

Comparative Efficacy of Topical Tacrolimus Versus Tyrosine as Co-Therapy to NB-UVB in Vitiligo: A Randomized Intra-Individual Controlled Clinical Trial

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Abstract

Aim: This study aimed to investigate the efficacy of topical tyrosine versus tacrolimus as co-therapies in vitiligo patients undergoing narrowband ultraviolet B (NB-UVB) therapy.

Materials and Methods: Three comparable vitiligo patches were selected from each patient ($n = 67$) and randomly assigned to tyrosine 2% plus NB-UVB (group I), tacrolimus 0.1% plus NB-UVB (group II), and NB-UVB alone (control). Topical treatments were applied twice daily, while NB-UVB phototherapy was administered twice weekly at the minimal erythema dose for three months.

Results: Repigmentation differed significantly among the study groups ($P < 0.001$). The tacrolimus plus NB-UVB group showed the highest repigmentation [median (interquartile range): 60.0% (37.0–70.0)], followed by the tyrosine plus NB-UVB group [28.0% (16.0–46.0)], while the NB-UVB alone group demonstrated the lowest repigmentation [12% (10.0–21.0)]. Estimated effect size showed that pairwise comparisons between each active treatment group (groups I and II) and the control group for responder status ($\geq 25\%$ repigmentation) were significant (McNemar's test, $P < 0.001$). Odds ratios were 5.5 (95% confidence interval: 2.3–13.1) for group I vs. control, and 89 for group II vs. control. Across all study groups, the stepwise linear regression model demonstrated that a shorter time since the last disease activity and a lower vitiligo area scoring index were the strongest predictors of a higher vitiligo extent score by target area.

Conclusion: Combination therapy appears to be more effective for the management of vitiligo. Tacrolimus combined with NB-UVB achieved the highest repigmentation outcomes, whereas tyrosine combined with NB-UVB may represent a promising, safe, and potentially beneficial adjunct. Early initiation of the treatment may improve repigmentation, particularly in patients with limited disease severity.

Keywords: Vitiligo, narrowband UVB, phototherapy, tacrolimus, tyrosine

INTRODUCTION

Vitiligo is a chronic, acquired pigmentary disorder characterized by autoimmune destruction of melanocytes, resulting in hypochromic or achromic macules and patches affecting the skin and mucous membranes.¹

The pathogenesis of vitiligo is multifactorial. A central mechanism involves an autoimmune response in which melanocyte-specific autoantibodies and cytotoxic CD8⁺ T cells

contribute to melanocyte destruction. In addition, impaired melanocyte adhesion, associated with reduced expression of adhesion molecules, may increase melanocyte detachment and susceptibility to immune-mediated damage.²

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Although several therapeutic options are available, few treatments effectively achieve both disease stabilization and repigmentation. Phototherapy remains one of the most effective treatment modalities for vitiligo. Ultraviolet (UV) radiation, particularly narrowband ultraviolet B (NB-UVB; 311–312 nm), has demonstrated significant efficacy in suppressing autoreactive cytotoxic T cells, inducing melanocyte differentiation, and stimulating residual melanocytes in perilesional skin and melanocyte precursors in hair follicles, thereby promoting repigmentation.^{3,4}

Calcineurin inhibitors also contribute to repigmentation through immunomodulatory mechanisms. By suppressing T-cell activation, these agents reduce inflammation-mediated melanocyte damage and may indirectly enhance melanogenesis. Tyrosinase, the key enzyme in melanin synthesis, plays a central role in this process, as its activity directly determines melanin production.⁵

Tyrosine, an essential amino acid and the primary substrate for melanin synthesis, has been explored *in vitro* as a potential therapeutic adjunct for vitiligo. Furthermore, tyrosine has been shown to influence tyrosinase activity in both normal and vitiligo-affected skin, supporting its possible role in melanogenesis.^{6,7}

Evidence from human studies further indicates that topically applied tyrosine can penetrate the epidermis and contribute to melanin production. In a pilot study, the application of a 0.2% tyrosine cream to sun-exposed forearm skin produced visible tanning in all volunteers after 24 hours, whereas a tyrosine-free control produced erythema alone.⁷ Additionally, tyrosine-derived nanospheres have been shown to effectively transport lipophilic agents across the stratum corneum into the deep dermis, achieving up to ninefold greater delivery than conventional formulations.⁸ Collectively, these findings support the principle that tyrosine-based compounds can penetrate human skin and serve as substrates for melanin production.

