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Clinical outcomes and Th17-associated immunomodulation in vitiligo treated with tacrolimus ointment plus narrow-band ultraviolet light

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Abstract: **Background**: Vitiligo, an autoimmune disorder causing skin depigmentation, has Narrow-Band Ultraviolet B (NB-UVB) and tacrolimus with limitations, warranting further research on the long-term efficacy, safety and T helper cell (Th) 17-related mechanisms of their combination. **Objectives**: This study assessed the Th17-related immunomodulation, efficacy and tolerability of tacrolimus plus NB-UVB in vitiligo. **Methods**: Retrospectively collected 132 vitiligo patients from our hospital (Jan 2020-Dec 2023); 124 were enrolled after excluding. Patients were divided into tacrolimus combined with NB-UVB group (n=63) and tacrolimus group (n=61). Primary outcomes: Vitiligo Area Scoring Index (VASI) scores and clinical efficacy. Secondary outcomes: Th17 cell proportion, serum Interleukin (IL)-17/IL-22 levels, Rretinoic Acid Receptor-Related Orphan Receptor γt (RORγt)-positive cell proportion, Dermatology Life Quality Index (DLQI) scores, Hospital Anxiety and Depression Scale (HADS) scores and adverse event incidence. **Results**: The combination group showed a greater reduction in VASI scores (P=0.041) and a higher effective rate (P=0.010) compared with the tacrolimus-group alone. The combination group had a significantly lower Th17 cell proportion (P=0.003), IL-17 levels (P<0.001), IL-22 levels (P=0.047), RORγt-positive cell proportion (P=0.029). Adverse event incidence was not different between groups (P=0.714), while the combination group had a lower DLQI (P<0.001), HADS-A (P=0.018) and HADS-D (P=0.006) scores. **Conclusion**: Tacrolimus plus NB-UVB is more effective than tacrolimus alone for vitiligo, reducing lesion size and disease activity, down regulating Th17-associated immunity and improving systemic immune profile.

Keywords: Immunomodulation; Narrow-band ultraviolet B; Tacrolimus ointment; Th17 cells; Vitiligo

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INTRODUCTION

Vitiligo is an autoimmune disease characterized by the selective destruction of melanocytes. Its global prevalence remains consistently between 0.5% and 2.0%, with significant variations in incidence across different ethnic groups and geographical regions. The incidence rate among the Asian population is approximately 1.0% to 1.5% and there is a distinct trend toward younger onset-about 50% of patients manifest before the age of 30, with the 20-30 years age group being the peak period for onset (LeWitt and Kundu, 2021, Manoj *et al*., 2024). This disease not only causes well-demarcated milky-white macules on the skin and mucous membranes but also exerts a profound impact on patients' psychosocial status. A multicenter cross-sectional study in Europe showed that vitiligo patients are significantly affected by concerns about disfigurement and the average score of the disfigurement concern questionnaire in female patients is significantly higher than that in male patients (Sampogna *et al*., 2025). In addition to impairing skin barrier function and reducing ultraviolet (UV) protection capacity, vitiligo poses multiple challenges to patients in social interactions, career development and romantic relationships. Therefore, optimizing treatment regimens has become an urgent clinical issue to be addressed.

Vitiligo pathogenesis is a complex process driven by genetic predisposition and environmental influences. In recent years, research advances have continuously deepened our understanding of this disease. At the genetic level, genome-wide association studies (GWAS) have identified more than 50 susceptibility genes, including Foxp3, HLA-DRB1 and CTLA4. Among these, Foxp3, a key transcription factor regulating the function of regulatory T cells (Treg), has genetic polymorphisms that can increase the risk of vitiligo by 1.8-fold. Carriers of the HLA-DRB1*04 allele have an even higher disease risk, which is 2.3-fold that of the general population. The MHC class II molecule encoded by this gene enhances the ability of antigen-presenting cells to recognize melanocyte autoantigens, thereby initiating autoimmune T cell-mediated immune attacks (Okamura and Suzuki, 2025). In addition, environmental factors play a crucial triggering role on this genetic basis. Mental stress, excessive UV exposure and contact with phenolic compounds can all induce abnormal elevation of reactive oxygen species (ROS) levels in skin tissue, leading to the dysfunction of the antioxidant system in melanocytes. A 2024 study by Professor Chengfeng Zhang's team from Fudan University further revealed that cell metabolic disorders and autophagic dysfunction associated with skin aging may contribute to vitiligo pathogenesis by affecting melanocyte homeostasis, providing a new perspective for research on the disease mechanism (Liu *et al*., 2024). Immune dysregulation occupies a central position in the pathological progression of vitiligo and the imbalance between helper T cell 17 (Th17) and Treg cells has been at the forefront of recent scholarly inquiry. The lineage commitment and functional characteristics of Th17 cells are regulated by retinoic acid-related orphan receptor γt

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(RORγt), a transcription factor that binds to the promoter region of the IL-17 gene, thereby upregulating the expression of IL-17A and IL-17F. In local lesions, IL-17A can damage melanocytes through a dual mechanism: on one hand, it activates keratinocytes to secrete chemokines such as CXCL10 and CCL20, recruiting more Th17 cells and neutrophils to form an inflammatory amplification loop; on the other hand, it directly acts on IL-17 receptors on the surface of melanocytes, triggering NF-κB signaling, while inhibiting the transcription of key melanin synthesis genes MITF and TYR. In sharp contrast to the abnormal process of Th17 cell activation is the functional deficiency of Treg cells. A 2024 review by Professor Chengfeng Zhang's team pointed out that in vitiligo patients, Treg cells in both lesions and peripheral blood not only show a reduced quantity but also exhibit impaired function and decreased stability. This functional deficiency prevents Treg cells from effectively inhibiting the activation and proliferation of autoreactive $CD8^+$ T cells, resulting in sustained immune attacks on melanocytes. Notably, the team also found that the metabolic status (e.g., glycolysis level) and post-translational modifications of Treg cells may be key factors affecting their function, providing new insights for therapeutic strategies targeting Treg cells (Liu *et al*., 2024). Given their pivotal role in the pathogenesis of vitiligo, dendritic cells (DCs) represent a promising therapeutic target. Relevant studies have mentioned that in patients with progressive vitiligo, the number of pro-inflammatory CD11b+CD11c+ DCs increases in lesions, while the number of anti-inflammatory CD11b+ DCs decreases. This imbalance in DC subsets leads to the massive secretion of pro-inflammatory cytokines such as IL-17A and IL-12p70, further deteriorating the local immune microenvironment (Yang *et al*., 2025). Together, these studies have clarified the immune imbalance in vitiligo and provided a clear direction for targeted therapy.

