, comparisons of treatment means were done by using the one-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. 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 by 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 and .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.

RESULTS

Baseline characteristics

Three hundred ninety-three men with AGA were enrolled in the trial. Patient demographic and hair loss features at baseline were similar among the treatment groups (Table I). The average age of the population was 36 years, and most (80%) patients were white. Patients had hair loss for an average of 9 years (range, 1-28 years). According to the Savin Male Pattern and Density Scale,[5] the mean vertex pattern score was 4.6 in each treatment group; and the mean vertex density scores were 6.0, 5.8, and 5.8 in the 5% topical minoxidil, 2% topical minoxidil, and placebo groups, respectively.

A total of 351 patients completed the entire 48-week trial, and 352 were included in the efficacy-evaluable population (Table II). One patient treated with 2% topical minoxidil was withdrawn from the study because of a nondrug-related serious adverse event (angina, see safety results) after completing 46 weeks of treatment but was retained in the efficacy-evaluable population. All patients enrolled were included in the safety analyses (intent-to-treat). The most common reasons that patients were withdrawn from the trial were patient request, nonserious adverse events, and loss 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 22 target area hair counts were missing for 13 patients over the 48-week trial period. Also, questionnaire information was unavailable in some instances because the patients missed a clinic visit, the questionnaire was not administered properly, or the patient or investigator skipped questions. Consequently, the number of patients in the evaluable population varies over time for the affected end points. Twenty-five patients used protocol-prohibited concomitant medications (mostly systemic corticosteroids of short duration with tapering doses) during the trial: 1 (7%) of the 157 patients in the 5% topical minoxidil group, 11 (7%) of the 158 patients in the 2% topical minoxidil group, and 3 (4%) of the 78 patients in the placebo group. None of these deviations was thought to have an impact on the trial results and conclusions.

Efficacy (protocol-specified)

Nonvellus hair count. The mean change from baseline in target area nonvellus hair count at week 48 (primary efficacy measure, Table III) showed that results in the 5% topical minoxidil group were sig-

Table I. Demographic and hair loss features at baseline

Variable	5% Minoxidil (n = 157)	2% Minoxidil (n = 158)	Placebo (n = 78)	Treatment *P* value
Age (y)				
Mean (SD)	36.2 (6.4)	36.5 (6.5)	36.8 (6.4)	.797
Range	21-49	20-49	23-49	
Race/ethnic group [No. (%) of patients]				.139*
White	118 (75.2)	133 (84.2)	62 (79.5)	
Black	1 (0.6)	4 (2.5)	0	
Oriental/Asian	2 (1.3)	0	1 (1.3)	
Hispanic	34 (21.7)	21 (13.3)	13 (16.7)	
Other	2 (1.3)	0	2 (2.6)	
Duration of hair loss (y)				
Mean (SD)	9.3 (5.4)	9.3 (5.2)	9.4 (5.4)	.977
Range	1-25	1-25	1-28	
Vertex pattern score† [No. (%) of patients]				.974
3	18 (11.5)	27 (17.1)	9 (11.5)	
4	55 (35.0)	41 (25.9)	25 (32.1)	
5	50 (31.8)	53 (33.5)	29 (37.2)	
6	34 (21.7)	35 (22.2)	15 (19.2)	
Mean (SD)‡	4.6 (0.9)	4.6 (1.0)	4.6 (0.9)	
Vertex density score† [No. (%) of patients]				.223
4	5 (3.2)	13 (8.2)	7 (9.0)	
5	41 (26.1)	45 (28.5)	18 (23.1)	
6	66 (42.0)	53 (33.5)	39 (50.0)	
7	45 (28.7)	45 (28.5)	14 (17.9)	
Mean (SD)‡	6.0 (0.8)	5.8 (0.9)	5.8 (0.9)	
Pattern of hair loss (Hamilton-Norwood scale)§ [No. (%) of patients]				ND
Type IIA	1 (0.6)	0	0	
Type III	1 (0.6)	3 (1.9)	0	
Type III vertex	64 (40.8)	69 (43.7)	29 (37.2)	
Type IV	55 (35.0)	53 (33.5)	32 (41.0)	
Type V	19 (12.1)	18 (11.4)	7 (9.0)	
Type VA	11 (7.0)	10 (6.3)	6 (7.7)	
Type VI	4 (2.5)	4 (2.5)	4 (5.1)	
Type VII	2 (1.3)	1 (0.6)	0	
Nonvellus hair count at baseline§				
Mean (SD)	151.1 (45.9)	143.6 (45.0)	152.4 (42.3)	.258
No. of patients	139	142	71	

ND, Not done.

