A Retrospective Study of 231 Japanese Vitiligo Patients with Special Reference to Phototherapy

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SUMMARY Although the outcomes of various treatment modalities for vitiligo have been studied extensively, the influence of the participant's characteristics on treatment response has not been thoroughly investigated. Therefore, we retrospectively investigated treatment effects and their association with clinical characteristics in Japanese patients with vitiligo. The charts of patients with vitiligo treated in our institution were reviewed. Clinical response was evaluated as a marked response rate, defined as repigmentation in >75% of the initial lesional area. 162 patients were treated with phototherapy, while 69 were treated with topical mono-therapy. The patients treated with phototherapy and those treated with both phototherapy and topical treatment demonstrated significantly higher clinical response rates compared to patients treated solely with topical mono-therapy (marked response rate: 19.1% vs. 5.8%, $P<0.05$; and 23.5% vs. 5.8%, $P<0.01$, respectively). Among the phototherapy-treated patients, younger subjects (≤15 years old) were more responsive to phototherapy compared to older patients (37.0% vs. 15.6%; $P=0.015$). The disease subtypes did not affect treatment response. In conclusion, phototherapy appears to have a therapeutic effect superior to topical mono-therapy on both focal and generalized vitiligo, especially in younger patients. Thus, any type of psychosocially devastating lesions in a pediatric patient may be a good target for phototherapy.

KEY WORDS: excimer laser, focal vitiligo, generalized vitiligo, narrow-band UVB, pediatric.

INTRODUCTION

Vitiligo is a common, acquired, depigmenting disease caused by selective destruction of cutaneous melanocytes. This disfiguring disease affects both sexes equally and can be developed at any age. The reported prevalence of vitiligo is 0.5% to 1%, and this disorder significantly impairs the patients' quality of life (1). While genetic, autoimmune, neuronal, biochemical, oxidative stress-induced, and viral mechanisms have been proposed, the precise etiology remains to be determined. There are various treatment options for vitiligo that include phototherapy (psoralen and ultraviolet A (PUVA), narrow band ultraviolet B (NBUVB), and 308-nm excimer laser), topical therapy (topical corticosteroids, topical vitamin D3 analogues, and topical calcineurin inhibitors), and surgical therapy (suction blister grafts, split thickness grafts, and minigrafts). Several review articles concluded that topical corticosteroids are the

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intervention of choice for localized vitiligo, and that phototherapy is the intervention of choice for generalized vitiligo (2,3). However, since previous studies had varied designs and outcome measurements, no definitive treatment strategy has been established to date (4). In addition, variations in participants' characteristics, including skin color, age or duration of the disease, and extent and type of vitiligo may cause the response to treatment to vary (4). Thus, it is important to accumulate enough evidence to create a standardized treatment protocol. With this in mind, we conducted a retrospective study of vitiligo patients in our institution in order to evaluate the response to various types of treatments and their association with the clinical characteristics of the patients.

METHODS

The study included patients with vitiligo who visited the Department of Dermatology at the Juntendo University Hospital from 2006 to 2011. We obtained written, informed consent from each patient as well as approval from the institutional review board. The patients' characteristics (age, age of onset, duration, sex, family history, comorbidities, disease localization, disease subtypes (1), and the presence of halo nevi and the Kobner phenomenon) and the treatment course were recorded. Laboratory results, including thyroid function tests (thyroid stimulating hormone, free T4, anti-thyroglobulin antibodies, and anti-thyroid peroxidase antibodies) and the presence of other autoantibodies, were also assessed.

When phototherapy was used, the modalities, treatment duration, frequency, initial dose, total amount of irradiation, adverse events (AEs), and concomitant use of topical therapy (corticosteroids, calcineurin inhibitors, and vitamin D3 analogues) were noted. The mean initial doses were 0.28 J/cm^2 for PUVA, 0.24 J/cm^2 for NBUVB, and 0.14 J/cm^2 for excimer laser. The optimal maintenance dose was set below the minimal erythema dose. Topical methoxypsoralen was applied prior to PUVA exposure. Liver and renal function tests were also performed before PUVA was started. Over 6-months of topical treatment, either as the sole treatment or along with phototherapy, were taken into account. Due to the potential risk of carcinogenesis, topical calcineurin inhibitors were not used with phototherapy.

