Title: Retrospective review of diphencyprone in the treatment of alopecia areata.

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ABSTRACT

Background: Contact immunotherapy with diphencyprone (DCP) is used in the management of alopecia areata (AA). The treatment, given weekly, induces dermatitis and requires a prolonged treatment course over months. Reported efficacy is variable and an individual's response cannot currently be accurately predicted.

Objective: Identify patient and treatment course variables that may affect outcome to DCP treatment.

Methods We performed a retrospective review of patient data from our DCP service over a 20-year period from 1991-2010, including patient and treatment course variables, with the aim of identifying factors relevant to treatment outcome.

Results Complete data was available for 205 treatment courses. 162 (79%) treatment courses were completed for 133 patients. Overall, 72.2% (96/133) of completed treatment courses resulted in some degree of hair re-growth (any grade). In 15.8% (21/133) of completed courses, hair growth response was >90% re-growth. However, 27.1% (36/133) of courses resulted in no hair growth response. During a further 13.5% (18/133) of courses, a response to DCP was obtained initially but patients relapsed during treatment. We found extent of alopecia at baseline and duration of disease to be statistically significant when comparing those with an optimal outcome with those who did not ($p<0.05$). In contrast to other reports, we found variables such as atopy, age at onset of disease and the presence of nail changes were not of statistical significance with regard to outcome. For patients receiving more than one course of treatment, response to DCP treatment tended to be broadly consistent for each treatment course. DCP was generally well tolerated with 43% of patients reporting no side effects. However, 5.9% (12/205) of DCP treatment courses were terminated early due to side effects. Cervical lymphadenopathy was the most common side effect (39%).

Limitations of this study include that this was a retrospective study and the lack of long term follow up looking at relapse.

Conclusion Our findings add to published data on DCP outcome, assisting clinicians and patients in the decision as to whether to undertake a course of DCP treatment and show that extent of alopecia at baseline and duration of disease are important factors in predicting response to treatment.

Key Words: alopecia areata, diphencyprone, DCP, immunotherapy

Capsule Summary:

What is already known on this topic:

- There is a lack of robust evidence for many of the treatments used in AA.
- Spontaneous re-growth occurs in 34-50%
- Treatment with immunotherapy results in widely varied response rates
- Patient and treatment variables may predict outcome to immunotherapy

What this article adds to our knowledge:

- More extensive AA at baseline predicts poorer response to treatment.
- Longer duration of disease at baseline predicts poorer response to treatment
- Atopy should not be considered a negative prognostic factor
- Patients receiving more than one course of treatment have similar response to treatment in subsequent courses
- Failure to respond to one treatment course should not preclude a further trial.

How this information impacts clinical practice and or changes patient care:

- This study provides us with further information with can be provided to patients considering undertaking a course of DCP including likelihood of response
- This study also provides insight into outcome for those patients who may which to have further treatments.

INTRODUCTION

Alopecia areata (AA) is considered to be a CD8+ T-cell dependent organ specific autoimmune disorder affecting the hair follicle[1] with a clinical disease spectrum ranging from limited patchy scalp hair loss to complete loss of scalp and body hair. Commonly used treatments include topical and intra-lesional corticosteroids, dithranol and topical immunotherapy.[2] The mechanism of action of immunotherapy using diphencyprone (DCP) is unclear but has been described as an immune-deviation strategy.[1] The protocol for DCP contact immunotherapy in alopecia areata was first described by Happle in 1983.[3] He reported 50% of patients had some response to treatment, with a cosmetically acceptable result in 29%. Subsequent reports reveal widely variable treatment responses (9-85% complete response rates).[4] Possible explanations for these variations in response include definition of treatment response, disease duration and severity, and duration of treatment. We reviewed 20 years data on DCP treatment courses for AA in Glasgow with an aim of identifying predictors of treatment outcome.