*Because the majority of the patients were white, race categories were collapsed to form the dichotomy of white and nonwhite for analysis.

†Savin Male Pattern and Density Scale.[5]

‡Missing values are not included in the calculation of mean and SD.

§Data are presented for the efficacy-evaluable population.

nificantly superior to results in the 2% topical minoxidil and placebo groups. The results in the 5% topical minoxidil group were also significantly superior to those in the 2% topical minoxidil and placebo groups, beginning at the first evaluation time point (week 8), indicating an earlier response to treatment with 5% topical minoxidil (Fig 1).

Patient evaluation

The results in the 5% topical minoxidil group were significantly superior to those in the 2% topical minoxidil and placebo groups for 2 primary efficacy measures: patients' assessment of change in scalp coverage and benefit of treatment at week 48 (Table III). The change in scalp coverage for the 5% topical minoxidil group was also significantly superior to the changes in the 2% topical minoxidil and placebo groups at weeks 16 and 32 ($P < .001$). The ratio of satisfaction/expectation with treatment (calculated from patient perspectives before and after treatment) demonstrated a marginally significant difference favoring the 5% topical minoxidil group over the 2% topical minoxidil group and a significant

Table II. Disposition of patients

Disposition	Patients [No. (%)]		
	5% Minoxidil (n = 157)	2% Minoxidil (n = 158)	Placebo (n = 78)
Completion of 48-wk trial	139 (88.5)	141 (89.2)	71 (91.0)
Efficacy-evaluable population	139 (88.5)	142 (89.9)*	71 (91.0)
Did not complete trial	18 (11.5)	17 (10.8)	7 (9.0)
Reasons for not completing trial			
Patient request	3 (1.9)	7 (4.4)	2 (2.6)
Adverse events			
Nonserious	7 (4.5)	1 (0.6)	0
Serious	0	1 (0.6)	0
Lost to follow-up	2 (1.3)	3 (1.9)	3 (3.8)
Protocol noncompliance/violation	1 (0.6)	2 (1.3)	2 (2.6)
Other	4 (2.5)	3 (1.9)	0
Lack of efficacy	1 (0.6)	0	0

*One patient was discontinued because of a serious adverse event after completing 46 weeks of treatment but was retained in the efficacy-evaluable population.

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)	18.6 ± 25.4	12.7 ± 20.7	3.9 ± 21.7	.025	<.001	.013
Change in scalp coverage (patient)†	62.0 ± 17.0	56.9 ± 11.0	51.0 ± 14.9	.002	<.001	.009
Benefit from treatment (patient)‡	50.5 ± 28.6	41.2 ± 25.3	26.1 ± 27.9	.004	<.001	<.001
Secondary						
Change in scalp coverage (investigator) (calculated mean change from baseline)	12.3 ± 23.1	7.0 ± 20.4	2.5 ± 19.5	.042	.002	.157
Benefit from treatment (investigator)‡	33.7 ± 28.2	30.2 ± 28.4	12.6 ± 20.3	.342	<.001	.001
Treatment benefit S/E ratio (patient)§	0.83 ± 0.61	0.72 ± 0.60	0.41 ± 0.42	.071	<.001	.001

S/E, Satisfaction/expectation; *VAS*, visual analog scale.
*Pairwise comparisons are displayed when overall treatment *P* value was ≤ .1.
†Based on a 100-mm 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.
§Calculated from patient perspectives before and after treatment. A score of 1 is an indication of equal expectation and satisfaction.

difference over the placebo group (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 by using responses to all questions or to selected questions within each category (Table IV). The composite score for the 5% topical minoxidil group was significantly superior to composite scores for the 2% topical minoxidil and placebo groups at week 48 with regard to quality of life, global benefit, and hair growth. For the hair styling composite score, the 5% topical minoxidil group was significantly superior to the placebo group but not to the 2% topical minoxidil group.

Although 5% topical minoxidil did not achieve statistical superiority over 2% topical minoxidil and placebo for each individual patient questionnaire end point, there was a strong trend for increased efficacy with 5% topical minoxidil. The treatment means (visual analog responses only) generally showed a dose-related effect; that is, 5% topical minoxidil was superior to 2% topical minoxidil and placebo (Table V).

