Effectiveness of Paint Psoralen and Ultraviolet-A in Alopecia Areata - Our Experience in the National Skin Center

Lucinda Siyun Tan, Melissa Mei Hsia Chan¹, Daryl Jian An Tan¹, Joyce Siong See Lee, Wei-Sheng Chong

Abstract

Background: Alopecia areata (AA) is usually a benign cause of patchy hair loss that often resolves within a few weeks to months. Most treatment modalities are ineffective in the treatment of severe AA. The use of paint psoralen and ultraviolet-A (PUVA) in the treatment of patients with severe forms of AA has been reported in the literature. Aims and Objective: The aim of this study was to evaluate the effectiveness of paint PUVA therapy in the treatment of AA in Singapore. Materials and Methods: We performed a 10-year retrospective analysis of patients who underwent paint PUVA for AA. We evaluated patient demographics and treatment outcomes in the form of percentage change in baseline severity of alopecia tool score and final amount of hair regrowth and relapse rate. Results: Ten patients were included in this study. With paint PUVA therapy, significant hair regrowth was seen in six patients. Paint PUVA therapy in our study showed minimal side effects. Conclusion: PUVA gives fair response in AA in a reasonable time as per our center’s experience in Singapore.

Key Words: Alopecia areata, psoralen plus ultraviolet-A, treatment

Introduction

Alopecia areata (AA) is a nonscarring recurrent type of hair loss that can affect any hair-bearing area at any time.¹,² AA itself and the treatment can lead to psychosocial stress in patients and family, resulting in a negative quality of life.³,⁴ There are multiple treatment modalities, ranging from conservative treatment, topicals with minoxidil and/or steroidal lotions, intralesional steroids, immunotherapy with diphenylcyclopropenone (DCP), and use of psoralen and ultraviolet-A (PUVA).⁵ The course of AA may be extremely variable, with spontaneous remissions and relapses complicating the interpretation of treatment efficacy. The severe forms of AA, with complete and persistent hair loss, appear to be seen more frequently in young adults with a history of atopy or autoimmune disorders. These severe presentations of AA seem to respond poorly to conventional treatment options.⁶

PUVA in the treatment of patients with severe forms of AA has been reported in the literature.⁶–⁸ Oral PUVA treatment is often limited by systemic side effects. Bath/topical-PUVA offers an alternative solution because of negligible systemic absorption of psoralen.⁸ The objective of this study was to evaluate the effectiveness of paint PUVA therapy in the treatment of AA in the National Skin Center (NSC), Singapore. The study results would allow for more accurate counseling for patients considering paint PUVA as an alternative treatment.

Materials and Methods

NSC is a tertiary referral center for dermatological diseases in Singapore, catering to approximately 1000 cases of AA annually. The National Healthcare Group Domain Specific Review Board, Singapore, approval was obtained before the commencement of the study (NHG DSRB Ref: 2014/01017). We performed a 10-year (March 2004 to February 2014) retrospective review of data of all patients who have undergone paint PUVA for AA at NSC. The diagnosis of AA was made clinically by experienced dermatologists. Case records of the patients were retrieved to collect data on patient profile, treatment tolerability, complications, and success and relapse rates with regard to paint PUVA therapy for the treatment of AA.

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Following the widely accepted quantitative assessment of baseline hair loss proposed by Olsen et al., the ten patients were categorized according to their baseline hair loss reflective of their severity of AA as 0%–24%, 25%–49%, 50%–74%, 75%–99%, 100%, alopecia totalis or universalis. Treatment outcomes were focused on the final amount of hair regrowth measured by percentage of terminal hair regrowth and percentage change in baseline SALT score. The severity of alopecia tool (SALT) score is a quantitative scale used to evaluate the severity of AA by assessing the degree of scalp hair loss. The SALT score for each patient was assessed by an experienced dermatologist and the percentage change in SALT score was calculated by subtracting the SALT score obtained after treatment from the SALT score obtained before treatment. Likewise, the final amount of hair regrowth was clinically assessed by an experienced dermatologist.

The paint PUVA therapy involved the application of 0.1% 8-methoxypsoralen (8-MOP) solution (Meladinine® CLS Pharma) as a thin layer with a cotton swab over the scalp. Following 20 min after application, patients received UVA irradiation. A curve-panel UVA unit (Waldmann UV 200; Herbert Waldmann GmbH and Co. KG, Villingen-Schwenningen, Germany) and a flat-panel UVA unit (Waldmann UV 181AL; Herbert Waldmann GmbH and Co. KG) were utilized concurrently for the scalp irradiation, with the main emission set at 320–410 nm and the peak emission at 351 nm. Each patient received paint PUVA therapy twice a week. The patients’ Fitzpatrick skin type was assessed and the starting UVA dose was adjusted accordingly.