METHODS

Medical and nursing caserecords were reviewed for patients commencing treatment with DCP between January 1991 and December 2010. Data recorded included age at start of treatment; age at disease onset; gender; history of atopy (asthma, allergic rhinitis and atopic eczema); evidence of nail changes; baseline severity of hair loss (graded 1-5: 1-limited patchy; 2–extensive patchy; 3–subtotal scalp hair loss; 4–alopecia totalis; 5–alopecia universalis; or diffuse loss) as per MacDonald-Hull;[5] duration of alopecia; previous treatments; number of DCP treatments; concentrations of DCP used; patient-reported inflammatory response (1 - nil, 2 - barely perceptible, 3 - mild, 4 - moderate 5 - intense, 6 - very intense) and treatment response (0 – no hair growth; 1 - vellus hair growth; 2 - sparse terminal pigmented hair; 3 – pigmented terminal hair re-growth but some persistent patches of alopecia; 4 - 90-99% hair re-growth; 5 - complete re-growth; grade 6: any response followed by relapse). An optimal outcome was defined by

outcome groups 4 and 5 (i.e. >90% hair re-growth). In addition, for the period 2001-2010, side effects recorded during treatment were documented.

Data for patients receiving more than one treatment course during the 20 year period were included only once for statistical analysis (first course only). This group were reviewed separately to assess reproducibility of DCP response over multiple treatment courses.

All patients had a clinical diagnosis of alopecia areata made by a consultant dermatologist and/or by a consultant in a tertiary referral hair clinic. All patients were treated with topical DCP according to a standard protocol. This consisted of sensitisation with 2% DCP on the scalp (if DCP naïve) followed by weekly treatments with DCP. The aim was to induce an eczematous reaction consisting of erythema and pruritus persisting for 48 hours. Initially, half the scalp was treated. If hair growth was observed, the entire scalp would be treated. There was some flexibility regarding end point of treatment course, however treatment would be discontinued in the following situations: if no hair growth was achieved after 6 months treatment; at full re-growth (if occurring before 6 months); when no further re-growth could be obtained despite treatment or at patient request.

Statistical Analysis: Factors possibly related to outcome were compared between those with an optimal treatment response (grade4&5) and those without (grade0-3 and grade6). These between-group comparisons were done using t-test or Mann-Whitney tests for numerical variables, and chi-squared for categorical variables. All analyses were done using Minitab (version 16) at a 5% significance level.

This retrospective review of data did not require institutional review board / human subjects committee approval but was registered with the local audit, research and development committee.

RESULTS

In the 20-year-period from 1991-2010, 253 treatment courses were undertaken, with available data on 205. Of 205 treatment courses, 162 were completed on 133 patients (18 patients received 2 courses; 2 patients received 3 courses; 1 patient received 4 courses; 1 patient received 5 courses).
Forty-three courses (21%) were not completed. This represents a dropout rate of 1 in 5. All patients dropping out after sensitisation or after less than 5 sessions were classed as incomplete and therefore excluded from the analysis. Reasons for discontinuation included failure to attend/unknown (19/205 courses); social reasons (12/205 courses) and treatment side effects (12/205 courses). No patients were found to be DCP anergic.

Patient data

Patient demographics, baseline clinical information and treatment data are shown in table I and figure 1. Most patients had tried more than one treatment before referral for DCP, however 8.3% (11/133) had no previous treatment. Patients trying DCP as a first line treatment tended to have more severe AA at baseline (63.4% [7/11] grade 4/5/diffuse).

Response to Treatment

Treatment course information for the cohort is summarised in table 1. With respect to treatment response, 36/133 (27.1%) had no response to treatment, 27/133 (20.3%) developed vellus hair, 8/133 (6.0%) developed sparse pigmented hair, 22/133 (16.5%) developed terminal re-growth with patchy alopecia, 7/133 (5.3%) developed 90-99% re-growth and 14/133 (10.5%) patients developed complete re-growth (figure 2). Final treatment outcome was unrecorded for 1 patient. In 18/133 (13.5%) courses, initial hair re-growth was followed by significant hair loss during treatment.

Patient and Treatment variables

Differences in outcome with respect to patient and treatment variables are shown in tables IIa-c. For statistical analysis, course outcomes were categorised as optimal response (>90% re-growth: groups 4 & 5) and non-optimal response (groups 0-3 and group 6).

