

Predictive Model for Immunotherapy of Alopecia Areata With Diphencyprone

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Background: Immunotherapy with diphencyprone (diphenylcyclopropenone) is used in the treatment of alopecia areata (AA). Response rates have varied in the literature.

Objectives: To determine the efficacy of diphencyprone therapy for AA in the largest reported cohort of patients; to identify patient and treatment factors predictive of therapeutic success; and to develop a practical model for predicting patient response.

Methods: The medical records of 148 consecutive patients treated with diphencyprone were reviewed. A clinically significant response to diphencyprone therapy was defined as a cosmetically acceptable response or greater than 75% terminal hair regrowth. Survival analyses using the Kaplan-Meier method and the Cox proportional hazards model were performed to determine significant factors predictive of regrowth and relapse.

Results: Using a survival analysis model, the cumulative patient response at 32 months was 77.9% (95% con-

fidence interval, 56.8%-98.9%). Variables independently associated with clinically significant regrowth were age at onset of disease and baseline extent of AA. Older age at onset of AA portended a better prognosis. A cosmetically acceptable end point was obtained in 17.4% of patients with alopecia totalis/universalis, 60.3% with 75% to 99% AA, 88.1% with 50% to 74% AA, and 100% with 25% to 49% AA. A lag of 3 months was present between initiation of therapy and development of significant hair regrowth in the first responders. Relapse after achieving significant regrowth developed in 62.6% of patients.

Conclusions: Response to diphencyprone treatment in AA is affected by baseline extent of AA and age at disease onset. A prolonged treatment course might be necessary. A predictive model has been developed to assist with patient prognostication and counseling.

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TOPICAL immunotherapy was first introduced as treatment for alopecia areata (AA) in 1978 in 2 patients treated with dinitrochlorobenzene.¹ Squaric acid dibutylester²⁻⁸ and diphencyprone (diphenylcyclopropenone)⁹⁻¹⁸ have since been used extensively as contact sensitizers for AA. Reported response rates to diphencyprone therapy are highly variable, ranging from 5% to 85%,^{11,12,17-21} which has led to considerable confusion surrounding the therapeutic value and efficacy of diphencyprone. This variation in outcome might in part be due to differences in patient demographics, treatment protocols, definitions of positive outcomes and end points, and statistical analysis. This retrospective study was undertaken to assess the efficacy of diphencyprone treatment in AA in the largest reported patient cohort to date; to identify patient and treatment fac-

tors associated with therapeutic success; and to establish a sound and practical model for predicting patient response to diphencyprone use.

RESULTS

PATIENT DEMOGRAPHICS

Disease duration ranged from 0.5 months to 55.0 years (mean, 9.6 years), and the duration of the current episode of AA immediately before immunotherapy varied from 0.5 months to 41.0 years (mean, 5.6 years). The age range at initiation of diphencyprone therapy was 8.0 to 77.0 years (mean, 36.3 years), and the age at onset of AA varied from 1.0 to 69.0 years (mean, 26.8 years). As a percentage of patients for whom the status was known, 61.5% (91/148) were female, 44.1% (52/118) were atopic, 33.0% (38/115) experienced nail involvement, and 27.8% (20/72) had a family member with

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PATIENTS AND METHODS

This is a retrospective study based on a review of treatment records and telephone interviews with 148 consecutive patients treated with topical diphencyprone between January 1, 1989, and December 31, 1999, at the University of British Columbia Hair Research and Treatment Centre, Vancouver. A minimum of 25% scalp involvement by AA was necessary for diphencyprone treatment eligibility and study participation. Informed consent was obtained from all participants. Women of childbearing age were required to use a reliable form of birth control. Individuals with AA were ineligible for diphencyprone treatment if they presented with less than 25% scalp involvement, significant cardiovascular disease, pregnancy, or serious intercurrent medical illnesses. All immunotherapy treatments were performed under a study protocol approved by the University of British Columbia Clinical Research Ethics Board.

DIPHENCYPRONE FORMULATION

The diphencyprone was obtained from Sel-Win Chemicals (London, Ontario) and prepared at Royal Oak Pharmacy (Burnaby, British Columbia). It was dissolved in acetone at serial dilutions of 0.0001%, 0.001%, 0.01%, 0.02%, 0.05%, 0.1%, 0.25%, 0.5%, 1.0%, 2.0%, and 4.0% and stored in tightly sealed dark vials to prevent UV light degradation and evaporation.

