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Comparative Study between the Efficacy of Trichloroacetic Acid 30% versus Intradermal 5 Fluorouracil Injection in Treatment of Vitiligo with or without Narrow Band Ultraviolet B Phototherapy

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ABSTRACT

Background: Vitiligo is a challenging disease, which significantly impaired quality of life (QoL). In recent years, there are numerous therapeutic modalities available that aim to stop progression with a subsequent induction of skin re-pigmentation. Combination among different modalities could improve the response, reduces the adverse events, and reduces the course required to achieve re-pigmentation in vitiligo.

Objective: To compare the efficacy of trichloroacetic acid (TCA) chemical peel (30% concentration) versus intradermal injection of 5 Fluorouracil Injection (5-FU) both with and without Narrow Band Ultraviolet B (NB-UVB) Phototherapy (PT) in management of stable non-segmental vitiligo (NSV).

Patients and Methods: This comparative prospective interventional study comprised 60 patients with stable NSV. Patients were divided into two equal groups: Group I and group II. Lesion 1 in both groups was treated with only TCA 30%, while, lesion 2 was treated with only intradermal injection of 5-FU. In group II, each lesion was followed by the application of NBUVB sessions twice/week.

Results: Based on the Physician's Global Assessment (PGA) score, the present study demonstrated a highly statistically significant increase in the percentage of improvement among group II compared to group I. According to the PGA score, our study demonstrated a statistically significant increase in the percentage of improvement among the subgroup 5-FU II+ NBUVB compared to 5-FU I.

Conclusion: It could be concluded that the combination therapies of each of TCA or 5-FU with NBUVB ranked higher than monotherapy with either TCA or 5-FU in inducing successful re-pigmentation in stable NSV patients.

Keywords: Trichloroacetic Acid, 5 Fluorouracil Injection, Vitiligo, Narrow band ultraviolet B phototherapy.

INTRODUCTION

Vitiligo is a chronic dermal lesion, featured by the lack of cutaneous pigmentation, it is caused by the destruction of melanocytes or reduced their function, as well as it may result from psychological stress and those affected may be stigmatized [1].

Vitiligo can occur at any age. Vitiligo prevalence is ranging from 0.5% to 2% globally [2].

A lot of treatment options are suggested for vitiligo, as its pathophysiology remains enigmatic. On the other hand, phototherapy (PT) is apparently the most efficient and favored therapeutic modality. PT with NB-UVB has become the backbone with regard to vitiligo treatment, with higher efficacy compared to psoralen-ultraviolet A (PUVA) [3]. Numerous treatment modalities for vitiligo involve topical and systemic steroids, calcineurin inhibitors, PUVA, NB-UVB, different surgical and laser approaches, antioxidants, and so on [4].Koebner's phenomenon (KP) is described as the development of isomorphic lesions at traumatized unaffected skin of cases with dermal lesions. This lesion (KP) is recorded in cases with vitiligo. On the other hand, other authors have recorded that there is a reverse Koebner's phenomenon (RKP) in vitiligo cases where there is spontaneous re-pigmentation of vitiligo patches following skin grafts. In addition, trauma is recorded to induce hyperpigmentation [5].

Such facts (trauma-associated pigmentations in addition to the RKP) could open avenue for the development of novel approaches in the context of vitiligo management. Traumas induced by dermal abrasion, thermal traumas by utilizing fractional laser therapy [6], and chemical traumas by phenol and TCA [7].

Topical 5-flurouracil (5-FU) may enhance melanocytic proliferations and migrations. In addition, it could cause overstimulation of melanocytic proliferation with a subsequent immunomodulation, which induces stabilization of the disease activity [8]. The current study was done to compare the efficacy of TCA chemical peel (30% concentration) versus intradermal injection of 5-FU both with and without NB-UVB phototherapy in treatment of stable NSV.

PATIENTS AND METHODS

This was a comparative interventional study that comprised 60 adult cases with stable NSV and fulfilling the inclusion criteria. They were recruited from Mansoura University Hospital Outpatient Clinic of Dermatology.

Inclusion criteria: Patients of both genders > 18 years with stable NSV having at least two discrete vitiliginous patches, stable means absence of novel areas of depigmentation, enlarged preexisting lesion, or absence of KP for 6 monthes.

