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THERAPEUTIC HOTLINE

Clinical utility and validity of minoxidil response testing in androgenetic alopecia

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ABSTRACT: Clinical response to 5% topical minoxidil for the treatment of androgenetic alopecia (AGA) is typically observed after 3–6 months. Approximately 40% of patients will regrow hair. Given the prolonged treatment time required to elicit a response, a diagnostic test for ruling out nonresponders would have significant clinical utility. Two studies have previously reported that sulfotransferase enzyme activity in plucked hair follicles predicts a patient's response to topical minoxidil therapy. The aim of this study was to assess the clinical utility and validity of minoxidil response testing. In this communication, the present authors conducted an analysis of completed and ongoing studies of minoxidil response testing. The analysis confirmed the clinical utility of a sulfotransferase enzyme test in successfully ruling out 95.9% of nonresponders to topical minoxidil for the treatment of AGA.

KEYWORDS: androgenetic alopecia, minoxidil, response test

Introduction

Androgenetic alopecia (AGA) is a common dermatological condition affecting approximately 50% of the population by the age of 50 (1). Currently, the only drug approved by the US Food and Drug Administration for the treatment of AGA in both men and women is topical minoxidil. Clinical trials have demonstrated that following 16 weeks of 5% minoxidil therapy approximately 30–40% of patients regrow hair (2). Other studies (3) have reported higher response rates after 48 weeks of treatment but the placebo group also showed larger improvements. Given the lengthy treatment time required to ascertain individual efficacy of minoxidil, a diagnostic test for ruling out nonresponders would have significant clinical utility. It is important to note that over the course of an ineffective treatment, AGA may continue to progress. Additionally, ruling out nonresponders will reduce the potential side effects, emotional stress, and expense associated with using an ineffective drug.

Although the exact mechanism of action of minoxidil in the treatment of AGA is not completely understood, research has demonstrated that

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minoxidil sulfate is the active compound that stimulates hair follicles (4). Minoxidil is converted to its active form, minoxidil sulfate, in the outer root sheath of the hair follicle by endogenous sulfotransferase enzymes (5,6). Previously, two studies have reported a correlation between sulfotransferase activity in plucked hair follicles and minoxidil response for AGA patients (7,8). Combined data from both studies demonstrates the diagnostic is 94% sensitive and 76% specific for predicting response to minoxidil treatment for AGA. The aim of this study was to demonstrate the clinical utility and validity of minoxidil response testing in AGA patients.

Methods

New patients

A total of 15 patients (eight male, seven female) were included in our analysis of minoxidil response testing. These patients are part of a current prospective clinical study of androgenetic alopecia patients treated with 5% topical minoxidil and assessed a priori with a sulfotransferase activity assay of plucked hairs. Patients were treated with 5% minoxidil, twice daily, for a minimum duration of 6 months. Patients were excluded for active thyroid disease, hormone therapies, use of other AGA treatments, and failure to comply with the trial protocol. Patient progress was thoroughly documented including global photography at regular intervals. After 24 weeks, global photographs were assessed by an independent expert; a standard scale was utilized: (i) no change or decrease in hair and (ii) increase in hair.

Sulfotransferase assay

Plucked anagen hairs were collected from the border between the most prominent area of thinning and non-thinning at the vertex scalp and inspected visually for an intact bulb. Suitable anagen hairs were trimmed to a length of ~1 cm and immersed, bulb first, in 100 µL of the assay solution (50 mM phosphate buffer (pH 8), 5 mM potassium p-nitrophenyl sulfate, 20 µM adenosine 3′,5′-diphosphate, 100 µM minoxidil and 5 mM $MgCl_2$). Hairs were allowed to react with the solution for 24 hours at room temperature. After incubation, hairs were removed and the optical absorbance of the solution at 405 nm was determined with a spectrophotometer (Shimadzu UV-1700, Kyoto, Japan) using a single scan and 1 cm path length.

Meta-analysis

Data from 70 patients was used in meta-analysis (55 patients from two previously published studies (7,8) and 15 patients from our ongoing study). All patients were treated with 5% minoxidil therapy (twice daily) for a minimum duration of 6 months. The sex and distribution of hair loss was not available in all cases (7) and was not included in our analysis. Minoxidil response was determined, in all cases by blinded assessment of global photography. Data from Goren et al. (7) was converted from a three point scale to match a standard scale: (i) no change or decrease in hair and (ii) increase in hair.

Statistics

We chose the value reported by Goren et al. (7) of less than 0.4 absorbance units (AU) as a marker for low follicular sulfotransferase activity. The 0.4 AU cutoff was used to determine a positive or negative test result. The clinical accuracy of the test was determined using Bayes' theorem:

$$\Pr(\sim R|\sim T)=\frac{\Pr(\sim T|\sim R)\Pr(\sim \mathrm{R})}{\Pr(\sim \mathrm{T}|\sim \mathrm{R})\Pr(\sim \mathrm{R})+\Pr(\sim \mathrm{T}|\mathrm{R})\Pr(\mathrm{R})},$$

where $\Pr(\sim R|\sim T)$ is the clinical accuracy of a negative test result, $\Pr(\sim T|\sim \mathrm{R})\Pr(\sim \mathrm{R})$ is the probability of a true negative, $\Pr(\sim R)$ is the prevalence of negative minoxidil responders (60%), $\Pr(\sim T|R)\Pr(R)$ is the probability of a false positive, and $\Pr(R)$ is the is the prevalence of positive minoxidil responders (40%).