APPLICATION METHOD

For each patient, half of the scalp was arbitrarily assigned as the treatment side, with the contralateral half of the scalp

serving as an untreated control. Patients were sensitized to diphencyprone treatment at the initial visit by application of 2.0% diphencyprone to a 4-cm-diameter circular area on the control side of the scalp. The control side was selected for sensitization because of a potential for a delayed eczematous flare at the sensitization site. After sensitization, weekly treatments commencing at 0.0001% were initiated on the treatment side of the scalp. A reinforced cotton-tipped applicator was saturated with diphencyprone, and a double coat of diphencyprone was applied to the treatment side of the scalp, first anteroposteriorly and then in a lateral direction. With each successive treatment, the concentration of diphencyprone was serially titrated upward to produce mild inflammation that manifested as pruritus and erythema lasting 36 hours. The concentration of diphencyprone that produced this mild inflammatory response was then maintained for subsequent treatments. Only 1 patient required use of greater than 2% diphencyprone. Occasionally, further upward or downward titration of the diphencyprone concentration was required to achieve transient mild inflammation.

The first 13 patients in this series were previously described by Shapiro et al.¹⁶ These patients underwent half-scalp treatments with diphencyprone for 24 weeks, after which, if terminal hair growth was noted, the entire scalp was then treated under the same weekly protocol. For all subsequent 135 patients in this study, diphencyprone was applied unilaterally until any initial hair growth was detected. At that time, regardless of duration of treatment, the entire scalp was treated with diphencyprone.

During diphencyprone therapy, 20 patients who demonstrated a clinically unequivocal terminal hair growth response to diphencyprone but who had incomplete hair

AA. The estimated baseline extent of scalp involvement by AA was 25% to 49%, 50% to 74%, 75% to 99%, or 100% in 26, 39, 48, and 35 patients, respectively. The mean overall duration of therapy for this cohort was 7.2 months, with a range of 1 day (discontinuation of therapy after initial treatment) to 43 months. In general, patients themselves usually determined when therapy was to be discontinued in consultation with one of us (J.S., H.L.), and the most common reasons were lack of response and inconvenience of attending the clinic for weekly therapy. The wide range of times at which patients discontinued therapy reflects the varying motivation among patients for ongoing treatment.

OVERALL RESPONSE

According to the survival analysis, the cumulative patient response to diphencyprone immunotherapy is 77.9% (95% confidence interval [CI], 56.8%-98.9%) at 32 months (**Figure 1A**). There is a lag of approximately 3 months from initiation of therapy to the first patients demonstrating clinically significant regrowth. After this initial interval, cosmetically acceptable regrowth was observed in 2.3% of patients at 3 months, 22.5% at 6 months, 44.4% at 9 months, 52.0% at 12 months, 63.5% at 18 months, and 70.3% at 24 months (**Table 1**). The me-

dian time required to achieve significant regrowth was 12.2 months (95% CI, 7.0-17.4 months). The residual probabilities of regrowth at given times after initiation of therapy are also specified in Table 1.

PATIENT VARIABLES

Using the Cox proportional hazards model, the only patient variables that were independently associated with clinically significant regrowth were age at onset of AA and baseline extent of AA (**Table 2**). When analyzed as a continuous variable, younger age at onset portended a poorer therapeutic prognosis ($P=.04$). In the group with 25% to 49% AA, all patients obtained clinically significant regrowth by 20 months; for 50% to 74% AA, 88.1% (95% CI, 67.7%-100%) achieved clinically significant regrowth by 16 months; for 75% to 99% AA, 60.3% (95% CI, 26.4%-94.2%) experienced clinically significant regrowth by 33 months; and, finally, for individuals with alopecia totalis or universalis, only 17.4% (95% CI, 0.0%-43.0%) ultimately obtained clinically significant regrowth at 8 months (**Figure 1B**, **Table 3**). The likelihood of differences in responses between these groups was also assessed using the Wald test and pairwise comparisons. Statistically significant higher likelihoods of response were seen only when comparing groups with ei-

regrowth manifesting as persistent localized patches of AA also received intralesional corticosteroids (triamcinolone acetonide, 5 mg/mL, up to a maximum 2 mL) at 4- to 6-week intervals.