Exclusion criteria: Pregnant or lactating females, cases with history of skin malignancy, keloids, hypertrophic

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scar, photosensitivity condition, or KP, patient with any systematic disease and cases with active viral and bacterial infections.

Methods:

Entire patients were subjected to full history taking comprising onset, course, duration, family history of vitiligo, past history of precedding therapeutic approaches and the result. General examination was done to rule out systemic diseases. Dermatologic examination included detection of lesion site, size and skin phenotype.

Assessment of the patients at the base line by staging, which has been evaaluted according to skin and hair pigmentation in vitiligo patches, and the lesion was staged from zero to three on the largest macule in all body areas where s**tage zero** as normal pigmentation, s**tage I** was partial depigmentation (comrpising spotty depigmentation, trichrome, and homogeneous lighter pigmentation), s**tage II** was total depigmentation (may involve hair whitening in a limited numbers of hairs (< 30%) and s**tage III** was total depigmentation in additon to signification hair whitening (> 30%). Patients were divided haphazardly into two equal groups (A and B) each composed 30 cases. Group A included patients with two vitiliginous lesions in each patient and were given numbers. Vitiliginous lesion number 1 in all patients was treated with TCA 30%. The area to be managed was degreased by acetone or alcohols. Vitiliginous lesion number 2 in all patients was managed with intradermal injection of 5-FU every 14 days for four months. Group B included patients with two vitiliginous lesions in each patient and were given numbers. Vitiliginous lesion number 1 in all patients was treated with TCA 30% as in lesion number 1 in group A. While, vitiliginous lesion number 2 in all patients was treated with intradermal injection of 5-FU every two weeks as in lesion number 2 in group A. But patients in group B received narrow-band ultraviolet B sessions twice weekly up to four months or when full re-pigmentation was achieved.

Ethical approval: The Ethics Committee of Faculty of Medicine, Mansoura University granted the study approval. All participants signed informed consents after a thorough explanation of the goals of the study. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

The data were collected, processed, coded, and inserted into a special sofware to analyse the gathered information by utilizing SPSS 23 (Chicago, IL, USA) for windows software. For descriptive statistics, mean ± SD, percent and frequencies were used to represent the gathered data of the outcomes. Quantitative data were expressed as median (IQR) because the data were not normally distributed. Mann Whitney U test (MW) was used when comparing between two groups (for abnormally distributed data), Chi-square test was utilized when comparing between non-parametric data. In terms of all the previous tests, $p \leq 0.05$ was considered significant.

RESULTS

To date, this was the first research that apply multiple comparisons with different interventions of vitiligo macules that included treatment with TCA alone, 5-FU alone, combination between TCA and NBUVB or combination between 5-FU and NB-UVB. This comparative prospective interventional study comprised 60 cases with stable NSV. Table (1) showed that there was no significant difference ($p = 0.343$) between studied groups regarding age, sex, family history, skin type and presence of systemic disease. While, there was a statistically significant increase in percentage of previous treatment in group II (30 patients, 100%) as compared to group I (26 patients, 86.7%).

Table (1): Comparison of sociodemographic data between studied groups (group I and group II)

		Group I (N = 30)		Group II (N = 30)		Stat. test	P-value
Age (years)	**Median**	22		25		MW = 386	0.343 NS
	IQR	16 - 40		16 – 30			
Sex	**Male**	8	26.7%	8	26.7%	$X^2 = 0.0$	1.0 NS
	Female	22	73.3%	22	73.3%		
Family history	**Negative**	16	53.3%	16	53.3%	$X^2 = 0.0$	1.0 NS
	Positive	14	46.7%	14	46.7%		
Skin type	**Type III**	12	40%	6	20%	$X^2 = 3.1$	0.207 NS
	Type IV	12	40%	14	46.7%		
	Type V	6	20%	10	33.3%		
Systemic diseases	**Negative**	30	100%	28	93.3%	$X^2 = 2.06$	0.150 NS
	Positive	0	0%	2	6.7%		
Previous treatment	**No**	4	13.3%	0	0%	**$X^2 = 4.3$**	**0.038 S**
	Yes	26	86.7%	30	100%		

MW: Mann Whitney test, **S:** $p < 0.05$ is considered significant. **X^2:** Chi-square test, **NS:** $p > 0.05$ is considered non-significant.