Those with an optimal response were found to have had a significantly lower median duration of disease than those without (2 years vs. 4.5 years, p=0.046). There was also a significant association between baseline disease extent and optimal response (p=0.003). Those with grade 1 AA were more likely to have an optimal response and those with grade 3-5 are less likely (figure III). All the other variables were not significant, as shown in table IId.

Side effects

Treatment side effects in the cohort of patients treated between 2001-2010 (n=95) were documented. Additionally, those experienced by patients that did not complete the course were reviewed. Overall 5.9% (12/205) of treatment courses were terminated early due to side effects.

No side effects were reported in 42/95 patients (44%). Mild eczema outwith the scalp was reported during 17/95 treatments (18%) and severe eczema (defined as blistering, weeping, +/- widespread secondary sensitisation) occurred in 11/95 treatments (12%). Cervical lymphadenopathy was the commonest side effect reported in 37/95 patients (39%). Headache occurred in 14/95 (15%) treatments, and otalgia in 2/95 (2%) patients.

Other side effects included flare of a facial acneiform eruption; postinflammatory hyperpigmentation of the scalp and 2 cases of severe peri-orbital / facial swelling. Both the latter cases occurred at or shortly after sensitisation with 2% DCP. In both cases, a moderate (therapeutic) dermatitic scalp reaction to DCP was associated with severe periorbital and facial oedema requiring a course of oral prednisolone. Whether the facial swelling represented a type 1 reaction to DCP is uncertain. Neither patient continued with treatment.

Relapse

Data on relapse following completion of treatment was not routinely documented however, those patients relapsing during treatment following an initial response, were recorded. In total, 18/133 (13.5%) patients achieved initial hair re-growth but then lost hair during treatment. In addition, 22 patients had more than one course of DCP during the 20 year study period (18 patients had 2 courses, 2 patients had 3 courses, 1 patient had 4 courses, 1 patient had 5 courses [n = 51 courses]). The median grade for disease extent in this group was extensive patchy. The mean time between the end of one course and start of next course was 16 months (median 14 months). 20 patients had consistent responses to DCP in all courses. 19 had re-growth in all courses, 1 no re-growth in all courses. Thus 91% (20/22) showed consistent responses to DCP treatment. However, for 2 patients who had a dissimilar response, both responded poorly in the first course but were treated successfully in a second course.

DISCUSSION

Spontaneous re-growth in patchy localised AA is estimated to occur in 34-50% of patients.[2] However, patients with more extensive disease often wish to pursue treatment and topical immunotherapy has been recommended as a first line treatment option if locally available.[2] The allergic contact dermatitis caused by DCP is thought to attenuate the T-cell mediated immune reaction against the hair bulb allowing re-growth of the hair.[7]

It is not possible to accurately predict an individual`s response to immunotherapy with DCP. Before committing to an often prolonged treatment course, in addition to the uncertainty of treatment response, patients must consider factors such as the impact of once weekly hospital attendance for a minimum 6-month period, strict photo-protection of the scalp for 48 hours after treatment and a heightened scrutiny of, and emotional response to, hair gain and loss.

Patient and treatment variables have been reported as being relevant in response to DCP treatment.[5, 8-13] With the aim of providing better information on outcome for both clinician and patient in making the decision to embark on DCP treatment, we reviewed 20 years data on DCP treatment courses. The

variables assessed included baseline severity of hair loss, disease duration, the presence of atopy, nail changes and hair growth response.

The DCP service has been provided in our Department for over 20 years and has run in conjunction with a dedicated Hair Clinic for the last 14 years, with a small cohort of doctors and nursing staff. Given the small numbers of clinic staff since the service began (5 experienced senior nurses) documentation and interpretation of patient responses has been consistent. This DCP service appears to be one of the larger services provided in the UK and is perhaps one of the few services with as yet no reported cases of staff sensitisation due to strict protocols for protective clothing worn by clinical and pharmacy staff. Additionally this appears to be one of the larger cohorts of patients receiving DCP treatment performed to date.[8-13] Limitations of this study include use of retrospective data and limited longterm follow up with respect to disease relapse.