The records of ten patients were included in this study. The patient demographics and relevant medical history of the recruited patients are listed in Table 1. Of the ten patients, eight were Chinese with Fitzpatrick skin type IV. Aside one patient having atopic dermatitis and another having vitiligo, all other patients in the study had no significant medical history or family history of AA. The mean duration of alopecia before diagnosis was 3.7 months (range: 0–12 months). The patient demographics in this study were in concordance with the demographics in the epidemiology study of AA conducted in the same center.

Table 2 describes the paint PUVA treatment regimens undertaken by the ten patients in accordance to the severity of their AA. Four patients of baseline hair loss of 0%–24% received a mean maximum UVA dose of 4.88 J/cm² of mean energy and mean cumulative UVA dose of 167.75 J/cm², over an average of 50 therapy sessions with earliest sign of hair regrowth after a mean of 16 sessions.

One patient with baseline hair loss of 25%–49% received a maximum UVA mean energy dose of 4.75 J/cm² and cumulative UVA dose of 116 J/cm² over 47 therapy sessions with treatment response seen on the 28th session. Three patients with alopecia totalis received a mean maximum UVA dose of 3.75 J/cm² and mean cumulative UVA dose of 136.42 J/cm², over an average of 60 therapy sessions with earliest signs of hair regrowth after 12 sessions. Finally, two patients of alopecia universalis received a mean maximum UVA dose of 2.88 J/cm² and mean cumulative UVA dose of 276.88 J/cm² over an average of 133 therapy sessions with earliest signs of hair regrowth after a mean of 14 sessions.

Table 3 shows the treatment outcomes of paint PUVA therapy in each patient, categorized according to the severity of disease. With paint PUVA therapy, patients of baseline hair loss of 0%–24% and alopecia universalis managed to successfully regrow their hair by 75%–100%, with percentage change in baseline SALT score of 15.5%–20% among the four patients with baseline hair

### Results

The ten patients received PUVA treatment in the same center. The mean duration of alopecia before diagnosis was 3.7 months (range: 0–12 months). The patient demographics in this study were in concordance with the demographics in the epidemiology study of AA conducted in the same center.

Three patients had previously undergone intralesional steroidal injections over a period ranging 1–2 months. Nine patients received immunotherapy with DCP over a period ranging 7–36 months. Four patients received topical minoxidil 5% and three patients received topical potent steroids over a period of 6–12 months. Notably, eight out of the ten recruited patients employed more than one treatment modality before paint PUVA with unsuccessful outcomes.

### Table 1: Patient demographics and medical history (n=10)

| Variables                        | Figure |
|----------------------------------|--------|
| Age (years), mean (range)        | 36.1 (13.0-56.0) |
| Gender no. (%)                   |        |
| Female                           | 4 (40.0) |
| Male                             | 6 (60.0) |
| Ethnicity no. (%)                |        |
| Chinese                          | 8 (80.0) |
| Malay                            | 1 (10.0) |
| Indian                           | 1 (10.0) |
| Fitzpatrick skin type no. (%)    |        |
| IV                               | 8 (80.0) |
| V                                | 2 (20.0) |
| Age of diagnosis (years) mean (range) | 27.7 (5.0-51.0) |
| Age at the first PUVA treatment (years) mean (range) | 30.5 (8.0-52.0) |
| Duration of alopecia before diagnosis (months) mean (range) | 3.7 (0.0-12.0) |
| Extent of AA before PUVA no. (%) |        |
| Baseline hair loss of 0-24       | 5 (50.0) |
| Baseline hair loss of 25-49      | 1 (10.0) |
| Alopecia totalis or universalis  | 4 (40.0) |

AA: Alopecia areata, PUVA: Psoralen and ultraviolet-A.
Tan, et al.: Use of paint psoralen UVA in alopecia areata