Three of 6 quality-of-life questions showed that the results in the 5% topical minoxidil group were significantly superior to those in the 2% topical mi-

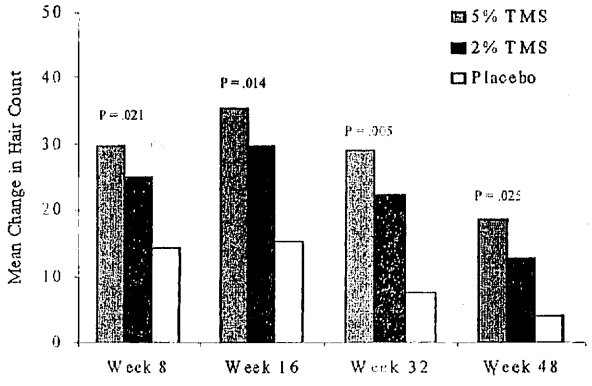

Fig 1. Change from baseline in nonvellus hair count. *P* values reflect statistically significant differences favoring 5% topical minoxidil over 2% minoxidil. *TMS*, Topical minoxidil solution.

noxidil and placebo groups: effect of hair loss condition on social life, effect of treatment of hair loss condition on first impressions in social situations, and effect of treatment of hair loss condition on first impressions made in job (Table VI). Two of 6 global benefit questions showed that the results in the 5% topical minoxidil group were significantly superior to those in the 2% topical minoxidil and placebo groups: patient's description of current attitude of hair loss condition and feeling about present hair loss condition (Table VI). In one case (effect of hair loss condition on life), 5% topical minoxidil achieved a marginally significant difference over 2% topical minoxidil and a significant difference over placebo.

Investigators' evaluation

The results in the 5% topical minoxidil group were significantly superior to those in the 2% topical minoxidil and placebo groups for the investigators' rating of change in scalp coverage at week 48 (secondary efficacy measure, Table III) and at earlier time points (weeks 16 and 32, $P < .05$). The investigators' assessment of benefit of treatment at week 48 (secondary efficacy measure) showed that the results in the 5% topical minoxidil group were significantly superior to those in the placebo group but not to those in the 2% topical minoxidil group (Table III).

Efficacy (retrospective assessment)

Global photographs. Assessment of clinical global photographs by 2 independent reviewers showed that a greater percentage of patients in the 5% topical minoxidil group achieved hair regrowth (mild, moderate, and dense growth) relative to the 2% topical minoxidil and placebo groups (Table VII). For the first reviewer, the percentages of patients with hair regrowth at 48 weeks were 62% (86/139 patients), 44% (62/142 patients), and 30% (21/71 patients) in the 5% topical minoxidil, 2% topical minoxidil, and placebo groups, respectively. The percentages of patients with hair regrowth at 48 weeks for the second reviewer were 54% (75/139 patients), 38% (54/142 patients), and 17% (12/71 patients) in the 5% topical minoxidil, 2% topical minoxidil, and placebo groups, respectively. Greater percentages of patients achieved moderate or dense hair regrowth in the 5% topical minoxidil group relative to the 2% topical minoxidil and placebo groups: respectively, 40% (55/139), 32% (32/142), and 7% (5/71) as rated by the first reviewer and 30% (42/139), 16% (22/142), and 7% (5/71) as rated by the second reviewer.

Safety

Adverse events. Drug-related adverse events of a dermatologic nature (eg, pruritus and dermatitis) were more prevalent in the 5% topical minoxidil group (9/157 patients, 6%) than in the 2% topical minoxidil group (3/158 patients, 2%) and placebo group (2/78 patients, 3%). The most frequent drug-related dermatologic event was pruritus, affecting 6 (4%) of 157 patients in the 5% topical minoxidil group, 2 (1%) of 158 patients in the 2% topical minoxidil group, and no patients in the placebo group. Five patients in the 5% topical minoxidil group and one patient in the 2% topical minoxidil group dropped out because of drug-related local intolerance (ie, itching, dryness, flaking, and other symptoms of dermatitis of the scalp).

Headache was the only other drug-related adverse event that occurred in more than one patient within at least one treatment group: 5 (3%) of the 157 patients in the 5% topical minoxidil group, including one who dropped out because of this adverse event, 1 (0.6%) of the 158 patients in the 2% topical minoxidil group, and 1 (1%) of the 78 patients in the placebo group.