DATA COLLECTION

Baseline information obtained before initiation of treatment included age at commencement of diphencyprone therapy, duration of disease, duration of the current episode of AA, presence of atopy, and family history of AA. Data compiled at the time of initial physical examination included the baseline extent of scalp AA (categorized as 25%-49%, 50%-74%, 75%-99%, or 100% hair loss); personal history of atopy, defined by atopic dermatitis, asthma, or hay fever; and nail involvement. Treatment data included highest concentration of diphencyprone applied, treatment number and concentration of diphencyprone at first eczematous response, presence and type of adverse events, total number of treatments, diphencyprone concentration when any hair growth was first detected, cumulative number of treatments, hair loss status at time of treatment discontinuation, concomitant intralesional corticosteroid administration to persistent patches, and relapse after clinically significant regrowth.

An initial hair growth response was declared at the first unequivocal sign of any new unilateral hair within treated sites. The primary study end point, clinically significant regrowth with diphencyprone therapy, was defined as a cosmetically acceptable response (as judged by the patient) or significant regrowth resulting in greater than 75% of the scalp being covered with terminal hair (as determined by the investigators). Cosmetically

acceptable regrowth, as judged by the patient, was often heralded by the abandonment of hairpieces or head coverings. For patients who achieved clinically significant regrowth, subsequent disease relapse was defined as greater than 25% hair loss. Maintenance topical immunotherapy, defined as ongoing therapy once every 1 to 4 weeks, was generally recommended for patients who achieved significant regrowth, although the final decision for this was left to the patient.

STATISTICAL ANALYSIS

Survival analysis was performed using the Kaplan-Meier method to estimate the probability of regrowth caused by diphencyprone therapy as a function of time or treatment number. A Cox proportional hazards model was used to determine factors that independently affected regrowth. Patient factors analyzed using the Cox model included sex, age at onset of disease, duration of the current episode, age at initiation of diphencyprone therapy, baseline extent of AA, presence of atopy or nail changes, and family history of AA. Treatment factors analyzed using the Cox model included highest concentration of diphencyprone applied, treatment number and time at initial regrowth, treatment number and diphencyprone concentration at first eczematous response, concomitant administration of intralesional corticosteroids, and the presence or type of adverse events.

For patients who achieved significant regrowth due to diphencyprone therapy, the rate of relapse over time was also analyzed using the Kaplan-Meier method, with Cox regression being used to assess the effects of maintenance treatment and baseline extent of AA on relapse.

ther 25% to 49% or 50% to 74% AA with patients with totalis or universalis scalp involvement (**Table 4**). Other patient variables, including sex, age at initiation of immunotherapy, duration of the current AA episode, duration of disease, atopy, nail involvement, and family history, did not affect the probability of regrowth (Table 2).

TREATMENT VARIABLES

Four treatment variables independently predicted the development of clinically significant regrowth: the highest concentration of diphencyprone applied, treatment number and time when any initial new hair regrowth was apparent, and concomitant intralesional corticosteroid administration (Table 2). Overall, a higher peak concentration of diphencyprone was associated with a diminished chance of clinically significant regrowth ($P = .049$). Patients who developed initial terminal hair regrowth with diphencyprone therapy either earlier ($P = .03$) or with fewer diphencyprone treatments ($P = .005$) had better therapeutic outcomes. The concomitant administration of intralesional corticosteroids in some patients with persistent patches of AA was associated with a significantly better therapeutic outcome ($P = .01$; odds ratio, 2.23; 95% CI, 1.19-4.17), and this effect of corticosteroid administration seemed to be independent of the baseline extent of AA.

ADVERSE EVENTS

Clinically significant adverse events were experienced by 56.8% of patients and included blistering (45.3%), hyperpigmentation (12.2%), autoeczematization (10.1%), hypopigmentation (2.0%), and symptomatic lymphadenopathy (2.0%). Autoeczematization was managed with topical corticosteroid administration, and oral corticosteroids were administered to 4.7% of patients for blistering and severe autoeczematization. The presence of any of these adverse events did not affect clinically significant regrowth ($P = .38$).

RELAPSE

Relapse after achievement of clinically significant regrowth with diphencyprone therapy was defined as the subsequent loss of greater than 25% of regrown hair. Overall, 62.6% (95% CI, 36.1%-89.1%) of patients who had developed significant regrowth with diphencyprone relapsed after 37 months of follow-up (**Figure 2**), and the median time to relapse was 30.7 months (95% CI, 2.4-58.9 months). The risk of relapse was not significantly related to the baseline extent of AA at the initiation of therapy ($P = .54$) or to ongoing maintenance diphencyprone immunotherapy after clinically significant regrowth was achieved ($P = .48$).

