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Research Article

Tofacitinib for the Treatment of Refractory Progressive Vitiligo: A Retrospective Case Series

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Treatment of progressive vitiligo aims to halt the spread of the disease and facilitate repigmentation of lesions. JAK inhibitor has been shown some therapeutic effects on vitiligo, but the data for the progressive vitiligo are limited. This retrospective study was performed to evaluate the efficacy and safety of oral tofacitinib in 25 refractory progressive vitiligo patients who experienced failure to previous steroid treatments. 16 (64%) of the 25 patients noted stopping disease progression, and nearly half of the 16 cases halted progression within one month. 10 (40%) patients had repigmentation in varying degrees. Combination with phototherapy was a key factor affecting the rate of repigmentation. Oral tofacitinib might be a potentially effective treatment for intractable progressive vitiligo. The limitations of the study include the retrospective, single-centre study with small sample size and lack of comparison with other systemic therapies.

1. Introduction

Vitiligo is an autoimmune disease resulting from the loss of melanocytes [1]. This is a disfiguring disease that usually causes anxiety and depression in patients, especially those with progressive stages. Treatment of progressive vitiligo aims to halt the spread of the disease and facilitate the repigmentation of affected lesions. Topical medicines and narrow-band ultraviolet B (NB-UVB) phototherapy are the mainstays of treatment for vitiligo. Still, in some cases, these treatments cannot control the progress of the disease. Systemic glucocorticoid treatment may have a role in halting vitiligo progression. However, steroids have proved to be double-edged weapons. Other systemic treatments, such as methotrexate, minocycline, ciclosporin, and Janus kinase (JAK) inhibitors, may be also useful as mono or adjunctive therapy [2].

JAK inhibitors target the Janus kinase and signal transducer and activator of the transcription (JAK/STAT) pathway, which is closely related to the development of immune-mediated conditions such as vitiligo, alopecia areata, and atopic dermatitis [3]. So, besides rheumatoid arthritis, JAK inhibitors can also treat these inflammatory dermatoses [4]. Tofacitinib, a JAK1/3 inhibitor, has shown some therapeutic effects on vitiligo [5–7]. However, the data for the progressive vitiligo are limited. This study was performed to evaluate the efficacy and safety of tofacitinib in progressive vitiligo patients who experienced failure to previous steroid treatments.

2. Methods

This was a retrospective case series reviewing the progressive vitiligo patients treated with tofacitinib. Twenty-five patients with vitiligo were included in this study. They were from the Department of Dermatology, Hangzhou Third People's Hospital from April 2022 to October 2022. The study was approved by the Ethics Committee of the Researcher's Hospital. Patients were included if they had progressive vitiligo and experienced failure to previous steroid treatments. Patients were excluded if they (i) had severe liver or kidney or heart dysfunction; (ii) had infection, such as active tuberculosis, hepatitis B virus infection, or HIV infection; (iii) had cancer; (iv) were pregnant or breastfeeding; or (v)