Clinical outcomes were evaluated using the following repigmentation grading: no response, mild response (<25% repigmentation), moderate response (25% to 50% repigmentation), good response (50% to 75% repigmentation), and marked response (>75% repigmentation) (5). Statistical analyses were performed using the Mann–Whitney U-test for two-group comparisons and Fisher's exact probability test for the analysis of frequencies. Bonferroni correction was used in multiple comparisons. Statistical significance was defined as a *P* value of <0.05.

RESULTS

Patient characteristics are summarized in Table 1. We analyzed the data of 121 men and 110 women. The most common lesional site was the face (56.7%), followed by the chest and abdomen (35.6%), hands (26.6%), and the neck (25.8%). Vitiligo vulgaris was the most common subtype (42.9%). Topical vitamin D_3 derivatives were used for 48.9% of the patients, as well as topical corticosteroids (39.1%) and topical cal-

Table 1. Subject characteristics

Characteristc	Value n = 231
Age (years)	38.2 ± 23.0
Age at onset (years)	33.1 ± 23.0
Duration (years)	4.9 ± 9.0
Sex (male/female)	121/110
Halo nevi (%)	2.1
Family history of vitiligo (%)	3.4
ANA titer >160 (%)	2.6
Abnormal TFTs (%)	10.3
Subtypes (%)	
Acrofacial	7.7
Focal	29.6
Segmental	18.9
Universal	0.9
Vulgaris	42.9
Localization (%)	
Head	14.2
Face	56.7
Neck	25.8
Chest/abdomen	35.6
Back	15.5
Upper extremities	18.9
Lower extremities	15.0
Groin	19.3
Hands	26.6
Feet	7.7
Comorbidities (%)	
Hypothyroidism	3.0
Hyperthyroidism	0.4
Alopecia areata	4.3
Atopic dermatitis	6.1

ANA = Anti-nuclear antibody; TFTs = thyroid function tests.

Table 2. Clinical efficacy of different treatment options in vitiligo

	N	Marked response	Good response	Moderate response	Mild response	No response
Phototherapy	162	31 (19.1%)*	56 (34.6%)	23 (14.2%)	43 (26.5%)	9 (5.6%)
Phototherapy with topical therapy	81	19 (23.5%)†	25 (30.9%)	14 (17.3%)	19 (23.5%)	4 (4.9%)
Mono-phototherapy	81	12 (14.8%)	31 (38.3%)	9 (11.1%)	24 (29.6%)	5 (6.2%)
Topical mono-therapy	69	4 (5.8%)*†	37 (53.6%)	3 (4.3%)	18 (26.1%)	7 (10.1%)
Subtypes of phototherapy-treated patients						
Acrofacial	14	3 (21.4%)	6 (42.9%)	0 (0%)	4 (28.6%)	1 (7.1%)
Focal	50	11 (22.0%)	24 (48.0%)	1 (2.0%)	12 (24.0%)	2 (4.0%)
Segmental	25	4 (16.0%)	11 (44.0%)	0 (0%)	10 (40.0%)	0 (0%)
Universal	2	0 (0%)	0 (0%)	1 (50.0%)	1 (50.0%)	0 (0%)
Vulgaris	71	13 (18.3%)	15 (21.1%)	21 (29.6%)	16 (22.5%)	6 (8.5%)
PUVA	14	6 (42.9%)	4 (28.6%)	1 (8.3%)	2 (14.3%)	1 (7.1%)
NBUVB	39	5 (12.8%)	12 (30.8%)	8 (20.5%)	11 (28.2%)	3 (7.7%)
Excimer	109	20 (18.3%)	40 (36.7%)	14 (12.8%)	30 (27.5%)	5 (4.6%)

PUVA = Proralen and ultraviolet A; NBUVB = Narrow band ultraviolet B

cineurin inhibitors (7.3%). A small percentage of the patients (2.1%) underwent suction blister grafts as a surgical procedure. Atopic dermatitis was the most common comorbidity (6.8% men and 5.8% women) followed by alopecia areata (3.4% men and 5.8% women), asthma (3.4% men and 3.9% women), and hypothyroidism (0.9% men and 5.8% women).