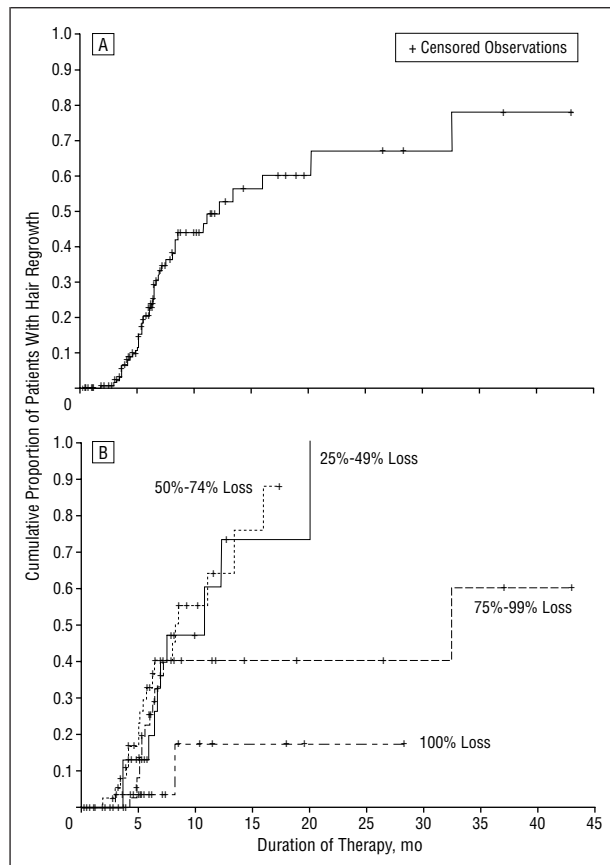


Figure 1. Cumulative proportion of patients with clinically significant hair regrowth during diphenylpyrone topical immunotherapy. A, Overall for all patients. B, Stratified by baseline extent of alopecia areata.

Table 1. Cumulative Patient Response Rate to Diphenylpyrone Immunotherapy Over Time

Duration of Diphenylpyrone Therapy, mo	Clinically Significant Hair Regrowth (95% Confidence Interval), %	Residual Probability of Hair Regrowth, %
3	2.3 (0-4.9)	76
6	22.5 (14.6-30.4)	55
9	44.4 (32.7-55.8)	34
12	52.0 (38.9-65.1)	26
18	63.5 (47.5-79.5)	14
24	70.3 (51.9-88.7)	8

COMMENT

Alopecia areata is an autoimmune disorder affecting the hair follicle that manifests along a spectrum ranging from focal areas of balding to complete loss of all scalp and body hair. Current therapeutic options²² include topical immunotherapy, corticosteroids, psoralen-UV-A, anthralin, minoxidil, and cyclosporine.^{23,24} Because all of these options are associated with specific adverse effects and limitations, detailed outcome data are important for obtaining informed consent, guiding therapy, and counseling patients. In this study we modeled the therapeutic outcome of diphenylpyrone immunotherapy according to a broad range of patient and treatment variables.

Table 2. Patient and Treatment Variables Analyzed Using the Cox Proportional Hazards Model*

Significant ($P < .05$)	Not Significant
Patient Variables	
Baseline extent of AA (.01)	Sex (.56)
Age at AA onset (.04)	Age at diphenylpyrone initiation (.09)
	Duration of disease (.09)
	Duration of current AA episode (.08)
	Atopy (.63)
	Nail changes (.27)
	Family history AA (.49)
Treatment Variables	
Highest concentration (.049)	Concentration at first eczematous response (.44)
Treatment number at initial response (.005)	Treatment number at first eczematous response (.90)
Time of initial response (.03)	Adverse events (.38)
Intralesional corticosteroid therapy (.01)	

*AA indicates alopecia areata. P values are given in parentheses.

Table 3. Clinically Significant Hair Regrowth Stratified by Baseline Extent of Alopecia Areata

Baseline Extent of Alopecia Areata, %	Clinically Significant Regrowth, % (95% Confidence Interval)	Median Time to Regrowth, mo
25-49	100.0 (NA*)	10.8
50-74	88.1 (67.7-100.0)	8.3
75-99	60.3 (26.4-94.2)	32.4
100	17.4 (0-43.0)	...