Table 2: Psoralen and ultraviolet-A treatment regimens of the patients according to the severity of their alopecia areata

| Number of patients | Baseline hair loss 0%-24% | Baseline hair loss 25%-49% | Alopecia totalis | Alopecia universalis |
|--------------------|---------------------------|-----------------------------|-----------------|---------------------|
| Maximum UVA dose (J/cm²) | 4.88 (3.0-8.0) | 4.75 | 3.75 (1.3-6.8) | 2.88 (2.0-3.8) |
| Cumulative UVA dose (J/cm²) | 167.75 (23.0-293.5) | 116.0 | 136.42 (24.0-272.5) | 276.88 (195.0-358.8) |
| Total number of sessions | 49.5 (21.0-75.0) | 47.0 | 59.67 (41.0-77.0) | 133.0 (115.0-151.0) |
| Earliest session that hair regrowth is seen | 16 (8.0-24.0) | 28.0 | 12.0 | 14 (8.0-20.0) |

Data are represented in mean (range). UVA: Ultraviolet-A, AA: Alopecia areata

Table 3: The patient’s percentage change in baseline severity of alopecia tool score and final amount of hair regrowth after psoralen and ultraviolet-A therapy

| Patients | SALT score | Final amount of hair regrowth (percentage of terminal hair regrowth) |
|----------|------------|---------------------------------------------------------------|
| Before treatment | After treatment | Percentage change | |
| Baseline hair loss 0%-24% | | | |
| Patient 1 | 20 | 4.5 | 15.5 | 75-100 |
| Patient 2 | 20 | 0 | 20 | 75-100 |
| Patient 3 | 20 | 0 | 20 | 75-100 |
| Patient 4 | 20 | 4.5 | 15.5 | 75-100 |
| Baseline hair loss 25%-49% | | | |
| Patient 5 | 30 | 30 | 0 | <30 |
| Alopecia totalis | | | |
| Patient 6 | 100 | 100 | 0 | <30 |
| Patient 7 | 100 | 95.5 | 4.5 | <30 |
| Patient 8 | 100 | 100 | 0 | <30 |
| Alopecia universalis | | | |
| Patient 9 | 100 | 4.5 | 95.5 | 75-100 |
| Patient 10 | 100 | 4.5 | 95.5 | 75-100 |

SALT: Severity of alopecia tool, AA: Alopecia areata

loss of 0%-24% and 95.5% among both patients with alopecia universalis.

Interestingly, both alopecia universalis patients suffered relapse of alopecia after 16 months and 4 months into remission separately. It was with the restarting of paint PUVA therapy that both patients managed to achieve their successful hair regrowth of 75%-100%, along with eyebrow and body hair regrowth and a significant percentage change in baseline SALT score of 95.5%. Full hair regrowth was observed after 10 months of treatment, prompting treatment cessation. However, multiple patches of hair loss following an ophiasis pattern were seen after 4 months of treatment cessation, with the largest patch measuring 6 cm in diameter. Paint PUVA therapy was then restarted and full hair regrowth was again achieved after 14 months of treatment.

Table 3 also shows that patients of baseline hair loss of 25%-49% and alopecia totalis had 0% change in baseline SALT score and <30% of terminal hair regrowth. The apparent lack of efficacy in this group of alopecia totalis patients compared to the alopecia universalis patients may be in part attributed to the lack of treatment follow-ups in the former group who cited time constraint and loss of confidence in treatment as the main reasons for the premature termination of paint PUVA treatment, compared to the alopecia universalis patients who persisted with a longer treatment schedule.

Aside the three patients with alopecia totalis who discontinued paint PUVA therapy due to the aforementioned reasons, one patient with baseline hair loss of 0%-24% and another patient with baseline hair loss of 25%-49% also discontinued paint PUVA therapy due to time constraint and loss of confidence. In terms of side effects, only one patient with alopecia totalis was unable to tolerate higher doses of paint PUVA due to tenderness over treatment area. Fortunately, the
other nine patients in this study did not report any side effects from the paint PUVA therapy such as painful burns or bullous reactions.

**Discussion**

The use of PUVA in dermatology is not uncommon. PUVA has been used in the treatment of psoriasis, lichen planus, mycosis fungoides, and vitiligo. In the treatment of AA, PUVA is reported to work through eradication of the inflammatory cell infiltrates surrounding the affected hair follicles, which may play an integral role in the pathogenesis of AA. While many treatment modalities currently exist in the treatment of AA, many of them do not work well in the face of severe AA. PUVA, on the other hand, serves to be a promising alternative in the treatment of severe AA.