The occurrence of cardiovascular adverse events (ie, chest pain, palpitations, increase in blood pressure, angina, electrocardiogram abnormalities) was clearly not dose- or medication-related, affecting 1% (2/157), 6% (9/158), and 4% (3/78) of the patients in the 5% topical minoxidil, 2% topical minoxidil, and placebo groups, respectively. One patient in the 5% topical minoxidil group dropped out because of hypertension, but this was not considered drug-related by the investigator. One patient in the 2% topical minoxidil group had electrocardiographic abnormalities reported as possibly drug-related by the investigator. On follow-up, the patient was seen by a cardiologist and was thought to have mitral

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

Category	Mean composite score			Treatment comparison *P* value	Pairwise comparison *P* value		
	5% Minoxidil	2% Minoxidil	Placebo		5% vs 2%	5% vs Placebo	2% vs Placebo
Hair growth*	60.4	56.8	50.7	<.001	.010	<.001	.002
Global benefit†	58.3	53.5	48.3	<.001	.015	<.001	.023
Hair styling‡	59.0	55.6	53.6	.060	.102	.025	.365
Quality of life§	54.9	52.2	50.0	.004	.026	.002	.179

*Composite score was calculated based on 8 of 8 hair growth questions.
†Composite score was calculated based on 11 of 16 global benefit questions.
‡Composite score was calculated based on 5 of 8 styling questions.
§Composite score was calculated based on 6 of 6 quality of life questions.

regurgitation caused by a minor degree of mitral valve prolapse, papillary muscle dysfunction, or both. The cardiologist did not relate this event to 2% topical minoxidil. Application of the product was not interrupted, and the patient completed the trial.

Seven patients had serious adverse events; all were unrelated to study medication but all occurred in the 2% topical minoxidil group. One patient dropped out because of angina associated with coronary artery disease, which led to coronary artery bypass surgery. Five other patients underwent surgical procedures, and one patient had an inhalation injury from a chemical mixture.

Local tolerance

According to the investigators' assessment of signs and symptoms of contact dermatitis (ie, stinging/burning, itching, dryness/scaling), severe scalp symptoms were more prevalent in the 5% topical minoxidil group (10/157 patients, 6%) than in the 2% topical minoxidil group (2/158 patients, 1%) and placebo group (0/78 patients, 0%). Three patients in the 5% topical minoxidil group had patch tests done and were subsequently withdrawn from the trial: 2 of the 3 patients had positive patch test reactions to propylene glycol (vehicle component), as well as 2% and 5% topical minoxidil; the test results were equivocal in the third patient.

Laboratory tests

Application of the study medications 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 1.9 ng/mL, which was 2.7 times the level seen in the 2% topical minoxidil group (0.7 ng/mL). Among all 393 patients, serum minoxidil levels were less than 10 ng/mL in all but 5 (3%) of the 157 patients in the 5% topical minoxidil group. These 5 patients were examined for signs of systemic effects of minoxidil. Three of these patients had some minor, fluctuating changes in blood pressure and pulse rate; all changes were well within expected physiologic limits. Serum minoxidil levels in these 3 patients ranged from 10.5 ng/mL to 15.2 ng/mL. All 5 patients completed the trial. The highest serum minoxidil concentration reported was 16.5 ng/mL, which is below the level (21.7 ng/mL) that minor hemodynamic effects (pulse rate changes) have been first reported.[7]

Table V. Patient questionnaire outcome means (VAS responses only) showing a dose-related effect at week 48* (efficacy-evaluable population)

Questionnaire category	No. of responses showing a dose-related effect	Total No. of VAS questions
Hair growth	6 (86%)	7
Global benefit	13 (93%)	14
Styling	4 (67%)	6
Quality of life	6 (100%)	6

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

DISCUSSION

This 48-week trial clearly showed that 5% topical minoxidil was significantly superior to 2% topical minoxidil (4/6 efficacy measures) and placebo (6/6 efficacy measures) in increasing hair growth in men with AGA. Five percent topical minoxidil produced 45% more hair regrowth compared with 2% topical minoxidil as determined by target area hair counts at 48 weeks (18.6 and 12.7 nonvellus hairs, respectively, Table III). A more rapid hair growth response was also apparent, with an equivalent response at week 8 for the 5% topical minoxidil group (29.7 nonvellus hairs cm^2) versus week 16 for the 2% topical minoxidil group (29.8 nonvellus hairs cm^2).