*NA indicates not applicable.

Table 4. Likelihood of Obtaining Clinically Significant Hair Regrowth

Baseline Extent of Alopecia Areata, %	Odds Ratio (95% Confidence Interval)
25-49 vs 100	6.4* (1.4-28.8)
50-74 vs 100	7.4* (1.7-31.6)
75-99 vs 100	3.8 (0.9-16.8)

* $P < .05$.

Although the mechanism of action of diphenylpyrone has not been clearly delineated, it has been proposed that this immunogen recruits a different T-cell subpopulation to the treated area, which in turn enhances the clearance of the putative follicular antigen.^{7,18,25} Specific hypotheses put forth have included “antigenic competition”²⁶ and interference with the production of proinflammatory cytokines by the immunogen.^{23,24}

The efficacy of diphenylpyrone in the treatment of AA was first reported by Happle et al¹⁸ in 1983 and later confirmed by Hull and Norris.¹¹ This study detected a raw response rate in 50% of patients and a cosmetically acceptable result in 29%. A 6-month posttreatment follow-up study²⁷ of responders demonstrated that 37% (7/19) did not experience further hair loss, 68% maintained a cosmetically acceptable response, 53% developed patchy AA, and 10% lost all the hair that they had regrown. In a sub-

sequent series¹² of 78 patients with extensive AA, 62% demonstrated a treatment response and 32% had complete regrowth. van der Steen et al,¹⁹ in a series of 139 patients, reported a raw response rate of 50.4% and, using multivariate analysis, identified extensive AA, prolonged disease duration, and the presence of nail changes as factors predictive of a poorer response. Relapse and resistance to therapy developed in 28% (30/107) of patients.¹⁹ Weise et al²⁸ subsequently demonstrated 5 factors of prognostic significance: type of AA, presence of nail changes, duration of AA, age at onset of disease, and the presence of atopic dermatitis. Our findings showed lack of correlation between response and disease duration and the presence of nail changes or atopy but confirmed a positive correlation with extent of scalp involvement and age at onset of disease. Shapiro et al¹⁶ demonstrated a raw response to diphenycprone of 38% in AA and found no benefit from the addition of topical 5% minoxidil. Pericin and Trueb¹⁵ reported a somewhat impressive response of 70.6% in a series of 68 patients with AA, with complete remission achieved in 30.9%. Other studies^{11,12,17-20} have had success ranging from 5% to 85%.

The literature clearly indicates a high degree of inconsistency with respect to patient response to diphenycprone therapy. This variability can be explained by several methodologic or reporting factors. First, a uniform definition for “response” does not exist. Some studies have left the definition ambiguous, whereas others have defined response as total hair regrowth, cosmetically acceptable hair regrowth, or a specific percentage of hair regrowth. The Alopecia Areata Investigational Guidelines have helped provide some uniformity when studying AA.²⁹ For the purpose of this study, the primary end point of clinically significant regrowth was specifically achieved when either of 2 criteria were satisfied: the patient perceived cosmetically acceptable hair regrowth (including abandonment of wigs if appropriate) or the investigators’ clinical impression was that regrowth resulted in greater than 75% of the scalp being covered with hair. The cosmetically acceptable end point, although somewhat subjective, is an important concept because it is the most clinically practical and relevant end point from a social perspective, and the key patient motive for seeking therapy. Our definition included provision for an objective assessment by the investigators to account for patients with unrealistic hair regrowth expectations. A second explanation for interstudy differences in reported responses to diphenycprone therapy is the significant variability in immunotherapy protocols, treatment durations, and follow-up periods. Finally, different groups have used variable and primarily basic statistical methods for data analysis and reporting therapeutic responses.