A stepped treatment system has been established for the clinical management of vitiligo, yet the limitations of single therapeutic approaches have become increasingly prominent. According to the 2023 Global Expert Recommendations on Diagnosis and Management of Vitiligo, topical calcineurin inhibitors (TCIs) such as tacrolimus ointment are the first-line treatment option for localized vitiligo in both adults and children (van Geel *et al*., 2023). As a non-hormonal agent, tacrolimus exerts its effects by inhibiting the activity of calcineurin, reducing the secretion of pro-inflammatory cytokines-this mechanism of action is completely distinct from that of hormonal drugs. Meta-analysis data show that the total effective rate of 0.1% tacrolimus ointment monotherapy is approximately 45%-60% (Duplaine *et al*., 2025); however, some patients discontinue treatment due to adverse reactions such as local burning sensation and erythema. Narrow-band ultraviolet B (NB-UVB), the preferred phototherapy modality, exerts therapeutic effects by activating tyrosinase activity, promoting the migration and proliferation of melanocytes and inducing T cell apoptosis. The response rate of NB-UVB monotherapy ranges from 50% to 70% (Narayan *et al*., 2023), but its treatment course lasts as long as 3-6 months and it is prone to causing uneven pigmentation. Given the limitations of single treatments, the combination of topical medication and phototherapy has become a research focus and their synergistic mechanism has been initially elucidated. Tacrolimus can regulate the local immune microenvironment to reduce the risk of inflammatory reactions in the early stage of NB-UVB treatment, while enhancing the protective effect of phototherapy on melanocytes; conversely, NB-UVB can promote the skin absorption of tacrolimus, increasing the local drug concentration and enhancing the immunosuppressive effect (Alshiyab *et al*., 2023, Pourriyahi *et al*., 2024). Despite the promising prospects of combined therapy, research on its immunomodulatory mechanism remains insufficient and the regulatory effect of the combined regimen on the Th17 pathway has not been clearly defined.

Based on the aforementioned research status, the innovation of this study is reflected in three aspects: (1) adopting a standardized evaluation system, using the vitiligo area scoring index (VASI) to quantify changes in the area of skin lesions; (2) conducting an in-depth exploration of the immune mechanism, comprehensively analyzing the regulatory effect of combined therapy on the Th17 pathway; (3) integrating quality of life assessment, using the dermatology life quality index (DLQI) combined with the hospital anxiety and depression scale (HADS) to evaluate the impact of treatment on patients' psychosocial functions. As a complex autoimmune disease, the treatment of vitiligo has shifted from simple pigment restoration to a comprehensive goal of immune regulation - pigment regeneration-quality of life improvement. By combining clinical observation with in-depth mechanism research, this study not only provides evidence for optimizing combined treatment regimens but also paves the way for the development of novel Th17-targeted therapies, with the ultimate goal of improving the clinical management of vitiligo.

MATERIALS AND METHODS

General information

Vitiligo patients who received treatment in our hospital from January 2020 to December 2023 were included. Their medical records were screened through the hospital's electronic medical record (EMR) system. Fig. 1 and Table 1 depicts the study flowchart. Initially, 132 patients underwent screening, 128 patients remained after exclusion and 4 patients were excluded due to abnormal data. Finally, 124 patients were enrolled and stratified into two groups according to the treatment method: the tacrolimus ointment group (including 61 patients) and the tacrolimus ointment combined with NB-UVB group (including 63 patients).