Despite growing evidence regarding the potential role of tyrosine metabolism in vitiligo, its clinical relevance in enhancing repigmentation of human vitiliginous skin remains insufficiently explored. Therefore, the present study aimed to investigate the efficacy and safety of topical tyrosine 2% compared with those of topical tacrolimus 0.1% in promoting skin repigmentation among patients with vitiligo who were candidates for NB-UVB therapy.

MATERIALS AND METHODS

Study Design, Setting, and Study Period

This randomized, intra-individual, controlled clinical trial was conducted in patients with non-segmental vitiligo (NSV) at the outpatient dermatology clinic of a university hospital between August 2025 and February 2026. Sample size was calculated with G*Power software (version 3.1.9.4) for paired proportions using McNemar's test, assuming a two-tailed α of 0.05, 80% power, an odds ratio (OR) of 3.5, and a discordant proportion of 0.40; these assumptions were based on previously reported efficacy rates of 74.35% for combined tacrolimus and phototherapy and 45.3% for phototherapy.⁹ The minimum required sample size was 63 patients; to account for a 10% anticipated dropout, 69 patients were enrolled, of whom 67 completed the study.

Ethical Considerations and Consent

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Faculty of Medicine, Minia University, Egypt (Approval No: 1614/07/2025; Date: 14 June 2025). The study was registered at ClinicalTrials.gov (Identifier: NCT07532330). Written informed consent, including consent for clinical photography, was obtained from all participants prior to enrollment. Participants were thoroughly informed about the treatment procedures, assessment methods, expected outcomes, and potential adverse effects.

Eligibility Criteria

Patients aged 18–65 years with NSV who were candidates for NB-UVB therapy were eligible for inclusion in the study. Pregnant or lactating women and patients who had received any systemic or topical treatment within the preceding three months were excluded.

Baseline Assessment

A full medical history was obtained from all participants, including personal history (age and sex), present history (disease duration and time since the last episode of disease activity), and family history of vitiligo.

A general clinical and dermatological examination was performed for all participants, including confirmation of the diagnosis of vitiligo using Wood's lamp examination, assessment of disease extent using the vitiligo area scoring index (VASI),¹⁰ and determination of Fitzpatrick skin type.

Treatment Protocol

For each patient, three comparable vitiligo patches, matched as closely as possible for lesion duration and anatomical site, were selected and randomly assigned to one of the following treatment groups using a manual shuffling method (drawing cards), which was repeated independently for each patient:

Group I: NB-UVB combined with topical tyrosine 2% cream (Tyromax® Cream, Vaxil Pharma, Egypt), a liposomal formulation designed to enhance skin penetration, applied twice daily to the first patch.

Group II: NB-UVB combined with topical tacrolimus 0.1% ointment (Treczimus® 0.1% ointment, Marcyrl Pharmaceutical Industries, Egypt) applied twice daily to the second patch.

Group III: NB-UVB alone to the third patch as a control.

NB-UVB phototherapy was delivered twice weekly over a three-month period. All patients started treatment at a fixed dose of 200 mJ/cm². Subsequent dose adjustments ranged from 10% to 20% per session, with the goal of achieving a mild, non-painful pink erythema lasting less than 24 hours (minimal erythema dose). In the absence of erythema, the dose was increased; conversely, if bright red, persistent, or painful erythema occurred, phototherapy was withheld until complete resolution.

Patches were clearly marked and monitored to ensure adherence to treatment, and care was taken to avoid overlap between patches.

Clinical Assessment of Treatment Outcome

Standardized photographs were obtained at baseline and after three months of treatment using the same camera for all patients. Imaging parameters, including lighting, background, and distance, were kept consistent across all sessions. Treatment outcomes were subsequently evaluated by two independent, non-blinded physicians using the following measures:

The Vitiligo Extent Score by Target Area (VESTA): It is a semi-objective assessment tool that uses reference images to evaluate the percentage of repigmentation within a target lesion. It accounts for both marginal and perifollicular repigmentation patterns. The vitiligo extent score by target area (VESTA) comprises three components: (1) reference images for marginal repigmentation; (2) reference images illustrating perifollicular repigmentation; and (3) a formula used to calculate the total percentage of repigmentation. This calculation combines the fully repigmented area (%) with the percentage of perifollicular repigmentation within the remaining depigmented area.¹¹

Clinical Improvement Grade: Clinical improvements grading is a subjective assessment tool based on physician visual assessment, generally categorized as follows:

< 25% Improvement: Mild.