had coagulation function abnormalities. If the vitiliginous lesion enlarged or new lesions were seen, the disease was regarded as progressive. Wood's lamp examination to analyze the presence of confetti-like lesions or trichome lesions was also considered. The disease activity was assessed using a vitiligo disease activity score (VIDA) [8]. VIDA score is a 6 points score and assesses the activity of vitiligo based on the presence of new lesions or expansion of existing lesions. If vitiligo activity is seen in the preceding 6 weeks or less, a VIDA score of +4 is given. Similarly, the score is +3 if active disease is present in the preceding 6–12 weeks, +2 if active disease is present in the preceding 3–6 months, and +1 if active disease is present in the preceding 6–12 months. In the present study, all patients were diagnosed as nonsegmental progressive vitiligo with a VIDA score of +4. These patients had experienced no improvement after 2–4 months of systemic corticosteroids, mainly oral minipulse (OMP) therapy or betamethasone injection. Oral methylprednisolone was given on two consecutive days every week with a 5-day rest between the two minipulses. Methylprednisolone was used in a dose of 0.5 mg/kg body weight on each day of the minipulse [9]. As for betamethasone injection therapy, Diprospan® (suspension of 7 mg compound betamethasone) was injected intramuscularly for patients with vitiligo, at an interval of 3-4 weeks [10]. All of them also failed with previous topical corticosteroids and calcineurin inhibitors. Some of them have taken phototherapy but cannot achieve halting of disease progression. After a thorough clinical and laboratory assessment, the patients were initiated on tofacitinib therapy at a dose of 5 mg twice daily. Tests of complete blood counts, liver and kidney function tests, blood glucose measurement, blood lipid measurement, T-cell-enzyme-linked immuno-spot assay (T-SPOT.TB), HIV testing, and lung CT examination were conducted before the tofacitinib treatment. The complete blood counts, liver and kidney function tests, blood glucose, and lipid measurements were rechecked after one month and three months of treatment. 12 patients took on NB-UVB phototherapy as a concomitant treatment. The radiation source was the Waldmann UV therapy system, which used Phillips TL-01 fluorescent lamps with a radiation spectrum of 310–315 nm and a peak of 311 nm. The patients were exposed to NB-UVB therapy 1-2 times per week, on nonconsecutive days for 13–50 sessions. The initial dose was 200 mJ/cm^2 and increased gradually until reaching the minimal erythema dose.

The efficacy of treatment was judged on two counts: an arrest of the disease process as well as the extent of repigmentation of lesions. Arrest of vitiligo progression, in this study, is defined as a decrease of at least 1 point in the VIDA score. The percentage of repigmentation after treatment was defined as follows: (area of repigmented vitiligo lesion/area of vitiligo lesion prior to therapy) × 100%. The main outcomes of interest were an excellent response (≥75% repigmentation), good response (50%–75% repigmentation), moderate response (25%–50% repigmentation), and poor response (<25% repigmentation).

3. Results

3.1. Patients. In total, 25 patients (10 men and 15 women) were included in the study. The characteristics and outcomes of these patients are listed in Table 1. The mean age at presentation was 39.6 years (between 12 and 62 years). Depigmented lesions involved 5–50% of the body surface area. 12 patients took on NB-UVB phototherapy as a concomitant treatment. Tofacitinib treatment durations varied from 2 to 9 months. After tofacitinib treatment, there was a clinical effect as shown in the representative photographs in Figure 1.

3.2. Outcome

3.2.1. Arrest of Progression. Arrest of vitiligo progression, in this study, is defined as a decrease of at least 1 point in the VIDA score. After the tofacitinib therapy, 16 (64.0%) of the 25 patients noted stopping disease progression, with VIDA score decreased to +3, +2, or +1. The duration of disease control ranged from one to four months. Among them, 7 patients stopped progress in one month, 3 in two months, 4 in three months, and 2 in four months.

Nine patients had no response to tofacitinib in this series.

3.2.2. Repigmentation. Of the 16 patients who achieved disease control mentioned above, 10 patients had repigmentation in varying degrees within 1–5 months of starting the oral tofacitinib therapy. The response was excellent (≥75% repigmentation) in 2 patients, good (50%–75% repigmentation) in 3 patients, and moderate (25%–50% repigmentation) in 3 patients, while 2 patients showed a poor response (<25% pigmentation). Tofacitinib could only control the disease progression but without repigmentation in the other 6 cases.