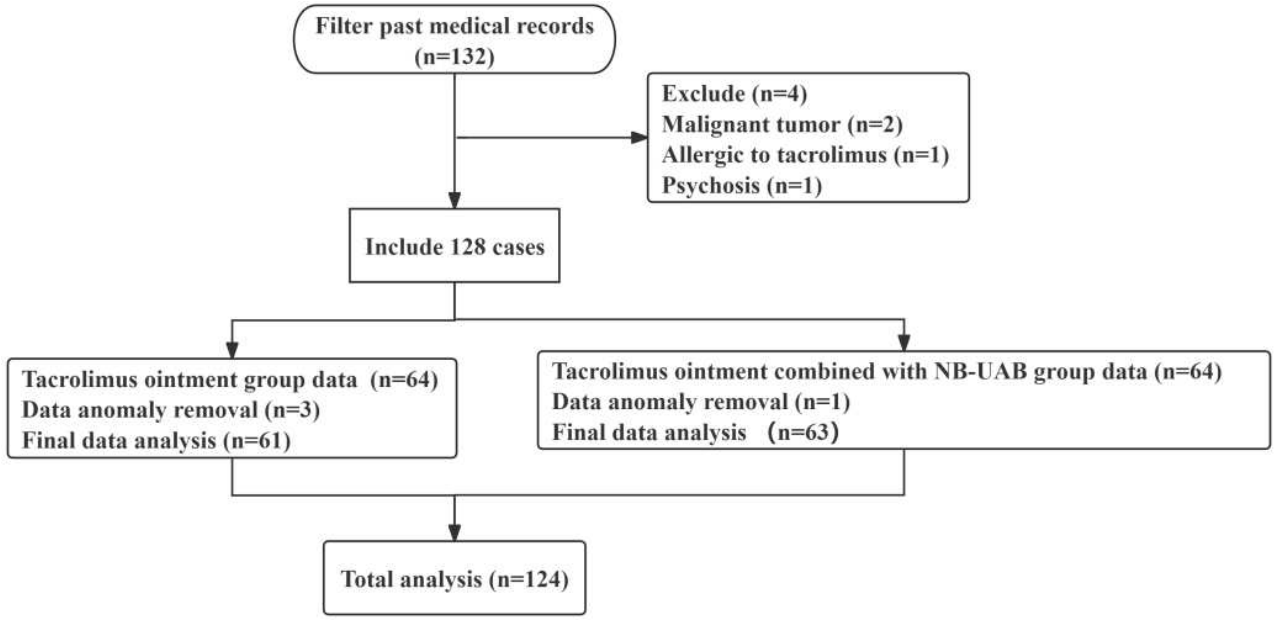

Fig. 1: Research flowchart
Initially, 132 patients were screened out based on their medical records. According to the exclusion criteria, 4 patients were excluded, and during the data analysis phase, another 4 patients were removed due to abnormal data. Finally, a total of 124 patients were included in the analysis, among whom 61 were in the tacrolimus ointment group and 63 were in the tacrolimus ointment combined with NB-UVB group.

Table 1: Endpoint flow table

Group	Endpoint	Enrolled	Completed assessment	Analyzed	Missing	Reasons for missing
Tacrolimus ointment group	VASI/DLQI/HADS/Th17%/RORγt%/IL-17/IL-22/adverse events/clinical Efficacy	64	61	61	3	Data anomaly
Tacrolimus ointment combined with NB-UVB group	VASI/DLQI/HADS/Th17%/RORγt%/IL-17/IL-22/adverse events/ clinical efficacy	64	61	63	1	Data anomaly

Note: VASI: vitiligo area scoring index; Th17: T helper cell 17; RORγt: retinoic acid receptor-related orphan receptor γt; IL-17: interleukin-17; IL-22: interleukin-22; DLQI: dermatology life quality index; HADS: hospital anxiety and depression scale.

Inclusion criteria

(1) Meeting the diagnostic criteria for vitiligo specified in the Chinese Clinical Consensus on Diagnosis and Treatment of Vitiligo (2024 Version) (Pigmentary Disorder Group, 2024); (2) Aged 18-65 years; (3) Lesion type being non-segmental vitiligo (including generalized type, acral type and facial-cervical type); (4) No targeted treatment for vitiligo received within 3 months before the study, including topical glucocorticoids, other calcineurin inhibitors, systemic immunosuppressants, phototherapy, or traditional Chinese medicine; (5) No contraindications to NB-UVB treatment, specifically: no porphyria, severe photosensitive dermatitis, history of skin cancer, or active infection and no photosensitive drugs taken within 2 weeks before treatment; (6) No history of autoimmune diseases (Saki *et al*., 2022); (7) Not participating in other concurrent clinical trials.

Exclusion criteria

(1) Complicated with other infectious diseases; (2) Complicated with malignant tumors; (3) Allergic to tacrolimus ointment or its excipients, or abnormally sensitive to skin reactions after NB-UVB treatment; (4) Pregnant or lactating women; (5) Complicated with severe underlying diseases; (6) Patients with lesions involving special sites or in a state of severe skin lesions (Ebrahim *et al*., 2021);(7) Complicated with mental diseases or cognitive impairment.

Treatment regimens

According to the medical records, all patients first optimized the condition of the lesioned skin and surrounding skin before treatment, including cleaning and moisturizing, strict sun protection and avoidance of irritation.

Tacrolimus Ointment Group: Patients assigned to this group underwent 0.1% tacrolimus ointment (Protopic, Astellas Pharma Co., Ltd., China), administered twice daily (morning and evening) as routine. If patients developed obvious irritative symptoms such as burning sensation, pruritus, or erythema after application, the dosage was adjusted to once a day (in the evening); after the skin achieved tolerance, the administration frequency was restored to twice a day and the treatment was continued for 6 consecutive months (Alshaikh *et al*., 2025).

Tacrolimus Ointment Combined with NB-UVB Group: Patients assigned to this group underwent 0.1% tacrolimus ointment (Protopic, Astellas Pharma Co., Ltd., China) twice daily (morning and evening) and meanwhile received NB-UVB phototherapy using an NB-UVB phototherapeutic apparatus (UV1000L, Waldmann, Germany) with a wavelength of 311-313 nm and a fixed dose of 200 mJ/cm². Special UV-protective glasses were worn before irradiation and the phototherapy was delivered three times per week, separated by a minimum of 24 hours. The NB-UVB treatment was continued for a cumulative period of 6 months (Bhatia *et al*., 2021). If NB-UVB irradiation was performed on a given day, the ointment was applied 30 minutes before phototherapy and an additional application was given 2 hours after phototherapy. The actual average number of treatments for the patients was (64.9 ± 7.5) sessions and the average cumulative irradiation dose was (12980 ± 1500) mJ/cm². Meanwhile, according to the patients' medical records, erythema occurred during the treatment period, leading to a 1-2 session suspension of irradiation. There were no multiple adjustments to the treatment plan. All erythema symptoms subsided within 3-5 days, did not progress to severe reactions and did not affect the patients' subsequent treatment or the completion of the overall treatment course.

All post-treatment measurements of the endpoints for all patients were conducted 6 months after the initiation of treatment.