Table (2) demonstrated highly statistically significant difference ($p < 0.001$) between group I sub-groups (TCA and FU) as regards improvement/Physician's Global Assessment (PGA). In TCA sub-group I, there were two patients (13.3%) with mild improvement, four patients (26.7%) with moderate improvement and 9 patients (60%) with good improvement, while in FU sub-group I there were six patients (40%) with no change, 7 patients (46.7%) with mild improvement and two patients (13.3%) with moderate improvement. Highly statistical significant ($p < 0.001$) increased percentage of improvement in TCA sub-group I (median = 60, IQR = 50 - 75) when compared to FU sub-group I (median = 20, IQR = 0 - 25).

Table (2): Comparison of improvement between group I sub-groups (TCA and FU)

			Group I				**Stat. test**	**P-value**
			TCA (N = 15)		**FU (N = 15)**			
Improvement / PGA	**No change**		0	0%	6	40%	**$X^2 = 18.4$**	**< 0.001 HS**
	Mild		2	13.3%	7	46.7%		
	Moderate		4	26.7%	2	13.3%		
	Good		9	60%	0	0%		
Improvement %		**Median**	60		20		**MW = 10**	**< 0.001 HS**
		IQR	50 - 75		0 – 25			

X^2: Chi-square test.

Table (3) showed that there was no statistically significant difference **(p = 1.0)** between group II sub-groups (TCA and FU) as regards improvement/PGA. In group II sub-groups (TCA and FU), there were 12 patients (80%) of excellent improvement and 3 patients (20%) of good improvement in both sub-groups, and no statistically significant difference **(p= 1.0)** between group II sub-groups (TCA and FU) as regards improvement %. In group II sub-groups (TCA and FU), the mean improvement % was 85.3 ± 7.8 % in both sub-groups.

Table (3): Comparison of improvement between group II sub-groups (TCA and FU)

		Group II				**Stat. test**	**P-value**
		TCA (N = 15)		**FU (N = 15)**			
Improvement / PGA	**Good**	3	20%	3	20%	$X^2 = 0.0$	1.0 NS
	Excellent	12	80%	12	80%		
Improvement %	**Mean**	85.3		85.3		MW = 0.0	1.0 NS
	±SD	7.8		7.8			

X2: Chi-square test. NS: $p>0.05$ is considered non-significant.

Table (4) showed that there was highly statistically significant difference ($p < 0.001$) between studied groups (TCA I and TCA II) as regards improvement/PGA. In TCA I, there were 2 patients (13.3%) with mild improvement, 4 patients (26.7%) with moderate improvement, 9 patients (60%) with good improvement and 0 patients (0%) with excellent improvement. While, in TCA II there were 3 patients (20%) with good improvement and 12 patients (80%) with excellent improvement and highly statistically significant increased percentage of improvement in TCA II (median = 85, IQR = 80 - 90) when compared with TCA I (median = 60, IQR = 50 - 75).

Table (4): Comparison of improvement between studied groups (TCA I and TCA II)

			TCA I (N = 15)		**TCA II (N = 15)**		**Stat. test**	**P-value**
Improvement / PGA	**Mild**		2	13.3%	0	0%	**$X^2 = 21$**	**< 0.001 HS**
	Moderate		4	26.7%	0	0%		
	Good		9	60%	3	20%		
	Excellent		0	0%	12	80%		
Improvement %		**Median**	60		85		**MW = 9**	**< 0.001 HS**
		IQR	50 – 75		80 – 90			

X2: Chi-square test. HS: $p<0.001$ is considered highly significant.

Table (5) showed that there was highly statistically significant difference ($p < 0.001$) between studied groups (FU I and FU II) as regards improvement/PGA. In FU I, there were 6 patients (40%) with no change, 7 patients (46.7%) with mild improvement and 2 patients (13.3%) with moderate improvement. While in FU II, there were 3 patients (20%) with good improvement and 12 patients (80%) with excellent improvement and highly statistically significant ($p < 0.001$) increased percentage of improvement in FU II (median = 85, IQR = 80 - 90) when compared with FU I (median = 20, IQR = 0 - 25).