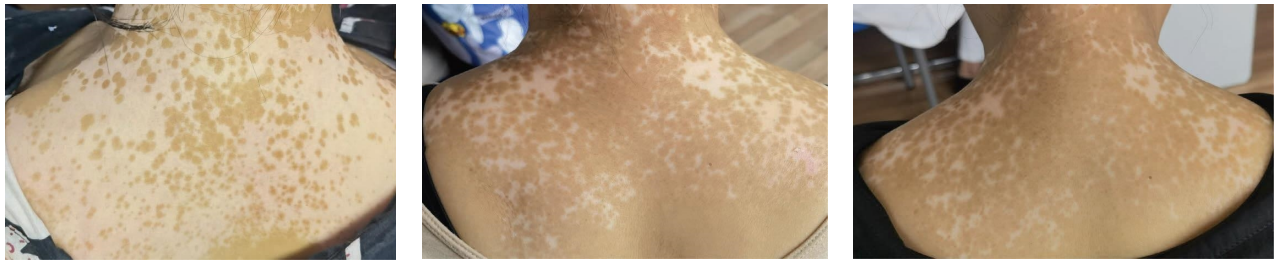
As for the factors affecting repigmentation, we found phototherapy might be a key factor affecting the rate of repigmentation during the tofacitinib treatment. Of the 10 patients with successful repigmentation, 9 patients had experienced NB-UVB phototherapy. On the contrary, of the 6 patients without repigmentation, just one patient had received phototherapy.

3.3. Follow-Up. During the follow-up of six months, 3 patients continued to take low-dose tofacitinib (5 mg every day), and 22 patients discontinued the treatment. Those 9 patients with no response to tofacitinib abandoned this therapy. 4 patients remained in remission six months after discontinuation, and 9 patients relapsed 2–5 months after discontinuation, most of them received treatment with tofacitinib again when relapse occurred.

3.4. Side Effects of the Oral Tofacitinib Therapy. Adverse events were a transient common cold in two patients. No obvious abnormality of biochemistry metabolism was found.

Table 1: Clinical characteristics of the vitiligo patients and outcomes of tofacitinib treatment.

Patient no.	Age (y)/ sex	Disease duration (y)	Location of lesion	VIDA score at baseline	Tofacitinib treatment duration (m)	Concomitant NB-UVB	VIDA score after therapy	Arrest of progression	Repigmentation
1	F/34	17	Entire body	4	5	No	3	Yes	No
2	M/33	15	Entire body	4	5	No	2	Yes	No
3	F/12	5	Limbs and crotch	4	6	1/W	2	Yes	Yes
4	F/29	2	Face, neck, chest, and arms	4	7	1/W	2	Yes	Yes
5	F/18	0.5	Neck, trunk, and hands	4	9	1/W	1	Yes	Yes
6	F/56	7	Entire body	4	9	2/W	1	Yes	Yes
7	M/26	10	Limbs and trunk	4	5	2/W	2	Yes	Yes
8	F/62	30	Entire body	4	6	1/W	2	Yes	Yes
9	M/57	8	Hands	4	4	No	2	Yes	No
10	F/46	26	Neck and limbs	4	3	1/W	3	Yes	No
11	M/26	4	Entire body	4	7	No	2	Yes	No
12	F/50	2	Face, neck, trunk, and hands	4	7	1/W	2	Yes	Yes
13	F/50	0.5	Arms	4	2	No	2	Yes	No
14	F/50	10	Entire body	4	7	1/W	3	Yes	Yes
15	M/46	3	Face and hands	4	9	No	1	Yes	Yes
16	F/49	4	Entire body	4	8	1/W	2	Yes	Yes
17	M/57	10	Scalp, face, and hands	4	4	No	4	No	No
18	F/56	18	Entire body	4	2	No	4	No	No
19	F/31	5	Scalp, face, neck, and limbs	4	3	1/W	4	No	No
20	F/40	20	Entire body	4	2	1/W	4	No	No
21	M/30	12	Face, neck, and limbs	4	2	No	4	No	No
22	F/33	7	Face, trunk, and limbs	4	2	No	4	No	No
23	M/29	6	Entire body	4	2	No	4	No	No
24	M/49	7	Trunk and limbs	4	3	No	4	No	No
25	M/21	1.5	Face, hands, feet, and crotch	4	3	No	4	No	No



(a) (b) (c)

Figure 1: Representative photographs of vitiligo lesions shown at baseline (a) and following tofacitinib treatment with NB-UVB phototherapy after 5 months (b) and 7 months (c).