Outcome measures

Primary outcome measures

VASI

The VASI score was used to quantitatively evaluate the recovery of vitiligo. The definition of the VASI score is as follows:

VASI=Σ (Number of palm units in each body part)×Degree of depigmentation in that area.

VASI scores range from 0 to 100, with higher scores reflecting greater disease severity. One palm-sized area of skin corresponds to roughly 1% of the patient's total body surface area. According to the percentage of pigment loss, each skin lesion can be classified into 7 grades, 100%: complete loss of pigment with no evidence of residual melanin; 90%: only punctate pigment remaining; 75%: depigmented area larger than non-depigmented area; 50%: depigmented area equal to non-depigmented area; 25%: non-depigmented area larger than depigmented area; 10%: only punctate depigmentation; 0%: no depigmentation (Guo *et al*., 2025).

In this study, the VASI scoring was independently conducted by 2 clinicians, rather than a single assessor. This approach was adopted to reduce subjective bias and ensure the objectivity of the scoring results. The consistency test of 248 pieces of VASI scoring data (covering pre-intervention and post-intervention periods) from 124 patients, evaluated by the 2 clinicians, showed that the intraclass correlation coefficient (ICC) was 0.92 (95%CI: 0.87-0.95).

Clinical efficacy

Clinical efficacy was evaluated with reference to the efficacy evaluation criteria established in the Clinical Consensus on Diagnosis and Treatment of Vitiligo (2024 Version) (Pigmentary Disorder Group, 2024). In this study, the following four terms were used to define treatment responses, (1) complete recovery: white patch lesions completely resolved, skin color nearly returned to normal or fully normalized and accompanying symptoms such as pruritus and pain disappeared; (2) marked improvement: most of the white patch lesions resolved and the area of restored normal skin color accounted for more than 50% of the pre-treatment lesion area; (3) improvement: a small area of the white patch lesions resolved and the area of restored skin color accounted for 25%-50% of the original lesion area; (4) no improvement: failure to meet the above criteria, no pigment regeneration in the white patches and the lesion range expanded compared with that before treatment. The formula for calculating the total effective rate is: (number of cases with complete recovery +number of cases with marked improvement +number of cases with improvement)/total number of cases×100% (Guo *et al*., 2025).

Secondary outcome measures

Proportions of Th17 cells and RORγt-positive cells

Five milliliters of peripheral venous blood was collected using an anticoagulant tube. A BD FACSAria™ Fusion flow cytometer was used to capture fluorescent signals and the proportions of Th17 cells and RORγt-positive cells were calculated.Th17 cells are defined as the cell population of CD3+CD4+IL-17A+. The gating strategy refers to conventional standards (lymphocyte population → mononuclear cells → CD3+T cells → CD4+T cells → IL-17A+ cells) and isotype controls are used to exclude non-

specific binding. The cell population from which RORγt-positive cells are derived is CD3+CD4+T cells. The detection procedure is consistent with that of Th17 cells, except that the fluorescent antibody is replaced with RORγt-PE. Gating is based on the difference in fluorescence intensity between the RORγt antibody and the isotype control in the CD4+T cell population.

Interleukin-17 (IL-17) and interleukin-22 (IL-22)

The peripheral venous blood of 5 mL was collected using a coagulation-promoting tube. Serum was separated by centrifugation at 3000 r/min for 10 minutes using a Beckman Microfuge® 20R centrifuge. Human IL-17 ELISA Kit (sensitivity: 11.3 pg/ml, Cat. No.: PI550, Beyotime) was used for IL-17 detection and Human IL-22 ELISA Kit (sensitivity: 22.4 pg/ml, Cat. No.: PI595, Beyotime) was used for IL-22 detection.

DLQI

DLQI is the world's leading questionnaire for assessing the impact of skin disease on patients' quality of life. It consists of 10 items and each item provides 4 options corresponding to different scores, 0 points: no pain/itching, no disease-related symptoms and no impact; 1 point: mild pain/itching, no impact on daily life, symptoms are present but tolerable and no interference with basic activities such as sleep and work; 2 points: moderate pain/itching, partial impact on daily life, obvious symptoms, occasional impact on sleep or reduced work efficiency, but major activities can still be completed; 3 points: severe pain/itching, severe impact on daily life, intense symptoms, frequent insomnia, inability to work/study normally, or dependence on medication for relief to maintain basic life (Fekete *et al*., 2024, Gupta *et al*., 2021). Scores on the DLQI range from 0 to 30, with higher values representing a more substantial decrement in quality of life.

HADS

The HADS is an emotional screening tool specifically designed for hospital patients, widely employed to measure anxiety and depression levels in patients without psychotic disorders. It consists of 14 items, comprised two distinct subscales: the Anxiety Subscale (HADS-A) includes 7 items to evaluate anxiety and the Depression Subscale (HADS-D) includes 7 items to evaluate depression. Each item corresponds to 4 options, with a scoring range of 0-3 points. The total score for each of the two subscales ranges from 0-21 points. Scores increase in parallel with the severity of anxiety and depressive symptoms (Cao *et al*., 2024).

Incidence of adverse events

Adverse events occurring during treatment included skin pruritus, erythema, dryness, etc. (Alqifari *et al*., 2025, Hu *et al*., 2025). Adverse event rates were calculated as the number of affected cases divided by the total number of cases.

Sample size calculation method

In a randomized controlled clinical trial evaluating NB-UVB phototherapy combined with medication for vitiligo (Guo *et al*., 2025), Cohen's d was estimated to be 0.65 based on changes in VASI. The sample size was calculated using the analysis software G*Power 3.1.9.7. With an α value set at 0.05, a power of 90% and a two-tailed test, the calculation showed that 51 cases were required per group, thus yielding an overall sample size of 102 cases. Considering potential data loss in retrospective studies, The final analysis comprised 61 patients in the tacrolimus ointment group and 63 patients in the combination group (tacrolimus ointment plus NB-UVB), both of which were higher than the theoretically estimated numbers and met the statistical requirements. Moreover, the total sample size (124 cases) was larger than the theoretical total sample size (102 cases), thereby enhancing the credibility and robustness of the results.