Out of all patients, 162 were treated with phototherapy, and the remaining 69 patients were treated with topical mono-therapy. The efficacy of phototherapy was clearly superior to that of topical mono-therapy, with marked response rates of 19.1% and 5.8%, respectively ($P < 0.05$, Table 2). There were no differences in therapeutic response to phototherapy based on disease subtypes. Marked response rates were 21.4% (acrofacial), 22% (focal), 16% (segmental), and 18.3% (vulgaris). Among the 162 patients who received phototherapy, 14, 39, and 109 were treated with PUVA, NBUVB, and excimer laser, respectively. The mean number of irradiations in each modality was 21.6, 34.5, and 39.3, respectively. Of those treated with PUVA, 42.9% showed marked improvement, whereas 12.8% of those treated with NBUVB and 18.3% of those treated with excimer laser showed marked responses (Table 2). Thus, the marked response rate to PUVA (42.9%) was significantly higher compared with non-PUVA phototherapy (15.9%; $P = 0.023$).

Concomitant use of topical medicine with phototherapy has been reported to improve the therapeutic outcome in some cases (6,7). Therefore, we also investigated whether administering topical therapy in addition to phototherapy improved therapeutic outcomes in this study population. Among the 162 patients treated with phototherapy, 81 were also treated with topical therapy, whereas the remaining 81 were treated with mono-phototherapy. Concomitant use of phototherapy and topical ointment demonstrated significantly higher treatment efficacy compared to topical mono-therapy, and tended to show better efficacy than mono-phototherapy (marked response: 23.5% vs. 5.8%, $P = 0.0029$; 23.5% vs. 14.8%; $P = 0.17$; Table 2).

A previous study reported that vitiligo patients under 15 years of age were more susceptible to phototherapy (5). Thus, we performed a separate analysis of this population. As expected, patients ≤15 years of age (n = 26) were more responsive to phototherapy compared with patients >15 years old (n = 136; marked response: 37.0% vs. 15.6%; $P = 0.015$). There were no significant differences in disease duration, sex, or disease subtypes between the two age groups (Table 3).

Adverse reactions to either therapy were mild, and no patients discontinued the treatment. In patients treated with phototherapy, there were 20 cases

(12.3%) of mild burns and 14 cases (8.6%) of skin irritation. In topically treated patients, four cases of telangiectasia, two cases of skin irritation, one case of hypertrichosis, and one case of skin atrophy were also observed.

DISCUSSION

Currently, no optimal therapeutic strategy for the treatment of vitiligo has been defined. Phototherapy markedly improves the clinical picture in many cases, but a cure has not been achieved. In addition, the therapeutic effect varies among patients, and the treated patients often fail to maintain their initial response to phototherapy (8). However, considering the psychologically devastating nature of the disease, improvement in treatment outcomes is highly desirable.