4. Discussion

Vitiligo involves the destruction of melanocytes via cell-mediated immunity, of which interferon (IFN)-γ and CD8+ T cells are key players [11]. IFN-γ-induced expression of C-X-C-motif chemokine-10 (CXCL10) in keratinocytes has been proposed as an intermediary of vitiligo depigmentation [12]. The IFN-γ signal transduction occurs through JAK [13]. Therefore, it is postulated that the JAK inhibitor tofacitinib blocks IFN-γ signalling and downstream CXCL10 expression, resulting in repigmentation [5].

This retrospective review showed that disease activity was stopped by oral tofacitinib in 16 of 25 patients with refractory progressive vitiligo. The response rate to tofacitinib was 64.0% if the halting of the progression of vitiligo is taken as the criterion for judging the response to therapy. In our study, these vitiligo patients received systemic steroid treatments but had no significant improvement. However, after treatment with tofacitinib, the VIDA score of 64.0% of these patients decreased by more than 1 point, which suggested that tofacitinib might play a powerful anti-inflammatory role in vitiligo. Meanwhile, the quick effect of tofacitinib was noted, with 43.8% of the 16 patients halting progression within one month. For our cases that were refractory, it was supposed to be more efficient to tofacitinib in stopping the disease in those not so recalcitrant cases.

In this study, 10 patients (40.0%) had repigmentation in varying degrees. In Song et al.'s study [7], 15 patients were given tofacitinib 5 mg twice a day and NB-UVB phototherapy for vitiligo. At the 16th week after treatment, the percentage of repigmentation ≥50% was achieved in 14 of 15 patients. Our results did not show such outstanding repigmentation response compared with Song et al.'s study, partly because their patients were not all in the active stage and were treated with NB-UVB phototherapy three times weekly. While our patients were all in active stage, resistant to systemic steroids therapy, and not all of them underwent phototherapy, these factors may contribute to the difference in outcomes between our study and Song et al.'s study on tofacitinib treatment for vitiligo.

In Liu et al.'s study [14], treatment of vitiligo using tofacitinib seemed to require light exposure. However, another case report showed that long-term tofacitinib could be effective as monotherapy without sun exposure or phototherapy [15]. We found in this study that more patients achieved successful repigmentation if combined with NB-UVB phototherapy, although the effect of once or twice weekly NB-UVB therapy might be limited. Tofacitinib, as a blocker of inflammatory pathway, could inhibit the autoimmune reaction of vitiligo but could not restore melanocytes in a short time. It seemed to be more efficient with a combination of phototherapy. In addition, the locations of repigmentation in this study included the face, neck, trunk, and limbs, with better facial repigmentation. Among the 10 patients with repigmentation, 7 had lesions on the face, and 6 had varying degrees of repigmentation. The face is well known to have better responses than other areas after treatment. The results of this study also showed better facial efficacy by the treatment of tofacitinib, which might be related to sunlight exposure.

The data from follow-up showed a high relapse rate of 69.2% (9/13) on discontinuation of tofacitinib treatment. These relapsed patients receiving retreatment with tofacitinib achieved remission again. Probably continuous treatment will be needed in this line of therapy.

The most common adverse reaction of JAK inhibitors is infection. Tofacitinib is reportedly also associated with malignancies, cytopenias, and hyperlipidemia in some patients with rheumatoid arthritis [16]. Among the 25 patients we observed, 2 patients had upper respiratory tract infections. However, based on the short-term research results, further research was needed to explore the impact of long-term use. No other severe adverse effects were reported, showing that tofacitinib was safe for treating vitiligo.

In conclusion, based on our observations, for patients with progressive vitiligo but not responsive to traditional treatment, tofacitinib might be a new therapeutic option. Oral tofacitinib could arrest the progression of vitiligo and induce repigmentation when combined with phototherapy.

The limitations of our study include the retrospective, single-centre study with a small sample size, and our findings thus may not be representative of the treatment outcome in other populations. A better design would have been a comparison of tofacitinib with other systemic treatment options in vitiligo like oral corticosteroids or oral methotrexate. We look forward to seeing more studies with high evidence levels on the treatment of vitiligo with JAK inhibitors.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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