Statistical analysis

Statistical analysis of patients' baseline data and outcome measures was performed using SPSS 27 software. For quantitative data: if they conformed to a normal distribution, they were expressed as mean±SD; independent samples t-test was used for comparisons between groups and paired t-test was used for comparisons within the same group before and after treatment. For quantitative data with a non-normal distribution, they were expressed as M (IQR); Between-group comparisons of continuous variables were performed using the Mann-Whitney U test and Wilcoxon signed rank test was used for comparisons within the same group before and after treatment. Categorical data were presented as n(%) and Chi-Square test was adopted to make between-group comparisons. Two-tailed tests were used for all analyses, with a significance threshold of $P<0.05$.

RESULTS

Comparison of patients' baseline data

Baseline characteristics were abstracted from the medical record database, all data are presented in table 2. A comparison of the data between the two groups showed that there were no significant between-group differences in the aforementioned baseline data (all $P>0.05$). This indicates that the two groups of patients are well comparable, allowing for the comparison of outcome measures.

Comparison of VASI scores between the two groups

Table 3 compares the VASI scores between the two groups, both groups were balanced at baseline, after treatment, the VASI scores of both groups showed a decreasing trend (*95% CI*: 2.18, 2.85, $P<0.001$, *95% CI*: 2.67, 3.40, $P<0.001$). In addition, compared with the tacrolimus ointment group after treatment, the VASI score of the tacrolimus ointment combined with NB-UVB group decreased more significantly (*95%CI*: 0.02, 0.77, $P=0.041$).

Table 2: Baseline Data [*mean ± SD*, *n (%)*]

Variables	Tacrolimus ointment group (n=61)	Tacrolimus ointment combined with NB-UVB group (n=63)	*95%CI*	*P*	*Effect size*
Age (years)	47.34±8.35	47.29±8.35	-2.91,3.03	0.969	0.007
BMI (kg/m^2)	24.01±1.58	24.03±1.54	-0.57,0.54	0.952	-0.011
Gender					
Male	26(42.6)	24(38.1)		0.607	0.046
Female	35(57.4)	39(61.9)			
Family history					
Yes	16(26.2)	19(30.2)		0.627	-0.044
No	45(73.8)	44(69.8)			
Duration of disease (years)					
Less than 1	11(18.0)	9(14.3)		0.872	0.075
1-5	25(41.0)	24(38.1)			
5-10	15(24.6)	17(27.0)			
More than 10	10(16.4)	13(20.6)			
Staging of disease					
Active	26(42.6)	31(49.2)		0.462	-0.066
Stable	35(57.4)	32(50.8)			
Lesion location					
Generalized	34(55.7)	32(50.8)		0.755	0.067
Acral	13(21.3)	17(27.0)			
Facial-cervical	14(23.0)	14(22.2)			

Note: BMI: body mass index.

Table 3: Comparison of VASI score (*mean ± SD*, scores)

Variables	Time	Tacrolimus ointment group (n=61)	Tacrolimus ointment combined with NB-UVB group (n=63)	*95%CI*	*P*	*Effect size*
VASI score	Before treatment	6.45±0.80	6.58±0.80	-0.41,0.16	0.391	-0.155
	After treatment	3.93±1.04	3.54±1.09	0.02,0.77	0.041	0.371
Change score		-2.52±1.31	1.41±0.18			
95%CI		2.18,2.85	2.67,3.40			
P		<0.001	<0.001			
Effect size		1.926	2.097			

Note: VASI: vitiligo area scoring index.

Table 4: Comparison of clinical effectiveness [n(%)]

Variables	Tacrolimus ointment group (n=61)	Tacrolimus ointment combined with NB-UVB group (n=63)	*P*	*Effect size*
Complete repigmentation	7(11.5)	11(17.5)	0.034	0.264
Marked improvement	13(21.3)	24(38.1)		
Moderate improvement	19(31.1)	18(28.6)		
No improvement	22(36.1)	10(15.9)		
Total effective	39(63.9)	53(84.1)	0.010	-0.231

These statistics highlight the area of vitiligo lesions was reduced in both groups after treatment and the effect of reducing vitiligo lesion area was better in the tacrolimus ointment combined with NB-UVB phototherapy group.

Comparison of clinical efficacy between the two groups

The clinical efficacy results are shown in table 4. In the tacrolimus ointment group, 7 patients achieved complete recovery, 13 achieved marked improvement, 19 achieved improvement and 22 showed no improvement, with a total effective rate of 63.9%.

Table 5: Comparison of the proportions of Th17 cells and RORγt-positive cells (*mean ±SD*, %)

Variables	Time	Tacrolimus ointment group (n=61)	Tacrolimus ointment combined with NB-UVB group (n=63)	*95%CI*	*P*	*Effect size*
Th17 cells	Before treatment	3.60±0.39	3.71±0.39	-0.25,0.02	0.103	-0.295
	After treatment	3.06±0.33*	2.88±0.33*	0.06,0.30	0.003	0.551
RORγt-positive cells	Before treatment	4.17±0.47	4.26±0.47	-0.26,0.08	0.284	-0.193
	After treatment	3.60±0.35*	3.46±0.37*	0.02,0.27	0.029	0.398

Note: *P<0.05 vs. before treatment; Th17: T helper cell 17; RORγt: retinoic acid receptor-related orphan receptor γt.