Cohort characteristics appear broadly similar to those of other studies. The median age of our group (33.5 years) and gender split (74% female) is similar to that of several other large studies .[10, 13] Mean duration of disease (6.8 years) is similar to studies by El- Zawahry (6.61 years), Ohlmeier (6 years) and Wiseman (9.6 years) thus our group is comparable in terms of disease chronicity.

Atopy was present in 36.1% of patients, similar to numbers reported in several other larger DCP studies[10, 13] and in keeping with current European data on atopy prevalence in the general population,[15] but significantly higher than observed by El-Zawahry's group (9.6%).[11]

We suspect the documentation of nail changes in this study (18.8%) may have been an overestimation as this parameter was recorded only in nursing documentation and may have included changes other than pitting and trachonychia, possibly explaining the lack of significance with respect to outcome compared with other studies.[8,9] Other studies have documented nail changes ranging from 12.6%[11] to 33.0%[13] of patients receiving DCP and are thought to occur in around 10% of areata patients.[2]

No patients were found to be anergic in contrast with other studies which quote rates of anergy in immunotherapy ranging from 5-19%.[10, 16-18] Reasons for this finding are unclear.

With respect to patient variables predicting outcome, we found both baseline severity of hair loss (p=0.003) and duration of disease (p=0.043) to be significant similar to Van der Steen and Weise *et al*.[8,9] However both these authors and others have found variables in addition to disease severity and duration of disease to be significant.[5, 10-13] Atopy coincident with AA is postulated to be associated with a poorer disease prognosis[20, 21] and possibly a worse outcome with DCP treatment.[9, 12] However, in common with Wiseman *et al*[13] our study did not find atopy to be of statistical significance with regard to outcome. The criteria by which patients were considered to be atopic has varied between studies: while we included a history of hayfever, childhood asthma or eczema as consistent with atopy, other studies looked only at atopic eczema and outcome.[9]

Many studies, including this, have found gender to be unimportant in predicting outcome.[4] The greater proportion of women completing treatment in our cohort (74.4%) and others may reflect the cosmetic impact of AA in women and a greater desire for treatment.[10, 13]

Treatment variables such as requiring higher concentrations of DCP to maintain an inflammatory response have also been thought to be an unfavorable prognostic factor.[9, 13, 22] However, this was not true of our cohort. While optimal responders (n=21) required a median concentration of DCP of 0.025% to maintain an inflammatory response compared with 0.01% for non-optimal responders (n=111), this was not statistically significance. It has been suggested that if a higher DCP concentration is required to achieve active inflammation this may signify greater difficulty inducing sufficient cytokine and inflammatory mediator release required to induce hair growth.[13] The greater concentration used in the optimal response group cannot be explained by differences in treatment course length (median no. treatments for both was 27). A further intriguing finding was that all groups had the same median median inflammatory responses (grade 4) suggesting factors additional to induction and maintenance of inflammation are important in inducing hair re-growth.

Comparisons between published studies can be difficult. While an optimal response of 15.8% may appear low, this may relate to definition of optimal response.[8, 10, 11, 13] In this study, optimal response was defined as >90% re-growth. Other studies have used a variety of definitions of optimal response ranging from >75% re-growth,[11 13] to less well defined criteria such as "subtotal or total re-growth."[8] In addition, there may be variation in disease severity at baseline: achieving >90% re-growth in a patient with limited patchy disease may not be directly comparable, in terms of treatment success, with baseline AA totalis achieving >90% re-growth. The largest group in this study were those with severe loss at baseline (totalis/universalis n=53 [39.8%]). Other studies have involved more individuals with less severe disease. Ohlmeier *et al* reported complete response rates of 37.8% but only 17.8% had totalis/universalis at baseline.[10]