Table VI. 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	49.9	47.3	45.4	.029	.065	.012	.320
Effect of hair loss condition on social life	52.5	48.9	46.3	.003	.016	.001	.208
Degree of self confidence	68.2	67.0	63.0	.326	.663	.138	.259
Effect of treatment of hair loss condition on first impressions in social situations	54.3	49.9	47.1	<.001	.004	<.001	.150
Effect of hair loss condition on job	51.5	50.0	49.2	.186	.162	.098	.614
Effect of treatment of hair loss condition on first impressions made in job	53.1	50.2	48.9	.006	.013	.004	.392
Global benefit							
Description of current attitude about hair loss condition	56.7	51.8	46.5	<.001	.012	<.001	.037
Feeling about overall personal appearance	64.6	60.1	57.8	.083	.105	.038	.460
Feeling about being in bright light	56.8	54.2	50.0	.153	.470	.053	.179
Feeling about present hair loss condition	55.7	51.3	47.7	.009	.047	.003	.180
Feeling about being photographed	60.9	57.9	53.1	.108	.375	.035	.167
Feeling about being in the wind	56.4	52.7	50.2	.201	.244	.085	.444

*Based on a 100-mm visual analog scale in which a score of 0 = negative, 50 = neutral, and 100 = positive.

Table VII. Retrospective photographic evaluation of clinical response at week 48*

Variable	Patients [No. (%)]					
	Reviewer No. 1			Reviewer No. 2		
	5% Minoxidil (n = 139)	2% Minoxidil (n = 142)	Placebo (n = 71)	5% Minoxidil (n = 139)	2% Minoxidil (n = 142)	Placebo (n = 71)
Dense growth	3 (2.2)	4 (2.8)	0	14 (10.1)	5 (3.5)	0
Moderate growth	52 (37.4)	28 (19.7)	5 (7.0)	28 (20.1)	17 (12.0)	5 (7.0)
Minimal growth	31 (22.3)	30 (21.1)	16 (22.5)	33 (23.7)	32 (22.5)	7 (9.9)
No change	44 (31.7)	71 (50.0)	43 (60.6)	40 (28.8)	67 (47.2)	43 (60.6)
Hair loss	7 (5.0)	4 (2.8)	7 (9.9)	9 (6.5)	2 (1.4)	10 (14.1)
Unable to rate	2 (1.4)	5 (3.5)	0	15 (10.8)	19 (13.4)	6 (8.5)

*Comparison of baseline (week 0) with week 48; grading of week 48 results compared with baseline may not total 100% because of rounding.

This finding was further supported by the global photographic review data (Table VII): mild, moderate, and dense hair growth was greater in the 5% topical minoxidil group (mean of 57%) than in the 2% topical minoxidil and placebo groups (means of 41% and 23%, respectively).

The finding of increased target area hair counts over the course of the 48-week trial provides evidence that 5% topical minoxidil not only reverses hair loss but also slows the progression of hair loss. This effect is further supported by the global photographic review data and by findings from another

5% topical minoxidil clinical trial in men with AGA. This latter trial, which used both hair weight and hair count measures to assess efficacy, showed a minimal placebo effect.[8]

Unlike previous clinical trials of topical minoxidil, the present trial used an extensive patient questionnaire to evaluate aspects of quality of life, global benefit, hair growth, and hair styling. These data demonstrated that 5% topical minoxidil helped improve psychosocial perceptions of hair loss in men with AGA.

A dose-dependent increase in local irritation (eg, pruritus, itching, burning) was apparent, which may be in part a function of the vehicle and increased percentage of propylene glycol rather than the concentration of minoxidil in the formulation. Indeed, 2 of 3 patients in the 5% topical minoxidil group had positive patch test reactions to propylene glycol, as well as to both 2% and 5% topical minoxidil, suggesting the role of propylene glycol in these cutaneous reactions.

The mechanism by which topical minoxidil induces hair growth in AGA has not been fully characterized. Topical minoxidil increases hair density either by induction of anagen or an increase in anagen duration. Hair diameter is also increased by topical minoxidil.[9,10] The net result is reversal of the miniaturization process of AGA and/or slowing the progression of hair loss.

In conclusion, this trial clearly demonstrates the enhanced efficacy of 5% topical minoxidil versus 2% topical minoxidil in men with AGA. Both concentrations of topical minoxidil were well tolerated without evidence of systemic effects.

Pharmacia Corporation provided the topical minoxidil solutions and placebo used in the trial.

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