Table 6: Comparison of the IL-17 and IL-22 (*mean ±SD*, pg/mL)

Variables	Time	Tacrolimus ointment group (n=61)	Tacrolimus ointment combined with NB-UVB group (n=63)	*95%CI*	*P*	*Effect size*
IL-17	Before treatment	39.59±4.42	40.71±4.07	-2.63,0.39	0.143	-0.265
	After treatment	33.40±4.00*	27.60±3.75*	4.42,7.18	<0.001	1.496
IL-22	Before treatment	44.23±5.17	45.35±4.82	-2.90,0.66	0.215	-0.224
	After treatment	36.40±4.00*	35.00±3.75*	0.02,2.78	0.047	0.361

Note: *P<0.05 vs. before treatment; IL-17: interleukin-17; IL-22: interleukin-22.

Table 7: Comparison of DLQI Score [*M(IQR)*, scores]

Variables	Time	Tacrolimus ointment group (n=61)	Tacrolimus ointment combined with NB-UVB group (n=63)	*P*	*Z*
DLQI score	Before treatment	9.00(8.00,10.00)	9.00(8.00,11.00)	0.275	-1.092
	After treatment	5.00(4.50,6.50)*	3.00(3.00,4.00)*	<0.001	-7.450
Change score		-3.38±0.49	-5.98±1.06		
95%CI		3.25,3.50	5.72,6.25		
P		<0.001	<0.001		
Effect size		6.911	5.673		

Note: *P<0.05 vs. before treatment; DLQI: dermatology life quality index.

Table 8: Comparison of HADS-A score and HADS-D scores [*M(IQR)*, scores]

Variables	Time	Tacrolimus ointment group (n=61)	Tacrolimus ointment combined with NB-UVB group (n=63)	*P*	*Z*
HADS-A scores	Before treatment	9(8,10)	10(8.75,11)	0.334	-0.966
	After treatment	5(4,5)*	4(3,5)*	0.018	-2.375
HADS-D scores	Before treatment	9(8,10)	9(8,10)	0.093	-1.678
	After treatment	6(6,7.5)*	5(4,8)*	0.006	-2.774

Note: *P<0.05 vs. before treatment; HADS-A: hospital anxiety and depression scale-anxiety; HADS-D: hospital anxiety and depression scale-depression.

Table 9: Comparison of adverse events [n(%)]

Variables	Tacrolimus ointment group (n=61)	Tacrolimus ointment combined with NB-UVB group (n=63)	*P*	*Effect size*
Pruritus	7(11.5)	8(12.7)		
Erythema	0(0.0)	4(6.3)		
Dryness	4(6.6)	1(1.6)		
Total	11(18.0)	13(20.6)	0.714	-0.033

In the tacrolimus ointment combined with NB-UVB group, 11 patients achieved complete recovery, 24 achieved marked improvement, 18 achieved improvement and 10 showed no improvement, with a total effective rate of 84.1%. A statistically significant difference in the overall response rate was observed between the two groups (P=0.010) and the total effective rate of the tacrolimus ointment combined with NB-UVB group was higher than that of the tacrolimus ointment group. These results indicate that the therapeutic effect of tacrolimus ointment combined with NB-UVB phototherapy is better than that of tacrolimus ointment alone.

Comparison of the proportions of Th17 cells and RORγt-positive cells between the two groups

Table 5 shows that after treatment, the proportions of Th17 cells and RORγt-positive cells in both groups decreased (all P<0.05). Moreover, compared with the tacrolimus ointment group, the decreases in the proportions of Th17 cells and RORγt-positive cells in the tacrolimus ointment combined with NB-UVB group were more significant (*95%CI*: 0.06, 0.30, P= 0.003; *95%CI*: 0.02, 0.27, P=0.029). These results indicate that both treatment methods can control inflammation and improve immune function in vitiligo patients, but the effect of tacrolimus ointment combined with NB-UVB phototherapy is superior to that of tacrolimus ointment alone.

Comparison of IL-17 and IL-22 levels between the two groups

Table 6 illustrates the alterations in IL-17 and IL-22 concentrations. Treatment led to a decrease in IL-17 and IL-22 levels in both groups (all P<0.05) and the degrees of decrease in IL-17 and IL-22 levels in the tacrolimus ointment combined with NB-UVB group were higher than those in the tacrolimus ointment group (*95%CI*: 4.42, 7.18, P<0.001; *95%CI*: 0.02, 2.78, P=0.047). The above results indicate that both tacrolimus ointment combined with NB-UVB phototherapy and tacrolimus ointment alone can reduce the inflammatory response in vitiligo patients and the effect of tacrolimus ointment combined with NB-UVB phototherapy in reducing the inflammatory response is better.

Comparison of DLQI scores between the two groups

As shown in table 7, After treatment, the DLQI scores of both groups decreased (all P<0.05) and compared with the tacrolimus ointment group, the DLQI score of the tacrolimus ointment combined with NB-UVB group decreased more significantly (P<0.001). These results indicate that both tacrolimus ointment combined with NB-UVB phototherapy and tacrolimus ointment alone can improve the quality of life of vitiligo patients and the combined use has a better effect on improving the quality of life.

Comparison of HADS scores between the two groups

As shown in table 8, After treatment, the HADS-A and HADS-D scores of both groups decreased (all P<0.05). Moreover, compared with the tacrolimus ointment group, the decreases in HADS-A and HADS-D scores in the tacrolimus ointment combined with NB-UVB group were more significant (P=0.018, P=0.006). These results are indicative of both tacrolimus ointment combined with NB-UVB phototherapy and tacrolimus ointment alone can alleviate anxiety and depressive emotions in vitiligo patients and the combined use has a better effect on relieving patients' anxiety and depressive emotions.