Results

Selected results from our ongoing study are shown in Table 1. The AU of the assay solution after 24 hours of incubation with each patient's hair is shown in line with the independent investigators assessment of global photography (nonresponder (i), responder (ii)). The sulfotransferase activity assay was able to predict responders to 5% topical minoxidil therapy with a sensitivity of 100% and a specificity of 71% (Student's t-test $p < 0.005$).

Figure 1 depicts a scatter plot of the responder and nonresponder data from the 70 patients included in our analysis. Each data point is plotted vertically based on the result from a sulfotransferase activity assay (optical absorbance at 405 nm). A line is drawn at 0.4 AU to denote the cutoff for nonresponders. Using the reported prevalence of minoxidil response after 16 weeks (2), Bayes' statistical analysis predicts the test to have 95.9% accuracy for ruling out nonresponders

Table 1. Results from new patients completing a prospective clinical trial

Patient	Age	Sex	AGA duration (years)	Treatment duration (weeks)	AU (405 nm)	Response
1	24	Male	3	24	1.296	1
2	19	Female	3	30	1.004	1
3	20	Female	1	27	0.996	1
4	28	Male	4	26	0.840	0
5	35	Male	3	30	0.800	1
6	35	Male	2	29	0.740	1
7	32	Female	0.5	26	0.736	1
8	28	Female	1	26	0.644	1
9	28	Female	0.5	29	0.612	1
10	33	Male	6	26	0.444	0
11	24	Male	1	26	0.392	0
12	32	Female	2	26	0.388	0
13	23	Male	2	27	0.248	0
14	34	Female	0.5	25	0.204	0
15	26	Male	5	26	0.088	0

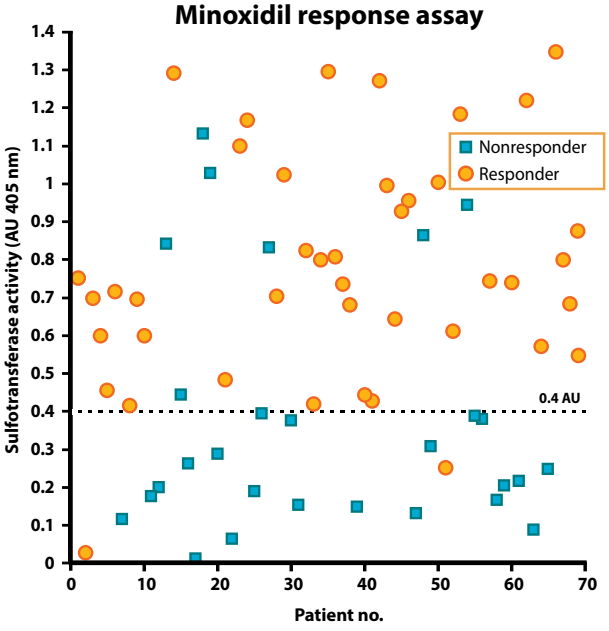

FIG. 1. Scatter plot of responder and nonresponder data from the 70 patients. Each data point is plotted vertically based on the result from a sulfotransferase activity assay (optical absorbance at 405 nm). A dashed line is drawn at 0.4 AU to denote the cutoff for nonresponders reported in Goren et al. (7).

to minoxidil. Table 2 summarizes the performance of the diagnostic test based on our analysis.

Discussion

Because of the limited number of patients in the general population that will exhibit visible hair regrowth following topical minoxidil therapy, a test to rule out nonresponders will have significant clinical utility. In this study, we aimed to determine the clinical utility and validity of a sulfotransferase activity assay in guiding AGA treatment. Since the accuracy of a diagnostic test is determined in the context of population prevalence, we applied Bayes' analysis to the data. The results of this study confirm the clinical validity of the test. Goren et al. (7), Roberts et al. (8), and data from 15 new patients all show similar accuracies of 95.8%, 95.3%, and 100%, respectively, for ruling out nonresponders.

In addition, the meta-analysis of the results from all three studies (70 patients total), yielded an accuracy of 95.9% in ruling out nonresponders to

Table 2. Meta-analysis of minoxidil response studies in 70 patients

	AU < 0.4	AU > 0.4
Responder	2	40
Nonresponder	21	7
Bayesian	Minoxidil works	Minoxidil fails
Prevalence	**0.4**	**0.6**
Test positive	0.95	0.25
Test negative	0.05	0.75
True positive	0.38	
False positive	0.15	
True negative	0.45	
False negative	0.02	
Rule out	**95.94%**	

minoxidil; thus, demonstrating the clinical utility of minoxidil response testing prior to initiating prolonged therapy for AGA. Given the prevalence of over-the-counter minoxidil use, the test could also provide a unique opportunity to protect consumers from the potential side effects, emotional stress, and expense associated with the use of an ineffective drug. Minoxidil response testing could also direct patients to seek medical consultation earlier and ultimately improve outcomes for AGA patients.

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