Dermatology Practical & Conceptual

Stabilizing Progressive Vitiligo with Systemic Treatment: Identifying Factors Associated With Patients Requiring Prolonged Treatment Duration

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Key words: Active vitiligo, Immunosuppression medications, Repigmentation

Citation: Yang TT, Lan CC. Stabilizing Progressive Vitiligo With Systemic Treatment: Identifying Factors Associated With Patients Requiring Prolonged Treatment Duration. *Dermatol Pract Concept*. 2025;15(4):5210. DOI: https://doi.org/10.5826/dpc.1504a5210

Accepted: March 6, 2025; **Published:** October 2025

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Patients with active vitiligo are treated with systemic immunosuppressants to halt disease progression. However, clinical features associated with patients whose condition is more difficult to control are unknown.

Objective: This study aimed to identify the clinical features of patients requiring extended periods of systemic immunosuppressants and the real-world clinical course of active vitiligo patients receiving systemic treatments.

Methods: This was a single-center retrospective study. Records of actively progressing vitiligo patients from September 2017 to August 2023 were reviewed.

Results: One hundred and fifty-nine patients with non-segmental actively progressing vitiligo were enrolled. In the six-month follow-up period, 101 (63.52%) patients required oral systemic immunosuppressants for ≤ 16 weeks without reactivation (Group 1), 51 (32.08%) patients required continuous systemic immunosuppressants for more than 16 weeks to achieve disease stabilization (Group 2), and seven (4.4%) patients achieved disease stabilization ≤16 weeks of oral immunosuppressants but recurred within nine months after stabilization (Group 3). Patients in Group 2 were significantly younger (39.69±11.51 vs. 46.47±14.91 years old; *P*=0.013) and had a lower proportion of facial involvement (56.86% vs. 76.24%; *P*=0.016) compared to Group 1. Similarly, both age (odds ratio

(OR): 0.968; *P*=0.016) and facial involvement (OR: 0.432; *P*=0.023) were identified as significant factors associated with decreased risk for Group 2. At one-year follow-up, 10.89% of Group 1 patients experienced disease reactivation.

Conclusions: Older patients and patients with facial involvement were more likely to achieve disease stabilization. Careful photo documentation is essential to optimal vitiligo management as disease reactivation is common after systemic treatment, even if initial disease stabilization is achieved.

Introduction

Vitiligo affects approximately 1% of the world's population and significantly impacts patients' quality of life [1,2]. Currently, treatment of vitiligo includes topical and/or oral immunosuppressants in combination with phototherapy [3,4]. For chronic stable vitiligo, topical corticosteroids or topical calcineurin inhibitors in combination with phototherapy are suggested [3,4]. For patients with rapidly progressing disease, however, systemic oral immunosuppressants for three to six months are recommended to suppress immune-mediated destruction of melanocytes in addition to phototherapy [3,4]. Various regimens of systemic immunosuppressants have been proposed. Oral mini-pulse corticosteroid therapy with doses equivalent to 2–10 mg dexamethasone/ betamethasone twice weekly on two consecutive days has been shown to halt disease progression while minimizing steroid-induced side effects [3-7]. Low-dose methotrexate, ranging from 7.5 to 25 mg weekly, is also effective [3,5,7-9]. However, the required length of treatment varies among patients, and some patients experience relapsing disease, making multiple courses of systemic treatments necessary [6,10]. Until now, there have been no known clinical features associated with actively progressive vitiligo patients whose condition is more difficult to control with systemic treatments. The proportion of patients experiencing disease reactivation after systemic immunosuppressants is also seldom documented.

Objective

In this study, we aimed to evaluate the clinical features associated with vitiligo patients who require prolonged or multiple courses of systemic immunosuppressants to control disease activity and to report the recurrence rate after systemic treatment.