A drop out rate of 1 in 5 (43/205 [21%]) perhaps reflects the prolonged commitment to treatment required of patients. As we offer treatment to individuals from a wide geographic area, this commitment may involve long journeys on a weekly basis and patients may dropout sooner as a result. Dropout due to side effects was 5.9% [12/205], broadly similar to other centres. Ohlmejer *et al* found 1.5% of patients (2/135) discontinued therapy due to side effects.[10] In our cohort, cervical lymphadenopathy was the commonest side effect reported in 37/95 patients (39%), significantly higher than 2% incidence in some studies[13] but similar to others (50%).[11] Additionally, we identified 2 patients with a possible Type I reaction to DCP, a phenomenon rarely reported.[23, 24] It has been suggested that this may be dose-dependent, with patients able to continue treatment without side effects at a lower doses. We also report 2 cases of severe peri-orbital / facial swelling which occurred at or shortly after sensitisation with 2% DCP and required treatment with oral prednisolone. In both, this was associated with only a moderate (therapeutic) dermatitic scalp reaction to DCP. Whether the facial swelling represented a type 1 reaction to DCP is uncertain however, neither patient wished to continue treatment. A further unusual side effect not previously reported was the development of an acneiform facial eruption in a 41-year-old man after

21 treatments with DCP. There was a history of facial acne previously, however this had been entirely settled prior to DCP treatment being commenced. The eruption settled following a 3-month course of oral minocycline and cessation of DCP therapy.

Although we lack long-term follow up data for the majority of patients, 22 patients received multiple courses of DCP over the 20 year period (n=51 courses). This group achieved a mean remission period of 16 months between courses. Of those receiving more than one treatment course, 91% of patients had a broadly similar response to DCP with each treatment course (19 had re-growth in all courses, 1 had no re-growth in all courses). While our department has not offered on-going maintenance therapy for individuals who have successfully completed a course of DCP treatment, this is recommended by some centres.[11. 19, 22, 25,] However, the benefit of this strategy has been questioned. [13, 22] Given the continuity of response observed in repeat courses it would be interesting to assess hether DCP maintenance would result in a more prolonged remission compared with no maintenance therapy and further study of the role of maintenance therapy is warranted. For the two patients who had a dissimilar response, both responded poorly in the first course but were treated successfully in the second course. Thus, a poor initial response should not necessarily preclude a second trial of DCP treatment

CONCLUSIONS:

We found extent of alopecia at baseline and duration of disease are predictors of outcome, findings which may assist patients in the decision to commit to undertaking DCP treatment. Atopy was not found to be a negative predictive factor and should not preclude trial of treatment. We recognise the need for improved follow up and now send questionnaires to all patients completing successful courses 1 year after completion of treatment. Further studies assessing maintenance therapy are required. Additionally in the group not responding despite adequate immune response/inflammation, further comparative

studies may help elucidate the immunological mechanisms by which DCP immune deviation permits hair re-growth.

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Figure 1: Distribution of severity of hair loss at baseline (n=133)

The figure shows that the distribution of severity of hair loss in this group is weighted towards the more severe end of the spectrum in AA, with only 19% (25/133) having limited patchy disease and 77% (103/133) with extensive patchy, subtotal hair loss, alopecia totalis or alopecia universalis.

Figure 2: Response to treatment in those completing the course.

Figure showing an optimal outcome (complete re-growth or 90-99% re-growth) was achieved in 16% (21/133) of patients completing the course of DCP. However 27% of patients had no response (36/133) to treatment.

Figure 3: Severity of Hair Loss at Baseline and Outcome

Figure showing that fewer patients with severe hair loss at baseline (alopecia totalis and universalis) appear to achieve an optimal response (shaded in red in the figure) after treatment compared with those with less severe hair loss at baseline (limited patchy AA).

Table I: Patient Demographics, Clinical and Treatment Data of whole cohort (n=133)

Demographic data		
Number of treatment courses with available data		205
Number of completed treatment courses		162
Number of patients completing course		133
Number of incomplete treatment courses		43
Gender of those competing treatment course:	Female	99/133 (74.4%)
	Male	34/133 (25.6%)
Age at beginning of treatment (years)		
	Mean	35
	Median	33.5
	Range	13-69
Clinical Data		
History of Atopy		48/133 (36.1%)
Nail changes		25/133 (18.8%)
Severity of AA at baseline (fig. 1):		
	Limited patchy	25/133 (18.8%)
	Extensive patchy	35/133 (26.3%)
	Subtotal hair loss	15/133 (11.3%)
	AA Totalis	33/133 (24.8%)
	AA Universalis	20/133 (15.0%)
	Diffuse AA	3/133 (2.3%)
	Unknown/Undefined	2/133(1.5%)
Disease Duration at baseline:	Mean	6.8 years
	> 10 years	37/133 (27.8%)
	< 1 year	25/133 (18.8%)
	> 1 year and < 10 years	68/133 (51.1%)
	Unknown	3/133 (2.3%)
Treatment Data		
Average number of treatments per course		34
Range		10-115
Median median concentration of DCP used		0.01%.
Median median inflammation achieved		4