25%–50% Improvement: Moderate.

51%–75% Improvement: Good.

> 75% Improvement: Excellent.¹²

Treatment response was assessed at 3 months for each lesion. The percentage of repigmentation was calculated relative to the baseline lesion area. A patient was considered a responder for a given treatment if the lesion treated with that agent achieved $\geq 25\%$ repigmentation (based on VESTA score repigmentation percent) at the 3-month follow-up. Lesions with < 25% repigmentation were classified as non-responders. This threshold was chosen based on studies demonstrating that at least 25% repigmentation constitutes a clinically meaningful improvement and correlates with patients' satisfaction and willingness to continue treatment.¹³ Therefore, this cut-off is considered clinically valid.

Side-effect monitoring: patients were monitored for side effects at each follow-up visit. Monitoring included assessment of visible, persistent erythema, as well as patient-reported, long-lasting (> 24 hours) erythema, irritation, or itching associated with application of topical treatment.

Statistical Analysis

All data were collected, tabulated, and analyzed using SPSS version 26 for Windows (SPSS Inc., Chicago, IL, USA) and R version 4.5.0 (R Core Team, 2025). Normality of quantitative data was assessed using the Shapiro-Wilk test. Qualitative variables were expressed as frequencies and percentages, and differences between groups were evaluated using Fisher's exact test. For quantitative variables (repigmentation percentage), values were expressed as the median [interquartile range (IQR)] when the data were non-normally distributed. The Friedman test was used for overall comparison among the three paired groups, followed by the Wilcoxon signedrank test for pairwise comparisons. The median difference between each pair was estimated using the Hodges-Lehmann estimator with 95% confidence intervals (CIs). Stepwise linear regression was performed to identify independent predictors of the VESTA score; standardized coefficients (β) and *P* values were reported, and model fit was assessed using *R*² and the *F* test. For the binary outcome (responder status, defined as $\geq 25\%$ repigmentation based on VESTA score), pairwise comparisons between each active treatment group (groups I and II) and the control group were performed

using McNemar’s test for paired proportions (R version 4.5.0, McNemar’s test function). When zero discordant cells were present, a continuity correction (adding 0.5 to each cell) was applied to calculate the matched OR. The proportion of discordant pairs was reported as an additional measure of withinsubject effect size. A twotailed *P*-value < 0.05 was considered statistically significant.

RESULTS

A total of 69 patients were enrolled in the study. One patient was lost to follow-up, and another discontinued treatment because of a non-study-related accident. Consequently, 67 patients completed the study and were included in the final analysis.

Baseline Demographic and Clinical Characteristics

The patients’ age mean ± standard deviation (SD) was 32.4 ± 11.1 years. Males constituted 59.7% of the sample, while females constituted 40.3%. The disease durations mean ± SD was 5.3 ± 4.9 years, and the time elapsed since the last disease activity mean ± SD was 4.0 ± 4.4 months. A positive family history of vitiligo was reported in 37.3% of patients. The VASI score mean ± SD was 8.1 ± 4.4, and majority of patients had Fitzpatrick skin type III (67.2%), followed by type IV (32.8%).

Clinical Evaluation

The VESTA score intraclass correlation coefficient was 0.974 (95% CI: 0.966–0.980, *P* < 0.001), indicating excellent agreement between raters. It demonstrated a statistically significant difference in repigmentation among the study groups *P*-value < 0.001. Group II (combined tacrolimus and NB-UVB) exhibited the highest repigmentation, with a median (IQR) of 60.0% (37.0–70.0). This was followed by Group I (combined tyrosine and NB-UVB) with a median (IQR) of 28.0% (16.0–46.0). In contrast, group III (NB-UVB alone) showed the lowest repigmentation, with a median (IQR) of 12% (10.0–21.0). Pairwise comparisons revealed statistically significant differences between all groups. The median difference between group I and group II was -19.0% [95% CI: -24.0–(-14.5); *P* < 0.001], indicating significantly higher repigmentation in group II. Group I showed a median increase of 15.5% (95% CI: 9.5–23.5) compared with Group III (*P* < 0.001). The largest effect was observed between groups II and III, with a median difference of 40.13% (95% CI: 31.0–47.0) in favor of group II (*P* < 0.001) (Table 1).