Methods

This was a single-center retrospective study. Patient records from September 2017 to August 2023 at a specialized pigmentary disease clinic in a tertiary teaching hospital were retrospectively reviewed. All patients over age 18 years with non-segmental active vitiligo and who had received follow-up for more than six months starting from the day of treatment initiation were included. Our treatment protocol for active vitiligo is as follows: oral dexamethasone 2 mg on two consecutive days weekly or oral methotrexate 7.5 mg weekly for 12 to 16 weeks. If continuous disease progression is observed, oral immunosuppressants are prolonged until stabilization. Active vitiligo is defined as having any newly developed depigmented lesions or nontreated vitiligo lesions within the preceding three months. Disease stabilization is defined as no new depigmented lesion observed for three months. Systemic therapy was resumed if a recurrence of disease activity was observed. All patients received low-dose maintenance phototherapy for repigmentation [11]. Patients who refused systemic therapy, were under immunosuppressants for other diseases, or were receiving treatment for active cancer were excluded. This study was approved by the hospital institutional review board (KMUHIRB-E(I)-20240106).

To identify patients whose condition was more difficult to stabilize under the above treatment protocol, the enrolled patients were grouped into three groups. The first group included patients who only required oral systemic immunosuppressants for ≤16 weeks, without reactivation within six months from treatment initiation. The second group included patients who required continuous systemic immunosuppressants for more than 16 weeks. Patients whose disease activity could be controlled with ±16 weeks of oral immunosuppressants but which recurred within six months from treatment initiation were included in the third group.

Statistical analyses were performed by R software version 3.6.3. One-way ANOVA was used to compare the mean ages, and Fisher's exact test was used to compare the percentage frequencies among categorical variables. A p-value equal to or less than 0.05 was considered significant. Post hoc analyses were adjusted using Tukey's post hoc test or Bonferroni correction. In order to control for confounding factors, multivariate logistic regression was implemented to identify factors associated with active vitiligo more difficult to stabilize (Group 2). Bidirectional stepwise selection was used to select relevant variables for the logistic regression model.

Results

A total of 166 patients with active vitiligo received follow-up for more than six months in the study period. After excluding two patients under concomitant cancer treatment, two patients who refused systemic treatment, two patients under immunosuppressants for other diseases (Sjögren's syndrome and psoriasis), and one pregnant patient, a total of 159 patients were enrolled. The first group consisted of 101 (63.52%) patients, the second group included 51 (32.08%) patients, and the third group consisted of seven (4.4%) patients. The characteristics of patients are summarized in Table 1. Patients in Group 2 were significantly younger than patients in Group 1 (39.69±11.51 vs. 46.47±14.91 years; Tukey's post hoc test p=0.013). After post-hoc analysis with the Bonferroni correction (p< 0.05/3 = 0.017 was considered significant), the proportion of patients with facial involvement was significantly lower in Group 2 compared to Group 1 (56.86% vs. 76.24% vs.; P=0.016).

Age and facial involvement were independent variables selected in the multivariate logistic regression model to predict patients in Group 2 using bidirectional stepwise selection. Both age (β= -0.033; odds ratio (OR): 0.968; 95% confidence interval (CI): -0.059– -0.006; P=0.016) and facial involvement (β= - 0.84; OR: 0.432; 95% CI: -1.568– -0.115; P=0.023) were identified as significant factors associated with decreased risk for Group 2.

We further examined the number of patients requiring subsequent systemic treatment due to disease reactivation at 1-year follow-up despite initial disease stabilization. At 1-year follow-up, 70 patients remained in Group 1, and 11 (10.89%) patients experienced disease reactivation. To summarize, 108 (101+7; 67.92%) patients had their active vitiligo stabilized at month 3, and 101 (63.52%) patients remained inactive at month 6 from treatment initiation. At least 69 (51+7+11; 43.4%) patients required extended or additional systemic treatment at 1-year follow-up from treatment initiation. Patients experiencing disease reactivation despite initial stabilization were significantly younger (39.8±11.39 vs. 44.85≤14.32 years; P=0.03) and were more likely to have lesions involving the upper limbs (68.12% vs. 49.15%; P=0.046).

Conclusion

Patients with actively progressing vitiligo often require systemic treatments in addition to phototherapy to achieve good disease stabilization and induce repigmentation. There remains no standard systemic treatment for active vitiligo. However, mini-pulse therapy with oral dexamethasone and low-dose methotrexate have been demonstrated to provide good disease control with minimal adverse events in active vitiligo patients [5,6,12]. Currently, the recommended treatment duration for these systemic immunosuppressants is three to six months [3,4]. Nevertheless, the clinical profiles of difficult-to-control patients and the likelihood of recurrence once stabilization has been achieved have not been well-documented.

In the present study, both univariate and multivariate analyses showed that older patients and patients with facial

Table 1. Patient characteristics.