Table (5): Comparison of improvement between studied groups (FU I and FU II)

			FU I (N = 15)		**FU II (N = 15)**		**Stat. test**	**P-value**
Improvement / PGA	**No change**		6	40%	0	0%	**$X^2 = 30$**	**< 0.001 HS**
	Mild		7	46.7%	0	0%		
	Moderate		2	13.3%	0	0%		
	Good		0	0%	3	20%		
	Excellent		0	0%	12	80%		
Improvement %		**Median**	20		85		**MW = 0.0**	**< 0.001 HS**
		IQR	0 - 25		80 – 90			

X^2: Chi-square test. HS: $p<0.001$ is considered highly significant.

Table **(6)** showed that there was highly statistically significant difference ($p < 0.001$) between studied groups (group I and group II) as regards improvement/PGA. In group I, there were 6 patients (20%) with no change, 9 patients (30%) with mild improvement, 6 patients (20%) with moderate improvement, 9 patients (30%) with good improvement and 0 patients (0%) with excellent improvement. While in group II, there were 6 patients (20%) with good improvement and 24 patients (80%) with excellent improvement and highly statistical significant ($p < 0.001$) increased percentage of improvement in group II (median = 85, IQR = 80 - 90) when compared with group I (median = 32.5, IQR = 17.5 - 60).

Table (6): Comparison of improvement between studied groups (group I and group II)

			Group I (N = 30)		**Group II (N = 30)**		**Stat. test**	**P-value**
Improvement / PGA	**No change**		6	20%	0	0%	**$X^2 = 45.6$**	**< 0.001 HS**
	Mild		9	30%	0	0%		
	Moderate		6	20%	0	0%		
	Good		9	30%	6	20%		
	Excellent		0	0%	24	80%		
Improvement %		**Median**	32.5		85		**MW = 18**	**< 0.001 HS**
		IQR	17.5 - 60		80 – 90			

X^2: Chi-square test. HS: $p<0.001$ is considered highly significant.

DISCUSSION

Vitiligo is an autoimmune skin lesion induced by dysfunction of pigment-producing melanocytes attacked by immune cells, which ultimately ends in achromic macules and patches. In recent years, there are numerous therapeutic modalities available, that aim to stop progression and induce skin re-pigmentation [9]. It has been demonstrated that vitiligo treatment is challenging considering its complicated pathogenesis. In addition, there is no specific cure available in the context of vitiligo treatment. The therapeutic modalities in vitiligo involve: topical corticosteroids, immunomodulators, PT, oral corticosteroids, Januskinase inhibitors, surgical interference, lasers, and depigmentation therapies. In spite of the novel advances in vitiligo treatment, outcomes remain mostly not satisfied and several cases demonstrate no or mild response [10].

Among the various topical therapies used for vitiligo, the utilization of TCA in the context of vitiligo treatment has been considered as a recent entity and limited numbers of researches have assessed its efficacy as a therapeutic modality. Of note, till now, no well-established explanation is available for TCA role in re-pigmentation of vitiligo. All the suggested mechanisms are mainly reliant on its capability for induction of inflammation at the application area that could, as a result, trigger any remaining active melanocytes [11].

5-Flurouracil (5-FU) is mostly utilized for the treatment of premalignant and malignant skin diseases. The hyperpigmentation noticed following the utilization of 5-FU has been considered as the primary cause behind utilizing it as a vitiligo treatment. The pigmentation induced by 5-FU is potentially owing to the migration of melanocytes from the nearby pigmented skin throughout the re-epithelialization process. In addition, 5-FU might induce re-pigmentation by overstimulation of follicular melanocytes with a subsequent increase in melanosomes numbers in keratinocytes nearby the hair follicles [12].

NB-UVB phototherapy acts as an efficient treatment modality to induce skin re-pigmentation in stable vitiligo. Although NB-UVB phototherapy was confirmed to be an efficient treatment option, the re-pigmentation responses to that PT differs significantly in various vitiligo cases and re-pigmentation might only appear after several months of treatment [13]. Thus, the combination of NBUVB and another treatment modality could be used in an effort to achieve faster and greater re-pigmentation. To the best of our knowledge, this is to date the first research that applies multiple comparisons with different interventions on treating vitiligo macules as follows: treatment with TCA 30% alone, intradermal 5-FU injection alone, combination between TCA 30% and NBUVB and combination between intradermal 5-FU injection and NBUVB.