A statistically significant difference in the distribution of clinical improvement grades was observed among the three groups (*P* < 0.001). Group II (combined tacrolimus and NB-UVB) demonstrated the most favorable clinical outcomes, with the majority of patients achieving either good (50.7%) or excellent (14.9%) improvement. In contrast, group I (combined tyrosine and NB-UVB) showed predominantly mild (37.4%) to moderate (38.8%) improvement, with only 13.4% and 10.4% of patients demonstrating good and

	Group I tyrosine 2% + NB-UVB	Group II Tacrolimus 0.1% + NB-UVB	Group III NB-UVB (control)	Group I vs. group II	Group I vs. group III	Group II vs. group III
VESTA score (%):	Median (IQR)			Median differences (CI)		
	28.0 (16–46)	60.0 (37–70)	12.0 (10.0–21)	-19 [-24.0– (-14.5)]	15.5 (9.5–23.5)	40.13 (31.0–47.0)
P-value	< 0.001*			< 0.001*	< 0.001*	< 0.001*
Clinical improvement grade:	n (%)					
Mild	25 (37.4%)	8 (11.9%)	43 (64.2%)			
Moderate	26 (38.8%)	15 (22.5%)	24 (35.8%)			
Good	9 (13.4%)	34 (50.7%)	0 (0.0%)			
Excellent	7 (10.4%)	10 (14.9%)	0 (0.0%)			
P-value	< 0.001*			< 0.001*	< 0.001*	< 0.001*
Friedman’s test for non-parametric quantitative data between the three groups ^Wilcoxon test for non-parametric quantitative data between each two groups HodgesLehmann test for median differences and confidence interval Positive median differences indicate higher repigmentation in the first group compared to the second Fisher’ exact test for qualitative data NB-UVB: Narrowband ultraviolet B, VESTA: Vitiligo extent score by target area, IQR: Inter quartile range, CI: Confidence interval *Statistically significant <i>P</i> -value (<i>P</i> < 0.05)						

excellent improvement, respectively. Group III (NB-UVB alone) exhibited predominantly mild improvement (64.2%), while the remaining 35.8% showed moderate improvement; no patients achieved good or excellent responses. Pairwise comparisons revealed a significantly greater improvement in group II compared with both groups I and III ($P < 0.001$ for both comparisons). Additionally, group I demonstrated significantly greater improvement than Group III ($P < 0.001$; Table 1, Figures 1–3).

None of the patients included in the present study reported any clinically significant or treatment-limiting side effects.

The best-fitting stepwise linear regression model demonstrated the effects of different variables on the VESTA score. Across the studied groups, shorter time since the last disease activity and lower VASI scores were the strongest predictors of higher VESTA scores, with standardized coefficients (β) of -0.37 ($P = 0.016$) and -0.66 ($P < 0.001$), respectively in group I, standardized coefficients (β) of -0.41 ($P = 0.001$) and -0.61 ($P < 0.001$), respectively in group II, and standardized coefficients (β) of -0.38 ($P = 0.014$) and -0.65 ($P < 0.001$), respectively in group III (Table 2).

Effect Size Estimation

For the binary outcome (responder status defined as $\geq 25\%$ VESTA repigmentation score), the responder proportions were 59.7% (40/67) in group I (tyrosine plus NB-UVB), 85.1% (57/67) in group II (tacrolimus plus NB-UVB), and 19.4% (13/67) in group III (NB-UVB alone). These proportions differ from those obtained with clinical improvement grading owing to differences in methodology between the two assessment tools. These proportions were analyzed using McNemar's paired comparisons, which showed statistically significant differences between each active treatment group (groups I and II) and the control group ($P < 0.001$ for each). Between group I and the control group, 33 subjects responded only to tyrosine plus NB-UVB, and 6 subjects responded only to NB-UVB (OR = 5.5; 95% CI: 2.3–13.1; discordant proportion 0.582). Between group II and the control group, 44 patients responded only to tacrolimus plus NB-UVB, and none responded only to NB-UVB (OR = 89; continuity correction; discordant proportion 0.657; 95% CI not estimable due to zero_cell) (Table 3).