	Group 1 N = 101	Group 2 N = 51	Group 3 N = 7	P-value
Age, mean (SD)	46.47 (14.91)	39.69 (11.51)	40.71 (9.46)	**0.02**
Sex (female)	61 (60.40%)	28 (54.90%)	5 (71.43%)	0.71
Positive family history of vitiligo	4 (3.96%)	4 (7.84%)	0 (0%)	0.61
Positive family history of thyroid disease	11 (10.89%)	4 (7.84%)	2 (28.57%)	0.21
Abnormal thyroid tests	29 (28.71%)	14 (27.45%)	3 (42.86%)	0.71
Abnormal ANA	8 (7.92%)	3 (5.88%)	0 (0%)	1
Concomitant autoimmune disease	6 (5.94%)	2 (3.92%)	0 (0%)	1
Anatomic location				
Face	77 (76.24%)	29 (56.86%)	6 (85.71%)	**0.03**
Neck	36 (35.64%)	16 (31.37%)	1 (14.29%)	0.55
Trunk	40 (39.60%)	27 (52.94%)	5 (71.43%)	0.11
Upper limbs	52 (51.49%)	34 (66.66%)	5 (71.43%)	0.14
Hands	40 (39.60%)	26 (50.98%)	2 (28.57%)	0.34
Lower limbs	26 (25.74%)	21 (41.18%)	3 (42.86%)	0.11

Bold numbers indicate P<0.05. Abnormal ANA test was defined as ANA titer >1:80. Abbreviations: ANA: antinuclear antibody; SD: standard deviation.

involvement were less likely to require continuous systemic treatment for more than 16 weeks to achieve disease stabilization. However, within six months from treatment initiation, more than one-third of active vitiligo patients required prolonged systemic treatment or multiple courses of systemic treatments to stabilize their disease. In many clinical studies, the efficacy of systemic treatment is evaluated at the sixth month of treatment, and information regarding the clinical course of vitiligo beyond the follow-up period is lacking [5,6,12]. In this study, we further examined the number of patients requiring subsequent systemic treatment due to disease reactivation one year after stabilization had been achieved by systemic treatment. Although 12 to 16 weeks of systemic immunosuppressant is adequate to induce stabilization for approximately 60% of vitiligo patients with active disease, flare-up of disease activity may occur in more than 10% of patients who showed initial stabilization at 1-year follow-up from treatment initiation. In previous studies, the 1-year recurrence rate of non-segmental vitiligo treated with topical tacrolimus 0.1% and narrowband UVB were reported to be 40% and 44%, respectively [13,14]. Recently, Xu et al. reported recurrence rates of 23.7% and 26.3% at 6-month and 1-year follow-up in vitiligo patients with >80% repigmentation receiving treatment with traditional Chinese medicine [15]. The lower reactivation rate in the present study may be due to the difference in treatment modalities.

This study has several limitations. First, the retrospective nature of this study may have resulted in potential biases in data collection. Second, the number of patients included in Group 3 is relatively small compared with the other groups, which may potentially have reduced statistical power. Thirdly, the progression of vitiligo lesions was not evaluated using standardized severity assessment tools such as vitiligo area scoring index (VASI) or vitiligo extent score (VES) but based on clinical documentation and photos during each visit, which may have produced less objective results. Lastly, patients were not stratified by treatment (oral mini-pulse corticosteroid or methotrexate), which may have influenced treatment outcomes. However, both treatments are recommended by several guidelines and are equally effective in suppressing the activity of active vitiligo [5]. In the present study, treatment choice was determined through shared-decision making with the patient. Of the 42 patients who received methotrexate treatment, only one patient did not receive any oral mini-pulse corticosteroid therapy, and 38 patients received mini-pulse corticosteroid therapy prior to methotrexate, making it difficult to isolate the effect of each medication.

Currently, it is difficult to predict which specific patient will require extended treatment. Given that vitiligo patients often require a long treatment course to obtain satisfactory repigmentation [1], and unsynchronized repigmentation [16] is often observed among different vitiligo lesions, careful photo documentation is essential to optimal vitiligo management so that immunosuppressants may be given promptly when disease activity flare occurs after initial stabilization.

Ethical Approval: This study was approved by the hospital institutional review board (KMUHIRB-E(I)-20240106).

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