As expected, phototherapy, especially the combination of phototherapy and topical therapy, was significantly more effective than topical mono-therapy. Importantly, in the group treated with phototherapy, patients under 15 years of age were significantly more responsive to treatment. Although there is no consensus on the superior efficacy of phototherapy in younger patients, there are two previous studies that also support our finding. In an observational, prospective study, Percivalle *et al.* (5) demonstrated that 14.3% of 28 patients between 3 and 15 years of age achieved repigmentation of ≥75%. This result was better than that of their previous study in an adult population, which showed that 3.8% of 53 adult patients achieved repigmentation of ≥75% (9). Furthermore, Brazzelli *et al.* (10) showed in a prospective study of 60 cases that patients under 20 years achieved a higher repigmentation rate in lesions of the neck and the extremities than patients >20 years old. Although the mechanism underlying improved outcomes in younger patients has not been elucidated, it may be partly attributed to the aging of residual melanocytes in the lesional skin. While vitiligo is caused by a selective destruction of melanocytes, these cells are unlikely to be completely lost even in the lesional skin of vitiligo (11). The density of melanocytes is reported to decrease progressively during adulthood by approximately 10% per decade (12). Although both PUVA and NBUVB promote melanocyte migration and proliferation, and create a favorable environment for melanocyte growth (13,14), aging may diminish these effects on residual melanocytes in the lesional skin. Taken together, phototherapy appears to be a good treatment option, especially for pediatric vitiligo patients.

In our study, phototherapy was considered as a treatment of choice only in adult and pediatric patients who could not be adequately managed with topical treatment. Since previous studies have demonstrated the effectiveness and safety of phototherapy, including NBUVB and excimer laser, both in pediatric patients and adults (15,17), we used these treatments for pediatric patients with vitiligo, while carefully observing adverse reactions. A recent guideline also suggests phototherapy as a treatment of choice when more conservative treatment is ineffective (18). In our study, the safety assessment revealed mild burns in 12.3% and skin irritation in 8.6% of the phototherapy-treated patients, all of which resolved spontaneously. So far, skin cancer did not emerge in neither adults nor children treated with phototherapy in our institution. However, unlike NBUVB (19), PUVA carries a slightly increased risk of both non-melanoma skin cancer and melanoma (20-22). Premature photoaging of the skin is also a concern with prolonged use of phototherapy (23). Therefore, it is necessary to provide patients with an extensive explanation of these possible long-term adverse effects, and obtain written informed consent before the use of phototherapy. Long-term follow-up is also necessary, especially for children.

With regard to the modalities of phototherapy, many previous studies have shown that NBUVB has equivalent or higher rates of repigmentation compared to PUVA (63% vs. 51%), although PUVA may yield a quicker response (3). According to Hong *et al.*

Table 3. Comparison of pediatric and adult patients with vitiligo treated with phototherapy

	≤15 years old n = 26	>15 years old n = 136
Duration (years)	1.4 ± 1.5	5.6 ± 12.0
Sex (male/female ratio)	0.9	1.7
Subtypes (%)		
Acrofacial	0	10.4
Focal	0	1.5
Segmental	42.3	27.6
Universal	64.6	12.7
Vulgaris	26.9	47.8
Treatment response (%)		
Marked response	37.0*	15.6*
Good response	44.4	32.6
Moderate response	0	17.0
Mild response	18.5	28.1
No response	0	6.7

*$P < 0.05$

(24), excimer laser has a better clinical outcome than NBUVB. In contrast, the clinical efficacy of PUVA was superior to that of both NBUVB and excimer laser in our study. However, the number of the patients treated with PUVA was relatively small compared with those treated with NBUVB or excimer laser, because the latter two modalities are now the most frequently used in our institution. The small number of PUVA-treated patients may be partly responsible for the difference in treatment efficacy between the two studies. However, PUVA may be more effective for a certain population of patients with vitiligo, and thus further investigation is needed.

Our results showed that the clinical subtypes of vitiligo did not affect the response to phototherapy. Although several previous studies reported that segmental vitiligo is less likely to respond to phototherapy, this finding is not always consistent with other observations (25). As excimer laser can only be applied to a limited, small, depigmented lesion, phototherapy should be considered for both focal and generalized depigmentation.

CONCLUSION

Our retrospective study suggests that phototherapy has a positive therapeutic effect on both focal and generalized vitiligo, especially in younger patients. Therefore, even a small, limited, depigmented lesion in a pediatric patient can be a good target for phototherapy if the symptom is psychosocially devastating. Since our study has some limitations due to its retrospective nature and the small number of patients, further accumulation of evidence is recommended.

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