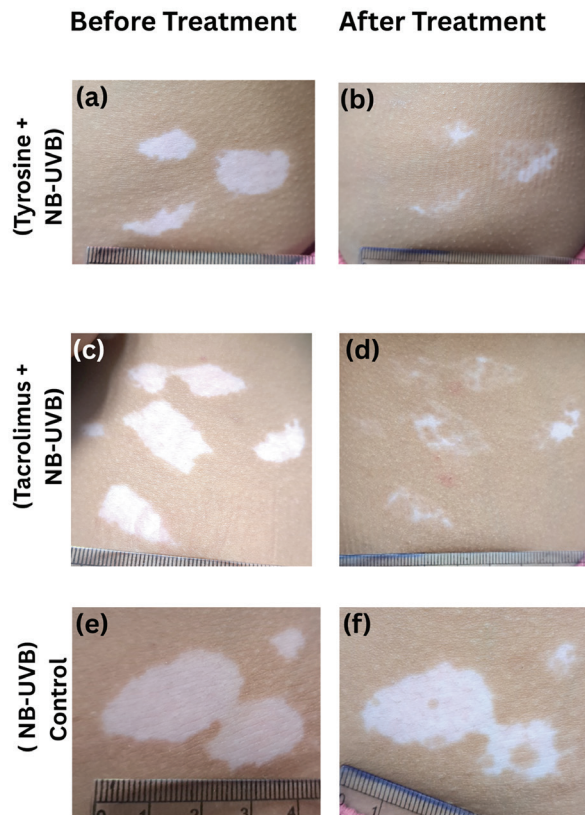


Figure 1. Clinical outcomes of the three treatment modalities in a female patient with non-segmental vitiligo. (a, b) Tyrosine 2% plus narrowband ultraviolet B (NB-UVB) group, showing baseline lesion on the trunk (a) and excellent improvement after 3 months (b). (c, d) Tacrolimus 0.1% plus NB-UVB group, showing baseline lesion on the trunk (c) and excellent improvement after 3 months (d). (e, f) NB-UVB only group, displaying baseline lesion on the trunk (e) and mild improvement after 3 months (f)

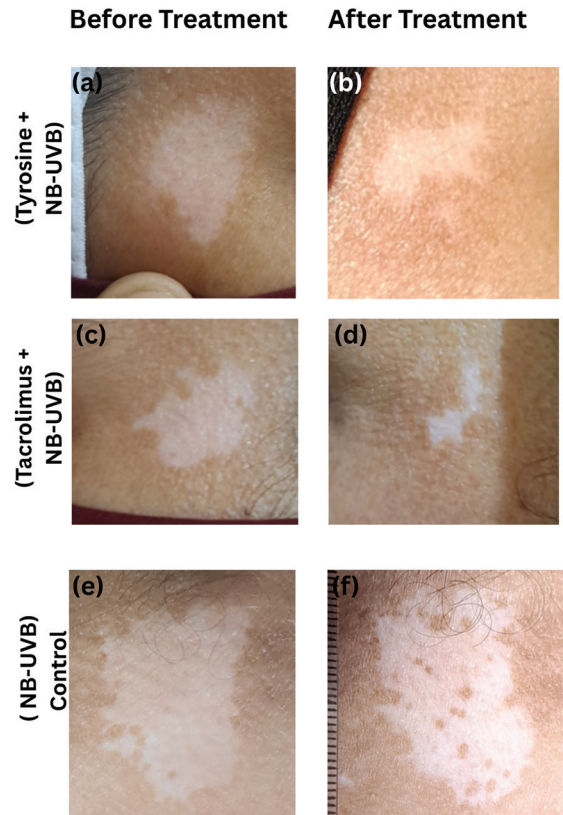


Figure 2. Clinical outcomes of the three treatment modalities in a female patient with non-segmental vitiligo. (a, b) Tyrosine 2% plus narrowband ultraviolet B (NB-UVB) group, showing baseline lesion on the face (a) and good improvement after 3 months (b). (c, d) Tacrolimus 0.1% plus NB-UVB group, showing baseline lesion on the face (c) and excellent improvement after 3 months (d). (e, f) NB-UVB only group, displaying baseline lesion on the neck (e) and mild improvement after 3 months (f)