Comparison of the incidence of adverse events between the two groups

Table 9 records the adverse events of patients in the two groups. During the treatment period, in the tacrolimus ointment group, 7 patients experienced skin pruritus and 4 patients had dry skin, with a total of 11 adverse events and an incidence rate of 18%. In the tacrolimus ointment combined with NB-UVB group, 8 patients had skin pruritus, 4 patients had erythema and 1 patient had dry skin, with a total of 13 adverse events and an incidence rate of 20.6%. Through comparison, the two groups exhibited a comparable safety profile with respect to adverse events between tacrolimus ointment combined with NB-UVB phototherapy and tacrolimus ointment alone (P=0.714).

DISCUSSION

Vitiligo, a common autoimmune depigmenting disorder, seriously impairs patients' appearance and mental health. Its pathogenesis is complex, involving multiple factors such as genetics, autoimmunity and oxidative stress, among which abnormal autoimmunity is considered to play a key role in disease progression (Bergqvist and Ezzedine, 2021, Feng and Lu, 2022). Currently, there are numerous treatment methods for vitiligo; however, single therapies often have limitations and are difficult to achieve ideal therapeutic effects. This study sought to compare the efficacy of tacrolimus ointment monotherapy versus combination therapy with NB-UVB in vitiligo and to clarify their effects on the Th17 immune axis, providing evidence-based support for clinical decision-making.

In this study, the treatment data of 124 vitiligo patients were analyzed retrospectively. At baseline, the two groups were comparable with respect to all measured variables, indicating good comparability. After treatment, in terms of clinical efficacy, the tacrolimus ointment combined with NB-UVB group exhibited a more pronounced decrease in VASI score and a higher total effective rate of clinical efficacy, which indicated that the combination therapy had superior efficacy in reducing the area of vitiligo lesions and improving depigmentation; in terms of immune regulation.

The percentage of Th17 cells, levels of IL-17 and IL-22 and share of RORγt-positive cells in the tacrolimus ointment combined with NB-UVB group were significantly lower

than those in the tacrolimus ointment group, suggesting that the combined therapy had a stronger inhibitory effect on Th17-related immune pathways; in terms of quality of life and mental state, the DLQI and HADS scores in the tacrolimus ointment combined with NB-UVB group decreased significantly, indicating that the combined therapy could more effectively improve patients' quality of life and alleviate negative emotions; The overall safety profile was comparable between the two groups, with no serious adverse events leading to treatment discontinuation.

The advantage of combined therapy in clinical efficacy stems from the synergistic and complementary effects of tacrolimus ointment and NB-UVB, which jointly improve the pathological state of vitiligo through two core links: immune protection and melanocyte activation (Sarkar *et al*., 2024). NB-UVB is ultraviolet light with a wavelength of 311-313 nm, which can penetrate the epidermal layer of the skin to reach the superficial layer of the dermis and act directly on melanocytes. On the one hand, it exerts to upregulate the proliferation and differentiation of melanocyte precursors, promote their migration to the lesioned area to supplement the damaged melanocytes in the lesions. On the other hand, NB-UVB can activate the activity of tyrosinase in melanocytes. Tyrosinase is a key rate-limiting enzyme in melanin synthesis and the enhancement of its activity can accelerate the conversion of tyrosine to dopa and dopaquinone, ultimately promoting the synthesis and maturation of melanin granules and realizing the pigment recovery in the lesioned area(Shah and McMichael, 2024), thereby reducing the VASI score and improving the clinical effective rate. The core pathological mechanism of vitiligo is the damage of melanocytes caused by abnormal autoimmunity. As a calcineurin inhibitor, tacrolimus ointment can inhibit the activation signaling pathway of T lymphocytes and reduce the release of pro-inflammatory cytokines. These cytokines can induce the apoptosis of melanocytes via the induction of apoptosis-related signaling cascades and at the same time inhibit the expression of melanin synthesis-related enzymes (Zhu *et al*., 2023, Ashrafizadeh, 2024). By inhibiting immune damage, tacrolimus ointment provides a protective barrier for melanocytes activated by NB-UVB, preventing newly generated melanocytes from being attacked by autoimmunity again, thereby consolidating the therapeutic effect and further improving the clinical effective rate. RORγt is the core switch for Th17 cell differentiation and its expression level directly determines the differentiation efficiency of Th17 cells. Tacrolimus ointment can indirectly down-regulate the transcriptional expression of RORγt gene through the inhibition of NFAT activity, thereby reducing the synthesis of RORγt protein. At the same time, NB-UVB can activate skin keratinocytes to secrete anti-inflammatory cytokines such as IL-10. IL-10 further inhibits the expression of RORγt by activating the STAT3 signaling pathway (Du *et al*., 2025, Wang *et al*., 2024), thereby reducing the differentiation source of Th17 cells at the transcriptional level. The differentiation of naive CD4+T cells into Th17 cells requires the synergistic effect of RORγt and cytokines such as IL-6 and IL-23(Liu *et al*., 2021). Tacrolimus ointment diminishes the capacity of IL-6 and IL-23 to activate T cells, meanwhile, NB-UVB can induce the apoptosis of Th17 cells. Ultraviolet light can damage the DNA of Th17 cells by generating ROS, activate the p53 apoptotic pathway and reduce the number of Th17 cells. IL-17 and IL-22 are core effector factors of Th17 cells. IL-17 can recruit neutrophils to the lesioned area, amplify the local inflammatory response and destroy the structure of melanocytes; IL-22 can inhibit the proliferation of melanocytes and melanin synthesis (Shah *et al*., 2024). Through reducing the number of Th17 cells and inhibiting the expression of cytokine genes (IL-17 and IL-22 genes) in Th17 cells, combined therapy can dualistically reduce the levels of these two cytokines and alleviate the damage of melanocytes caused by inflammation.