Weissmann et al. were the pioneers to report successful results in five patients who underwent PUVA to the scalp. Since then, their study encouraged other investigators to explore the use of PUVA therapy in patients with AA. Our study explored the treatment outcomes of patients with differing severity of AA who underwent paint PUVA therapy. As seen from the results obtained, all the patients who continued treatment with paint PUVA without premature termination were successful in hair regrowth to more than 75%. They included three patients with baseline hair loss of 0%–24% and two patients with alopecia universalis, with percentage change in baseline SALT score of 15.5%–20% among the former group and 95.5% among the latter group. On the average, the patients with baseline hair loss of 0%–24% required 16 sessions of paint PUVA to show earliest signs of hair regrowth, and patients with alopecia universalis required 14 sessions. Although our study is relatively small with ten patients recruited, the response rates of paint PUVA therapy are comparable to those of larger studies such as the study of 149 patients conducted by Mohamed et al. in 2005 that reported more than 50% hair regrowth in 84% of AA Grade I (<30% baseline hair loss) or Grade II patients (>30% baseline hair loss) and 56% of AA Grade III patients (alopecia totalis or universalis). Similarly, Whitmont et al. performed a retrospective cohort study in patients with alopecia totalis and universalis using 8-MOP with UVA therapy and showed complete hair regrowth in 53% of patients with alopecia totalis and 55% of patients in alopecia universalis.

As mentioned previously, five patients in our study had discontinued with paint PUVA therapy prematurely because of time constraint and loss of confidence in treatment efficacy. These reasons are understandable given that paint PUVA therapy requires repeated treatment over a long duration for efficacy. Prospective patients have to be well-informed of the time frame expected for paint PUVA therapy to accomplish results to set realistic expectations and reduce frustration with time and economical loss.

Aside from cautioning patients of the long treatment course, the risk of AA relapse is also another concern that needs to be conveyed to patients. A study by Broniarczyk-Dyla et al. reported that recurrence after turban PUVA was seen in 26% of AA patients over a 15-month follow-up period. In our study, both alopecia universalis patients who had significant hair regrowth after paint PUVA therapy had recurrence of AA. Other patients in our study, however, did not develop any recurrence. Therefore, we recommend longer follow-up periods to assess durable efficacy of PUVA.

Paint PUVA therapy offers a convenient method of applying the 8-MOP solution to the scalp without inducing photosensitivity to other areas. It also has a shorter duration of skin photosensitivity and requires lower UVA doses to achieve therapeutic effects in comparison to orally administered psoralen. Therefore, decreased phototoxic side effects and lack of systemic side effects allow paint PUVA to be considered as a well-tolerated therapeutic alternative for the treatment of AA. All the side effects of PUVA encountered by the patients in our study were minimal and reversible. In fact, only one patient with alopecia totalis was unable to tolerate higher doses of PUVA due to pain. This is consistent with other studies that show the self-limited and mild side effects of paint PUVA such as prolonged erythema, burning sensation, and postinflammatory hyperpigmentation. This is in contrast to oral PUVA therapy where nausea, vomiting, and photosensitization are often seen.

One of the concerns with use of PUVA is the associated increased risk of skin malignancies. It is hypothesized that the mechanism of therapeutic action of PUVA in AA is through the induction of thymidine dimerization in DNA. In this process there is production of reactive oxygen species, that can also be carcinogenic to neighboring skin cells. Several published studies have shown the increased incidence of cutaneous squamous cell carcinoma and basal cell carcinoma associated with PUVA therapy. In our 10-year retrospective analysis, none of the ten patients exhibited any signs of obvious skin malignancy. However, this may be due to the short follow-up duration of 10 years in contrast to other studies with evidence of skin malignancies after 300 PUVA sessions and 20-year follow-up. Therefore, the increased risk of skin malignancies associated with PUVA therapy remains a significant concern to be investigated and addressed.

Our study is not without its limitations. It is noteworthy that our retrospective study is dependent on the integrity of the clinical notes of the patients. Hence, there would be bias associated with this mode of retrospective analysis. Moreover, our small sample size is vulnerable to many confounders and type II errors owing to the low power of our study. Nonetheless, we hope that our study can serve
as a fresh perspective into the treatment of AA with paint PUVA therapy in the Southeast Asian population.

**Conclusion**

This study serves to report our experiences of treating patients with AA using paint PUVA therapy at the NSC, Singapore. Persisting with treatment for a longer period of time in patients with AA universalis may increase the chances of significant hair regrowth in this cohort who would otherwise have limited treatment options. We hope that this study detailing our experiences with the use of PUVA in the treatment of AA will allow for more accurate counseling for patients considering paint PUVA as an alternative treatment.

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**Conflicts of interest**

There are no conflicts of interest.

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