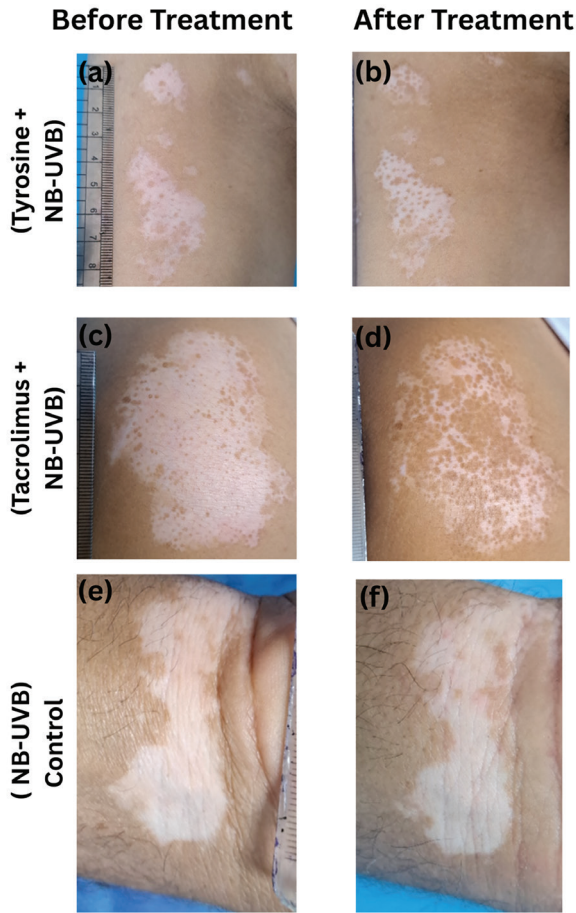


Figure 3. Clinical outcomes of the three treatment modalities in a male patient with non-segmental vitiligo. (a, b) Tyrosine 2% plus narrowband ultraviolet B (NB-UVB) group, showing baseline lesion on the upper limb (a) and Moderate improvement after 3 months (b). (c, d) Tacrolimus 0.1% plus NB-UVB group, showing baseline lesion on the upper limb (c) and excellent improvement after 3 months (d). (e, f) NB-UVB only group, displaying baseline lesion on the upper limb (e) and mild improvement after 3 months (f)

DISCUSSION

Vitiligo is a complex disorder characterized by a multifactorial pathogenesis arising from the interplay of genetic predisposition, metabolic influences, and immune responses, ultimately leading to the destruction of melanocytes.¹⁴ Therefore, therapeutic strategies that target immune suppression, stimulate melanocyte activity, and modulate the metabolic environment are essential for effective disease management.

In the present study, NB-UVB demonstrated efficacy in the treatment of vitiligo when used alone or in combination with tyrosine or tacrolimus.

Phototherapy represents a cornerstone in the management of generalized vitiligo, acting not only to stabilize active disease but also to promote repigmentation. The primary mechanisms

include the induction of T-cell apoptosis, the downregulation of inflammatory cytokines and the stimulation, migration, and proliferation of melanocyte stem cells originating from hair follicles. Furthermore, phototherapy enhances the production of melanogenic growth factors, such as endothelin-1 (ET-1).¹⁵

Notably, our result revealed that, patients receiving tyrosine plus NB-UVB had a substantially higher chance of achieving a clinical response compared to NB-UVB alone.