Table IIa: Table showing patient variables Age and Sex in each response group

	All patients completing treatment course	Any response (grade 1-6)	No response	Optimal response (>90% re-growth: grade 4+5)	Non-Optimal Response (grade 0-3 and grade 6)
Number of patients	133	96 (72%)	36 (27.1%)	21 (15.8%)	111 (83.5%)
Median Age (years)	33.5	30	37	34	33
Females	99/133 (74%)	71/96 (74%)	27/36 (75%)	14/21 (67%)	84/111 (75.7%)

Table IIb: Table showing treatment variables in each response group:

	All patients completing treatment course	Any Response (grade 1-6) n= 96/133	No response (grade 0) n= 36/133	Optimal response (>90% growth: grade 4&5) n= 21/133	Non-Optimal Response (grade 0-3 and grade 6) n= 111/133
Mean Number of treatments per course	34	37	25	34	34
Median number of treatments per course	27	27	23	27	27
Median median % DCP	0.01%	0.01%	0.0025%	0.025%	0.0100%
Median grade of inflammation (1-6)	4	4	4	4	4

Table IIc: Table showing patient variables in each response group

Patient Variable	Any Response (Grade 1-6) n = 96/133	No Response (Grade 0) n = 36/133	Optimal Response (Grade 4 & 5) n = 21/133	Non-Optimal Response (grade 0-3 and grade 6) n= 111/133
Atopic	32/48 (66.6%)	16/48 (33.3%)	7/48 (14.6%)	41/48 (85.4%)
Non-atopic†	59/79 (70%)	19/79 (24.1%)	12/79 (15.2%)	66/79 (83.5%)
Severity of Alopecia§				
• Alopecia Universalis/ Totalis	34/53 (64%)	19/53 (35.8%)	4/53 (7.5%)	49/53 (92.5%)
• Mild AA	19/25 (76%)	6/25 (24.0%)	9/25 (36.0%)	16/25 (64.0%)
Length of time with AA‡				
• >10 yrs	28/37 (75%)	9/37 (24.3%)	3/37 (8.1%)	34/37 (91.9%)
• <1 yr	18/25 (72%)	7/25 (28.0%)	6/25 (24.0%)	19/25 (76.0%)
Nail Changes#	17/25 (68%)	8/25 (32.0%)	5/25 (20.0%)	20/25 (80%)

† Atopic status of 6/133 patients unknown and 1 non-atopic patient had an unknown outcome, § 1/133 patients had an unknown severity of hair loss and 1 patient with totalis/universalis had an unknown outcome, ‡ 3/133 had an unknown disease duration. # nail changes unknown for 75 patients.

Table IId: Statistical analysis of patient and treatment variables: optimal vs. non-optimal response

Patient Variable	Statistical test used	p value
Age	Mann-Whitney	p = 0.932
Age at Onset	Mann-Whitney	p = 0.966
Gender	Pearson Chi-Square	p = 0.397
Extent of disease*	Pearson Chi-Square	p = 0.003* Those with grade ≥ 3 loss are less likely to have an optimal outcome
Duration of disease*	Mann-Whitney	p = 0.046* Those with the optimal response had a significantly lower median duration of disease
Atopy	Pearson Chi-Square	p = 0.903
Nail Changes	Pearson Chi-Square	p = 0.906
Treatment Variable		
Median Strength of DCP	Mann-Whitney	p = 0.386
Median Inflammatory Response	Pearson Chi-Square	p = 0.358
Total Number of treatments	Mann-Whitney	p = 0.794

* Denotes statistically significant results