Our model used a survival analysis approach to characterize patient response to maximally account for all of the treatment data and follow-up periods that were available in our cohort. This method, which is used extensively in oncology, provides appropriate weighting to the duration of time that patients are being treated and followed up. Thus, rather than simply considering patients who abandoned therapy before an expected response as treatment failures, this statistical model provides a more

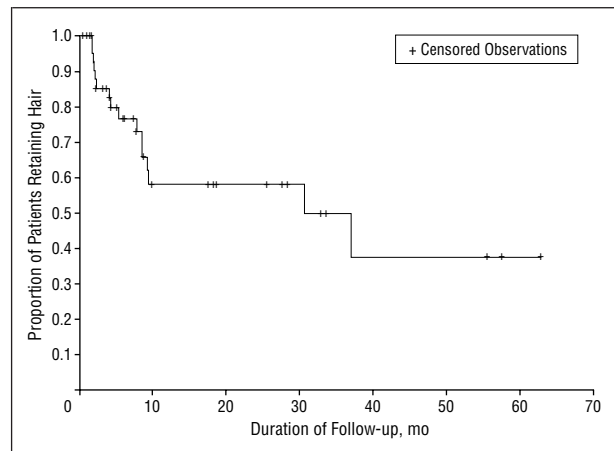


Figure 2. Relapse of alopecia areata after clinically significant hair regrowth (n=45).

accurate and meaningful estimate of the “true” response rate. In addition, survival analysis also provides a means by which the expected time to response can be derived.

Overall, we found that the estimated primary response to diphenycprone therapy is excellent, with 77.9% of all patients obtaining a clinically significant response by 32 months. The model also indicates that a prolonged therapeutic period might be necessary for achieving this result. When patients commence diphenycprone therapy, the 3-month interval between initiation of treatment and the first possible achievement of clinically significant regrowth should be considered as the absolute minimum time commitment required, assuming weekly treatments. At the other end of the spectrum, most patients (ie, 90%) who developed a clinically significant response did so by 24 months of treatment, thus providing little support for continuing therapy in nonresponders beyond this point. In contrast, if therapy is abandoned at 1 year or at 18 months, we estimate that one third and one fifth of responders, respectively, will not be identified.

The only baseline patient characteristics that affected the therapeutic response to diphenycprone were baseline extent of AA and age at onset of disease. Patients with earlier onset of disease or more extensive baseline scalp AA had a poorer response to diphenycprone therapy. Price and Colombe³⁰ similarly distinguished 2 separate groups of patients and suggested that those with early onset of AA and alopecia totalis and universalis should be considered different prognostically. From an HLA perspective, they are a separate subgroup, potentially implicating a somewhat different immunologic basis for their disease, and possibly accounting for the lack of response in those with early onset. In addition, the time to achieving regrowth was also significantly longer for patients with alopecia totalis and universalis. Use of higher concentrations of diphenycprone and a prolonged treatment interval or number before an initial response also portended a less favorable therapeutic outcome. Patients in whom an eczematous response can be elicited and maintained using lower diphenycprone concentrations are more likely to demonstrate a regrowth response. One can speculate that production of cytokines or factors that are specifically responsible for hair growth might be at a higher level in these more “haptensensitive” individu-

als. Polymorphisms in the tumor necrosis factor α^{31} and interleukin 1 antagonist³² genes have been linked to the severity of AA, and this could potentially affect the extent and degree of diphencyprone-induced inflammation, thereby affecting the clinical outcome. Administration of intraleisional corticosteroids to persistent patches that were slower to respond to diphencyprone therapy seems to increase the likelihood of achieving clinically significant regrowth, independent of baseline extent of AA.

A subsequent relapse after the initial achievement of clinically significant regrowth with diphencyprone therapy was not affected by implementation of maintenance therapy. However, there might have been insufficient power in our relapse analysis to detect a statistical effect of maintenance therapy if it existed. Taking into account the primary response and relapse results, the overall rate of success was 29.1% for all those who initiated diphencyprone immunotherapy (ie, 77.9% response rate times 37.4% rate of long-term remission).

By extrapolating data from the Kaplan-Meier survival analysis, it is possible to estimate the conditional residual probabilities of regrowth at a given time for patients who have not yet achieved significant regrowth up to that specific point in time (Table 1). For example, if a patient has not yet achieved regrowth by 6 months of continuous weekly therapy, there is still a 55% probability of regrowing hair if treatment is continued. These residual probabilities can be particularly useful in counseling patients because they provide reasonable estimates of the ongoing likelihood of therapeutic success as a function of treatment duration. Thus, reference to these data will enable each patient to individually decide whether to continue or abandon treatment at any given time depending on his or her own specific thresholds for success and consideration of treatment limitations such as frequent clinic visits and the potential for adverse events. A practical model based on clinical experience for guiding clinicians and patients undertaking diphencyprone immunotherapy for AA did not heretofore exist in the literature.

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