Tyrosine serves as the principal amino acid precursor for all forms of melanin, including eumelanin and pheomelanin, in the skin, hair, and eyes. In melanocytes, tyrosine is converted by the enzyme tyrosinase into L-DOPA and subsequently into dopaquinone, initiating the melanogenesis pathway.¹⁶ Both L-tyrosine and L-DOPA function not only as substrates but also as positive regulators of melanogenesis, contributing to melanogenic homeostasis within melanocytes.¹⁷

UV radiation enhances melanogenesis in part by upregulating tyrosinase expression and increasing its utilization of L-tyrosine.¹⁶ Because tyrosinase uses L-tyrosine as its rate-limiting substrate, variations in tyrosine availability or competition at this step can directly influence melanin production and overall pigmentation.¹⁸ Moreover, metabolomic analyses of plasma from patients with vitiligo have demonstrated an enrichment of the tyrosine metabolism pathway, suggesting potential alterations of this pathway in vitiligo pathophysiology. Notably, evidence indicates that vitiliginous skin retains the capacity to synthesize melanin from tyrosine.¹⁹

These mechanisms may account for the therapeutic benefit of tyrosine observed in the present study. By increasing the availability of a critical substrate for melanin synthesis, tyrosine may enhance melanogenic activity in residual or partially functional melanocytes, particularly when combined with phototherapy-induced stimulation. Accordingly, the addition of tyrosine to NB-UVB may facilitate repigmentation primarily through the metabolic enhancement of melanogenesis.

Moreover, our results demonstrated that patients treated with tacrolimus combined with NB-UVB were substantially more likely to achieve a clinically meaningful repigmentation compared with NB-UVB alone. This finding is consistent with multiple randomized trials and meta-analyses showing greater repigmentation with tacrolimus combined with NB-UVB or excimer light than with phototherapy alone. In particular, the meta-analyses by Arora et al.²⁰ and Dong et al.²¹ reported that combining tacrolimus with phototherapy significantly increased the proportion of patients achieving $\geq 75\%$ repigmentation (excellent response) compared with phototherapy alone.

Table 2. Linear regression for factors affecting VESTA score in in each group (n = 67)

		Standardized coefficient β	(95% CI)	P-value
Group I tyrosine 2% + NB-UVB	Age	-0.153	(-0.78–0.11)	0.131
	Sex	-0.04	(-14.44–13.85)	0.967
	Disease duration	0.28	(-0.20–2.86)	0.088
	Time since last disease activity	-0.37	[-3.55–(-0.38)]	0.016*
	Family history	-0.03	(-12.09–15.14)	0.823
	VASI score	-0.66	[-4.87–(-2.16)]	< 0.001*
	Fitzpatrick skin type	0.05	(-8.21–13.30)	0.638
Group II tacrolimus 0.1% + NB-UVB	Age	-0.12	(-0.67–0.12)	0.166
	Sex	0.00	(-12.50–12.51)	0.999
	Disease duration	0.18	(-0.43–2.28)	0.175
	Time since last disease activity	-0.41	[-3.74–(-0.94)]	0.001*
	Family history	0.05	(-9.54–14.54)	0.679
	VASI score	-0.61	[-4.66–(-2.27)]	< 0.001*
	Fitzpatrick skin type	-0.05	(-12.30–6.72)	0.560
Group III NB-UVB (control)	Age	-0.12	(-0.22–0.06)	0.273
	Sex	-0.06	(-5.41–3.56)	0.682
	Disease duration	0.27	(-0.08–0.89)	0.103
	Time since last disease activity	-0.38	[-1.14–(-0.13)]	0.014*
	Family history	-0.01	(-4.45–4.19)	0.953
	VASI score	-0.65	[-1.51–(-0.65)]	< 0.001*
	Fitzpatrick skin type	0.07	[-4.51–(-2.32)]	0.523

Dependent variable; vitiligo extent score by target area (VESTA)
 VASI: Vitiligo area scoring index, CI: Confidence interval, NB-UVB: Narrowband ultraviolet B
 Reference categories: female sex, negative family history, and Fitzpatrick skin type IV
 *Statistically significant P-value ($P < 0.05$)

Table 3. McNemar paired comparisons for responder status ($\geq 25\%$ repigmentation) (n = 67)

Comparison	OR (95% CI)	P-value	Discordant proportion
Group I (tyrosine 2% + NB-UVB) vs. Group III (NB-UVB only)	5.5 (2.3–13.13)	< 0.001*	0.582 (58.2%)
Group II (tacrolimus 0.1% + NB-UVB) vs. Group III (NB-UVB only)	89[^]	< 0.001*	0.657 (65.7%)