The reduction in DLQI and HADS scores essentially reflects a positive cycle of improved skin lesions, optimized mental state and enhanced quality of life. The negative emotions (anxiety, depression) and decreased quality of life in vitiligo patients mainly stem from social pressure and self-identity crisis caused by changes in skin appearance. Combined therapy significantly reduces the area of vitiligo lesions, promotes pigment recovery, improves patients' appearance, reduces peculiar glances in social situations, alleviates patients' self-denial psychology and lays a foundation for the improvement of mental state and quality of life (Ghalamkarpour *et al*., 2024). Tacrolimus ointment alone has a relatively slow onset of action. Some patients develop anxiety and abandon treatment due to the failure to see therapeutic effects for a long time. In contrast, combined therapy shortens the onset time due to synergistic effects and achieves more stable efficacy. Patients can observe the improvement of skin lesions more quickly (Tarafdar *et al*., 2025), which enhances their confidence in treatment, reduces worries about disease prognosis and further alleviates anxiety and depressive emotions. Notably, combined therapy does not increase treatment-emergent adverse events, avoiding the decline in quality of life and psychological pressure caused by adverse reactions. This allows patients to receive treatment with greater peace of mind, further optimizing their quality of life.

The results of this study are consistent with the conclusions of most studies on combined therapy for vitiligo in recent years, further verifying the advantages of combined therapy. In terms of efficacy-related studies: A randomized controlled study by Yang *et al*.(Yang et al., 2024) on 96 vitiligo patients showed that the total effective rate of tacrolimus ointment combined with NB-UVB treatment (97.92%) was significantly higher than that of the tacrolimus monotherapy group (85.42%), with a greater

reduction in VASI score, which corroborates our findings. The possible reason is that the irradiation dose of NB-UVB and the administration method of tacrolimus ointment were similar across different studies, ensuring the consistency of synergistic effects. (Zhang and Qiao, 2024) performed a randomized controlled trial involving 80 patients with progressive vitiligo, dividing them into a phototherapy group and a tacrolimus ointment combined with NB-UVB group. The combination therapy group achieved a higher overall response rate (92.50%) than the phototherapy group (75.00%); the immune function of patients in the combined therapy group was significantly improved, the overall incidence of adverse reactions did not differ significantly between the combination therapy group (2.50%) and the phototherapy group (7.50%) (P=0.305), an observation that corroborates our findings.

Critical evaluation of the study's strengths and limitations

This study not only evaluated clinical efficacy but also incorporated immunomodulatory indicators, quality of life and mental state indicators and safety indicators. It comprehensively assessed the value of combined therapy from three dimensions: pathological mechanism, clinical effect and patients' subjective feelings, avoiding the limitations of single-indicator evaluation and making the results more convincing. A total of 124 patients were included in this study, which improved the statistical reliability of the results. The treatment regimen adopted in this study is relatively consistent with routine clinical regimens and the study also conducted a detailed analysis of the causes of changes in various indicators. This provides specific references for clinicians to select treatment regimens and monitor efficacy and safety and thus has strong practical guiding value.

This study is a retrospective study. The treatment regimens for patients were selected by clinicians based on the specific conditions of the patients rather than being randomly assigned, which may lead to selection bias. Meanwhile, retrospective studies rely on data extraction from hospital's EMR system and data missing may occur, which affects the integrity of the results. This study did not report the long-term follow-up results after treatment; thus, the long-term efficacy and stability of the combined therapy could not be assessed. Vitiligo is characterized by a high recurrence rate; although some patients achieve significant short-term therapeutic effects, recurrence may occur due to the reactivation of immune abnormalities after treatment withdrawal. In addition, whether chronic use of tacrolimus ointment can contribute to skin atrophy and increased risk of infection and whether long-term NB-UVB irradiation can heighten the risk of cutaneous malignancies, also require long-term follow-up for evaluation. This study did not conduct subgroup analysis based on patients' age, lesion location, or disease duration, so it is impossible to clarify the differences in the efficacy of combined therapy among patients in different subgroups, which limits the guiding value of combined therapy in individualized treatment. This study only detected the changes in the levels of Th17-related immune indicators, did not further explore the impact of combined therapy on other immune pathways and did not verify the protective mechanism of combined therapy on melanocytes through in vitro experiments. This results in an insufficiently comprehensive explanation of the immunomodulatory mechanism and makes it difficult to fully clarify the action targets of combined therapy.In this study, the detailed data collection protocol for Th17 cells and RORγt-positive cells is insufficiently comprehensive in retaining all detailed data, including flow cytometry gating plots, event counts and detection CV values. A prospective randomized controlled study will be conducted in the future to further validate the conclusions of this study.

CONCLUSION

In conclusion, the clinical efficacy of tacrolimus ointment combined with NB-UVB in the treatment of vitiligo is superior to that of tacrolimus ointment monotherapy. It can effectively reduce the area of vitiligo and decrease disease activity, while suggesting a systemic downregulation of Th17-associated immunity, improving the systemic immune profile. Therefore, this combined therapy has good clinical application value.

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None

Authors' contributions

Lifen Chen: Developed and planned the study, performed experiments and interpreted results. Edited and refined the manuscript with a focus on critical intellectual contributions; Shuyi Shen and Songyu Wang: Participated in collecting, assessing and interpreting the date. Made significant contributions in the interpretation and manuscript preparation. All authors have read and approved the final manuscript.

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Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval

This study is a retrospective cohort study, which strictly adheres to the relevant guidelines of the Declaration of Helsinki. The study protocol has been reviewed and approved by the Medical Ethics Committee of The First Affiliated Hospital of Fujian Medical University. This study extracted patients' diagnosis and treatment data from

January 2020 to December 2023 based on the hospital's electronic medical record system. No additional interventional procedures were performed on the patients, and all data were anonymized. All patients have signed the informed consent form (ethical approval number: LC2024-15).

Conflict of interest

The authors declare that they have no conflicts of interest.

Consent to participate

We secured a signed informed consent form from every participant.

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