Regarding the sociodemographic data, the current study demonstrated no significant differences between the studied groups with regard to age, gender, family history, skin type and the presence of systemic diseases (P value > 0.05). The present findings revealed positive family history of similar condition among 53.3% of the studied cases. Such findings are in agreement with **Azzazi *et al.*** [14] who reported positive family history in 32% of vitiligo cases, and **El-taweel *et al.*** [15] who indicated positive family history in 35% of vitiligo cases.

Based on the Physician's Global Assessment (PGA) score, the current study displayed a highly statistically significant increase in the degree of improvement among group II compared to group I (83% versus 32.5%, P value < 0.001). In group II, excellent and good improvements were achieved in 80% and 20% of treated patients respectively, while in group I, mild, moderate and good improvements were achieved in 30%, 20% and 30% of treated patients respectively. Nil response to treatment at the end of the study duration was noted in 20% of patients of group I. Such findings highlighted that the combination therapies of TCA or 5-FU with NB-UVB ranked higher than monotherapy with either TCA or 5-FU in inducing efficient re-pigmentation and avoiding failed treatment among cases with vitiligo. In addition, a novel research conducted by **Zhu *et al.*** [16] revealed that all combined therapies ranked greater than NBUVB monotherapy in inducing efficient re-pigmentation and avoiding failure of therapy among cases with vitiligo as follows: (1) NBUVB + Er:YAG laser + topical 5% 5-FU, (2) NBUVB + topical Vitamin D analogues, (3) NBUVB + needling/micro-needling, (4) NBUVB + fractional CO_2 laser, (5) NBUVB + topical tacrolimus and (6) NBUVB+ oral Chinese herbal medicine compound were of great efficiency compared to NBUVB alone with regard to ≥ 75% re-pigmentation response rate. Additionally, a prospective comparative study conducted among cases with generalized stable vitiligo in acral regions and extremities by **Farajzadeh *et al.*** [17] demonstrated that adding carboxy-therapy to NBUVB has been demonstrated to be accompanied by a significant increase in efficiency of treatment without any complications in comparison with monotherapy with NBUVB. Good and excellent response rates were noticed in combined therapy group only. Moreover, **El-Domyati *et al.*** [18] revealed that intralesional corticosteroid injections combined with NBUVB demonstrated a good and well-tolerated treatment modality in the context of vitiligo.

The comparison between lesion 1 treated with TCA and lesion 2 treated with 5-FU in group A regarding PGA score, the present study demonstrated a significant increase in the percentage of improvement among the subgroup patients treated with TCA alone compared to treatment with 5-FU alone (60% vs. 20%, respectively) (P value<0.001). Good, moderate, mild and no change improvement were reported in 60% vs.

26.7% vs. 13.3% vs. 0% respectively within the subgroup treated with TCA alone compared to 0% vs. 13.3% vs. 46.7% vs. 40% respectively within the subgroup treated with 5-FU alone, with highly statistically significant differences between both subgroups ($P < 0.001$). Of note, there are no previous researches that compared between the monotherapy with TCA 30% and 5-FU in vitiligo treatment. **Nofal *et al.*** [11] studied the efficacy of TCA as a monotherapy on 100 cases with acral/non-acral stable vitiligo and revealed that eyelid vitiligo displayed the greatest response to TCA treatment, then the face, trunk, and limbs. Minimal response rates were observed in the hands and feet vitiligo. Complications were temporary and not significant in few cases. Additionally, a previous study by **Zohdy and Hussein** [19] that compared the efficiency of intradermal 5-FU, triamcinolone acetonide (TAA) or a comparable mixture of both medications and revealed that intradermal 5-FU demonstrated the best overall improvement when compared to triamcinolone and the drug mixture. Throughout follow-up, the patches of vitiligo remained to re-pigment for six months in 5-FU and the drug mixture groups, while the improvement stopped one month following the last session in the TAA group.