McNemar’s chi-squared test was applied for binary outcome (responder status defined as $\geq 25\%$ repigmentation)
[^]Continuity correction applied (0.5) due to zero cell; 95% CI estimate is unstable and not calculable
 *Statistically significant P-value ($P < 0.05$)
 CI: Confidence interval, OR: Odds ratio, NB-UVB: Narrowband ultraviolet B

Tacrolimus plays a key role in inhibiting T-cell-mediated autoimmunity by blocking the calcineurin/nuclear factor of activated T-cells signaling pathway, which is essential for T-cell activation and the production of pro-inflammatory cytokines. This immunosuppressive effect reduces the autoimmune response responsible for melanocyte destruction in vitiligo. In addition, tacrolimus promotes melanocyte growth, migration, and function. It has been shown to increase the expression of

endothelin-B (ETB) receptors on melanoblasts and enhance the production of matrix metalloproteinases (MMP-2 and MMP-9), which facilitate melanocyte migration and contribute to repigmentation.²²

Moreover, the dual action of UVB-induced ET-1 production and tacrolimus-induced ETB receptor expression creates a favorable microenvironment for melanocyte recruitment and

repigmentation.^{23,24} This synergistic interaction may explain the enhanced therapeutic efficacy observed when these two modalities are combined in the treatment of vitiligo.

However, our results demonstrated that the addition of tacrolimus to NB-UVB produced significantly greater repigmentation than tyrosine. This difference may be attributed to tacrolimus's ability to target multiple pathogenic mechanisms of vitiligo through its potent immunomodulatory effects and stimulatory effect on melanocyte migration and proliferation.²² In contrast, tyrosine acts primarily via a single targeted pathway in its role as a melanin precursor.¹⁷

The influence of the treatment modalities studied, NB-UVB alone or combined with tyrosine or tacrolimus, on the progression of vitiligo suggests that early initiation of these therapies may be beneficial in limiting disease progression and enhancing repigmentation. This effect appears to be more pronounced in patients with limited disease severity. This is supported by the regression findings, which identified shorter time since last disease activity and lower VASI scores as significant predictors of higher VESTA scores across the studied groups.

Study Limitations

This study is limited by its short follow-up, lack of external funding, and single-center design, which may limit generalizability and preclude assessment of the long-term durability of repigmentation. Although the intra-individual design reduces inter-patient variability, residual site-specific differences in treatment response cannot be excluded. Additionally, the non-blinded design of this controlled clinical trial may represent a source of assessment bias. Moreover, the discrepancy between the semi-objective VESTA assessment and the subjective clinical grading, particularly near the 25% response threshold, represents an additional limitation. Therefore, VESTA-based responder analysis was prioritized for effect size estimation.

CONCLUSION

Combination therapy appears to offer superior efficacy in the management of vitiligo, potentially shortening the time required to achieve noticeable repigmentation, with NB-UVB phototherapy remaining the therapeutic cornerstone. Tacrolimus in combination with NB-UVB achieved the highest repigmentation outcomes, whereas tyrosine combined with NB-UVB may represent a safe and potentially beneficial adjunct. Early initiation of NB-UVB, with or without tyrosine or tacrolimus, may improve repigmentation and limit disease progression, particularly in patients with less severe disease.

Recommendation

Given that this is, to our knowledge, the first clinical study evaluating topical tyrosine in vitiligo, these findings require further validation through large-scale, multicenter trials with extended follow-up to confirm these results and delineate potential synergistic effects of combining NB-UVB, tacrolimus, and tyrosine. Furthermore, comprehensive mechanistic studies are needed to elucidate the role of topical tyrosine in melanogenesis and repigmentation.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Faculty of Medicine, Minia University, Egypt (Approval No: 1614/07/2025; Date: 14 June 2025). The study was retrospectively registered at ClinicalTrials.gov (Identifier: NCT07532330).

Informed Consent: Written informed consent, including consent for clinical photography, was obtained from all participants prior to enrollment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.M.A., Concept: M.H.A.M., Design: M.H.A.M., A.M.A., H.A.Z., Data Collection or Processing: A.M.A., Analysis or Interpretation: H.A.Z., Literature Search: M.H.A.M., A.M.A., Writing: M.H.A.M., A.M.A., H.A.Z.

Conflict of Interest: The authors declare that they have no conflict of interest.

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