The comparison between lesion 1 treated with TCA+NBUVB and lesion 2 treated with 5-FU+NBUVB in group B regarding PGA score, our study displayed no significant difference among the subgroup patients treated with TCA + NBUVB compared to treatment with 5-FU+ NBUVB ($P > 0.05$). Such findings highlighted the equal efficacy of the combining treatment of NBUVB with either TCA 30% or 5-FU, with statistically significant increase in the burning sensation among TCA + NBUVB-treated lesions and a statistically significant increase in the perilesional hyperpigmentation among 5-FU + NBUVB treated lesions. A comparative study by **Elgarhy *et al.*** [20] revealed that both 5-FU injection plus NBUVB and $FrCO_2$ plus 5-FU plus NBUVB were effective therapeutic modalities for vitiligo. Patients were more compliant with $FrCO_2$ plus 5-FU plus NBUVB in the management of stable vitiligo. Moreover, **Pazyar *et al.*** [21] compared the efficiency of microneedling in association with topical 5-FU vs topical tacrolimus ointment in treatment of vitiligo patches and recorded that utilizing microneedling together with 5-FU may manage vitiligo cases more effectively compared to tacrolimus monotherapy.

The comparison between lesion 1 treatment in each of group I and group II regarding the PGA score, the current study demonstrated a statistically significant increase in the degree of improvement among the subgroup TCA II compared with TCA I (85% vs. 60% respectively, $P < 0.001$). Excellent, good, moderate, mild and no change improvement were reported as 80%, 20%, 0% and 0% respectively within the TCA II compared to 0%, 60%, 26.7% and 13.3% respectively within the TCA I, with highly statistically significant differences between both subgroups ($P < 0.001$). Such findings highlighted that the combination therapy of TCA 30% with NBUVB give better efficacy compared to the TCA 30% monotherapy. A previous study by **El Mofty *et al.*** [5] that compared the efficacy of combined TCA 15% + NBUVB Vs TCA 25% + NBUVB for 10 cases with stable NSV revealed that the initial lesions managed with TCA 15% + NBUVB demonstrated significant improvement in seventy per cent of cases, moderate improvement in 10% and mild response in 20%. While, the second managed lesions with TCA 25% + NBUVB revealed marked improvement in 20% of patients, moderate improvement in 40%, mild improvement in 10% and minimal in 30%, emphasizing that the beginning of vitiligo therapy with TCA 15% could improve the overall response accomplished by NBUVB. Moreover, **Elnokaly *et al.*** [22] study on 60 vitiligo patients revealed that the mix of microneedling with either TCA 25% or tacrolimus is efficient and safe in vitiligo treatment. On the other hand, TCA achieved a slight increase in percentage of re-pigmentation compared to tacrolimus.

The comparison between lesion 2 treatment in each of group I and group II regarding the PGA score, the present study displayed a statistically significant increase in the percentage of improvement among the subgroup 5-FU II + NBUVB compared to 5-FU I (85% vs. 20% respectively, P value < 0.001). Excellent, good, moderate, mild and no change improvement were reported in 80%, 20%, 0%, 0%, and 5%, respectively within the 5-FU II+ NBUVB compared to 0% , 0%, 13.3%, 46.7% and 40%, respectively within the FU I subgroup, with highly statistically significant differences between both subgroups (P value < 0.001). Such findings highlighted that the combination therapy of 5-FU with NBUVB gave better efficacy compared to the 5-FU monotherapy. Such findings are in agreement with **Abd El-Samad and Shaaban**[23] who assessed the efficiency and safety of intradermal injection of 5-FU combined with NBUVB as a therapeutic modality in 60 vitiligo cases and revealed that the overall re-pigmentation was significantly greater in the 5-FU plus NBUVB in comparison with the NB-UVB alone in all body areas with exception of the acral lesions in which the change wasn't significant.

CONCLUSION

It could be concluded that the combination therapies of each of TCA or 5-FU with NBUVB ranked higher than monotherapy with either TCA or 5-FU in inducing successful re-pigmentation in stable NSV cases. Moreover, the therapeutic response of stable NSV patients treated with intradermal 5-FU injection followed by the application of NBUVB was significantly efficient, less side effects and gave excellent improvement according to the PGA score with cosmetically accepted re-pigmentation compared to the treatment with TCA in combination with NBUVB.

RECOMMENDATIONS

Further evaluation in larger-scale studies evaluating the efficacy and safety using 5-FU combined with NBUVB in the treatment of NSV is warranted. Further studies regarding the use of combination treatment of vitiligo using 5-FU combined with NBUVB including performing pretreatment and posttreatment pathological or electron microscopic examination are recommended for confirmation of the clinical results.

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